National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pancreatic Adenocarcinoma

Version 2.2021 — February 25, 2021

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NCCN Guidelines Version 2.2021
Pancreatic Adenocarcinoma

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NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN Member Institutions, https://www.nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2021 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2021 include:

MS-1
- **The Discussion section corresponding to the following topics has been updated: Overview, risk factors and genetic predisposition, premalignant tumors of the pancreas, and systemic therapy approaches for locally advanced or metastatic disease.**

Updates in Version 1.2021 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2020 include:

General Changes:
- **Changed "Unresectable at surgery" to "unresectable disease at surgery."**
- **Algorithm for locally advanced disease has been moved after the algorithm for borderline resectable disease, and before unresectable disease at surgery. Page numbers and links have been updated.**

PANC-1
- **Footnote a, modified to include: "...(see Principles of Palliation and Supportive Care [PANC-H])."**

PANC-2
- **Treatment, second option modified: EUS-guided biopsy if considering neoadjuvant thearpy *and consider stent if clinically indicated*.**
- **After "consider neoadjuvant therapy..." bullet removed: "Consider stent if clinically indicated"**

PANC-5
- **Heading modified "~~Second-line~~ *Subsequent* Therapy" (Also on PANC-9)**
- **Good PS, no disease progression, subsequent therapy option added: Continue systemic therapy**

PANC-6
- **Title heading changed from Locally Advanced to Unresectable Disease At Surgery**
- **No jaundice, treatment modified: Consider gastrojejunostomy, if clinically indicated ~~(category 2B for prophylactic gastrojejunostomy)~~**
- **If jaundice present, treatment modified: Gastrojejunostomy, *if clinically indicated* ~~(category 2B for prophylactic gastrojejunostomy)~~**

PANC-7
- **Footnote modified: "...may be candidates for additional chemotherapy *(or chemoradiation if none was delivered neoadjuvantly)* following surgery...**
- **Footnote added: CA 19-9 elevation, without other evidence of disease recurrence, is not a clear indication for treatment.**

PANC-A 5 of 8
- **Location added: Neck (anterior to SMV/PV confluence)**
- **Footnote added" See Management of Neck Lesions on PANC-D (2 of 2).**

PANC-D 2 of 2
- **Added section: Surgery for Locally Recurrent Pancreatic Ductal Adenocarcinoma:**
- **Footnote added: Moletta L, Serafini S, Valmasoni M, et al. Surgery for recurrent pancreatic cancer: Is it effective? Cancers (Basel) 2019;11(7):991.**

PANC-E
- **This section has been significantly revised.**
- **References have been updated.**

Continued

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Updates in Version 1.2021 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2020 include:

PANC-F 4 of 8
- Pembrolizumab, reference added: Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase 2 KEYNOTE-158 study. J Clin Oncol 2020;38:1-10.

PANC-F 5 of 8
- Removed: Good PS
- Olaparib (only for germline *BRCA1/2* mutations) moved from "useful in certain circumstances" to "preferred"
- Regimens moved from "useful in certain circumstances" to "other recommended":
  - ◊ Capecitabine
  - ◊ Gemcitabine + nab-paclitaxel modified schedule (category 2B)
  - ◊ Gemcitabine single agent (category 2B)
- FOLFIRI (preferred regimen) was removed and replaced with 5-FU ± irinotecan (useful in certain circumstances)
- FOLFOX (category 2B) moved from "other recommended regimens" to "useful in certain circumstances"
- Footnote removed: ECOG 0-2 for combination regimens; ECOG 0-3 for single agent options.
- Footnote added: 5-FU ± irinotecan may be considered for maintenance therapy in the case of oxaliplatin-related progressive neuropathy or allergy to oxaliplatin.
- Footnote added: While FOLFOX is not commonly used in the maintenance setting, it may be considered as an alternative to irinotecan-based therapy when GI toxicity is a concern.

PANC-F 6 of 8
- Heading modified: ~~Second-line~~ *Subsequent* Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

PANC-F 8 of 8
- Reference added; Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase 2 KEYNOTE-158 study. J Clin Oncol 2020;38:1-10.

PANC-G
- This section has been significantly revised.
- References have been updated.

PANC-H
- Depression, pain, and malnutrition
  - Bullet modified: Formal Palliative Medicine Service evaluation when ~~appropriate~~ *available*
  - Bullet modified: Nutritional evaluation with a registered dietitian when ~~appropriate~~ *available*
  - Symptom, modified: *Exocrine* pancreatic ~~exocrine~~ insufficiency
- Footnote added: Consider encouraging advanced care planning.

INTRODUCTION

Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with use of appropriate imaging studies.

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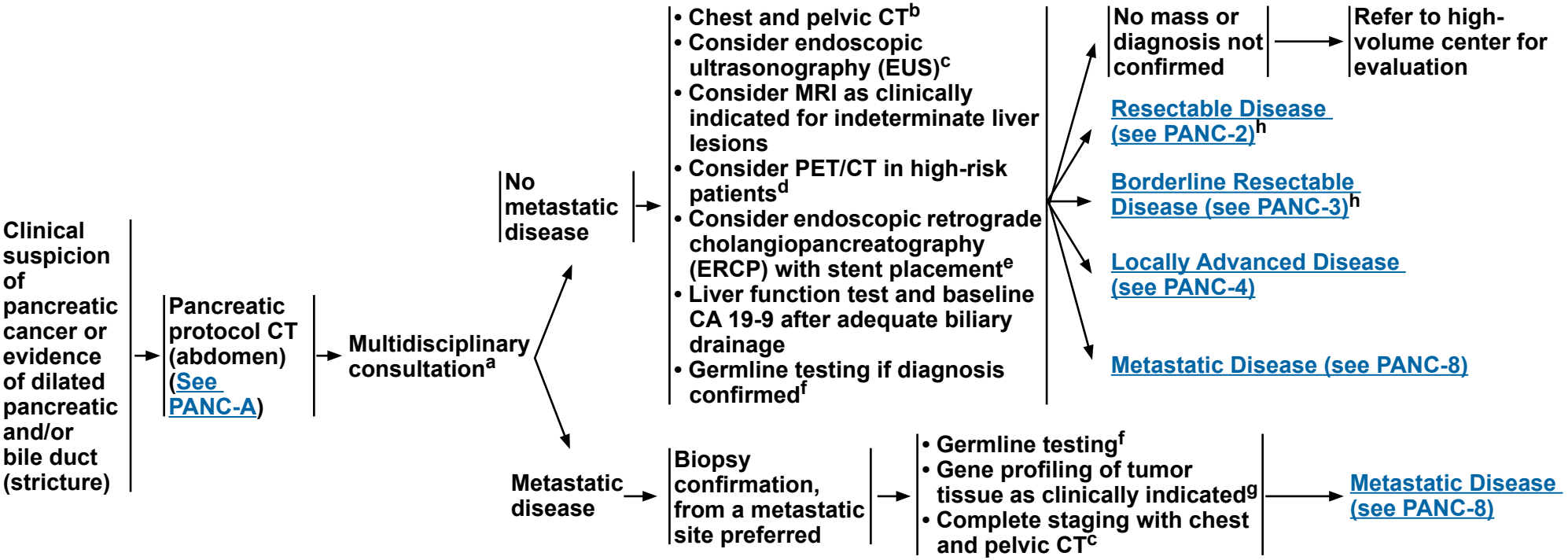
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL PRESENTATION AND WORKUP



[a] Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, pathology, geriatric medicine, and palliative care (see Principles of Palliation and Supportive Care [PANC-H]).Consider consultation with a registered dietitian. See NCCN Guidelines for Older Adult Oncology and NCCN Guidelines for Palliative Care.

[b] Imaging with contrast unless contraindicated.

[c] EUS to confirm primary site of involvement; EUS-guided biopsy if clinically indicated.

[d] 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. See Principles of Diagnosis, Imaging, and Staging (PANC-A).

[e] See Principles of Stent Management (PANC-B).

[f] Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. Okur V, et al. Cold Spring Harb Mol Case Stud 2017;3(6):a002154. See Discussion and NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic.

[g] Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for actionable somatic findings including, but not limited to: fusions (*ALK, NRG1, NTRK, ROS1*), mutations (*BRAF, BRCA1/2, HER2, KRAS, PALB2*), and mismatch repair (MMR) deficiency (detected by tumor IHC, PCR, or NGS). Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. See Discussion.

[h] See Criteria Defining Resectability Status at Diagnosis (PANC-C).

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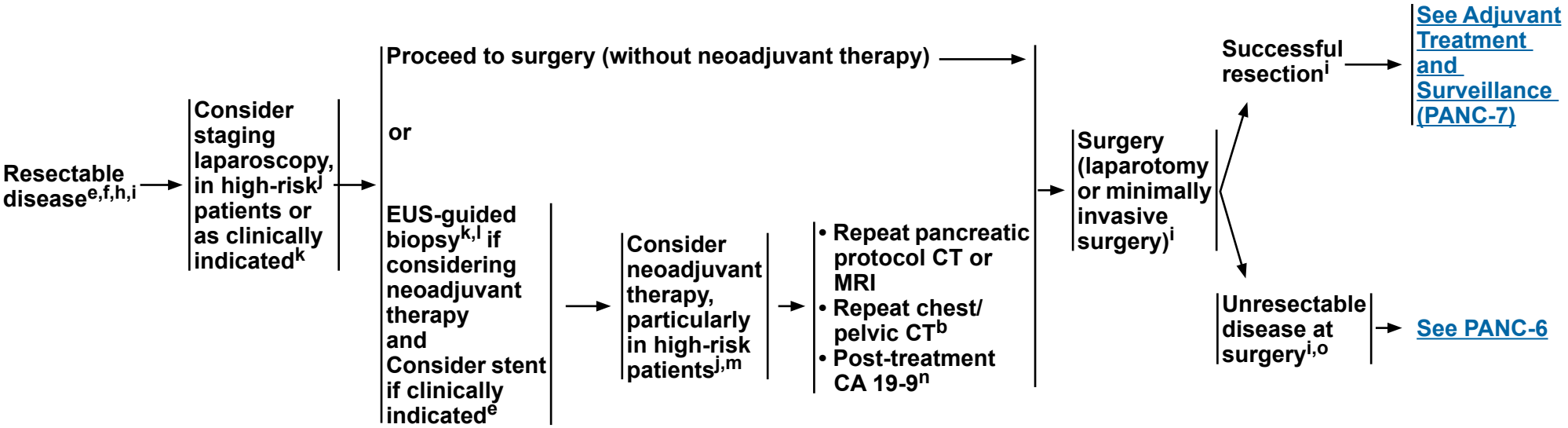
RESECTABLE DISEASE **TREATMENT**



[b] Imaging with contrast unless contraindicated.
[e] See Principles of Stent Management (PANC-B).
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[h] See Criteria Defining Resectability Status at Diagnosis (PANC-C).
[i] See Principles of Surgical Technique (PANC-D) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-E).
[j] High-risk features include imaging findings, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain.
[k] See Principles of Diagnosis, Imaging, and Staging (PANC-A).
[l] Core biopsy recommended, if possible, to obtain adequate tissue for possible ancillary studies.
[m] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. See Principles of Systemic Therapy (PANC-F) for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included; see Principles of Radiation Therapy (PANC-G). Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center.
[n] Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary infection (cholangitis), inflammation, or obstruction, benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (See Discussion).
[o] See Principles of Palliation and Supportive Care (PANC-H).

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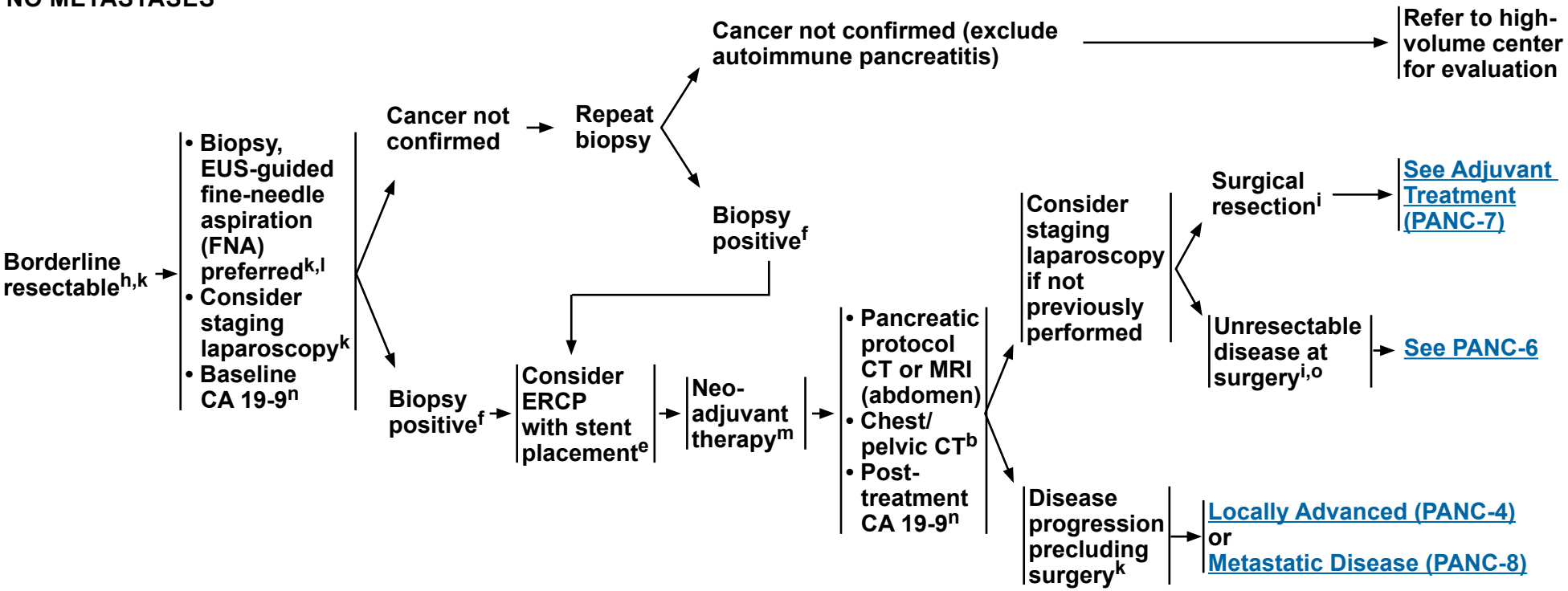
BORDERLINE RESECTABLE DISEASE
NO METASTASES

TREATMENT



[b] Imaging with contrast unless contraindicated.
[e] See Principles of Stent Management (PANC-B).
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[h] See Criteria Defining Resectability Status at Diagnosis (PANC-C).
[i] See Principles of Surgical Technique (PANC-D) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-E).
[k] See Principles of Diagnosis, Imaging, and Staging (PANC-A).
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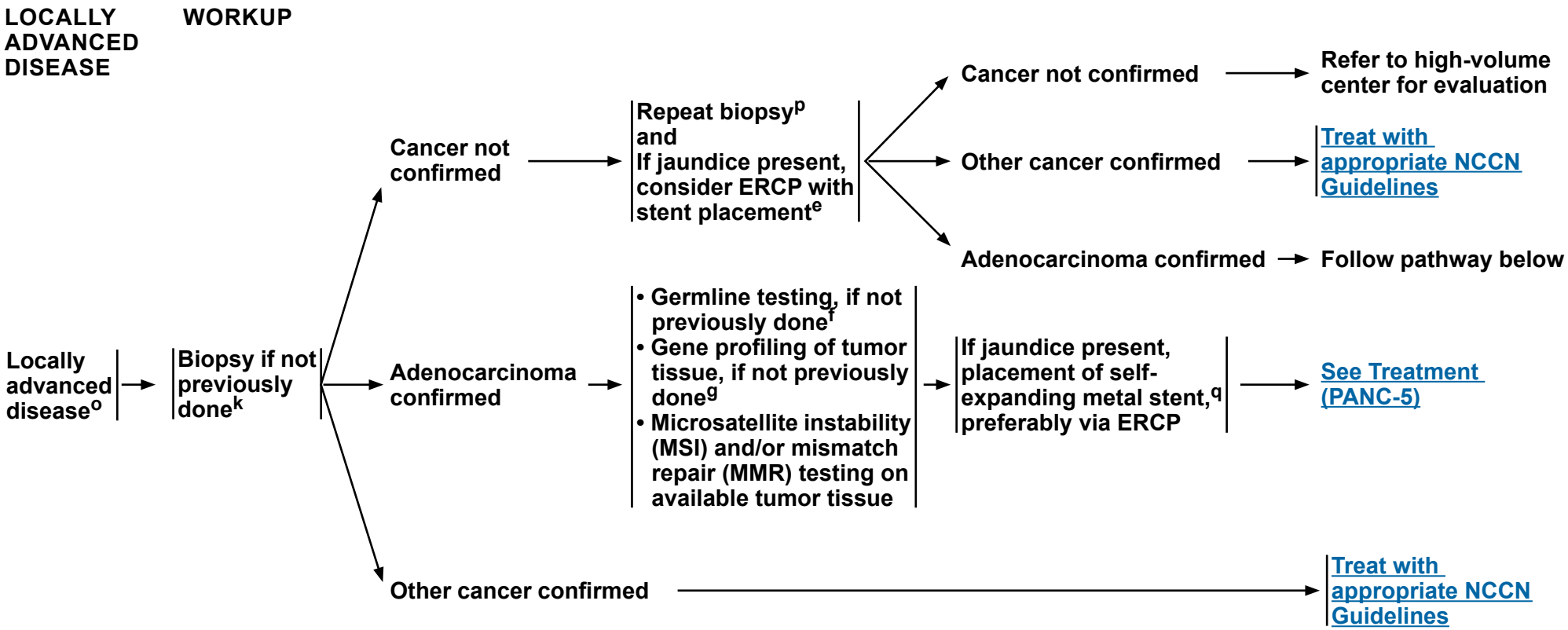

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[k] See Principles of Diagnosis, Imaging, and Staging (PANC-A).

[o] See Principles of Palliation and Supportive Care (PANC-H).

[p] EUS-guided FNA and core biopsy at a center with multidisciplinary expertise is preferred. When EUS-guided biopsy is not feasible, CT-guided biopsy can be done.

[q] Unless biliary bypass performed at time of laparoscopy or laparotomy.

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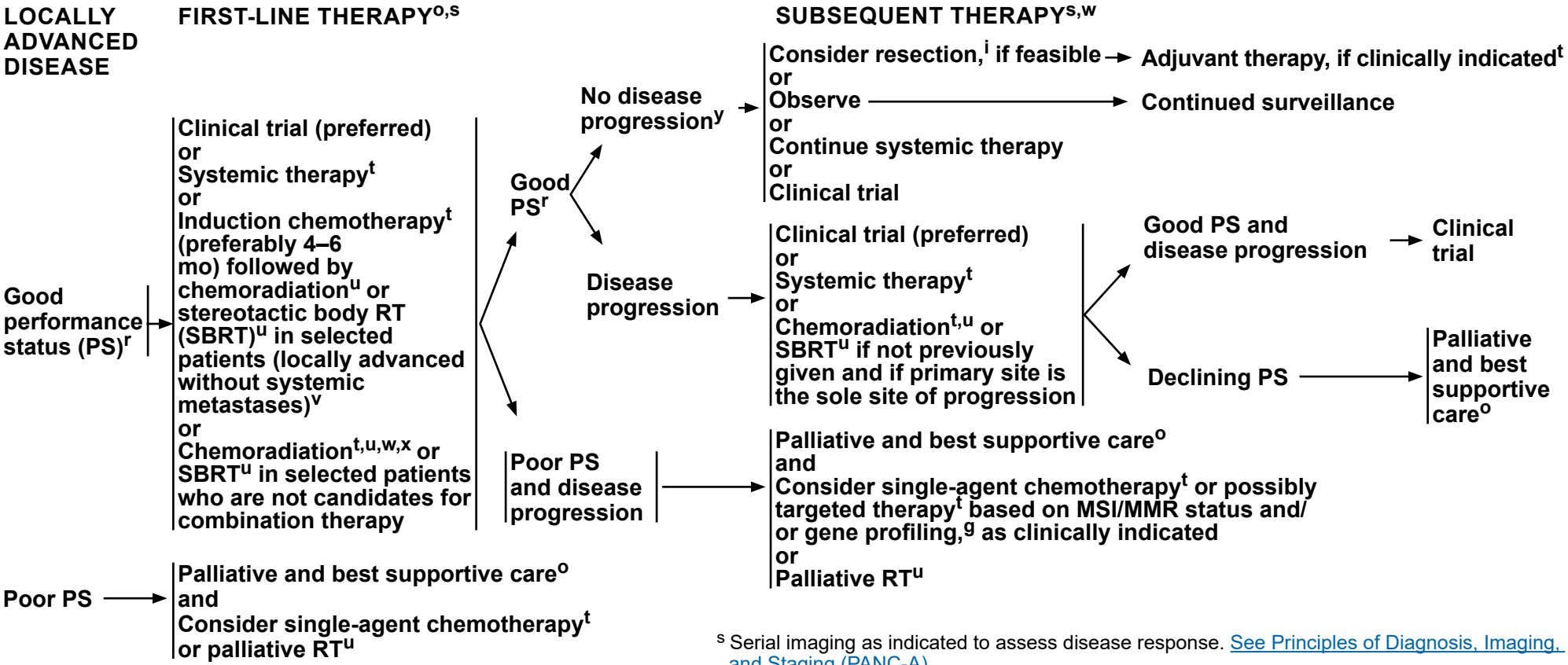

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[i] See Principles of Surgical Technique (PANC-D) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-E).

[o] See Principles of Palliation and Supportive Care (PANC-H).

[r] Defined as ECOG 0-1, with good biliary drainage and adequate nutritional intake, and ECOG 0-2 if considering gemcitabine + albumin-bound paclitaxel.

[s] Serial imaging as indicated to assess disease response. See Principles of Diagnosis, Imaging, and Staging (PANC-A).

[t] See Principles of Systemic Therapy (PANC-F).

[u] See Principles of Radiation Therapy (PANC-G).

[v] Laparoscopy as indicated to evaluate distant disease.

[w] Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy.

[x] Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy. (Hammel P, et al. AMA 2016;315:1844-1853.)

[y] In the presence of marked radiographic improvement, the patient should be referred to a high-volume center for consideration of surgery. However, the primary site often does not regress radiographically even in the setting of effective treatment. If there is radiographic stability and marked clinical improvement or decline in CA19-9, the patient should still be referred for evaluation.

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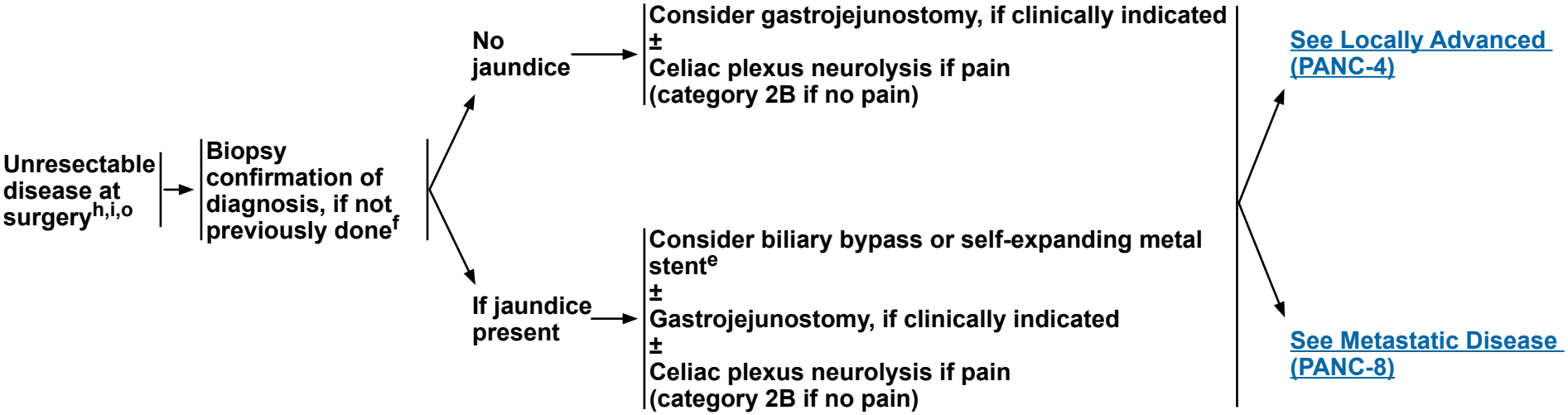
UNRESECTABLE DISEASE AT SURGERY **TREATMENT**



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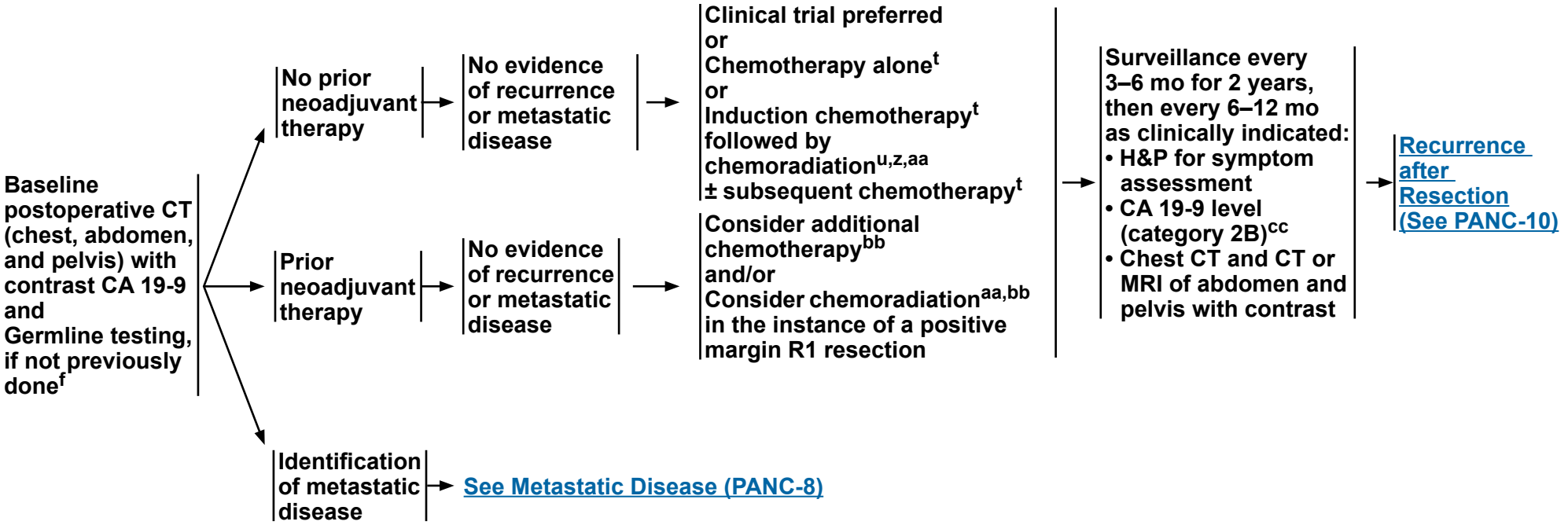
POSTOPERATIVE ADJUVANT TREATMENT

SURVEILLANCE



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[t] See Principles of Systemic Therapy (PANC-F).

[u] See Principles of Radiation Therapy (PANC-G).

[z] Adjuvant treatment should be administered to patients who have adequately recovered from surgery; treatment should be initiated within 12 weeks. If systemic chemotherapy precedes chemoradiation, restaging with imaging should be done after each treatment modality.

[aa] If considering chemoradiation due to positive margins, chemotherapy should be given prior to the administration of chemoradiation.

[bb] Patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy (or chemoradiation if none was delivered neoadjuvantly) following surgery and multidisciplinary review. The adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

[cc] CA 19-9 elevation, without other evidence of disease recurrence, is not a clear indication for treatment.

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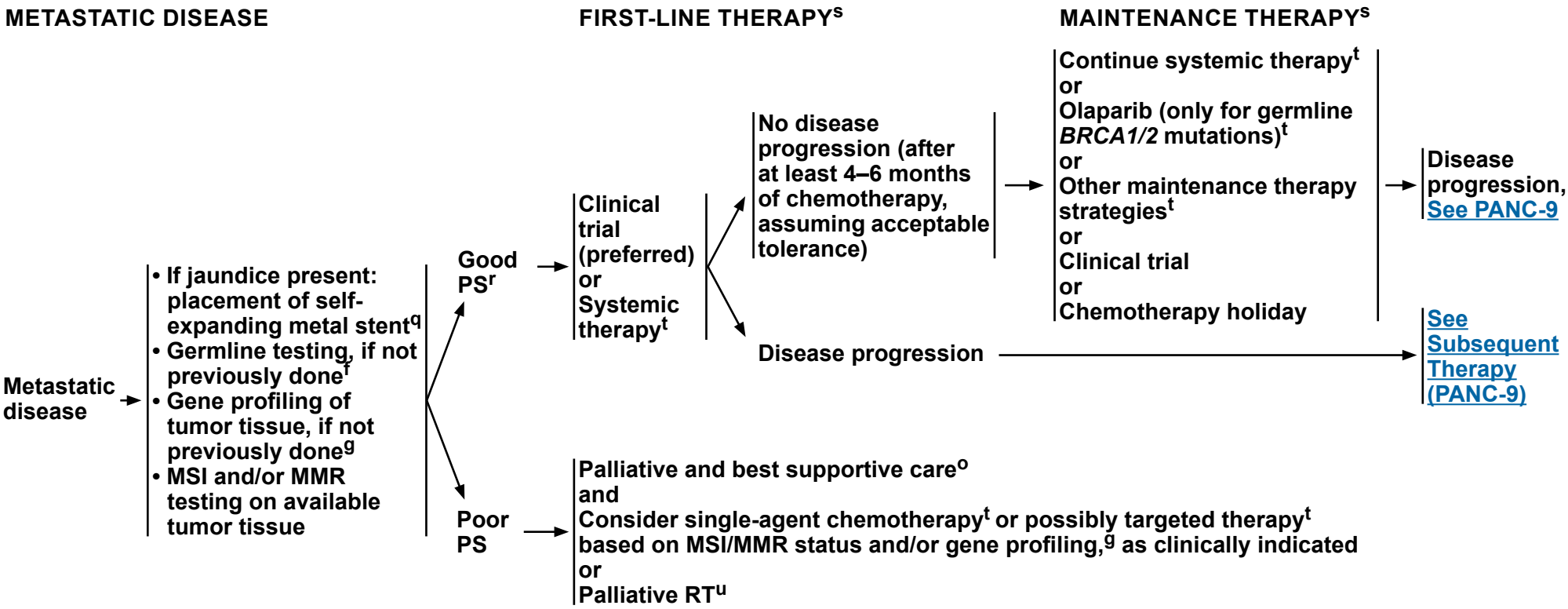
Discussion



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[o] See Principles of Palliation and Supportive Care (PANC-H).

[q] Unless biliary bypass performed at time of laparoscopy or laparotomy.

[r] Defined as ECOG 0-1, with good biliary drainage and adequate nutritional intake, and ECOG 0-2 if considering gemcitabine + albumin-bound paclitaxel.

[s] Serial imaging as indicated to assess disease response. See Principles of Diagnosis, Imaging, and Staging (PANC-A).

[t] See Principles of Systemic Therapy (PANC-F).

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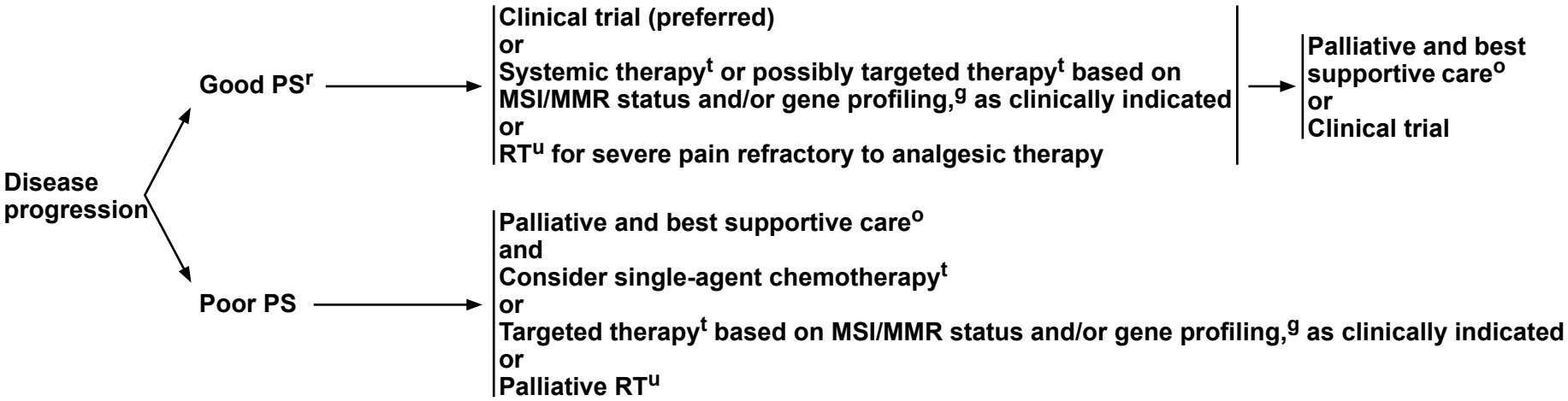
DISEASE PROGRESSION **SUBSEQUENT THERAPY[s]**



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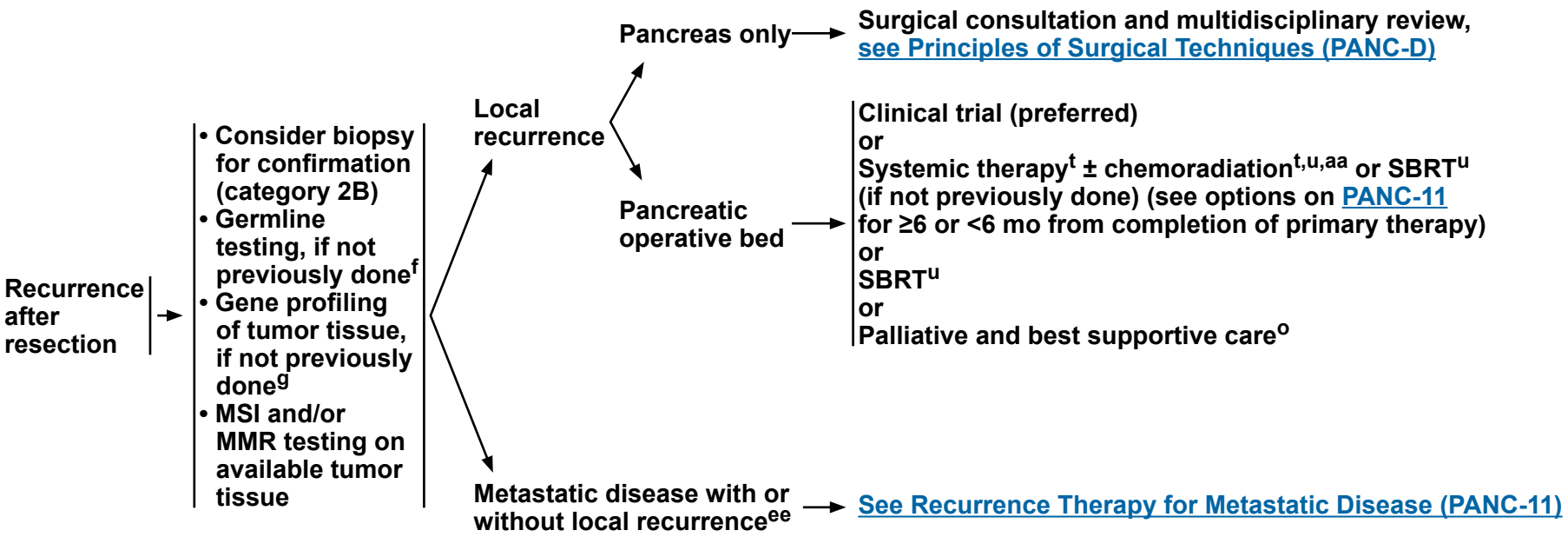
RECURRENCE AFTER RESECTION

RECURRENCE THERAPY[dd]



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[o] See Principles of Palliation and Supportive Care (PANC-H).

[t] See Principles of Systemic Therapy (PANC-F).

[u] See Principles of Radiation Therapy (PANC-G).

[aa] If considering chemoradiation due to positive margins, chemotherapy should be given prior to the administration of chemoradiation.

[dd] Best reserved for patients who maintain a good performance status.

[ee] For more information about the treatment of isolated pulmonary metastases, see Discussion.

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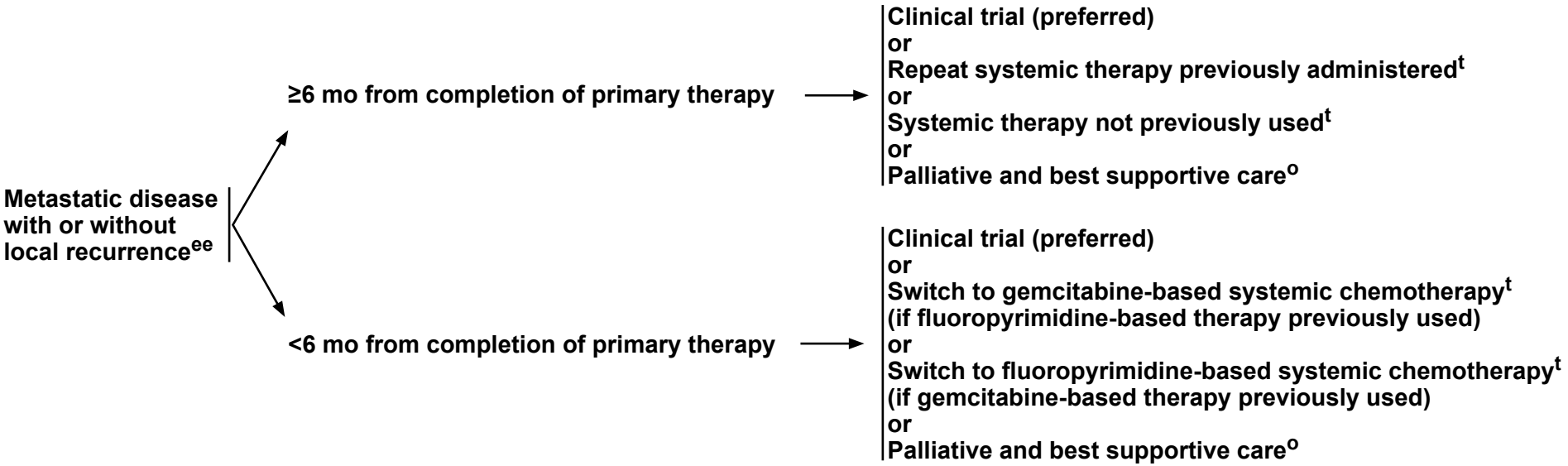
METASTATIC DISEASE

RECURRENCE THERAPY[dd]



[o] See Principles of Palliation and Supportive Care (PANC-H).
[t] See Principles of Systemic Therapy (PANC-F).
[dd] Best reserved for patients who maintain a good performance status.
[ee] For more information about the treatment of isolated pulmonary metastases, see Discussion.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

- **Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a 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 (at least 15–20) of pancreatic resections annually.**

- **High-quality dedicated imaging of the pancreas should be performed at presentation (even if standard CT imaging is already available), preferably within 4 weeks of surgery, and following neoadjuvant treatment to provide adequate staging and assessment of resectability status. Imaging should be done prior to stenting, when possible.**

- **Imaging should include dedicated pancreatic CT of abdomen (preferred) or MRI with contrast.**
  - **Multidetector computed tomography (MDCT) angiography, performed by acquiring thin, preferably sub-millimeter, axial sections using a dual-phase pancreatic protocol, with images obtained in the pancreatic and portal venous phase of contrast enhancement, is the preferred imaging tool for dedicated pancreatic imaging.a Scan coverage can be extended to cover the chest and pelvis for complete staging as per institutional preferences. Multiplanar reconstruction is preferred as it allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits. See MDCT Pancreatic Adenocarcinoma Protocol, PANC-A (3 of 8).**
  - **MRI is most commonly used as a problem-solving tool, particularly for characterization of CT-indeterminate liver lesions and when suspected pancreatic tumors are not visible on CT or when contrast-enhanced CT cannot be obtained (as in cases with severe allergy to iodinated intravenous contrast material). This preference for using MDCT as the main imaging tool in many hospitals and imaging centers is mainly due to the higher cost and lack of widespread availability of MRI compared to CT. See MRI Pancreatic Adenocarcinoma Protocol, PANC-A (4 of 8).**

- **The decision regarding resectability status should be made by consensus at multidisciplinary meetings/discussions following the acquisition of dedicated pancreatic imaging including complete staging. Use of a radiology staging reporting template is preferred to ensure complete assessment and reporting of all imaging criteria essential for optimal staging, which will improve the decision-making process.[a] See Pancreatic Cancer Radiology Reporting Template, PANC-A (5 of 8).**

[a] Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270(1):248-260.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

- **The role of PET/CT (without iodinated intravenous contrast) remains unclear. Diagnostic CT or MRI with IV contrast as discussed above in conjunction with functional PET imaging can be used per institutional preference. PET/CT scan may be considered after formal pancreatic CT protocol in high-risk[b] patients to detect extra-pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT.**
- **EUS is not recommended as a routine staging tool. In select cases, EUS may be complementary to CT for staging.**
- **EUS-FNA/fine-needle biopsy (FNB) 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/FNB 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.**
- **Diagnostic staging laparoscopy to rule out metastases not detected on imaging (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[b] for disseminated disease. Intraoperative ultrasound can be used as a diagnostic adjunct during staging laparoscopy.**
- **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.**
- **For locally advanced/metastatic disease, the panel recommends serial CT with contrast (routine single portal venous phase or dedicated pancreatic protocol if surgery is still contemplated) or MRI with contrast of known sites of disease to determine therapeutic benefit. However, it is recognized that patients can demonstrate progressive disease clinically without objective radiologic evidence of disease progression.**
- **Recent retrospective studies suggest that imaging characteristics may not be a reliable indicator of resectability in borderline resectable and locally advanced patients who have received neoadjuvant therapy. Determinations of resectability and surgical therapy should be made on an individualized basis in a multidisciplinary setting. (See Discussion for references)**

[b] Indicators of high-risk patients may include borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes.

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MDCT Pancreatic Adenocarcinoma Protocol[c]

Parameters	Details
Scan type	Helical (preferably 64-multidetector row scanner or more)
Section thickness	Thinnest possible (<3 mm). Preferably submillimeter (0.5–1 mm) if available
Interval	Same as section thickness (no gap)
Oral contrast agent	Neutral contrast (positive oral contrast may compromise the three-dimensional [3D] and maximum intensity projection [MIP] reformatted images)
Intravenous contrast	Iodine-containing contrast agents (preferably high concentration [>300 mg I/L]) at an injection rate of 3–5 mL/sec. Lower concentration contrast can be used if low Kv setting is applied.
Scan acquisition timing	Pancreatic parenchymal phase at 40–50 sec and portal venous phase at 65–70 sec, following the commencement of contrast injection
Image reconstruction and display	- Axial images and multiplanar reformats (in the coronal, and per institutional preference, sagittal plane) at 2- to 3-mm interval reconstruction - MIP or 3D volumetric thick section for vascular evaluation (arteries and veins)

[c] Adapted from: Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270(1):248-260.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

MRI Pancreatic Adenocarcinoma Protocol[d]

Sequences	Plane	Slice Thickness
T2-weighted single-shot fast spin-echo (SSFSE)	Coronal +/- axial	<6 mm
T1-weighted in-phase and opposed-phase gradient echo (GRE)	Axial	<6 mm
T2-weighted fat-suppressed fast spin-echo (FSE)	Axial	<6 mm
Diffusion-weighted imaging (DWI)	Axial	<6 mm
Pre and dynamic post IV contrast administration (gadolinium[e]) 3D T1-weighted fat-suppressed gradient-echo (in pancreatic, portal venous, and equilibrium phases)	Axial	Thinnest possible 2–3 mm (4–6 mm if overlapping)
T2-weighted MR cholangiopancreatography (MRCP) (preferably 3D, fast relaxation fast spin-echo sequence [FRFSE])	Coronal	<3 mm

[d] Sheridan MB, Ward J, Guthrie JA, et al. Dynamic contrast-enhanced MR imaging and dual-phase helical CT in the preoperative assessment of suspected pancreatic cancer: a comparative study with receiver operating characteristic analysis. AJR Am J Roentgenol 1999;173(3):583-90.

[e] Unenhanced MRI can be obtained in cases of renal failure or contraindication to gadolinium intravenous contrast if enhanced CT cannot be obtained due to severe iodinated contrast allergy.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING
PANCREATIC CANCER RADIOLOGY REPORTING TEMPLATE[c]

Morphologic Evaluation			
Appearance (in the pancreatic parenchymal phase)	☐ Hypoattenuating	☐ Isoattenuating	☐ Hyperattenuating
Size (maximal axial dimension in centimeters)	☐ Measurable	☐ Nonmeasurable (isoattenuating tumors)	
Location	☐ Head/uncinate (right of SMV)	☐ Neck (anterior to SMV/PV confluence)[f]	☐ Body/tail (left of SMV)
Pancreatic duct narrowing/abrupt cutoff with or without upstream dilatation	☐ Present	☐ Absent	
Biliary tree abrupt cutoff with or without upstream dilatation	☐ Present	☐ Absent	

[c] Adapted from: Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270(1):248-260.

[f] See Management of Neck Lesions on PANC-D (2 of 2).

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING
PANCREATIC CANCER RADIOLOGY REPORTING TEMPLATE[c]

Arterial Evaluation				
SMA Contact	☐ Present	☐ Absent		
Degree of solid soft-tissue contact	☐ ≤180	☐ >180		
Degree of increased hazy attenuation/stranding contact	☐ ≤180	☐ >180		
Focal vessel narrowing or contour irregularity	☐ Present	☐ Absent		
Extension to first SMA branch	☐ Present	☐ Absent		
Celiac Axis Contact	☐ Present	☐ Absent		
Degree of solid soft-tissue contact	☐ ≤180	☐ >180		
Degree of increased hazy attenuation/stranding contact	☐ ≤180	☐ >180		
Focal vessel narrowing or contour irregularity	☐ Present	☐ Absent		
CHA Contact	☐ Present	☐ Absent		
Degree of solid soft-tissue contact	☐ ≤180	☐ >180		
Degree of increased hazy attenuation/stranding contact	☐ ≤180	☐ >180		
Focal vessel narrowing or contour irregularity	☐ Present	☐ Absent		
Extension to celiac axis	☐ Present	☐ Absent		
Extension to bifurcation of right/left hepatic artery	☐ Present	☐ Absent		
Arterial Variant	☐ Present	☐ Absent		
Variant anatomy	☐ Accessory right hepatic artery	☐ Replaced right hepatic artery	☐ Replaced common hepatic artery	☐ Others (origin of replaced or accessory artery) _____
Variant vessel contact	☐ Present	☐ Absent		
Degree of solid soft-tissue contact	☐ ≤180	☐ >180		
Degree of increased hazy attenuation/stranding contact	☐ ≤180	☐ >180		
Focal vessel narrowing or contour irregularity	☐ Present	☐ Absent		

[c] Adapted from: Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270(1):248-260.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING
PANCREATIC CANCER RADIOLOGY REPORTING TEMPLATE[c]

Venous Evaluation			
MPV Contact	☐ Present	☐ Absent	☐ Complete occlusion
Degree of solid soft-tissue contact	☐ ≤180	☐ >180	
Degree of increased hazy attenuation/stranding contact	☐ ≤180	☐ >180	
Focal vessel narrowing or contour irregularity (tethering or tear drop)	☐ Present	☐ Absent	
SMV Contact	☐ Present	☐ Absent	☐ Complete occlusion
Degree of solid soft-tissue contact	☐ ≤180	☐ >180	
Degree of increased hazy attenuation/stranding contact	☐ ≤180	☐ >180	
Focal vessel narrowing or contour irregularity (tethering or tear drop)	☐ Present	☐ Absent	
Extension	☐ Present	☐ Absent	
Other			
Thrombus within vein (tumor, bland)	☐ Present ☐ MPV ☐ SMV ☐ Splenic vein	☐ Absent	
Venous collaterals	☐ Present ☐ Around pancreatic head ☐ Porta hepatis ☐ Root of the mesentery ☐ Left upper quadrant	☐ Absent	

[c] Adapted from: Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270(1):248-260.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING
PANCREATIC CANCER RADIOLOGY REPORTING TEMPLATE[c]

Extrapancreatic Evaluation		
Liver lesions	☐ Present ☐ Suspicious ☐ Indeterminate ☐ Likely benign	☐ Absent
Peritoneal or omental nodules	☐ Present	☐ Absent
Ascites	☐ Present	☐ Absent
Suspicious lymph nodes	☐ Present ☐ Porta hepatis ☐ Celiac ☐ Splenic hilum ☐ Paraaortic ☐ Aortocaval ☐ Other_____	☐ Absent
Other extrapancreatic disease (invasion of adjacent structures)	☐ Present • Organs involved: _____	☐ Absent
Impression		
	Tumor size: _____	Tumor location: _____
Vascular contact	☐ Present • Vessel involved: _____ • Extent: _____	☐ Absent
Metastasis	☐ Present (Location _____)	☐ Absent

[c] Adapted from: Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270(1):248-260.

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PRINCIPLES OF STENT MANAGEMENT

- **Stent placement is not routinely recommended prior to planned surgery; however, a stent may be considered for symptoms of cholangitis/fever or severe symptomatic jaundice (intense pruritus), or if surgery is being delayed for any reason, including neoadjuvant therapy.**
- **ERCP-guided biliary drainage is preferred. If ERCP is not possible, a percutaneous transhepatic cholangiography (PTC) approach may be used.**
- **Stents should be as short as feasible.**
- **Self-expanding metal stents (SEMS) should only be placed if tissue diagnosis is confirmed.**
- **For neoadjuvant therapy, fully covered SEMS are preferred since they can be removed/exchanged.**
- **During ERCP, common bile duct brushings may be done if no prior definitive diagnosis, and an EUS-guided biopsy can be done or repeated.**

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CRITERIA DEFINING RESECTABILITY STATUS AT DIAGNOSIS[a]

• Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions.

Resectability Status	Arterial	Venous
Resectable	• No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	• No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	<u>Pancreatic head/uncinate process</u>: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. <u>Pancreatic body/tail</u>: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure (some panel members prefer these criteria to be in the locally advanced category).	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced[b,c]	<u>Head/uncinate process</u>: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° <u>Pancreatic body/tail</u>: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

[a] Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014; 270:248-260.
[b] Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans.
[c] Distant metastasis (including non-regional lymph node metastasis), regardless of anatomic resectability, implies disease that should not be treated with upfront resection.

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CRITERIA FOR RESECTION FOLLOWING NEOADJUVANT THERAPY[a-f]

- **Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions.**
- **Our understanding of the value of neoadjuvant therapy is evolving. Medical technology is advancing the boundaries for resection, but we are still unclear about whether this can lead to increased cure rates.**

Following neoadjuvant therapy:

- **Resection may be considered only if there is no evidence of metastatic disease.**
- **Mild increases in perivascular soft tissue can be observed, but alone should not represent a contraindication to surgical exploration.**
- **Exploration following clear local progression on neoadjuvant therapy should be undertaken only after careful consideration in a multidisciplinary conference given its implications of aggressive tumor biology.**
- **Patients who initially presented with resectable or borderline resectable (BR) disease should be explored if their carbohydrate antigen (CA) 19-9 is at least stable or has decreased and radiographic findings do not demonstrate clear progression.**
- **For patients with borderline resectable tumors, exploration may be undertaken if there is involvement of, or thrombus in, the superior mesenteric vein (SMV)/portal vein (PV) as long as there is suitable patent vessel for vascular reconstruction proximal and distal to the site of involvement.**
  - **For borderline resectable tumors involving the pancreatic head/uncinate process, mild increases in soft tissue around the superior mesenteric artery (SMA)/common hepatic artery (CHA)/variant arterial anatomy (replaced right hepatic artery [RHA] or CHA, CA, gastroduodenal artery [GDA], or aorta) should not be considered a contraindication to surgical exploration in the setting of other signs of clinical improvement (ie, improvement in performance status, pain, early satiety, weight/nutritional status).**
- **For patients who presented with locally advanced disease (LAD), exploration for resection should be considered if there is a >50% decrease in CA 19-9 level and clinical improvement (ie, improvement in performance status, pain, early satiety, weight/nutritional status) indicating response to therapy. For LAD, patients should be counseled that the long-term benefit (ie, chance for cure) is unknown. LAD cases should always always be handled in highly specialized centers.**
- **Note that for all clinical stages, radiographic findings may appear stable despite dramatic falls in CA 19-9.**

[a] Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261(1):12-7.
[b] Macedo FI, Ryon E, Maithel SK, et al. Survival outcomes associated with clinical and pathological response following neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel chemotherapy in resected pancreatic cancer. Ann Surg 2019;270(3):400-413.
[c] Tsai S, George B, Wittmann D, et al. Importance of normalization of CA19-9 levels following neoadjuvant therapy in patients with localized pancreatic cancer. Ann Surg 2020;271:740-747.
[d] Michelakos T, Pergolini I, Castillo CF, et al. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. Ann Surg 2019;269(4):733-740.
[e] Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. Ann Surg 2019 Apr 5. [Epub ahead of print]
[f] Gilbert JW, Wolpin B, Clancy T, et al. Borderline resectable pancreatic cancer: conceptual evolution and current approach to image-based classification. Ann Oncol. 2017;28(9):2067-2076.

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PRINCIPLES OF SURGICAL TECHNIQUE

The goals of surgery for adenocarcinoma of the pancreas include an oncologic resection of the primary tumor and regional lymph nodes. Careful intraoperative staging should rule out peritoneal, liver, and distant lymph node metastases, and resection of the primary tumor should only be done in the absence of distant disease. Surgery should be done efficiently, optimizing quality of life and cost. The surgical procedure required is based on the location of the primary tumor and relationship to blood vessels. Therefore, a pancreas protocol CT is critical for preoperative planning.

Consider frozen section analysis of the pancreatic neck and bile duct. To avoid cautery artifact that may confound the frozen section, assess the pancreatic neck and bile duct at time of surgery by frozen section approximately 5 mm from the transection margin. If tumor is located within 5 mm of margins, consider further excision of the pancreas and bile duct to ensure at least 5 mm of clearance.
For cancers of the pancreas head and uncinate, a pancreatoduodenectomy (Whipple procedure) is done. For cancers of the pancreas body and tail, a distal pancreatectomy with en-bloc splenectomy is done.

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 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). Skeletalization of the lateral, posterior, and anterior borders of the SMA 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 SMV 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 PV 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.**
- **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.**

1 Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. J Am Coll Surg 2008;207:510-519.
2 Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg 2006;10:1199-1210; discussion 1210-1191.
3 Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. Curr Probl Cancer 2002;26:176-275.
4 Nakeeb A, Lillemoe KD, Grosfeld JL. Surgical techniques for pancreatic cancer. Minerva Chir 2004;59:151-163.

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PRINCIPLES OF SURGICAL TECHNIQUE

Surgery for Locally Recurrent Pancreatic Ductal Adenocarcinoma[5]

Pancreatic cancer may relapse in the form of a local, regional, or distant recurrence. A local recurrence is usually defined as being isolated to the bed of the pancreatic margin, the pancreatic remnant, or the mesenteric root.

There is a potential benefit of re-resection for pancreatic ductal adenocarcinoma recurrences in selected subgroups of patients. These patients should be carefully evaluated in the multidisciplinary clinic where following a detailed restaging assessment, a multimodality therapy care plan consisting of neoadjuvant chemotherapy, possible radiation therapy, and possible surgical resection can be formulated.

Distal Pancreatectomy with En-bloc Splenectomy

The goals of left-sided resection are similar to those of pancreatoduodenectomy, although they are often more difficult to achieve due to the advanced stage at which most of these cancers are discovered. Plane of dissection anterior to adrenal gland or en bloc resection of left adrenal gland with plane of dissection posterior to Gerota's fascia is recommended as clinically indicated.

- **An R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.**[6,7]
- **Similar to the Whipple procedure, lateral venorrhaphy, vein excision and reconstruction, and dissection to the level of the CA and SMA adventitia should be performed if complete tumor clearance can be achieved.**[6,8]
- **Spleen preservation is not indicated in adenocarcinoma.**

Management of Neck Lesions

Pancreas neck adenocarcinomas are especially difficult to manage. Cancers in the pancreas neck are located anterior to the superior mesenteric vessels and PV. Depending on the extent of involvement, a pancreaticoduodenectomy extending to the left of the SMV (extended pancreaticoduodenectomy), a distal pancreatectomy extending to the right of the SMV (extended distal pancreatectomy), or a total pancreatectomy may be required to obtain an R0 resection.[9]

The precise extent of involvement often cannot be determined prior to surgery; therefore, complex intraoperative decisions are required, and the surgeon must anticipate this. Complexity of surgery for pancreas neck cancers is compounded by the frequent involvement of the SMV/PV.[9,10] **Surgeons who operate on pancreas neck cancers must anticipate possible SMV/PV involvement and be prepared to manage it.**

[5] Moletta L, Serafini S, Valmasoni M, et al. Surgery for recurrent pancreatic cancer: Is it effective? Cancers (Basel) 2019;11(7):991.
[6] Shoup M, Conlon KC, Klimstra D, at al. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? J Gastro Surg 2003;7:946-952; discussion 952.
[7] Christein JD, Kendrick ML, Iqbal CW, et al. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. J Gastrointest Surg 2005;9:922-927.
[8] Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. J Am Coll Surg 2007;204:244-249.
[9] Hirono S, Kawai M, Okada K, et al. Pancreatic neck cancer has specific and oncologic characteristics regarding portal vein invasion and lymph node metastasis. Surgery 2016;159:426-440.
[10] Strasberg SM, Sanchez LA, Hawkins WG, et al. Resection of tumors of the neck of the pancreas with venous invasion: the "Whipple at the Splenic Artery (WATSA)" procedure. J Gastrointest Surg 2012;16:1048-1054.

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

The primary purpose of pathologic analysis of the pancreatic specimen is to determine the pathologic 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 the 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 (eg, written on the pathology requisition); for example: the distal and proximal margins of the SMV and SMA and the bile duct margin should be marked.**
- **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 SMA. 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 uncinate margin should be inked. Rather than being submitted en face, the uncinate margin tissue should be shaved/amputated, then the portion of tissue should be sectioned perpendicular to the ink and submitted entirely for histologic examination.**
    - **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 encompass the full thickness of the vein wall, demonstrating the depth of tumor invasion, as this has been shown to have prognostic value.[1]**
    - **Pancreatic Neck (transection) Margin: This is the en face section of the transected pancreatic neck. Care should be taken when placing the section into the cassette to document the orientation of the section with respect to the true margin (eg, facing down so that the initial section into the block represents the true margin, or facing up so that the initial section represents the surface opposite the true 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 care should be taken when placing the section into the cassette to document the orientation of the section with respect to the true margin (eg, facing down so that the initial section into the block represents the true margin, or facing up so that the initial section represents the surface opposite the true margin).**
  - **Other margins analyzed in Whipple specimens include the proximal (gastric or enteric) and distal enteric margins (en face sections).**
  - **Collectively, these margins and pancreatic tissue surfaces constitute the circumferential surface of the specimen. Designating the various specific margins and surfaces with different colored inks will allow recognition on microscopy.**

References

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

- **Other Circumferential Surfaces**
  - **Posterior (non-SMA margin) Surface: This surface consists of the posterior caudad aspect of the pancreatic head that is not part of the SMA margin and that appears to be covered by loose connective tissue. Radial, rather than en face, sections of this surface will more clearly demonstrate whether it is involved by tumor. In some instances, this surface may already be included in sections of the SMA margin.**
  - **SMV Groove: Also referred to as the vascular groove surface (and in previous versions of the Guidelines as the Portal Vein Groove Margin), this is the smooth-surfaced groove on the posterior-medial surface of the pancreatic head that rests over the SMV. Radial, rather than en face, sections of this surface will more clearly demonstrate whether it is involved by tumor, and also will provide the distance of the tumor from the surface. As is true for the posterior (non-SMA margin) surface, in some instances, this surface may be included in the same sections as the SMA margin.**
  - **Anterior Surface: 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 is therefore strongly recommended, but not currently required.[2-5] In some cases where the anterior surface is adherent to other structures, from which it is surgically dissected or transected, it should be considered an additional circumferential margin, for which the closest distance from tumor should be reported.**
- **Histologic Sectioning**
  - **The approach to histologic 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 slicing. 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. However, knowledge of the clinically suspected lesion is helpful in choosing the best dissection method for examination and appropriate characterization of the lesion. The most important aspects of dissection are clear and accurate assessment of the margins, size of the tumor, and relationship to the relevant structures, such as pancreatic surfaces, margins, bile duct, main pancreatic duct, duodenum, etc.**
  - **Per the current CAP protocol, the presence of tumor at or within 1 mm of resection margin constitutes a positive margin,[2,6] although this recommendation is based primarily on extrapolating from data on rectal adenocarcinoma. There is currently a lack of definitive evidence for 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 RT might be indicated if not received preoperatively. Tumor clearance should be reported with millimeter accuracy for all margins where tumor is close (within 1.0 cm or less of the tumor). This may be done using either mm (eg, “2 mm”) or cm (eg, “0.2 cm”). For margins distant from tumor (>1.0 cm from tumor), tumor clearance may be reported with centimeter accuracy.**
  - **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.**

References

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

Distal Pancreatectomy

- **In left-sided resections, the peripancreatic soft tissue surfaces and the pancreatic neck are assessed. Additionally, involvement of the splenic vessels should be documented, along with invasion of the spleen. Additionally, the margins of the splenic vein and artery can be shaved and submitted for histologic examination.**
- **Margin and Circumferential Surface Definitions**
  - **Proximal Pancreatic (transection) Margin: A full en face section of the pancreatic body along the plane of transection, if the tumor is grossly >1.0 cm from this margin. Care should be taken when placing the section into the cassette to document the orientation of the section with respect to with the true margin (eg, facing down so that the initial section into the block represents the true surgical margin, or facing up so that the initial section represents the surface opposite the true margin). More than one block may be needed. If the tumor is grossly close to the margin (eg, within 1.0 cm or less), radial (eg, perpendicular) sections to this margin are recommended for millimeter-level accuracy in documenting the distance to the margin.**
  - **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 gross involvement.**
  - **Posterior (caudad) Peripancreatic (peripheral) Surface: This surface demonstrates the relationship between the tumor and the posterior or caudad 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 gross involvement.**

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References

PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND 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.[7,8]**
- **Treatment effect should be assessed and reported by the pathologist, as tumor viability may impact postoperative therapy options. For more information about pathologic analysis, refer to the CAP Cancer Protocol Template for carcinoma of the pancreas. (Burgart LJ, Shi C, Adsay VN, et al. Protocol for the Examination of Specimens from Patients with Carcinoma of the Pancreas. College of American Pathologists. Cancer Protocol Templates; 2020.)**

Specimen Type

- **Tumor size (obtained from careful gross measurement of the largest dimension of the tumor in cm, and corroborated on microscopic exam)**
- **Histologic type (H)[9]**
- **Histologic grade [G (x-3)]**
- **Primary tumor stage [T (x-4)]**
- **Regional lymph nodes [N (x-2)][a]**
  - **# nodes recovered**
  - **# nodes involved**
- **Metastases [M (0-1)]**
- **Margins and Other Circumferential Surfaces: Involvement should be defined and surgical clearance measured with mm accuracy for close (within 1.0 cm of tumor) margin**
  - **Whipple resection:**
    - ◊ **SMA (retroperitoneal/uncinate) margin**
    - ◊ **Posterior surface**
    - ◊ **SMV groove**
    - ◊ **Pancreatic neck (transection) margin**
    - ◊ **Bile duct margin**
    - ◊ **Gastric/Enteric margins**
    - ◊ **Anterior surface**
  - **Distal pancreatectomy:**
    - ◊ **Proximal pancreatic (transection) margin**
    - ◊ **Anterior (cephalad) peripancreatic (peripheral) surface**
    - ◊ **Posterior (caudad) peripancreatic (peripheral) surface**
- **Lymphovascular invasion (L)**
  - **Lymphatic (small vessel) invasion (optional) and vascular (large vessel) invasion (optional)**
- **Additional pathologic findings**
  - **Pancreatic intraepithelial neoplasia**
  - **Chronic pancreatitis**
- **Tumor regression score following prior chemotherapy and/or RT**

Final stage: T, N, M (per AJCC)

[a] Every effort should be made to identify all regional lymph nodes within the pancreatectomy specimen (see Discussion).

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References

PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING
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PRINCIPLES OF SYSTEMIC THERAPY

General Principles:

- **Systemic therapy is used in all stages of pancreatic cancer. This includes neoadjuvant therapy (resectable or borderline resectable), adjuvant therapy, and first-line or subsequent therapy for locally advanced, metastatic, and recurrent 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.**
- **For regimens where RT or chemoradiation is included, see Principles of Radiation Therapy (PANC-G) for more details related to radiation delivery, including recommended technique and dose.**
- **To optimize the care of older adults, see NCCN Guidelines for Older Adult Oncology.**

Neoadjuvant Therapy (Resectable/Borderline Resectable Disease)

- **There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and radiation. Subsequent chemoradiation is sometimes included. When considering neoadjuvant therapy, consultation at a high-volume center is preferred. If neoadjuvant therapy is recommended, treatment at or coordinated through a high-volume center is preferred, when feasible. Participation in a clinical trial is encouraged.**

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• FOLFIRINOX or modified FOLFIRINOX[a] ± subsequent chemoradiation[b] • Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation[b] **Only for known BRCA1/2 or PALB2 mutations:** • FOLFIRINOX or modified FOLFIRINOX[a] ± subsequent chemoradiation[b] • Gemcitabine + cisplatin (≥2–6 cycles) ± subsequent chemoradiation[b]	• None	• None

[a] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1.
[b] See Chemoradiation (PANC-F, 7 of 8).

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References

PRINCIPLES OF SYSTEMIC THERAPY

Adjuvant Therapy

- **The CONKO 001 trial demonstrated significant improvements in DFS and OS with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[1]**
- **ESPAC-3 study results showed no significant difference in OS 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.[2]**
- **Data from ESPAC-4 support the use of gemcitabine combined with capecitabine (1,660 mg/m2/day days 1–21 every 4 weeks) with superiority demonstrated compared to gemcitabine alone (HR, 0.82; 95% CI, 0.68, 0.98; P = .032).[3]**
- **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 postoperative adjuvant treatment.[4]**
- **Recommended adjuvant therapy options apply to patients who did not receive prior neoadjuvant therapy. For those who received prior neoadjuvant therapy, the adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.**

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Modified FOLFIRINOX (category 1)[a] • Gemcitabine + capecitabine (category 1)	• Gemcitabine (category 1) • 5-FU + leucovorin (category 1) • Continuous infusion 5-FU • Capecitabine (category 2B) • Induction chemotherapy (gemcitabine, 5-FU + leucovorin, or continuous infusion 5-FU) followed by chemoradiation[b,c] • Induction chemotherapy (gemcitabine, 5-FU + leucovorin, or continuous infusion 5-FU) followed by chemoradiation[b,c] followed by subsequent chemotherapy:[4] ▸ Gemcitabine followed by chemoradiation[b,c] followed by gemcitabine ▸ Bolus 5-FU + leucovorin followed by chemoradiation[b,c] followed by bolus 5-FU + leucovorin ▸ Continuous infusion 5-FU followed by chemoradiation[b,c] followed by continuous infusion 5-FU	• None

[a] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1.
[b] See Chemoradiation (PANC-F, 7 of 8).
[c] If considering chemoradiation due to positive margins, chemotherapy should be given prior to the administration of chemoradiation.

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References

PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced Disease (First-Line Therapy)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	• FOLFIRINOX or modified FOLFIRINOX[d,e,f,6] • Gemcitabine + albumin-bound paclitaxel[d,f,7] **Only for known BRCA1/2 or PALB2 mutations:** • FOLFIRINOX or modified FOLFIRINOX[d,e,f,6] • Gemcitabine + cisplatin[10]	• Gemcitabine + erlotinib[g,8] • Gemcitabine + capecitabine[9] • Gemcitabine • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B) • Fluoropyrimidine + oxaliplatin (5-FU + leucovorin + oxaliplatin [OFF][12] or CapeOx[13]) (category 2B)	• Induction chemotherapy with any of the preferred/other regimens (≥4–6 cycles) followed by chemoradiation[b,h] or SBRT[14] (in selected patients, locally advanced disease without systemic metastases)[15] • Chemoradiation[b,i] or SBRT[i] (in select patients who are not candidates for combination therapy)
Poor PS	• Gemcitabine ▸ 1000 mg/m2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B)	• None	• None

See Subsequent Therapy on PANC-F (6 of 8)

[b] See Chemoradiation (PANC-F, 7 of 8).
[d] The recommendations for FOLFIRINOX or modified FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.
[e] Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[f] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.
[g] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[h] Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy.[16]
[i] If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation or SBRT. See Principles of Radiation Therapy (PANC-G).

References

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PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

- **Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes.**

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	• FOLFIRINOX (category 1) or modified FOLFIRINOX[e,f,6] • Gemcitabine + albumin-bound paclitaxel[f,7] (category 1) **Only for known BRCA1/2 or PALB2 mutations:** • FOLFIRINOX (category 1) or modified FOLFIRINOX[e,f,6] • Gemcitabine + cisplatin[10]	• Gemcitabine + erlotinib[g,8] (category 1) • Gemcitabine (category 1) • Gemcitabine + capecitabine[9] • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B) • Fluoropyrimidine + oxaliplatin (eg, 5-FU + leucovorin + oxaliplatin [OFF][12] or CapeOx[13]) (category 2B)	• None
Poor PS	• Gemcitabine ▸ 1000 mg/m2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B)	• None	• Pembrolizumab[j,16] (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if NTRK gene fusion positive) (category 2B)

See Maintenance Therapy for Metastatic Disease on PANC-F (5 of 8)

See Subsequent Therapy on PANC-F (6 of 8)

[e] Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[f] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.
[g] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[j] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

References

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PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (Maintenance Therapy)

- **Patients who have response or stable disease after 4–6 months of chemotherapy may undergo maintenance therapy.**

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• If previous platinum-based chemotherapy: ▸ Olaparib (only for germline *BRCA1/2* mutations)	• Clinical trial or • If previous first-line FOLFIRINOX: ▸ Capecitabine or • If previous first-line gemcitabine + nab-paclitaxel: ▸ Gemcitabine + nab-paclitaxel modified schedule (category 2B) ▸ Gemcitabine single agent (category 2B)	• If previous first-line FOLFIRINOX: ▸ 5-FU ± irinotecan[k] ▸ FOLFOX[l] (category 2B)

See Subsequent Therapy on PANC-F (6 of 8)

[k] 5-FU ± irinotecan may be considered for maintenance therapy in the case of oxaliplatin-related progressive neuropathy or allergy to oxaliplatin.
[l] While FOLFOX is not commonly used in the maintenance setting, it may be considered as an alternative to irinotecan-based therapy when GI toxicity is a concern.

References

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PRINCIPLES OF SYSTEMIC THERAPY

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

	Preferred Regimens	Other Recommended Regimens		Useful in Certain Circumstances
Good PS	• None	(If prior gemcitabine-based therapy) • 5-FU + leucovorin + liposomal irinotecan[f,17] (category 1 for metastatic disease) • 5-FU + leucovorin + irinotecan (FOLFIRI)[18-20] • FOLFIRINOX or modified FOLFIRINOX[f] • Oxaliplatin + 5-FU + leucovorin (OFF) • FOLFOX • Capecitabine + oxaliplatin • Capecitabine • Continuous infusion 5-FU	(If prior fluoropyrimidine-based therapy) • Gemcitabine • Gemcitabine + albumin-bound paclitaxel[f] • Gemcitabine + cisplatin (only for known BRCA1/2 or PALB2 mutations) • Gemcitabine + erlotinib • 5-FU + leucovorin + liposomal irinotecan[f] (if no prior irinotecan)	• Pembrolizumab[j] (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if *NTRK* gene fusion positive) • Chemoradiation,[b,c] if not previously given, only an option for: ▸ Locally advanced disease if primary site is the sole site of progression ▸ Select patients with recurrent disease in combination with systemic therapy
Poor PS	• None	• Gemcitabine ▸ 1000 mg/m2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B)		• Pembrolizumab[j] (only for MSI-H or dMMR tumors) • Larotrectinib (if *NTRK* gene fusion positive) • Entrectinib (if *NTRK* gene fusion positive) (category 2B)

[b] See Chemoradiation (PANC-F, 7 of 8).
[c] If considering chemoradiation due to positive margins, chemotherapy should be given prior to the administration of chemoradiation.
[f] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.
[j] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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References

PRINCIPLES OF SYSTEMIC THERAPY

Chemoradiation

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Capecitabine + concurrent RT • Continuous infusion 5-FU + concurrent RT	• Gemcitabine + concurrent RT[5]	• None

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References

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

PRINCIPLES OF RADIATION THERAPY

General Principles:

- **Patients with pancreatic cancer are best managed by a multidisciplinary team.[1]**
- **Prior to initiation of RT, staging is optimally determined with a contrast-enhanced abdominal CT (3D-CT) and/or MRI.[2] See Principles of Diagnosis, Imaging, and Staging (PANC-A).**
- **Recommendations for RT for patients with pancreatic cancer are typically made based on five clinical scenarios:**
  - **Resectable/borderline resectable**
  - **Resected (adjuvant)**
  - **Locally advanced**
  - **Palliative**
  - **Recurrent**

For definitions of these scenarios, See Criteria Defining Resectability Status at Diagnosis (PANC-C).

- **In these scenarios, the goal of delivering RT is to sterilize vessel margins, enhance the likelihood of a margin-negative resection, and/or provide adequate local control to prevent or delay progression or prevent local disease recurrence while minimizing the risk of RT exposure to surrounding organs at risk (OARs). Radiation can also be used to palliate pain and bleeding or relieve obstructive symptoms in patients who have progressed or recurred locally.**

****Note: It is not known whether one regimen is necessarily more effective than another in the five clinical scenarios mentioned above. Therefore, the following recommendations are given as examples of commonly utilized regimens. However, other recommendations based on similar principles are acceptable. See Principles of Systemic Therapy (PANC-F) for details on chemotherapy regimens used for chemoradiation.**

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References

PRINCIPLES OF RADIATION THERAPY
TREATMENT PLANNING: RADIATION DELIVERY

Simulation:

- For localized, intact pancreatic cancer (resectable, borderline, and locally advanced), placement of 1–5 (preferably ≥3) fiducial markers may be useful for targeting purposes. Placement of fiducial markers directly into the tumor and/or periphery under EUS is preferred. Stents can assist with targeting; however, they can shift and are therefore less reliable than fiducials.
- Position patient supine with arms up in an immobilization device that will be custom-made for each patient. The simulation scan range should include the target structures and OARs.
- CT simulation (2- to 3-mm slices) is often performed with IV contrast (assuming adequate kidney function) and oral contrast may also be utilized. Multiphase IV contrast delivery may facilitate disease delineation. MRI imaging may be complementary to CT in target delineation.
- Simulation and treatment of patient with nothing by mouth (NPO) may facilitate setup reproducibility. If the patient receives oral contrast, consider giving the same volume of water prior to treatment each day to mimic simulation anatomy.

Motion Management:[3]

- A motion management strategy should be considered.
- Respiratory motion should be accounted for in determining the internal target volume (ITV). These strategies may include using a 4D-CT scan, respiratory gating, breath-hold, respiratory tracking, or abdominal compression.

Planning, Dose and Fractionation:

- 3-D conformal RT (3D-CRT), intensity-modulated RT (IMRT), and SBRT can result in improved planning target volume (PTV) coverage with decreased dose to OARs.[4,5] The exact planning strategy used should be individualized to patient anatomy, clinical scenario, treatment goals, and dose goals.
- It is imperative to evaluate the dose-volume histogram (DVH) of the target structures and the critical OARs such as the duodenum, stomach, liver, kidneys, spinal cord, and bowel. See Table 1. Normal Tissue Dose Volume Recommendations (PANC-G, 5 of 7). No definitive dose constraints for SBRT currently exist; however, they are emerging and are dependent on a variety of factors including dose per fraction and total dose.
- While these examples of limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable).

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References

PRINCIPLES OF RADIATION THERAPY
RECOMMENDATIONS BASED ON TREATMENT SETTING

Resectable/Borderline Resectable:

- Data are limited to support specific treatment options for resectable or borderline resectable pancreatic cancer; however, data suggest that RT in the neoadjuvant setting may lead to an increased likelihood of a margin-negative resection and local control.[2,6,7,8] If RT is being administered in the neoadjuvant setting, it is generally recommended that patients receive neoadjuvant chemotherapy prior to RT (See Principles of Systemic Therapy [PANC-F]).
- Neoadjuvant therapy for patients with resectable tumors should ideally be conducted in a clinical trial.
- Subsequent chemoradiation is sometimes an option following neoadjuvant chemotherapy[9,10] (See Principles of Systemic Therapy [PANC-F]).
- The optimal timing for surgical resection following RT has not been firmly established.
- RT Dosing/Planning:
  - For chemoradiation, the following RT doses have been reported: 36 Gy in 2.4 Gy fractions to 45–54 Gy in 1.8–2.0 Gy fractions (doses higher than 54 Gy may be considered on a clinical trial).
  - The role of elective nodal irradiation (ENI) is controversial for resectable/borderline resectable/locally advanced disease.[11]

Resected (Adjuvant):[a]

- In the adjuvant setting, treatment with chemotherapy is recommended; the role of radiation is being evaluated in clinical studies.
- After resection, patients may receive adjuvant RT for features that portend high risk for local recurrence (eg, positive resection margins).
- If no prior neoadjuvant therapy and no evidence of recurrence or metastatic disease after resection, RT is included in the following adjuvant therapy option:
  - Adjuvant chemotherapy followed by chemoradiation ± subsequent chemotherapy (See Principles of Systemic Therapy [PANC-F])
- RT Dosing/Planning:
  - For chemoradiation, RT dose generally consists of 45–46 Gy in 1.8–2.0 Gy fractions to the tumor bed, surgical anastomoses (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), and adjacent lymph node basins, with potential dose escalation to the high-risk regions, if clinically appropriate.[12,13] Careful attention to the bowel and stomach dose is warranted and normal tissue dose constraints should always be considered.
  - Several clinical trials (RTOG) now refer to atlases to assist with contouring and adjuvant RT planning: (https://www.nrgoncology.org/About-Us/Center-for-Innovation-in-Radiation-Oncology).
  - Preoperative CT scans and strategically placed surgical clips may be used to determine the tumor bed, ideally with the surgeon's assistance.

[a] Adjuvant options listed apply only to patients who did not receive prior neoadjuvant therapy. For those who received prior neoadjuvant therapy, the adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

References

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PRINCIPLES OF RADIATION THERAPY
RECOMMENDATIONS BASED ON TREATMENT SETTING

Locally Advanced[14,15]

- The goal of RT is to prevent or delay local progression (that may result in pain or local obstructive symptoms) and facilitate local disease control, and in some instances help facilitate R0 resection in patients considered for surgery.
- Data are limited to support specific RT recommendations for locally advanced disease. Options may include:
  - Induction chemotherapy followed by chemoradiation or SBRT in select patients (locally advanced without systemic metastases)[b,c,17-21]
  - Chemoradiation[16] or SBRT[b,c] in selected patients who are not candidates for combination chemotherapy.
- RT Dosing/Planning:
  - For chemoradiation, RT dose generally consists of 45–54 Gy in 1.8–2.0 Gy fractions.
  - There are limited data to support a specific RT dosing for SBRT; therefore, it should preferably be utilized as part of a clinical trial or at an experienced, high-volume center. SBRT doses of 3 fractions (total dose 30–45 Gy) or 5 fractions (total dose 25–45 Gy) have been reported as have more protracted courses delivering high doses through a hypofractionated approach.[22] However, caution is warranted when utilizing higher doses and normal tissue constraints must be respected.[21] This approach is optimally performed in the setting of a clinical trial.

Recurrent Pancreatic Cancer (pancreatic bed):

- Data are limited to support specific RT recommendations for locally recurrent pancreatic cancer; the options for patients with recurrent, unresectable disease may include:
  - Induction chemotherapy followed by chemoradiation or SBRT (if not previously performed) (See Principles of Systemic Therapy [PANC-F])
  - Chemoradiation[16] or SBRT[b,c] in selected patients who are not candidates for induction chemotherapy.

- RT Dosing/Planning:
  - For chemoradiation, RT dose generally consists of 45–54 Gy in 1.8–2.0 Gy fractions.
  - There are limited data to support a specific RT dosing for SBRT; therefore, it should preferably be utilized as part of a clinical trial or at an experienced, high-volume center. SBRT doses of 3 fractions (total dose 30–45 Gy) or 5 fractions (total dose 25–45 Gy) have been reported as have more protracted courses delivering high doses through a hypofractionated approach.
  - However, caution is warranted when utilizing higher doses and normal tissue constraints must be respected.[21] This approach is optimally performed in the setting of a clinical trial.

[b] SBRT should be delivered at an experienced, high-volume center with technology that allows for image-guided radiation therapy or in a clinical trial.[23,24] Furthermore, since patients with locally advanced disease are less likely to undergo surgery, every effort should be made to limit dose to the duodenum and stomach in order to limit treatment-related toxicity.

[c] SBRT should be avoided if direct invasion of the bowel or stomach is observed on CT, MRI, and/or endoscopy.

References

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PRINCIPLES OF RADIATION THERAPY

Palliative

- The goal of palliative RT is often to relieve pain and bleeding and/or ameliorate local obstructive symptoms in patients with non-metastatic or metastatic disease. See Principles of Palliation and Supportive Care (PANC-H).
  - Non-Metastatic Disease: Palliative RT can be considered for patients who are elderly and/or not candidates for definitive therapy due to poor performance status or comorbidities.
  - Metastatic Disease:
    - Metastatic sites causing pain (ie, osseous) may be palliated with a short course of RT.
    - RT is reasonable for patients with metastatic disease who require local palliation for symptoms such as obstruction, pain refractory to analgesic therapy, or bleeding.[25]
- RT Dosing/Planning:
  - Palliative RT is commonly used, although specific dose and fractionation recommendations should take into account burden of metastatic disease, normal tissue tolerance, and expected survival.

Table 1: Normal Tissue Dose Volume Recommendations for Chemoradiation Utilizing Conventional Fractionation

Organ at Risk (OAR)	Neoadjuvant/Definitive/Palliative and Recurrent Recommendations[d]	Adjuvant Recommendations[e]
Kidney (right and left)	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.	For 3D conformal plans in patients with two normally functioning kidneys, at least 50% of the right kidney and at least 65% of the left kidney must receive <18 Gy. For IMRT planning, mean dose to bilateral kidneys must be <18 Gy. If only one kidney is present, not more than 15% of the volume of that kidney can receive ≥18 Gy and not more than 30% can receive ≥14 Gy.
Stomach, duodenum, jejunum	Max dose 55 Gy.	Max dose ≤54 Gy; <10% of each organ volume can receive between 50 and 53.99 Gy; <15% of the volume of each organ can receive between 45 and 49.99 Gy.
Liver	Mean dose cannot exceed 30 Gy.	Mean liver dose must be ≤25 Gy.
Spinal cord	Max dose to a volume of at least 0.03 cc must be ≤45 Gy.	Max dose ≤45 Gy.

[d] Adapted from RTOG 1102 (IMRT, 2.2–54 Gy).
[e] Adapted from RTOG 0848 (3D or IMRT).

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References

PRINCIPLES OF RADIATION THERAPY

Table 2: Commonly Used Radiation Therapy Abbreviations

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

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References

PRINCIPLES OF RADIATION THERAPY
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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE[a]

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

SYMPTOM	THERAPY
Biliary obstruction	• Endoscopic biliary metal stent (preferred method) • Percutaneous biliary drainage with subsequent internalization • Open biliary-enteric bypass
Gastric outlet/duodenal obstruction	• Good performance status ▸ Gastrojejunostomy (open or laparoscopic) ± J-tube ▸ Consider enteral stent[b] • Poor performance status ▸ Enteral stent[b] ▸ Venting percutaneous endoscopic gastrostomy (PEG) tube for gastric decompression
Severe tumor-associated abdominal pain unresponsive to optimal, around-the-clock analgesic administration, or if patient experiences undesirable analgesic-associated side effects (See NCCN Guidelines for Adult Cancer 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. See Principles of Radiation Therapy (PANC-G).
Depression, pain, and malnutrition (See NCCN Guidelines for Supportive Care)	• Formal Palliative Medicine Service evaluation when available[d] • Nutritional evaluation with a registered dietitian when available
Exocrine pancreatic insufficiency	Pancreatic enzyme replacement
Thromboembolic disease	• Low-molecular-weight heparin preferred over warfarin[c] • Consider direct oral anticoagulants for select patients
Bleeding from the primary tumor site	• Therapeutic endoscopy, if clinically indicated • RT, if not previously done • Angiography with embolization, if clinically indicated

[a] Palliative surgical procedures are best reserved for patients with a longer life expectancy.
[b] Placement of an enteral stent is particularly important for patients with poor performance status and should be done after biliary drainage is assured.
[c] A randomized trial examing the effects of prophylactic low-molecular-weight heparin showed a decrease in venous thromboembolism but no effect on survival (Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: Outcomes from the CONKO-004 trial. J Clin Oncol 2015;33:2028-2034).
[d] Consider encouraging advanced care planning.

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Table 1. **Definitions for T, N, M**
American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017)

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

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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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 2.2021
Pancreatic Adenocarcinoma

Discussion

Sections of this discussion were updated on February 25, 2021 to correspond with the latest algorithm.
The remainder of the discussion was last updated on July 10, 2018.

Table of Contents

Overview

During the year 2021 in the United States, an estimated 60,430 people will be diagnosed with pancreatic cancer, and approximately 48,220 people are expected to die from the disease.[1] Pancreatic cancer 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] Although the incidence is roughly equal in both sexes, African Americans have a higher incidence of pancreatic cancer than white Americans.[2,3]The incidence of pancreatic cancer in the United States increased from 1999 to 2008, possibly because of the increasing prevalence of obesity, an aging population, and other unknown factors.[3-5] Mortality rates have remained largely unchanged.[6,7]

In the 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 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.[8]

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 use of appropriate imaging studies. In addition, the panel believes that increasing participation in clinical trials (only 4.6% of patients enroll in a pancreatic cancer trial[9]) is critical to making progress in this disease. Thus, the panel unanimously endorses participation in a clinical trial over standard or accepted therapy.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Pancreatic Adenocarcinoma, an electronic search of the PubMed database was performed to obtain key literature in the field of pancreatic cancer using the following search terms: (pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreas adenocarcinoma) OR (pancreas cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[10]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search citations over the past year was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Risk Factors and Genetic Predisposition

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.[11-16] Exposure to chemicals and heavy metals such as beta-naphthylamine, benzidine, pesticides, asbestos, benzene, and chlorinated hydrocarbons is associated with increased risk for pancreatic cancer,[17,18] as is heavy alcohol consumption.[11,13,19-21] Periodontal disease is associated with pancreatic cancer, even when controlling for other risk factors such as gender, smoking, body mass index (BMI), diabetes, and alcohol consumption.[22]

An increased BMI is associated with an increased risk for pancreatic cancer,[19,23-25] with BMI during early adulthood being associated with increased pancreatic cancer mortality.[26] A meta-analysis including 22 cohort studies with 8,091 patients with pancreatic cancer showed that those who engage in low levels of physical activity have an increased risk for pancreatic cancer, relative to those who engage in high levels of physical activity (relative risk [RR], 0.93; 95% CI, 0.88–0.98).[27] Regarding diet, there is some evidence that increased consumption of red/processed meat and dairy products is associated with an elevation in pancreatic cancer risk,[28,29] although other studies have failed to identify dietary risk factors for the disease.[15,30,31] The association between tea consumption and pancreatic cancer risk has been examined, with mostly null associations being found.

Studies examining the association between vitamin D and risk for pancreatic cancer have shown contradictory results. Some data suggest that low plasma 25-hydroxyvitamin D levels may increase the risk for pancreatic cancer.[32] A pooled analysis of 9 case-control studies, including 2,963 patients with pancreatic cancer and 8.527 control subjects, showed a positive association between vitamin D intake and pancreatic cancer risk (odds ratio [OR], 1.13; 95% CI, 1.07–1.19; $P < .001$).[33] This association may be stronger in those with low retinol/vitamin A intake.

Chronic pancreatitis has been identified as a risk factor for pancreatic cancer,[34-37] with one study demonstrating a 7.2-fold increased risk for pancreatic cancer for patients with a history of pancreatitis.[38] A meta-analysis including two case-control studies and one cohort study (1,636 patients with pancreatic cancer) showed that hepatitis B infection is associated with pancreatic cancer (OR, 1.50; 95% CI, 1.21–1.87).[39] Patients with systemic lupus erythematosus (SLE) are also suggested to be at an increased risk for pancreatic cancer. In a meta-analysis of 11 cohort studies, patients with SLE were found to be an increased risk for developing pancreatic cancer (CI 1.32-1.53, HR 1.43).[40] However, 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.

Diabetes and Pancreatic Cancer

The association between diabetes mellitus and pancreatic cancer is particularly complicated. A population-based study of 2122 patients with diabetes found that approximately 1% of patients diagnosed with diabetes who are aged 50 years or younger will be diagnosed with pancreatic cancer within 3 years.[41] Prediabetes may also be associated with increased risk for pancreatic cancer.[42] A systematic review and dose-response meta-analysis including 9 prospective studies ($N = 2,408$) showed that every 0.56 mmol/L increase in fasting blood glucose is associated with a 14% increase in pancreatic cancer incidence.[43]

Numerous studies have shown an association between new-onset non-insulin–dependent diabetes and the development of pancreatic cancer,[41,44-47] especially in those who are elderly, have a lower BMI, experience weight loss, or do not have a family history of diabetes.[48] In these short-onset cases of diabetes diagnosed prior to pancreatic cancer diagnoses, diabetes is thought to be caused by the cancer, although the physiologic basis for this effect is not yet completely understood.[49]

Long-term diabetes, on the other hand, appears to be a risk factor for pancreatic cancer, as some studies have shown an association of pancreatic cancer with diabetes of 2- to 8-year duration.[50] However, certain risk factors such as obesity, associated with both diabetes and pancreatic cancer, may confound these analyses.[51] A meta-analysis including 44 studies showed that the strength of the association between diabetes and pancreatic cancer risk decreases with duration of diabetes, potentially due to the effects of long-term treatment of diabetes.[52]

The use of diabetic medications such as insulin and sulfonylureas has been found to be associated with an increased risk for pancreatic cancer.[53-55] On the other hand, metformin may be associated with a reduced risk for pancreatic and other cancers,[53-58] though a retrospective cohort study (*N* = 980) showed that metformin did not significantly improve survival in diabetic patients diagnosed with pancreatic cancer.[59]

In addition, diabetes and diabetic medication may affect outcomes in patients with pancreatic cancer. 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 months; *P* = .009).[60] The OS difference was significant only in patients without distant metastases and remained significant when insulin users were excluded. In contrast, data from a meta-analysis of more than 38,000 patients show that those with pancreatic cancer and diabetes have a significantly lower OS than those without diabetes (14.4 vs. 21.7 months; *P* < .001).[46] A similar result was seen in a prospective cohort study, in which the survival of 504 patients with and without diabetes who developed pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was compared.[61] After multivariable adjustment, mortality was significantly higher in participants with diabetes compared to those without (hazard ratio [HR], 1.52; 95% CI, 1.14–2.04; *P* < .01).

Genetic Predisposition

Pancreatic cancer is thought to have a familial component in approximately 10% of cases, and familial excess of pancreatic cancer is associated with high risk.[15,62-65] A retrospective review of 175 families in which a family history of pancreatic cancer was present showed that a genetic mutation was present in 28% of families.[66] A prospective registry-based study of 5179 individuals from 838 kindreds found that having just 1 first-degree relative with pancreatic cancer raises the risk for pancreatic cancer by 4.6-fold, whereas having 2 affected first-degree relatives raises the risk by about 6.4-fold.[67] An analysis of 9.040 family members of 1,718 kindreds with pancreatic cancer showed that a family history of early-onset pancreatic cancer (ie, <50 years) was associated with greater risk of pancreatic cancer (standardized incidence ratio [SIR], 9.31; 95% CI, 3.42–20.28; *P* < .001), and lifetime risk of pancreatic cancer increases as the age of onset decreases (HR, 1.55; 95% CI, 1.19–2.03 per year).[68] The genetic basis of this inherited predisposition is not known in most cases, and as many as 80% of patients with a family history of pancreatic cancer have no known genetic cause.[62] The genes most commonly associated with pathogenic germline alterations (PGAs) are *BRCA1, BRCA2, ATM, PALB2, MLH1, MSH2, MSH6, PMS2, CDKN2A*, and *TP53*.[69] Germline mutations in the *STK11* gene result in Peutz-Jeghers syndrome, in which individuals have gastrointestinal (GI) polyps and an increased risk for colorectal cancer.[70-72] These individuals also have a highly elevated risk for developing pancreatic cancer, reported to be increased by as much as 132-fold.[73,74] Furthermore, *STK11* undergoes somatic mutation in approximately 5% of pancreatic cancers.[75]

As with non-hereditary forms of pancreatitis, familial pancreatitis is also associated with an increased risk for pancreatic cancer.[76] Several genes

are associated with the familial form of pancreatitis, including *PRSS1*, *SPINK1*, and *CFTR*.[77] The increased risk for the development of pancreatic cancer in these individuals is estimated to be 26-fold to as high as 87-fold.[35,78-80]

Familial malignant melanoma syndrome (also known as melanoma-pancreatic cancer syndrome or familial atypical multiple mole melanoma [FAMMM]) syndrome is caused by germline mutation of the *CDKN2A* (p16INK4a/p14ARF) gene.[81] This syndrome is associated with a 20-fold to 47-fold increased risk for pancreatic cancer.[82,83] In addition, patients with Melanoma-Pancreatic Cancer syndrome may experience an earlier onset of pancreatic cancer than the general population.[84]

Lynch syndrome is the most common form of genetically determined colorectal cancer predisposition and is caused by germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).[85-90] Patients with Lynch syndrome also have an estimated 9- to 11-fold elevated risk for pancreatic cancer.[91,92] In a sample of 96 patients with pancreatic cancer, two mutations were found in the *MSH6* MMR gene.[93]

Microsatellite instability (MSI) is also a prognostic factor for survival in many cancers, notably for colon cancer although rare in pancreatic adenocarcinoma. Microsatellites are regions of coding and noncoding DNA where short sequences or single nucleotides of DNA are repeated. MSI is caused by a loss of DNA MMR activity. Mutations in germline MMR genes result in a lack of repair of any errors, such as destabilizing errors introduced during DNA replication that shorten or lengthen microsatellites, which then persist in somatic cells. Tumor samples can be assessed for the sizes of microsatellite markers and classified as MSI high (MSI-H), low (MSI-L), and stable (MSS).[87,90] The NCCN Panel recommends MSI testing and/or MMR testing on available tumor tissue for patients with locally advanced or metastatic pancreatic adenocarcinoma.

An excess of pancreatic cancer is also seen in families harboring *BRCA1/2* (breast cancer susceptibility gene-1 and -2) mutations, although the link with *BRCA2* is better established.[93-100] Studies of unselected patients with pancreatic cancer have detected *BRCA1/2* mutations at a frequency of 4% to 7%.[101,102] The risk for pancreatic cancer is elevated 2- to 6-fold in these patients, and the age of onset is younger than average in the general population.[94,98,99] Patients with pancreatic cancer who have Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a *BRCA1/2* mutation, with prevalence of detected mutations in this group ranging from 5.5% to 19%, with mutations being more common for *BRCA2*.[96,102-104]

BRCA1/2 is also involved in the Fanconi DNA anemia/*BRCA* pathway. This pathway is responsible for the repair of DNA interstrand cross-links, and particular mutations in other Fanconi anemia/*BRCA* pathway genes, including in *PALB2*, *FANCC*, and *FANCG,* have also been identified as increasing pancreatic cancer susceptibility.[100,105-107]

Whole-genome sequencing allowed for the identification of germline mutations in *ATM*, a DNA damage response gene, in 2 kindreds with familial pancreatic cancer.[108] Further analyses then revealed *ATM* mutations in 4 of 166 individuals with familial pancreatic cancer. In a sample of 96 patients with pancreatic cancer, 4% had a mutation in *ATM*.[93]

Patients with pancreatic cancer for whom a hereditary cancer syndrome is suspect should be considered for genetic counseling.[109] The panel emphasizes the importance of taking a thorough family history when seeing a new patient with pancreatic cancer. In particular, a family history of pancreatitis, melanoma, and cancers of the pancreas, colorectum, breast, and ovaries should be noted. A free online pancreatic cancer risk prediction tool, called PancPRO, is available and may help determine risk.[65] Referral for genetic counseling may be considered for patients diagnosed with pancreatic cancer, especially those who have a family

history of cancer or who are young, as well as those of Ashkenazi Jewish ancestry. The panel recommends germline testing in any patient with confirmed pancreatic cancer and in those in whom there is a clinical suspicion for inherited susceptibility (see the NCCN Guidelines for Genetic/Familial High Risk Assessment, Breast and Ovarian, available at www.NCCN.org). The panel currently does not identify a specific age to define early-onset pancreatic cancer, though age 50 has been used in previous studies of familial pancreatic cancer.[68] If a cancer syndrome is identified, at-risk relatives should be offered genetic counseling. With or without a known syndrome, individuals with a suspicious family history should be advised on risk-reducing strategies including smoking cessation and weight loss. In addition, the possibility of screening for pancreatic (see below) and other cancers should be discussed. For patients with locally advanced or metastatic disease who are candidates for anticancer therapy, the NCCN Panel recommends testing for actionable somatic mutations, including but not limited to: fusions (*ALK, NRG1, NTRK, ROS1*), mutations (*BRAF, BRCA 1/2, HER2, KRAS, PALB2*), and MMR deficiency.

Premalignant Tumors of the Pancreas

Mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are cystic lesions that can be small and asymptomatic and are often discovered incidentally; MCNs have an ovarian-like stroma.[110-112] IPMNs can occur in the main duct and/or in the branch ducts. Lesions involving the main duct have a higher malignant potential than those in the branches, with the risk of malignancy at around 62%.[113] The risk of malignancy in MCNs is <15%.[113]

An international group of experts has established guidelines for the management of pancreatic IPMNs and MCNs,[114] as has a European group.[115] The international group strongly recommends resection in fit patients with main duct IPMNs ≥ 10 mm.[113] For branch-duct IPMNs, surveillance is considered an appropriate option in patients who are older or unfit or for cysts lacking high-risk stigmata. Branch-duct IPMNs that have an enhancing mural nodule ≥ 5 mm, or are in the head of the pancreas causing obstructive jaundice should be considered for resection.[113] Patients with resected IPMNs are followed with imaging studies to identify recurrences. For MCNs, the international group recommends resection for all fit patients, and recurrences are not observed.[113] The European group gives similar recommendations.[115]

Pancreatic Cancer Screening

Routine screening for pancreatic cancer is generally not recommended for asymptomatic individuals. However, a systematic review including 5 studies showed that screening asymptomatic individuals with a family history of pancreatic cancer was associated with more curative resections ($P = 0.011$) and longer median survival ($P < .001$).[118] 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.[119] 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 reported results of its CAPS3 study, in which 225 asymptomatic high-risk individuals were independently (in a blinded manner) screened once with CT, MRI, and EUS.[120] 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 IPMNs 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 showed that, although 32% of 262 participants were found to have pancreatic abnormalities, and some IPMNs and intraepithelial neoplasias were resected, 3 patients developed pancreatic adenocarcinoma (2 metastatic, 1 recurrent 30 months post-resection) despite screening.[121] These results could be due to rapid malignant progression, but they are more likely a result of inadequate imaging by MRI.

The diagnostic yield of pancreatic cancer screening with EUS in asymptomatic individuals at high risk for familial disease was also investigated in the Netherlands,[122] while a German study used EUS plus MRI/magnetic resonance cholangiopancreatography (MRCP) in a similar high-risk population.[123] 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. Results suggest that MRI/MRCP may be a useful adjunct or a noninvasive alternative to EUS for pancreatic cancer screening.

Newer screening methods to identify patients with early pancreatic cancer rather than those with preinvasive lesions may prove to be beneficial in the future. Examples of techniques being investigated are microRNA biomarkers in whole blood and serum metabolism profiling.[124-127] In addition, circulating cell-free DNA is being investigated as a possible biomarker for screening. One study showed that methylation patterns in cell-free plasma DNA can differentiate between pancreatitis and pancreatic cancer with a sensitivity of 91.2% and specificity of 90.8%.[128] In addition, carbohydrate antigen (CA) 19-9 levels may be elevated in patients up to 2 years before a pancreatic cancer diagnosis, indicating that CA 19-9 has potential as a biomarker for screening high-risk patients.[129]

An international CAPS Consortium summit with 49 multidisciplinary experts was held in 2011 to develop consensus guidelines for pancreatic cancer screening.[130] The group recommends screening with EUS and/or MRI/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 with pancreatic cancer. 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, vomiting, and occasionally pancreatitis; 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 (see *Diabetes and Pancreatic Cancer*, above). Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss.

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.[131] All patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should therefore undergo initial evaluation by CT performed according to a dedicated pancreas protocol of the abdomen.[132] In addition, the panel recommends imaging after neoadjuvant treatment to provide adequate staging and assessment of resectability status. Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation, with use of 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, pathology, geriatric medicine, and palliative care.

The AJCC has developed staging criteria for adenocarcinoma of the pancreas that follow the tumor/node/metastasis (TNM) system.[133,134] 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.[134,135] [135] In the 8th edition of the AJCC Cancer Staging Manual, the definition of N category has been revised; N1 is defined as 1–3 metastatic lymph nodes and N2 as >4 metastatic lymph nodes. Additionally, the T category now has a size-based definition and the T4 category no longer incorporates resectability.[136] Validation studies of the changes to the 8th edition of the AJCC T and N staging found that it better stratifies patients with resected tumors according to their lymph node involvement[137] and retains prognostic accuracy,[138] compared to the 7th edition.

For clinical purposes, however, most NCCN Member Institutions use a clinical classification system based mainly on results of presurgical imaging studies. Following staging by pancreatic protocol CT of abdomen, chest, and pelvis CT (and EUS with biopsy if clinically indicated, and/or MRI for indeterminate liver lesions, and/or PET/CT in high-risk patients to detect extra-pancreatic metastases), or endoscopic retrograde cholangiopancreatography (ERCP) to place stent if jaundiced or undiagnosed on previous placement (or percutaneous transhepatic cholangiography [PTC]) in some cases), liver function tests and baseline CA 19-9 in a decompressed patient, and genetic counseling and germline testing if the diagnosis is confirmed or if patient has metastatic disease, 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 with a high chance of an R1 resection); 3) locally advanced (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) metastatic, and this system is used throughout the guidelines. See *Criteria for Resection* below for more detailed definitions.

Imaging Evaluations

Pancreatic Protocol CT and MRI

Multi-detector CT angiography, performed by acquiring thin, preferably sub-millimeter, axial sections using a dual-phase pancreatic protocol, with images obtained in the pancreatic and portal venous phase of contrast enhancement, is the preferred imaging tool for dedicated pancreatic imaging. Scan coverage can be extended to cover the chest and pelvis for complete staging as per institutional preferences. Multiplanar reconstruction is preferred as it allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits.[131,132,139] Studies have shown that 70% to 85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.[131,140-144] However, the sensitivity of CT for small hepatic and peritoneal metastases is limited. High-quality CT imaging should occur no more than 4 weeks before surgery.[145]

The difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the pancreatic 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 enhanced visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], hepatic artery) 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.[143]

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 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.[146] 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. See *PET/CT*, below, for more details about these procedures. Pancreas protocol MRI with contrast can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for characterization of CT-indeterminate liver lesions and when suspected pancreatic tumors are not visible on CT or in cases of contrast allergy.[147,148]

Recently, a multidisciplinary expert consensus group defined standardized language for the reporting of imaging results.[132] Such uniform reporting can help improve the accuracy and consistency of staging to determine optimal treatment strategies for individual patients and can allow cross-study and cross-institutional comparisons for research purposes. Use of the template also ensures a complete assessment and reporting of all imaging criteria essential for optimal staging and can therefore aid in determining optimal management. The use of the radiology staging reporting template is thus recommended by the panel. The template recommended by the panel includes morphologic, arterial, venous, and extrapancreatic evaluations.[132] The morphologic evaluation includes documentation of tumor appearance, size, and location, as well as the

presence of narrowing or abrupt cut-off of pancreatic duct or biliary tree. The arterial evaluation should include assessment of the celiac axis, the SMA, and the common hepatic artery. Arterial variations should also be noted, such as vessel contact, solid soft-tissue contact, hazy attenuation or stranding contact, and focal vessel narrowing or contour irregularity. Venous evaluation should include an assessment of the main PV and the SMV. Documentation of thrombus within the vein and venous collaterals should also be done. The extrapancreatic evaluation should include documentation of liver lesions, peritoneal or omental nodules, ascites, suspicious lymph nodes, and other present extrapancreatic disease sites.

Endoscopic Ultrasound

NCCN Member Institutions vary in the use of additional staging technologies, such as EUS. An analysis of 20 studies and 726 cases of pancreatic cancer showed that EUS for T1-2 staging has a sensitivity and specificity of 0.72 and 0.90, respectively.[149] Sensitivity and specificity for T3-4 staging is 0.90 and 0.72, respectively. [150-153] EUS may be used to discriminate between benign and malignant strictures or stenosis, because severe stenosis and marked proximal dilatation most often indicate malignancy.[154] EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. In addition, EUS plays a role in better characterizing cystic pancreatic lesions due to the ability to aspirate the cyst contents for cytologic, biochemical, and molecular analysis. 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 neurolysis, removal of ascites). Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

The role of EUS in staging is felt to be complementary to pancreas protocol CT, which is considered the gold standard. The primary role of EUS is to procure tissue for cytologic diagnosis, but sometimes additional diagnostic information is identified. EUS provides additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes.[150-153] Because variations in hepatic arterial anatomy occur in up to 45% of individuals, and EUS is highly operator dependent, EUS is not recommended as a routine staging tool and should not be used to assess vascular involvement.

Endoscopic Retrograde Cholangiopancreatography and Percutaneous Transhepatic Cholangiography

ERCP is a technique that combines endoscopic and fluoroscopic procedures and is generally limited to therapeutic interventions.[155] ERCP is a preferred recommendation for patients who are jaundiced or diagnosed on previous biopsy and without evidence of metastatic disease who require biliary decompression and who undergo additional imaging with EUS to help establish a diagnosis.[156] Thus, from a therapeutic standpoint ERCP allows for stent placement and can be used to palliate biliary obstruction when surgery is not elected or if surgery must be delayed. However, biliary decompression in those without symptomatic hyperbilirubinemia receiving upfront surgery may be avoided.[157-159]

There are occasional anatomic considerations that preclude ERCP stent placement. In these cases, palliation of biliary obstruction can be achieved by placing a stent through the liver using PTC.[160]

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.[161] 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.[162,163] PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered as an adjunct to a formal pancreatic CT protocol in high-risk patients. Indicators of high risk for metastatic disease may include borderline resectable disease, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, and patients who are very symptomatic.

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.[164-166] 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, which can be accomplished in an estimated 23% of patients in whom curative intent surgery is planned,[165] although routine use of staging laparoscopy is controversial. There is some concern that laparoscopy may promote trocar-site recurrences and peritoneal disease progression, but these concerns are based on clinical observation and experimental data from animal and in vitro studies, and one retrospective study (*N* = 235) found that staging laparoscopy was not significantly associated with poor outcomes.[167] The panel does not consider staging laparoscopy to be a substitute for poor-quality preoperative imaging.

Some 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).[168] For example, preoperative serum CA 19-9 levels >100 U/mL or >215 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.[169,170] In a 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.[171] 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 metastases not detected on imaging (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 (ie, imaging findings; borderline resectable disease; markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; highly symptomatic; excessive weight loss; extreme pain). Thus, the panel believes that staging laparoscopy can be considered for patients staged with resectable pancreatic cancer who are considered to be at increased risk for disseminated disease and for patients with borderline resectable disease prior to administration of neoadjuvant therapy. Intraoperative ultrasound may be used as a diagnostic adjunct during staging laparoscopy to further evaluate the liver and tumor and vascular involvement. The panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[172]

Biopsy

Although a pathologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy and for patients staged with locally advanced pancreatic cancer or metastatic disease. A pathologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either EUS guidance (preferred) or CT. EUS-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.[173-175] 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-FNA also gives the benefit of additional staging information at the time of biopsy.

EUS-FNA is highly accurate and reliable for determining malignancy. A meta-analysis including 20 studies and 2761 patients showed sensitivity and specificity values of 90.8% and 96.5%, respectively, for diagnosis of solid pancreatic lesions.[176] In rare cases when EUS-FNA cannot be obtained from a patient with borderline resectable or unresectable disease, other acceptable methods of biopsy exist. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy.[177] A percutaneous approach[174] or a laparoscopic biopsy[178] 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 and a core needle biopsy at a high-volume center is preferred, though new methods are being developed for diagnosis of pancreatobiliary malignancies (eg, cholangiopancreatoscopy) when repeat biopsy is needed.[179] Core needle biopsy is recommended, if possible, for patients with borderline resectable disease to obtain adequate tissue for possible ancillary studies, such as genomic analysis or MSI testing. 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 disease 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.

Evolving changes in molecular analyses of pancreatic cancer have led some institutions to attempt to procure additional tumor-rich, formalin-fixed, paraffin-embedded tissue to bank for future genomic studies. Several methods can be used to obtain such tissue samples, including core biopsy, but the panel believes that core biopsies should not replace EUS-guided FNA, but rather can be done in addition to EUS-guided FNA. Some of the most common somatic mutations in pancreatic cancer are *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*.[180,181] Molecularly targeted therapies for pancreatic cancer are being developed and investigated.[182]

Biomarkers

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal antigen, tissue polypeptide antigen, CA 125, and CA 19-9. The panel recognizes the importance of identifying biomarkers for early detection of this difficult disease, and they emphasize the need for collection and sharing of tissue to help accelerate the discovery of prognostic biomarkers (see *Future Clinical Trials: Recommendations for Design*, below). For example, a

meta-analysis including 8 studies found that S100 calcium-binding protein P (S100P) shows high sensitivity (0.87; 95% CI, 0.83–0.90) and specificity (0.88; 95% CI, 0.82–0.93) for diagnosis of pancreatic cancer.[183] A biomarker panel consisting of the immunoassays TIMP1 and LRG1, along with CA 19-9 improved the detection of early-stage pancreatic cancer, relative to CA 19-9 alone.[184]

CA 19-9

The best-validated and most clinically useful biomarker for early detection and surveillance of pancreatic cancer 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).[185] 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.[186]

CA 19-9 is a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 80% to 90% in symptomatic patients,[187] but its low positive predictive value makes it a poor biomarker for screening.[188] 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.[189-191]

CA 19-9 also seems to have value as a prognostic and a predictive marker for pancreatic cancer in various settings. In resectable disease, for instance, low postoperative serum CA 19-9 levels or a serial decrease in CA 19-9 levels following surgery have been found to be prognostic for survival for patients undergoing resection.[188,189,191-197] 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; $P < .0001$).[193]

Also in the resectable setting, data from an analysis of 260 consecutive patients support the predictive role of postoperative CA 19-9 levels for benefit of adjuvant therapy.[196] 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 (DFS) 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 DFS 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 less than 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 DFS of 19.6 months, suggesting a possible prognostic benefit of post-adjuvant therapy CA 19-9 levels in this setting.

In the neoadjuvant/borderline resectable setting, a recent study of 141 patients treated at MD Anderson Cancer Center found that post-treatment CA 19-9 levels were a good prognostic marker in patients receiving neoadjuvant therapy with or without subsequent resection.[198] This study found that a normalization of CA 19-9 to less than 40 U/mL was associated with improvements in OS in non-resected (15 months vs. 11 months; $P = .02$) and resected (38 months vs. 26 months; $P = .02$) disease.

In the advanced disease setting, data support the role of CA 19-9 as a prognostic marker.[192,199,200] 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.[199] In addition, the change in CA 19-9 levels during chemotherapy in patients with advanced disease

has been shown to be useful for evaluating the benefit of treatment, although the data are not entirely consistent.[199-204] For example, a 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 were associated with a better outcome.[192] 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.[205] Furthermore, CA 19-9 may be falsely positive in cases of biliary infection (cholangitis), inflammation, or biliary obstruction (regardless of etiology) and does not necessarily indicate cancer or advanced disease.[206,207] Preoperative measurement of CA 19-9 levels (category 3) is therefore best performed after biliary decompression is complete and bilirubin is normal. If biliary decompression is not performed in a patient with jaundice, 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 after neoadjuvant treatment, prior to surgery, following surgery immediately prior to administration of adjuvant therapy, and for surveillance (category 2B). The panel emphasizes the importance of obtaining a CA 19-9 measurement immediately before the therapeutic intervention to have an accurate baseline from which to follow response; for example, before and after neoadjuvant therapy in patients with tumors that are borderline resectable. Of note, a number of different methods are commercially available for quantifying this tumor-associated antigen. Measurements of serum levels of CA 19-9 using one testing method cannot be extrapolated to results obtained using a different procedure.

Differential Diagnoses

Chronic pancreatitis and other benign conditions are possible differential diagnoses of patients suspected of having pancreatic cancer.[208-212] 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.[210,213-215] 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.[214] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis.

In addition, fine-needle aspirates can be misinterpreted as malignant or suspicious for malignancies.[216,217] 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.[216-219]

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.[220] A recent study found that IgG4 levels of >1.0 g/L combined with CA 19-9 levels of <74 U/mL distinguished patients with autoimmune pancreatitis from those with adenocarcinoma with 94% sensitivity and 100% specificity.[221] 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. Consultation with an expert pancreatologist is also recommended.

Systemic Therapy Approaches for Locally Advanced or Metastatic Disease

The data supporting the regimens used in pancreatic cancer are described below (also summarized in Table 2).

FOLFIRINOX and modified 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.[116] 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.[117] A later randomized phase II trial showed a response rate of greater than 30% to FOLFIRINOX in patients with metastatic pancreatic cancer.[118]

Results from the randomized phase III PRODIGE trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median PFS (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.[119] Eligibility criteria for this trial, however, were stringent, limiting real-world generalizability.[120] For example, patients with abnormal bilirubin levels were excluded from participating.

A systematic review including 11 studies and 315 patients with locally advanced pancreatic cancer showed a pooled median OS of 24.2 months (95% CI, 21.7–26.8).[121] An observational study including 101 patients with locally advanced unresectable disease who were treated with FOLFIRINOX as induction therapy showed that 29% of the sample (20% without administration of chemoradiation) had a reduction in tumor size of greater than 30%, and half of the patients who experienced a reduction in tumor size underwent resection.[122] Out of the patients who underwent resection, 55% achieved an R0 resection.

Because of the strong results from the PRODIGE trial, FOLFIRINOX is included as a preferred, category 1 recommendation for first-line treatment of patients with good performance status (ie, ECOG 0-1) with metastatic pancreatic cancer. It is listed as a category 2A recommendation for patients with locally advanced disease by extrapolation. The panel also lists this regimen as an acceptable option in the neoadjuvant/borderline resectable setting.

There are 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.[119] Despite the high levels of toxicity, no toxic deaths have been reported.[117-119] 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%, $P < .01$).[119] A more detailed analysis of the quality of life of patients in this trial was published and showed that FOLFIRINOX maintained and even improved quality of life more so than gemcitabine.[123]

The panel appreciates that the toxicity of FOLFIRINOX can be managed with a variety of approaches. For example, a group from Memorial Sloan Kettering Cancer Center reported good activity and acceptable toxicity of first-line FOLFIRINOX at 80% dose intensity with routine growth factor support in carefully selected patients with metastatic or locally advanced disease.[124] Median OS was 12.5 months in the metastatic setting and 13.7 months in patients with locally advanced disease.

The efficacy and toxicity of a modified FOLFIRINOX regimen in which the initial dosing of bolus 5-FU and irinotecan were each reduced by 25% were assessed in a phase II single-arm prospective trial (*N* = 75).[125] In patients with metastatic disease, the efficacy of the modified regimen was comparable to that of the standard regimen (median OS = 10.2 months). In patients with locally advanced disease, the median OS was 26.6 months. Patients who received the modified regimen experienced significantly less neutropenia, fatigue, and vomiting, relative to patients who received the standard FOLFIRINOX regimen. Thus to reduce the toxicity associated with FOLFIRINOX and improve its tolerability, the modified FOLFIRINOX regimen is also included as a preferred treatment option.

Gemcitabine Monotherapy

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.[126] The panel recommends gemcitabine monotherapy as one option for front-line therapy for patients with locally advanced or metastatic disease (category 1) disease and a good performance status. Because the approved indications for gemcitabine include the relief of symptoms, the panel also recommends gemcitabine monotherapy as a reasonable first-line and second-line option for symptomatic patients with locally advanced or metastatic disease with poor performance status (category 1).

Gemcitabine monotherapy also has category 1 evidence supporting its use 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 DFS was met (13.4 months vs. 6.9 months; $P < .001$, log rank).[127] 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; HR, 0.76; 95% CI, 0.61–0.95; $P = .01$).[128] An absolute survival difference of 10.3% was observed between the two groups at 5 years (20.7% vs. 10.4%).[128]

Gemcitabine Response: hENT1

Human equilibrative nucleoside transporter 1 (hENT1) is a nucleoside transporter that has been studied as a predictor for response to gemcitabine.[129] Preliminary clinical data showed that hENT1 expression may in fact predict response to gemcitabine.[130-135]

hENT1 was validated as a predictive biomarker for benefit from gemcitabine in the adjuvant setting. A meta-analysis including 7 studies with 770 patients with resected pancreatic cancer showed that hENT1 expression was associated with DFS (HR, 0.58; 95% CI, 0.42–0.79) and OS (HR, 0.52; 95% CI, 0.38–0.72) in patients who received adjuvant gemcitabine, but not in patients who received adjuvant fluoropyrimidine-based therapy.[136] Two retrospective analyses from ESPAC-3 and RTOG-9704 found the same results, although results from the adjuvant CONKO-001 trial and the AIO-PK0104 trial were unable to confirm these results using a different antibody for the IHC analysis (SP120).[137,138]

Unfortunately, hENT1 could not be validated in the metastatic setting in the LEAP trial, which also used the SP120 assay to determine hENT1 expression.

Further studies based on hENT1 expression using the 10D7G2 assay are limited by the fact that no commercial source of the antibody and no CLIA-approved testing are available.

Fixed-Dose-Rate Gemcitabine

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.[139] In a randomized phase II trial of patients with locally advanced or metastatic pancreatic cancer, the infusion of gemcitabine at an FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.[140] In the phase III randomized ECOG-6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine versus standard gemcitabine (6.2 months vs. 4.9 months; $P = .04$), although this outcome did not satisfy the protocol-specified criteria for superiority.[141] 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 and oxaliplatin]; GTX [gemcitabine, docetaxel, and capecitabine]). See *Gemcitabine Combinations*, below.[142,143] The combination of FDR gemcitabine and capecitabine has also been found to be active and well-tolerated.[144]

Gemcitabine Combinations

The NCCN Panel acknowledges that, historically, combination chemotherapy did not appear to be superior to monotherapy in the era of 5-FU–based therapy. However, because gemcitabine is superior to bolus 5-FU in the advanced setting 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).[141-143,145-155] Two meta-analyses of randomized controlled trials (RCTs) found that gemcitabine combinations give a marginal benefit in OS over gemcitabine monotherapy in the advanced setting, with a significant increase in toxicity.[156,157]

Combinations recommended in the advanced setting are discussed below. The panel does not consider the combination of gemcitabine plus docetaxel[158] or gemcitabine plus irinotecan[155,158,159] to meet the criteria for inclusion in the guidelines. In addition, gemcitabine plus sorafenib is not recommended. The 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.[160] This trial did not meet its primary endpoint of progression-free survival (PFS) in its 104 patients (5.7 months vs. 3.8 months; $P = .90$). Gemcitabine combinations are currently being used and studied in the adjuvant setting.

Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.[149,150,152]

Gemcitabine Plus Albumin-Bound Paclitaxel

Albumin-bound paclitaxel is a nanoparticle form of paclitaxel. In a publication of a phase I/II trial, 67 patients with advanced pancreatic cancer received gemcitabine plus albumin-bound paclitaxel. At the maximum tolerated dose, the partial response rate was 48%, with an additional 20% of patients demonstrating stable disease for 16 or more weeks. The median OS at this dose was 12.2 months.[161]

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.[162] Participants were randomized to receive gemcitabine plus albumin-bound paclitaxel or gemcitabine alone. The trial met its primary endpoint of OS (8.7 months vs. 6.6 months; *P* < .0001; HR, 0.72).[162] The addition of albumin-bound paclitaxel also improved other endpoints, including 1-year survival, 2-year survival, response rate, and PFS. OS was associated with a decrease in CA 19-9 (HR, 0.53; 95% CI, 0.36–0.78; *P* = .001).[163] Tumor response was validated with PET imaging.[164] The most common grade 3 or higher adverse events attributable to albumin-bound paclitaxel were neutropenia, fatigue, and neuropathy. Development of peripheral neuropathy was associated with longer treatment duration and greater treatment efficacy.[165] Updated results of the MPACT trial show that long-term survival is possible with gemcitabine plus albumin-bound paclitaxel, as 3% of patients from that arm were alive at 42 months, whereas no patients were alive from the control arm at that time.[166] Factors associated with survival in this trial include KPS score and absence of liver metastases.[167]

Gemcitabine plus albumin-bound paclitaxel is a category 1 recommendation for the treatment of patients with metastatic disease and good performance status based on these results, and is listed as a preferred option in this setting. Good performance status for this regimen is defined as ECOG 0-2, since the clinical trial used KPS ≥70 as an eligibility criterion.[162,166] Therefore, some patients with an ECOG score of 2 may be eligible to receive this regimen.[168,169] By extrapolation of the data, the panel recommends this combination in the locally advanced, good performance status setting as well (category 2A). The panel also notes that this combination is an acceptable option in the neoadjuvant/borderline resectable setting

Gemcitabine Plus Cisplatin

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of RCTs 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.[146,147,150]

Nevertheless, selected patients may benefit from this regimen because patients with breast and ovarian cancers who are carriers of a *BRCA* mutation[170-172] and selected patients with inherited forms of pancreatic cancer[96] 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.[173] 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).[173] Furthermore, a report of 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.[174] 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 patients with metastatic or locally advanced disease, only for known *BRCA1/2* or *PALB2* mutations. FOLFIRINOX and modified FOLFIRINOX are also possible treatment options for patients with *BRCA 1/2* and *PALB2* mutations.

Gemcitabine Plus Erlotinib and Other Targeted Therapeutics

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.[175-179] 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 PFS (HR, 0.77; *P* = .004) when compared to patients receiving gemcitabine alone.[175] 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.[175] 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.[175,180,181]

The NCCN Panel recommends the gemcitabine-erlotinib combination therapy as a treatment option, under other recommended regimens, for patients with locally advanced or metastatic disease and good performance status, with this combination being a category 1 recommendation for patients with metastatic disease. However, the panel notes that although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

Gemcitabine Plus Capecitabine

A number of randomized trials have investigated the combination of gemcitabine with capecitabine, a fluoropyrimidine, in patients with advanced pancreatic cancer. A randomized study in 533 patients with advanced disease found that PFS 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.[148] 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.[152] Results from a third randomized phase III trial also showed that gemcitabine with capecitabine did not significantly improve OS, compared with gemcitabine alone, though patients who received gemcitabine with capecitabine had a greater overall response rate, compared to patients who received gemcitabine only (43.7% vs. 17.6%, respectively; *P* = .001).[182] In a meta-analysis of 8 RCTs, OS was better in patients receiving gemcitabine plus capecitabine than in patients receiving gemcitabine alone (HR, 0.87; *P* = .03).[183] Although there are concerns about dosing and toxicity of capecitabine in a U.S population, a biweekly regimen of fixed-dose gemcitabine in combination with capecitabine may be both effective and well-tolerated in patients with advanced disease.[144]

The panel includes the combination of gemcitabine, docetaxel, and capecitabine (GTX regimen) as a category 2B recommendation for the treatment of patients with metastatic or locally 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.[143] 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 retrospective case-review study at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins 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.[184]

Gemcitabine combined with capecitabine and oxaliplatin (GEMOXEL) was recently assessed in a randomized phase II trial (N = 67) for the metastatic setting.[185] Disease control rate (P = .004), PFS (P < .001), and OS (P < .001) were all superior in patients randomized to receive the GEMOXEL regimen, compared to patients randomized to receive gemcitabine alone.

The NCCN Panel considers gemcitabine-based combination therapy with capecitabine to be a reasonable option (category 2A) for patients with locally advanced or metastatic disease and a good performance status who are interested in pursuing more aggressive therapy outside a clinical trial.

Gemcitabine and Other Fluoropyrimidine-Based Therapies

Gemcitabine has been examined in combination with other fluoropyrimidine-based therapies. A recent meta-analysis of 8 RCTs, including more than 2000 patients, found that OS was significantly improved when a fluoropyrimidine was added to gemcitabine.[183] In a phase II randomized trial, the effects of the FIRGEM regimen [irinotecan delivered before and after infusion of 5-FU/leucovorin (FOLFIRI.3), alternating with FDR gemcitabine] were assessed in 98 patients with metastatic pancreatic cancer.[186] Patients were randomized to receive the FIRGEM regimen or FDR gemcitabine monotherapy. The primary objective of a 45% PFS rate at 6 months was reached, and PFS was a median of 5.0 months in those randomized to receive the FIRGEM regimen, while those randomized to receive only gemcitabine had a median PFS of 3.4 months (HR, 0.59; 95% CI, 0.38–0.90). Rates of hematologic toxicity were higher in those who received the FIRGEM regimen, relative to those who received gemcitabine only. Study investigators deemed FIRGEM to be effective and feasible in the metastatic setting.

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.[145]

Recent randomized trials from Asia show that gemcitabine combined with the oral fluoropyrimidine S-1 may improve response and survival in patients with locally advanced pancreatic cancer, though trial results are inconsistent regarding whether outcomes are improved over gemcitabine monotherapy.[187-189]

Capecitabine and Continuous Infusion 5-FU

The panel lists capecitabine monotherapy and continuous infusion 5-FU as first-line and second-line treatment options for patients with locally advanced disease (category 2B), and for patients with poor performance status and metastatic disease (category 2B). They are also recommended as options in the adjuvant settings (category 2A for continuous infusion 5-FU and category 2B for capecitabine). 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.[190]

Note that the capecitabine dose recommended by the panel (1000 mg/m^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).[191]

Fluoropyrimidine Plus Oxaliplatin

The combination of a fluoropyrimidine (5-FU/leucovorin or capecitabine) with oxaliplatin is 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 [OFF] vs. best supportive care) and on a phase II study (CapeOx).[192,193] 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).

Maintenance Therapy in Advanced Disease

With the success of more effective regimens in patients with advanced disease, questions have been raised about how best to manage the treatment-free interval prior to disease progression. Options include continuing systemic therapy, stopping treatment, dropping the most toxic agents, and using different agents for maintenance therapy.

Based on the fact that the BRCA genes encode for proteins involved in homologous recombination repair and that cells with mutations are sensitive to poly (ADP ribose) polymerase (PARP) inhibitors, the efficacy of olaparib, a PARP inhibitor, was investigated. In a phase II trial assessing its efficacy and safety, the tumor response rate for patients with metastatic pancreatic cancer and a germline *BRCA1/2* mutation (*n* = 23) was 21.7% (95% CI, 7.5–43.7).[194] Following this, in the randomized, double-blind, placebo-controlled phase 3 POLO trial, olaparib was found to be an effective maintenance therapy agent for patients with metastatic pancreatic cancer and germline BRCA 1/2 mutations and no disease progression following at least 16 weeks of first-line platinum-based therapy. A total of 154 patients were randomized to receive either olaparib or placebo. In the olaparib arm, the median PFS was 7.4 months compared to 3.8 months in the placebo arm (95% CI 0.35-0.82, P=0.004). At interim, however, there was found to be no difference in OS between the olaparib and placebo groups (18.9 months vs. 16.1 months, 95% CI 0.56-1.46, P=0.68). Adverse events, such as those grade 3 or higher, were found to be higher in the olaparib arm than in the placebo arm (40% vs. 23%).[195] Based on this data, olaparib is recommended by the NCCN Panel as a preferred targeted maintenance therapy for patients with germline *BRCA*-mutated metastatic disease and no disease progression after 4-6 months of first-line platinum-based therapy. Other maintenance therapy options for patients include clinical trial enrollment; gemcitabine-based therapy for patients who received previous first-line gemcitabine and nab-paclitaxel; or capecitabine, 5-FU with or without irinotecan, or FOLFOX for patients who received previous FOLFIRINOX. The NCCN Panel has included 5-FU with or without irinotecan for patients who exhibited oxaliplatin-related progressive neuropathy or allergy. Finally, if irinotecan-related GI toxicity is of concern, then FOLFOX may be a suitable maintenance therapy.

Subsequent Therapy in the Advanced Setting

A systematic review of clinical trials that assessed the efficacy of subsequent therapy after gemcitabine in pancreatic cancer concluded that, while data are very limited, evidence suggests an advantage of additional chemotherapy over best supportive care.[196] For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable subsequent options.[192,193,197,198] Gemcitabine-based therapy can be given to those previously treated with fluoropyrimidine-based therapy.

Results from the phase III CONKO-003 trial showed significant improvements in both median PFS (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,[199,200] making this regimen the standard approach for subsequent therapy for patients without prior exposure to fluoropyrimidine-based therapy at that time. Final results of the trial were published in 2014.[201] The median OS in the OFF arm was 5.9 months (95% CI, 4.1–7.4), whereas it was 3.3 months (95% CI, 2.7–4.0) in the 5-FU/leucovorin arm, for a significant improvement in the HR (0.66; 95% CI, 0.48–0.91; *P* = .01).

However, results from the open-label phase III PANCREOX trial show that the addition of oxaliplatin to 5-FU/leucovorin (OFF) in subsequent treatment may be detrimental.[202] In this trial, 108 patients with advanced pancreatic cancer who progressed on gemcitabine-based treatment were randomized to receive second-line mFOLFOX6 or infusional 5-FU/ leucovorin. No difference was seen in median PFS (3.1 vs. 2.9 months; *P* = .99), but median OS was worse in those in the FOLFOX arm (6.1 vs. 9.9 months; *P* = .02). Furthermore, the addition of oxaliplatin resulted in increased toxicity, with rates of grade 3/4 adverse events of 63% in the FOLFOX arm and of 11% in the 5-FU/ leucovorin arm. However, this trial was limited by imbalances in PS 2 proportion between the study arms and possible crossover in treatment delivered following progression.[203] The randomized phase II SWOG S1115 trial showed that patients with metastatic disease that failed to respond to gemcitabine-based therapy (*n* = 62) who received mFOLFOX (fluorouracil and oxaliplatin) had a median OS of 6.7 months, which is comparable to the median OS rates found in the CONKO-003 and PANCREOX trials.[204]

In the NAPOLI-1 phase III randomized trial, the effects of nanoliposomal irinotecan were examined in patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy.[205] Patients were randomized to receive nanoliposomal irinotecan monotherapy, 5-FU/leucovorin, or both (*N* = 417). Median PFS (3.1 months vs. 1.5 months; HR, 0.56; 95% CI, 0.41–0.75; *P* < .001) was significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin, compared to patients who did not receive irinotecan. Updated analyses showed that median OS (6.2 months vs. 4.2 months; HR, 0.75; *P* = .042) was significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin, compared to patients who received 5-FU/leucovorin without irinotecan.[206] Grade 3 or 4 adverse events that occurred most frequently with this regimen were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).[205] Irinotecan liposomal injection, combined with 5-FU/leucovorin, was later approved by the FDA to be used as a subsequent treatment option following gemcitabine-based therapy in patients with metastatic disease. The panel recommends this regimen as a subsequent treatment option for patients with good performance status and disease progression.

Another subsequent therapy option in patients with good performance status and locally advanced or metastatic disease is 5-FU + leucovorin + irinotecan (FOLFIRI). A phase II trial found comparable efficacy and safety in patients treated with mFOLFOX (n = 30) and modified FOLFIRI-3 (n = 21) regimens whose disease had failed previous gemcitabine treatment; OS was 14.9 and 16.6 weeks, respectively.[207] Another phase II trial studied 63 patients with metastatic disease and failure in 1 to 3 lines of gemcitabine- and platinum-based chemotherapies, who received FOLFIRI (in 2 different schedules reported together; FOLFIRI-1 and -3).[208] The median OS was 6.6 months (95% CI, 5.3–8.1 months). Patients who had grade 3-4 toxicities (23.8%) experienced mainly hematologic or digestive toxicities. A GISCAD multicenter phase II study of locally advanced or metastatic disease evaluated the FOLFIRI-2 regimen in patients previously treated with gemcitabine with or without platinum-based therapies.[209] The OS was 5 months and the toxicity was manageable; patients experienced grade 3–4 neutropenia (20%) and diarrhea (12%).

The AIO-PK0104 trial also assessed subsequent therapy in a randomized crossover trial and found capecitabine to be efficacious after progression on gemcitabine/erlotinib in patients with advanced disease.[210] In this trial, capecitabine/erlotinib followed by gemcitabine gave similar outcomes to the aforementioned sequence.

Advances in research have revealed that human immune-checkpoint–inhibitor antibodies that inhibit the interactions between immune cells and antigen-presenting cells may also do so in tumor cells.[211] There is evidence that PD-1 blockade with pembrolizumab may be effective in

tumors with mismatch repair deficiency (dMMR).[212] Pembrolizumab is an anti-PD-1 receptor antibody and blocks its interaction with PD-L1 and PD-L2, releasing the PD-1–mediated inhibition of the immune response, which improves antitumor immunity. The results of a phase II study in patients with 12 different dMMR advanced cancers, including pancreas, found that treatment with pembrolizumab resulted in durable responses (ORR in 53% of patients, with 21% complete response).[213] There were 6 patients with pancreatic cancer with an ORR in 62% of patients (2 had complete response and 3 had progressive disease). Adverse events were experienced by 74% of all patients receiving pembrolizumab; most were low grade (20% experienced grade 3 or 4 adverse events, such as diarrhea/colitis, pancreatitis/hyperamylasemia, fatigue, arthritis/arthralgias, or anemia).[213] Adverse events, however, for immune checkpoint inhibitors can be significant; please see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org.

Based on these data, pembrolizumab was granted accelerated FDA approval in 2017 for patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Similar results were reported from the phase II KEYNOTE-158 study. Among 27 noncolorectal tumor types, including pancreatic cancer, with a median follow-up of 13.4 months, the ORR was reported to be 34.3% (95% CI 28.3%-40.8%), the median PFS was 4.1 months (95% CI 2.4-4.9 months), and the median OS was 23.5 months.[214] Pembrolizumab is recommended by the NCCN Panel for the advanced disease setting for first-line and subsequent treatment as appropriate.

Finally, neurotrophin receptor kinase (NTRK) gene fusions, although rare, have been implicated in the oncogenesis of pancreatic cancer. In three multicenter, open-label, single-arm trials (a phase 1 study with adults, a phase 1/2 study with children, and a phase 2 study with adolescents and adults), the efficacy and safety of larotrectinib, an NTRK inhibitor, was investigated.[215,216] The primary endpoint was set to be ORR and the secondary endpoints were determined to be PFS, duration of response, and safety. Among 17 tumor types, the ORR during independent review was 75% (95% CI 61-85). After 9.4 months, 86% of participants had either underwent curative surgery or were continuing treatment. At one year, 55% of patients were progression-free and the toxicity profile of the agent was found to be minimal.[215] Based on this data, larotrectinib was approved by the FDA in 2018 for the treatment of NTRK gene fusion positive solid tumors in adult and pediatric patients with known acquired resistance and advanced or morbid disease that has progressed despite treatment.[216] Updated data published in 2020 reported that the percentage of patients with an objective response was 79% (95% CI 72-85) with 16% of patients showing a complete response.[217]Similarly, entrectinib is another NTRK inhibitor approved in 2019 by the FDA for adult and pediatric patients (ages 12 years and older) with advanced, morbid, or unresectable NTRK gene fusion positive solid tumors with acquired resistance to standard treatment.[218] Data from three phase 1-2 trials (ALKA-372-001, STARTRK-1, and STARTRK-2) revealed that entrectinib had an ORR of 57.4% and a median duration of response (DOR) of 10.4 months. Like its predecessor, it had a tolerable safety profile.[219,220] Thus the NCCN Panel recommends larotrectinib and entrectinib as first-line and subsequent treatment options for patients with NTRK gene fusion positive locally advanced or metastatic pancreatic adenocarcinoma.

To summarize, subsequent treatment options for patients with good performance status and previously treated with gemcitabine-based therapy include: 5-FU/leucovorin/liposomal irinotecan (category 1 for metastatic disease), FOLFIRI, FOLFIRINOX or modified FOLFIRINOX, 5-FU/leucovorin/oxaliplatin (OFF), FOLFOX, CapeOx, capecitabine, orcontinuous infusion 5-FU.Options for patients with good performance status and previously treated with fluoropyrimidine-based therapy include:

5-FU/leucovorin/nanoliposomal irinotecan (if no prior irinotecan administered), gemcitabine/albumin-bound paclitaxel, gemcitabine/cisplatin, gemcitabine/erlotinib, or gemcitabine monotherapy. Chemoradiation may be a subsequent treatment option in select patients (see *Management of Locally Advanced Disease* below). For MSI-H or dMMR tumors, pembrolizumab is an option whereas for NTRK gene fusion positive disease, larotrectinib or entrectinib may be considered. Subsequent treatment options for patients with poor performance status include: gemcitabine (standard infusion as a category 1 and fixed-dose-rate as a category 2B recommendation), capecitabine (category 2B recommendation), and continuous infusion 5-FU (category 2B recommendation).

Radiation and Chemoradiation Approaches

In patients with pancreatic cancer, radiation is usually given concurrently with gemcitabine- or fluoropyrimidine-based chemotherapy. Chemotherapy is used as a radiosensitizer, increasing the toxicity of radiation to tumor cells. Although the mechanism of radiosensitization is not entirely clear, it is postulated that gemcitabine and fluoropyrimidines decrease the number of tumor cells in the S phase of the cell cycle, a stage at which cells are resistant to radiation damage.[331]

Radiation and chemoradiation are sometimes used for pancreatic cancer in the resectable and adjuvant settings, because of the potential of these treatment methods to decrease the likelihood of local recurrence. A major goal of radiation therapy (RT) in these settings is to sterilize vessel margins and increase the likelihood of a margin-negative resection. It also may be used to enhance local control and prevent disease progression, while minimizing the risk of RT exposure to surrounding organs at risk. Chemoradiation is also often incorporated into neoadjuvant regimens, although randomized trials demonstrating the role of chemoradiation in this setting have not been done. Chemoradiation can also be given as second-line therapy in patients with locally advanced disease, if chemoradiation was not previously given and if the primary site is the sole site of progression. Finally, radiation without chemotherapy is used in the metastatic setting as palliation for pain refractory to analgesic therapy. Varying levels of evidence support the use of chemoradiation in each setting, as discussed in more detail below.

Stereotactic body RT (SBRT) is another technique aimed at increasing dose to the gross tumor while sparing radiation to nearby healthy tissue.[332-339] Retrospective analyses from the National Cancer Database (NCDB) including patients with locally advanced pancreatic cancer (n = 988) showed that patients treated with SBRT had better median OS (13.9 vs. 11.6 months, respectively; P < .001) and 2-year OS (21.7% vs. 16.5%, respectively; P = .001), compared to patients treated with conventionally fractionated RT.[340] Analyses of patient-reported outcomes from a phase II trial in which patients with locally advanced pancreatic cancer received SBRT either upfront or following gemcitabine showed that SBRT did not significantly impact global quality of life and improved pancreatic pain (P = .001) and body image (P = .007), based on assessment at 4 to 6 weeks following treatment.[341] However, 4 months after treatment, role functioning was negatively impacted (P = .002). Results from a prospective trial showed that SBRT was associated with less severe radiation-induced lymphopenia one month after beginning treatment, relative to conventional chemoradiation (13.8% vs. 71.7%, respectively; P < .001).[342] SBRT should not be used if direct invasion of the bowel or stomach is observed on imaging, and care should be taken to limit dose to these areas to reduce treatment-related toxicity, particularly in patients with unresectable disease. SBRT delivered in 3 to 5 fractions may reduce toxicity, though longer follow-up may then be needed.[338] Since the data regarding appropriate use of SBRT are evolving, the panel recommends that SBRT should be used preferably in the context of a clinical trial and at an experienced high-volume center.

Adjuvant Chemoradiation

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.[343,344] 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/m^2 daily for 3 days, was given concurrently with each 2,000-cGy segment of RT. The 5-FU regimen was then continued weekly for a full 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 42%, compared with 15% in the control group.[343]

Other studies have also shown an advantage to adjuvant chemoradiation over observation after resection. EORTC conducted a phase III trial (40891) in patients with both ampullary and pancreatic adenocarcinoma assessing adjuvant RT 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.[345] At a median follow-up of 11.7 years, no statistically significant differences were observed in the different study arms with respect to PFS or OS for the subset of patients with pancreatic cancer.[346]

More contemporary studies have compared different regimens incorporating chemoradiation. 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.[347] This trial, which utilized daily fractionated RT, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[348] 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 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.[349]

The Role of Radiation in Adjuvant Regimens

The majority of the data comparing chemotherapy to chemoradiation in the adjuvant setting do not generally show an advantage to the addition of radiation. Results of ESPAC-1 suggested that the addition of radiation to adjuvant 5-FU chemotherapy may be unnecessary and perhaps even harmful (OS, 13.9, 21.6, and 19.9 months for chemoradiation, chemotherapy, and chemotherapy plus chemoradiation, respectively),[350] although the ESPAC-1 trial has been criticized for lack of attention to quality control for RT.[351-353] A phase II study by GERCOR randomized patients to adjuvant gemcitabine or adjuvant gemcitabine-based chemoradiation.[354] No differences were seen in OS (24.4 months vs. 24.3 months) or DFS (10.9 months vs. 11.8 months) between the groups, but with only 45 patients in each arm no *P* values were reported. In addition, the multicenter, open-label, randomized phase III CapRI trial found that adjuvant chemoradiation with 5-FU, cisplatin, and interferon alfa-2b (IFN α-2b) followed by 5-FU chemotherapy gave outcomes no better than adjuvant treatment with 5-FU alone.[355]

A 2012 meta-analysis of 15 prospective, randomized trials found that adjuvant chemoradiation did not improve DFS, 2-year survival, or OS (OR, 0.99; $P = .93$) compared to surgery alone, while adjuvant chemotherapy improved all 3 outcomes (OR for OS, 1.98; $P < .001$).[356] A 2013 meta-analysis of 9 trials found similar results, with HRs for death compared to no adjuvant treatment of 0.62 for 5-FU (95% CI, 0.42–0.88), 0.68 for gemcitabine (95% CI, 0.44–1.07), 0.91 for chemoradiation (95% CI, 0.55–1.46), 0.54 for chemoradiation plus 5-FU (95% CI, 0.15–1.80), and 0.44 for chemoradiation plus gemcitabine (95% CI, 0.10–1.81).[357]

However, a population-based assessment of outcomes of patients in the NCDB with pancreatic cancer resected from 1998 to 2002 found the opposite result: chemoradiation gave better OS than chemotherapy in a performance-status–matched comparison to no adjuvant treatment (HR, 0.70; 95% CI, 0.61–0.80 vs. HR, 1.04; 95% CI, 0.93–1.18).[358] A multi-institutional pooled analysis of 955 consecutive patients who had R0-1 resections for pancreatic cancer also supports the supposition that

adjuvant chemoradiation improved survival compared to chemotherapy alone (OS, 39.9 months vs. 27.8 months; $P < .001$).[359]

To definitively clarify the role of chemoradiation following gemcitabine monotherapy in the adjuvant setting, RTOG is conducting trial 0848 (ClinicalTrials.gov NCT01013649). Patients without evidence of progressive disease after 5 cycles of gemcitabine-based chemotherapy are being randomized to 1 additional round of chemotherapy or 1 additional round of chemotherapy followed by chemoradiation with capecitabine or 5-FU. The primary endpoint is OS, and the trial is estimated to be completed in 2020. Studies are presently investigating the potential role of SBRT in the adjuvant setting (eg, NCT02461836).

Benefit of Adjuvant Chemoradiation in Patient Subsets

It has been suggested that subsets of patients (eg, patients with R1 resections or positive lymph nodes) may be more likely to benefit from adjuvant chemoradiation.

Studies that have looked at R0 or R1 subsets of patients have found mixed results. For instance, patients treated in the ESPAC-1 trial did not derive a benefit from the addition of radiation to adjuvant chemotherapy, irrespective of margin status.[360] In contrast, results from a prospectively collected database of 616 patients with resected pancreatic cancer at the Johns Hopkins Hospital found that adjuvant chemoradiation benefited both the R0 and R1 subsets compared to observation alone.[361] The Mayo Clinic performed a retrospective review of 466 patients who had R0 resections for pancreatic adenocarcinoma, and found an OS benefit of adjuvant chemoradiation over observation.[362] In addition, a retrospective review of greater than 1200 resected patients from the Johns Hopkins Hospital and the Mayo Clinic who received adjuvant 5-FU–based chemoradiation or were observed following resection found that chemoradiation improved outcomes regardless of margin status (R0: RR, 0.61; 95% CI, 0.47–0.77; $P < .001$; R1: RR, 0.52; 95% CI, 0.36–0.74; $P < .001$).[363] A meta-analysis of 4 RCTs found evidence for an increased survival benefit of adjuvant chemoradiation in the R1 subset (HR for death, 0.72; 95% CI, 0.47–1.10) over the R0 subset (HR for death, 1.19; 95% CI, 0.95–1.49).[364]

Fewer analyses have looked at the role of chemoradiation in resected patients with positive lymph nodes. One retrospective review compared outcomes of 94 patients who underwent distal pancreatectomy at the Johns Hopkins Hospital and either received adjuvant chemoradiation or were just observed following resection.[365] An exploratory subset analysis suggested that patients with positive lymph nodes derived greater benefit from adjuvant chemoradiation than those with negative nodes. In addition, a meta-analysis of 4 randomized controlled adjuvant trials found that chemoradiation had a similar lack of benefit in patients with positive and negative lymph nodes.[366]

Chemoradiation and SBRT for Locally Advanced Disease

Chemoradiation is a conventional option for the management of locoregional pancreatic cancer, although the utility of chemoradiation in this population of patients is controversial.[367] It is mainly used in selected patients who do not develop metastatic disease during initial chemotherapy.

A meta-analysis identified 15 RCTs (1128 patients) that compared chemoradiation to either chemotherapy or radiation in the locally advanced setting.[368] Whereas combined modality therapy significantly improved survival compared to radiation alone, survival was the same when compared to those receiving chemotherapy alone. Increased toxicity was observed in the chemoradiation group.

The role of chemoradiation in locoregional pancreatic cancer was initially defined in a trial conducted in locally advanced disease by GITSG.[344] 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.[369] Gemcitabine has also been used as a radiation sensitizer in the locally advanced setting.[370-374] Some evidence suggests that concurrent gemcitabine and radiation can yield similar or better outcomes when compared with 5-FU–based chemoradiation in the setting of locally advanced disease.[369,372,375,376] The use of capecitabine as a radiosensitizer has also been assessed in this setting and appears to be effective.[377] Recently reported results of the phase II SCALOP trial showed that health-related quality-of life scores (ie, cognitive functioning, fatigue, bloating, dry mouth, body image, future health concerns) tended to favor capecitabine-based chemoradiation, compared to gemcitabine-based chemoradiation.[378] Therefore, when chemoradiation is recommended by the panel, fluoropyrimidine-based chemoradiation is generally preferred, compared to gemcitabine-based chemoradiation.

Upfront Chemoradiation or SBRT in Locally Advanced Disease

Results of 2 early randomized trials comparing upfront chemoradiation to chemotherapy in locally advanced disease were contradictory.[379,380] Three phase II trials also assessed the upfront chemoradiation approach in locally advanced pancreatic adenocarcinoma, with median survival rates ranging from 8.2 to 9 months.[370,381-383] Results from small, single-arm trials of upfront chemotherapy followed by chemoradiation in locally advanced disease have been discussed.[384]

The phase III randomized ECOG-4201 trial, which assessed gemcitabine compared with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced 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).[374] However, the poor accrual rate decreased its statistical power, there was no difference in PFS, 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.[385]

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.[386] 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.

Upfront SBRT may be used in patients with locally advanced disease who are not candidates for combination systemic treatment. A 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.[332] However, another retrospective review of 71 patients reported a median OS of 10.3 months with only 3 patients (4%) experiencing grade 3 toxicity.[335] Hypofractionated dosing may also be used in these patients, with acceptable toxicity.[387] The

incorporation of simultaneous integrated boost is being investigated to improve the potential of SBRT for downstaging.[388]

Thus, the role of upfront chemoradiation in the setting of locally advanced pancreatic cancer is still undefined. If patients present with poorly controlled pain or local invasion with bleeding, then starting with upfront chemoradiation therapy or SBRT is an option.[370,374]

Chemoradiation or SBRT Following Chemotherapy in Locally Advanced Disease

Starting with 2 to 6 cycles of systemic chemotherapy followed by chemoradiation or SBRT is an option for selected patients with locally advanced disease and good performance status who have not developed metastatic disease.[389-391] 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/celiac arteries); 2) there are suspicious metastases; or 3) the patient may not be able to tolerate chemoradiation. Employing an initial course of chemotherapy may improve systemic disease control in these cases. In addition, the natural history of the disease can become apparent during the initial chemotherapy, thus allowing the selection of patients most likely to benefit from subsequent chemoradiation. 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.[389]

In the randomized phase II SCALOP trial, patients with locally advanced pancreatic cancer received gemcitabine and capecitabine combination chemotherapy, followed by either gemcitabine-based chemoradiation or capecitabine-based chemoradiation (n = 74).[377,392] Though OS and PFS did not significantly differ between the two treatment arms, results favored capecitabine-based chemoradiation, with a median OS of 17.6 months and a median PFS of 12 months.[392]

In the international phase III LAP-07 RCT, patients with locally advanced pancreatic cancer (n = 269) received chemoradiation with capecitabine following 4 months of induction chemotherapy with either gemcitabine monotherapy or gemcitabine and erlotinib.[393] Chemoradiation in this setting provided no survival benefit, compared to chemotherapy only (HR, 1.03; 95% CI, 0.79–1.34; P = .83). Differences were noted in other potentially meaningful outcomes such as time to reinitiation of therapy (159 days in the chemoradiation arm vs. 96 days in the control arm; P = .05) and local tumor progression (34% in the chemoradiation arm vs. 65% in the chemotherapy only arm; P < .0001).[393]

SBRT following gemcitabine monotherapy in patients with locally advanced pancreatic cancer has been examined in phase II trials.[394,395] This regimen was associated with low toxicity and favorable freedom from local disease progression.[394,395] Because there are now more active chemotherapy regimens than gemcitabine monotherapy, additional studies are planned to assess the role of radiation after more active chemotherapy.

Advanced Radiation Techniques

Intensity-modulated RT (IMRT) is increasingly being applied for therapy of locally advanced pancreatic adenocarcinoma and in the adjuvant setting with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues.[396-400] 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.[400] 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. A recent systematic review including 13 IMRT studies showed that IMRT does not improve survival outcomes, compared to 3D-CRT.[401] However, toxicities grade 3 or greater were more numerous in 3D-CRT, relative to IMRT (*P* = .017). These toxicities were mainly GI, specifically nausea/vomiting and diarrhea. IMRT resulted in reduced grade 3/4 toxicities when the authors made a cross-study comparison of toxicities in patients who received a similar 5-FU–based regimen with 3-D conformal radiation in the RTOG 9704 trial.[347,402] Comparing the 2 trials, rates of grade 3/4 nausea and vomiting were 0% vs. 11% (*P* = .024), and rates of grade 3/4 diarrhea were 3% vs. 18% (*P* = .017),[402] suggesting that IMRT may be well-tolerated and allow for higher radiation doses to the tumor.[402] There is no clear consensus on the appropriate maximum dose of radiation when IMRT technique is used.

Intraoperative RT (IORT) can allow for higher doses of radiation because sensitive structures can be excluded from the radiation fields. IORT is sometimes administered to patients with borderline resectable disease who have received maximal neoadjuvant therapy to sterilize close or involved margins at the time of surgery, although data in this setting are lacking. It is also sometimes used when a patient is found to be unresectable at the time of surgery and in cases of locally recurrent disease. Most studies of IORT in patients with locally advanced pancreatic cancer found that while local control may be improved, no change in survival is evident with use of IORT because of the high frequency at which metastatic disease develops.[403-406] Some groups, however, believe that IORT can offer benefits in very carefully selected patients with non-metastatic disease.[407-409] Overall, there is no clear established role for IORT in patients with pancreatic cancer,[410] and the panel believes it should only be performed at specialized centers.

Management of Metastatic Disease

The primary goals of treatment for metastatic pancreatic cancer are palliation and lengthened survival. Survival benefits are usually limited to patients with adequate performance status (ECOG 0-1, with good biliary drainage, and adequate nutritional intake). Systemic therapy is therefore recommended for patients with metastatic disease and good performance status, as described in *Systemic Therapy Approaches for Locally Advanced or Metastatic Disease*, above, and in the algorithm.

Patients who present with poor performance status may benefit from single-agent chemotherapy (gemcitabine is a category 1 recommendation), but comfort-directed measures are always paramount (see *Palliative and Supportive Care*, below, and the NCCN Guidelines for Supportive Care, available at www.NCCN.org). An alternative option for these patients is palliative and best supportive care.

Patients with metastatic disease are generally not candidates for RT. However, palliative RT may be administered to patients who present with poor performance status (ie, patients who are elderly and/or not candidates for definitive treatment), instead of single-agent chemotherapy. A short course of RT may be administered to metastatic sites that cause pain (eg, osseous pain).[411]

Before initiating cytotoxic therapy, an open dialogue regarding the goals and side effects of treatment should take place and, if needed, adjunctive strategies can be used (see *Palliative and Supportive Care*, below). Of note, 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/or as constipation.

For patients who do well on initial therapy, a chemotherapy holiday is appropriate, or maintenance therapy can be considered (see *Possible Role of Maintenance Therapy in Advanced Disease*, above). After progression, second-line therapy is possible, especially in patients who maintain a good performance status (see *Second-Line Systemic Therapy in the Advanced Setting*, above). Prior to commencing second-line therapy, serial 3D CT or MRI imaging of known sites of disease to determine therapeutic benefit is recommended by the panel. However, patients may demonstrate progressive disease clinically without objective evidence of progression (also for *Management of Locally Advanced Disease*; see below).

Management of Locally Advanced Disease

As in the metastatic setting, the primary goals of treatment of patients with locoregionally advanced pancreatic cancer are palliation and lengthened survival. Also, as in metastatic disease, patients with locally advanced disease are treated with systemic therapy based on their performance status. Palliative and best supportive care and single-agent chemotherapy or palliative RT are options for patients with poor or declining performance status, whereas patients with good performance status can be treated with more intensive therapy, as described in *Systemic Therapy Approaches for Locally Advanced or Metastatic Disease*, above, and in the guidelines.

Historically, most studies in the locally advanced setting used gemcitabine monotherapy. However, there is an increasing emphasis on understanding the role of modern, more active regimens in locoregionally advanced disease. The experience with FOLFIRINOX in 22 patients with locally advanced pancreatic cancer at the Massachusetts General Hospital Cancer Center through February 2012 was reported.[412] An overall response rate of 27% was observed, and the median PFS was 11.7 months. Five patients (23%) were able to undergo R0 resections, although 3 of these patients experienced distant recurrence by 5 months. It was also reported that 32% of patients receiving FOLFIRINOX required greater than or equal to 1 hospitalization or visit to the emergency department during treatment.

Other studies and case reports addressing the use of chemotherapy with or without chemoradiation in patients with locally unresectable disease have noted that the opportunity for curative intent resection occasionally arises.[412-421] The panel believes that patients with a significant response to chemotherapy and/or chemoradiation may be considered for surgical resection, but acknowledges that such conversions are rare in patients with true locally advanced disease. Following resection, these patients have similar survival rates as those initially determined to be resectable.[422]

Upfront chemoradiation or SBRT may be used in select patients (see *Chemoradiation and SBRT for Locally Advanced Disease*). The use of chemoradiation or SBRT following chemotherapy in locally advanced disease is also discussed above. If disease progression occurs in patients with locally advanced disease, chemoradiation or SBRT are treatment options if all of the following are true: good performance status is maintained, chemoradiation or SBRT were not previously given, and the primary site is the sole site of progression.

Irreversible electroporation (IRE) is an ablative technique in which electric pulses are used to create nanopores that induce cell death similar to apoptosis. This technique has been used in patients with locally advanced pancreatic cancer.[423,424] IRE may be safe and feasible[425] and may improve

survival outcomes.[424] However, due to concerns about complications and technical expertise,[426] the panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer.

Management of Resectable and Borderline Resectable Disease

Surgical Management

The goals of surgery for adenocarcinoma of the pancreas include an oncologic resection of the primary tumor and regional lymph nodes. 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.[427] Surgery should be done efficiently, optimizing quality of life and cost. Early concerns about high mortality associated with various pancreatic resection procedures[428] have now been lessened by studies demonstrating an acceptably low (<5%) mortality in experienced centers (see *Effect of Clinical Volume*, below).[429] Even under the most optimal clinical trial conditions, the median survival of resected patients following adjuvant therapy ranges from 20.1 to 28.0 months.[223,347,350,430,431] Negative margin status (ie, R0 resection), tumor DNA content, small tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[432-434] 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.[435-437]

Criteria for Resection

The NCCN Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation at high-volume centers with use of 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 differ in their approaches to patients with locoregional disease involvement (pancreas and peripancreatic lymph nodes).

Careful intraoperative staging should rule out peritoneal, liver, and distant lymph node metastases, and resection of the primary tumor should only be done in the absence of distant disease. The surgical procedure required is based on the location of the primary tumor and relationship to blood vessels. Therefore, a pancreas protocol CT is critical for preoperative planning.

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.[131,438] Other groups have also put forth definitions of resectability of pancreatic cancer.[439-441] A more restrictive definition of borderline resectable pancreatic tumors has also been described.[442] This definition uses degrees of contact (eg, interface between tumor and SMA measuring ≤180° of vessel wall circumference) and contour deformity/narrowing (eg, tear drop deformity in the main PV [MPV] or SMV) to ascribe likelihood of vascular invasion rather than subjective terms such as abutment and impingement. The panel endorses this definition for use in clinical trials. Using a combination of these sets of criteria, tumors are classified as resectable, borderline resectable, locally advanced, or metastatic disease.

Analysis of the pancreatic neck and bile duct at time of surgery by frozen section may be considered. A review of 4 studies with 2580 patients showed that additional resection to achieve a negative surgical margin was not associated with improved survival.[443] Frozen sections should be taken approximately 5 mm from the transection margin, with the clean-cut side facing down, to avoid cautery artifact that may confound analysis and result in false negatives. If tumor is located within 5 mm of margins, further

excision of the pancreas should be considered to ensure at least 5 mm of clearance.

For cancers of the pancreas head and uncinate, a pancreatoduodenectomy (Whipple procedure) is done. For cancers of the pancreas body and tail, a distal pancreatectomy with en-bloc splenectomy is done.

The panel has adapted the criteria put forth by other groups and lists its recommended criteria for defining resectability status in the guidelines. 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 negative (R0) resection margins. Overall, the likelihood of attaining negative margins is the key criterion for consideration when determining whether a patient is a potential candidate for resection.[441,444] In this context, a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete resection. Patients at high risk for positive surgical margins are not considered to be good candidates for an upfront resection but may be potentially downstaged and safely resected following neoadjuvant therapy [see *Preoperative (Neoadjuvant) Therapy* below]. Furthermore, the panel recommends that patient factors be considered when deciding whether a patient is a surgical candidate. Comorbidities, performance status, and frailty are all things to be discussed during the multidisciplinary review. Please refer to the NCCN Guidelines for Older Adult Oncology (available at www.NCCN.org) 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 pancreatic 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 minimally invasive pancreaticoduodenectomy (ie, the Whipple procedure).[445,446]

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 previously performed. If a patient with jaundice is found to be unresectable at surgery, then the panel recommends surgical biliary bypass at that time. If a stent has been previously placed, then surgical biliary bypass could be considered. In addition, gastrojejunostomy can be considered if appropriate regardless of jaundice (category 2B for prophylactic gastrojejunostomy). Celiac plexus neurolysis can also be performed, especially when indicated by pain in a patient with jaundice (category 2B if no pain). See *Severe Tumor-Associated Abdominal Pain*, below, for more details about these procedures.

In patients with suspected borderline resectable disease for whom cancer is not confirmed following repeated biopsy with EUS-FNA (preferred), intraoperative biopsy is recommended. If resectable disease is found in these patients, then surgical resection followed by adjuvant therapy is recommended. If unresectable disease is found, then recommendations for management of locally advanced or metastatic disease should be followed (see above). If these patients present with jaundice, surgical biliary bypass and gastrojejunostomy (category 2B for prophylactic gastrojejunostomy) should be considered, as well as celiac plexus neurolysis for pain (category 2B if no pain).

Pancreatoduodenectomy (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).[447,448] 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 result in suboptimal clearance and increase the risk of an R1 resection.[449,450]

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.[451-453] 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 numbers are more limited, similar findings have been noted with respect to hepatic arterial resection and reconstruction.[453,454] Others, however, have noted poor short- and long-term outcomes with arterial resection.[455,456] 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 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.[456] No difference in mortality was seen.

Distal Pancreatectomy with En-bloc Splenectomy

The goals of left-sided resection are similar to those of pancreatoduodenectomy, although they are often more difficult to achieve because of the advanced stage at which most of these cancers are discovered. Plane of dissection anterior to adrenal gland or en bloc resection of left adrenal gland with plane of dissection posterior to Gerota's fascia is recommended as clinically indicated. Spleen preservation is not indicated in distal pancreatectomy for adenocarcinoma, and an R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.[457,458] 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.[458,459] 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.[457-459] 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.[458,459] Local recurrence, however, remains problematic even with pathologically negative margins.[459]

There is an increasing role for laparoscopic distal pancreatectomy. A meta-analysis including 29 observational studies with 3,701 patients showed that laparoscopic distal pancreatectomy may decrease intraoperative blood loss ($P < .01$), time to first oral intake ($P < .01$), and length of hospital stay ($P < .01$), as compared to open distal pancreatectomy.[460] Results from 172 patients treated at the Mayo Clinic found significant benefits in the patients who had laparoscopic versus open resections in blood loss, the need for blood transfusions, and the length of hospital and intensive care unit stays without any difference in oncologic outcomes.[461] In addition, results from a meta-analysis of 4 studies of 665 total patients suggest that the laparoscopic method is safe and results in shorter hospital stays.[462] Furthermore, results from a population-based, retrospective cohort study that included 8957 patients showed similarly that the laparoscopic approach can decrease complication rates and shorten hospital stays.[463]

Management of Neck Lesions

Pancreas neck adenocarcinomas are especially difficult to manage. Cancers in the pancreas neck are located anterior to the superior mesenteric vessels and PV. Depending on the extent of involvement, a pancreaticoduodenectomy extending to the left of the SMV (extended pancreaticoduodenectomy), a distal pancreatectomy extending to the right of the SMV (extended distal pancreatectomy), or a total pancreatectomy may be required to obtain an R0 resection.[464]

The precise extent of involvement often cannot be determined prior to surgery; therefore, complex intraoperative decisions are required, and the surgeon must anticipate this. Complexity of surgery for pancreas neck cancers is compounded by the frequent involvement of the SMV/PV.[464,465] Surgeons who operate on pancreas neck cancers must anticipate possible SMV/PV involvement and be prepared to manage it.

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.[466] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreatoduodenectomy decreased, a subset was identified of patients 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.[467] Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.[468]

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.[469-472] 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.[453] A meta-analysis of 22 retrospective studies (2890 patients) found that vein resection resulted in perioperative morbidity and mortality equal to that of standard resection, but R0 resection rates were lower in that group.[473] In a multi-institutional database analysis of 492 patients undergoing pancreaticoduodenectomy, R0 resection rates were no different between the 14% who had vein resection compared to those without venous involvement (66% vs. 75%; *P* = NS).[474] 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[475] 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.[476] A systematic review comparing a classic Whipple operation to pylorus-preserving pancreaticoduodenectomy (including 8 RCTs with 512 patients) showed no significant differences for mortality, morbidity, and survival, but some perioperative measures (ie, operating time, intraoperative blood loss, red blood cell transfusion) were better in patients who received pylorus-preserving pancreaticoduodenectomy, relative to those who received a classic Whipple.[476] Therefore, though more data from high-quality RCTs are needed, pylorus-preserving pancreatoduodenectomy is an acceptable alternative to classic pancreatoduodenectomy performed with antrectomy.

Pancreatic Anastomosis

Efforts have focused on preventing pancreatic leaks and fistulas, which are morbid and potentially lethal complications of pancreatoduodenectomy. Pancreaticojejunostomy has traditionally been the standard reconstruction and is the major focus of morbidity and mortality after pancreatoduodenectomy because of leaks, abscess formation, and fistulas from this anastomosis. A randomized study at Johns Hopkins Hospital found no difference in fistula rates after pancreaticojejunostomy and pancreaticogastrostomy.[477] However, a more recent multicenter, randomized, superiority trial compared the outcomes of 329 patients undergoing pancreaticoduodenectomy with either pancreaticojejunostomy or pancreaticogastrostomy.[478] A significant difference was seen in the primary outcome measure of postoperative fistulas, which occurred in 19.8% of patients in the pancreaticojejunostomy group and 8.0% of patients in the pancreaticogastrostomy group (OR, 2.86; 95% CI, 1.38–6.17; *P* = .002). An increase in grade ≥3a postoperative complications was seen, however, in the pancreaticogastrostomy group (24% vs. 21%). Criticisms of this trial have been published.[479] Although a meta-analysis of 4 RCTs (676 patients) concluded that pancreaticogastrostomy is associated with a lower risk of fistula formation than pancreaticojejunostomy (RR, 0.41; 95% CI, 0.21–0.62),[480] the optimal approach to anastomosis remains undefined.[481]

Surgeons have also 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.[482,483] 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.[484] Stents used in the 1930s and 1940s continue to be used today, but data suggest that they do not decrease leak rates.[485]

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).[486,487] Pasireotide, in contrast, significantly decreased the rate of grade ≥3 fistula, leak, or abscess in a single-center, double-blind RCT of 300 patients (9% in pasireotide group vs. 21% in placebo group; RR, 0.44; 95% CI, 0.24–0.78; P = .006).[488] Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.[489]

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.[490,491] 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.[492] 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.[493]

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.[494] A larger randomized prospective trial was performed at Johns Hopkins Hospital from 1996 through 2001 to evaluate the role of extended lymph node dissections.[495] 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.[495-497] A randomized multicenter trial in Japan came to similar conclusions.[498] Furthermore, multiple systematic literature reviews and meta-analyses of RCTs comparing pancreatoduodenectomy with standard versus extended lymphadenectomy support the conclusion that the extended procedure does not have any impact on survival.[499-501] In addition, patients undergoing extended lymphadenectomy have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.[502]

The information to date thus does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.[503] 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.[504,505]

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis and to potentially make surgery less

morbid by improving liver function preoperatively. Although controversial, several studies have suggested that pancreatoduodenectomy is associated with higher perioperative mortality when done in the setting of hyperbilirubinemia.[506-508] 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.[509-515] A retrospective analysis from a prospective database of 593 patients treated with pancreatoduodenectomy at MD Anderson Cancer Center found that self-expandable metal stents did not affect postoperative complications, 30-day mortality, length of stay, anastomotic leak, margin status, or determination of unresectability during resection, although more wound infections and longer operative times were observed in this group.[516] In contrast, a 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%; RR 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.[159]

Based on these reports, most groups who perform resection without neoadjuvant treatment advocate selective use of decompression only in patients who are symptomatic, septic, coagulopathic, have renal insufficiency, 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 longer than 1 week.

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.[517] 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.[518-521]

The panel notes that stents are an evolving technology. The choice of stents includes plastic and self-expanding metal (fully covered, partially covered, or uncovered) (also see the discussion on stents in *Palliative and Supportive Care*, below). While any stent can become occluded, several groups have reported better patency with metal stents.[519-521] Covered metal stents may give more durable patency, since the cover prevents tumor ingrowth,[522] but the reported differences between covered and uncovered stents are not dramatic.[522,523] Furthermore, migration is more of an issue with covered stents.[523] This issue has led to the introduction of partially covered stents,[524] though these stents may still migrate in a substantial number of patients.[525,526] Most metal stents used today are self-expanding. Their small initial diameters make them easy to place, and their placement rarely requires dilation.[524] Several panel members reported that their institutions use plastic stents in patients with short life expectancies (<3 months).[524] 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). In the absence of level-1 data, the panel consensus is that short, self-expanding metal stents (SEMS) are preferred because they are easy to place without dilation, are unlikely to interfere with the subsequent resection, and have a

significantly longer patency rate than plastic stents. The panel recommends that a plastic stent or a fully covered self-expandable metal stent be placed if tissue diagnosis has not been confirmed, as fully covered metal stents are removable endoscopically.

Effect of Clinical Volume

Several studies have examined the effect of institutional volume on patient outcomes. The fundamental premise was that the decreasing morbidity and mortality seen in the 1980s and 1990s were the direct result of large, single-institution experiences. Moreover, the concern was that if surgeons performed pancreatoduodenectomy less frequently, patients might have increased morbidity and mortality. 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% vs. 12.3%).[527] High volume was defined as more than 50 cases per year, and this relationship correlated in a regression analysis. Of note, 75% of the cases in New York State were performed in low-volume centers. Several other studies have assessed regional outcomes with pancreatoduodenectomy from U.S. hospitals.[528-532] 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.[533-535]

The definitions of high and low volume varied among all these studies. However, a striking difference was seen when the mortality rates from pancreatoduodenectomy in very-low-volume (0–1 procedure/year) and low-volume (1–2 procedures/year) hospitals were compared with rates in higher-volume hospitals (>5 procedures/year).[536] In-hospital mortality rates at these very-low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, vs. 4%; $P < .001$). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreatoduodenectomy is compared to other major surgeries. In a retrospective analysis of data from the national Medicare claims database and the Nationwide Inpatient Sample, hospitals performing 6 to 16 and greater than 16 procedures per year were classified as “high” and “very-high” volume centers.[537] 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 pancreatoduodenectomy, as compared to major surgery at any other site, further reinforcing the magnitude of the effect that high-volume centers can have specifically 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.[538] In addition, a 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 ($P = .008$).[539] This review also found that 5-year survival rates were higher in high-volume centers. In contrast, hospital readmission after pancreatoduodenectomy appears to be more of a function of patient characteristics than hospital or surgeon volume.[540]

The NCCN Panel recommendation is that pancreatic resections should be done at institutions that perform a large number (at least 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.[541] 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 pathologic 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.

Specimen Orientation, Sectioning, Pathologic Analysis, and Reporting

The primary purpose of pathologic analysis of the pancreatic specimen is to determine the pathologic stage of the tumor by evaluating the type, grade, size, and extent of the cancer. Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. In 2004, the Commission on Cancer (CoC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. The pathology synoptic reports from the College of American Pathologists (CAP) comply with the CoC requirements, and the latest revisions to the CAP Pancreatic (Exocrine) protocol were issued in August 2016.[542] The NCCN Pancreatic Adenocarcinoma Panel currently supports the CAP pathology synoptic reports. The proposal included in the guidelines (see *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* in the algorithm) 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.[543,544]

Lymph Node Counts and Lymph Node Ratio

Number of positive lymph nodes and lymph node ratio are associated with OS in patients with pancreatic cancer.[545] The CAP recommendations include a count of the number of lymph nodes recovered and the number of involved nodes.[546] Retrospective database analyses have found that patients with N0 disease have a better prognosis with an increasing number of examined lymph nodes.[547-549] 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 to be from 11 to 17 to provide optimal staging and to serve as a quality indicator.[547,549,550] The panel believes that every effort should be made to identify all regional lymph nodes within the pancreatectomy specimen.

For patients with N1 disease, lymph node ratio (positive node/nodes examined) appears to be related to prognosis.[547-554] For instance, in one analysis, patients with less than 15% of examined positive nodes had a 5-year survival rate of 21.7%, while those with greater than 15% positive nodes had a 5.2% 5-year survival rate (P = .0017).[552]

Whipple Specimen

Specimen orientation and inking involves both a 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 (ie, written on the pathology

requisition). For example, the distal and proximal margins of the SMV and SMA, as well as the bile duct margin, should be marked.

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 algorithm. 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.[541,555-557] 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. There is no one correct way to dissect a Whipple specimen. Options include axial, bi- or multi-valve slicing, and perpendicular slicing (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).

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 RT might be indicated if not received preoperatively. The panel strongly recommends reporting tumor clearance in mm for all margins (as noted in the *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* section of the algorithm) to allow prospective accumulation of these important data for future analysis.

A 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; $P < .001$).[558] In fact, patients with close-margin R0 resections had a median survival time similar to that of the R1 population (16 months vs. 14 months; $P = .6$). Consistent with these results, another retrospective review of 285 patients found that those with R1 resections, defined as tumor ≤1 mm from the margin, had a significantly worse local recurrence-free survival than those with R0 resections (HR, 4.27; 95% CI, 2.07–8.81).[559,560] Finally, a recent study, which used a standardized pathologic protocol that involved multicolor inking and careful evaluation of multiple margins distances, found that patients with R1 resections (tumor at 0 mm) had a median survival of 17.7 months, while those with R0 resections had a median survival of 32.9 months ($P = .10$).[561] Together, these results suggest that an appropriate definition of a negative margin may be greater than 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 pT3 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 (caudad) peripancreatic (peripheral) margin are included in the guidelines (see *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* in the algorithm).

Perioperative Therapy

Even with R0 resections, recurrence rates are very high in this disease. Therefore, additional therapy is required for all patients with resected pancreatic adenocarcinoma.

Postoperative (Adjuvant) Therapy

Results of many trials have shown that adjuvant therapy improves outcomes over observation following resection (see sections on *Systemic Therapy Approaches for Locally Advanced or Metastatic Disease* and *Radiation and Chemoradiation Approaches*, above). While 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, timing of imaging, and 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 CA 19-9 or CEA levels[223]), 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. Results of the ESPAC-4 phase III randomized trial (N = 730), in which gemcitabine combined with capecitabine was compared to gemcitabine monotherapy for the adjuvant setting, showed that median survival was greater for participants randomized to receive the combination regimen (28.0 months), relative to patients randomized to receive gemcitabine monotherapy (25.5 months) (HR, 0.82; 95% CI, 0.68–0.98; P = .032).[431] In the CONKO-005 phase III randomized trial, gemcitabine administered with erlotinib was compared to gemcitabine administered alone in the adjuvant setting.[562] This combination regimen did not significantly improve OS or DFS, compared to gemcitabine monotherapy. A phase II prospective trial including 22 patients with resected pancreatic cancer showed that gemcitabine/cisplatin is feasible, with a median OS of 35.5 months and median recurrence-free survival of 16.7 months.[563]

Based on the data discussed above, no definite standard has been established in the adjuvant treatment of pancreatic cancer at this time. Chemotherapy alone with gemcitabine (category 1), 5-FU/leucovorin (category 1), gemcitabine/capecitabine (category 1), or continuous infusion 5-FU are listed in the guidelines as options for adjuvant treatment. Capecitabine monotherapy is also a treatment option for the adjuvant setting (category 2B). The panel considers capecitabine to be 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. Gemcitabine, 5-FU/leucovorin, or continuous infusion 5-FU before gemcitabine- or fluoropyrimidine-based chemoradiation is also recommended as an adjuvant treatment, with subsequent chemotherapy

being an option. To date, no studies have demonstrated superiority of giving chemoradiation before versus after chemotherapy in the adjuvant setting.

Regardless of the therapy being considered it is important to evaluate the patient for extent of disease prior to therapy, because some patients have early recurrence within the first few weeks following surgery. In addition, the panel recommends restaging a patient with imaging following systemic chemotherapy if chemoradiation is planned.

A recent retrospective analysis of data from patients in the ESPAC-3 trial found that completion of the full course of chemotherapy was an independent prognostic factor for survival, but that time to treatment initiation after surgery was not.[564] These results suggest that delaying chemotherapy until patients adequately recover could possibly improve outcomes. The panel therefore recommends that adjuvant treatment be initiated within 12 weeks, after adequate recovery from surgery.

S-1 is an oral chemotherapy drug that is being used in Asia. Results of the phase III RCT JASPAC-01 trial (*N* = 385), in which S-1 was compared to gemcitabine in the adjuvant setting, showed that median OS was greater for S-1 (46.5 months; 95% CI, 37.8–63.7) compared to gemcitabine (25.5 months; 95% CI, 22.5–29.6).[565] Three- and 5-year survival rates were 59.7% and 44.1%, respectively, for S-1, and 38.8% and 24.4%, respectively, for gemcitabine. S-1 was generally well-tolerated, and the treatment of patients randomized to receive gemcitabine was more likely to be discontinued, relative to the treatment of patients randomized to receive S-1 (*P* = .005). Grade 3 or 4 adverse events that were more likely to be reported in patients receiving gemcitabine include leucopenia, neutropenia, aspartate aminotransferase, and alanine aminotransferase, while stomatitis and diarrhea were more common in patients receiving S-1.

Results of the PRODIGE 24/CCTG PA.6 phase III trial (n = 493) were recently presented, comparing adjuvant chemotherapy with gemcitabine versus mFOLFIRINOX to treat resected pancreatic adenocarcinoma in patients with good performance status.[566] The median follow-up was 30.5 months (95% CI, 29.5–33.7). The median DFS was greater for mFOLFIRINOX (21.6 months; 95% CI, 17.5–26.7) compared to gemcitabine (12.8 months; 95% CI, 11.7–15.2). The median OS (54.4 vs. 35.0 months, respectively) and metastasis-free survival (30.4 months vs. 17.7 months, respectively) were also greater for mFOLFIRINOX compared to gemcitabine. Grade 3 or 4 adverse events in mFOLFIRINOX or gemcitabine treatment arms were reported in 75.5% versus 51.1% of patients, including 12% grade 4 in each arm, with one death due to toxicity in the gemcitabine arm.

Ongoing clinical trials in the adjuvant setting include RTOG 0848 (ClinicalTrials.gov NCT01013649), which is assessing gemcitabine with or without subsequent chemoradiation, and a phase II study comparing FOLFIRINOX with albumin-bound paclitaxel (ClinicalTrials.gov NCT02243007).

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levo-leucovorin is equivalent to 400 mg/m^2 of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when

given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.[567] Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) leucovorin.[568] Also, the Mayo Clinic and North Central Cancer Treatment Group (NCCTG) determined that there was no therapeutic difference between the use of high- (200 mg/m^2) or low- (20 mg/m^2) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.[569] Finally, if none of the above options is 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.

Preoperative (Neoadjuvant) Therapy

The standard approach to therapy in patients with resectable disease has been postoperative treatment, with median survivals in the range of 20.1 to 23.6 months under the most optimal clinical trial conditions.[223,347,350,430] However, it is becoming increasingly apparent that patients with borderline resectable disease, who are at higher risk for R1 resections, are potentially in need of a different management approach. Contemporary approaches to perioperative treatment have focused on neoadjuvant therapy for patients with borderline resectable disease with the goal of improving OS.[417,420] Neoadjuvant therapy is also sometimes used in patients with resectable disease, especially in those with high-risk features. The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of patients with resectable disease will receive chemotherapy 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.[419,421,441,570] Moreover, surgery following neoadjuvant treatment appears to be safe.[571,572]

EUS-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 neoadjuvant therapy. Furthermore, patients for whom neoadjuvant therapy is planned should be assessed for jaundice, and placement of a stent (preferably a short, SEMS, as discussed in *Preoperative Biliary Drainage* above) is recommended prior to initiation of neoadjuvant therapy in patients with jaundice or after neoadjuvant therapy if clinically indicated.[519-521]

Retrospective analyses from patients at one NCCN Member Institution showed that neoadjuvant chemoradiation is associated with better local control, relative to neoadjuvant chemotherapy, though significant differences in survival were not found.[573] Practices vary with regard to chemotherapy and chemoradiation. Acceptable regimens include FOLFIRINOX, gemcitabine/albumin-bound paclitaxel, and gemcitabine/cisplatin (for patients with known *BRCA1/2* mutations).

Chemoradiation following chemotherapy is sometimes included in the neoadjuvant setting. Doses for neoadjuvant chemoradiation that have been reported include 36 Gy in 2.4 Gy/fraction, or 45 to 54 Gy in 1.8 to 2.0 Gy/fraction.[421,574] The role of chemoradiation with more active chemotherapy regimens needs to be tested.

Pancreatic protocol CT or MRI of the abdomen, and chest/pelvic CT should be repeated following neoadjuvant therapy, and staging laparoscopy can be considered at this time if not previously performed. 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. Importantly, results from retrospective studies suggest that radiographic response does not correlate with pathologic response.[575,576] Therefore, if no apparent tumor shrinkage is observed after neoadjuvant treatment and no extrapancreatic progressive disease is evident, surgery should still be attempted.

Neoadjuvant Therapy in Borderline Resectable Disease

Patients with borderline resectable disease should be considered for neoadjuvant therapy, followed by restaging and resection in patients without disease progression precluding surgery. The use of neoadjuvant therapy in the setting of borderline resectable disease has been a highly debated topic. However, although there is no high-level evidence supporting its use, most NCCN Member Institutions now prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease. If neoadjuvant therapy is recommended, treatment should preferably be administered at or coordinated through a high-volume center, when feasible. Upfront resection in patients with borderline resectable disease is no longer recommended, as of the 2016 version of these guidelines.

Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerated.[577-584] A phase I/II trial of neoadjuvant therapy in borderline resectable disease allowed 4 of 26 patients (15%) to be resected.[581] 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.[580] A multi-institutional phase II trial found that full-dose gemcitabine, oxaliplatin, and radiation given preoperatively to patients with resectable (n = 23), borderline resectable (n = 39), or unresectable disease (n = 6) found the approach to be feasible with an overall R0 resection rate of 53%.[579] In this study, 63% of all evaluable patients underwent resection, with 84% of those patients achieving an R0 resection.

In 2 retrospective reviews, 31% to 35% of patients with borderline resectable disease who completed neoadjuvant therapy had R0 resections.[585,586] A systematic review and meta-analysis of 19 cohort studies found that patients with unresectable disease (including both borderline resectable and unresectable) undergoing neoadjuvant chemoradiation therapy had similar 1-year survival outcomes as patients who were initially deemed resectable.[587] 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). In addition, the Alliance A021101 trial (NCT01821612) is a single-arm pilot study evaluating the safety and efficacy of FOLFIRINOX before capecitabine-based chemoradiation and surgery in this population.[442] Preliminary results including 22 patients from multiple centers showed that median OS was 21.7 months, and 68% of patients underwent resection.[583] Out of the 15 patients who underwent resection, all but one had negative margins, and 2 had a complete response. However, the number of grade 3 or higher adverse events was considerable, with 64% of patients experiencing one of these events. Other initial results in patient series suggest that neoadjuvant regimens including FOLFIRINOX are a promising approach in

patients with borderline resectable disease.[588-590] Chemotherapy followed by SBRT may also be safe and feasible in the neoadjuvant setting, and may improve the potential for resection in patients with borderline resectable or locally advanced disease.[338,591] However, further studies are needed before SBRT is recommended as a treatment option for patients with borderline resectable disease.

Neoadjuvant Therapy in Resectable Disease

An observational retrospective propensity score that matched analyses of 15,237 patients with resected pancreatic cancer showed that those who received neoadjuvant therapy had better OS than those who received upfront resection (median survival 26 months vs. 21 months, respectively; HR, 0.72; 95% CI, 0.68–0.78; $P < .01$).[592] A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[419,420,593-601] 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.[594] The authors suggest that preoperative therapy gives a selection advantage because 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.[594] 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.[594] The MD Anderson group has continued to champion this approach both for its ability to select patients for resection and for cost-effectiveness.[602]

Other potential advantages of the neoadjuvant approach in patients with resectable disease 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.[572,603,604]

Although most studies investigating the neoadjuvant experience in patients with resectable pancreatic cancer are retrospective, several small phase II studies have been published.[572,603,605,606] 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.[599]

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.[596] 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.[520] 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.[570] 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,[607] results of randomized trials addressing this issue are needed. A recent randomized phase II trial, which was terminated early because of slow accrual, compared gemcitabine/cisplatin neoadjuvant chemoradiation with upfront surgery; both arms received adjuvant chemotherapy.[608] With only 66 patients eligible for analysis, no significant differences were seen in R0 resection rate (52% vs. 48%), (y)pN0 rate (39% vs. 30%), or OS (25.0 months vs. 18.9 months), although all results favored the neoadjuvant arm and no safety issues were noted. The phase III NEOPA trial, with OS as the primary endpoint, is currently recruiting patients with resectable pancreatic cancer to compare neoadjuvant gemcitabine chemoradiation therapy to upfront surgery in this population (ClinicalTrials.gov NCT01900327)[609] and the randomized phase II SWOG 1505 trial, which is intended to establish benchmarking data for fluorouracil, irinotecan, and oxaliplatin and gemcitabine and albumin-bound paclitaxel (ClinicalTrials.gov NCT02562716). A phase II trial with R0 resection as the primary endpoint is also ongoing (ClinicalTrials.gov NCT01389440).

At this time, the panel does not recommend neoadjuvant therapy for clearly resectable patients without high-risk features, except in a clinical trial. There is limited evidence to recommend specific neoadjuvant regimens off study, and practices vary with regard to the use of chemotherapy and chemoradiation. For selected patients who appear technically resectable but have poor prognostic features (ie, markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; excessive weight loss; extreme pain) consideration can be given to neoadjuvant therapy after biopsy confirmation, and therapy should be administered preferably at or coordinated through a high-volume center.

Adjuvant Treatment After Neoadjuvant Therapy

For patients who received neoadjuvant treatment, data supporting additional therapy after surgery 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 and other clinical considerations, such as performance status and patient tolerability.

Adjuvant chemotherapy or adjuvant chemoradiation should only be considered for patients who have adequately recovered from surgery and have no evidence of recurrence or metastatic disease; treatment should ideally be initiated within 12 weeks. It is recommended that the patient undergo a pretreatment baseline assessment following surgery, including pancreas protocol CT scan (abdomen) and chest/pelvic CT with contrast, 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 imaging following systemic chemotherapy, if it will precede chemoradiation.

Surveillance of Patients with Resected Disease

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited,[610-612] 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 every 6 to 12 months as clinically indicated. CA 19-9 determinations and follow-up CT scans (chest, abdomen, and pelvis) with contrast 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, an analysis of the SEER-Medicare database showed no significant survival benefit for patients who received regular surveillance CT scans.[613]

Management of Recurrent Disease After Resection

As cross-sectional body imaging has improved, small-volume metastatic disease or local recurrence is being detected in patients with resected pancreatic cancer who are otherwise maintaining good functional status. As many as 50% of them will continue to maintain a sufficiently good performance status to consider recurrence therapy.[614] These patients will, however, ultimately progress.

For patients experiencing a recurrence of disease following resection, the panel recommends consideration of confirmatory biopsy (category 2B). In all cases of recurrent disease, a clinical trial is the preferred option; palliative and best supportive care without additional therapy should also be an option, especially for patients with poor performance status. In a pooled analysis of 55 patients who underwent pancreatectomy for recurrent pancreatic cancer, 1-, 3-, and 5-year survival rates were 82.2%, 49.2%, and 40.6%, respectively.[615] Therefore, for patients with local disease recurrence, surgical resection may be considered in select cases (ie, good performance status, location of recurrence is in the pancreas only). Chemoradiation can be considered in patients with local disease recurrence in the pancreatic bed, if radiation has not been previously administered, or a systemic chemotherapy regimen can be given. However, there are limited data to support specific RT recommendations for recurrent disease. For patients for whom there is evidence of metastatic disease (with or without a local recurrence), treatment decisions are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed less than 6 months prior to development of metastatic disease, the panel recommends that an alternative chemotherapy option be administered (eg, switching to a gemcitabine-based regimen if fluoropyrimidine-based therapy was previously used, or vice versa). When this period is 6 months or greater, repeating systemic therapy as previously administered or switching to any other systemic regimen is recommended.

Management of Isolated Pulmonary Metastases

Some patients have isolated lung metastases after resection of localized pancreatic adenocarcinoma. A growing body of evidence in this population suggests that these patients have a prolonged survival compared to patients with metastases in other locations.[616,617] Preliminary data also suggest that pulmonary metastasectomy may be advantageous in this population.[618] More data are needed before recommendations can be made regarding the management of pulmonary metastases of pancreatic cancers.

Palliative and Supportive Care

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that are, in many respects, unique to the 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.[619] 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 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 an RCT of 100 patients at a single center randomly assigned to receive either a plastic stent or a covered SEMS inserted endoscopically indicated that median patency times were 1.8 and 3.6 months (P = .002), respectively.[620] A meta-analysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.[621] 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. Another randomized trial showed that covered SEMS had longer patency than uncovered SEMS in the setting of biliary obstruction due to pancreatic cancer, because covered stents prevented the ingrowth of tumor.[622]

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.[623] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.[623]

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors following laparotomy, an open biliary-enteric bypass provides durable palliation of biliary obstruction and can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain. The panel recommends stenting or an open biliary-enteric bypass with or without gastrojejunostomy (category 2B for prophylactic gastrojejunostomy[624,625]) and with or without celiac plexus neurolysis [626-628] (category 2B in patients without pain). 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.[619]

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 gastrojejunostomy (category 2B for prophylactic gastrojejunostomy[624,625]) and with or without celiac plexus neurolysis (category 2B in patients without pain). 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. If cancer has not been biopsy-confirmed in the setting of locally advanced disease in a patient with jaundice, brushings can be obtained at the time of stent placement.

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10% to 25% of patients with pancreatic cancer.[619] 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 after biliary drainage is assured.[623] 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.[629-631] 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 RCTs have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer, the majority arising from the head of the pancreas.[624,625] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. A 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.[632] 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.[628] General principles for cancer-related pain management can be found in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). Patients with severe tumor-associated abdominal pain should be treated with around-the-clock analgesics. However, some patients will be unresponsive to analgesics or will experience undesirable side effects. Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, celiac plexus neurolysis should be considered (category 2B, except when indicated by pain in a patient with jaundice who is found unresectable at surgery, for which the recommendation is a category 2A). In several RCTs, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.[626,628,633] In a 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.[627] These patients reported better pain relief at 3 months (P = .01), suggesting that early EUS-guided celiac plexus neurolysis may be beneficial. A recent meta-analysis of 7 RCTs concluded that celiac plexus neurolysis improved pain scores at 4 weeks but not at 8 weeks in patients with pancreatic cancer.[634] The effectiveness of ethanol celiac plexus neurolysis for pain in resectable pancreatic and periampullary adenocarcinoma was examined in a recent RCT (N = 467).[635] The use of this technique was not found to significantly impact postoperative pain. 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 analgesic therapy, palliative RT may be considered to ameliorate pain, bleeding, and/or local obstructive symptoms, in the settings of both metastatic and non-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. The dose used should take into account the burden of disease, normal tissue tolerance, and expected survival.

Pancreatic Exocrine Insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or blockage of the pancreatic duct, or by surgical removal of pancreatic tissue, and results in an inadequate production of digestive enzymes.[636,637] This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.[638] Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency. Because pancreatic exocrine insufficiency occurs in up to 94% of patients undergoing pancreatic surgery,[639,640] 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.[638] A prospective double-blind phase II RCT including 67 patients with unresectable pancreatic cancer showed no significant difference in weight loss between patients randomized to receive pancreatic exocrine replacement therapy and patients randomized to receive a placebo.[641] For patients with disease that does not respond to this therapy, doses of the enzyme preparation can be increased, and inhibition of gastric secretion with a proton pump inhibitor can also be considered.[638,639] Patients with a clinical suspicion of pancreatic exocrine 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.[642,643] 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.[644]

Results from the CONKO 004 trial showed that patients randomized to receive enoxaparin (n = 160) experienced fewer symptomatic VTEs, relative to patients receiving chemotherapy only (n = 152) (HR, 0.40; 95% CI, 0.19–0.83; P = .01).[645] PFS and OS did not significantly differ between the two groups, however. In a pilot trial conducted in preparation for the CONKO 004 trial, 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.[646] The panel does not recommend prophylactic LMWH at this time, due to the lack of evidence regarding impact on survival. Please see the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease for more information (available at www.NCCN.org).

Bleeding From the Primary Tumor Site

GI bleeding in patients with pancreatic adenocarcinoma is hard to study because it is rare, but can carry a serious prognosis. [647] Various causes of GI bleeding include segmental portal hypertension,[648] gastric or duodenal ulcer erosion, and radiation-induced gastritis.[647] Treatment options for GI

bleeding should be used according to clinical judgement regarding the specifics of the patient's case. Endoscopic techniques[649] or RT,[650] when other options are not feasible, may be an effective treatment for GI bleeding. As a final attempt, upper GI bleeding may be stopped with angiography with embolization.[651,652]

One study of 246 eligible patients with pancreatic cancer, included 32 patients with GI bleeding of varying grade.[647] The median OS of patients with GI bleeding was 9 months and in patients without GI bleeding was 14.5 months. Conservative care was given to patients with bad physical state (11 patients), endoscopic hemostasis was given to 20 patients, and angiography and embolization were given to 1 patient. Therapeutic endoscopy was successful in 37.5% of patients and angiography with embolization was successful in 1 patient. Overall, 10.2% (25 patients) succumbed due to bleeding. The average time from GI bleeding to death was 31.5 days and the average OS rate was 10 months.

The panel recommends the following treatment options for bleeding from the primary tumor site: therapeutic endoscopy, if clinically indicated; RT, if not previously done; and angiography with embolization, if clinically indicated.

Depression, Pain, and Malnutrition

For many patients, a diagnosis of pancreatic cancer may result in significant psychosocial distress, including anxiety, depression, and sleep disturbances.[653] In fact, the suicide rate in male patients with pancreatic cancer is reportedly 11 times that of the general population.[654] 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 with a registered dietitian 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).

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.[655]

- 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 2011 consensus report from a group of European experts came to many of the same conclusions.[656] 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 to discuss current and future pancreatic cancer research and came to similar conclusions.[614] 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.[657] 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.

ASCO also recently convened a working group to discuss designs for pancreatic cancer clinical trials that would accomplish meaningful clinical improvements.[658] This group concluded OS should be the primary endpoint of first-line, metastatic pancreatic cancer trials. They also concluded that trials should aspire to a 3- to 4-month improvement in OS in gemcitabine-eligible and gemcitabine/albumin-bound paclitaxel-eligible patients and a 4- to 5-month improvement in OS for FOLFIRINOX-eligible patients to give results with true clinical impact.

A systematic review including 32 phase III trials showed that the following benchmarks for phase II trials were most predictive of a clinically meaningful phase III trial: 50% improvement in OS, 90% increase in 1-year survival, or 80% to 100% increase in PFS.[659]

To determine appropriate historic controls for single-arm phase II trials based on gemcitabine, an algorithm has been developed based on an analysis of a database of cooperative group trials that can be used to calculate historic benchmarks for OS and PFS.[660]

Neoadjuvant Clinical Trials

For neoadjuvant trials, study populations should be well-defined and standardized. The panel endorses use of a restrictive definition of borderline resectable disease in clinical trials, such as that defined in an Intergroup trial.[442] Endpoints should also be standardized and could include resection rates, R0 resection rates, local recurrence rates, pathologic response rates, DFS, and OS.[661]

Summary

Patients with borderline resectable disease and select patients with resectable disease can undergo neoadjuvant therapy in the hopes of improving the chances for an R0 resection. Patients with locally advanced disease and good performance status can undergo chemotherapy and

chemoradiation or SBRT with second-line therapy if performance status is maintained after progression. Patients with good performance status 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 poor outcomes for patients with all stages of pancreatic cancer, the NCCN Panel recommends that investigational options be considered in all phases of disease management.

Table 1: Selected Genetic Syndromes with Associated Pancreatic Cancer Risk

Syndrome	Gene	Estimated Cumulative Risk of Pancreatic Cancer	Estimated Increased Risk Compared to General Population
Peutz-Jeghers syndrome	*STK11*	11%–36% by age 65–70 years[75]	132-fold[74]
Familial pancreatitis	*PRSS1, SPINK1, CFTR*	40%–53% by age 70–75 years[79-81]	26-fold to 87-fold[37,79-81]
Melanoma-pancreatic cancer syndrome	*CDKN2A*	14% by age 70[87] 17% by age 75 years[84]	20-fold to 47-fold[83,84]
Lynch syndrome	*MLH1, MSH2 (MSH6)*	4% by age 70 years[95]	9-fold to 11-fold[95,96]
Hereditary breast-ovarian cancer syndrome	*BRCA1, BRCA2*	1.4%–1.5% (women) and 2.1%–4.1% (men) by age 70[98,103]	2.4-fold to 6-fold[98,102,103]
Familial pancreatic cancer	Unknown in most families (family X is an exception)*	≥3 first-degree relatives with pancreatic cancer: 7%–16% by age 70[64] 2 first-degree relatives with pancreatic cancer: 3% by age 70[64]	≥3 first-degree relatives with pancreatic cancer: 32-fold[69] 2 first-degree relatives with pancreatic cancer: 6.4-fold[69] 1 first-degree relative with pancreatic cancer: 4.6-fold[69]

*One family (family X) with a mutation in the *palladin* (*PALLD*) gene has been identified.[667]

Table 2: Potential Indications for Various Therapies in the Treatment of Pancreatic Adenocarcinoma

Regimen	Resectable (adjuvant)	Borderline Resectable/ Resectable (neoadjuvant)	Locally Advanced (category recommendations for good performance status only unless otherwise noted)	Metastatic (category recommendations for good performance status only unless otherwise noted)	Second-Line Therapy (good performance status only unless otherwise noted)
Gemcitabine	√ (category 1)		√ (category 1 for poor performance status)	√ (category 1 for good and poor performance status)	√ (if previously treated with fluoropyrimidine-based therapy; or category 1 for poor performance status)
Gemcitabine/albumin-bound paclitaxel		√	√	√ (category 1; preferred)	√ (if previously treated with fluoropyrimidine-based therapy)
Gemcitabine/erlotinib			√	√ (category 1)	√ (if previously treated with fluoropyrimidine-based therapy)
Gemcitabine/cisplatin		√ (only for known *BRCA1/2* mutations)	√ (only for known *BRCA1/2* mutations)	√ (only for known *BRCA1/2* mutations)	√ (if previously treated with fluoropyrimidine-based therapy, only for known *BRCA1/2* mutations)
Gemcitabine/ capecitabine	√ (category 1)		√	√	
Fixed-dose-rate gemcitabine			√ (poor performance status only; category 2B)	√ (poor performance status only; category 2B)	√ (poor performance status only; category 2B)
GTX [fixed-dose-rate gemcitabine/docetaxel/ capecitabine]			√ (category 2B)	√ (category 2B)	

5-FU/leucovorin	√ (category 1)				
5-FU/ leucovorin/liposomal irinotecan					√ (if previously treated with fluoropyrimidine-based therapy and no prior irinotecan; or category 1 if previously treated with gemcitabine-based therapy and metastatic disease)
5-FU/ leucovorin/irinotecan (FOLFIRI)					√ (if previously treated with gemcitabine-based therapy)
FOLFIRINOX		√	√	√ (category 1; preferred)	√ (if previously treated with gemcitabine-based therapy)
Capecitabine	√ (category 2B)		√ (good and poor performance status; category 2B)	√ (poor performance status only; category 2B)	√ (if previously treated with gemcitabine-based therapy; or category 2B for poor performance status)
Continuous infusion 5-FU	√		√ (category 2B)	√ (poor performance status only; category 2B)	√ (if previously treated with gemcitabine-based therapy; or category 2B for poor performance)
Fluoropyrimidine/ oxaliplatin (eg, OFF, FOLFOX, CapeOx)			√ (category 2B)	√ (category 2B)	√ (if previously treated with gemcitabine-based therapy)
Chemoradiation	√ (following induction chemotherapy, with or without subsequent chemotherapy)	√ (subsequent chemoradiation is sometimes included)	√ (in select patients who are not candidates for combination therapy, and following induction chemotherapy in select patients without systemic metastases)		√ (if locally advanced disease; if not previously given; and if primary site is the sole site of progression)
Pembrolizumab					√ (only for MSI-H or dMMR tumors)

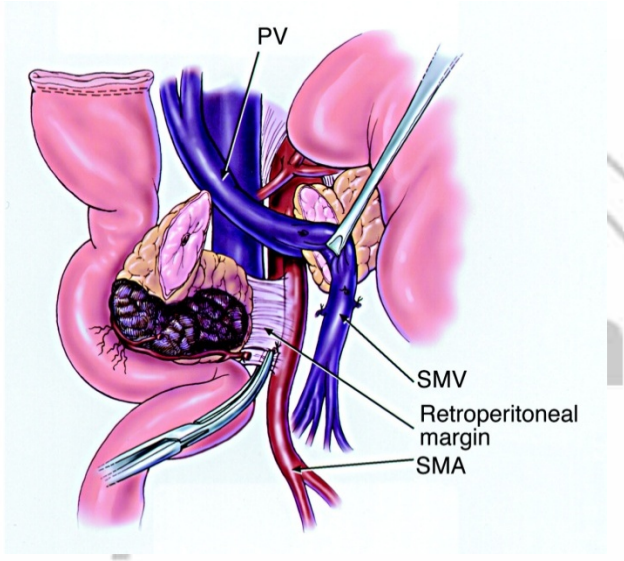


Figure 1. Complete mobilization of the superior mesenteric (SMV) and portal veins (PVs), and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA).[668]

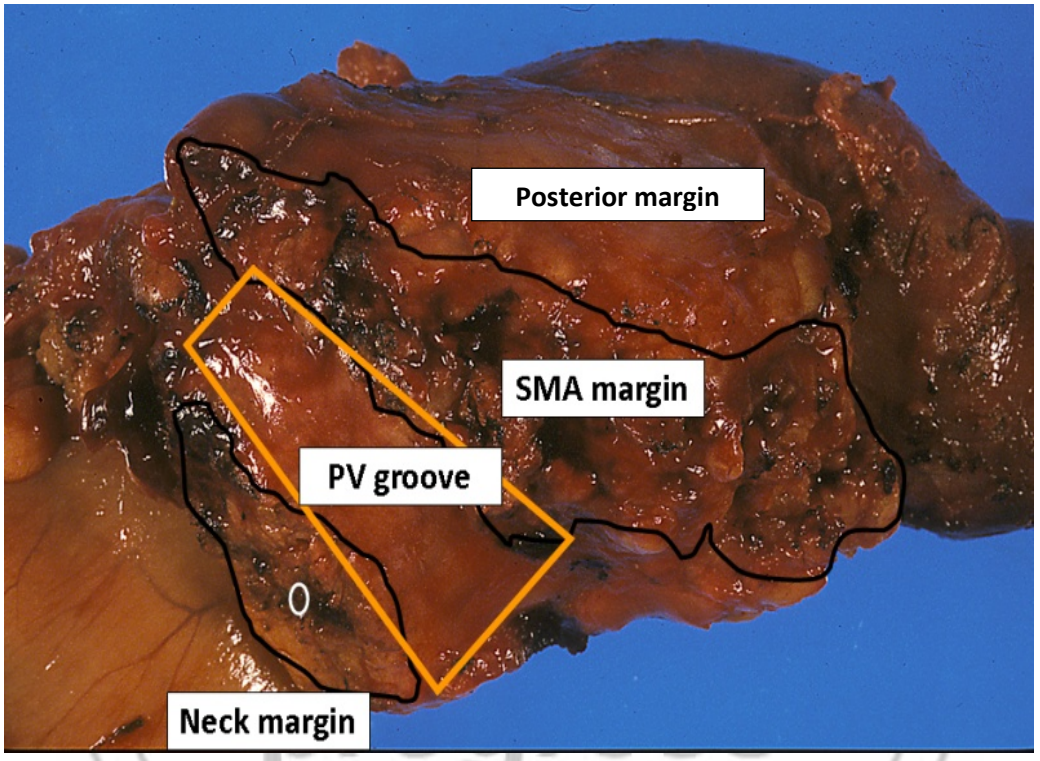
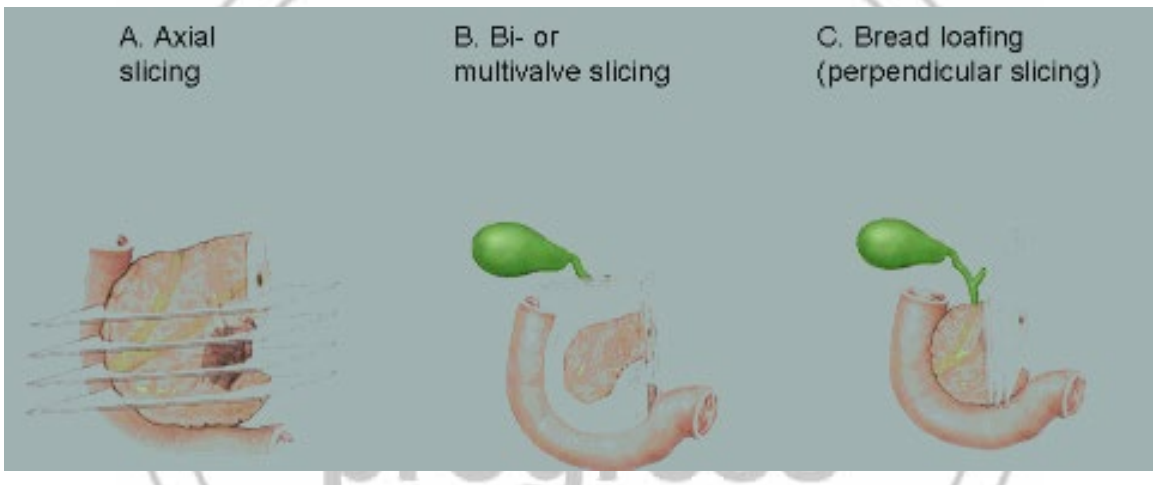


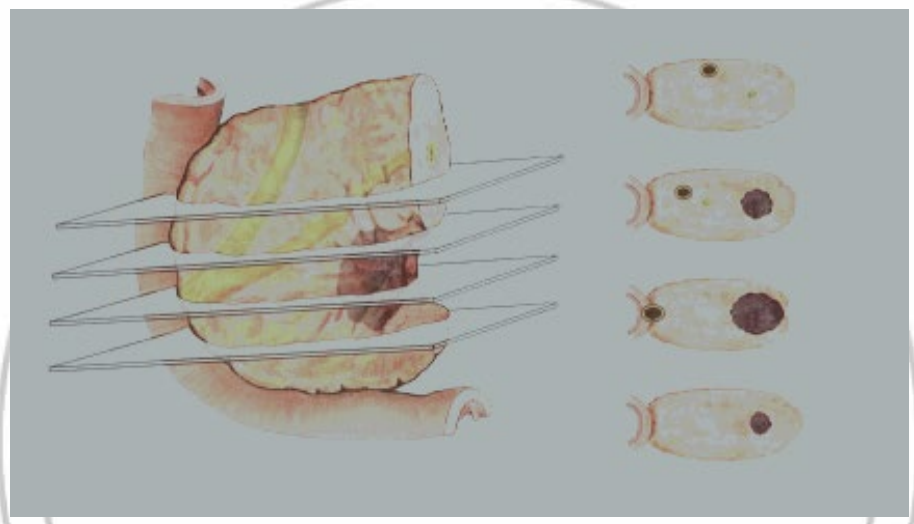
Image courtesy of Dr. N. Volkan Adsay

Figure 2. Whipple specimen with labeled margins.



Courtesy of Mr. Paul Brown, Specialist Medical Illustrator, St James's University Hospital Leeds

Figure 3. Slicing of pancreatoduodenectomy specimens.[541]



Courtesy of Mr. Paul Brown, Specialist Medical Illustrator, St James's University Hospital Leeds

Figure 4. Slicing of the pancreatoduodenectomy specimen in the axial plane to allow circumferential assessment of tumor.[541]

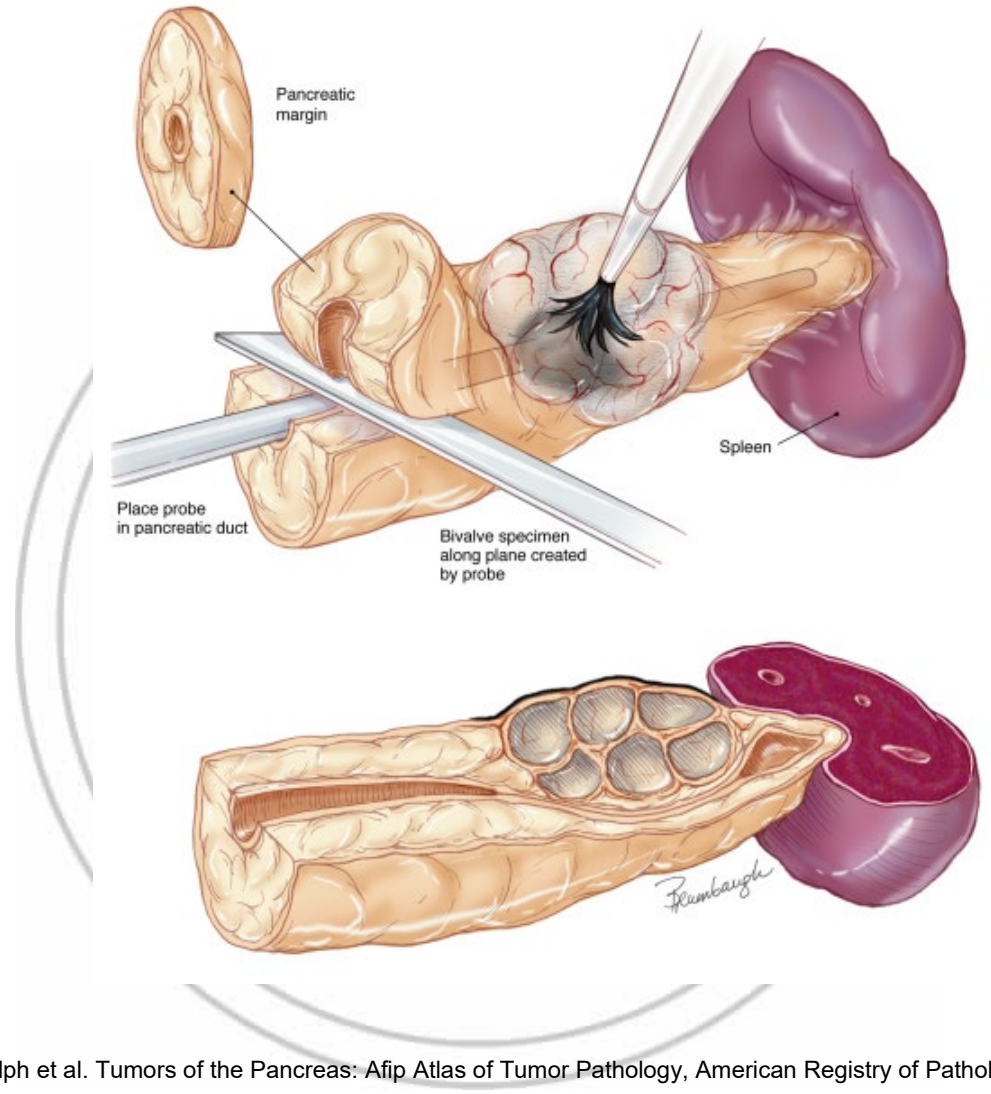


Figure 16-4, from Hruban, Ralph et al. Tumors of the Pancreas: Afip Atlas of Tumor Pathology, American Registry of Pathology, Washington DC 2007

Figure 5. Slicing of the distal pancreatectomy specimen.[557]

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NCCN Guidelines Version 2.2021
Pancreatic Adenocarcinoma

Discussion

Sections of this discussion were updated on February 25, 2021 to correspond with the latest algorithm.
The remainder of the discussion was last updated on July 10, 2018.

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Overview

During the year 2021 in the United States, an estimated 60,430 people will be diagnosed with pancreatic cancer, and approximately 48,220 people are expected to die from the disease.[1] Pancreatic cancer 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] Although the incidence is roughly equal in both sexes, African Americans have a higher incidence of pancreatic cancer than white Americans.[2,3]The incidence of pancreatic cancer in the United States increased from 1999 to 2008, possibly because of the increasing prevalence of obesity, an aging population, and other unknown factors.[3-5] Mortality rates have remained largely unchanged.[6,7]

In the 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 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.[8]

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 use of appropriate imaging studies. In addition, the panel believes that increasing participation in clinical trials (only 4.6% of patients enroll in a pancreatic cancer trial[9]) is critical to making progress in this disease. Thus, the panel unanimously endorses participation in a clinical trial over standard or accepted therapy.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Pancreatic Adenocarcinoma, an electronic search of the PubMed database was performed to obtain key literature in the field of pancreatic cancer using the following search terms: (pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreas adenocarcinoma) OR (pancreas cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[10]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search citations over the past year was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Risk Factors and Genetic Predisposition

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.[11-16] Exposure to chemicals and heavy metals such as beta-naphthylamine, benzidine, pesticides, asbestos, benzene, and chlorinated hydrocarbons is associated with increased risk for pancreatic cancer,[17,18] as is heavy alcohol consumption.[11,13,19-21] Periodontal disease is associated with pancreatic cancer, even when controlling for other risk factors such as gender, smoking, body mass index (BMI), diabetes, and alcohol consumption.[22]

An increased BMI is associated with an increased risk for pancreatic cancer,[19,23-25] with BMI during early adulthood being associated with increased pancreatic cancer mortality.[26] A meta-analysis including 22 cohort studies with 8,091 patients with pancreatic cancer showed that those who engage in low levels of physical activity have an increased risk for pancreatic cancer, relative to those who engage in high levels of physical activity (relative risk [RR], 0.93; 95% CI, 0.88–0.98).[27] Regarding diet, there is some evidence that increased consumption of red/processed meat and dairy products is associated with an elevation in pancreatic cancer risk,[28,29] although other studies have failed to identify dietary risk factors for the disease.[15,30,31] The association between tea consumption and pancreatic cancer risk has been examined, with mostly null associations being found.

Studies examining the association between vitamin D and risk for pancreatic cancer have shown contradictory results. Some data suggest that low plasma 25-hydroxyvitamin D levels may increase the risk for pancreatic cancer.[32] A pooled analysis of 9 case-control studies, including 2,963 patients with pancreatic cancer and 8.527 control subjects, showed a positive association between vitamin D intake and pancreatic cancer risk (odds ratio [OR], 1.13; 95% CI, 1.07–1.19; $P < .001$).[33] This association may be stronger in those with low retinol/vitamin A intake.

Chronic pancreatitis has been identified as a risk factor for pancreatic cancer,[34-37] with one study demonstrating a 7.2-fold increased risk for pancreatic cancer for patients with a history of pancreatitis.[38] A meta-analysis including two case-control studies and one cohort study (1,636 patients with pancreatic cancer) showed that hepatitis B infection is associated with pancreatic cancer (OR, 1.50; 95% CI, 1.21–1.87).[39] Patients with systemic lupus erythematosus (SLE) are also suggested to be at an increased risk for pancreatic cancer. In a meta-analysis of 11 cohort studies, patients with SLE were found to be an increased risk for developing pancreatic cancer (CI 1.32-1.53, HR 1.43).[40] However, 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.

Diabetes and Pancreatic Cancer

The association between diabetes mellitus and pancreatic cancer is particularly complicated. A population-based study of 2122 patients with diabetes found that approximately 1% of patients diagnosed with diabetes who are aged 50 years or younger will be diagnosed with pancreatic cancer within 3 years.[41] Prediabetes may also be associated with increased risk for pancreatic cancer.[42] A systematic review and dose-response meta-analysis including 9 prospective studies ($N = 2,408$) showed that every 0.56 mmol/L increase in fasting blood glucose is associated with a 14% increase in pancreatic cancer incidence.[43]

Numerous studies have shown an association between new-onset non-insulin–dependent diabetes and the development of pancreatic cancer,[41,44-47] especially in those who are elderly, have a lower BMI, experience weight loss, or do not have a family history of diabetes.[48] In these short-onset cases of diabetes diagnosed prior to pancreatic cancer diagnoses, diabetes is thought to be caused by the cancer, although the physiologic basis for this effect is not yet completely understood.[49]

Long-term diabetes, on the other hand, appears to be a risk factor for pancreatic cancer, as some studies have shown an association of pancreatic cancer with diabetes of 2- to 8-year duration.[50] However, certain risk factors such as obesity, associated with both diabetes and pancreatic cancer, may confound these analyses.[51] A meta-analysis including 44 studies showed that the strength of the association between diabetes and pancreatic cancer risk decreases with duration of diabetes, potentially due to the effects of long-term treatment of diabetes.[52]

The use of diabetic medications such as insulin and sulfonylureas has been found to be associated with an increased risk for pancreatic cancer.[53-55] On the other hand, metformin may be associated with a reduced risk for pancreatic and other cancers,[53-58] though a retrospective cohort study (*N* = 980) showed that metformin did not significantly improve survival in diabetic patients diagnosed with pancreatic cancer.[59]

In addition, diabetes and diabetic medication may affect outcomes in patients with pancreatic cancer. 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 months; *P* = .009).[60] The OS difference was significant only in patients without distant metastases and remained significant when insulin users were excluded. In contrast, data from a meta-analysis of more than 38,000 patients show that those with pancreatic cancer and diabetes have a significantly lower OS than those without diabetes (14.4 vs. 21.7 months; *P* < .001).[46] A similar result was seen in a prospective cohort study, in which the survival of 504 patients with and without diabetes who developed pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was compared.[61] After multivariable adjustment, mortality was significantly higher in participants with diabetes compared to those without (hazard ratio [HR], 1.52; 95% CI, 1.14–2.04; *P* < .01).

Genetic Predisposition

Pancreatic cancer is thought to have a familial component in approximately 10% of cases, and familial excess of pancreatic cancer is associated with high risk.[15,62-65] A retrospective review of 175 families in which a family history of pancreatic cancer was present showed that a genetic mutation was present in 28% of families.[66] A prospective registry-based study of 5179 individuals from 838 kindreds found that having just 1 first-degree relative with pancreatic cancer raises the risk for pancreatic cancer by 4.6-fold, whereas having 2 affected first-degree relatives raises the risk by about 6.4-fold.[67] An analysis of 9.040 family members of 1,718 kindreds with pancreatic cancer showed that a family history of early-onset pancreatic cancer (ie, <50 years) was associated with greater risk of pancreatic cancer (standardized incidence ratio [SIR], 9.31; 95% CI, 3.42–20.28; *P* < .001), and lifetime risk of pancreatic cancer increases as the age of onset decreases (HR, 1.55; 95% CI, 1.19–2.03 per year).[68] The genetic basis of this inherited predisposition is not known in most cases, and as many as 80% of patients with a family history of pancreatic cancer have no known genetic cause.[62] The genes most commonly associated with pathogenic germline alterations (PGAs) are *BRCA1, BRCA2, ATM, PALB2, MLH1, MSH2, MSH6, PMS2, CDKN2A*, and *TP53*.[69] Germline mutations in the *STK11* gene result in Peutz-Jeghers syndrome, in which individuals have gastrointestinal (GI) polyps and an increased risk for colorectal cancer.[70-72] These individuals also have a highly elevated risk for developing pancreatic cancer, reported to be increased by as much as 132-fold.[73,74] Furthermore, *STK11* undergoes somatic mutation in approximately 5% of pancreatic cancers.[75]

As with non-hereditary forms of pancreatitis, familial pancreatitis is also associated with an increased risk for pancreatic cancer.[76] Several genes

are associated with the familial form of pancreatitis, including *PRSS1*, *SPINK1*, and *CFTR*.[77] The increased risk for the development of pancreatic cancer in these individuals is estimated to be 26-fold to as high as 87-fold.[35,78-80]

Familial malignant melanoma syndrome (also known as melanoma-pancreatic cancer syndrome or familial atypical multiple mole melanoma [FAMMM]) syndrome is caused by germline mutation of the *CDKN2A* (p16INK4a/p14ARF) gene.[81] This syndrome is associated with a 20-fold to 47-fold increased risk for pancreatic cancer.[82,83] In addition, patients with Melanoma-Pancreatic Cancer syndrome may experience an earlier onset of pancreatic cancer than the general population.[84]

Lynch syndrome is the most common form of genetically determined colorectal cancer predisposition and is caused by germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).[85-90] Patients with Lynch syndrome also have an estimated 9- to 11-fold elevated risk for pancreatic cancer.[91,92] In a sample of 96 patients with pancreatic cancer, two mutations were found in the *MSH6* MMR gene.[93]

Microsatellite instability (MSI) is also a prognostic factor for survival in many cancers, notably for colon cancer although rare in pancreatic adenocarcinoma. Microsatellites are regions of coding and noncoding DNA where short sequences or single nucleotides of DNA are repeated. MSI is caused by a loss of DNA MMR activity. Mutations in germline MMR genes result in a lack of repair of any errors, such as destabilizing errors introduced during DNA replication that shorten or lengthen microsatellites, which then persist in somatic cells. Tumor samples can be assessed for the sizes of microsatellite markers and classified as MSI high (MSI-H), low (MSI-L), and stable (MSS).[87,90] The NCCN Panel recommends MSI testing and/or MMR testing on available tumor tissue for patients with locally advanced or metastatic pancreatic adenocarcinoma.

An excess of pancreatic cancer is also seen in families harboring *BRCA1/2* (breast cancer susceptibility gene-1 and -2) mutations, although the link with *BRCA2* is better established.[93-100] Studies of unselected patients with pancreatic cancer have detected *BRCA1/2* mutations at a frequency of 4% to 7%.[101,102] The risk for pancreatic cancer is elevated 2- to 6-fold in these patients, and the age of onset is younger than average in the general population.[94,98,99] Patients with pancreatic cancer who have Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a *BRCA1/2* mutation, with prevalence of detected mutations in this group ranging from 5.5% to 19%, with mutations being more common for *BRCA2*.[96,102-104]

BRCA1/2 is also involved in the Fanconi DNA anemia/*BRCA* pathway. This pathway is responsible for the repair of DNA interstrand cross-links, and particular mutations in other Fanconi anemia/*BRCA* pathway genes, including in *PALB2*, *FANCC*, and *FANCG,* have also been identified as increasing pancreatic cancer susceptibility.[100,105-107]

Whole-genome sequencing allowed for the identification of germline mutations in *ATM*, a DNA damage response gene, in 2 kindreds with familial pancreatic cancer.[108] Further analyses then revealed *ATM* mutations in 4 of 166 individuals with familial pancreatic cancer. In a sample of 96 patients with pancreatic cancer, 4% had a mutation in *ATM*.[93]

Patients with pancreatic cancer for whom a hereditary cancer syndrome is suspect should be considered for genetic counseling.[109] The panel emphasizes the importance of taking a thorough family history when seeing a new patient with pancreatic cancer. In particular, a family history of pancreatitis, melanoma, and cancers of the pancreas, colorectum, breast, and ovaries should be noted. A free online pancreatic cancer risk prediction tool, called PancPRO, is available and may help determine risk.[65] Referral for genetic counseling may be considered for patients diagnosed with pancreatic cancer, especially those who have a family

history of cancer or who are young, as well as those of Ashkenazi Jewish ancestry. The panel recommends germline testing in any patient with confirmed pancreatic cancer and in those in whom there is a clinical suspicion for inherited susceptibility (see the NCCN Guidelines for Genetic/Familial High Risk Assessment, Breast and Ovarian, available at www.NCCN.org). The panel currently does not identify a specific age to define early-onset pancreatic cancer, though age 50 has been used in previous studies of familial pancreatic cancer.[68] If a cancer syndrome is identified, at-risk relatives should be offered genetic counseling. With or without a known syndrome, individuals with a suspicious family history should be advised on risk-reducing strategies including smoking cessation and weight loss. In addition, the possibility of screening for pancreatic (see below) and other cancers should be discussed. For patients with locally advanced or metastatic disease who are candidates for anticancer therapy, the NCCN Panel recommends testing for actionable somatic mutations, including but not limited to: fusions (*ALK, NRG1, NTRK, ROS1*), mutations (*BRAF, BRCA 1/2, HER2, KRAS, PALB2*), and MMR deficiency.

Premalignant Tumors of the Pancreas

Mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are cystic lesions that can be small and asymptomatic and are often discovered incidentally; MCNs have an ovarian-like stroma.[110-112] IPMNs can occur in the main duct and/or in the branch ducts. Lesions involving the main duct have a higher malignant potential than those in the branches, with the risk of malignancy at around 62%.[113] The risk of malignancy in MCNs is <15%.[113]

An international group of experts has established guidelines for the management of pancreatic IPMNs and MCNs,[114] as has a European group.[115] The international group strongly recommends resection in fit patients with main duct IPMNs ≥ 10 mm.[113] For branch-duct IPMNs, surveillance is considered an appropriate option in patients who are older or unfit or for cysts lacking high-risk stigmata. Branch-duct IPMNs that have an enhancing mural nodule ≥ 5 mm, or are in the head of the pancreas causing obstructive jaundice should be considered for resection.[113] Patients with resected IPMNs are followed with imaging studies to identify recurrences. For MCNs, the international group recommends resection for all fit patients, and recurrences are not observed.[113] The European group gives similar recommendations.[115]

Pancreatic Cancer Screening

Routine screening for pancreatic cancer is generally not recommended for asymptomatic individuals. However, a systematic review including 5 studies showed that screening asymptomatic individuals with a family history of pancreatic cancer was associated with more curative resections ($P = 0.011$) and longer median survival ($P < .001$).[116] 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.[117] 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 reported results of its CAPS3 study, in which 225 asymptomatic high-risk individuals were independently (in a blinded manner) screened once with CT, MRI, and EUS.[118] 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 IPMNs 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 showed that, although 32% of 262 participants were found to have pancreatic abnormalities, and some IPMNs and intraepithelial neoplasias were resected, 3 patients developed pancreatic adenocarcinoma (2 metastatic, 1 recurrent 30 months post-resection) despite screening.[119] These results could be due to rapid malignant progression, but they are more likely a result of inadequate imaging by MRI.

The diagnostic yield of pancreatic cancer screening with EUS in asymptomatic individuals at high risk for familial disease was also investigated in the Netherlands,[120] while a German study used EUS plus MRI/magnetic resonance cholangiopancreatography (MRCP) in a similar high-risk population.[121] 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. Results suggest that MRI/MRCP may be a useful adjunct or a noninvasive alternative to EUS for pancreatic cancer screening.

Newer screening methods to identify patients with early pancreatic cancer rather than those with preinvasive lesions may prove to be beneficial in the future. Examples of techniques being investigated are microRNA biomarkers in whole blood and serum metabolism profiling.[122-125] In addition, circulating cell-free DNA is being investigated as a possible biomarker for screening. One study showed that methylation patterns in cell-free plasma DNA can differentiate between pancreatitis and pancreatic cancer with a sensitivity of 91.2% and specificity of 90.8%.[126] In addition, carbohydrate antigen (CA) 19-9 levels may be elevated in patients up to 2 years before a pancreatic cancer diagnosis, indicating that CA 19-9 has potential as a biomarker for screening high-risk patients.[127]

An international CAPS Consortium summit with 49 multidisciplinary experts was held in 2011 to develop consensus guidelines for pancreatic cancer screening.[128] The group recommends screening with EUS and/or MRI/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 with pancreatic cancer. 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, vomiting, and occasionally pancreatitis; 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 (see *Diabetes and Pancreatic Cancer*, above). Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss.

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.[129] All patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should therefore undergo initial evaluation by CT performed according to a dedicated pancreas protocol of the abdomen.[130] In addition, the panel recommends imaging after neoadjuvant treatment to provide adequate staging and assessment of resectability status. Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation, with use of 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, pathology, geriatric medicine, and palliative care.

The AJCC has developed staging criteria for adenocarcinoma of the pancreas that follow the tumor/node/metastasis (TNM) system.[131,132] 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.[132,133] [133] In the 8th edition of the AJCC Cancer Staging Manual, the definition of N category has been revised; N1 is defined as 1–3 metastatic lymph nodes and N2 as >4 metastatic lymph nodes. Additionally, the T category now has a size-based definition and the T4 category no longer incorporates resectability.[134] Validation studies of the changes to the 8th edition of the AJCC T and N staging found that it better stratifies patients with resected tumors according to their lymph node involvement[135] and retains prognostic accuracy,[136] compared to the 7th edition.

For clinical purposes, however, most NCCN Member Institutions use a clinical classification system based mainly on results of presurgical imaging studies. Following staging by pancreatic protocol CT of abdomen, chest, and pelvis CT (and EUS with biopsy if clinically indicated, and/or MRI for indeterminate liver lesions, and/or PET/CT in high-risk patients to detect extra-pancreatic metastases), or endoscopic retrograde cholangiopancreatography (ERCP) to place stent if jaundiced or undiagnosed on previous placement (or percutaneous transhepatic cholangiography [PTC]) in some cases), liver function tests and baseline CA 19-9 in a decompressed patient, and genetic counseling and germline testing if the diagnosis is confirmed or if patient has metastatic disease, 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 with a high chance of an R1 resection); 3) locally advanced (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) metastatic, and this system is used throughout the guidelines. See *Criteria for Resection* below for more detailed definitions.

Imaging Evaluations

Pancreatic Protocol CT and MRI

Multi-detector CT angiography, performed by acquiring thin, preferably sub-millimeter, axial sections using a dual-phase pancreatic protocol, with images obtained in the pancreatic and portal venous phase of contrast enhancement, is the preferred imaging tool for dedicated pancreatic imaging. Scan coverage can be extended to cover the chest and pelvis for complete staging as per institutional preferences. Multiplanar reconstruction is preferred as it allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits.[129,130,137] Studies have shown that 70% to 85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.[129,138-142] However, the sensitivity of CT for small hepatic and peritoneal metastases is limited. High-quality CT imaging should occur no more than 4 weeks before surgery.[143]

The difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the pancreatic 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 enhanced visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], hepatic artery) 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.[141]

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 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.[144] 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. See *PET/CT*, below, for more details about these procedures. Pancreas protocol MRI with contrast can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for characterization of CT-indeterminate liver lesions and when suspected pancreatic tumors are not visible on CT or in cases of contrast allergy.[145,146]

Recently, a multidisciplinary expert consensus group defined standardized language for the reporting of imaging results.[130] Such uniform reporting can help improve the accuracy and consistency of staging to determine optimal treatment strategies for individual patients and can allow cross-study and cross-institutional comparisons for research purposes. Use of the template also ensures a complete assessment and reporting of all imaging criteria essential for optimal staging and can therefore aid in determining optimal management. The use of the radiology staging reporting template is thus recommended by the panel. The template recommended by the panel includes morphologic, arterial, venous, and extrapancreatic evaluations.[130] The morphologic evaluation includes documentation of tumor appearance, size, and location, as well as the

presence of narrowing or abrupt cut-off of pancreatic duct or biliary tree. The arterial evaluation should include assessment of the celiac axis, the SMA, and the common hepatic artery. Arterial variations should also be noted, such as vessel contact, solid soft-tissue contact, hazy attenuation or stranding contact, and focal vessel narrowing or contour irregularity. Venous evaluation should include an assessment of the main PV and the SMV. Documentation of thrombus within the vein and venous collaterals should also be done. The extrapancreatic evaluation should include documentation of liver lesions, peritoneal or omental nodules, ascites, suspicious lymph nodes, and other present extrapancreatic disease sites.

Endoscopic Ultrasound

NCCN Member Institutions vary in the use of additional staging technologies, such as EUS. An analysis of 20 studies and 726 cases of pancreatic cancer showed that EUS for T1-2 staging has a sensitivity and specificity of 0.72 and 0.90, respectively.[147] Sensitivity and specificity for T3-4 staging is 0.90 and 0.72, respectively. [148-151] EUS may be used to discriminate between benign and malignant strictures or stenosis, because severe stenosis and marked proximal dilatation most often indicate malignancy.[152] EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. In addition, EUS plays a role in better characterizing cystic pancreatic lesions due to the ability to aspirate the cyst contents for cytologic, biochemical, and molecular analysis. 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 neurolysis, removal of ascites). Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

The role of EUS in staging is felt to be complementary to pancreas protocol CT, which is considered the gold standard. The primary role of EUS is to procure tissue for cytologic diagnosis, but sometimes additional diagnostic information is identified. EUS provides additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes.[148-151] Because variations in hepatic arterial anatomy occur in up to 45% of individuals, and EUS is highly operator dependent, EUS is not recommended as a routine staging tool and should not be used to assess vascular involvement.

Endoscopic Retrograde Cholangiopancreatography and Percutaneous Transhepatic Cholangiography

ERCP is a technique that combines endoscopic and fluoroscopic procedures and is generally limited to therapeutic interventions.[153] ERCP is a preferred recommendation for patients who are jaundiced or diagnosed on previous biopsy and without evidence of metastatic disease who require biliary decompression and who undergo additional imaging with EUS to help establish a diagnosis.[154] Thus, from a therapeutic standpoint ERCP allows for stent placement and can be used to palliate biliary obstruction when surgery is not elected or if surgery must be delayed. However, biliary decompression in those without symptomatic hyperbilirubinemia receiving upfront surgery may be avoided.[155-157]

There are occasional anatomic considerations that preclude ERCP stent placement. In these cases, palliation of biliary obstruction can be achieved by placing a stent through the liver using PTC.[158]

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.[159] 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.[160,161] PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered as an adjunct to a formal pancreatic CT protocol in high-risk patients. Indicators of high risk for metastatic disease may include borderline resectable disease, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, and patients who are very symptomatic.

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.[162-164] 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, which can be accomplished in an estimated 23% of patients in whom curative intent surgery is planned,[163] although routine use of staging laparoscopy is controversial. There is some concern that laparoscopy may promote trocar-site recurrences and peritoneal disease progression, but these concerns are based on clinical observation and experimental data from animal and in vitro studies, and one retrospective study (*N* = 235) found that staging laparoscopy was not significantly associated with poor outcomes.[165] The panel does not consider staging laparoscopy to be a substitute for poor-quality preoperative imaging.

Some 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).[166] For example, preoperative serum CA 19-9 levels >100 U/mL or >215 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.[167,168] In a 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.[169] 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 metastases not detected on imaging (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 (ie, imaging findings; borderline resectable disease; markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; highly symptomatic; excessive weight loss; extreme pain). Thus, the panel believes that staging laparoscopy can be considered for patients staged with resectable pancreatic cancer who are considered to be at increased risk for disseminated disease and for patients with borderline resectable disease prior to administration of neoadjuvant therapy. Intraoperative ultrasound may be used as a diagnostic adjunct during staging laparoscopy to further evaluate the liver and tumor and vascular involvement. The panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[170]

Biopsy

Although a pathologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy and for patients staged with locally advanced pancreatic cancer or metastatic disease. A pathologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either EUS guidance (preferred) or CT. EUS-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.[171-173] 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-FNA also gives the benefit of additional staging information at the time of biopsy.

EUS-FNA is highly accurate and reliable for determining malignancy. A meta-analysis including 20 studies and 2761 patients showed sensitivity and specificity values of 90.8% and 96.5%, respectively, for diagnosis of solid pancreatic lesions.[174] In rare cases when EUS-FNA cannot be obtained from a patient with borderline resectable or unresectable disease, other acceptable methods of biopsy exist. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy.[175] A percutaneous approach[172] or a laparoscopic biopsy[176] 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 and a core needle biopsy at a high-volume center is preferred, though new methods are being developed for diagnosis of pancreatobiliary malignancies (eg, cholangiopancreatoscopy) when repeat biopsy is needed.[177] Core needle biopsy is recommended, if possible, for patients with borderline resectable disease to obtain adequate tissue for possible ancillary studies, such as genomic analysis or MSI testing. 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 disease 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.

Evolving changes in molecular analyses of pancreatic cancer have led some institutions to attempt to procure additional tumor-rich, formalin-fixed, paraffin-embedded tissue to bank for future genomic studies. Several methods can be used to obtain such tissue samples, including core biopsy, but the panel believes that core biopsies should not replace EUS-guided FNA, but rather can be done in addition to EUS-guided FNA. Some of the most common somatic mutations in pancreatic cancer are *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*.[178,179] Molecularly targeted therapies for pancreatic cancer are being developed and investigated.[180]

Biomarkers

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal antigen, tissue polypeptide antigen, CA 125, and CA 19-9. The panel recognizes the importance of identifying biomarkers for early detection of this difficult disease, and they emphasize the need for collection and sharing of tissue to help accelerate the discovery of prognostic biomarkers (see *Future Clinical Trials: Recommendations for Design*, below). For example, a

meta-analysis including 8 studies found that S100 calcium-binding protein P (S100P) shows high sensitivity (0.87; 95% CI, 0.83–0.90) and specificity (0.88; 95% CI, 0.82–0.93) for diagnosis of pancreatic cancer.[181] A biomarker panel consisting of the immunoassays TIMP1 and LRG1, along with CA 19-9 improved the detection of early-stage pancreatic cancer, relative to CA 19-9 alone.[182]

CA 19-9

The best-validated and most clinically useful biomarker for early detection and surveillance of pancreatic cancer 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).[183] 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.[184]

CA 19-9 is a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 80% to 90% in symptomatic patients,[185] but its low positive predictive value makes it a poor biomarker for screening.[186] 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.[187-189]

CA 19-9 also seems to have value as a prognostic and a predictive marker for pancreatic cancer in various settings. In resectable disease, for instance, low postoperative serum CA 19-9 levels or a serial decrease in CA 19-9 levels following surgery have been found to be prognostic for survival for patients undergoing resection.[186,187,189-195] 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; $P < .0001$).[191]

Also in the resectable setting, data from an analysis of 260 consecutive patients support the predictive role of postoperative CA 19-9 levels for benefit of adjuvant therapy.[194] 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 (DFS) 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 DFS 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 less than 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 DFS of 19.6 months, suggesting a possible prognostic benefit of post-adjuvant therapy CA 19-9 levels in this setting.

In the neoadjuvant/borderline resectable setting, a recent study of 141 patients treated at MD Anderson Cancer Center found that post-treatment CA 19-9 levels were a good prognostic marker in patients receiving neoadjuvant therapy with or without subsequent resection.[196] This study found that a normalization of CA 19-9 to less than 40 U/mL was associated with improvements in OS in non-resected (15 months vs. 11 months; $P = .02$) and resected (38 months vs. 26 months; $P = .02$) disease.

In the advanced disease setting, data support the role of CA 19-9 as a prognostic marker.[190,197,198] 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.[197] In addition, the change in CA 19-9 levels during chemotherapy in patients with advanced disease

has been shown to be useful for evaluating the benefit of treatment, although the data are not entirely consistent.[197-202] For example, a 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 were associated with a better outcome.[190] 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.[203] Furthermore, CA 19-9 may be falsely positive in cases of biliary infection (cholangitis), inflammation, or biliary obstruction (regardless of etiology) and does not necessarily indicate cancer or advanced disease.[204,205] Preoperative measurement of CA 19-9 levels (category 3) is therefore best performed after biliary decompression is complete and bilirubin is normal. If biliary decompression is not performed in a patient with jaundice, 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 after neoadjuvant treatment, prior to surgery, following surgery immediately prior to administration of adjuvant therapy, and for surveillance (category 2B). The panel emphasizes the importance of obtaining a CA 19-9 measurement immediately before the therapeutic intervention to have an accurate baseline from which to follow response; for example, before and after neoadjuvant therapy in patients with tumors that are borderline resectable. Of note, a number of different methods are commercially available for quantifying this tumor-associated antigen. Measurements of serum levels of CA 19-9 using one testing method cannot be extrapolated to results obtained using a different procedure.

Differential Diagnoses

Chronic pancreatitis and other benign conditions are possible differential diagnoses of patients suspected of having pancreatic cancer.[206-210] 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.[208,211-213] 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.[212] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis.

In addition, fine-needle aspirates can be misinterpreted as malignant or suspicious for malignancies.[214,215] 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.[214-217]

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.[218] A recent study found that IgG4 levels of >1.0 g/L combined with CA 19-9 levels of <74 U/mL distinguished patients with autoimmune pancreatitis from those with adenocarcinoma with 94% sensitivity and 100% specificity.[219] 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. Consultation with an expert pancreatologist is also recommended.

Systemic Therapy Approaches for Locally Advanced or Metastatic Disease

The data supporting the regimens used in pancreatic cancer are described below (also summarized in Table 2).

FOLFIRINOX and modified 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.[220] 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.[221] A later randomized phase II trial showed a response rate of greater than 30% to FOLFIRINOX in patients with metastatic pancreatic cancer.[222]

Results from the randomized phase III PRODIGE trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median PFS (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.[223] Eligibility criteria for this trial, however, were stringent, limiting real-world generalizability.[224] For example, patients with abnormal bilirubin levels were excluded from participating.

A systematic review including 11 studies and 315 patients with locally advanced pancreatic cancer showed a pooled median OS of 24.2 months (95% CI, 21.7–26.8).[225] An observational study including 101 patients with locally advanced unresectable disease who were treated with FOLFIRINOX as induction therapy showed that 29% of the sample (20% without administration of chemoradiation) had a reduction in tumor size of greater than 30%, and half of the patients who experienced a reduction in tumor size underwent resection.[226] Out of the patients who underwent resection, 55% achieved an R0 resection.

Because of the strong results from the PRODIGE trial, FOLFIRINOX is included as a preferred, category 1 recommendation for first-line treatment of patients with good performance status (ie, ECOG 0-1) with metastatic pancreatic cancer. It is listed as a category 2A recommendation for patients with locally advanced disease by extrapolation. The panel also lists this regimen as an acceptable option in the neoadjuvant/borderline resectable setting.

There are 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.[223] Despite the high levels of toxicity, no toxic deaths have been reported.[221-223] 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%, $P < .01$).[223] A more detailed analysis of the quality of life of patients in this trial was published and showed that FOLFIRINOX maintained and even improved quality of life more so than gemcitabine.[227]

The panel appreciates that the toxicity of FOLFIRINOX can be managed with a variety of approaches. For example, a group from Memorial Sloan Kettering Cancer Center reported good activity and acceptable toxicity of first-line FOLFIRINOX at 80% dose intensity with routine growth factor support in carefully selected patients with metastatic or locally advanced disease.[228] Median OS was 12.5 months in the metastatic setting and 13.7 months in patients with locally advanced disease.

The efficacy and toxicity of a modified FOLFIRINOX regimen in which the initial dosing of bolus 5-FU and irinotecan were each reduced by 25% were assessed in a phase II single-arm prospective trial (*N* = 75).[229] In patients with metastatic disease, the efficacy of the modified regimen was comparable to that of the standard regimen (median OS = 10.2 months). In patients with locally advanced disease, the median OS was 26.6 months. Patients who received the modified regimen experienced significantly less neutropenia, fatigue, and vomiting, relative to patients who received the standard FOLFIRINOX regimen. Thus to reduce the toxicity associated with FOLFIRINOX and improve its tolerability, the modified FOLFIRINOX regimen is also included as a preferred treatment option.

Gemcitabine Monotherapy

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.[230] The panel recommends gemcitabine monotherapy as one option for front-line therapy for patients with locally advanced or metastatic disease (category 1) disease and a good performance status. Because the approved indications for gemcitabine include the relief of symptoms, the panel also recommends gemcitabine monotherapy as a reasonable first-line and second-line option for symptomatic patients with locally advanced or metastatic disease with poor performance status (category 1).

Gemcitabine monotherapy also has category 1 evidence supporting its use 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 DFS was met (13.4 months vs. 6.9 months; $P < .001$, log rank).[231] 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; HR, 0.76; 95% CI, 0.61–0.95; $P = .01$).[232] An absolute survival difference of 10.3% was observed between the two groups at 5 years (20.7% vs. 10.4%).[232]

Gemcitabine Response: hENT1

Human equilibrative nucleoside transporter 1 (hENT1) is a nucleoside transporter that has been studied as a predictor for response to gemcitabine.[233] Preliminary clinical data showed that hENT1 expression may in fact predict response to gemcitabine.[234-239]

hENT1 was validated as a predictive biomarker for benefit from gemcitabine in the adjuvant setting. A meta-analysis including 7 studies with 770 patients with resected pancreatic cancer showed that hENT1 expression was associated with DFS (HR, 0.58; 95% CI, 0.42–0.79) and OS (HR, 0.52; 95% CI, 0.38–0.72) in patients who received adjuvant gemcitabine, but not in patients who received adjuvant fluoropyrimidine-based therapy.[240] Two retrospective analyses from ESPAC-3 and RTOG-9704 found the same results, although results from the adjuvant CONKO-001 trial and the AIO-PK0104 trial were unable to confirm these results using a different antibody for the IHC analysis (SP120).[241,242]

Unfortunately, hENT1 could not be validated in the metastatic setting in the LEAP trial, which also used the SP120 assay to determine hENT1 expression.

Further studies based on hENT1 expression using the 10D7G2 assay are limited by the fact that no commercial source of the antibody and no CLIA-approved testing are available.

Fixed-Dose-Rate Gemcitabine

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.[243] In a randomized phase II trial of patients with locally advanced or metastatic pancreatic cancer, the infusion of gemcitabine at an FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.[244] In the phase III randomized ECOG-6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine versus standard gemcitabine (6.2 months vs. 4.9 months; *P* = .04), although this outcome did not satisfy the protocol-specified criteria for superiority.[245] 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 and oxaliplatin]; GTX [gemcitabine, docetaxel, and capecitabine]). See *Gemcitabine Combinations*, below.[246,247] The combination of FDR gemcitabine and capecitabine has also been found to be active and well-tolerated.[248]

Gemcitabine Combinations

The NCCN Panel acknowledges that, historically, combination chemotherapy did not appear to be superior to monotherapy in the era of 5-FU–based therapy. However, because gemcitabine is superior to bolus 5-FU in the advanced setting 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).[245-247,249-259] Two meta-analyses of randomized controlled trials (RCTs) found that gemcitabine combinations give a marginal benefit in OS over gemcitabine monotherapy in the advanced setting, with a significant increase in toxicity.[260,261]

Combinations recommended in the advanced setting are discussed below. The panel does not consider the combination of gemcitabine plus docetaxel[262] or gemcitabine plus irinotecan[259,262,263] to meet the criteria for inclusion in the guidelines. In addition, gemcitabine plus sorafenib is not recommended. The 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.[264] This trial did not meet its primary endpoint of progression-free survival (PFS) in its 104 patients (5.7 months vs. 3.8 months; *P* = .90). Gemcitabine combinations are currently being used and studied in the adjuvant setting.

Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.[253,254,256]

Gemcitabine Plus Albumin-Bound Paclitaxel

Albumin-bound paclitaxel is a nanoparticle form of paclitaxel. In a publication of a phase I/II trial, 67 patients with advanced pancreatic cancer received gemcitabine plus albumin-bound paclitaxel. At the maximum tolerated dose, the partial response rate was 48%, with an additional 20% of patients demonstrating stable disease for 16 or more weeks. The median OS at this dose was 12.2 months.[265]

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.[266] Participants were randomized to receive gemcitabine plus albumin-bound paclitaxel or gemcitabine alone. The trial met its primary endpoint of OS (8.7 months vs. 6.6 months; *P* < .0001; HR, 0.72).[266] The addition of albumin-bound paclitaxel also improved other endpoints, including 1-year survival, 2-year survival, response rate, and PFS. OS was associated with a decrease in CA 19-9 (HR, 0.53; 95% CI, 0.36–0.78; *P* = .001).[267] Tumor response was validated with PET imaging.[268] The most common grade 3 or higher adverse events attributable to albumin-bound paclitaxel were neutropenia, fatigue, and neuropathy. Development of peripheral neuropathy was associated with longer treatment duration and greater treatment efficacy.[269] Updated results of the MPACT trial show that long-term survival is possible with gemcitabine plus albumin-bound paclitaxel, as 3% of patients from that arm were alive at 42 months, whereas no patients were alive from the control arm at that time.[270] Factors associated with survival in this trial include KPS score and absence of liver metastases.[271]

Gemcitabine plus albumin-bound paclitaxel is a category 1 recommendation for the treatment of patients with metastatic disease and good performance status based on these results, and is listed as a preferred option in this setting. Good performance status for this regimen is defined as ECOG 0-2, since the clinical trial used KPS ≥70 as an eligibility criterion.[266,270] Therefore, some patients with an ECOG score of 2 may be eligible to receive this regimen.[272,273] By extrapolation of the data, the panel recommends this combination in the locally advanced, good performance status setting as well (category 2A). The panel also notes that this combination is an acceptable option in the neoadjuvant/borderline resectable setting

Gemcitabine Plus Cisplatin

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of RCTs 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.[250,251,254]

Nevertheless, selected patients may benefit from this regimen because patients with breast and ovarian cancers who are carriers of a *BRCA* mutation[274-276] and selected patients with inherited forms of pancreatic cancer[96] 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.[277] 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).[277] Furthermore, a report of 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.[278] 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 patients with metastatic or locally advanced disease, only for known *BRCA1/2* or *PALB2* mutations. FOLFIRINOX and modified FOLFIRINOX are also possible treatment options for patients with *BRCA 1/2* and *PALB2* mutations.

Gemcitabine Plus Erlotinib and Other Targeted Therapeutics

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.[279-283] 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 PFS (HR, 0.77; *P* = .004) when compared to patients receiving gemcitabine alone.[279] 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.[279] 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.[279,284,285]

The NCCN Panel recommends the gemcitabine-erlotinib combination therapy as a treatment option, under other recommended regimens, for patients with locally advanced or metastatic disease and good performance status, with this combination being a category 1 recommendation for patients with metastatic disease. However, the panel notes that although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

Gemcitabine Plus Capecitabine

A number of randomized trials have investigated the combination of gemcitabine with capecitabine, a fluoropyrimidine, in patients with advanced pancreatic cancer. A randomized study in 533 patients with advanced disease found that PFS 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.[252] 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.[256] Results from a third randomized phase III trial also showed that gemcitabine with capecitabine did not significantly improve OS, compared with gemcitabine alone, though patients who received gemcitabine with capecitabine had a greater overall response rate, compared to patients who received gemcitabine only (43.7% vs. 17.6%, respectively; *P* = .001).[286] In a meta-analysis of 8 RCTs, OS was better in patients receiving gemcitabine plus capecitabine than in patients receiving gemcitabine alone (HR, 0.87; *P* = .03).[287] Although there are concerns about dosing and toxicity of capecitabine in a U.S population, a biweekly regimen of fixed-dose gemcitabine in combination with capecitabine may be both effective and well-tolerated in patients with advanced disease.[248]

The panel includes the combination of gemcitabine, docetaxel, and capecitabine (GTX regimen) as a category 2B recommendation for the treatment of patients with metastatic or locally 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.[247] 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 retrospective case-review study at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins 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.[288]

Gemcitabine combined with capecitabine and oxaliplatin (GEMOXEL) was recently assessed in a randomized phase II trial (*N* = 67) for the metastatic setting.[289] Disease control rate (*P* = .004), PFS (*P* < .001), and OS (*P* < .001) were all superior in patients randomized to receive the GEMOXEL regimen, compared to patients randomized to receive gemcitabine alone.

The NCCN Panel considers gemcitabine-based combination therapy with capecitabine to be a reasonable option (category 2A) for patients with locally advanced or metastatic disease and a good performance status who are interested in pursuing more aggressive therapy outside a clinical trial.

Gemcitabine and Other Fluoropyrimidine-Based Therapies

Gemcitabine has been examined in combination with other fluoropyrimidine-based therapies. A recent meta-analysis of 8 RCTs, including more than 2000 patients, found that OS was significantly improved when a fluoropyrimidine was added to gemcitabine.[287] In a phase II randomized trial, the effects of the FIRGEM regimen [irinotecan delivered before and after infusion of 5-FU/leucovorin (FOLFIRI.3), alternating with FDR gemcitabine] were assessed in 98 patients with metastatic pancreatic cancer.[290] Patients were randomized to receive the FIRGEM regimen or FDR gemcitabine monotherapy. The primary objective of a 45% PFS rate at 6 months was reached, and PFS was a median of 5.0 months in those randomized to receive the FIRGEM regimen, while those randomized to receive only gemcitabine had a median PFS of 3.4 months (HR, 0.59; 95% CI, 0.38–0.90). Rates of hematologic toxicity were higher in those who received the FIRGEM regimen, relative to those who received gemcitabine only. Study investigators deemed FIRGEM to be effective and feasible in the metastatic setting.

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.[249]

Recent randomized trials from Asia show that gemcitabine combined with the oral fluoropyrimidine S-1 may improve response and survival in patients with locally advanced pancreatic cancer, though trial results are inconsistent regarding whether outcomes are improved over gemcitabine monotherapy.[291-293]

Capecitabine and Continuous Infusion 5-FU

The panel lists capecitabine monotherapy and continuous infusion 5-FU as first-line and second-line treatment options for patients with locally advanced disease (category 2B), and for patients with poor performance status and metastatic disease (category 2B). They are also recommended as options in the adjuvant settings (category 2A for continuous infusion 5-FU and category 2B for capecitabine). 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.[294]

Note that the capecitabine dose recommended by the panel (1000 mg/m^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).[295]

Fluoropyrimidine Plus Oxaliplatin

The combination of a fluoropyrimidine (5-FU/leucovorin or capecitabine) with oxaliplatin is 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 [OFF] vs. best supportive care) and on a phase II study (CapeOx).[296,297] 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).

Maintenance Therapy in Advanced Disease

With the success of more effective regimens in patients with advanced disease, questions have been raised about how best to manage the treatment-free interval prior to disease progression. Options include continuing systemic therapy, stopping treatment, dropping the most toxic agents, and using different agents for maintenance therapy.

Based on the fact that the BRCA genes encode for proteins involved in homologous recombination repair and that cells with mutations are sensitive to poly (ADP ribose) polymerase (PARP) inhibitors, the efficacy of olaparib, a PARP inhibitor, was investigated. In a phase II trial assessing its efficacy and safety, the tumor response rate for patients with metastatic pancreatic cancer and a germline *BRCA1/2* mutation (*n* = 23) was 21.7% (95% CI, 7.5–43.7).[298] Following this, in the randomized, double-blind, placebo-controlled phase 3 POLO trial, olaparib was found to be an effective maintenance therapy agent for patients with metastatic pancreatic cancer and germline BRCA 1/2 mutations and no disease progression following at least 16 weeks of first-line platinum-based therapy. A total of 154 patients were randomized to receive either olaparib or placebo. In the olaparib arm, the median PFS was 7.4 months compared to 3.8 months in the placebo arm (95% CI 0.35-0.82, P=0.004). At interim, however, there was found to be no difference in OS between the olaparib and placebo groups (18.9 months vs. 16.1 months, 95% CI 0.56-1.46, P=0.68). Adverse events, such as those grade 3 or higher, were found to be higher in the olaparib arm than in the placebo arm (40% vs. 23%).[299] Based on this data, olaparib is recommended by the NCCN Panel as a preferred targeted maintenance therapy for patients with germline *BRCA*-mutated metastatic disease and no disease progression after 4-6 months of first-line platinum-based therapy. Other maintenance therapy options for patients include clinical trial enrollment; gemcitabine-based therapy for patients who received previous first-line gemcitabine and nab-paclitaxel; or capecitabine, 5-FU with or without irinotecan, or FOLFOX for patients who received previous FOLFIRINOX. The NCCN Panel has included 5-FU with or without irinotecan for patients who exhibited oxaliplatin-related progressive neuropathy or allergy. Finally, if irinotecan-related GI toxicity is of concern, then FOLFOX may be a suitable maintenance therapy.

Subsequent Therapy in the Advanced Setting

A systematic review of clinical trials that assessed the efficacy of subsequent therapy after gemcitabine in pancreatic cancer concluded that, while data are very limited, evidence suggests an advantage of additional chemotherapy over best supportive care.[300] For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable subsequent options.[296,297,301,302] Gemcitabine-based therapy can be given to those previously treated with fluoropyrimidine-based therapy.

Results from the phase III CONKO-003 trial showed significant improvements in both median PFS (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,[303,304] making this regimen the standard approach for subsequent therapy for patients without prior exposure to fluoropyrimidine-based therapy at that time. Final results of the trial were published in 2014.[305] The median OS in the OFF arm was 5.9 months (95% CI, 4.1–7.4), whereas it was 3.3 months (95% CI, 2.7–4.0) in the 5-FU/leucovorin arm, for a significant improvement in the HR (0.66; 95% CI, 0.48–0.91; *P* = .01).

However, results from the open-label phase III PANCREOX trial show that the addition of oxaliplatin to 5-FU/leucovorin (OFF) in subsequent treatment may be detrimental.[306] In this trial, 108 patients with advanced pancreatic cancer who progressed on gemcitabine-based treatment were randomized to receive second-line mFOLFOX6 or infusional 5-FU/ leucovorin. No difference was seen in median PFS (3.1 vs. 2.9 months; *P* = .99), but median OS was worse in those in the FOLFOX arm (6.1 vs. 9.9 months; *P* = .02). Furthermore, the addition of oxaliplatin resulted in increased toxicity, with rates of grade 3/4 adverse events of 63% in the FOLFOX arm and of 11% in the 5-FU/ leucovorin arm. However, this trial was limited by imbalances in PS 2 proportion between the study arms and possible crossover in treatment delivered following progression.[307] The randomized phase II SWOG S1115 trial showed that patients with metastatic disease that failed to respond to gemcitabine-based therapy (*n* = 62) who received mFOLFOX (fluorouracil and oxaliplatin) had a median OS of 6.7 months, which is comparable to the median OS rates found in the CONKO-003 and PANCREOX trials.[308]

In the NAPOLI-1 phase III randomized trial, the effects of nanoliposomal irinotecan were examined in patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy.[309] Patients were randomized to receive nanoliposomal irinotecan monotherapy, 5-FU/leucovorin, or both (*N* = 417). Median PFS (3.1 months vs. 1.5 months; HR, 0.56; 95% CI, 0.41–0.75; *P* < .001) was significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin, compared to patients who did not receive irinotecan. Updated analyses showed that median OS (6.2 months vs. 4.2 months; HR, 0.75; *P* = .042) was significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin, compared to patients who received 5-FU/leucovorin without irinotecan.[310] Grade 3 or 4 adverse events that occurred most frequently with this regimen were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).[309] Irinotecan liposomal injection, combined with 5-FU/leucovorin, was later approved by the FDA to be used as a subsequent treatment option following gemcitabine-based therapy in patients with metastatic disease. The panel recommends this regimen as a subsequent treatment option for patients with good performance status and disease progression.

Another subsequent therapy option in patients with good performance status and locally advanced or metastatic disease is 5-FU + leucovorin + irinotecan (FOLFIRI). A phase II trial found comparable efficacy and safety in patients treated with mFOLFOX (n = 30) and modified FOLFIRI-3 (n = 21) regimens whose disease had failed previous gemcitabine treatment; OS was 14.9 and 16.6 weeks, respectively.[311] Another phase II trial studied 63 patients with metastatic disease and failure in 1 to 3 lines of gemcitabine- and platinum-based chemotherapies, who received FOLFIRI (in 2 different schedules reported together; FOLFIRI-1 and -3).[312] The median OS was 6.6 months (95% CI, 5.3–8.1 months). Patients who had grade 3-4 toxicities (23.8%) experienced mainly hematologic or digestive toxicities. A GISCAD multicenter phase II study of locally advanced or metastatic disease evaluated the FOLFIRI-2 regimen in patients previously treated with gemcitabine with or without platinum-based therapies.[313] The OS was 5 months and the toxicity was manageable; patients experienced grade 3–4 neutropenia (20%) and diarrhea (12%).

The AIO-PK0104 trial also assessed subsequent therapy in a randomized crossover trial and found capecitabine to be efficacious after progression on gemcitabine/erlotinib in patients with advanced disease.[314] In this trial, capecitabine/erlotinib followed by gemcitabine gave similar outcomes to the aforementioned sequence.

Advances in research have revealed that human immune-checkpoint–inhibitor antibodies that inhibit the interactions between immune cells and antigen-presenting cells may also do so in tumor cells.[315] There is evidence that PD-1 blockade with pembrolizumab may be effective in

tumors with mismatch repair deficiency (dMMR).[316] Pembrolizumab is an anti-PD-1 receptor antibody and blocks its interaction with PD-L1 and PD-L2, releasing the PD-1–mediated inhibition of the immune response, which improves antitumor immunity. The results of a phase II study in patients with 12 different dMMR advanced cancers, including pancreas, found that treatment with pembrolizumab resulted in durable responses (ORR in 53% of patients, with 21% complete response).[317] There were 6 patients with pancreatic cancer with an ORR in 62% of patients (2 had complete response and 3 had progressive disease). Adverse events were experienced by 74% of all patients receiving pembrolizumab; most were low grade (20% experienced grade 3 or 4 adverse events, such as diarrhea/colitis, pancreatitis/hyperamylasemia, fatigue, arthritis/arthralgias, or anemia).[317] Adverse events, however, for immune checkpoint inhibitors can be significant; please see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org.

Based on these data, pembrolizumab was granted accelerated FDA approval in 2017 for patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Similar results were reported from the phase II KEYNOTE-158 study. Among 27 noncolorectal tumor types, including pancreatic cancer, with a median follow-up of 13.4 months, the ORR was reported to be 34.3% (95% CI 28.3%-40.8%), the median PFS was 4.1 months (95% CI 2.4-4.9 months), and the median OS was 23.5 months.[318] Pembrolizumab is recommended by the NCCN Panel for the advanced disease setting for first-line and subsequent treatment as appropriate.

Finally, neurotrophin receptor kinase (NTRK) gene fusions, although rare, have been implicated in the oncogenesis of pancreatic cancer. In three multicenter, open-label, single-arm trials (a phase 1 study with adults, a phase 1/2 study with children, and a phase 2 study with adolescents and adults), the efficacy and safety of larotrectinib, an NTRK inhibitor, was investigated.[319,320] The primary endpoint was set to be ORR and the secondary endpoints were determined to be PFS, duration of response, and safety. Among 17 tumor types, the ORR during independent review was 75% (95% CI 61-85). After 9.4 months, 86% of participants had either underwent curative surgery or were continuing treatment. At one year, 55% of patients were progression-free and the toxicity profile of the agent was found to be minimal.[319] Based on this data, larotrectinib was approved by the FDA in 2018 for the treatment of NTRK gene fusion positive solid tumors in adult and pediatric patients with known acquired resistance and advanced or morbid disease that has progressed despite treatment.[320] Updated data published in 2020 reported that the percentage of patients with an objective response was 79% (95% CI 72-85) with 16% of patients showing a complete response.[321]Similarly, entrectinib is another NTRK inhibitor approved in 2019 by the FDA for adult and pediatric patients (ages 12 years and older) with advanced, morbid, or unresectable NTRK gene fusion positive solid tumors with acquired resistance to standard treatment.[322] Data from three phase 1-2 trials (ALKA-372-001, STARTRK-1, and STARTRK-2) revealed that entrectinib had an ORR of 57.4% and a median duration of response (DOR) of 10.4 months. Like its predecessor, it had a tolerable safety profile.[323,324] Thus the NCCN Panel recommends larotrectinib and entrectinib as first-line and subsequent treatment options for patients with NTRK gene fusion positive locally advanced or metastatic pancreatic adenocarcinoma.

To summarize, subsequent treatment options for patients with good performance status and previously treated with gemcitabine-based therapy include: 5-FU/leucovorin/liposomal irinotecan (category 1 for metastatic disease), FOLFIRI, FOLFIRINOX or modified FOLFIRINOX, 5-FU/leucovorin/oxaliplatin (OFF), FOLFOX, CapeOx, capecitabine, orcontinuous infusion 5-FU.Options for patients with good performance status and previously treated with fluoropyrimidine-based therapy include:

5-FU/leucovorin/nanoliposomal irinotecan (if no prior irinotecan administered), gemcitabine/albumin-bound paclitaxel, gemcitabine/cisplatin, gemcitabine/erlotinib, or gemcitabine monotherapy. Chemoradiation may be a subsequent treatment option in select patients (see Management of Locally Advanced Disease below). For MSI-H or dMMR tumors, pembrolizumab is an option whereas for NTRK gene fusion positive disease, larotrectinib or entrectinib may be considered. Subsequent treatment options for patients with poor performance status include: gemcitabine (standard infusion as a category 1 and fixed-dose-rate as a category 2B recommendation), capecitabine (category 2B recommendation), and continuous infusion 5-FU (category 2B recommendation).

Radiation and Chemoradiation Approaches

In patients with pancreatic cancer, radiation is usually given concurrently with gemcitabine- or fluoropyrimidine-based chemotherapy. Chemotherapy is used as a radiosensitizer, increasing the toxicity of radiation to tumor cells. Although the mechanism of radiosensitization is not entirely clear, it is postulated that gemcitabine and fluoropyrimidines decrease the number of tumor cells in the S phase of the cell cycle, a stage at which cells are resistant to radiation damage.[325]

Radiation and chemoradiation are sometimes used for pancreatic cancer in the resectable and adjuvant settings, because of the potential of these treatment methods to decrease the likelihood of local recurrence. A major goal of radiation therapy (RT) in these settings is to sterilize vessel margins and increase the likelihood of a margin-negative resection. It also may be used to enhance local control and prevent disease progression, while minimizing the risk of RT exposure to surrounding organs at risk. Chemoradiation is also often incorporated into neoadjuvant regimens, although randomized trials demonstrating the role of chemoradiation in this setting have not been done. Chemoradiation can also be given as second-line therapy in patients with locally advanced disease, if chemoradiation was not previously given and if the primary site is the sole site of progression. Finally, radiation without chemotherapy is used in the metastatic setting as palliation for pain refractory to analgesic therapy. Varying levels of evidence support the use of chemoradiation in each setting, as discussed in more detail below.

Stereotactic body RT (SBRT) is another technique aimed at increasing dose to the gross tumor while sparing radiation to nearby healthy tissue.[326-333] Retrospective analyses from the National Cancer Database (NCDB) including patients with locally advanced pancreatic cancer (n = 988) showed that patients treated with SBRT had better median OS (13.9 vs. 11.6 months, respectively; P < .001) and 2-year OS (21.7% vs. 16.5%, respectively; P = .001), compared to patients treated with conventionally fractionated RT.[334] Analyses of patient-reported outcomes from a phase II trial in which patients with locally advanced pancreatic cancer received SBRT either upfront or following gemcitabine showed that SBRT did not significantly impact global quality of life and improved pancreatic pain (P = .001) and body image (P = .007), based on assessment at 4 to 6 weeks following treatment.[335] However, 4 months after treatment, role functioning was negatively impacted (P = .002). Results from a prospective trial showed that SBRT was associated with less severe radiation-induced lymphopenia one month after beginning treatment, relative to conventional chemoradiation (13.8% vs. 71.7%, respectively; P < .001).[336] SBRT should not be used if direct invasion of the bowel or stomach is observed on imaging, and care should be taken to limit dose to these areas to reduce treatment-related toxicity, particularly in patients with unresectable disease. SBRT delivered in 3 to 5 fractions may reduce toxicity, though longer follow-up may then be needed.[332] Since the data regarding appropriate use of SBRT are evolving, the panel recommends that SBRT should be used preferably in the context of a clinical trial and at an experienced high-volume center.

Adjuvant Chemoradiation

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.[337,338] 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/m^2 daily for 3 days, was given concurrently with each 2,000-cGy segment of RT. The 5-FU regimen was then continued weekly for a full 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 42%, compared with 15% in the control group.[337]

Other studies have also shown an advantage to adjuvant chemoradiation over observation after resection. EORTC conducted a phase III trial (40891) in patients with both ampullary and pancreatic adenocarcinoma assessing adjuvant RT 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.[339] At a median follow-up of 11.7 years, no statistically significant differences were observed in the different study arms with respect to PFS or OS for the subset of patients with pancreatic cancer.[340]

More contemporary studies have compared different regimens incorporating chemoradiation. 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.[341] This trial, which utilized daily fractionated RT, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[342] 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 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.[343]

The Role of Radiation in Adjuvant Regimens

The majority of the data comparing chemotherapy to chemoradiation in the adjuvant setting do not generally show an advantage to the addition of radiation. Results of ESPAC-1 suggested that the addition of radiation to adjuvant 5-FU chemotherapy may be unnecessary and perhaps even harmful (OS, 13.9, 21.6, and 19.9 months for chemoradiation, chemotherapy, and chemotherapy plus chemoradiation, respectively),[344] although the ESPAC-1 trial has been criticized for lack of attention to quality control for RT.[345-347] A phase II study by GERCOR randomized patients to adjuvant gemcitabine or adjuvant gemcitabine-based chemoradiation.[348] No differences were seen in OS (24.4 months vs. 24.3 months) or DFS (10.9 months vs. 11.8 months) between the groups, but with only 45 patients in each arm no *P* values were reported. In addition, the multicenter, open-label, randomized phase III CapRI trial found that adjuvant chemoradiation with 5-FU, cisplatin, and interferon alfa-2b (IFN α-2b) followed by 5-FU chemotherapy gave outcomes no better than adjuvant treatment with 5-FU alone.[349]

A 2012 meta-analysis of 15 prospective, randomized trials found that adjuvant chemoradiation did not improve DFS, 2-year survival, or OS (OR, 0.99; *P* = .93) compared to surgery alone, while adjuvant chemotherapy improved all 3 outcomes (OR for OS, 1.98; *P* < .001).[350] A 2013 meta-analysis of 9 trials found similar results, with HRs for death compared to no adjuvant treatment of 0.62 for 5-FU (95% CI, 0.42–0.88), 0.68 for gemcitabine (95% CI, 0.44–1.07), 0.91 for chemoradiation (95% CI, 0.55–1.46), 0.54 for chemoradiation plus 5-FU (95% CI, 0.15–1.80), and 0.44 for chemoradiation plus gemcitabine (95% CI, 0.10–1.81).[351]

However, a population-based assessment of outcomes of patients in the NCDB with pancreatic cancer resected from 1998 to 2002 found the opposite result: chemoradiation gave better OS than chemotherapy in a performance-status–matched comparison to no adjuvant treatment (HR, 0.70; 95% CI, 0.61–0.80 vs. HR, 1.04; 95% CI, 0.93–1.18).[352] A multi-institutional pooled analysis of 955 consecutive patients who had R0-1 resections for pancreatic cancer also supports the supposition that

adjuvant chemoradiation improved survival compared to chemotherapy alone (OS, 39.9 months vs. 27.8 months; *P* < .001).[353]

To definitively clarify the role of chemoradiation following gemcitabine monotherapy in the adjuvant setting, RTOG is conducting trial 0848 (ClinicalTrials.gov NCT01013649). Patients without evidence of progressive disease after 5 cycles of gemcitabine-based chemotherapy are being randomized to 1 additional round of chemotherapy or 1 additional round of chemotherapy followed by chemoradiation with capecitabine or 5-FU. The primary endpoint is OS, and the trial is estimated to be completed in 2020. Studies are presently investigating the potential role of SBRT in the adjuvant setting (eg, NCT02461836).

Benefit of Adjuvant Chemoradiation in Patient Subsets

It has been suggested that subsets of patients (eg, patients with R1 resections or positive lymph nodes) may be more likely to benefit from adjuvant chemoradiation.

Studies that have looked at R0 or R1 subsets of patients have found mixed results. For instance, patients treated in the ESPAC-1 trial did not derive a benefit from the addition of radiation to adjuvant chemotherapy, irrespective of margin status.[354] In contrast, results from a prospectively collected database of 616 patients with resected pancreatic cancer at the Johns Hopkins Hospital found that adjuvant chemoradiation benefited both the R0 and R1 subsets compared to observation alone.[355] The Mayo Clinic performed a retrospective review of 466 patients who had R0 resections for pancreatic adenocarcinoma, and found an OS benefit of adjuvant chemoradiation over observation.[356] In addition, a retrospective review of greater than 1200 resected patients from the Johns Hopkins Hospital and the Mayo Clinic who received adjuvant 5-FU–based chemoradiation or were observed following resection found that chemoradiation improved outcomes regardless of margin status (R0: RR, 0.61; 95% CI, 0.47–0.77; *P* < .001; R1: RR, 0.52; 95% CI, 0.36–0.74; *P* < .001).[357] A meta-analysis of 4 RCTs found evidence for an increased survival benefit of adjuvant chemoradiation in the R1 subset (HR for death, 0.72; 95% CI, 0.47–1.10) over the R0 subset (HR for death, 1.19; 95% CI, 0.95–1.49).[358]

Fewer analyses have looked at the role of chemoradiation in resected patients with positive lymph nodes. One retrospective review compared outcomes of 94 patients who underwent distal pancreatectomy at the Johns Hopkins Hospital and either received adjuvant chemoradiation or were just observed following resection.[359] An exploratory subset analysis suggested that patients with positive lymph nodes derived greater benefit from adjuvant chemoradiation than those with negative nodes. In addition, a meta-analysis of 4 randomized controlled adjuvant trials found that chemoradiation had a similar lack of benefit in patients with positive and negative lymph nodes.[360]

Chemoradiation and SBRT for Locally Advanced Disease

Chemoradiation is a conventional option for the management of locoregional pancreatic cancer, although the utility of chemoradiation in this population of patients is controversial.[361] It is mainly used in selected patients who do not develop metastatic disease during initial chemotherapy.

A meta-analysis identified 15 RCTs (1128 patients) that compared chemoradiation to either chemotherapy or radiation in the locally advanced setting.[362] Whereas combined modality therapy significantly improved survival compared to radiation alone, survival was the same when compared to those receiving chemotherapy alone. Increased toxicity was observed in the chemoradiation group.

The role of chemoradiation in locoregional pancreatic cancer was initially defined in a trial conducted in locally advanced disease by GITSG.[338] 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.[363] Gemcitabine has also been used as a radiation sensitizer in the locally advanced setting.[364-368] Some evidence suggests that concurrent gemcitabine and radiation can yield similar or better outcomes when compared with 5-FU–based chemoradiation in the setting of locally advanced disease.[363,366,369,370] The use of capecitabine as a radiosensitizer has also been assessed in this setting and appears to be effective.[371] Recently reported results of the phase II SCALOP trial showed that health-related quality-of life scores (ie, cognitive functioning, fatigue, bloating, dry mouth, body image, future health concerns) tended to favor capecitabine-based chemoradiation, compared to gemcitabine-based chemoradiation.[372] Therefore, when chemoradiation is recommended by the panel, fluoropyrimidine-based chemoradiation is generally preferred, compared to gemcitabine-based chemoradiation.

Upfront Chemoradiation or SBRT in Locally Advanced Disease

Results of 2 early randomized trials comparing upfront chemoradiation to chemotherapy in locally advanced disease were contradictory.[373,374] Three phase II trials also assessed the upfront chemoradiation approach in locally advanced pancreatic adenocarcinoma, with median survival rates ranging from 8.2 to 9 months.[364,375-377] Results from small, single-arm trials of upfront chemotherapy followed by chemoradiation in locally advanced disease have been discussed.[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 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).[368] However, the poor accrual rate decreased its statistical power, there was no difference in PFS, 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.[379]

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.[380] 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.

Upfront SBRT may be used in patients with locally advanced disease who are not candidates for combination systemic treatment. A 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.[326] However, another retrospective review of 71 patients reported a median OS of 10.3 months with only 3 patients (4%) experiencing grade 3 toxicity.[329] Hypofractionated dosing may also be used in these patients, with acceptable toxicity.[381] The

incorporation of simultaneous integrated boost is being investigated to improve the potential of SBRT for downstaging.[382]

Thus, the role of upfront chemoradiation in the setting of locally advanced pancreatic cancer is still undefined. If patients present with poorly controlled pain or local invasion with bleeding, then starting with upfront chemoradiation therapy or SBRT is an option.[364,368]

Chemoradiation or SBRT Following Chemotherapy in Locally Advanced Disease

Starting with 2 to 6 cycles of systemic chemotherapy followed by chemoradiation or SBRT is an option for selected patients with locally advanced disease and good performance status who have not developed metastatic disease.[383-385] 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/celiac arteries); 2) there are suspicious metastases; or 3) the patient may not be able to tolerate chemoradiation. Employing an initial course of chemotherapy may improve systemic disease control in these cases. In addition, the natural history of the disease can become apparent during the initial chemotherapy, thus allowing the selection of patients most likely to benefit from subsequent chemoradiation. 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.[383]

In the randomized phase II SCALOP trial, patients with locally advanced pancreatic cancer received gemcitabine and capecitabine combination chemotherapy, followed by either gemcitabine-based chemoradiation or capecitabine-based chemoradiation (n = 74).[371,386] Though OS and PFS did not significantly differ between the two treatment arms, results favored capecitabine-based chemoradiation, with a median OS of 17.6 months and a median PFS of 12 months.[386]

In the international phase III LAP-07 RCT, patients with locally advanced pancreatic cancer (n = 269) received chemoradiation with capecitabine following 4 months of induction chemotherapy with either gemcitabine monotherapy or gemcitabine and erlotinib.[387] Chemoradiation in this setting provided no survival benefit, compared to chemotherapy only (HR, 1.03; 95% CI, 0.79–1.34; P = .83). Differences were noted in other potentially meaningful outcomes such as time to reinitiation of therapy (159 days in the chemoradiation arm vs. 96 days in the control arm; P = .05) and local tumor progression (34% in the chemoradiation arm vs. 65% in the chemotherapy only arm; P < .0001).[387]

SBRT following gemcitabine monotherapy in patients with locally advanced pancreatic cancer has been examined in phase II trials.[388,389] This regimen was associated with low toxicity and favorable freedom from local disease progression.[388,389] Because there are now more active chemotherapy regimens than gemcitabine monotherapy, additional studies are planned to assess the role of radiation after more active chemotherapy.

Advanced Radiation Techniques

Intensity-modulated RT (IMRT) is increasingly being applied for therapy of locally advanced pancreatic adenocarcinoma and in the adjuvant setting with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues.[390-394] 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.[394] 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. A recent systematic review including 13 IMRT studies showed that IMRT does not improve survival outcomes, compared to 3D-CRT.[395] However, toxicities grade 3 or greater were more numerous in 3D-CRT, relative to IMRT (*P* = .017). These toxicities were mainly GI, specifically nausea/vomiting and diarrhea. IMRT resulted in reduced grade 3/4 toxicities when the authors made a cross-study comparison of toxicities in patients who received a similar 5-FU–based regimen with 3-D conformal radiation in the RTOG 9704 trial.[341,396] Comparing the 2 trials, rates of grade 3/4 nausea and vomiting were 0% vs. 11% (*P* = .024), and rates of grade 3/4 diarrhea were 3% vs. 18% (*P* = .017),[396] suggesting that IMRT may be well-tolerated and allow for higher radiation doses to the tumor.[396] There is no clear consensus on the appropriate maximum dose of radiation when IMRT technique is used.

Intraoperative RT (IORT) can allow for higher doses of radiation because sensitive structures can be excluded from the radiation fields. IORT is sometimes administered to patients with borderline resectable disease who have received maximal neoadjuvant therapy to sterilize close or involved margins at the time of surgery, although data in this setting are lacking. It is also sometimes used when a patient is found to be unresectable at the time of surgery and in cases of locally recurrent disease. Most studies of IORT in patients with locally advanced pancreatic cancer found that while local control may be improved, no change in survival is evident with use of IORT because of the high frequency at which metastatic disease develops.[397-400] Some groups, however, believe that IORT can offer benefits in very carefully selected patients with non-metastatic disease.[401-403] Overall, there is no clear established role for IORT in patients with pancreatic cancer,[404] and the panel believes it should only be performed at specialized centers.

Management of Metastatic Disease

The primary goals of treatment for metastatic pancreatic cancer are palliation and lengthened survival. Survival benefits are usually limited to patients with adequate performance status (ECOG 0-1, with good biliary drainage, and adequate nutritional intake). Systemic therapy is therefore recommended for patients with metastatic disease and good performance status, as described in *Systemic Therapy Approaches for Locally Advanced or Metastatic Disease*, above, and in the algorithm.

Patients who present with poor performance status may benefit from single-agent chemotherapy (gemcitabine is a category 1 recommendation), but comfort-directed measures are always paramount (see *Palliative and Supportive Care*, below, and the NCCN Guidelines for Supportive Care, available at www.NCCN.org). An alternative option for these patients is palliative and best supportive care.

Patients with metastatic disease are generally not candidates for RT. However, palliative RT may be administered to patients who present with poor performance status (ie, patients who are elderly and/or not candidates for definitive treatment), instead of single-agent chemotherapy. A short course of RT may be administered to metastatic sites that cause pain (eg, osseous pain).[405]

Before initiating cytotoxic therapy, an open dialogue regarding the goals and side effects of treatment should take place and, if needed, adjunctive strategies can be used (see *Palliative and Supportive Care*, below). Of note, 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/or as constipation.

For patients who do well on initial therapy, a chemotherapy holiday is appropriate, or maintenance therapy can be considered (see *Possible Role of Maintenance Therapy in Advanced Disease*, above). After progression, second-line therapy is possible, especially in patients who maintain a good performance status (see *Second-Line Systemic Therapy in the Advanced Setting*, above). Prior to commencing second-line therapy, serial 3D CT or MRI imaging of known sites of disease to determine therapeutic benefit is recommended by the panel. However, patients may demonstrate progressive disease clinically without objective evidence of progression (also for *Management of Locally Advanced Disease*; see below).

Management of Locally Advanced Disease

As in the metastatic setting, the primary goals of treatment of patients with locoregionally advanced pancreatic cancer are palliation and lengthened survival. Also, as in metastatic disease, patients with locally advanced disease are treated with systemic therapy based on their performance status. Palliative and best supportive care and single-agent chemotherapy or palliative RT are options for patients with poor or declining performance status, whereas patients with good performance status can be treated with more intensive therapy, as described in *Systemic Therapy Approaches for Locally Advanced or Metastatic Disease*, above, and in the guidelines.

Historically, most studies in the locally advanced setting used gemcitabine monotherapy. However, there is an increasing emphasis on understanding the role of modern, more active regimens in locoregionally advanced disease. The experience with FOLFIRINOX in 22 patients with locally advanced pancreatic cancer at the Massachusetts General Hospital Cancer Center through February 2012 was reported.[406] An overall response rate of 27% was observed, and the median PFS was 11.7 months. Five patients (23%) were able to undergo R0 resections, although 3 of these patients experienced distant recurrence by 5 months. It was also reported that 32% of patients receiving FOLFIRINOX required greater than or equal to 1 hospitalization or visit to the emergency department during treatment.

Other studies and case reports addressing the use of chemotherapy with or without chemoradiation in patients with locally unresectable disease have noted that the opportunity for curative intent resection occasionally arises.[406-415] The panel believes that patients with a significant response to chemotherapy and/or chemoradiation may be considered for surgical resection, but acknowledges that such conversions are rare in patients with true locally advanced disease. Following resection, these patients have similar survival rates as those initially determined to be resectable.[416]

Upfront chemoradiation or SBRT may be used in select patients (see *Chemoradiation and SBRT for Locally Advanced Disease*). The use of chemoradiation or SBRT following chemotherapy in locally advanced disease is also discussed above. If disease progression occurs in patients with locally advanced disease, chemoradiation or SBRT are treatment options if all of the following are true: good performance status is maintained, chemoradiation or SBRT were not previously given, and the primary site is the sole site of progression.

Irreversible electroporation (IRE) is an ablative technique in which electric pulses are used to create nanopores that induce cell death similar to apoptosis. This technique has been used in patients with locally advanced pancreatic cancer.[417,418] IRE may be safe and feasible[419] and may improve

survival outcomes.[418] However, due to concerns about complications and technical expertise,[420] the panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer.

Management of Resectable and Borderline Resectable Disease

Surgical Management

The goals of surgery for adenocarcinoma of the pancreas include an oncologic resection of the primary tumor and regional lymph nodes. 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.[421] Surgery should be done efficiently, optimizing quality of life and cost. Early concerns about high mortality associated with various pancreatic resection procedures[422] have now been lessened by studies demonstrating an acceptably low (<5%) mortality in experienced centers (see *Effect of Clinical Volume*, below).[423] Even under the most optimal clinical trial conditions, the median survival of resected patients following adjuvant therapy ranges from 20.1 to 28.0 months.[231,341,344,424,425] Negative margin status (ie, R0 resection), tumor DNA content, small tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[426-428] 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.[429-431]

Criteria for Resection

The NCCN Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation at high-volume centers with use of 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 differ in their approaches to patients with locoregional disease involvement (pancreas and peripancreatic lymph nodes).

Careful intraoperative staging should rule out peritoneal, liver, and distant lymph node metastases, and resection of the primary tumor should only be done in the absence of distant disease. The surgical procedure required is based on the location of the primary tumor and relationship to blood vessels. Therefore, a pancreas protocol CT is critical for preoperative planning.

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.[129,432] Other groups have also put forth definitions of resectability of pancreatic cancer.[433-435] A more restrictive definition of borderline resectable pancreatic tumors has also been described.[436] This definition uses degrees of contact (eg, interface between tumor and SMA measuring ≤180˚ of vessel wall circumference) and contour deformity/narrowing (eg, tear drop deformity in the main PV [MPV] or SMV) to ascribe likelihood of vascular invasion rather than subjective terms such as abutment and impingement. The panel endorses this definition for use in clinical trials. Using a combination of these sets of criteria, tumors are classified as resectable, borderline resectable, locally advanced, or metastatic disease.

Analysis of the pancreatic neck and bile duct at time of surgery by frozen section may be considered. A review of 4 studies with 2580 patients showed that additional resection to achieve a negative surgical margin was not associated with improved survival.[437] Frozen sections should be taken approximately 5 mm from the transection margin, with the clean-cut side facing down, to avoid cautery artifact that may confound analysis and result in false negatives. If tumor is located within 5 mm of margins, further

excision of the pancreas should be considered to ensure at least 5 mm of clearance.

For cancers of the pancreas head and uncinate, a pancreatoduodenectomy (Whipple procedure) is done. For cancers of the pancreas body and tail, a distal pancreatectomy with en-bloc splenectomy is done.

The panel has adapted the criteria put forth by other groups and lists its recommended criteria for defining resectability status in the guidelines. 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 negative (R0) resection margins. Overall, the likelihood of attaining negative margins is the key criterion for consideration when determining whether a patient is a potential candidate for resection.[435,438] In this context, a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete resection. Patients at high risk for positive surgical margins are not considered to be good candidates for an upfront resection but may be potentially downstaged and safely resected following neoadjuvant therapy [see *Preoperative (Neoadjuvant) Therapy* below]. Furthermore, the panel recommends that patient factors be considered when deciding whether a patient is a surgical candidate. Comorbidities, performance status, and frailty are all things to be discussed during the multidisciplinary review. Please refer to the NCCN Guidelines for Older Adult Oncology (available at www.NCCN.org) 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 pancreatic 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 minimally invasive pancreaticoduodenectomy (ie, the Whipple procedure).[439,440]

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 previously performed. If a patient with jaundice is found to be unresectable at surgery, then the panel recommends surgical biliary bypass at that time. If a stent has been previously placed, then surgical biliary bypass could be considered. In addition, gastrojejunostomy can be considered if appropriate regardless of jaundice (category 2B for prophylactic gastrojejunostomy). Celiac plexus neurolysis can also be performed, especially when indicated by pain in a patient with jaundice (category 2B if no pain). See *Severe Tumor-Associated Abdominal Pain*, below, for more details about these procedures.

In patients with suspected borderline resectable disease for whom cancer is not confirmed following repeated biopsy with EUS-FNA (preferred), intraoperative biopsy is recommended. If resectable disease is found in these patients, then surgical resection followed by adjuvant therapy is recommended. If unresectable disease is found, then recommendations for management of locally advanced or metastatic disease should be followed (see above). If these patients present with jaundice, surgical biliary bypass and gastrojejunostomy (category 2B for prophylactic gastrojejunostomy) should be considered, as well as celiac plexus neurolysis for pain (category 2B if no pain).

Pancreatoduodenectomy (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).[441,442] 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 result in suboptimal clearance and increase the risk of an R1 resection.[443,444]

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.[445-447] 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 numbers are more limited, similar findings have been noted with respect to hepatic arterial resection and reconstruction.[447,448] Others, however, have noted poor short- and long-term outcomes with arterial resection.[449,450] 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 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.[450] No difference in mortality was seen.

Distal Pancreatectomy with En-bloc Splenectomy

The goals of left-sided resection are similar to those of pancreatoduodenectomy, although they are often more difficult to achieve because of the advanced stage at which most of these cancers are discovered. Plane of dissection anterior to adrenal gland or en bloc resection of left adrenal gland with plane of dissection posterior to Gerota's fascia is recommended as clinically indicated. Spleen preservation is not indicated in distal pancreatectomy for adenocarcinoma, and an R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.[451,452] 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.[452,453] 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.[451-453] 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.[452,453] Local recurrence, however, remains problematic even with pathologically negative margins.[453]

There is an increasing role for laparoscopic distal pancreatectomy. A meta-analysis including 29 observational studies with 3,701 patients showed that laparoscopic distal pancreatectomy may decrease intraoperative blood loss ($P < .01$), time to first oral intake ($P < .01$), and length of hospital stay ($P < .01$), as compared to open distal pancreatectomy.[454] Results from 172 patients treated at the Mayo Clinic found significant benefits in the patients who had laparoscopic versus open resections in blood loss, the need for blood transfusions, and the length of hospital and intensive care unit stays without any difference in oncologic outcomes.[455] In addition, results from a meta-analysis of 4 studies of 665 total patients suggest that the laparoscopic method is safe and results in shorter hospital stays.[456] Furthermore, results from a population-based, retrospective cohort study that included 8957 patients showed similarly that the laparoscopic approach can decrease complication rates and shorten hospital stays.[457]

Management of Neck Lesions

Pancreas neck adenocarcinomas are especially difficult to manage. Cancers in the pancreas neck are located anterior to the superior mesenteric vessels and PV. Depending on the extent of involvement, a pancreaticoduodenectomy extending to the left of the SMV (extended pancreaticoduodenectomy), a distal pancreatectomy extending to the right of the SMV (extended distal pancreatectomy), or a total pancreatectomy may be required to obtain an R0 resection.[458]

The precise extent of involvement often cannot be determined prior to surgery; therefore, complex intraoperative decisions are required, and the surgeon must anticipate this. Complexity of surgery for pancreas neck cancers is compounded by the frequent involvement of the SMV/PV.[458,459] Surgeons who operate on pancreas neck cancers must anticipate possible SMV/PV involvement and be prepared to manage it.

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.[460] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreatoduodenectomy decreased, a subset was identified of patients 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.[461] Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.[462]

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.[463-466] 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.[447] A meta-analysis of 22 retrospective studies (2890 patients) found that vein resection resulted in perioperative morbidity and mortality equal to that of standard resection, but R0 resection rates were lower in that group.[467] In a multi-institutional database analysis of 492 patients undergoing pancreaticoduodenectomy, R0 resection rates were no different between the 14% who had vein resection compared to those without venous involvement (66% vs. 75%; *P* = NS).[468] 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[469] 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.[470] A systematic review comparing a classic Whipple operation to pylorus-preserving pancreaticoduodenectomy (including 8 RCTs with 512 patients) showed no significant differences for mortality, morbidity, and survival, but some perioperative measures (ie, operating time, intraoperative blood loss, red blood cell transfusion) were better in patients who received pylorus-preserving pancreaticoduodenectomy, relative to those who received a classic Whipple.[470] Therefore, though more data from high-quality RCTs are needed, pylorus-preserving pancreatoduodenectomy is an acceptable alternative to classic pancreatoduodenectomy performed with antrectomy.

Pancreatic Anastomosis

Efforts have focused on preventing pancreatic leaks and fistulas, which are morbid and potentially lethal complications of pancreatoduodenectomy. Pancreaticojejunostomy has traditionally been the standard reconstruction and is the major focus of morbidity and mortality after pancreatoduodenectomy because of leaks, abscess formation, and fistulas from this anastomosis. A randomized study at Johns Hopkins Hospital found no difference in fistula rates after pancreaticojejunostomy and pancreaticogastrostomy.[471] However, a more recent multicenter, randomized, superiority trial compared the outcomes of 329 patients undergoing pancreaticoduodenectomy with either pancreaticojejunostomy or pancreaticogastrostomy.[472] A significant difference was seen in the primary outcome measure of postoperative fistulas, which occurred in 19.8% of patients in the pancreaticojejunostomy group and 8.0% of patients in the pancreaticogastrostomy group (OR, 2.86; 95% CI, 1.38–6.17; *P* = .002). An increase in grade ≥3a postoperative complications was seen, however, in the pancreaticogastrostomy group (24% vs. 21%). Criticisms of this trial have been published.[473] Although a meta-analysis of 4 RCTs (676 patients) concluded that pancreaticogastrostomy is associated with a lower risk of fistula formation than pancreaticojejunostomy (RR, 0.41; 95% CI, 0.21–0.62),[474] the optimal approach to anastomosis remains undefined.[475]

Surgeons have also 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.[476,477] 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.[478] Stents used in the 1930s and 1940s continue to be used today, but data suggest that they do not decrease leak rates.[479]

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).[480,481] Pasireotide, in contrast, significantly decreased the rate of grade ≥3 fistula, leak, or abscess in a single-center, double-blind RCT of 300 patients (9% in pasireotide group vs. 21% in placebo group; RR, 0.44; 95% CI, 0.24–0.78; *P* = .006).[482] Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.[483]

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.[484,485] 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.[486] 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.[487]

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.[488] A larger randomized prospective trial was performed at Johns Hopkins Hospital from 1996 through 2001 to evaluate the role of extended lymph node dissections.[489] 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.[489-491] A randomized multicenter trial in Japan came to similar conclusions.[492] Furthermore, multiple systematic literature reviews and meta-analyses of RCTs comparing pancreatoduodenectomy with standard versus extended lymphadenectomy support the conclusion that the extended procedure does not have any impact on survival.[493-495] In addition, patients undergoing extended lymphadenectomy have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.[496]

The information to date thus does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.[497] 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.[498,499]

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis and to potentially make surgery less

morbid by improving liver function preoperatively. Although controversial, several studies have suggested that pancreatoduodenectomy is associated with higher perioperative mortality when done in the setting of hyperbilirubinemia.[500-502] 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.[503-509] A retrospective analysis from a prospective database of 593 patients treated with pancreatoduodenectomy at MD Anderson Cancer Center found that self-expandable metal stents did not affect postoperative complications, 30-day mortality, length of stay, anastomotic leak, margin status, or determination of unresectability during resection, although more wound infections and longer operative times were observed in this group.[510] In contrast, a 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%; RR 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.[157]

Based on these reports, most groups who perform resection without neoadjuvant treatment advocate selective use of decompression only in patients who are symptomatic, septic, coagulopathic, have renal insufficiency, 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 longer than 1 week.

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.[511] 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.[512-515]

The panel notes that stents are an evolving technology. The choice of stents includes plastic and self-expanding metal (fully covered, partially covered, or uncovered) (also see the discussion on stents in *Palliative and Supportive Care*, below). While any stent can become occluded, several groups have reported better patency with metal stents.[513-515] Covered metal stents may give more durable patency, since the cover prevents tumor ingrowth,[516] but the reported differences between covered and uncovered stents are not dramatic.[516,517] Furthermore, migration is more of an issue with covered stents.[517] This issue has led to the introduction of partially covered stents,[518] though these stents may still migrate in a substantial number of patients.[519,520] Most metal stents used today are self-expanding. Their small initial diameters make them easy to place, and their placement rarely requires dilation.[518] Several panel members reported that their institutions use plastic stents in patients with short life expectancies (<3 months).[518] 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). In the absence of level-1 data, the panel consensus is that short, self-expanding metal stents (SEMS) are preferred because they are easy to place without dilation, are unlikely to interfere with the subsequent resection, and have a

significantly longer patency rate than plastic stents. The panel recommends that a plastic stent or a fully covered self-expandable metal stent be placed if tissue diagnosis has not been confirmed, as fully covered metal stents are removable endoscopically.

Effect of Clinical Volume

Several studies have examined the effect of institutional volume on patient outcomes. The fundamental premise was that the decreasing morbidity and mortality seen in the 1980s and 1990s were the direct result of large, single-institution experiences. Moreover, the concern was that if surgeons performed pancreatoduodenectomy less frequently, patients might have increased morbidity and mortality. 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% vs. 12.3%).[521] High volume was defined as more than 50 cases per year, and this relationship correlated in a regression analysis. Of note, 75% of the cases in New York State were performed in low-volume centers. Several other studies have assessed regional outcomes with pancreatoduodenectomy from U.S. hospitals.[522-526] 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.[527-529]

The definitions of high and low volume varied among all these studies. However, a striking difference was seen when the mortality rates from pancreatoduodenectomy in very-low-volume (0–1 procedure/year) and low-volume (1–2 procedures/year) hospitals were compared with rates in higher-volume hospitals (>5 procedures/year).[530] In-hospital mortality rates at these very-low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, vs. 4%; $P < .001$). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreatoduodenectomy is compared to other major surgeries. In a retrospective analysis of data from the national Medicare claims database and the Nationwide Inpatient Sample, hospitals performing 6 to 16 and greater than 16 procedures per year were classified as “high” and “very-high” volume centers.[531] 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 pancreatoduodenectomy, as compared to major surgery at any other site, further reinforcing the magnitude of the effect that high-volume centers can have specifically 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.[532] In addition, a 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 ($P = .008$).[533] This review also found that 5-year survival rates were higher in high-volume centers. In contrast, hospital readmission after pancreatoduodenectomy appears to be more of a function of patient characteristics than hospital or surgeon volume.[534]

The NCCN Panel recommendation is that pancreatic resections should be done at institutions that perform a large number (at least 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.[535] 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 pathologic 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.

Specimen Orientation, Sectioning, Pathologic Analysis, and Reporting

The primary purpose of pathologic analysis of the pancreatic specimen is to determine the pathologic stage of the tumor by evaluating the type, grade, size, and extent of the cancer. Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. In 2004, the Commission on Cancer (CoC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. The pathology synoptic reports from the College of American Pathologists (CAP) comply with the CoC requirements, and the latest revisions to the CAP Pancreatic (Exocrine) protocol were issued in August 2016.[536] The NCCN Pancreatic Adenocarcinoma Panel currently supports the CAP pathology synoptic reports. The proposal included in the guidelines (see *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* in the algorithm) 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.[537,538]

Lymph Node Counts and Lymph Node Ratio

Number of positive lymph nodes and lymph node ratio are associated with OS in patients with pancreatic cancer.[539] The CAP recommendations include a count of the number of lymph nodes recovered and the number of involved nodes.[540] Retrospective database analyses have found that patients with N0 disease have a better prognosis with an increasing number of examined lymph nodes.[541-543] 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 to be from 11 to 17 to provide optimal staging and to serve as a quality indicator.[541,543,544] The panel believes that every effort should be made to identify all regional lymph nodes within the pancreatectomy specimen.

For patients with N1 disease, lymph node ratio (positive node/nodes examined) appears to be related to prognosis.[541-548] For instance, in one analysis, patients with less than 15% of examined positive nodes had a 5-year survival rate of 21.7%, while those with greater than 15% positive nodes had a 5.2% 5-year survival rate (P = .0017).[546]

Whipple Specimen

Specimen orientation and inking involves both a 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 (ie, written on the pathology

requisition). For example, the distal and proximal margins of the SMV and SMA, as well as the bile duct margin, should be marked.

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 algorithm. 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.[535,549-551] 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. There is no one correct way to dissect a Whipple specimen. Options include axial, bi- or multi-valve slicing, and perpendicular slicing (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).

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 RT might be indicated if not received preoperatively. The panel strongly recommends reporting tumor clearance in mm for all margins (as noted in the *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* section of the algorithm) to allow prospective accumulation of these important data for future analysis.

A 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; $P < .001$).[552] In fact, patients with close-margin R0 resections had a median survival time similar to that of the R1 population (16 months vs. 14 months; $P = .6$). Consistent with these results, another retrospective review of 285 patients found that those with R1 resections, defined as tumor ≤1 mm from the margin, had a significantly worse local recurrence-free survival than those with R0 resections (HR, 4.27; 95% CI, 2.07–8.81).[553,554] Finally, a recent study, which used a standardized pathologic protocol that involved multicolor inking and careful evaluation of multiple margins distances, found that patients with R1 resections (tumor at 0 mm) had a median survival of 17.7 months, while those with R0 resections had a median survival of 32.9 months ($P = .10$).[555] Together, these results suggest that an appropriate definition of a negative margin may be greater than 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 pT3 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 (caudad) peripancreatic (peripheral) margin are included in the guidelines (see *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* in the algorithm).

Perioperative Therapy

Even with R0 resections, recurrence rates are very high in this disease. Therefore, additional therapy is required for all patients with resected pancreatic adenocarcinoma.

Postoperative (Adjuvant) Therapy

Results of many trials have shown that adjuvant therapy improves outcomes over observation following resection (see sections on *Systemic Therapy Approaches for Locally Advanced or Metastatic Disease* and *Radiation and Chemoradiation Approaches*, above). While 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, timing of imaging, and 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 CA 19-9 or CEA levels[231]), 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. Results of the ESPAC-4 phase III randomized trial (N = 730), in which gemcitabine combined with capecitabine was compared to gemcitabine monotherapy for the adjuvant setting, showed that median survival was greater for participants randomized to receive the combination regimen (28.0 months), relative to patients randomized to receive gemcitabine monotherapy (25.5 months) (HR, 0.82; 95% CI, 0.68–0.98; P = .032).[425] In the CONKO-005 phase III randomized trial, gemcitabine administered with erlotinib was compared to gemcitabine administered alone in the adjuvant setting.[556] This combination regimen did not significantly improve OS or DFS, compared to gemcitabine monotherapy. A phase II prospective trial including 22 patients with resected pancreatic cancer showed that gemcitabine/cisplatin is feasible, with a median OS of 35.5 months and median recurrence-free survival of 16.7 months.[557]

Based on the data discussed above, no definite standard has been established in the adjuvant treatment of pancreatic cancer at this time. Chemotherapy alone with gemcitabine (category 1), 5-FU/leucovorin (category 1), gemcitabine/capecitabine (category 1), or continuous infusion 5-FU are listed in the guidelines as options for adjuvant treatment. Capecitabine monotherapy is also a treatment option for the adjuvant setting (category 2B). The panel considers capecitabine to be 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. Gemcitabine, 5-FU/leucovorin, or continuous infusion 5-FU before gemcitabine- or fluoropyrimidine-based chemoradiation is also recommended as an adjuvant treatment, with subsequent chemotherapy

being an option. To date, no studies have demonstrated superiority of giving chemoradiation before versus after chemotherapy in the adjuvant setting.

Regardless of the therapy being considered it is important to evaluate the patient for extent of disease prior to therapy, because some patients have early recurrence within the first few weeks following surgery. In addition, the panel recommends restaging a patient with imaging following systemic chemotherapy if chemoradiation is planned.

A recent retrospective analysis of data from patients in the ESPAC-3 trial found that completion of the full course of chemotherapy was an independent prognostic factor for survival, but that time to treatment initiation after surgery was not.[558] These results suggest that delaying chemotherapy until patients adequately recover could possibly improve outcomes. The panel therefore recommends that adjuvant treatment be initiated within 12 weeks, after adequate recovery from surgery.

S-1 is an oral chemotherapy drug that is being used in Asia. Results of the phase III RCT JASPAC-01 trial (*N* = 385), in which S-1 was compared to gemcitabine in the adjuvant setting, showed that median OS was greater for S-1 (46.5 months; 95% CI, 37.8–63.7) compared to gemcitabine (25.5 months; 95% CI, 22.5–29.6).[559] Three- and 5-year survival rates were 59.7% and 44.1%, respectively, for S-1, and 38.8% and 24.4%, respectively, for gemcitabine. S-1 was generally well-tolerated, and the treatment of patients randomized to receive gemcitabine was more likely to be discontinued, relative to the treatment of patients randomized to receive S-1 (*P* = .005). Grade 3 or 4 adverse events that were more likely to be reported in patients receiving gemcitabine include leucopenia, neutropenia, aspartate aminotransferase, and alanine aminotransferase, while stomatitis and diarrhea were more common in patients receiving S-1.

Results of the PRODIGE 24/CCTG PA.6 phase III trial (n = 493) were recently presented, comparing adjuvant chemotherapy with gemcitabine versus mFOLFIRINOX to treat resected pancreatic adenocarcinoma in patients with good performance status.[560] The median follow-up was 30.5 months (95% CI, 29.5–33.7). The median DFS was greater for mFOLFIRINOX (21.6 months; 95% CI, 17.5–26.7) compared to gemcitabine (12.8 months; 95% CI, 11.7–15.2). The median OS (54.4 vs. 35.0 months, respectively) and metastasis-free survival (30.4 months vs. 17.7 months, respectively) were also greater for mFOLFIRINOX compared to gemcitabine. Grade 3 or 4 adverse events in mFOLFIRINOX or gemcitabine treatment arms were reported in 75.5% versus 51.1% of patients, including 12% grade 4 in each arm, with one death due to toxicity in the gemcitabine arm.

Ongoing clinical trials in the adjuvant setting include RTOG 0848 (ClinicalTrials.gov NCT01013649), which is assessing gemcitabine with or without subsequent chemoradiation, and a phase II study comparing FOLFIRINOX with albumin-bound paclitaxel (ClinicalTrials.gov NCT02243007).

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levo-leucovorin is equivalent to 400 mg/m^2 of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when

given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.[561] Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) leucovorin.[562] Also, the Mayo Clinic and North Central Cancer Treatment Group (NCCTG) determined that there was no therapeutic difference between the use of high- (200 mg/m^2) or low- (20 mg/m^2) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.[563] Finally, if none of the above options is 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.

Preoperative (Neoadjuvant) Therapy

The standard approach to therapy in patients with resectable disease has been postoperative treatment, with median survivals in the range of 20.1 to 23.6 months under the most optimal clinical trial conditions.[231,341,344,424] However, it is becoming increasingly apparent that patients with borderline resectable disease, who are at higher risk for R1 resections, are potentially in need of a different management approach. Contemporary approaches to perioperative treatment have focused on neoadjuvant therapy for patients with borderline resectable disease with the goal of improving OS.[411,414] Neoadjuvant therapy is also sometimes used in patients with resectable disease, especially in those with high-risk features. The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of patients with resectable disease will receive chemotherapy 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.[413,415,435,564] Moreover, surgery following neoadjuvant treatment appears to be safe.[565,566]

EUS-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 neoadjuvant therapy. Furthermore, patients for whom neoadjuvant therapy is planned should be assessed for jaundice, and placement of a stent (preferably a short, SEMS, as discussed in *Preoperative Biliary Drainage* above) is recommended prior to initiation of neoadjuvant therapy in patients with jaundice or after neoadjuvant therapy if clinically indicated.[513-515]

Retrospective analyses from patients at one NCCN Member Institution showed that neoadjuvant chemoradiation is associated with better local control, relative to neoadjuvant chemotherapy, though significant differences in survival were not found.[567] Practices vary with regard to chemotherapy and chemoradiation. Acceptable regimens include FOLFIRINOX, gemcitabine/albumin-bound paclitaxel, and gemcitabine/cisplatin (for patients with known *BRCA1/2* mutations).

Chemoradiation following chemotherapy is sometimes included in the neoadjuvant setting. Doses for neoadjuvant chemoradiation that have been reported include 36 Gy in 2.4 Gy/fraction, or 45 to 54 Gy in 1.8 to 2.0 Gy/fraction.[415,568] The role of chemoradiation with more active chemotherapy regimens needs to be tested.

Pancreatic protocol CT or MRI of the abdomen, and chest/pelvic CT should be repeated following neoadjuvant therapy, and staging laparoscopy can be considered at this time if not previously performed. 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. Importantly, results from retrospective studies suggest that radiographic response does not correlate with pathologic response.[569,570] Therefore, if no apparent tumor shrinkage is observed after neoadjuvant treatment and no extrapancreatic progressive disease is evident, surgery should still be attempted.

Neoadjuvant Therapy in Borderline Resectable Disease

Patients with borderline resectable disease should be considered for neoadjuvant therapy, followed by restaging and resection in patients without disease progression precluding surgery. The use of neoadjuvant therapy in the setting of borderline resectable disease has been a highly debated topic. However, although there is no high-level evidence supporting its use, most NCCN Member Institutions now prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease. If neoadjuvant therapy is recommended, treatment should preferably be administered at or coordinated through a high-volume center, when feasible. Upfront resection in patients with borderline resectable disease is no longer recommended, as of the 2016 version of these guidelines.

Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerated.[571-578] A phase I/II trial of neoadjuvant therapy in borderline resectable disease allowed 4 of 26 patients (15%) to be resected.[575] 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.[574] A multi-institutional phase II trial found that full-dose gemcitabine, oxaliplatin, and radiation given preoperatively to patients with resectable (n = 23), borderline resectable (n = 39), or unresectable disease (n = 6) found the approach to be feasible with an overall R0 resection rate of 53%.[573] In this study, 63% of all evaluable patients underwent resection, with 84% of those patients achieving an R0 resection.

In 2 retrospective reviews, 31% to 35% of patients with borderline resectable disease who completed neoadjuvant therapy had R0 resections.[579,580] A systematic review and meta-analysis of 19 cohort studies found that patients with unresectable disease (including both borderline resectable and unresectable) undergoing neoadjuvant chemoradiation therapy had similar 1-year survival outcomes as patients who were initially deemed resectable.[581] 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). In addition, the Alliance A021101 trial (NCT01821612) is a single-arm pilot study evaluating the safety and efficacy of FOLFIRINOX before capecitabine-based chemoradiation and surgery in this population.[436] Preliminary results including 22 patients from multiple centers showed that median OS was 21.7 months, and 68% of patients underwent resection.[577] Out of the 15 patients who underwent resection, all but one had negative margins, and 2 had a complete response. However, the number of grade 3 or higher adverse events was considerable, with 64% of patients experiencing one of these events. Other initial results in patient series suggest that neoadjuvant regimens including FOLFIRINOX are a promising approach in

patients with borderline resectable disease.[582-584] Chemotherapy followed by SBRT may also be safe and feasible in the neoadjuvant setting, and may improve the potential for resection in patients with borderline resectable or locally advanced disease.[332,585] However, further studies are needed before SBRT is recommended as a treatment option for patients with borderline resectable disease.

Neoadjuvant Therapy in Resectable Disease

An observational retrospective propensity score that matched analyses of 15,237 patients with resected pancreatic cancer showed that those who received neoadjuvant therapy had better OS than those who received upfront resection (median survival 26 months vs. 21 months, respectively; HR, 0.72; 95% CI, 0.68–0.78; $P < .01$).[586] A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[413,414,587-595] 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.[588] The authors suggest that preoperative therapy gives a selection advantage because 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.[588] 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.[588] The MD Anderson group has continued to champion this approach both for its ability to select patients for resection and for cost-effectiveness.[596]

Other potential advantages of the neoadjuvant approach in patients with resectable disease 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.[566,597,598]

Although most studies investigating the neoadjuvant experience in patients with resectable pancreatic cancer are retrospective, several small phase II studies have been published.[566,597,599,600] 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.[593]

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.[590] 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.[514] 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.[564] 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,[601] results of randomized trials addressing this issue are needed. A recent randomized phase II trial, which was terminated early because of slow accrual, compared gemcitabine/cisplatin neoadjuvant chemoradiation with upfront surgery; both arms received adjuvant chemotherapy.[602] With only 66 patients eligible for analysis, no significant differences were seen in R0 resection rate (52% vs. 48%), (y)pN0 rate (39% vs. 30%), or OS (25.0 months vs. 18.9 months), although all results favored the neoadjuvant arm and no safety issues were noted. The phase III NEOPA trial, with OS as the primary endpoint, is currently recruiting patients with resectable pancreatic cancer to compare neoadjuvant gemcitabine chemoradiation therapy to upfront surgery in this population (ClinicalTrials.gov NCT01900327)[603] and the randomized phase II SWOG 1505 trial, which is intended to establish benchmarking data for fluorouracil, irinotecan, and oxaliplatin and gemcitabine and albumin-bound paclitaxel (ClinicalTrials.gov NCT02562716). A phase II trial with R0 resection as the primary endpoint is also ongoing (ClinicalTrials.gov NCT01389440).

At this time, the panel does not recommend neoadjuvant therapy for clearly resectable patients without high-risk features, except in a clinical trial. There is limited evidence to recommend specific neoadjuvant regimens off study, and practices vary with regard to the use of chemotherapy and chemoradiation. For selected patients who appear technically resectable but have poor prognostic features (ie, markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; excessive weight loss; extreme pain) consideration can be given to neoadjuvant therapy after biopsy confirmation, and therapy should be administered preferably at or coordinated through a high-volume center.

Adjuvant Treatment After Neoadjuvant Therapy

For patients who received neoadjuvant treatment, data supporting additional therapy after surgery 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 and other clinical considerations, such as performance status and patient tolerability.

Adjuvant chemotherapy or adjuvant chemoradiation should only be considered for patients who have adequately recovered from surgery and have no evidence of recurrence or metastatic disease; treatment should ideally be initiated within 12 weeks. It is recommended that the patient undergo a pretreatment baseline assessment following surgery, including pancreas protocol CT scan (abdomen) and chest/pelvic CT with contrast, 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 imaging following systemic chemotherapy, if it will precede chemoradiation.

Surveillance of Patients with Resected Disease

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited,[604-606] 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 every 6 to 12 months as clinically indicated. CA 19-9 determinations and follow-up CT scans (chest, abdomen, and pelvis) with contrast 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, an analysis of the SEER-Medicare database showed no significant survival benefit for patients who received regular surveillance CT scans.[607]

Management of Recurrent Disease After Resection

As cross-sectional body imaging has improved, small-volume metastatic disease or local recurrence is being detected in patients with resected pancreatic cancer who are otherwise maintaining good functional status. As many as 50% of them will continue to maintain a sufficiently good performance status to consider recurrence therapy.[608] These patients will, however, ultimately progress.

For patients experiencing a recurrence of disease following resection, the panel recommends consideration of confirmatory biopsy (category 2B). In all cases of recurrent disease, a clinical trial is the preferred option; palliative and best supportive care without additional therapy should also be an option, especially for patients with poor performance status. In a pooled analysis of 55 patients who underwent pancreatectomy for recurrent pancreatic cancer, 1-, 3-, and 5-year survival rates were 82.2%, 49.2%, and 40.6%, respectively.[609] Therefore, for patients with local disease recurrence, surgical resection may be considered in select cases (ie, good performance status, location of recurrence is in the pancreas only). Chemoradiation can be considered in patients with local disease recurrence in the pancreatic bed, if radiation has not been previously administered, or a systemic chemotherapy regimen can be given. However, there are limited data to support specific RT recommendations for recurrent disease. For patients for whom there is evidence of metastatic disease (with or without a local recurrence), treatment decisions are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed less than 6 months prior to development of metastatic disease, the panel recommends that an alternative chemotherapy option be administered (eg, switching to a gemcitabine-based regimen if fluoropyrimidine-based therapy was previously used, or vice versa). When this period is 6 months or greater, repeating systemic therapy as previously administered or switching to any other systemic regimen is recommended.

Management of Isolated Pulmonary Metastases

Some patients have isolated lung metastases after resection of localized pancreatic adenocarcinoma. A growing body of evidence in this population suggests that these patients have a prolonged survival compared to patients with metastases in other locations.[610,611] Preliminary data also suggest that pulmonary metastasectomy may be advantageous in this population.[612] More data are needed before recommendations can be made regarding the management of pulmonary metastases of pancreatic cancers.

Palliative and Supportive Care

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that are, in many respects, unique to the 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.[613] 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 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 an RCT of 100 patients at a single center randomly assigned to receive either a plastic stent or a covered SEMS inserted endoscopically indicated that median patency times were 1.8 and 3.6 months (P = .002), respectively.[614] A meta-analysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.[615] 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. Another randomized trial showed that covered SEMS had longer patency than uncovered SEMS in the setting of biliary obstruction due to pancreatic cancer, because covered stents prevented the ingrowth of tumor.[616]

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.[617] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.[617]

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors following laparotomy, an open biliary-enteric bypass provides durable palliation of biliary obstruction and can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain. The panel recommends stenting or an open biliary-enteric bypass with or without gastrojejunostomy (category 2B for prophylactic gastrojejunostomy[618,619]) and with or without celiac plexus neurolysis [620-622] (category 2B in patients without pain). 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.[613]

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 gastrojejunostomy (category 2B for prophylactic gastrojejunostomy[618,619]) and with or without celiac plexus neurolysis (category 2B in patients without pain). 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. If cancer has not been biopsy-confirmed in the setting of locally advanced disease in a patient with jaundice, brushings can be obtained at the time of stent placement.

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10% to 25% of patients with pancreatic cancer.[613] 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 after biliary drainage is assured.[617] 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.[623-625] 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 RCTs have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer, the majority arising from the head of the pancreas.[618,619] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. A 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.[626] 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.[622] General principles for cancer-related pain management can be found in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). Patients with severe tumor-associated abdominal pain should be treated with around-the-clock analgesics. However, some patients will be unresponsive to analgesics or will experience undesirable side effects. Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, celiac plexus neurolysis should be considered (category 2B, except when indicated by pain in a patient with jaundice who is found unresectable at surgery, for which the recommendation is a category 2A). In several RCTs, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.[620,622,627] In a 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.[621] These patients reported better pain relief at 3 months (P = .01), suggesting that early EUS-guided celiac plexus neurolysis may be beneficial. A recent meta-analysis of 7 RCTs concluded that celiac plexus neurolysis improved pain scores at 4 weeks but not at 8 weeks in patients with pancreatic cancer.[628] The effectiveness of ethanol celiac plexus neurolysis for pain in resectable pancreatic and periampullary adenocarcinoma was examined in a recent RCT (N = 467).[629] The use of this technique was not found to significantly impact postoperative pain. 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 analgesic therapy, palliative RT may be considered to ameliorate pain, bleeding, and/or local obstructive symptoms, in the settings of both metastatic and non-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. The dose used should take into account the burden of disease, normal tissue tolerance, and expected survival.

Pancreatic Exocrine Insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or blockage of the pancreatic duct, or by surgical removal of pancreatic tissue, and results in an inadequate production of digestive enzymes.[630,631] This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.[632] Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency. Because pancreatic exocrine insufficiency occurs in up to 94% of patients undergoing pancreatic surgery,[633,634] 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.[632] A prospective double-blind phase II RCT including 67 patients with unresectable pancreatic cancer showed no significant difference in weight loss between patients randomized to receive pancreatic exocrine replacement therapy and patients randomized to receive a placebo.[635] For patients with disease that does not respond to this therapy, doses of the enzyme preparation can be increased, and inhibition of gastric secretion with a proton pump inhibitor can also be considered.[632,633] Patients with a clinical suspicion of pancreatic exocrine 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.[636,637] 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.[638]

Results from the CONKO 004 trial showed that patients randomized to receive enoxaparin (*n* = 160) experienced fewer symptomatic VTEs, relative to patients receiving chemotherapy only (*n* = 152) (HR, 0.40; 95% CI, 0.19–0.83; *P* = .01).[639] PFS and OS did not significantly differ between the two groups, however. In a pilot trial conducted in preparation for the CONKO 004 trial, 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.[640] The panel does not recommend prophylactic LMWH at this time, due to the lack of evidence regarding impact on survival. Please see the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease for more information (available at www.NCCN.org).

Bleeding From the Primary Tumor Site

GI bleeding in patients with pancreatic adenocarcinoma is hard to study because it is rare, but can carry a serious prognosis. [641] Various causes of GI bleeding include segmental portal hypertension,[642] gastric or duodenal ulcer erosion, and radiation-induced gastritis.[641] Treatment options for GI

bleeding should be used according to clinical judgement regarding the specifics of the patient's case. Endoscopic techniques[643] or RT,[644] when other options are not feasible, may be an effective treatment for GI bleeding. As a final attempt, upper GI bleeding may be stopped with angiography with embolization.[645,646]

One study of 246 eligible patients with pancreatic cancer, included 32 patients with GI bleeding of varying grade.[641] The median OS of patients with GI bleeding was 9 months and in patients without GI bleeding was 14.5 months. Conservative care was given to patients with bad physical state (11 patients), endoscopic hemostasis was given to 20 patients, and angiography and embolization were given to 1 patient. Therapeutic endoscopy was successful in 37.5% of patients and angiography with embolization was successful in 1 patient. Overall, 10.2% (25 patients) succumbed due to bleeding. The average time from GI bleeding to death was 31.5 days and the average OS rate was 10 months.

The panel recommends the following treatment options for bleeding from the primary tumor site: therapeutic endoscopy, if clinically indicated; RT, if not previously done; and angiography with embolization, if clinically indicated.

Depression, Pain, and Malnutrition

For many patients, a diagnosis of pancreatic cancer may result in significant psychosocial distress, including anxiety, depression, and sleep disturbances.[647] In fact, the suicide rate in male patients with pancreatic cancer is reportedly 11 times that of the general population.[648] 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 with a registered dietitian 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).

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.[649]

- 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 2011 consensus report from a group of European experts came to many of the same conclusions.[650] 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 to discuss current and future pancreatic cancer research and came to similar conclusions.[608] 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.[651] 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.

ASCO also recently convened a working group to discuss designs for pancreatic cancer clinical trials that would accomplish meaningful clinical improvements.[652] This group concluded OS should be the primary endpoint of first-line, metastatic pancreatic cancer trials. They also concluded that trials should aspire to a 3- to 4-month improvement in OS in gemcitabine-eligible and gemcitabine/albumin-bound paclitaxel-eligible patients and a 4- to 5-month improvement in OS for FOLFIRINOX-eligible patients to give results with true clinical impact.

A systematic review including 32 phase III trials showed that the following benchmarks for phase II trials were most predictive of a clinically meaningful phase III trial: 50% improvement in OS, 90% increase in 1-year survival, or 80% to 100% increase in PFS.[653]

To determine appropriate historic controls for single-arm phase II trials based on gemcitabine, an algorithm has been developed based on an analysis of a database of cooperative group trials that can be used to calculate historic benchmarks for OS and PFS.[654]

Neoadjuvant Clinical Trials

For neoadjuvant trials, study populations should be well-defined and standardized. The panel endorses use of a restrictive definition of borderline resectable disease in clinical trials, such as that defined in an Intergroup trial.[436] Endpoints should also be standardized and could include resection rates, R0 resection rates, local recurrence rates, pathologic response rates, DFS, and OS.[655]

Summary

Patients with borderline resectable disease and select patients with resectable disease can undergo neoadjuvant therapy in the hopes of improving the chances for an R0 resection. Patients with locally advanced disease and good performance status can undergo chemotherapy and

chemoradiation or SBRT with second-line therapy if performance status is maintained after progression. Patients with good performance status 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 poor outcomes for patients with all stages of pancreatic cancer, the NCCN Panel recommends that investigational options be considered in all phases of disease management.

Table 1: Selected Genetic Syndromes with Associated Pancreatic Cancer Risk

Syndrome	Gene	Estimated Cumulative Risk of Pancreatic Cancer	Estimated Increased Risk Compared to General Population
Peutz-Jeghers syndrome	*STK11*	11%–36% by age 65–70 years[74]	132-fold[73]
Familial pancreatitis	*PRSS1, SPINK1, CFTR*	40%–53% by age 70–75 years[78-80]	26-fold to 87-fold[35,78-80]
Melanoma-pancreatic cancer syndrome	*CDKN2A*	14% by age 70[656] 17% by age 75 years[83]	20-fold to 47-fold[82,83]
Lynch syndrome	*MLH1, MSH2 (MSH6)*	4% by age 70 years[91]	9-fold to 11-fold[91,92]
Hereditary breast-ovarian cancer syndrome	*BRCA1, BRCA2*	1.4%–1.5% (women) and 2.1%–4.1% (men) by age 70[94,99]	2.4-fold to 6-fold[94,98,99]
Familial pancreatic cancer	Unknown in most families (family X is an exception)*	≥3 first-degree relatives with pancreatic cancer: 7%–16% by age 70[62] 2 first-degree relatives with pancreatic cancer: 3% by age 70[62]	≥3 first-degree relatives with pancreatic cancer: 32-fold[67] 2 first-degree relatives with pancreatic cancer: 6.4-fold[67] 1 first-degree relative with pancreatic cancer: 4.6-fold[67]

*One family (family X) with a mutation in the *palladin* (*PALLD*) gene has been identified.[657]

Table 2: Potential Indications for Various Therapies in the Treatment of Pancreatic Adenocarcinoma

Regimen	Resectable (adjuvant)	Borderline Resectable/ Resectable (neoadjuvant)	Locally Advanced (category recommendations for good performance status only unless otherwise noted)	Metastatic (category recommendations for good performance status only unless otherwise noted)	Second-Line Therapy (good performance status only unless otherwise noted)
Gemcitabine	√ (category 1)		√ (category 1 for poor performance status)	√ (category 1 for good and poor performance status)	√ (if previously treated with fluoropyrimidine-based therapy; or category 1 for poor performance status)
Gemcitabine/albumin-bound paclitaxel		√	√	√ (category 1; preferred)	√ (if previously treated with fluoropyrimidine-based therapy)
Gemcitabine/erlotinib			√	√ (category 1)	√ (if previously treated with fluoropyrimidine-based therapy)
Gemcitabine/cisplatin		√ (only for known *BRCA1/2* mutations)	√ (only for known *BRCA1/2* mutations)	√ (only for known *BRCA1/2* mutations)	√ (if previously treated with fluoropyrimidine-based therapy, only for known *BRCA1/2* mutations)
Gemcitabine/ capecitabine	√ (category 1)		√	√	
Fixed-dose-rate gemcitabine			√ (poor performance status only; category 2B)	√ (poor performance status only; category 2B)	√ (poor performance status only; category 2B)
GTX [fixed-dose-rate gemcitabine/docetaxel/ capecitabine]			√ (category 2B)	√ (category 2B)	

5-FU/leucovorin	√ (category 1)				
5-FU/ leucovorin/liposomal irinotecan					√ (if previously treated with fluoropyrimidine-based therapy and no prior irinotecan; or category 1 if previously treated with gemcitabine-based therapy and metastatic disease)
5-FU/ leucovorin/irinotecan (FOLFIRI)					√ (if previously treated with gemcitabine-based therapy)
FOLFIRINOX		√	√	√ (category 1; preferred)	√ (if previously treated with gemcitabine-based therapy)
Capecitabine	√ (category 2B)		√ (good and poor performance status; category 2B)	√ (poor performance status only; category 2B)	√ (if previously treated with gemcitabine-based therapy; or category 2B for poor performance status)
Continuous infusion 5-FU	√		√ (category 2B)	√ (poor performance status only; category 2B)	√ (if previously treated with gemcitabine-based therapy; or category 2B for poor performance)
Fluoropyrimidine/ oxaliplatin (eg, OFF, FOLFOX, CapeOx)			√ (category 2B)	√ (category 2B)	√ (if previously treated with gemcitabine-based therapy)
Chemoradiation	√ (following induction chemotherapy, with or without subsequent chemotherapy)	√ (subsequent chemoradiation is sometimes included)	√ (in select patients who are not candidates for combination therapy, and following induction chemotherapy in select patients without systemic metastases)		√ (if locally advanced disease; if not previously given; and if primary site is the sole site of progression)
Pembrolizumab					√ (only for MSI-H or dMMR tumors)

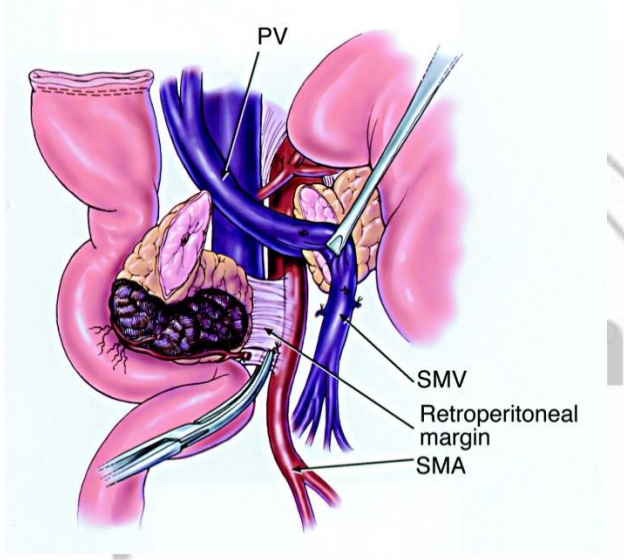


Figure 1. Complete mobilization of the superior mesenteric (SMV) and portal veins (PVs), and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA).[658]

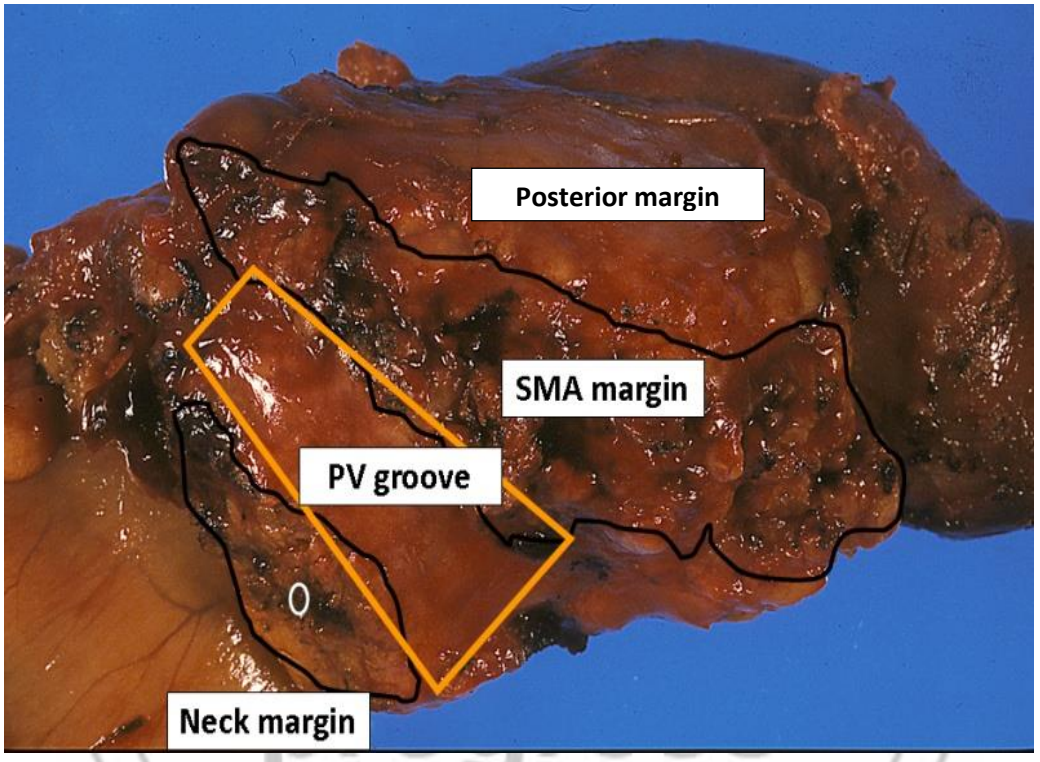
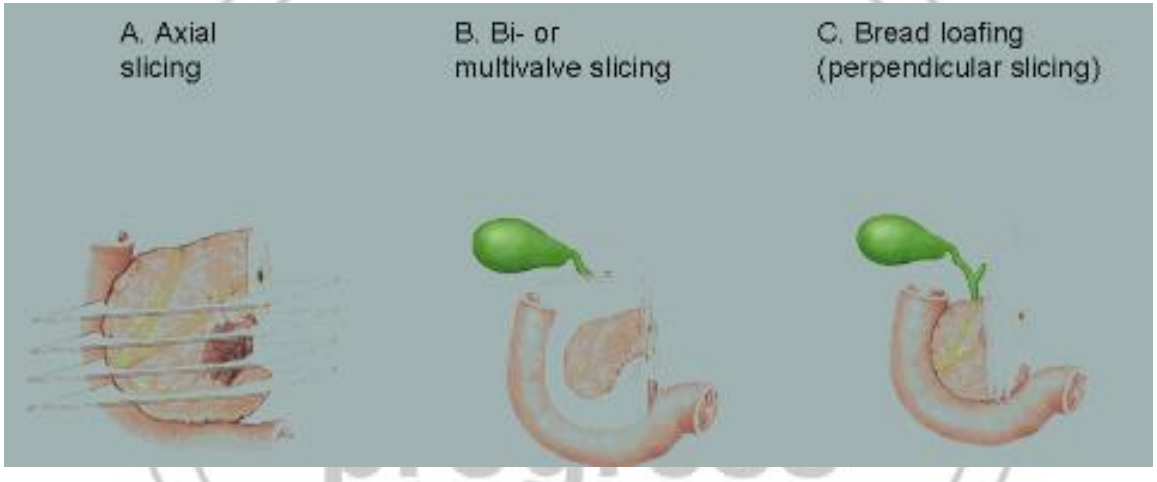


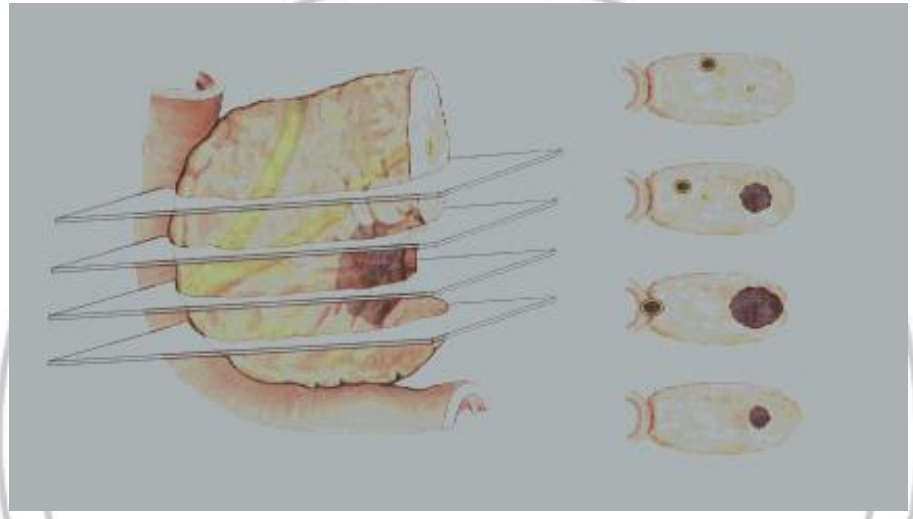
Image courtesy of Dr. N. Volkan Adsay

Figure 2. Whipple specimen with labeled margins.



Courtesy of Mr. Paul Brown, Specialist Medical Illustrator, St James's University Hospital Leeds

Figure 3. Slicing of pancreatoduodenectomy specimens.[535]



Courtesy of Mr. Paul Brown, Specialist Medical Illustrator, St James's University Hospital Leeds

Figure 4. Slicing of the pancreatoduodenectomy specimen in the axial plane to allow circumferential assessment of tumor.[535]

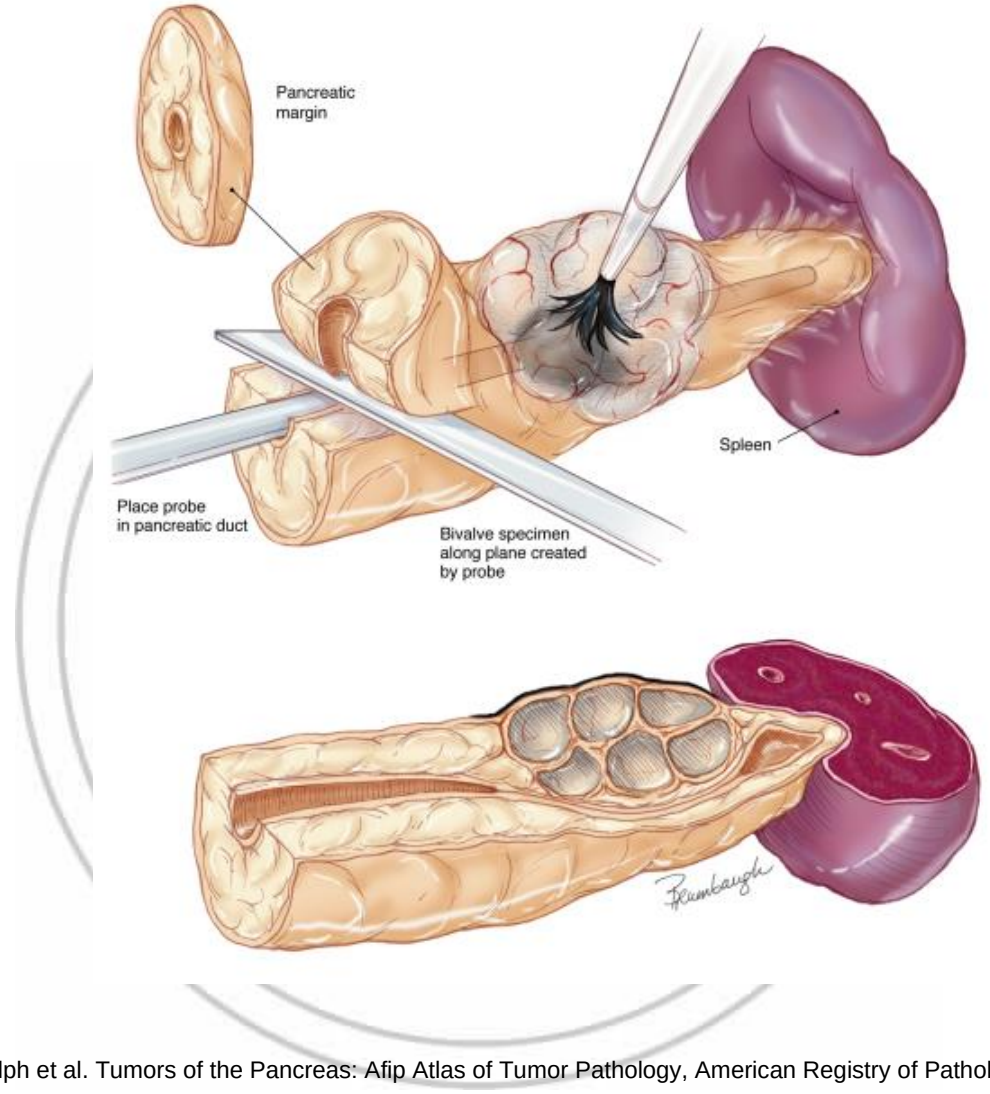


Figure 16-4, from Hruban, Ralph et al. Tumors of the Pancreas: Afip Atlas of Tumor Pathology, American Registry of Pathology, Washington DC 2007

Figure 5. Slicing of the distal pancreatectomy specimen.[551]

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