National Comprehensive Cancer Network®

NCCN

Pancreatic Adenocarcinoma, Version 2.2017

Clinical Practice Guidelines in Oncology

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Abstract

Ductal adenocarcinoma and its variants account for most pancreatic malignancies. High-quality multiphase imaging can help to preoperatively distinguish between patients eligible for resection with curative intent and those with unresectable disease. Systemic therapy is used in the neoadjuvant or adjuvant pancreatic cancer setting, as well as in the management of locally advanced unresectable and metastatic disease. Clinical trials are critical for making progress in treatment of pancreatic cancer. The NCCN Guidelines for Pancreatic Adenocarcinoma focus on diagnosis and treatment with systemic therapy, radiation therapy, and surgical resection.

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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 noted.

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

Overview

Pancreatic cancer is one of the most common causes of cancer-related death among men and women in the United States.[1] 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

Please Note

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Disclosures for the Pancreatic Adenocarcinoma Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Pancreatic Adenocarcinoma Panel members can be found on page 1061. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

factors[2–4]; mortality rates have remained largely unchanged.[5,6]

As an overall guiding principle of these NCCN Guidelines, the NCCN Pancreatic Adenocarcinoma 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. Multidisciplinary review should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, and pathology; consultation with a registered dietitian should also be considered. In addition, the panel believes that increasing participation in clinical trials is critical to making progress in this disease.

Diagnosis and Staging

Ductal adenocarcinoma and its variants account for >90% of all pancreatic malignancies. 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. Numerous studies have shown an association between new-onset non–insulin-dependent diabetes and the development of pancreatic cancer.[7–9] Therefore, new-onset diabetes in an otherwise fit individual might prompt consideration of early-stage pancreatic cancer. Screening for this disease is generally only recommended for asymptomatic individuals at increased risk.[10]

Text cont. on page 1045.

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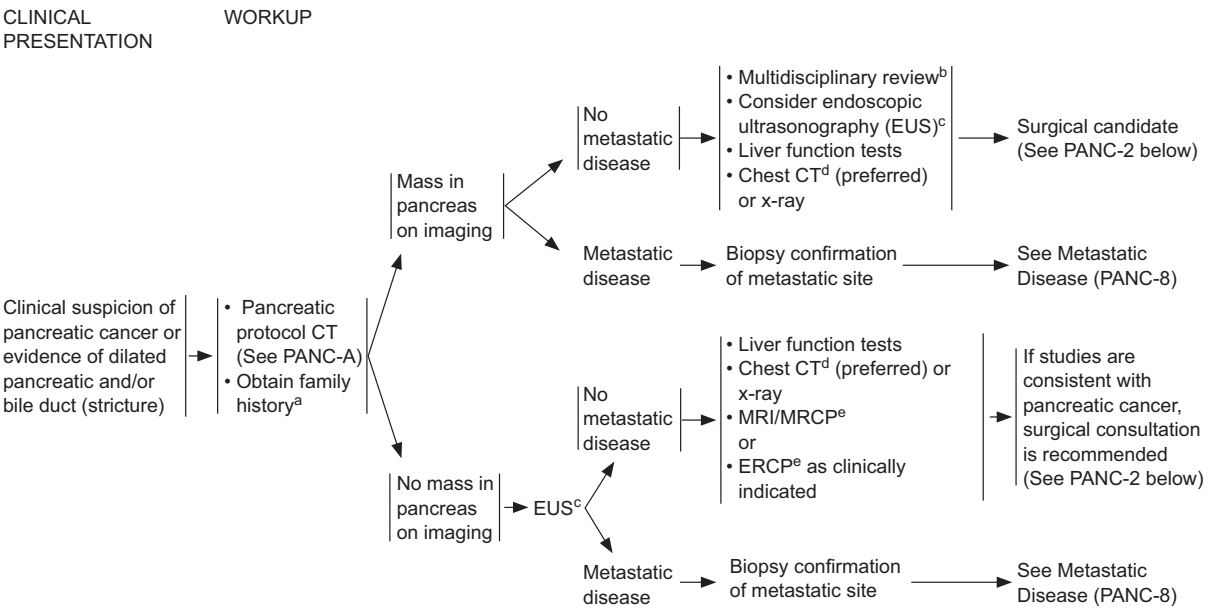


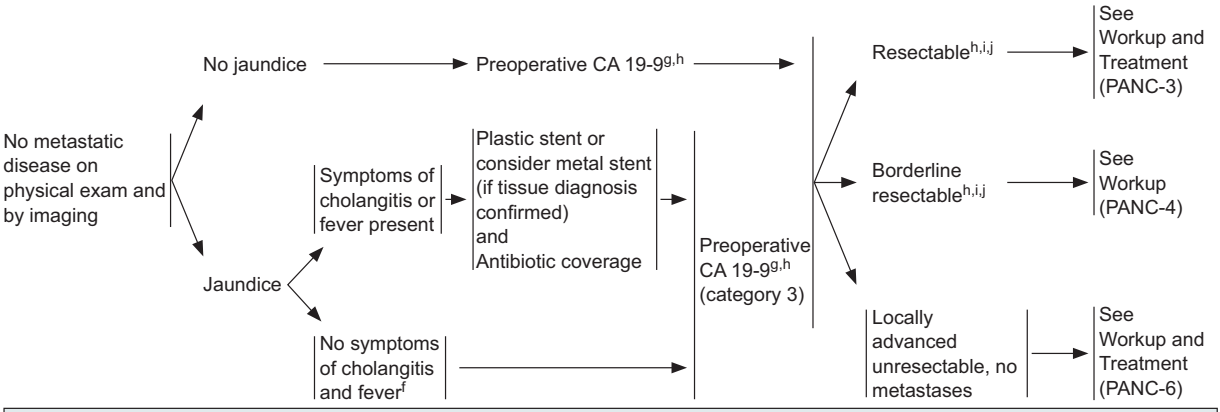
[a]If pancreatic cancer is diagnosed, consider referral for genetic counseling for patients who are young, those with a family history of cancer, or those of Ashkenazi Jewish ancestry.

[b]Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology. Consider consultation with a registered dietitian.

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

[d]Imaging with contrast unless contraindicated.

[e]MRCP = magnetic resonance cholangiopancreatography; ERCP = endoscopic retrograde cholangiopancreatography



[f]Plastic or consider self-expanding metal stent (if tissue diagnosis confirmed) as clinically indicated in patients with select comorbidities or when surgery may be delayed. (See Discussion)

[g]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)

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

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

[j]See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D, available online, in these guidelines, at NCCN.org).

PANC-1
PANC-2

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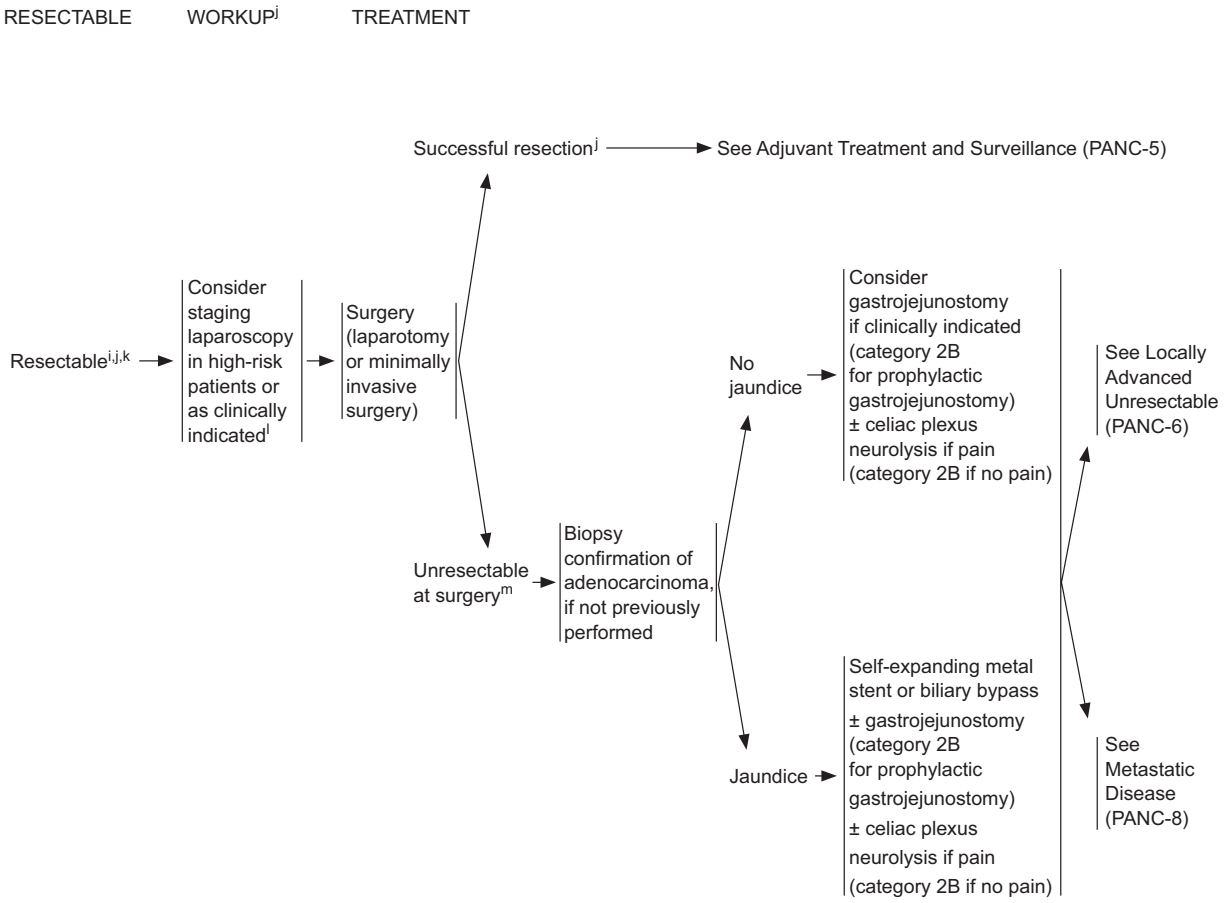


*Available online, in these guidelines, at NCCN.org.

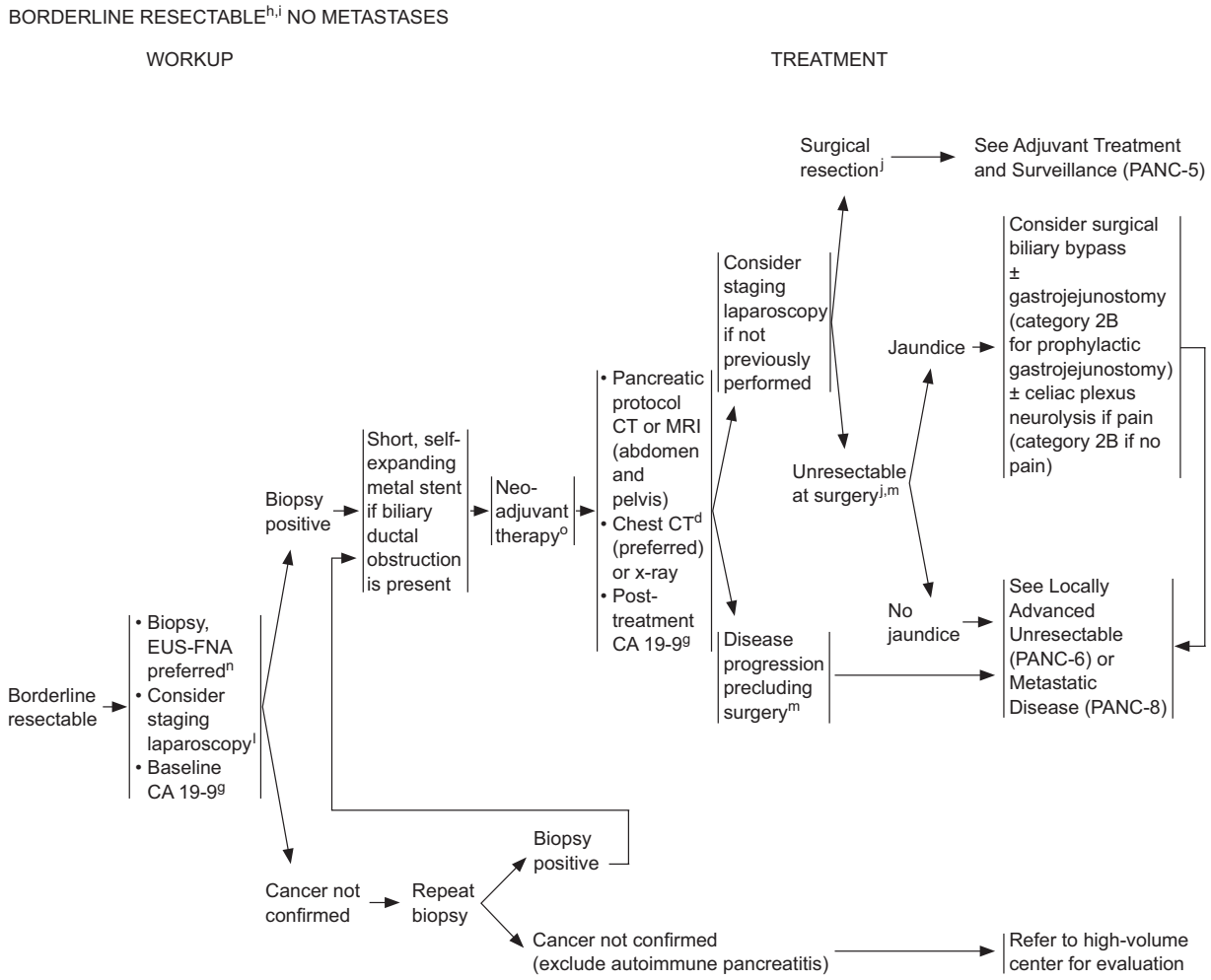
[i]See Criteria Defining Resectability Status (PANC-B).

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

[k]For patients with tumors that are clearly resectable and who do not have high-risk features, neoadjuvant therapy is only recommended in a clinical trial. For patients with high-risk features (ie, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain), neoadjuvant chemotherapy may be considered, which requires biopsy confirmation of adenocarcinoma (see PANC-4). See PANC-G for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included (see PANC-F*). Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center.

[l]See Principles of Diagnosis, Imaging, and Staging #8 (PANC-A, 2 of 8*).

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



*Available online, in these guidelines, at NCCN.org.

[d]Imaging with contrast unless contraindicated.

[g]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)

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

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

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

[l]See Principles of Diagnosis, Imaging, and Staging #8 (PANC-A, 2 of 8*).

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

[n]See Principles of Diagnosis, Imaging, and Staging #1 and #7 (PANC-A, 1 and 2 of 8*).

[o]There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. See PANC-G for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included (see PANC-F, available online, in these guidelines, at NCCN.org). Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.

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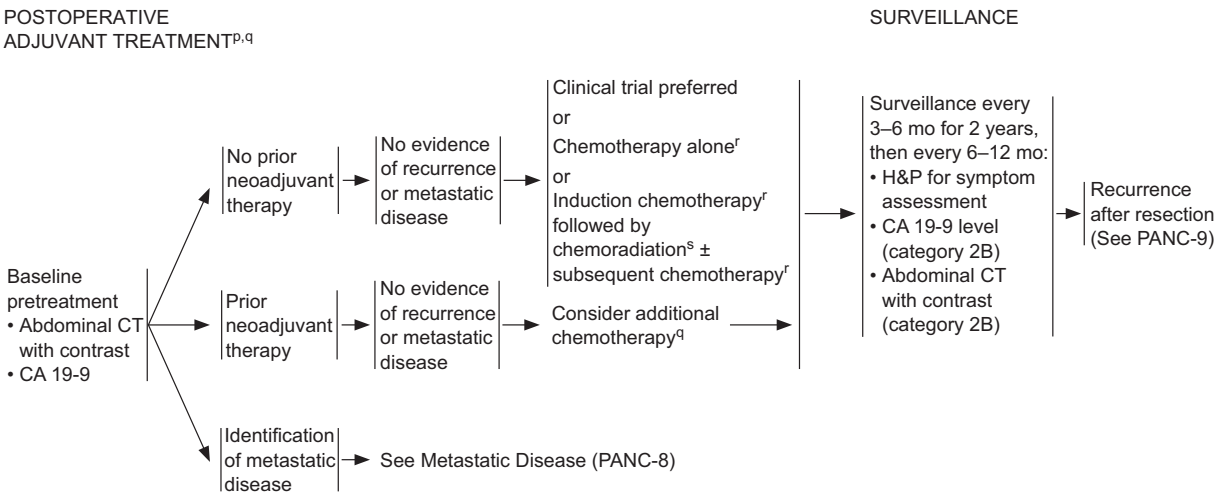
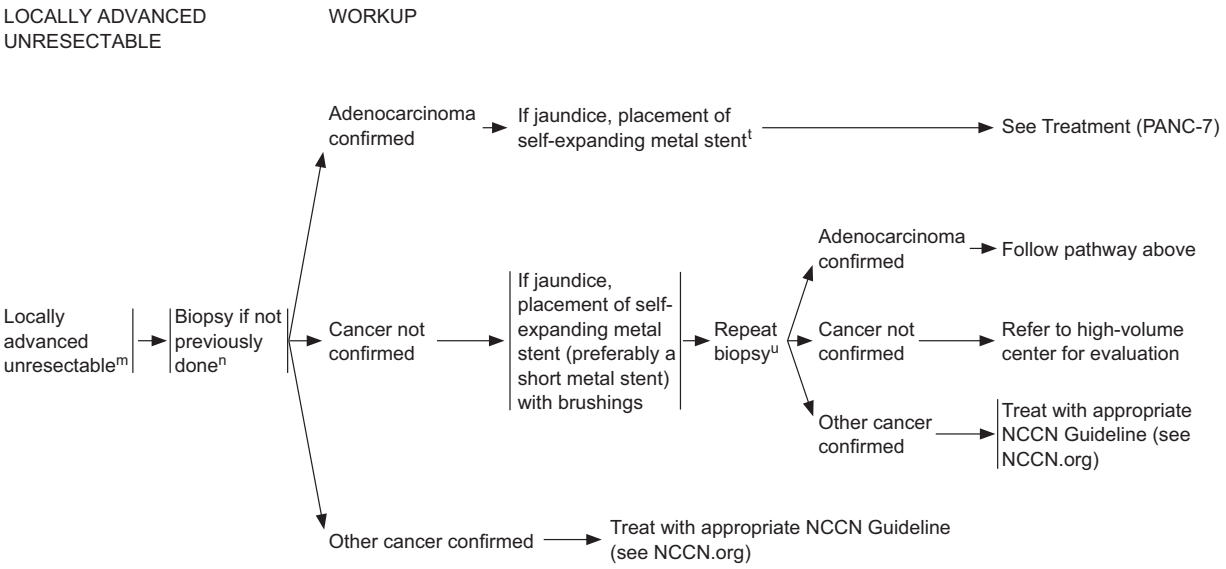


[p]Adjuvant treatment should be administered to patients who have not had neoadjuvant chemotherapy and who have adequately recovered from surgery; treatment should be initiated within 12 weeks. If systemic chemotherapy precedes chemoradiation, restaging with imaging should be done after each treatment modality.

[q]Patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. The adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

[r]See Principles of Chemotherapy (PANC-G).

[s]See Principles of Radiation Therapy (PANC-F, available online, in these guidelines, at NCCN.org).



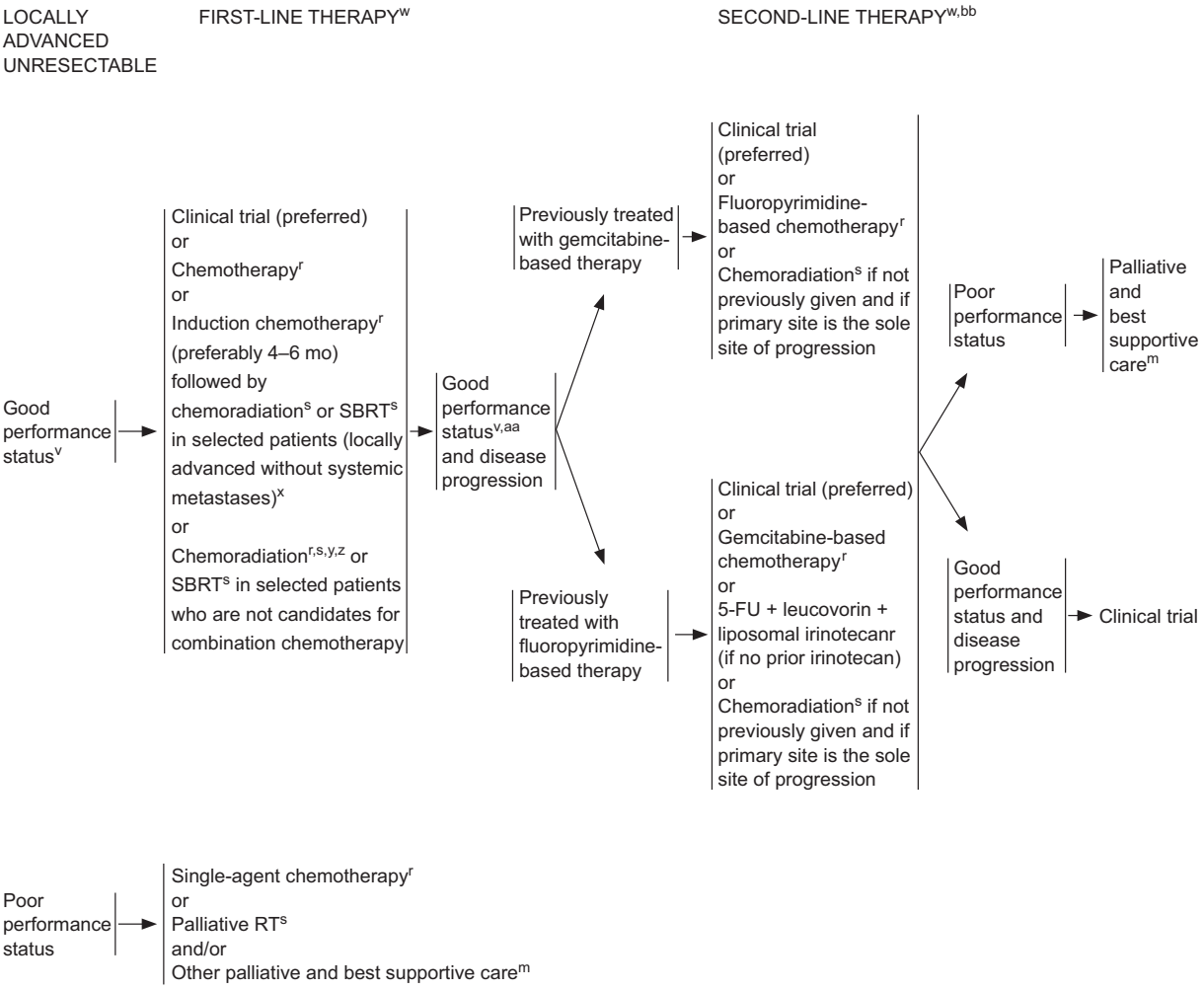
[m]See Principles of Palliation and Supportive Care (PANC-E, available online, in these guidelines, at NCCN.org).

[n]See Principles of Diagnosis, Imaging, and Staging #1 and #7 (PANC-A, 1 and 2 of 8, available online, in these guidelines, at NCCN.org).

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

[u]EUS-FNA ± core biopsy at a center with multidisciplinary expertise is preferred.

PANC-5
PANC-6



*Available online, in these guidelines, at NCCN.org.

[m]See Principles of Palliation and Supportive Care (PANC-E*).
[r]See Principles of Chemotherapy (PANC-G).
[s]See Principles of Radiation Therapy (PANC-F*).
[v]Defined as ECOG 0-1 with patent biliary stent and adequate nutritional intake.
[w]See Principles of Diagnosis, Imaging, and Staging #10 (PANC-A, 2 of 8*).
[x]Laparoscopy as indicated to evaluate distant disease.
[y]Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy.
[z]Based on preliminary data from the LAP-07 trial, 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. (Huguet F, et al. Impact of chemoradiotherapy on local control and time without treatment in patients with locally advanced pancreatic cancer included in the international phase III LAP 07 study [abstract]. J Clin Oncol 2014;32(Suppl):Abstract 4001.)
[aa]Patients with a significant response to therapy may be considered for surgical resection.
[bb]Best reserved for patients who maintain a good performance status.

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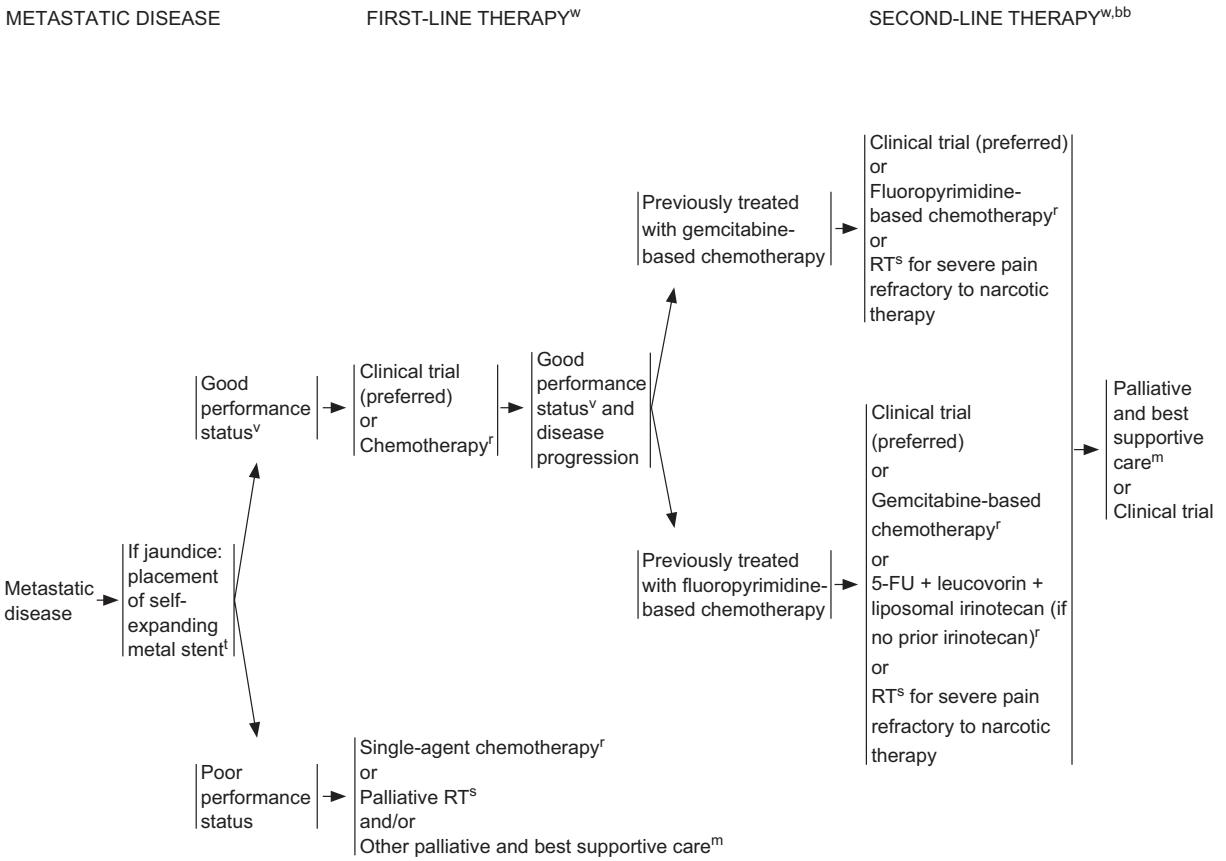

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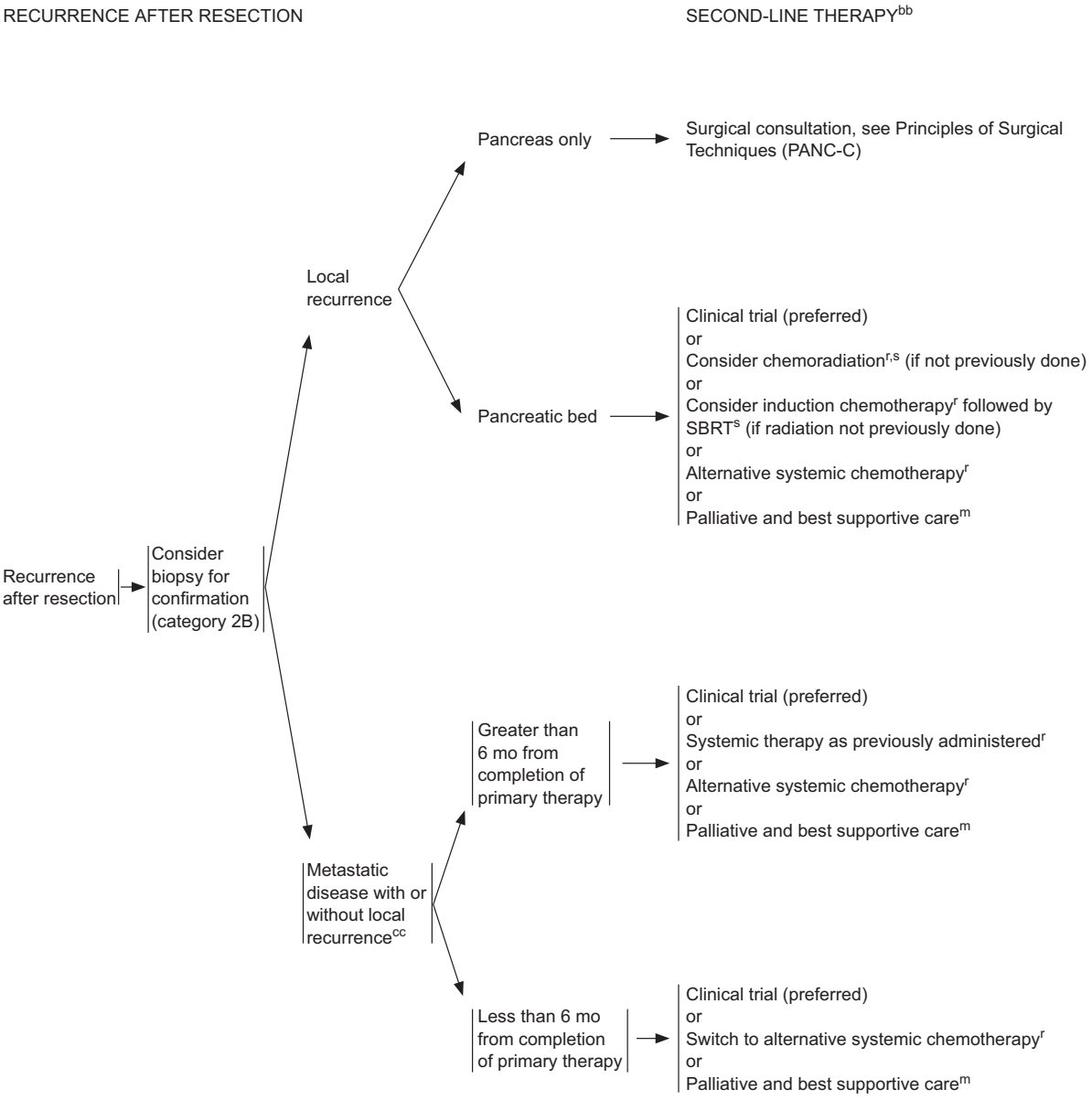
[m]See Principles of Palliation and Supportive Care (PANC-E*).
[r]See Principles of Chemotherapy (PANC-G).
[s]See Principles of Radiation Therapy (PANC-F*).
[t]Unless biliary bypass performed at time of laparoscopy or laparotomy.
[v]Defined as ECOG 0-1 with patent biliary stent and adequate nutritional intake.
[w]See Principles of Diagnosis, Imaging, and Staging #10 (PANC-A, 2 of 8*).
[bb]Best reserved for patients who maintain a good performance status.



*Available online, in these guidelines, at NCCN.org.

[m]See Principles of Palliation and Supportive Care (PANC-E*).
[r]See Principles of Chemotherapy (PANC-G).
[s]See Principles of Radiation Therapy (PANC-F*).
[bb]Best reserved for patients who maintain a good performance status.
[cc]For more information about the treatment of isolated pulmonary metastases, see Discussion.

PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING
PANCREATIC CANCER RADIOLOGY REPORTING TEMPLATE[1]

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)	☐ 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	

Reporting Template continued on following pages

[1]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;270:248-260.

PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING
PANCREATIC CANCER RADIOLOGY REPORTING TEMPLATE[1]

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		

Reporting Template continued on following page

[1]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;270:248-260.

PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING
PANCREATIC CANCER RADIOLOGY REPORTING TEMPLATE[1]

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	

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

[1]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;270:248-260.

PANC-A
7 AND 8 OF 8

CRITERIA DEFINING RESECTABILITY STATUS[1]

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[2]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis 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 should be noted if present as it may affect surgical planning. Pancreatic body/tail: • 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 members prefer this criteria to be in the unresectable 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).
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

[1]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.

[2]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. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions.

PANC-B

PRINCIPLES OF SURGICAL TECHNIQUE

Pancreatoduodenectomy (Whipple technique)

The goals of surgical extirpation of pancreatic carcinoma focus on the achievement of an R0 resection, as a margin-positive specimen is associated with poor long-term survival.[1,2] Achievement of a margin-negative dissection must focus on meticulous perivascular dissection of the lesion in resectional procedures, recognition of the need for vascular resection and/or reconstruction, and the potential need for 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 superior mesenteric artery down to the level of the adventitia will maximize uncinate yield and radial margin.[3,4]
- In the absence of frank venous occlusion noted on preoperative imaging, the need for lateral venorrhaphy or complete portal or 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, although acceptance of this concept (particularly with respect to vein resection) is not universal.
- While further data with respect to arterial resection are clearly needed, judicious utilization of this technique would appear to be reasonable in very select populations.

Distal Pancreatectomy

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

- An R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.[5,6]
- Similar to the Whipple procedure, lateral venorrhaphy, vein excision and reconstruction, and dissection to the level of the celiac axis and SMA adventitia should be performed if complete tumor clearance can be achieved.[5,7]
- Spleen preservation is not indicated in adenocarcinoma.

[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.

[5]Shoup M, Conlon KC, Klimstra D, et al. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? J Gastro Surg 2003;7:946-952; discussion 952.

[6]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.

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PRINCIPLES OF CHEMOTHERAPY (1 of 6 and 2 of 6)

General Principles:

- Systemic therapy is used in all stages of pancreatic cancer, including neoadjuvant (resectable or borderline resectable), adjuvant, locally advanced unresectable, and metastatic disease.
- Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.
- Close follow-up of patients undergoing chemotherapy is indicated.
- For regimens where RT or chemoradiation is included, see Principles of Radiation Therapy (PANC-F, available online, in these guidelines, at NCCN.org) for more details related to radiation delivery, including recommended technique and dose.

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, consulation at a high-volume center is preferred. When feasible, treatment with neoadjuvant therapy at or coordinated through a high-volume center is preferred. Participation in a clinical trial is encouraged.

- Options include:
  - FOLFIRINOX ± subsequent chemoradiation*
  - Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation*
  - Gemcitabine + cisplatin (≥2–6 cycles) followed by chemoradiation* (reserved for patients with *BRCA1/BRCA2* or other DNA repair mutations)

Adjuvant Therapy

- The CONKO 001 trial demonstrated significant improvements in disease-free survival and overall survival with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[1]
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[2]
- Data from ESPAC-4 support the use of gemcitabine combined with capecitabine (1,660 mg/m2/d d1–21 q 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.

- Options include:
  - Gemcitabine (category 1)
  - 5-FU/leucovorin (category 1)
  - Gemcitabine + capecitabine (category 1)
  - Continuous infusion 5-FU (CI 5-FU)
  - Capecitabine (category 2B)
  - Induction chemotherapy (gemcitabine, 5-FU/leucovorin, or CI 5-FU) followed by chemoradiation*
  - Induction chemotherapy (gemcitabine, 5-FU/leucovorin, or CI 5-FU) followed by chemoradiation* followed by subsequent chemotherapy:[4]
    - Gemcitabine followed by chemoradiation* followed by gemcitabine
    - Bolus 5-FU/leucovorin followed by chemoradiation* followed by bolus 5-FU/leucovorin
    - CI 5-FU followed by chemoradiation* followed by CI 5-FU

*Chemoradiation:
- Fluoropyrimidine (capecitabine, CI 5-FU, or 5-FU/cisplatin) + concurrent RT (preferred)
- Gemcitabine + concurrent RT[5]

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PRINCIPLES OF CHEMOTHERAPY (3 of 6 and 4 of 6)

Locally Advanced/Unresectable Disease (First-Line Therapy)

- Depending on performance status, mono- or combination systemic chemotherapy may be considered as initial therapy prior to radiation (chemoradiation or SBRT) for appropriate patients with locally advanced, unresectable disease.[a]
- Patients should be evaluated for recovery from hematologic and non-hematologic toxicity prior to initiation of chemoradiation.

- Options for patients with good performance status include:
  - FOLFIRINOX[a,b,6]
  - Gemcitabine + albumin-bound paclitaxel[a,7]
  - Gemcitabine + erlotinib[c,8]
  - Gemcitabine + capecitabine[9]
  - Gemcitabine + cisplatin[10] (especially for patients with *BRCA1/BRCA2* or other DNA repair mutations)
  - Gemcitabine
  - Capecitabine (category 2B)
  - CI 5-FU (category 2B)
  - Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B)
  - Fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin[12] or CapeOx[13])
  - Induction chemotherapy with any of the chemotherapy options above (≥4–6 cycles) followed by chemoradiation[*,d] or SBRT[14] (in selected patients, locally advanced disease without systemic metastases)[15]
  - Chemoradiation[*,e] or SBRT[e] (in select patients who are not candidates for combination therapy)

- Options for patients with poor performance status include:
  - Gemcitabine
    - 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1)
    - Fixed-dose-rate gemcitabine (10 mg/m^2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)
  - Capecitabine (category 2B)
  - CI 5-FU (category 2B)

Metastatic Disease (First-Line Therapy)

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

- Options for patients with good performance status include:
  - FOLFIRINOX[b,f,6] (category 1) (preferred)
  - Gemcitabine + albumin-bound paclitaxel[f,7] (category 1) (preferred)
  - Gemcitabine + erlotinib[c,8] (category 1)
  - Gemcitabine (category 1)
  - Gemcitabine + capecitabine[9]
  - Gemcitabine + cisplatin[10] (Can be considered as an alternative to FOLFIRINOX in patients with possible hereditary cancers involving DNA repair mutations)
  - Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B)
  - Fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin[12] or CapeOx[13])

- Options for patients with poor performance status include:
  - Gemcitabine
    - 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1)
    - Fixed-dose-rate gemcitabine (10 mg/m^2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)
  - Capecitabine (category 2B)
  - CI 5-FU (category 2B)

*Chemoradiation:
- Fluoropyrimidine (capecitabine, CI 5-FU, or 5-FU/cisplatin) + concurrent RT (preferred)
- Gemcitabine + concurrent RT[5]

See Second-Line Therapy on PANC-G (5 of 6)

[a]The recommendations for FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.

[b]Due to the high toxicity of this regimen, bolus 5-FU is often omitted.

[c]Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

[d]Based on preliminary data from the LAP-07 trial, 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]

[e]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-F, available online, in these guidelines, at NCCN.org).

[f]FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with KPS ≥70. 5-FU + leucovorin + liposomal irinotecan is a reasonable second-line option for patients with KPS ≥70.

PRINCIPLES OF CHEMOTHERAPY (5 of 6)

Second-line Therapy for Locally Advanced/Unresectable/Metastatic Disease and Good Performance Status

- If previously treated with gemcitabine-based therapy, options include:
  - 5-FU + leucovorin + liposomal irinotecan[f,17] (category 1 for metastatic disease)
  - FOLFIRINOX[f]
  - Oxaliplatin/5-FU/leucovorin
  - FOLFOX
  - Capecitabine/oxaliplatin
  - Capecitabine
  - CI 5-FU
  - Chemoradiation* (Only for locally advanced disease; if not previously given, and if primary site is the sole site of progression)
- If previously treated with fluoropyrimidine-based therapy, options include:
  - Gemcitabine + albumin-bound paclitaxel[f]
  - Gemcitabine
  - Gemcitabine + cisplatin
  - Gemcitabine + erlotinib
  - 5-FU + leucovorin + liposomal irinotecan (if no prior irinotecan)
  - Chemoradiation* (Only for locally advanced disease; if not previously given, and if primary site is the sole site of progression)

Recurrent Disease

- If resected patients with good performance status relapse after receiving adjuvant therapy, FOLFIRINOX or gemcitabine + albumin-bound paclitaxel are options depending on the length of time since completion of adjuvant therapy.

*Chemoradiation:
- Fluoropyrimidine (capecitabine, CI 5-FU, or 5-FU/cisplatin) + concurrent RT (preferred)
- Gemcitabine + concurrent RT[5]

[f]FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with KPS ≥70. 5-FU + leucovorin + liposomal irinotecan is a reasonable second-line option for patients with KPS ≥70.

PRINCIPLES OF CHEMOTHERAPY (6 of 6)

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PANC-G
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Cont. from page 1029.

Unlike many other cancers, imaging is the primary modality through which pancreatic cancer stage is determined. High-quality, multiphase 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 those with a potentially resectable tumor.[11] 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.[12]

Imaging Evaluations

Pancreatic Protocol CT and MRI: Multidetector CT angiography—performed by acquiring thin, preferably submillimeter, 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. Studies have shown that 70% to 85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.[11,13–16] 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 tumors are not visible on CT or in cases of contrast allergy.[17,18]

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 multiphasic pancreatic protocol also allows for enhanced visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], and hepatic artery) and venous structures (eg, superior mesenteric vein [SMV], splenic vein, portal vein), thereby providing an assessment of vascular invasion by the tumor. All of this information can improve the prediction of resectability.

Recently, a multidisciplinary expert consensus group defined standardized language for the reporting of imaging results.[12] 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 uniform reporting also ensures a complete assessment and reporting of all imaging criteria essential for optimal staging and can therefore aid in determining optimal management. Use of the radiology staging reporting template is thus recommended by the NCCN Panel.

Other Imaging Techniques: NCCN Member Institutions vary in the use of additional staging technologies, such as endoscopic ultrasound (EUS). An analysis of 20 studies and 726 cases of pancreatic cancer showed that EUS for T1–T2 staging has a sensitivity and specificity of 0.72 and 0.90, respectively.[19] Sensitivity and specificity for T3–T4 staging is 0.90 and 0.72, respectively. 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 lymph nodes outside the resection zone (ie, distant disease).[20–23] 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.

The role of endoscopic retrograde cholangiopancreatography (ERCP) is mainly therapeutic and used for relief of jaundice in select instances. It is recommended as clinically indicated for patients without a pancreatic mass and no evidence of metastatic disease who require biliary decompression and undergo additional imaging with EUS to help establish a diagnosis.[24] 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.[25–27] MRI/magnetic resonance cholangiopancreatography is considered to be equivalent to EUS/ERCP in the diagnostic setting.

Laparoscopy

Laparoscopy is another potentially valuable diagnostic tool for staging; it can identify peritoneal, capsu-

lar, or serosal implants or studding of metastatic tumor on the liver that may be missed with a pancreatic CT protocol.[28–30] Laparoscopic yield 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 for whom curative-intent surgery is planned,[29] although routine use of staging laparoscopy is controversial. The panel does not consider staging laparoscopy to be a substitute for poor-quality preoperative imaging.

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 before surgery or chemoradiation (chemoRT), or selectively in patients at higher risk for disseminated disease, such as those with markedly elevated CA 19-9 levels. Thus, the panel believes that staging laparoscopy can be considered for patients staged with resectable pancreatic cancer considered to be at increased risk for disseminated disease and for patients with borderline resectable disease before administration of neoadjuvant therapy.

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, unresectable pancreatic cancer or metastatic disease. A pathologic diagnosis of adenocarcinoma of the pancreas is most frequently 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 increased diagnostic yield, safety, and a potential lower risk of peritoneal seeding.[31–33] EUS-FNA also provides the benefit of additional staging information at time of biopsy and is highly accurate and reliable for determining malignancy.[34]

If a biopsy does not confirm malignancy, at least 1 repeat biopsy should be performed; EUS-FNA with or without a core needle biopsy at a high-volume center is preferred. A positive biopsy is required before chemotherapy administration. 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 there is high clinical suspicion of pancreatic cancer.

Biomarkers

The NCCN 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 "Design of Clinical Trials," page 1054). 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 a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 80% to 90% in symptomatic patients,[35] but its low positive predictive value makes it a poor biomarker for screening.[36] Furthermore, CA 19-9 may be falsely positive in cases of biliary infection (cholangitis), inflammation, or biliary obstruction (regardless of etiology), and it does not necessarily indicate cancer or advanced disease.[37,38] Preoperative CA 19-9 levels correlate with both AJCC staging and resectability and can thus provide additional information for staging and determining resectability, along with information from imaging, laparoscopy, and biopsy.[39–41] The panel recommends measurement of serum CA 19-9 levels before surgery (category 3 recommendation), after surgery immediately before administration of adjuvant therapy, and for surveillance (category 2B) if the level is abnormally elevated at diagnosis.

Systemic Therapy Approaches for Locally Advanced or Metastatic Disease

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.[42] The panel recommends gemcitabine monotherapy as an option for frontline therapy for patients with metastatic disease (category 1) or locally advanced disease and a good performance status (PS). Because the approved indications for gemcitabine include the relief of symptoms, the panel also recommends gemcitabine monotherapy as a reasonable option for symptomatic patients with

metastatic or locally advanced, unresectable disease with poor PS (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 radiation therapy (RT) were randomly assigned to adjuvant gemcitabine versus observation following macroscopically complete resection, an intent-to-treat analysis of the data showed that the primary end point of increased disease-free survival (DFS) was met (13.4 vs 6.9 months; $P<.001$, log rank).[43] Final results from this study showed median overall survival (OS) to be significantly improved for patients in the gemcitabine arm (22.8 vs 20.2 months; hazard ratio [HR], 0.76; 95% CI, 0.61–0.95; $P=.01$).[44] An absolute survival difference of 10.3% was observed between the 2 groups at 5 years (20.7% vs 10.4%).[44]

Fixed-Dose-Rate Gemcitabine

Clinical studies have shown that administering gemcitabine at a fixed dose rate (FDR) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.[45] 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 vs 4.9 months; $P=.04$), although this outcome did not satisfy the protocol-specified criteria for superiority.[46] When gemcitabine is considered for the treatment of advanced disease, the NCCN Panel views FDR gemcitabine (10 mg/m^2/min) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B). FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX [gemcitabine/oxaliplatin]; GTX [gemcitabine/docetaxel/capecitabine]) (see "Gemcitabine Combinations," next section).[47,48]

Gemcitabine Combinations

Because gemcitabine is superior to bolus 5-FU in the advanced setting when the efficacy end points of survival and symptom relief are used, it is now often combined with other chemotherapeutic agents for patients with good PS. 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.[49,50] Combinations recommended in the advanced setting are discussed in the following sections. Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good PS.[51–53]

Gemcitabine Plus Albumin-Bound Paclitaxel: Albumin-bound paclitaxel is a nanoparticle form of paclitaxel. In 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 weeks; median OS at this dose was 12.2 months.[54] Based on these results, the large, open-label, international, randomized phase III MPACT trial was initiated in 861 patients with metastatic pancreatic cancer with no prior chemotherapy.[55] Participants were randomized to receive gemcitabine plus albumin-bound paclitaxel or gemcitabine alone. The trial met its primary end point of OS (8.7 vs 6.6 months; $P<.0001$; HR, 0.72).[55] The addition of albumin-bound paclitaxel also improved other end points, including 1- and 2-year survival, response rate, and progression-free survival (PFS). OS was associated with a decrease in CA 19-9 levels (HR, 0.53; 95% CI, 0.36–0.78; $P=.001$).[56] 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.[57] Updated results of the MPACT trial show that long-term survival is possible with gemcitabine plus albumin-bound paclitaxel, because 3% of patients in that arm were alive at 42 months compared with no patients in the control arm.[58]

The panel considers the combination of gemcitabine plus albumin-bound paclitaxel a category 1 recommendation for the treatment of patients with metastatic disease and good PS based on these results, and it is listed as a preferred option in this setting. Good PS for this regimen is defined as Karnofsky PS ≥70,[58] thus some patients with an ECOG score of 2 may be eligible to receive this regimen.[59,60] By extrapolation of the data, the panel recommends this combination in the locally advanced, good PS setting as well (category 2A). The panel also notes

that this combination is an acceptable option in the neoadjuvant/borderline resectable setting.

Gemcitabine Plus Erlotinib: 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 (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 with patients receiving gemcitabine alone.[61] Median survival was 6.24 months and 1-year survival was 23% compared with 5.91 months and 17%, respectively, in the control arm. Adverse events, such as rash and diarrhea, were increased in those receiving erlotinib, but most were grade 1 or 2.[61]

The NCCN Panel recommends gemcitabine/erlotinib combination therapy as another option for patients with locally advanced or metastatic disease and good PS (category 1 for 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 Cisplatin: Three phase III trials evaluating combination gemcitabine/cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination over the single agent.[52,62,63] Nevertheless, selected patients may benefit from this regimen because patients with breast or ovarian cancer who are *BRCA* mutation carriers[64–66] and selected patients with inherited forms of pancreatic cancer[67] 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.[68] 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).[68] The panel recommends gemcitabine plus cisplatin for patients with metastatic or locally advanced disease, especially as an alternative to FOLFIRINOX, in patients with a hereditary cancer syndrome involving a DNA repair mutation (eg, *BRCA* or *PALB2* mutations).

Gemcitabine Plus Capecitabine: A number of randomized trials have investigated the combination of gemcitabine with capecitabine, a fluoropyrimidine, in patients with advanced pancreatic cancer.[53,69] In a recent meta-analysis of 8 RCTs, OS was improved in patients receiving gemcitabine plus capecitabine than in patients receiving gemcitabine alone (HR, 0.87; *P*=.03).[70] 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 PS who are interested in pursuing more aggressive therapy outside a clinical trial.

The panel also includes the GTX regimen as a category 2B recommendation for the treatment of patients with metastatic or locally advanced disease and good PS. In a report of 35 patients with metastatic pancreatic cancer treated with GTX, the authors reported an overall response rate of 29% (all partial responses), with an additional 31% of patients exhibiting a minor response or stable disease.[48] 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.

FOLFIRINOX

Results from the randomized phase III PRODIGE trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good PS showed dramatic improvements in both median PFS (6.4 vs 3.3 months; *P*<.001) and median OS (11.1 vs 6.8 months; *P*<.001), in favor of those receiving FOLFIRINOX.[71] Eligibility criteria for this trial, however, were stringent, limiting real-world generalizability.[72] Because of the strong results from this trial, in 2011 the panel added FOLFIRINOX as a preferred category 1 recommendation for first-line treatment of patients with good PS (ie, ECOG 0–1) with metastatic pancreatic cancer. It is listed as a category 2A recommendation for patients with locally advanced unresectable disease by extrapolation. The panel also lists this regimen as an acceptable option in the neoadjuvant/borderline resectable setting.

Some concerns exist about the toxicity of the FOLFIRINOX regimen. In the PRODIGE trial, some grade 3/4 toxicity rates that were significantly greater in the FOLFIRINOX group compared with the gemcitabine group were 45.7% for neutropenia, 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9.0% for sensory neuropathy.[71] Despite the high levels of toxicity, no toxic deaths have been reported.[71,73,74] Furthermore, the PRODIGE trial determined that, despite this toxicity, fewer patients in the FOLFIRINOX group experienced a degradation in their quality of life at 6 months (31% vs 66%; $P<.01$).[71] A more detailed analysis shows that FOLFIRINOX maintained and even improved quality of life more so than gemcitabine.[75]

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.[76] 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 ($N=75$).[77] In patients with metastatic disease, 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 those who received the standard FOLFIRINOX regimen.

Capecitabine and Continuous Infusion 5-FU

The panel lists capecitabine monotherapy and continuous infusion 5-FU as first-line treatment options for patients with locally advanced unresectable disease (category 2B) and those with poor PS 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.[78] Note that the capecitabine dose recommended by the panel (1,000 mg/m^2 orally twice daily) is less than the dose described by Cartwright et al,[79] because the higher dose has been associated with increased toxicity (eg, diarrhea, hand and foot syndrome).

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 vs best supportive care) and on a phase II study (CapeOx).[80,81] 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).

Second-Line Systemic Therapy in the Advanced Setting

A systematic review of clinical trials that assessed the efficacy of second-line therapy after gemcitabine in pancreatic cancer concluded that, although data are very limited, evidence suggests an advantage of additional chemotherapy over best supportive care.[82] For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable second-line options.[80,81,83,84] Gemcitabine-based therapy can be given to those previously treated with fluoropyrimidine-based therapy. Second-line systemic therapy should be administered only to patients with good PS.

Results from the phase III CONKO-003 trial presented in 2008 showed significant improvements in both median PFS (13 vs 9 weeks; $P=.012$) and median OS (20 vs 13 weeks; $P=.014$) when oxaliplatin was added to 5-FU/leucovorin,[85,86] making this regimen the standard approach for second-line therapy in patients with no prior exposure to fluoropyrimidine-based therapy at that time. Final results of the trial showed that the median OS in the OFF (oxaliplatin/folinic acid/5-fluorouracil) arm was 5.9 months

(95% CI, 4.1–7.4) versus 3.3 months (95% CI, 2.7–4.0) in the 5-FU/LV arm, for a significant improvement in HR (0.66; 95% CI, 0.48–0.91; *P*=.01).[87] Results from the open-label phase III PANCREOX trial show that the addition of oxaliplatin to 5-FU/LV in second-line treatment may be detrimental.[88] However, this trial was limited by imbalances in PS 2 proportion between the study arms and possible crossover in treatment delivered after progression.[89]

In the recent 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.[90] Patients were randomized to receive the nanoliposomal irinotecan monotherapy, 5-FU/leucovorin, or both (N=417). Median PFS (3.1 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 with those who did not receive irinotecan. Updated analyses showed that median OS (6.2 vs 4.2 months; HR, 0.75; *P*=.042) was significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin compared with those who received 5-FU/leucovorin without irinotecan.[91] Grade 3 or 4 adverse events that occurred most frequently with this regimen were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).[90]

Second-line treatment options for patients previously treated with gemcitabine-based therapy include 5-FU/leucovorin/nanoliposomal irinotecan (category 1 for metastatic disease); FOLFIRINOX; 5-FU/leucovorin/oxaliplatin; FOLFOX; CapeOx; capecitabine; and continuous infusion 5-FU. Options for patients 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; and gemcitabine monotherapy.

Radiation and ChemoRT 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. Varying levels of evidence support the use of chemoRT in each setting, as discussed later.

Adjuvant ChemoRT

Most data comparing chemotherapy and chemoRT 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 chemoRT, chemotherapy, and chemotherapy plus chemoRT, respectively),[92] although the trial has been criticized for lack of attention to quality control for RT.[93–95]

A 2012 meta-analysis of 15 prospective, randomized trials found that adjuvant chemoRT did not improve DFS, 2-year survival, or OS (odds ratio [OR], 0.99; *P*=.93) compared with surgery alone, whereas adjuvant chemotherapy improved all 3 outcomes (OR for OS, 1.98; *P*<.001).[96] A 2013 meta-analysis of 9 trials found similar results, with HRs for death compared with 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 chemoRT (95% CI, 0.55–1.46), 0.54 for chemoRT plus 5-FU (95% CI, 0.15–1.80), and 0.44 for chemoRT plus gemcitabine (95% CI, 0.10–1.81).[97] However, a population-based assessment of outcomes of patients in the National Cancer Data Base with pancreatic cancer who underwent resection from 1998 to 2002 found the opposite result: chemoRT was associated with better OS than chemotherapy in a PS-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).[98] A multiinstitutional pooled analysis of 955 consecutive patients with resected pancreatic cancer also supports the supposition that adjuvant chemoRT improved survival compared with chemotherapy alone (OS, 39.9 vs 27.8 months; *P*<.001).[99]

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 chemoRT.[100–103] To definitively clarify the role of chemoRT following gemcitabine monotherapy in the adjuvant setting, RTOG is conducting trial 0848 (ClinicalTrials.gov identifier: NCT01013649). Studies are presently investigating the role of stereotactic body RT (SBRT) in the adjuvant setting (eg, NCT02461836).

ChemoRT and SBRT for Locally Advanced Disease

ChemoRT for the management of unresectable locoregional pancreatic cancer is mainly used in selected patients who do not develop metastatic disease during initial chemotherapy. Some evidence suggests that concurrent gemcitabine and radiation can yield similar or better outcomes when compared with 5-FU–based chemoRT in the setting of locally advanced disease.[104–107] The use of capecitabine as a radiosensitizer has also been assessed in this setting and appears to be effective.[108] 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 chemoRT over gemcitabine-based chemoRT.[109] Therefore, when chemoRT is recommended by the panel, fluoropyrimidine-based chemoRT is generally preferred over gemcitabine-based chemoRT.

Upfront ChemoRT or SBRT in Locally Advanced Disease: The phase III randomized ECOG 4201 trial, which assessed gemcitabine compared with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer, was closed early due to poor accrual. However, an intent-to-treat analysis of data for the 74 patients enrolled in this study showed that median OS was significantly longer in the chemoRT arm (11.1 vs 9.2 months; P=.017).[110] However, the poor accrual rate decreased its statistical power, there was no difference in PFS, and the confidence intervals for OS overlapped between the 2 groups of patients, leading some to state that the results do not rise to the level of evidence required to determine standard of care.[111]

The benefit of chemotherapy versus chemoRT 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 chemoRT with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[112] In this study, gemcitabine alone was associated with a significantly increased OS rate at 1 year compared with chemoRT (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 chemoRT arm had a lower survival rate. However, these patients 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 chemoRT regimen.

Thus, the role of upfront chemoRT 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 chemoRT therapy or SBRT is an option.[110,113]

ChemoRT or SBRT Following Chemotherapy in Locally Advanced Disease: Systemic chemotherapy followed by chemoRT or SBRT is an option for select patients with unresectable disease and good PS who have not developed metastatic disease.[114–116] This sequence is especially recommended in cases in which (1) it is highly unlikely that the patient will become resectable (ie, complete encasement of SMA/superior celiac artery); (2) there are suspicious metastases; or (3) the patient may not be able to tolerate chemoRT. Using 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 chemoRT.

In the international phase III LAP07 RCT, patients with locally advanced pancreatic cancer (n=269) received chemoRT with capecitabine after 4 months of induction chemotherapy with either gemcitabine monotherapy or gemcitabine and erlotinib.[117] ChemoRT in this setting provided no survival benefit compared with 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 chemoRT arm vs 96 days in the control arm; P=.05) and local tumor progression (34% in the chemoRT arm vs 65% in the chemotherapy only arm; P<.0001).[117]

SBRT following gemcitabine monotherapy in patients with locally advanced pancreatic cancer has been examined in phase II trials.[118,119] This regimen was associated with low toxicity and favorable freedom from local disease progression.[118,119] Because there are now more active chemotherapy regimens than gemcitabine monotherapy, additional studies are planned to assess the role of RT after more active chemotherapy.

Management of Resectable and Borderline Resectable Disease

Surgical Management

Surgical resection is the only potentially curative technique for managing pancreatic cancer. However, >80% of patients present with disease that cannot be cured with surgical resection.[120] Even under the most optimal clinical trial conditions, the median survival of resected patients after adjuvant therapy ranges from 20.1 to 28.0 months.[43,92,121–123] Negative margin status (ie, R0 resection), small tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[124–126]

Criteria for Resection: The NCCN Panel recommends that pancreatic resections be performed at institutions that perform a large number (at least 15–20) of pancreatic resections annually. It is again emphasized that institutions performing pancreatic resections should have a multidisciplinary team with focus in pancreatic cancer that actively participates in the decision-making process regarding which patients should undergo surgery. A key component of this team is also to have specific expertise in dealing with the postoperative complications, including interventional radiology procedures and critical care management. 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.[11,127] A more restrictive definition of borderline resectable pancreatic tumors has also been described,[128] which uses degrees of contact (eg, interface between tumor and SMA measuring ≤180° of vessel wall circumference) and contour deformity/narrowing (eg, teardrop deformity in 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; or unresectable (ie, locally advanced or metastatic disease).

The panel consensus is that patients should be selected for surgery based on curative intent as determined by the probability of obtaining negative resection (R0) margins at presentation. Overall, the likelihood of attaining negative margins is the key criterion for consideration when determining whether a patient is a potential candidate for resection.[129,130] 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 good candidates for an upfront resection, but may be potentially downstaged and safely resected after neoadjuvant therapy (see "Preoperative (Neoadjuvant) Therapy," page 1053]. Furthermore, the panel recommends that patient factors (eg, comorbidities, PS, and frailty) be considered when deciding whether a patient is a surgical candidate.

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, wherein 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).[131,132] Tumors located in the pancreatic neck (anterior to the superior mesenteric vessels) present a particular challenge because the type of resection is often not certain until laparotomy is done. Based on the extent of the disease, one of the following is possible: a Whipple procedure with division of the pancreas to the left of the superior mesenteric vessels; a distal pancreatectomy with division of the pancreas to the right of the mesenteric vessels; or a total pancreatectomy.

Data from several RCTs did not show any survival advantage to performing an extended regional lymphadenectomy in addition to the standard pancreaticoduodenectomy.[133] Overall, outside of a clinical trial, an extended 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, because those with positive nodes in these positions have inferior prognoses.[134,135]

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. Stenting of the biliary system can improve symptoms and liver function, but it is not clear whether these changes can decrease the mortality rate associated with the Whipple procedure. Several prospective and retrospective studies have failed to show decreased mortality in patients with preoperative biliary drainage.[136–142] Placement of a stent is required before administration of neoadjuvant therapy for patients with jaundice.[143–146]

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). A clinical trial is currently recruiting patients to compare metal and plastic stents for preoperative biliary decompression in patients with pancreatic cancer (ClinicalTrials.gov identifier: NCT01191814). In the absence of level 1 data, the panel consensus is that short, self-expanding metal stents 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, because fully covered metal stents are removable endoscopically.

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 "Systemic Therapy Approaches for Locally Advanced or Metastatic Disease" and "Radiation and ChemoRT Approaches," pages 1046 and 1050, respectively). Although results of RTOG 9704 cannot be directly compared with those of the CONKO-001, ESPAC-1, or ESPAC-3 trials because of differences in treatment design, timing of imaging, and patient characteristics, 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 with gemcitabine monotherapy in the adjuvant setting, showed that median survival was greater for participants randomized to receive the combination regimen (28.0 months), relative to those randomized to receive gemcitabine monotherapy (25.5 months; HR, 0.82; 95% CI, 0.68–0.98; P=.032).[123] The CONKO-005 phase III randomized trial compared gemcitabine administered with erlotinib versus gemcitabine administered alone in the adjuvant setting,[147] but found the combination regimen did not significantly improve OS or DFS compared with gemcitabine monotherapy.

Based on the data discussed, no definite standard has yet been established in the adjuvant treatment of pancreatic cancer. 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 chemoRT is also recommended as an adjuvant treatment, with subsequent chemotherapy being an option. To date, no studies have demonstrated superiority of delivering chemoRT before versus after chemotherapy in the adjuvant setting.

Preoperative (Neoadjuvant) Therapy: Although no high-level evidence supports its use, most NCCN Member Institutions now prefer an initial approach for patients with borderline resectable disease that involves neoadjuvant therapy as opposed to immediate surgery. Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerat-

ed.[148–155] Neoadjuvant therapy should preferably be administered at or coordinated through a high-volume center. Upfront resection in patients with borderline resectable disease is no longer recommended, as of the 2016 version of these guidelines. It is important to note that no randomized phase III trials have compared the approach of neoadjuvant therapy in borderline resectable disease versus surgery without initial therapy, and the best regimens to use in the borderline neoadjuvant setting are unknown.

Neoadjuvant therapy is also sometimes used in patients with resectable disease, especially in those with high-risk features. A number of studies have evaluated the use of neoadjuvant chemoRT in patients with resectable disease.[156–166] Although evidence suggests that there may be a better chance of margin-negative resection with preoperative therapy,[167] results of randomized trials addressing this issue are needed. Clinical trials to assess outcomes for specific regimens in the neoadjuvant setting are currently recruiting, such as the phase III NEOPA trial, which is comparing neoadjuvant gemcitabine chemoRT therapy to upfront surgery (ClinicalTrials.gov identifier: NCT01900327),[168] 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 (NCT02562716). Currently, the panel does not recommend neoadjuvant therapy for clearly resectable patients without high-risk features, except in a clinical trial. For selected patients who appear technically resectable but have poor prognostic features (eg, markedly elevated CA 19-9 levels, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain), neoadjuvant therapy can be considered after biopsy confirmation.

The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of patients with resectable disease will receive chemotherapy and/or RT; the potential to downsize tumors to increase the likelihood of a margin-free resection (ie, conversion to resectable status); the potential to select for surgery patients with more stable disease or disease that is more responsive to therapy; and the ability to treat micrometastases at an earlier stage.[130,162,169,170] Practices vary with regard to chemotherapy and chemoRT. Acceptable regimens include FOLFIRINOX, gemcitabine/albumin-bound paclitaxel, and gemcitabine/cisplatin (for patients with *BRCA1/2* or other DNA repair mutations). ChemoRT after chemotherapy is sometimes included in the neoadjuvant setting.

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 chemoRT or chemotherapy may be candidates for additional chemotherapy after surgery and multidisciplinary review. When chemotherapy is given, the choice of regimen may be based on the observed response to neoadjuvant therapy and other clinical considerations, such as PS and patient tolerability. Adjuvant chemotherapy or adjuvant chemoRT should only be considered for pretreated patients who have adequately recovered from surgery and have no evidence of recurrence or metastatic disease; treatment should ideally be initiated within 4 to 8 weeks.

Surveillance of Patients With Resected Disease

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited,[171–173] 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 a history and physical examination for symptom assessment every 3 to 6 months for 2 years, then every 6 to 12 months. CA 19-9 level testing and follow-up contrast-enhanced CT scans every 3 to 6 months for 2 years after surgical resection are category 2B recommendations, because data are not available to show that earlier treatment of recurrences, detected through increased tumor marker levels or CT scan, leads to better patient outcomes.

Future Directions

Design of Clinical Trials

In 2007, the NCI's Gastrointestinal Cancer Steering Committee convened a meeting 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. Several important themes emerged from this meeting, and the recommendations put forward by the committee are endorsed by the panel[174]:

- 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, tumor tissue sample banking 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 PS. Criteria for selecting study populations should take into account the putative differential efficacy of the agent (eg, 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 end point of OS.
- Quality control standards for preoperative imaging interpretation, pathologic assessment of tumor specimens, and surgical selection criteria are critical when evaluating adjuvant therapies.

An international expert panel also met to discuss current and future pancreatic cancer research and came to similar conclusions.[175] 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,[176] including the 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.[177] This group concluded that OS should be the primary end point 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.

Targeted Therapies

Poly(ADP-ribose) polymerase (PARP) inhibitors provide a promising avenue of treatment for cancers associated with *BRCA1/2* mutations.[178] In a phase II trial assessing the efficacy and safety of olaparib, an oral PARP, 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).[179] Data from the phase II RUCAPANC trial including 19 patients with a *BRCA1/2* mutation and relapsed disease showed an objective response rate of 11% in patients who were administered the PARP inhibitor rucaparib.[180] The ongoing phase III randomized POLO trial (ClinicalTrials.gov identifier: NCT02184195) is assessing the effectiveness of maintenance olaparib monotherapy after cisplatin, carboplatin, or oxaliplatin.

Summary

Patients with borderline resectable disease and select patients with resectable disease can undergo neoadjuvant therapy, with the hope of improving the chances for an R0 resection. Patients with locally advanced unresectable disease and good PS can undergo chemotherapy and chemoRT with second-line therapy if good PS is maintained after progression. Patients with good PS presenting with metastatic disease can undergo chemotherapy and second-line therapy if a good PS 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.

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Individual Disclosures for Pancreatic Adenocarcinoma Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
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Stephen W. Behrman, MD	None	None	None	4/17/17
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Eric K. Nakakura, MD[a]	None	Expert witness: review medical records for law fims and provide opinion of care	None	5/17/17
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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:
Eric Nakakura, MD: Bayer HealthCare

[b]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty conflict:
Robert Wolff, MD: McGraw-Hill