NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pancreatic Adenocarcinoma

Version 2.2012

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Pancreatic Adenocarcinoma

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To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 2.2012 Updates
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Updates in Version 2.2012 of the NCCN Guidelines from Version 1.2012 include:

PANC-2
- Footnote "e" is new to the guideline; "See Principles of Surgical Technique (PANC-C) and Pathological Analysis: Specimen Orientation, Histological Sections, and Reporting (PANC-D)."

PANC-C
- The addition of Principles of Surgical Technique is new to the Guidelines.

PANC-D
- The addition of Pathological Analysis: Specimen Orientation, Histological Sections, and Reporting is new to the Guidelines.

Discussion
- The Discussion section has been update to reflect the changes in the Guidelines.

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

PANC-1
- Footnote a: Added "interventional endoscopy" to multidisciplinary team. "Multidisciplinary consultation should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, and pathology."
- Workup: Added MRI as an option to pancreatic protocol CT.
- Workup: Changed "chest imaging" to "chest CT."
- Workup: Changed "Biopsy confirmation, metastatic site preferred" to "Biopsy confirmation of metastatic site."

PANC-4
- Changed "biopsy negative" to "cancer not confirmed."
- Added "exclude autoimmune pancreatitis" to cancer not confirmed following repeat biopsy.
- Modified footnote h: "There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended."

PANC-7
- Changed "permanent metal stent" to "expandable metal stent."

PANC-8
- Locally advanced, unresectable, good performance status added: gemcitabine + erlotinib (category 1).
- Locally advanced, unresectable, good performance status removed (category 1) following FOLFIRINOX.
- Locally advanced, unresectable, good performance status, salvage therapy added: Chemoradiation if not previously given and if primary site is the sole site of progression.

PANC-9
- For good performance status, added gemcitabine + erlotinib (category 1).

Continued on next page

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

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

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

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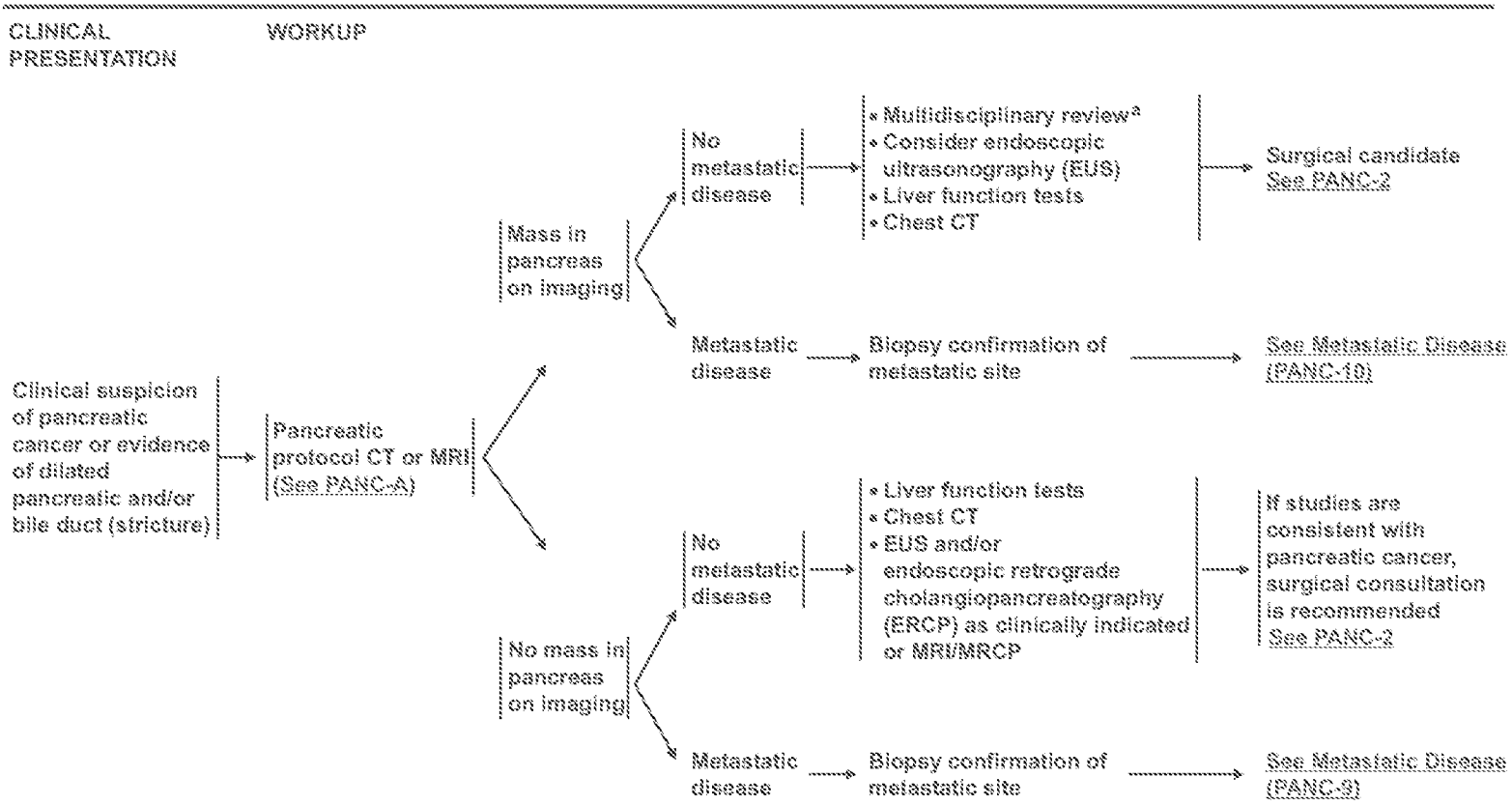

[a]Multidisciplinary review should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.

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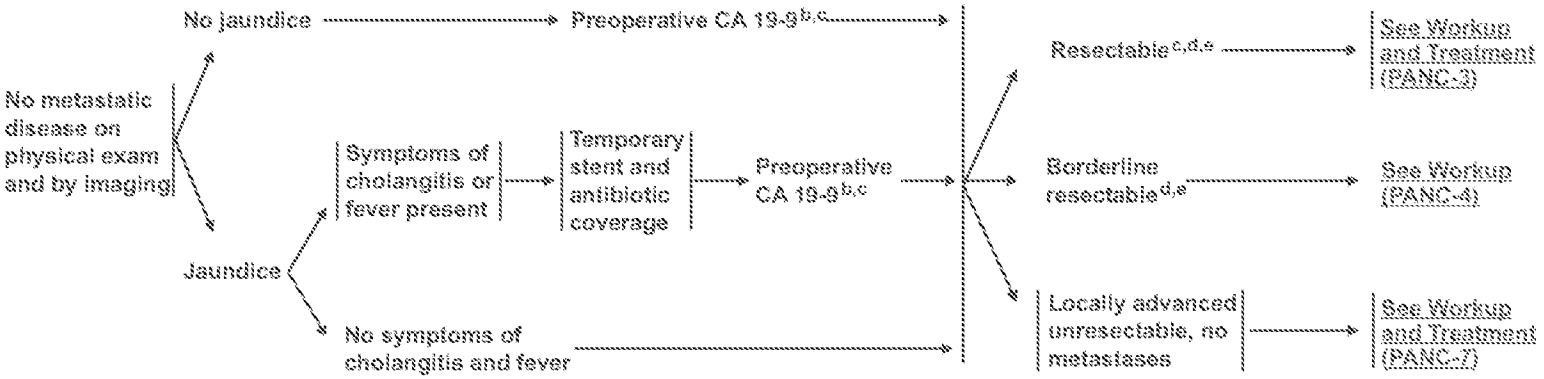
CLINICAL PRESENTATION

WORKUP



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

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

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

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

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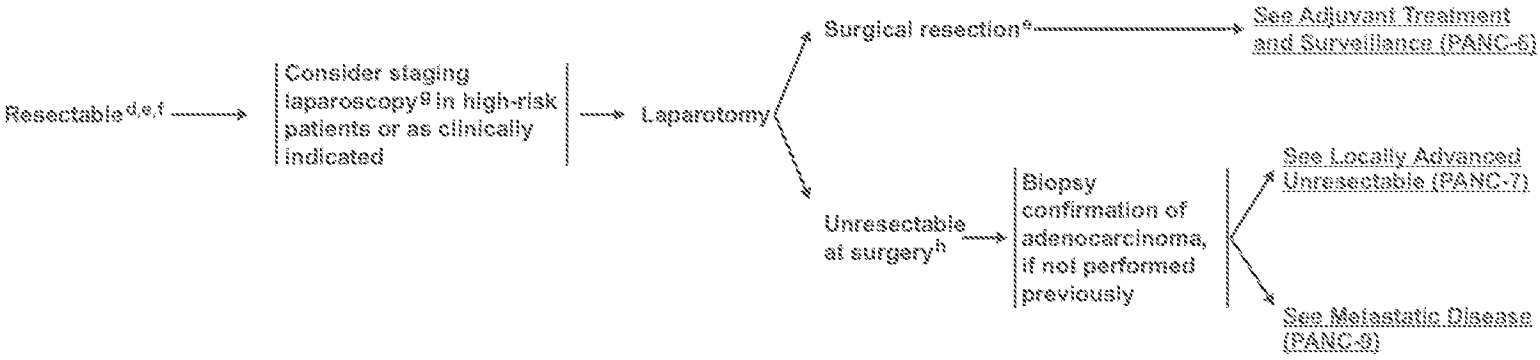
RESECTABLE | WORKUP | TREATMENT



[d] See Criteria Defining Resectability Status (PANC-B).
[e] See Principles of Surgical Technique (PANC-C) and Pathological Analysis: Specimen Orientation, Histological Sections, and Reporting (PANC-D).
[f] Consider neoadjuvant therapy on clinical trial, which requires biopsy confirmation of adenocarcinoma. For patients with biliary obstruction, durable biliary decompression is required.
[g] See Principles of Diagnosis and Staging #6 (PANC-A).
[h] See Principles of Palliation and Supportive Care (PANC-E).

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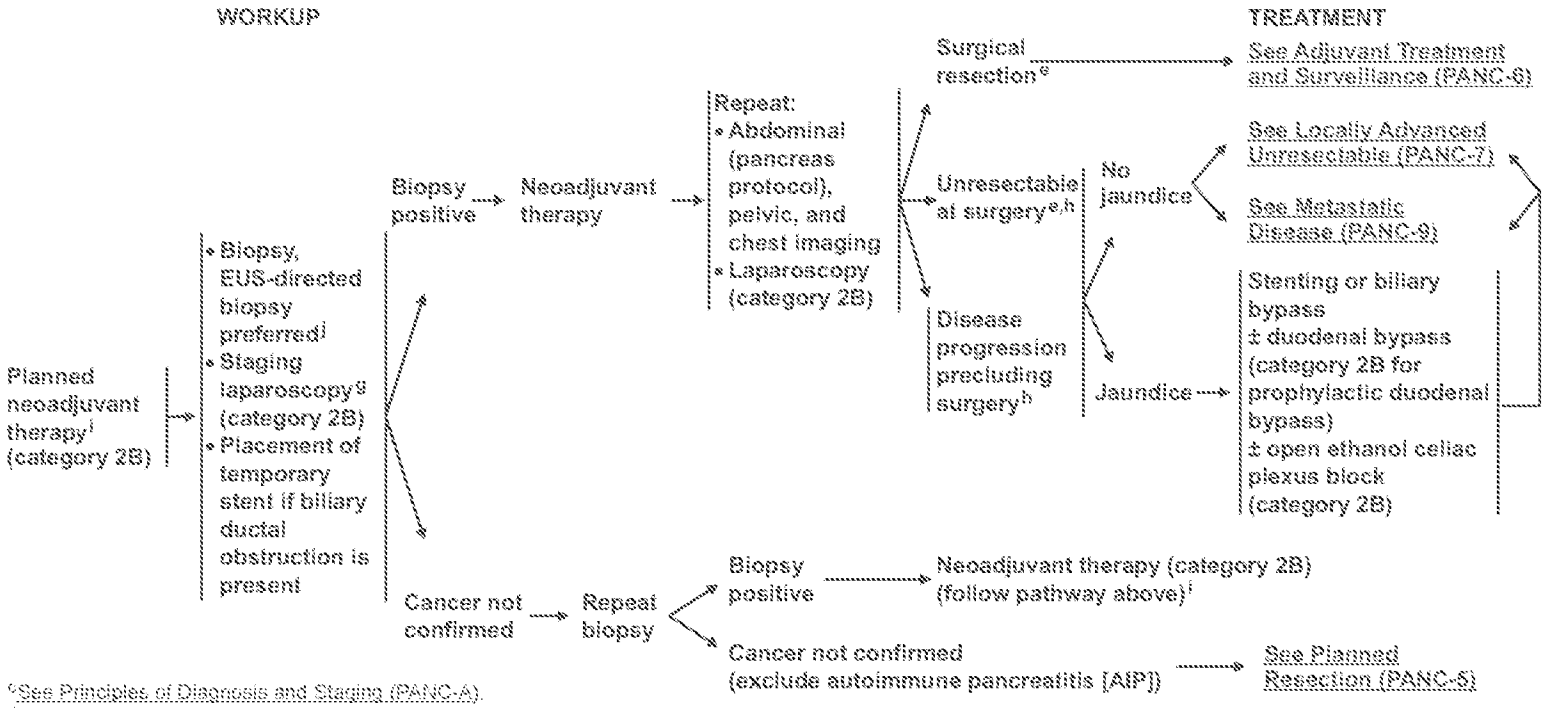
BORDERLINE RESECTABLE[c,d] NO METASTASES, PLANNED NEOADJUVANT THERAPY



[c] See Principles of Diagnosis and Staging (PANC-A).
[d] See Criteria Defining Resectability Status (PANC-B).
[e] See Principles of Surgical Technique (PANC-C) and Pathological Analysis: Specimen Orientation, Histological Sections, and Reporting (PANC-D).
[g] See Principles of Diagnosis and Staging #6 (PANC-A).
[h] See Principles of Palliation and Supportive Care (PANC-E).
[i] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[j] See Principles of Diagnosis and Staging #1 and #5 (PANC-A).

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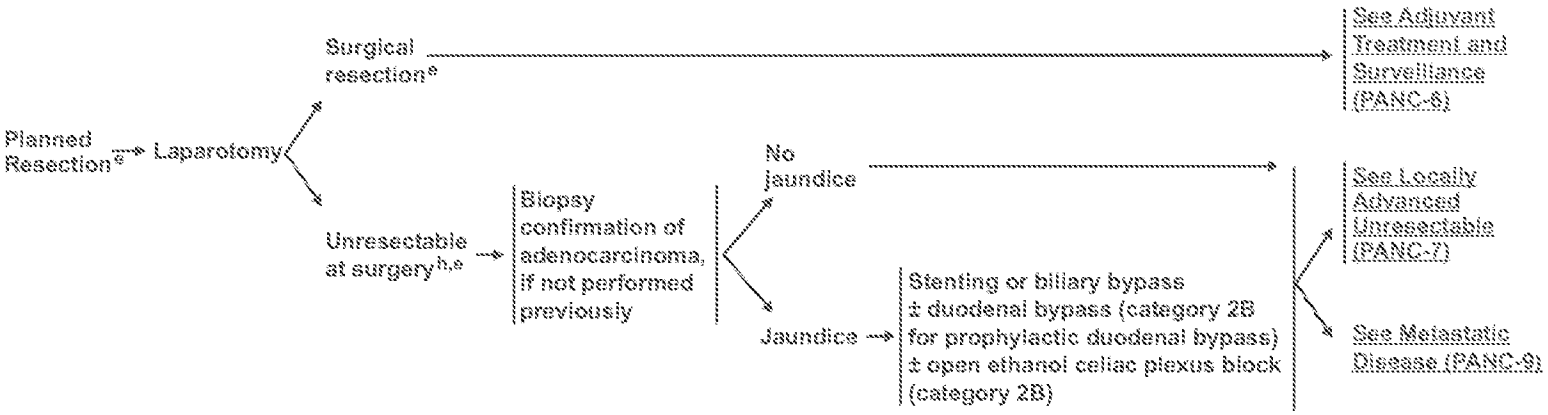
BORDERLINE RESECTABLE[c,d] NO METASTASES, PLANNED RESECTION



[c] See Principles of Diagnosis and Staging (PANC-A).
[d] See Criteria Defining Resectability Status (PANC-B).
[e] See Principles of Surgical Technique (PANC-C) and Pathological Analysis: Specimen Orientation, Histological Sections, and Reporting (PANC-D).
[h] See Principles of Palliation and Supportive Care (PANC-E).

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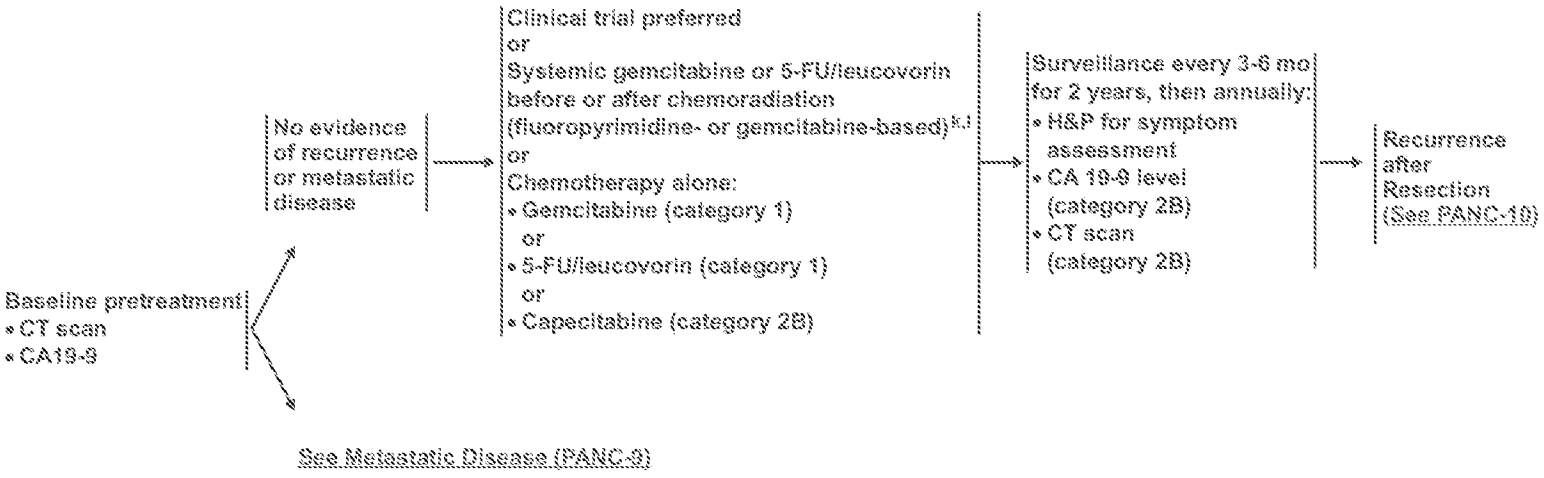
POST-OPERATIVE ADJUVANT TREATMENT[l]

SURVEILLANCE



[k]See Principles of Radiation Therapy (PANC-F).

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

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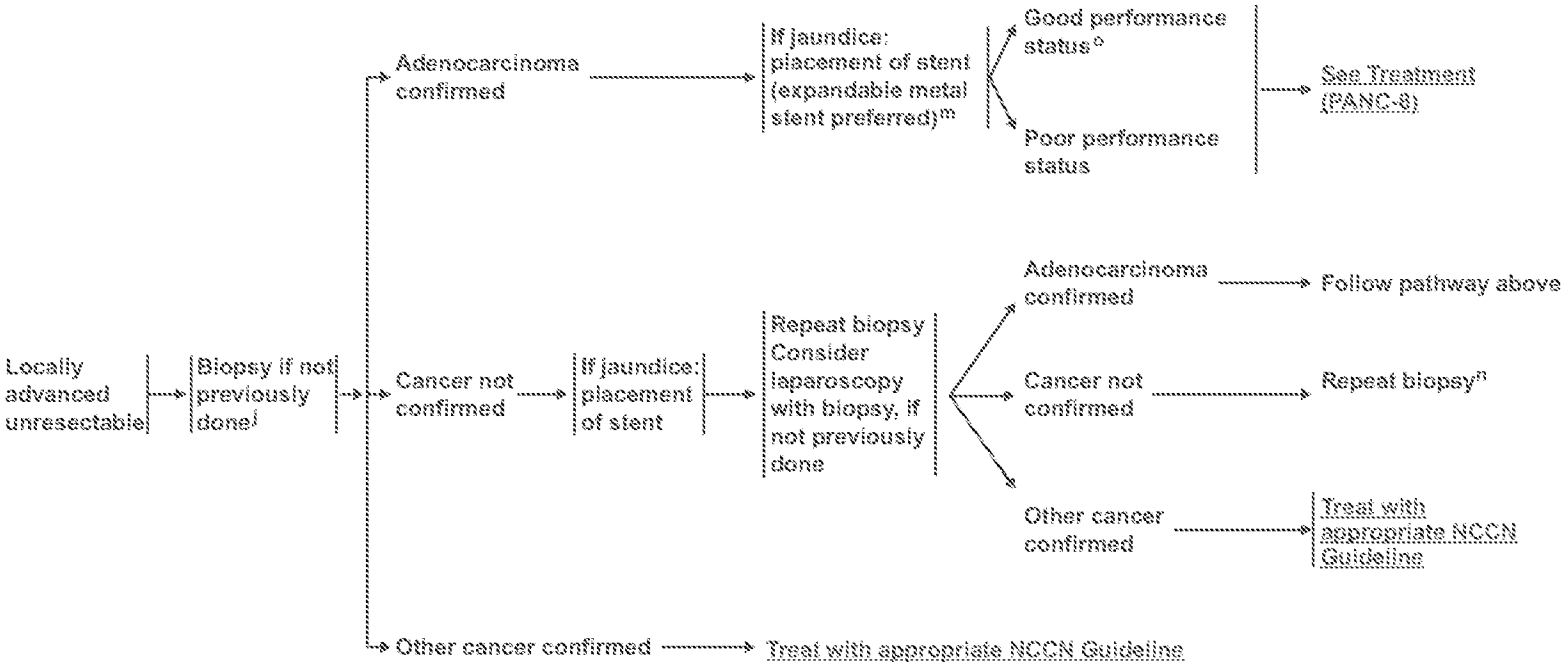
LOCALLY ADVANCED UNRESECTABLE

WORKUP



[l] See Principles of Diagnosis and Staging #1 and #5 (PANC-A).
[m] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[n] In this situation a laparscopic-directed biopsy may be useful.
[o] Defined as ECOG 0,1 with good pain management, patent biliary stent, and adequate nutritional intake.

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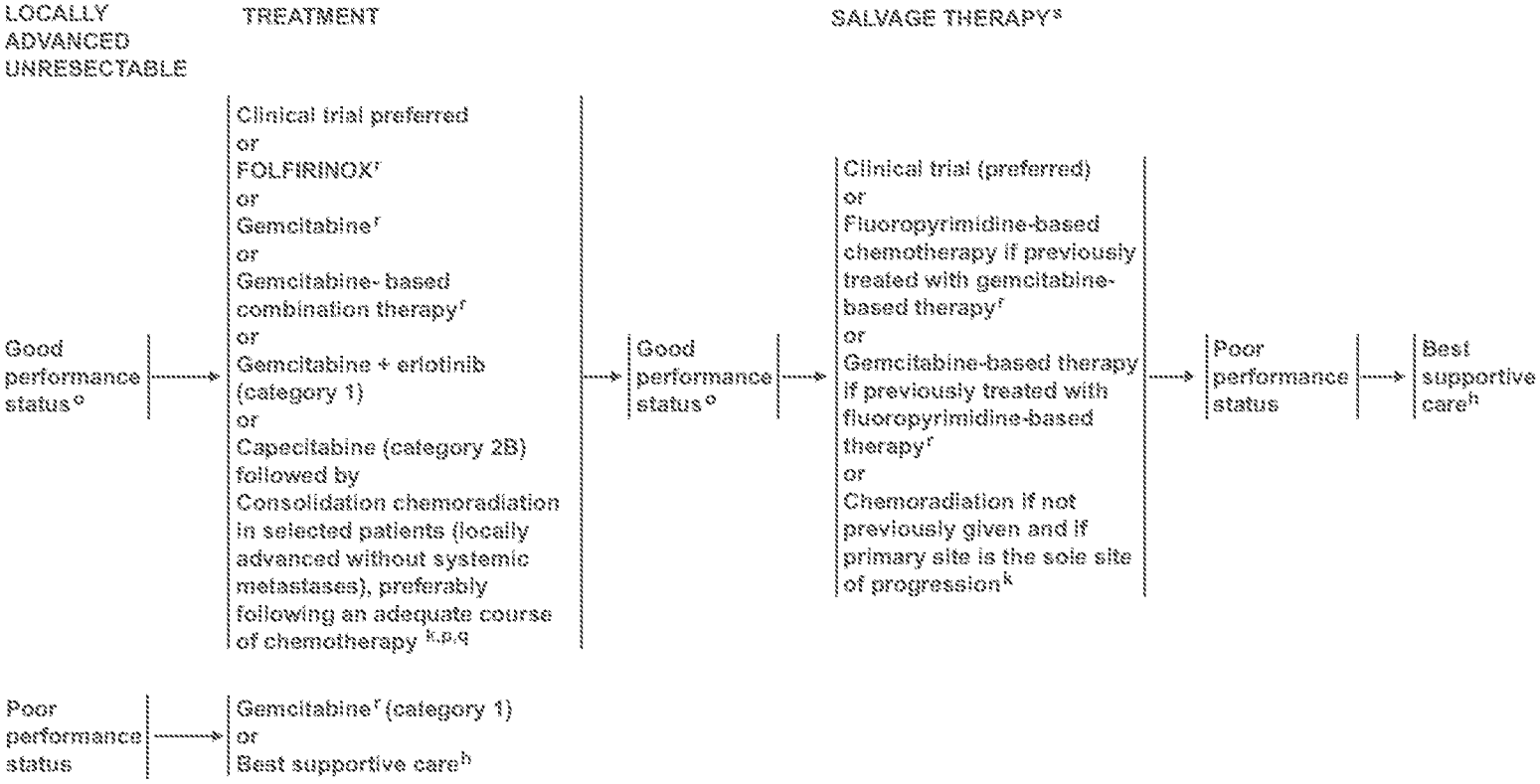

[h] See Principles of Palliation and Supportive Care (PANC-C).

[k] See Principles of Radiation Therapy (PANC-F).

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

[p] Laparoscopy as indicated to evaluate distant disease.

[q] Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy. Patients with a significant response to chemoradiation may be considered for surgical resection, although there is no definitive evidence at this time to support this intervention.

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

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

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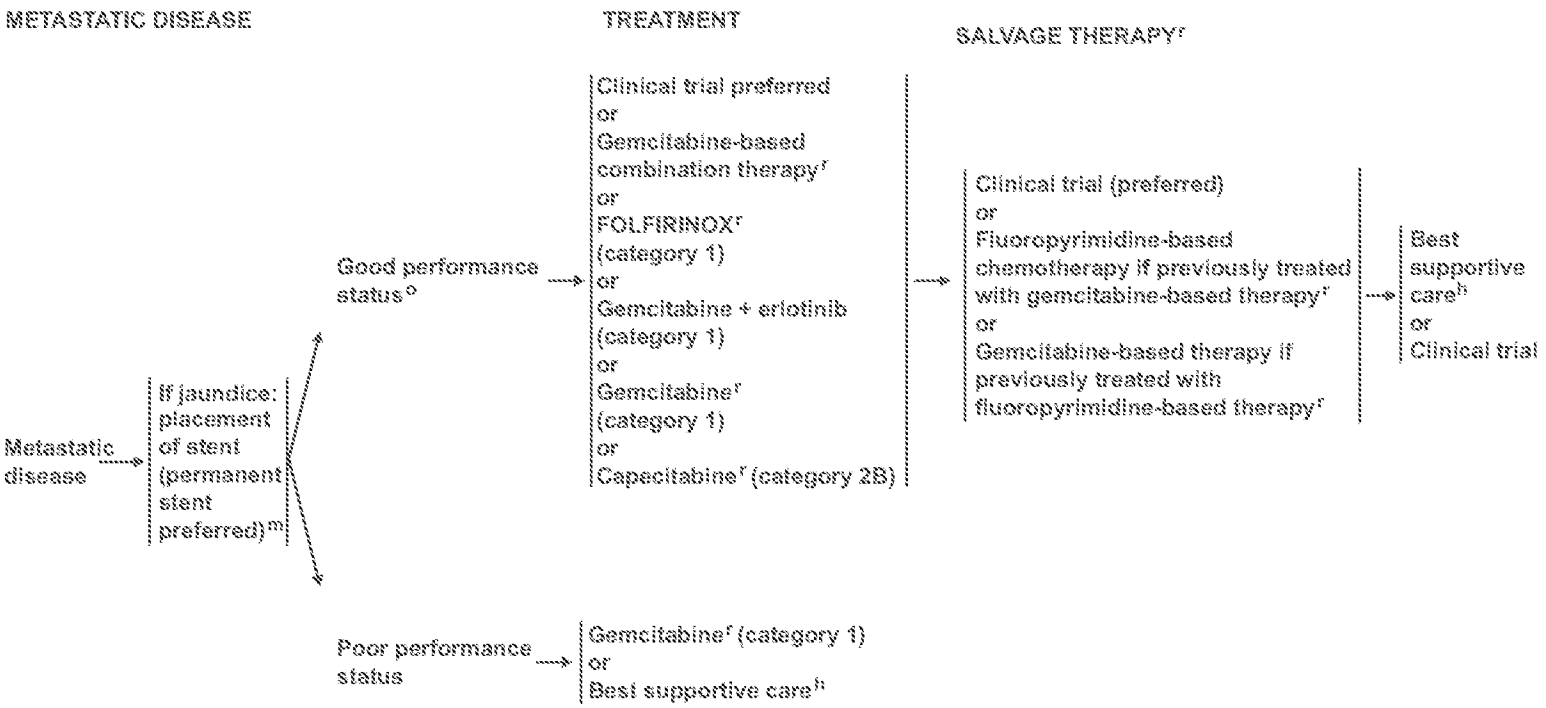

[h] See Principles of Palliation and Supportive Care (PANC-E).
[m] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[o] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[r] See Principles of Chemotherapy (PANC-G).
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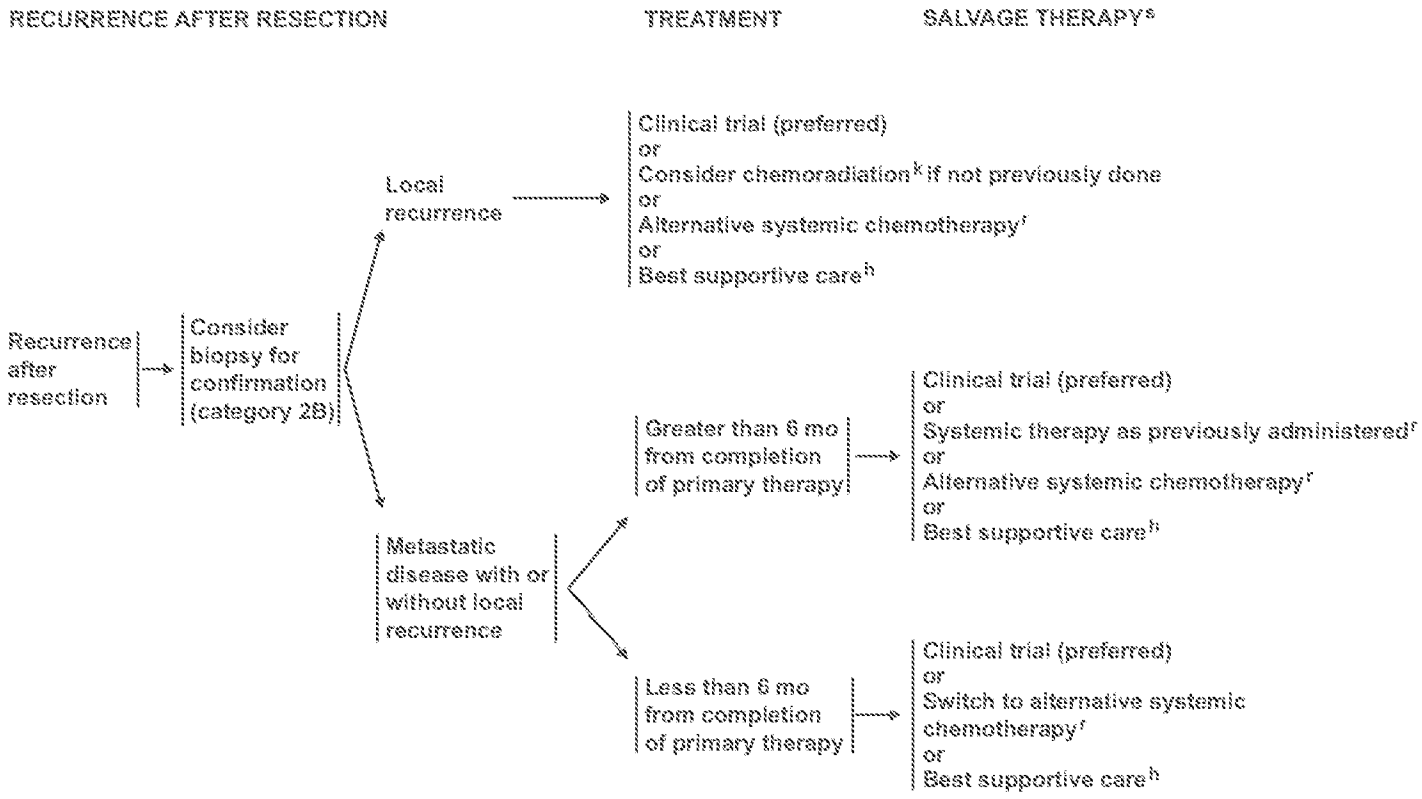

[h] See Principles of Palliation and Supportive Care (PANC-E).
[k] See Principles of Radiation Therapy (PANC-F).
[r] See Principles of Chemotherapy (PANC-G)
[s] Best reserved for patients who maintain a good performance status.

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PRINCIPLES OF DIAGNOSIS AND STAGING

#1 Decisions about diagnostic management and resectability should involve multidisciplinary consultation with reference to appropriate imaging studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (15-20) of pancreatic resections annually.

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

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

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

#5 EUS-directed FNA biopsy is preferable to a CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding with EUS FNA when compared with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection and a non-diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.

#6 Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used routinely in some institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes).

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

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CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and resectable should demonstrate the following:

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

Tumors considered borderline resectable include the following:

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

Adapted from: Callery MP, Chang KJ, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol 2009;16:1727-1733.

Tumors considered to be unresectable demonstrate the following:

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

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

Distal Pancreatectomy

The goals of left-sided resection are similar to those of 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]
- Utilization of radical resections is associated with an increase in blood loss, transfusion requirements, operating time, length of stay, and morbidity, but mortality remains exceptional.[5,7]

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PATHOLOGICAL ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGICAL SECTIONS AND REPORTING

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

Whipple Specimen

- Specimen orientation
  - Specimen orientation and inking involves both pathologist and surgeon as this will help to ensure accurate assessment of the size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method (e.g. written on the pathology requisition); for example: stitch on posterior margin, safety pin on the retroperitoneal/uncinate margin.
- Margins
  - Definitions of the margins and uniformity of nomenclature are critical to accurate reporting
    - SMA (Retroperitoneal/uncinate) Margin: The most important margin is the soft tissue directly adjacent to the proximal 3-4 cm of the superior mesenteric artery. This margin is often referred to as the "retroperitoneal margin" or "posterior margin", but has also been referred to as the "uncinate margin" or "mesenteric margin". More recently, this margin has been referred to as the "SMA margin" to correlate with its location on the specimen. Radial rather than en face sections of this margin will more clearly demonstrate how closely this margin is approached by tumor. The simple step of palpating the specimen can help guide the pathologist as to the best spot along the SMA margin to select for sampling.
    - Posterior Margin: This margin is from the posterior caudad aspect of the pancreatic head that merges with the uncinate margin and that appears to be covered by loose connective tissue. Radial rather than en face sections of this margin will more clearly demonstrate whether it is involved by tumor. In some instances this margin can be included in the same section as the SMA margin section.
    - Portal Vein Groove Margin: This is the smooth-surfaced groove on the posterior-medial surface of the pancreatic head that rests over the portal vein. Radial rather than en face sections of this margin will more clearly demonstrate whether it is involved by tumor and also will provide the distance of the tumor from the margin. As is true for the posterior margin, in some instances this margin can be included in the same section as the SMA margin section.
    - Portal Vein Margins: If an en bloc partial or complete vein resection is added to the surgical specimen it should be marked separately. En face proximal and distal end margins of the vein should be separately submitted as Proximal Portal Vein Margin and Distal Portal Vein Margin. A section documenting tumor invasion into the vein wall should also be submitted. If feasible, this section should be a full thickness of the vein wall demonstrating the depth of tumor invasion as this has been shown to have prognostic value.[8]
    - Pancreatic Neck (transection) Margin: This is the en face section of the transected pancreatic neck. The section should be placed into the cassette with true margin facing up so that the initial section into the block represents the true surgical margin.
    - Bile Duct Margin: This is the en face section of the bile duct end. The section should be removed from the unopened duct and placed into the cassette with true margin facing up so that the initial section into the block represents the true surgical margin.
  - Other margins analyzed in Whipple specimens include the proximal and distal enteric margins (en face sections) and anterior surface (closest representative). The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and so should be reported in all cases.[9-12]
  - Collectively, these pancreatic tissue surfaces constitute the circumferential transection margin. Designating the various specific margins with different colored inks will allow recognition on microscopy.

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PATHOLOGICAL ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGICAL SECTIONS AND REPORTING

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

Distal Pancreatectomy

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

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PATHOLOGICAL ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGICAL SECTIONS AND REPORTING

Reporting

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

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

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

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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE[2]

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

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

- Gastric outlet obstruction
  - Good performance status
    - Gastrojejunostomy (open or laparoscopic) ± J-tube
    - Consider enteral stent[1]
  - Poor performance status
    - Enteral stent[1]
    - Percutaneous endoscopic gastrostomy (PEG) tube

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

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

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

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

[1] Placement of an enteral stent is particularly important for patients with poor performance status.
[2] Palliative surgical procedures are best reserved for patients with a longer life expectancy.

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PRINCIPLES OF RADIATION THERAPY

General Principles:

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

Standard Recommendations:

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

Neoadjuvant resectable/borderline resectable:

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

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

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PRINCIPLES OF RADIATION THERAPY

Unresectable/Locally advanced (non-metastatic):

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

Options include:

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

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

Adjuvant:

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

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

Palliative:

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

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PRINCIPLES OF RADIATION THERAPY

Radiation Therapy Treatment Planning Principles

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

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PRINCIPLES OF RADIATION THERAPY

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

Table 1: Normal Tissue Dose Volume Constraints

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

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

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

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PRINCIPLES OF RADIATION THERAPY

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

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PRINCIPLES OF CHEMOTHERAPY (1 of 3)

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

- Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.

Close follow-up of patients undergoing chemotherapy is indicated.

Metastatic

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

Locally Advanced

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

See Adjuvant, and Neoadjuvant PANC-G (2 of 3)

See References on PANC-G 3 of 3

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF CHEMOTHERAPY (2 of 3)

Adjuvant

- The CONKO 001 trial demonstrated significant improvements in disease-free survival and overall survival with use of post-operative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[9]
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[10]
- The use of gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU based chemoradiotherapy.
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post- chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for post-operative adjuvant treatment.[11]
- For patients who relapse after receiving adjuvant therapy, subsequent therapy may consist of gemcitabine or gemcitabine based-combination therapy for patients previously treated with fluoropyrimidine-based therapy, or fluoropyrimidine-based therapy (eg, 5-FU/leucovorin/oxaliplatin[7] or CapeOx)[8] for patients previously treated with gemcitabine-based therapy.

Neoadjuvant

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

See Metastatic and Locally Advanced PANC-G (1 of 3)

See References on PANC-G (3 of 3)

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PRINCIPLES OF CHEMOTHERAPY (3 of 3)

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Table 1

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

Because only a few patients with pancreatic cancer undergo surgical resection of the pancreas (and adjacent lymph nodes), a single TNM classification must apply to both clinical and pathologic staging.

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma *in situ**

T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension

T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension

T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

*This also includes the "PanIntIII" classification.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Stage Grouping

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

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: 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.

Overview

During the year 2011 in the United States, an estimated 44,030 people will be diagnosed with pancreatic cancer, and approximately 37,660 people will die of pancreatic cancer.[1] This disease is the fourth most common cause of cancer-related death among U.S. men (after lung, prostate, and colorectal cancer) and women (after lung, breast, and colorectal cancer).[1] Its peak incidence occurs in the seventh and eighth decades of life.[2] Although incidence is roughly equal in both sexes, African Americans appear to have a higher incidence of pancreatic cancer than white Americans.[3] Furthermore, the incidence and mortality rates of pancreatic cancer in the United States have remained approximately the same over the past 2 decades.[4]

The NCCN practice guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the Panel during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The Panel unanimously endorses participation in a clinical trial over standard or accepted therapy. In these NCCN Pancreatic Adenocarcinoma guidelines, only tumors of the exocrine pancreas are discussed; neuroendocrine tumors are not included (please see the NCCN Neuroendocrine Tumors Guideline).

Risk Factors and Genetic Predisposition

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.[5-8] There is some evidence that increased consumption of red meat and dairy products is also associated with an elevation in pancreatic cancer risk,[9] although other studies have failed to identify dietary risk factors for the disease.[7] An increased body mass index is associated with increased risk of pancreatic cancer,[10-12] as are occupational exposure to chemicals such as beta-naphthylamine and benzidine[13] and heavy alcohol consumption.[5, 14] Numerous studies have shown an association between new-onset diabetes and the development of pancreatic cancer.[15-17] However, certain risk factors such as obesity and the use of diabetic medications can impact insulin resistance and blood glucose levels, thereby confounding these analyses.[18, 19] Chronic pancreatitis has also been identified as a risk factor for pancreatic cancer,[20, 21] and a more recent study demonstrated a 7.2-fold increased risk of pancreatic cancer for patients with a history of pancreatitis.[22] Nevertheless, further epidemiologic studies involving careful evaluation of these possible risk factors with adjustments for potential confounders are needed to clarify their impact on pancreatic cancer risk.

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True familial pancreatic cancer is rare; however, a genetic predisposition may be present in up to 5%-10% of patients,[23-25] and familial excess of pancreatic cancer is associated with high risk.[7, 25] A germline mutation in the *CDKN2A* (p16) gene has been reported in families with pancreatic cancer and melanoma.[26, 27] An excess of pancreatic cancer is also seen in families harboring *BRCA2* (breast cancer susceptibility gene-2) mutations,[28, 29] and particular mutations in the *PALB2*[30] and *MSH2*[31] genes have recently been identified as possibly increasing pancreatic cancer susceptibility. 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.[32] Preinvasive pancreatic neoplasms were detected in 10% of high-risk patients suggesting that EUS may have a promising role in screening high-risk patients.[32] The diagnostic yield of pancreatic cancer screening with EUS or MRI in asymptomatic individuals at high risk of familial disease has also been investigated in 2 more recent studies, although the malignant potential of some preinvasive pancreatic lesions and the impact of screening on survival are presently unclear.[33, 34]

Diagnosis and Staging

Ductal adenocarcinoma and its variants account for over 90% of pancreatic malignancies. The presenting symptoms of this disease can include weight loss, jaundice, floating stools, pain, dyspepsia, nausea, and depression; however, no early warning signs of pancreatic cancer have been established. As previously noted, sudden onset of adult type 2 diabetes in patients 50 years or older may be linked to a new diagnosis of pancreatic cancer; patients with long-standing diabetes may also develop pancreatic cancer.[35] Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss.

All patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should undergo initial evaluation by CT or MRI performed according to a defined pancreas protocol.[36, 37] Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation, with reference to appropriate studies to evaluate the extent of disease. The Panel recommends that a multidisciplinary review ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, and pathology.

The American Joint Committee on Cancer (AJCC) has developed staging criteria for adenocarcinoma of the pancreas that follow the tumor/node/metastasis (TNM) system.[38] 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.[38, 39] Recent validation of concordance between AJCC stage and overall survival has been provided through evaluation of 121,713 patients with pancreatic adenocarcinoma included in the National Cancer Database (NCDB).[39]

For clinical purposes, however, most NCCN centers use a clinical classification system based mainly on results of presurgical imaging studies. Following staging by CT or MRI (and EUS/endoscopic retrograde cholangiopancreatography (ERCP) in some cases), liver function tests, and chest CT, disease is classified as: (1) resectable; (2) borderline resectable (ie, tumors which are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable); (3) locally advanced unresectable (ie, tumors which are involved with nearby structures to an extent that renders them

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unresectable despite the absence of evidence of metastatic disease); or (4) disseminated, and this system is used throughout the guidelines. See 'Criteria for Resection' below for more detailed definitions.

Imaging Evaluations

Pancreatic protocol CT and MRI

Pancreatic protocol CT is the most widely available and best-validated imaging modality for diagnosing and staging patients with pancreatic cancer.[40, 41] Studies have shown that 70%-85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.[40, 42-46] However, the sensitivity of CT for small hepatic and peritoneal metastases is limited. Pancreas protocol MRI is emerging as an equivalent alternative to CT and has been added to the 2012 guidelines as an option for the initial workup of patients for whom pancreatic cancer is suspected. MRI can also be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for detecting the presence of extra-pancreatic disease in high-risk patients.[47, 48]

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.[40] Optimal multi-phase imaging technique (CT or MRI) includes a non-contrast phase plus arterial, pancreatic parenchymal, and portal venous phases of contrast enhancement with thin cuts (3mm or less) through the abdomen. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3-5 mm.[40, 44, 48, 49] The difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the late arterial phase, thereby providing a clear distinction between a hypodense lesion in the pancreas and the rest of the organ. A multi-phasic pancreatic protocol also allows for selective visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], and peripancreatic arteries) and venous structures (eg, superior mesenteric vein [SMV], splenic vein, and portal vein), thereby providing an assessment of vascular invasion by the tumor. 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, although further development of this technology may be needed before it is routinely integrated into clinical practice.[45]

Patients commonly present to the oncologist with a non-pancreas protocol CT already performed. The Panel feels that if the CT scan is of high quality, it can be sufficient. If not, a pancreas protocol CT or MRI is recommended.

Endoscopic ultrasound (EUS)

NCCN institutions vary in the use of additional staging technologies, such as EUS. The role of EUS in staging is felt to be complementary to CT or MRI, providing additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes.[38] In particular, EUS may provide assessment of certain types of vascular invasion.[50, 51] It is the consensus of the Panel that whereas the accuracy of EUS in assessing involvement of certain veins (eg, portal vein) is high, this technique is less accurate in imaging tumor invasion of the SMA.[52]

EUS is also used to discriminate between benign and malignant strictures or stenosis, since severe stenosis and marked proximal

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dilatation most often indicate malignancy.[53] EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. In addition, EUS may have a role in better characterizing cystic pancreatic lesions. On EUS, malignant cystic lesions may present as a hypoechoic cystic/solid mass or as a complex cyst and are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions can also be done with EUS (eg, celiac block, removal of ascites). Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

Endoscopic retrograde cholangiopancreatography (ERCP) and MRI/magnetic resonance cholangiopancreatography (MRI/MRCP)

Endoscopic retrograde cholangiopancreatography (ERCP) is a technique that combines endoscopic and fluoroscopic procedures and is generally limited to therapeutic interventions.[54] In the guidelines, ERCP is recommended for patients without a mass in the pancreas and without evidence of metastatic disease who require biliary decompression and who undergo additional imaging with EUS. Stent placement at the time of ERCP can be used to palliate biliary obstruction when surgery is not elected, or if surgery must be delayed. MRI/magnetic resonance cholangiopancreatography (MRCP) is considered to be equivalent to EUS/ERCP in this setting.

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.[55] The sensitivity of detecting metastatic disease for PET/CT alone, standard CT alone, and the combination of PET/CT and standard CT were 61%, 57%, and 87%, respectively. In this study, the clinical management of 11% of patients with invasive pancreatic cancer was changed as a result of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established. PET/CT is not a substitute for high-quality contrast-enhanced CT or MRI, although it can be considered as an adjunct to a formal pancreatic CT or MRI protocol in high-risk patients.

Laparoscopy

Laparoscopy is another potentially valuable diagnostic tool for staging; it can identify peritoneal, capsular, or serosal implants or studding of metastatic tumor on the liver that may be missed even with the use of a pancreatic CT protocol.[56, 57] The yield of laparoscopy is dependent on the quality of preoperative imaging and the likelihood of metastatic disease. A key goal is to avoid unnecessary laparotomy, although routine use of staging laparoscopy is controversial. The Panel does not consider staging laparoscopy to be a substitute for poor quality preoperative imaging.

Some recent evidence provides support for a selective approach to staging laparoscopy (ie, it is performed if the presence of occult metastatic disease is suggested by high-quality imaging or certain clinical indicators).[58] For example, preoperative serum CA 19-9 levels >100 U/mL (see discussion of 'Tumor-Associated Antigens,' below) have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.[58] In a recent prospective review of 838 patients who were diagnosed with resectable pancreatic tumors on imaging evaluation between 1999 and 2005, 14% were found to have unresectable disease (21% yield if only pancreatic adenocarcinoma was considered) following subsequent laparoscopy.[60] Characteristics associated with an increased laparoscopic yield of unresectable disease include the

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location of the tumor, tumor histology, the presence of weight loss and jaundice, and the facility conducting the imaging evaluation.

Diagnostic staging laparoscopy to rule out sub-radiologic metastases (especially for patients with body and tail lesions) is used routinely in some NCCN institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (eg, borderline resectable disease; markedly elevated CA 19-9; large primary tumors). The value of a staging laparoscopy in patients with resectable or borderline resectable disease was debated by the Panel, and it is included as a category 2A recommendation for patients staged with resectable pancreatic cancer considered to be at increased risk of disseminated disease, and as a category 2B recommendation for patients with borderline resectable disease prior to and following administration of neoadjuvant therapy since it is not uniformly done at all NCCN institutions. The Panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[61]

Biopsy

Although a histologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy and for patients staged with locally advanced and unresectable pancreatic cancer or metastatic disease. A histologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either EUS guidance (preferred) or CT. EUS-directed FNA biopsy 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.[62] Additional risks of CT-directed FNA biopsy include the potential for greater bleeding and infection due to the need to traverse vessels and bowel. EUS-directed FNA biopsy also gives the benefit of additional staging information at the time of biopsy.

In patients without obstructive jaundice at initial presentation, EUS-FNA is highly accurate and reliable for determining malignancy; in patients with obstructive jaundice and biliary stricture, EUS-FNA is less accurate.[36] EUS-guided FNA of cystic pancreatic lesions can also be useful in the differential diagnosis of non-neoplastic and neoplastic lesions that are difficult to discriminate with imaging studies.[63]

In rare cases when an EUS-directed biopsy cannot be obtained from a borderline resectable or unresectable patient, there are other acceptable methods of biopsy. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy.[64] A percutaneous approach[62] or a laparoscopic biopsy[65] 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. Although alternative diagnoses including autoimmune pancreatitis should be considered (see 'Differential Diagnoses,' below), laparotomy may still be recommended following 2 negative or indeterminate biopsies, especially if there is clinical and radiological evidence strongly suggestive of pancreatic cancer.[40] In situations where clinical and imaging findings indicate that locally advanced disease is present, laparoscopy with biopsy can be considered if repeat FNA biopsy does not confirm cancer. A positive biopsy is required before administration of chemotherapy.

It is important to reiterate that biopsy proof of malignancy is not required before surgical resection for clearly resectable patients and

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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.

Tumor-Associated Antigens

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal antigen, tissue polypeptide antigen, cancer antigen (CA) 125, and carbohydrate antigen (CA) 19-9. A sialylated Lewis a blood group antigen, CA 19-9, is commonly expressed and shed in pancreatic and hepatobiliary disease, as well as in many malignancies; thus, it is not tumor specific. However, the degree of increase in CA 19-9 levels may be useful in differentiating pancreatic adenocarcinoma from inflammatory conditions of the pancreas (see 'Differential Diagnoses,' below).[66] It is important to note that CA 19-9 may be undetectable in Lewis antigen-negative individuals.[67] Furthermore, CA 19-9 may be falsely positive in cases of benign or malignant biliary obstruction.[68, 69] Preoperative measurement of CA 19-9 levels should therefore be performed after biliary decompression is complete and bilirubin is normal. If biliary decompression is not performed in a jaundiced patient, CA 19-9 levels should not be assessed as they would not represent an appropriate baseline.

Data are conflicting regarding the predictive significance of CA 19-9 response following chemotherapy in patients with advanced disease[70-74]; however, CA 19-9 seems to have value as a prognostic marker. Low postoperative serum CA 19-9 levels and a decrease in serial CA 19-9 levels following surgery have been found to correlate with survival for patients undergoing resection for pancreatic cancer.[75-78] In a prospective study of patients undergoing surgery with curative intent, median survival for the group of patients with post-resectional CA 19-9 levels of <180 U/mL was significantly higher compared with the group with higher levels of CA 19-9 following surgery (hazard ratio=3.53; P<0.0001).[75] Similarly, in a prospective study of patients with advanced pancreatic cancer, a dichotomized pretreatment CA 19-9 serum level was shown to be an independent prognostic factor for survival.[71]

The Panel recommends measurement of serum CA 19-9 level prior to surgery (if bilirubin levels are normal), following surgery prior to administration of adjuvant therapy, and for surveillance (category 2B). Of note, a number of different methods are commercially available for quantifying this tumor-associated antigen. Measurements of serum levels of CA 19-9 using one testing method cannot be extrapolated to results obtained using a different procedure.

Differential Diagnoses

Chronic pancreatitis and other benign conditions are possible differential diagnoses of patients suspected of having pancreatic cancer.[79-83] 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.[81, 84-86] A benign disease that can be effectively treated with corticosteroids, autoimmune pancreatitis must be distinguished from pancreatic cancer to avoid unnecessary surgery and prevent delay in the initiation of appropriate treatment.

The finding of increased serum immunoglobulin (Ig) G levels is supportive of a diagnosis of autoimmune pancreatitis, although an

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elevated level of serum IgG4 specifically is the most sensitive and specific laboratory indicator.[87] 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.[85] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis. Jaundiced patients with locally advanced disease should be reviewed for autoimmune pancreatitis, and IgG4 levels should be assessed.

Autoimmune pancreatitis can, however, be negative for IgG4, thus closely mimicking pancreatic adenocarcinoma when there is a large pancreatic mass. For patients with borderline resectable disease and cancer not confirmed after 2 or 3 biopsies, a second-opinion is recommended. Alternative diagnoses should be considered, especially autoimmune pancreatitis, and a short course of steroid treatment may be an appropriate first approach. If no response is seen, the patient should undergo laparotomy for removal of the mass.

Surgical Management

Criteria for Resection

Surgical resection is the only potentially curative technique for managing pancreatic cancer. However, more than 80% of patients present with disease that cannot be cured with surgical resection.[88] Early concerns about high mortality associated with various pancreatic resection procedures[89] have now been lessened by studies demonstrating an acceptably low (< 5%) mortality in experienced centers (see 'Effect of Clinical Volume,' below).[90] Even under the most optimal conditions, however, the median survival of resected patients ranges from 15 to 19 months, and the actuarial 5-year survival rate is approximately 20%.[91] Negative margin status (ie, R0 resection), tumor DNA content, tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[92-94] 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.[95-97]

The NCCN Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation. Although it is clear that patients with visceral, peritoneal, or pleural metastases or with metastases to nodes beyond the field of resection derive no benefit from resection, institutions appear to differ in their approaches to patients with locoregional disease involvement (pancreas and peripancreatic lymph nodes). Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group developed criteria to define tumor resectability so as to improve patient selection for surgery and increase the likelihood of an R0 resection.[46] Using these criteria, tumors are classified as resectable; borderline resectable; or unresectable (ie, locally advanced or metastatic disease). The NCCN Panel has adopted these definitions.[46]

The absence of evidence of peritoneal or hepatic metastases following a thorough radiological assessment is a criterion for both resectable and borderline resectable disease. Radiological findings of tumor abutment on the portal vein or SMV with venous deformity, and limited encasement of the mesenteric vein and portal vein (ie, short segment occlusion with suitable vessel for anastomosis above and below) represent the extent of venous involvement that would categorize a tumor as borderline resectable. Radiological findings suggesting borderline arterial involvement include encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac

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axis and/or tumor abutment of the SMA involving ≤180 degrees of the artery circumference. Patients with resectable disease have clear fat planes around the celiac axis, hepatic artery, and SMA and no radiological evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement.[46] Overall, the likelihood of attaining negative surgical margins (ie, R0 resection) is the key criterion for consideration when determining whether a patient is a potential candidate for resection.[98, 99] In this context, a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete resection.

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

Primary Surgery for Pancreatic Cancer

The nature and the extent of the surgery for resectable tumors depend on the location and size of the tumor. If the tumor is found to be unresectable during surgery, the Panel recommends biopsy confirmation of adenocarcinoma at this time, if a biopsy was not performed previously.

Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and are rarely resectable. When tumors in the pancreatic tail are resectable, distal pancreatectomy, in which the surgeon removes the tail and body of the pancreas, as well as the spleen, is commonly performed. If the cancer diffusely involves the pancreas or is present at multiple sites within the pancreas, a total pancreatectomy may be required, where the surgeon removes the entire pancreas, part of the small intestine, a portion of the stomach, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes. Patients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with open or laparoscopic pancreatoduodenectomy (ie, the Whipple procedure).[100]

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 portal and superior mesenteric veins from the uncinate process (assuming no evidence of tumor infiltration). Further, 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 (see Figure 1).[101, 102]

In the absence of frank venous occlusion noted on preoperative imaging, the need for lateral venorrhaphy or complete portal or superior mesenteric vein resection and reconstruction to achieve an R0 resection may be suggested, but it is often not known until division of the pancreatic neck has occurred. Tethering of the carcinoma to the lateral wall of the portal vein is not uncommon and requires careful dissection to free the vein from the pancreatic head if in fact it is

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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.[103-105] On evaluation of excised vein specimens, only 60-70% had histologic evidence of frank tumor involvement and R0 resections were still not obtainable in 10-30% of patients despite increasing the magnitude of the operative procedure. However, if an R0 resection is obtained with vein excision, longevity appears similar to those with R0 resections without venous involvement, with no significant increase in morbidity and mortality. These data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected, although acceptance of this concept (particularly with respect to vein resection) is not universal.

Although numbers are more limited, similar findings have been noted with respect to hepatic arterial resection and reconstruction.[105, 106] 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.[107, 108] 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.[108, 109] 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.[107-109] Encouragingly, tumor clearance (R0 resection) has been reported in up to 72-91% of patients, with long-term survival equivalent to those having standard resection for more localized disease.[108, 109] Local recurrence, however, remains problematic even with pathologically negative margins.[109]

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.[110] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreatoduodenectomy decreased, a subset of patients was identified who were in need of resection of the SMV wall to achieve negative margins during removal of their tumors. Thus, in the 1990s, there was renewed interest in vein resection for complete resections. The group from the University of Texas MD Anderson Cancer Center has championed this approach, demonstrating that vein resection and reconstruction can allow for complete resection and is not associated with increased morbidity or mortality when compared with patients who did not require vein resection.[111] Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.[112] 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.[113-118] A recent study found that properly selected patients with adenocarcinoma of the pancreatic head who required vein resection (n = 141) had a median survival of

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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.[105] 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[117] reported the modern use of pylorus preservation in 1978. The hypothesis was that preservation would improve emptying and provide nutritional benefit, but the benefits have been inconsistent to date. Yeo et al reported no adverse affects of pylorus preservation[118]; however, van Berge Henegouwen et al reported longer nasogastric drainage times.[119] In several randomized and nonrandomized studies,[120-124] the pylorus-preserving procedure seemed to be associated with shorter surgical duration. No consistent data suggest that pylorus preservation leads to a better quality of life or nutritional status in patients after resection. Thus, pylorus-preserving pancreatoduodenectomy remains an unproven but certainly acceptable alternative to classic pancreatoduodenectomy performed with antrectomy.

Pancreatic anastomosis

Efforts in this area have focused on preventing pancreatic leaks and fistulas, which are morbid and potentially lethal complications of pancreatoduodenectomy. 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.[125] Furthermore, surgeons have examined various other options for the pancreaticojejunal anastomosis; end-to-end, end-to-side, duct-to-mucosa, and invaginating techniques have all proven to be safe and effective.[126, 127] 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.[128] Stents used in the 1930s and 1940s continue to be used today, but data suggests that they do not decrease leak rates.[129] Pancreatic fistula rates are similar among studies (ranging in most studies from 6% to 16%),[118, 127, 130] although the exact way to define a pancreatic leak in terms of volume and duration of drainage remains controversial.[131]

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).[132, 133] Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.[134]

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.[135, 136] A standard lymphadenectomy in patients undergoing pancreatoduodenectomy entails removal of nodes at the duodenum and pancreas and on the right side of the hepatoduodenal ligament, the right side of the superior mesenteric artery, and the anterior and posterior pancreatoduodenal lymph

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nodes.[137] An extended lymphadenectomy is most commonly performed in the United States by removing not only the nodes removed in the standard procedure, but also the soft tissue in the retroperitoneum from the hilum of the right kidney to the left lateral border of the aorta on the right side, and from the portal vein to the origin of the inferior mesenteric artery on the left.[138]

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.[139] A larger randomized prospective trial was performed at Johns Hopkins Hospital from 1995 through 2001 to evaluate the role of extended lymph node dissections.[140] 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.[140-142] Furthermore, a meta-analysis of randomized controlled trials comparing pancreatoduodenectomy with standard versus extended lymphadenectomy supports the conclusion that the extended procedure does not have any impact on survival.[143] In addition, patients undergoing extended lymphadenectomy have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.[144]

The information to date thus does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.[145] At this point in time, data suggest that nodal metastases are a marker of systemic disease and that their removal is unlikely to alter overall survival. One exception might be in the situation of an otherwise R0 resection with clinically positive adenopathy outside the standard field of dissection. Overall, outside of a clinical trial, a regional lymphadenectomy should not be considered as a routine part of the Whipple procedure, although consideration can be given to sampling of the aortocaval and common hepatic artery nodes, as those with positive nodes in these positions have inferior prognoses.[146, 147]

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis as well as to potentially make surgery less morbid by improving liver function preoperatively. Although controversial, several studies have suggested that pancreatoduodenectomy is associated with higher perioperative mortality when done in the setting of hyperbilirubinemia.[148-150] 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.[151-157] In 1999, a retrospective study from Memorial Sloan-Kettering Cancer Center examined 240 consecutive pancreaticoduodenectomies where 53% of patients underwent preoperative biliary decompression.[158] This study found a statistical relationship between the use of preoperative drainage (irrespective of the method used) and increased postoperative complications, including death, compared to patients who went straight to surgery. In addition, a recent multicenter, randomized trial comparing preoperative biliary drainage with surgery alone for 202 patients with cancer of the pancreatic head characterized by obstructive jaundice showed a nearly 2-fold increase in the rate of serious complications in the stented group (74% vs. 39%; relative risk in the surgery alone group=0.54; 95% CI,

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0.41-0.71; P<0.001), although no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.[163]

Based on these reports, most groups who perform resection without neoadjuvant treatment advocate selective use of decompression only in patients who are symptomatic or septic or in whom surgical resection is significantly delayed. The Panel includes in this group patients who present with jaundice and potentially resectable disease if symptoms of cholangitis or fever are present or if they have significant pruritus and an expected delay to surgery of >1 week. Most Panel members endorse use of a plastic stent in these cases, since such patients may undergo surgery shortly thereafter and do not require the longer patency time of a metal stent. If metal stents are used, short stents are preferred by some Panel members because they may be less likely to interfere with the subsequent resection.

For patients with jaundice undergoing neoadjuvant induction therapy before pancreatic resection, biliary decompression is necessary before initiation of therapy and appears to be well tolerated with minimal increase in perioperative morbidity. The University of Texas MD Anderson Cancer Center reported on their experience with more than 300 patients, of whom 57% had preoperative biliary drainage as part of a neoadjuvant chemoradiation program.[160] 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 and borderline resectable disease that is biopsy-positive.[161-162]

The Panel pointed out that stents are an evolving technology. The choice of stents includes plastic and metal; fully covered, partially covered, or uncovered; rigid or self-expanding (also see the discussion on stents in 'Palliation of Locally Advanced and Metastatic Disease,' below). While any stent can become occluded, several groups have reported better patency with metal stents.[161-163] Metal stents are generally viewed as more permanent than plastic stents. Covered metal stents may give more durable patency, since the cover prevents tumor ingrowth,[164] but the reported differences between covered and uncovered stents are not dramatic.[164, 165] Furthermore, migration is more of an issue with covered stents.[165] This issue has lead to the introduction of partially covered stents,[166] though these stents may still migrate in a substantial number of patients.[167, 168] Most metal stents used today are self-expanding. Their small initial diameters make them easy to place, and their placement rarely requires dilation.[166] Several Panel members reported that their institutions use plastic stents in patients with short life expectancies (<3 months).[166] The Panel could not reach a consensus on which type of stent is best used in each preoperative circumstance, since level-1 evidence is lacking. A clinical trial is currently recruiting patients to compare metal and plastic stents for preoperative biliary decompression in patients with pancreatic cancer (ClinicalTrials.gov NCT01191814).

Effect of Clinical Volume

Several studies have examined the effect of institutional volume on patient outcomes. The fundamental premise was that the decreasing morbidity and mortality seen in the 1980s and 1990s were the direct result of large single institution experiences. Moreover, the concern was that if surgeons performed pancreatoduodenectomy less frequently, patients might have increased morbidity and mortality. In 1993, Edge and colleagues assessed 223 pancreaticoduodenectomies from 26 U.S. hospitals, but they found that caseload did not correlate with mortality.[169] However, surgeons who performed fewer than 4 resections

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over the 2-year period of the study had more complications. The group from Memorial Sloan-Kettering Cancer Center examined the issue in 1995 and found that in a cohort of 1,972 patients, high-volume centers in New York State had significantly less mortality than low-volume centers (4% versus 12.3%).[170] 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.[171-175] 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.[176-178]

The definitions of high and low volume varied among all these studies. However, a striking difference is seen when the mortality rates from pancreatoduodenectomy in very-low-volume (0-1 procedure/year) and in low-volume (1-2 procedures/year) hospitals are compared with rates in higher-volume hospitals (> 5 procedures/year).[179] In-hospital mortality rates at these very-low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, versus 4%; $P < 0.001$). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreatoduodenectomy is compared to other major surgeries. In a retrospective analysis of data from the national Medicare claims database and the Nationwide Inpatient Sample, hospitals performing 6-16 and >16 procedures per year were classified as "high" and "very-high" volume centers.[180] In this study, 6 or more pancreatic resections were performed at only 6.3% of hospitals. The largest difference in operative mortality between very-low-volume (16.3%) and high-volume (3.8%) centers is seen for pancreatoduodenectomy, as compared to major surgery at any other site, further reinforcing the magnitude of the effect that high-volume centers can specifically have on pancreatic cancer outcomes.

Furthermore, a study involving 301,033 patients with pancreatic adenocarcinoma included in the National Cancer Data Base (NCDB) that evaluated the treatment patterns of 1,667 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.[181]

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

Pathology

Progress in treating pancreatic adenocarcinoma is encumbered by a lack of uniformity among treating physicians in defined areas that include pathologic analysis and reporting.[182] 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 pathological evaluation of the resected pancreatic specimen from gross examination to pathological report will provide better communication among the various treating physicians. It will also provide a clear and specific understanding of the individual patient's malignancy, including critical margin status, which will then allow a more accurate comparison of the existing and evolving treatment regimens for this lethal disease.

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Specimen orientation, sectioning, pathologic analysis, and reporting

The primary purpose of pathological analysis of the pancreatic specimen is to determine the pathological stage of the tumor by evaluating the type, grade, size, and extent of the cancer. 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. On January 1, 2004, the Commission on Cancer (COC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. The 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 February, 2011.[183] The NCCN Pancreatic Adenocarcinoma Panel currently supports the CAP pathology synoptic reports. The proposal included in the guidelines (see 'Pathological Analysis: Specimen Orientation, Histological Sections and Reporting,' above) 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.[184, 185]

Whipple specimen

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

One of the impediments to comparison of data across institutions is the variability in the names given to various margins. Definitions of the margins and uniformity of nomenclature are critical to accurate reporting. The Panel's recommended definitions are included in the 'Pathological Analysis: Specimen Orientation, Histological Sections and Reporting,' section in the guidelines. Margins defined include the SMA (retroperitoneal/uncinate) margin, the posterior margin, the portal vein groove margin, the proximal and distal portal vein 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.[182, 186-188] 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 histological sectioning of a Whipple specimen is determined by the unique characteristics of the tumor, but is also influenced by institutional preferences, expertise, and experience. Options include axial, bi- or multi-valve slicing, and perpendicular sliding (see Figure 3). Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas. Axial slicing provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum and pancreas, and all of the pancreatic circumferential tissue margins (see Figure 4). There is no one correct way to dissect a Whipple specimen. The most important aspects of

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dissection are clear and accurate assessment of the margins. It is currently unknown what constitutes an adequate margin in pancreatic carcinoma resection specimens. A standardized definition of this would allow better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if less than 1mm clearance is associated with an unacceptably high incidence of local recurrence then strong consideration for post-operative radiation therapy might be indicated if not received pre-operatively. The Panel strongly recommends reporting tumor clearance in millimeters for all margins (as noted in the 'Pathological Analysis: Specimen Orientation, Histological Sections and Reporting,' section of the guidelines) to allow prospective accumulation of this important data for future analysis.

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

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, as direct tumor invasion constitutes a pT4 pathological 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 'Pathological Analysis: Specimen Orientation, Histological Sections and Reporting').

Adjuvant Therapy

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The Panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/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.[189] 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.[190] Also, the Mayo Clinic and North Central Cancer Treatment (NCTTG) group determined that there was no therapeutic difference between the use of high (200 mg/m^2) or low (20 mg/m^2) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.[191] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

Postoperative Therapy

In 1985, the Gastrointestinal Tumor Study Group (GITSG) initially reported that the median survival of patients undergoing

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pancreatoduodenectomy could be prolonged almost 2-fold by postoperative chemoradiation.[192, 193] In this study, patients were randomly assigned to either observation or radiation therapy (RT) combined with an intermittent bolus of 5-fluorouracil (5-FU) after resection. A standard split course of 4,000 cGy was used. 5-FU, 500 mg/m^2 daily for 3 days, was given concurrently with each 2,000-cGy segment of RT. The 5-FU regimen was then continued weekly for a full 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 42%, compared with 15% in the control group.[192]

The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase III trial (40891) in patients with both ampullary and pancreatic adenocarcinoma assessing adjuvant radiotherapy and 5-FU versus observation alone after surgery; however, they found the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant.[194] At a median follow-up of 11.7 years, no statistically significant differences were observed in the different study arms with respect to progression-free survival or overall survival for the subset of patients with pancreatic cancer.[195]

Provocative but controversial results from the European Study Group for Pancreatic Cancer (ESPAC)-1 trial have been reported by Neoptolemos and colleagues.[196] Results of this study suggested that 5-FU/leucovorin is superior to observation and that chemoradiation is unnecessary and perhaps harmful. However, the ESPAC-1 trial has been criticized for lack of attention to quality control for RT.[197-199] Therefore, these latest results do not eliminate 5-FU-based chemoradiation as an acceptable choice in the adjuvant setting.

In the large phase III CONKO-001 trial in which 368 patients without prior chemotherapy or radiation therapy were randomly assigned to adjuvant gemcitabine versus observation following macroscopically complete resection, an intention-to-treat (ITT) analysis of the data showed that the primary endpoint of increased disease-free survival was met (median DFS 13.4 months vs. 6.9 months; P<0.001, log rank).[200] Final results from this study showed median overall survival to be improved significantly for patients in the gemcitabine arm (22.8 months vs. 20.2 months; P=0.005).[201] An absolute survival difference of 12.0% was observed between the two groups at 5 years (21% vs. 9%).[201]

The Radiation Therapy Oncology Group study RTOG 9704 was a phase III study that evaluated post-operative 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.[202] This trial, which utilized daily fractionated radiotherapy, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[203] Results of this study showed that, for patients with tumors of the pancreas head (representing 388 of the 451 patients enrolled in the trial), there was a non-statistically significant increase in overall survival in the gemcitabine arm compared with the 5-FU arm (median and 3-year survival of 20.5 months and 31% vs. 16.9 months and 22%; P=0.09); this benefit became more pronounced on multivariate analysis (hazard ratio = 0.80; 95% CI, 0.63-1.00; P=0.05). The recently published 5-year analysis of RTOG 9704 showed that there was in fact no difference in overall survival between the two groups, although patients with tumors in the head of the pancreas showed a trend toward improved overall survival with gemcitabine (P=0.08) upon multivariate analysis.[204]

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Whereas results from the RTOG trial suggest a possible small advantage for adjuvant therapy with gemcitabine over infusional 5-FU in patients with tumors in the pancreatic head, results from the prospective randomized trial of bolus 5-FU/leucovorin versus gemcitabine following surgery (ESPAC-3) showed no difference in overall survival when the 2 groups were compared (median survival was 23.0 months and 23.6 months, respectively).[205]

Results of RTOG 9704 cannot be directly compared with the results of the CONKO-001, ESPAC-1, or ESPAC-3 trials because of differences in treatment design, in timing of imaging, and in patient characteristics (eg, patients enrolled in CONKO-001 were more likely to be lymph node-negative and to have positive resection margins than those in RTOG 9704, and CONKO-001 excluded patients with high postoperative CA19-9 or CEA levels[200]). However, it is interesting to note that median overall survival for patients in the gemcitabine arm of CONKO-001 (22.8 months), the gemcitabine-containing arm of RTOG 9704 (20.5 months), the bolus 5-FU/leucovorin arm of ESPAC-1 (20.1 months), and the gemcitabine and 5-FU/leucovorin arms of the ESPAC-3 study (23.6 and 23.0 months) are remarkably similar.

Therefore, at this time, no definite standard has been established in the adjuvant treatment of pancreatic cancer. Gemcitabine- or fluoropyrimidine-based chemoradiation with additional gemcitabine or 5-FU/leucovorin[203] chemotherapy, as well as chemotherapy alone with gemcitabine (category 1) or 5-FU/leucovorin (category 1) are listed in the guidelines as options for adjuvant treatment. It was the consensus of the Panel that when chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over 5-FU/leucovorin for most patients due to its more favorable toxicity profile. In the adjuvant setting, capecitabine monotherapy is also listed in the guidelines (category 2B). The Panel considered capecitabine a reasonable alternative to 5-FU/leucovorin only in this setting as a last choice in patients for whom other options are inappropriate or unacceptable.

Although the optimal combination and sequencing of adjuvant RT has yet to be defined, the NCCN Panel recommends that postoperative RT, when given, should be administered at a dose of 45 to 46 Gy (1.8-2.0 Gy/day) with high energy photons (>4 MV) to the tumor bed, surgical anastomoses, and adjacent lymph node regions, followed by an additional 5-15 Gy to the tumor bed while paying careful attention to dose to the small bowel.[206, 207] The Panel strongly recommends use of CT simulation and 3-D treatment planning (thin slices through the pancreas/bed and locoregional basin) with intravenous (assuming adequate kidney function) and oral contrast. Treatment volumes should be based on preoperative CT scans and surgical clips (when placed). Radiation is usually given in combination with continuous infusion 5-FU, capecitabine, or gemcitabine, and can be given before or after systemic chemotherapy in the adjuvant setting. While no studies have demonstrated superiority of giving chemoradiation before versus after chemotherapy, when patients have a margin-positive resection, upfront chemoradiation followed by systemic chemotherapy is an appropriate option.[202, 206, 208]

Intensity-modulated radiotherapy (IMRT) is increasingly being applied for therapy of pancreatic adenocarcinoma in the adjuvant setting with the aim of increasing radiation dose to the gross tumor/tumor bed while minimizing toxicity to surrounding tissues.[209] Results of a recent study demonstrated that IMRT resulted in reduced grade 3/4 toxicities when compared to patients who received a similar 5-FU-based regimen with 3-D conformal radiation in the RTOG 9704 trial.[202, 210] Comparing the 2 trials, rates of grade 3/4 nausea and vomiting were 0% vs. 11% (P=0.024) and of grade 3/4 diarrhea were 3% vs. 18% (P=0.017),[210] suggesting that IMRT may be well tolerated and allow for higher

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radiation doses to the tumor.[210] There is no clear consensus on the appropriate maximum dose of radiation when IMRT technique is used.

Intraoperative radiation therapy (IORT) is sometimes used in resectable cases and may be best when resection may result is close or involved margins.[211] IORT is delivered with electron beam radiation (IOERT) or high dose rate brachytherapy (HDR-IORT). It is generally delivered in a single fraction of 15-20 Gy and in combination with adjuvant or neoadjuvant chemoradiation therapy. IORT can also be delivered in combination with external beam radiation therapy (EBRT, 10-20 Gy).

Patients who have received neoadjuvant chemoradiation or chemotherapy are candidates for additional chemotherapy following surgery. Adjuvant chemotherapy or adjuvant chemoradiation should only be considered for patients who have adequately recovered from surgery; treatment should ideally be initiated within 4 to 8 weeks. It is recommended that the patient undergo a pretreatment baseline assessment following surgery, including CT scan and CA 19-9 level, to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Further, the Panel recommends restaging a patient with a CT scan following systemic chemotherapy, if it will precede chemoradiation.

Preoperative (Neoadjuvant) Therapy

Novel contemporary approaches to adjuvant therapy have focused on preoperative (neoadjuvant) therapy for patients with borderline resectable disease with the goal of improving overall survival.[212, 213] The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of resectable patients will receive chemotherapy and/or radiation, the potential to downsize tumors so as to increase the likelihood of a margin-free resection (ie, conversion 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.[99, 214-216]

Neoadjuvant therapy in resectable disease

A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[213, 214, 217-225] 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.[218] The authors suggest that preoperative therapy gives a selection advantage, in that approximately 25% of patients who are restaged after therapy are found to have progressive disease and are therefore spared the morbidity of a surgical procedure that would not benefit them.[218] 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.[218]

Although most studies investigating the neoadjuvant experience in patients with pancreatic cancer are retrospective, several small phase II studies have been published. In a randomized phase II trial evaluating the safety and efficacy of gemcitabine-based chemotherapy regimens as neoadjuvant therapy for patients with resectable pancreatic cancer, more patients receiving combination therapy were able to undergo resection compared with those in the gemcitabine-only arm.[223]

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.[225] Although all patients were able to complete neoadjuvant therapy, at the time of restaging, only 73 (85%) patients

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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.[182] 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.[215] 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,[227] results of randomized trials addressing this issue have yet to be reported. A phase III trial with a PFS endpoint comparing adjuvant therapy with a combination of neoadjuvant and adjuvant therapy is currently recruiting patients (Clinicaltrials.gov NCT01314027).[228] A phase II trial with R0 resection as the primary endpoint is also recruiting patients with resectable disease (NCT01389440). At this time, the Panel does not recommend neoadjuvant therapy for resectable patients, except on a clinical trial.

Neoadjuvant therapy in borderline resectable disease

The use of neoadjuvant therapy in the setting of borderline resectable disease is a highly debated topic. Although there is no high-level evidence supporting its use, many NCCN centers prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease, and the Panel recommends neoadjuvant therapy as an option (category 2B) to upfront resection following clinical staging of disease as borderline resectable. Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerated. A phase I/II trial of neoadjuvant therapy in borderline resectable disease allowed 4 of 26 patients (15%) to be resected.[229] A randomized phase II trial comparing 2 different neoadjuvant regimens in borderline resectable disease terminated early due to poor accrual, but 5 of 21 patients (24%) were resected.[230] In 2 recently published retrospective reviews, 31-35% of borderline resectable patients who completed neoadjuvant therapy had R0 resections.[231, 232] A recent systematic review and meta-analysis of 19 cohort studies found that unresectable patients (including both borderline and unresectable patients) undergoing neoadjuvant chemoradiation therapy had similar 1-year survival outcomes as patients who were initially deemed resectable.[233] 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 that 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 (ex, clinicaltrials.gov NCT01268384, NCT00557492, and NCT01359007). Additional randomized trials are needed.

EUS-directed biopsy is the preferred method of obtaining histological confirmation of disease in these patients, and such confirmation is

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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, is also recommended (category 2B) before and after neoadjuvant therapy. Furthermore, patients for whom neoadjuvant therapy is planned should be assessed for jaundice, and placement of a stent is recommended prior to initiation of neoadjuvant therapy in patients with jaundice.[161-163]

Although there is insufficient evidence to recommend specific neoadjuvant regimens, most neoadjuvant regimens incorporate RT, and practices vary with regards to chemotherapy and chemoradiation. Neoadjuvant therapy regimens are often similar to those used to treat locally advanced disease (see section on 'Chemoradiation for Locally Advanced Disease,' below) and include upfront continuous infusion 5-FU- or capecitabine-based chemoradiation,[215, 234] upfront gemcitabine-based chemoradiation,[226] or 2 to 4 cycles of induction chemotherapy followed by 5-FU- or gemcitabine-based chemoradiation.[162] Options for radiation include 45-54 Gy in 1.8-2.5 Gy fractions or 36 Gy in 2.4 Gy fractions.[225] Abdominal (pancreas protocol), pelvic, and chest imaging should be repeated following neoadjuvant therapy, and surgical resection should only be attempted if there is a high likelihood of achieving an R0 resection. Surgery is ideally performed 6 to 8 weeks following therapy. Surgery can be performed more than 8 weeks following therapy, but radiation-induced fibrosis may potentially make surgery more difficult.

Recurrent Disease

As cross-sectional body imaging has improved, small-volume metastatic disease or local recurrence is being detected in patients with pancreatic cancer who are otherwise maintaining good functional status. As many as 50% of them will continue to maintain a sufficiently good performance status to consider second-line therapy.[235] 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; best supportive care without salvage therapy should also be an option, especially for patients with poor performance status. Alternatively, chemoradiation can be considered in patients with local disease recurrence only, if not previously administered, or an alternative chemotherapy regimen can be given. For patients for whom there is evidence of metastatic disease (with or without a local recurrence), treatment decisions are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed less than 6 months prior to development of metastatic disease, the Panel recommends that an alternative chemotherapy option be administered. When this period is greater than 6 months, systemic therapy as previously administered or an alternative systemic regimen is recommended.

Recommended regimens are as for second-line therapy in metastatic disease (also see 'Principles of Chemotherapy' in the guidelines), and may consist of gemcitabine or gemcitabine-based combination therapy for patients previously treated with fluoropyrimidine-based therapy or fluoropyrimidine-based therapy for patients previously treated with gemcitabine-based therapy. Examples of appropriate second-line fluoropyrimidine-based therapies recommended by the Panel are 5-FU/leucovorin/oxaliplatin or CapeOx.[236, 237] Gemcitabine-based therapies include those listed in 'Chemotherapy for Locally Advanced or Metastatic Disease,' below.

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Chemotherapy for Locally Advanced or Metastatic Disease

Systemic therapy is used in the adjuvant setting and in the management of locally advanced unresectable and metastatic disease. The primary goals of treatment for advanced pancreatic cancer are palliation and improved survival. Although some effect on survival may be achieved, these benefits are usually limited to patients with adequate performance status (ECOG 0-1, with good pain management, patent biliary stent, and adequate nutritional intake). Patients who present with very poor performance status may benefit from the administration of gemcitabine (category 1 recommendation), but comfort-directed measures are always paramount (see NCCN Supportive Care Guidelines). Before initiating cytotoxic therapy, an open dialogue regarding the goals of treatment should take place, and adjunctive strategies should be discussed including nonsurgical bypass and celiac block for pain (see 'Palliation of Locally Advanced and Metastatic Disease,' below, and 'Principles of Palliation and Supportive Care' in the guidelines). Of note, debilitated patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumor progression may develop quickly, and tumor-related symptoms may be inappropriately attributed to chemotherapy or other causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or in its more subtle form, as abdominal bloating, decreased oral intake, and constipation.

For patients who derive clinical benefit from initial chemotherapy treatment in the setting of locally advanced disease without developing distant disease, subsequent chemoradiation may enhance local control (see 'Chemoradiation for Locally Advanced Disease,' below).

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

Leucovorin Shortage

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

FOLFIRINOX

In 2003, a French group reported the results of an open phase I study to assess the feasibility of a combination therapy consisting of 5-FU/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) for the treatment of patients with metastatic solid tumors.[238] 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.[239] A later randomized phase II trial showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.[240]

Results from the randomized phase III PRODIGE trial evaluating the regimen of FOLFIRINOX vs. gemcitabine alone in patients with metastatic pancreatic cancer and good performance status showed

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dramatic improvements in both median progression-free survival (6.4 months vs. 3.3 months; P<0.001) and median overall survival (11.1 months vs. 6.8 months; P<0.001), in favor of the group receiving FOLFIRINOX.[241] Because of these strong results, the Panel added FOLFIRINOX as a category 1 recommendation for first-line treatment of good performance status patients with metastatic pancreatic cancer in 2011. It is listed as a category 2A recommendation for patients with locally advanced unresectable disease by extrapolation.

There are, however, some concerns about the toxicity of the FOLFIRINOX regimen. In the PRODIGE trial, some of the grade 3/4 toxicity rates that were significantly greater in the FOLFIRINOX group than in the gemcitabine group were 45.7% for neutropenia, 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9.0% for sensory neuropathy.[241] Despite the high levels of toxicity, no toxic deaths have been reported.[239-241] 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% versus 66%, P<0.01).

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

Gemcitabine

For patients with locally advanced or metastatic disease, gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU.[242] The NCCN Panel recommends gemcitabine monotherapy as one option for front-line therapy for patients with metastatic disease (category 1). The NCCN Panel also recommends gemcitabine monotherapy as an option for patients with unresectable, locoregional disease and a good performance status (category 2A).

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

Fixed-Dose-Rate Gemcitabine

Recent studies have suggested that the infusion rate of gemcitabine may be important for its efficacy. Gemcitabine is a prodrug, which must be phosphorylated for antitumor activity. Clinical studies have shown that administering gemcitabine at a fixed-dose rate (FDR; 350 mg/m^2/minute) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.[243] In a randomized phase II trial, the infusion of gemcitabine at a FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.[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 vs. standard gemcitabine (6.2 months vs. 4.9 months; P=0.04), although this outcome did not satisfy the protocol-specified criteria for superiority.[245] When gemcitabine is considered for the treatment of advanced pancreatic cancer, the NCCN Panel views FDR gemcitabine (10 mg/m^2/minute) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B).

FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX; [gemcitabine, oxaliplatin] and GTX [gemcitabine, docetaxel, and capecitabine], see 'Gemcitabine Combinations,' below).[246, 247]

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Gemcitabine Combinations

The NCCN Panel also acknowledged that, historically, combination chemotherapy has not appeared to be superior to monotherapy in the era of 5-FU-based therapy. However, because gemcitabine is superior to bolus 5-FU when efficacy end points of survival and relief from symptoms are used, it is now often combined with other chemotherapeutic agents for patients with good performance status. Gemcitabine has been investigated in combination with potentially synergistic agents (such as cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan) or in a multidrug combination (eg, cisplatin, epirubicin, gemcitabine, and 5-FU).[245-258]

Recommended combinations are discussed below. The Panel does not consider the combination of gemcitabine plus docetaxel[259] or gemcitabine plus irinotecan[258-260] to meet the criteria for inclusion in the guidelines.

Gemcitabine plus erlotinib

Although phase II trial results of gemcitabine combined with new targeted drugs (eg, bevacizumab, cetuximab) were encouraging,[261, 262] 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.[263-267] Results of the Cancer and Leukemia Group B (CALGB) phase III trial, which evaluated gemcitabine and bevacizumab (an anti-VEGF [vascular endothelial growth factor] antibody) compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer, and the Southwest Oncology Group (SWOG) phase III randomized trial, which assessed cetuximab (which targets the epidermal growth factor receptor [EGFR]) plus gemcitabine versus gemcitabine alone did not reveal improvements in survival upon addition of the biologic agent.[264, 265] In a phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer, bevacizumab did not improve overall survival, although a significant improvement in progression-free survival was observed with the addition of bevacizumab to the gemcitabine/erlotinib combination.[267] A recent randomized phase III trial of another VEGF inhibitor, axitinib, in combination with gemcitabine also failed to show any improvement in overall survival of patients with advanced pancreatic adenocarcinoma.[268]

In contrast, in a phase III, double-blind, placebo-controlled 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 overall survival (hazard ratio=0.82; P=0.038) and progression-free survival (hazard ratio=0.77; P=0.004) when compared to patients receiving gemcitabine alone.[263] 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.[263]

Erlotinib in combination with gemcitabine has been approved by the Food and Drug Administration (FDA) for first-line treatment of patients with locally advanced unresectable or metastatic pancreatic cancer. The NCCN Panel recommends gemcitabine-erlotinib combination therapy as an option for patients with locally advanced or metastatic disease and good performance status (category 1).

Gemcitabine plus cisplatin

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

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trials have not provided support for use of gemcitabine plus cisplatin in the treatment of patients with advanced pancreatic cancer. Three phase III trials evaluating the combination of gemcitabine with cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination over the single agent.[249, 250, 253]

Nevertheless, selected patients may benefit from this regimen since patients with breast and ovarian cancers who are carriers of a *BRCA* mutation,[269, 269] and selected patients with inherited forms of pancreatic cancer[28] 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.[270] Patients with a family history of pancreatic cancer alone demonstrated a large survival advantage when treated with platinum-based chemotherapy (6.3 vs. 22.9 months, HR 0.34, 95% CI 0.15-0.74; $p < 0.01$).[270] Further, in a recent report, 5 of 6 patients with known BRCA mutations and metastatic pancreatic adenocarcinoma treated with a platinum-based regimen at Memorial Sloan-Kettering Cancer Center showed a radiographic partial response.[271] Thus, gemcitabine plus cisplatin may be a good choice in selected patients with disease characterized by hereditary risk factors (eg, *BRCA* or *PALB2* mutations). The Panel recommends gemcitabine plus cisplatin for metastatic patients, especially those with possible hereditary cancers, as a category 2A recommendation.

Gemcitabine plus fluoropyrimidine

A number of randomized trials have investigated the combination of gemcitabine with a fluoropyrimidine in patients with advanced pancreatic cancer. The ECOG E2297 trial compared gemcitabine monotherapy with gemcitabine and bolus 5-FU/leucovorin in patients with advanced pancreatic cancer; no statistically significant survival advantage was observed for patients receiving the combination regimen.[248] A randomized study in 533 patients with advanced cancer found that progression-free survival and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine when compared with gemcitabine alone, although a trend toward an improvement in overall survival for the combination arm did not reach statistical significance.[251] Similarly, results from another smaller phase III trial evaluating this combination did not demonstrate an overall survival advantage for overall study population receiving the combination of gemcitabine with capecitabine, although a post-hoc analysis showed overall survival to be significantly increased in the subgroup of patients with good performance status.[255] Although there are concerns about dosing and toxicity of capecitabine in a U.S population, results from a recent phase I study suggest that a biweekly regimen of fixed-dose gemcitabine in combination with capecitabine is both effective and well tolerated in patients with advanced disease.[272] Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.[252, 253, 255]

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

Gemcitabine plus nab-paclitaxel

The Panel includes the combination of gemcitabine plus nab-paclitaxel as a category 2B recommendation for the treatment of patients with advanced disease and good performance status. Nab-paclitaxel is an

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albumin-bound nanoparticle form of paclitaxel. In a publication of a phase I/II trial, 67 patients received gemcitabine plus nab-paclitaxel. At the maximum tolerated dose, the partial response rate was 48%, with an additional 20% of patients demonstrating stable disease for ≥16 weeks. The median overall survival at this dose was 12.2 months.[273]

GTX regimen

The Panel included the combination of gemcitabine, docetaxel, and capecitabine (GTX regimen) as a category 2B recommendation for the treatment of patients with advanced disease and good performance status. In a report of 35 patients with metastatic pancreatic cancer treated with this regimen, the authors reported an overall response rate of 29% (all had partial responses), with an additional 31% of patients exhibiting a minor response or stable disease.[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% with grade 3/4 anemia. A recent retrospective case-review study at Johns Hopkins found similar results, with a median overall survival of 11.6 months and grade 3 or greater hematologic and non-hematologic toxicity rates of 41% and 9%, respectively.[274]

Capecitabine

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

Fluoropyrimidine Plus Oxaliplatin

The combination of a fluoropyrimidine (5-FU/leucovorin or capecitabine) with oxaliplatin is also listed as a possible first-line treatment for metastatic or locally advanced disease (category 2B). The Panel bases these recommendations on the randomized phase III CONKO-003 trial (5-FU/leucovorin/oxaliplatin vs. best supportive care) and on a phase II study (CapeOx).[236, 237] Both of these studies only enrolled patients who had received 1 prior chemotherapy regimen, but the Panel feels the extrapolation to first-line therapy is appropriate (category 2B).

Chemoradiation for Locally Advanced Disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer, although the utility of chemoradiation in this population of patients is controversial.[276] It is used in selected patients who do not develop metastatic disease during initial chemotherapy and occasionally before chemotherapy. The role of chemoradiation was initially defined in a trial conducted by GITSG.[193] In this study, the combination of bolus 5-FU and split-course radiation (total dose, 4,000 cGy) was compared with radiation alone or with 6,000 cGy combined with 5-FU. A nearly 2-fold increase in median survival (42.2 versus 22.9 weeks) was observed with the regimen of bolus 5-FU and 4,000 cGy compared with radiation alone. Subsequent generations of studies have sought to optimize the use of 5-FU, and most contemporary studies no longer use split-course radiation.[277] Gemcitabine has also been used as a radiation sensitizer.[183, 226, 278-282] There is evidence to suggest that concurrent gemcitabine and radiation can yield similar or better outcomes when compared with 5-FU-based chemoradiation.[277, 281, 283, 284]

Chemotherapy without radiation therapy is also an option for patients with locally advanced pancreatic cancer, especially for patients with

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poor performance status. Results of 2 randomized trials comparing chemoradiation to chemotherapy in locally advanced disease were contradictory.[285, 286] The phase III randomized trial ECOG-4201, which assessed gemcitabine compared with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer, was closed early due to poor accrual. However, an ITT analysis of data for the 74 patients enrolled in this study showed that median overall survival was significantly longer in the chemoradiation therapy arm of the study (11.1 months vs. 9.2 months; P=0.017).[287] However, the poor accrual rate decreased its statistical power, there was no difference in progression-free survival, and the confidence intervals for overall survival overlap 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.[288] The benefit of chemotherapy versus chemoradiation was also addressed in the phase III FFCD-SFRO study from France, in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[289] In this study, gemcitabine alone was associated with a significantly increased overall survival rate at 1 year compared with chemoradiation (53% vs. 32%; HR=0.54, 0.31-0.96; P=0.006). This study was stopped before the planned accrual, because an interim analysis revealed that patients in the chemoradiation arm had a lower survival rate. Also, patients in the chemoradiation arm experienced severe toxicity and were more likely to receive a shorter course of maintenance therapy with gemcitabine, suggesting that the observed differences in survival were most likely attributable to the extreme toxicity of this particular chemoradiation regimen.

Chemoradiation as conversion therapy

Some studies have addressed the use of chemoradiation with or without chemotherapy to convert selected patients with locally unresectable disease to a resectable status.[212-214, 216, 290] Patients with a significant response to chemotherapy and/or chemoradiation may be considered for surgical resection, although there is no definitive evidence at this time to support this intervention. Following resection, these patients have similar survival rates as those initially determined to be resectable.[291]

Recommendations for Chemoradiation

Starting with 2 to 6 cycles of systemic chemotherapy (see 'Chemotherapy for Locally Advanced or Metastatic Disease,' above) followed by consolidation chemoradiation therapy is the preferred recommended option for patients with unresectable disease and good performance status who have not developed metastatic disease.[282-284] 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. If patients present with poorly controlled pain or local obstructive symptoms, however, it may be preferable to start with upfront chemoradiation therapy.[278, 280] Three phase II trials have assessed the upfront chemoradiation approach in locally advanced pancreatic adenocarcinoma, with median survival rates ranging from 8.2 to 9 months.[278, 295-297] Employing an initial course of chemotherapy may facilitate systemic disease control while simultaneously helping to uncover whether the disease is rapidly progressive. For example, a retrospective analysis of outcome from the GERCOR studies indicated that first-line treatment with chemotherapy may be a useful strategy for

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selecting patients with locally advanced disease who are more likely to benefit from subsequent chemoradiation therapy.[292]

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

Radiation is given with concurrent gemcitabine,[182, 236, 278-282, 298] capecitabine, or continuous infusion 5-FU.[277] For primary definitive chemoradiation therapy, the NCCN recommends one of two options: 1) 45-54 Gy in 1.8-2.5 Gy fractions for 5-FU-based chemoradiation regimens or 2) 36 Gy in 2.4 Gy fractions for gemcitabine-based chemoradiation regimens.[281] Use of CT simulation and 3-D treatment planning is strongly encouraged. Treatment volumes should be based on CT scans and surgical clips/fiducials (when placed).

Intensity-modulated radiotherapy (IMRT) is increasingly being applied for therapy of locally advanced pancreatic adenocarcinoma with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues.[299-301] 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.[301] While the authors concluded that the IMRT plans would allow for significant increase in target volume dose with substantial dose reductions to local organs at risk, there is no clear consensus on the appropriate maximum dose of radiation when IMRT is used.

Stereotactic body radiotherapy (SBRT) is another technique aimed at increasing dose to the gross tumor while sparing radiation to nearby healthy tissue. Retrospective analysis of 77 patients with unresectable disease demonstrated that while SBRT gave effective local control, it gave no improvement to overall survival and was associated with significant toxicities.[302] However, another retrospective review of 71 patients reported a median overall survival of 10.3 months with only 3 patients (4%) experiencing grade 3 toxicity.[303] There is no standard total dose or dose per fraction established for SBRT, and the Panel currently recommends that SBRT only be utilized as part of a clinical trial.

Second-Line Therapy

For patients who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable options.[236, 297, 304] The Panel includes capecitabine, 5-FU/leucovorin/oxaliplatin,[236] and CapeOx[237] as options. Note that the capecitabine dose recommended in the guidelines (1,000 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).[305] Chemoradiation can also be given as salvage therapy in patients with locally advanced unresectable disease if it was not previously given and if the primary site is the sole site of progression.

Of note, results from the phase III CONKO-003 trial presented in 2008 showed significant improvements in both median progression-free

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survival (13 weeks vs. 9 weeks; P=0.012) and median overall survival (20 weeks vs. 13 weeks; P=0.014) when oxaliplatin was added to 5-FU/leucovorin,[306, 307] making this regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy. Recently published results from this trial demonstrated the superiority of 5-FU/leucovorin/oxaliplatin over best supportive care in both median second-line survival (4.82 months vs. 2.30 months; P=0.008) and median overall survival (9.09 months vs.7.90 months; P=0.031).[236]

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.[308]

- With the emergence of new agents to treat pancreatic cancer, particularly biologics, clinical trial strategies incorporating principles of molecular biology and new imaging methods as well as results from preclinical studies are important.
- For patients enrolled in clinical trials, banking of tumor tissue samples should be required along with paired blood and serum samples.
- Biomarkers which serve as surrogate markers of the anticancer effects of investigational agents should be sought, and assays to measure such biomarkers should be well validated.
- Clinical trials should enroll homogeneous patient populations with respect to disease stage (ie, separate trials for patients with locally advanced disease and metastatic disease) and patient performance status; criteria for selecting study populations should take into account the putative differential efficacy of the agent (ie, vaccines in patients with early-stage disease).
- Phase III trials should not be initiated in the absence of clinically meaningful efficacy and safety signals in the phase II setting.
- Phase II and III clinical trials should have a primary endpoint of overall survival.
- Quality control standards for preoperative imaging interpretation, pathologic assessment of tumor specimens, and surgical selection criteria are critical when evaluating adjuvant therapies.

A more recent consensus report from a group of European experts came to many of the same conclusions.[309] Additionally, the group states that FOLFIRINOX can be considered as a new standard treatment option in selected patients in future clinical trials, but that gemcitabine should remain the standard for most patients. An international expert panel also met recently to discuss current and future pancreatic cancer research and came to similar conclusions.[235]

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Palliation of Locally Advanced and Metastatic Disease

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that are, in many respects, unique to the disease. For patients with locally advanced unresectable and metastatic disease, the multidisciplinary management of symptoms due to biliary obstruction, gastric outlet obstruction, and cancer-related pain is of primary importance. The main objective of palliative care is to prevent and ameliorate suffering, while ensuring optimal quality of life. Palliative surgical procedures are best reserved for patients with longer life expectancies.

Biliary Obstruction

Approximately 65-75% of patients with pancreatic cancer develop symptomatic biliary obstruction.[310] For patients diagnosed with unresectable disease and biliary obstruction on initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent self-expanding metal stent (SEMS) is recommended unless biliary bypass is performed (also see the discussion on stents in 'Preoperative Biliary Drainage,' above). Stent occlusion that causes recurrent cholangitis is a well-know complication of plastic (temporary) biliary stents and typically occurs within 3 months of insertion. Metal stents are wider in diameter than plastic stents (ie, less likelihood of blockage) and become embedded in the bile duct, whereas plastic stents are more likely to become occluded but can be replaced. Results of a randomized, controlled trial of 100 patients at a single center randomly assigned to receive either a plastic stent or a covered self-expanding metal stent inserted endoscopically indicated that median patency times were 1.8 and 3.6 months (P=0.002), respectively.[311] A metaanalysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.[312] This study suggested that the risk of recurrent biliary obstruction was lower for the metal stents (RR=0.52, 95% CI 0.39-0.69), although no significant differences in technical/therapeutic success, complications, or 30-day mortality were found.

When a biliary stent cannot be placed (often because the endoscope cannot be advanced passed the neoplasm that is obstructing the gastric outlet), percutaneous biliary drainage with subsequent internalization may be necessary. An alternative is to sequentially dilate the duodenum endoscopically, place a metallic biliary stent, and then place an enteral stent.[313] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.[312]

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors following laparotomy, an open biliary-enteric bypass provides durable palliation of biliary obstruction and can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain. The Panel recommends stenting or an open biliary-enteric bypass with or without duodenal bypass (category 2B for prophylactic duodenal bypass[314, 315]) and with or without open ethanol celiac plexus block[316-318] (category 2B). Please see 'Gastric Outlet Obstruction' and 'Severe Tumor-Associated Abdominal Pain,' below for more detailed information on these procedures. Bypass of the common bile duct (choledochojejunostomy) or common hepatic duct (hepaticojejunostomy) to the jejunum is preferred to bypass of the gallbladder (cholecystojejunostomy) since choledochojejunostomy / hepaticojejunostomy provide more durable and reliable palliation of biliary obstruction.[310]

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Biliary decompression is also required for jaundiced patients with disease progression precluding surgery with or without neoadjuvant therapy. Here, stenting or biliary bypass is recommended, with or without duodenal bypass (category 2B for prophylactic duodenal bypass[314, 315]) and with or without open ethanol celiac plexus block (category 2B). One final circumstance requiring biliary drainage is in jaundiced patients with locally advanced or metastatic disease (those for whom surgical resection will not be attempted). In this situation, a self-expandable metal stent (SEMS) is preferred, unless biliary bypass was performed at the time of laparoscopy or laparotomy. However, several Panel members reported that their institutions use plastic stents in patients with short life expectancies, due to the lack of concern about long-term patency.

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10%-25% of patients with pancreatic cancer.[310] 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.[313] 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 (i.e., 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.[319-321] 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. The role of prophylactic gastrojejunostomy in otherwise asymptomatic patients who are found to have unresectable cancers at the time of laparotomy has been evaluated. Two randomized controlled trials have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer, the majority arising from the head of the pancreas.[314, 315] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. In both studies, prophylactic retrocolic gastrojejunostomy significantly decreased the incidence of late gastric outlet obstruction but did not extend the length of stay or increase complication rates, such as delayed gastric emptying.

Severe Tumor-Associated Abdominal Pain

Most patients with locally advanced or metastatic pancreatic cancer experience cancer-related pain.[316] General principles for cancer-related pain management can be found in the NCCN Adult Cancer Pain Guidelines. Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, open ethanol celiac plexus neurolysis should be considered. In 2 randomized controlled trials, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.[316, 318] In a recent study of 96 patients with pain related to suspected pancreatic cancer, half were randomized to EUS-guided celiac plexus neurolysis at the time of EUS if unresectable adenocarcinoma was confirmed.[317] These patients reported better pain relief at 3 months (P=0.01), suggesting that early EUS-guided celiac plexus neurolysis may be beneficial. Minimally invasive techniques including EUS-guided (preferred if available) and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis are

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recommended, but laparoscopic, thoracoscopic, and open approaches can also be used.

In selected patients with severe local back pain, palliative radiation therapy may be considered, even in the setting of metastatic disease, if not already given as part of primary therapy. In such cases, radiation is given with or without concurrent chemotherapy to the primary tumor plus a margin (typically 30-36 Gy in 2.4-3.0 Gy fractions), or radiation alone is given to the metastatic site.

Pancreatic Insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or blockage of the pancreatic duct, as well as by surgical removal of pancreatic tissue, and results in an inadequate production of digestive enzymes.[322, 323] This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.[324] Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency. Because pancreatic insufficiency occurs in up to 94% of patients undergoing pancreatic surgery,[325, 326] therapy may be initiated without diagnostic tests. Enteric-coated mini-microspheres containing preparations of pancreatic enzymes are taken orally (25,000 to 75,000 units of lipase for a main meal and 10,000 to 25,000 units of lipase for a snack, depending on fat content), with half of the dose taken at the start of the meal and half taken in middle of the meal.[324] For patients failing this therapy, doses of the enzyme preparation can be increased, and inhibition of gastric secretion with a proton pump inhibitor can also be considered.[324, 325] Patients with a clinical suspicion of pancreatic insufficiency despite appropriate replacement may need a more thorough nutritional evaluation.

Thromboembolic Disease

The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.[327] 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.[328] In the CONKO 004 trial, VTE- and chemotherapy-naïve patients with advanced pancreatic cancer were randomized to receive palliative chemotherapy with or without the LMWH, enoxaparin.[329] The risk of developing symptomatic VTE was significantly lower for patients in the LMWH arm of the study with no significant increase in bleeding observed in this group compared to those not receiving enoxaparin.

Depression, Pain, Malnutrition

The Panel recommends that patients with locally-advanced or metastatic pancreatic cancer receive a formal evaluation by a Palliative Medicine Service, when appropriate. Additional resources are detailed in the NCCN Palliative Care Guidelines; NCCN Adult Cancer Pain Guidelines; and the NCCN Distress Management Guidelines.

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Surveillance

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited, recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The Panel recommends history and physical examination for symptom assessment every 3 to 6 months for 2 years, then annually. CA 19-9 determinations and follow-up CT scans every 3 to 6 months for 2 years after surgical resection are category 2B recommendations, because data are not available to show that earlier treatment of recurrences, following detection by increased tumor marker levels or CT scan, leads to better patient outcomes.

Summary

Resection remains the only chance for a cure of pancreatic adenocarcinoma, and resectable patients should under surgery without delay, followed by adjuvant therapy. Borderline resectable patients can undergo neoadjuvant therapy (category 2B) in the hopes of improving the chances for an R0 resection or can go immediately to surgery. Salvage therapy is an option for those patients whose disease recurs following surgery. Patients with locally advanced unresectable disease and good performance status can undergo chemotherapy and chemoradiation with second-line therapy if performance status is maintained after progression. Good performance status patients presenting with metastatic disease can undergo chemotherapy and can undergo second-line therapy if performance status is maintained after progression. Specific palliative measures are recommended for patients with advanced pancreatic adenocarcinoma characterized by biliary or gastric obstruction, severe abdominal pain, or other tumor-associated manifestations of the disease.

Overall, in view of the relatively high likelihood of a poor outcome for patients with all stages of pancreatic cancer, the NCCN Panel recommends that investigational options be considered in all phases of disease management.

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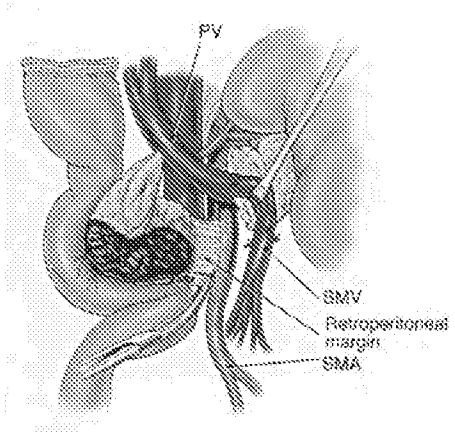

Figure 1. Complete mobilization of the superior mesenteric (SMV) and portal veins, and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA).[330]

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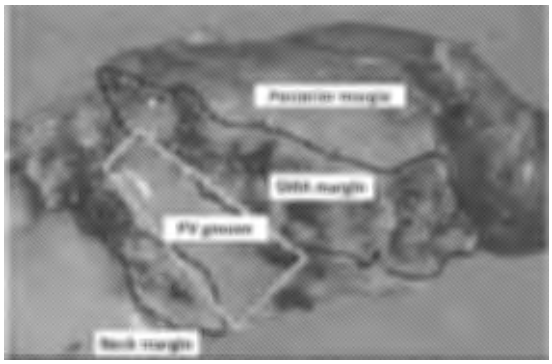

Image courtesy of Dr. N. Volkan Adsay

Figure 2. Whipple specimen with labeled margins.

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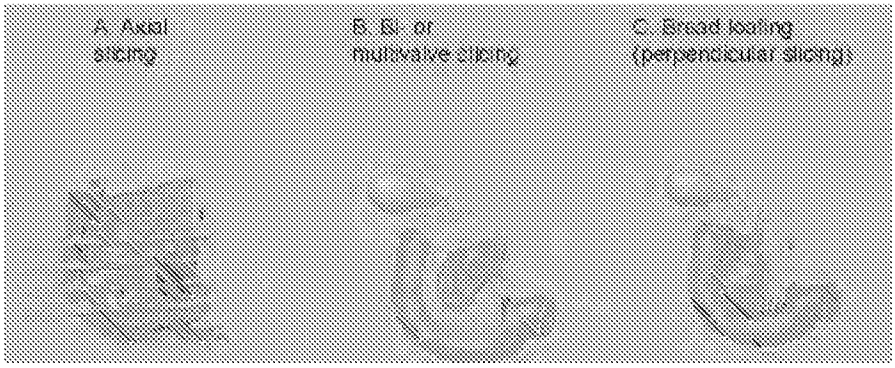

Figure 3. Slicing of pancreatoduodenectomy specimens.[182]

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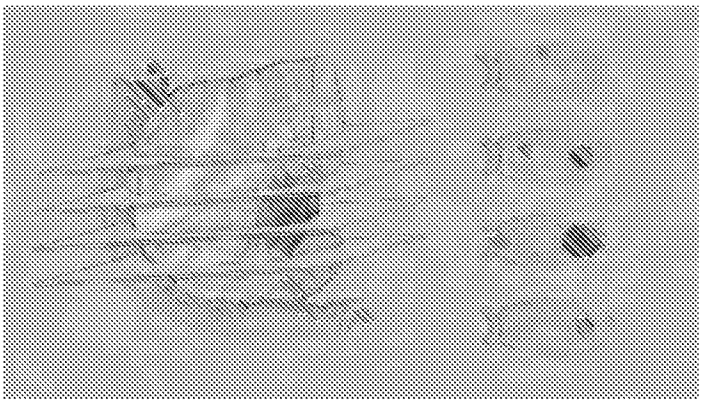

Figure 4. Slicing of the pancreatoduodenectomy specimen in the axial plane to allow circumferential assessment of tumor.[182]

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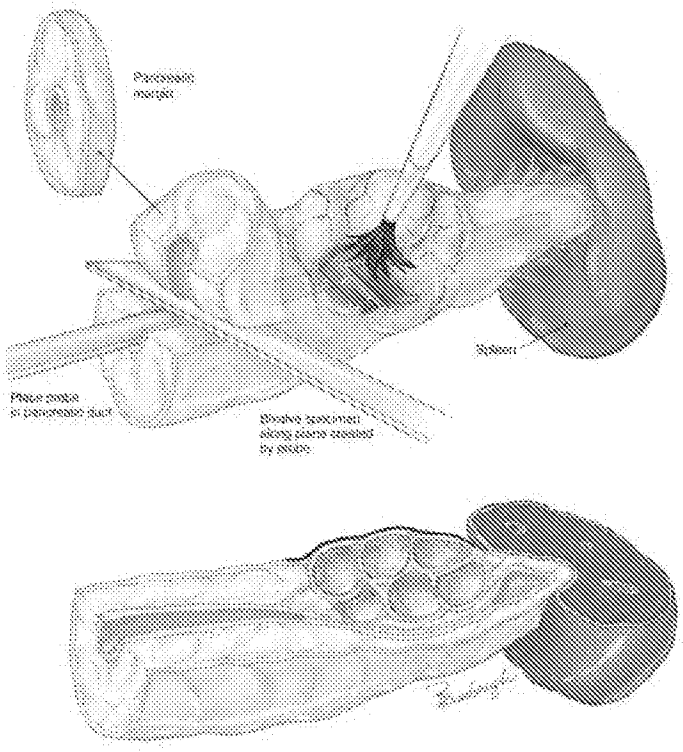

Figure 5. Slicing of the distal pancreatectomy specimen.[186]

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pancreatic Adenocarcinoma

Version 2.2014

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See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2014
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Pancreatic Table of Contents
Discussion

Updates in Version 2.2014 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2014 include:

General

- For clarification, "nab-paclitaxel" was changed to "albumin-bound paclitaxel" throughout the guidelines.

MS-1

- The discussion section was updated to reflect the changes in the algorithm.

Updates in Version 1.2014 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2013 include:

PANC-1

- Workup, following no mass in pancreas on imaging:
  - No metastatic disease: MRI/magnetic resonance cholangiopancreatography (MRCP) was moved before ERCP.
  - Metastatic disease: EUS was added as an option.

PANC-2

- To be consistent with the Preoperative CA 19-9 (category 3) recommendation for those patients with no symptoms of cholangitis and fever, "category 3" was added to Preoperative CA 19-9 for patients with symptoms of cholangitis or fever present.
- Footnote "c" was revised: "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 may be undetectable in Lewis antigen-negative individuals..."

PANC-3

- Footnote "g" was revised: "In selected patients who appear technically resectable but have poor prognostic features *(ie, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, or extreme pain)* consider neoadjuvant therapy (clinical trial preferred), which requires biopsy confirmation of adenocarcinoma (*see PANC-4*). For patients with biliary obstruction, durable biliary decompression is required."

PANC-4

- Workup
  - Following neoadjuvant therapy after a positive biopsy: "Staging laparoscopy" was modified: "Consider staging laparoscopy if not previously performed."

PANC-5

- Planned resection was changed to a category 2B recommendation.

PANC-6

- "Identification of metastatic disease" was added after "Baseline pretreatment."
- The last sentence of footnote "m" was modified: "If systemic chemotherapy precedes chemoradiation, restaging with ~~a CT scan~~ *imaging* should be done after each treatment modality."

PANC-7

- "Good performance status" and "Poor performance status" were removed after stent placement for confirmed adenocarcinoma.

PANC-8

- Treatment
  - Under chemotherapy, the 4th bullet was modified: "*Gemcitabine + albumin-bound paclitaxel or other* gemcitabine-based combination therapy."
  - Following poor performance status, "Best supportive care" was modified to be "Palliative and best supportive care."
- Footnotes
  - Footnote was added: "Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)"
  - Footnote was added: "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."

Continued on next page

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

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Updates in Version 1.2014 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2013 include:

PANC-3
- Footnote was added: "Although this combination significantly improved survival, the actual benefit was small, suggesting that only a *small* subset of patients benefit."

PANC-A
- Principle #1, the last sentence was revised: "Resections should be done at institutions that perform a large number (*at least* 15-20) of pancreatic resections annually."
- Footnote was added: Indicators of high-risk patients may include borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes.

PANC-B
- Footnote was added: "The panel endorses the use of a more restrictive definition of borderline resectable tumors in clinical trials. (Katz M, Marsh R, Herman J, et al. Borderline resectable pancreatic cancer: Need for standardization and methods for optimal clinical trial design. Ann Surg Oncol. 2013 Aug; 20(8):2787-95.)"

PANC-C
- Bullet was added to "Distal Pancreatectomy": "Spleen preservation is not indicated in adenocarcinoma."

PANC-D (2 of 4)
- Whipple Specimen, histologic sectioning:
  - The 4th sub-bullet was modified: "...Tumor clearance should be reported in millimeters for ~~the 6 MA~~ *all* margins described above to allow prospective accumulation of these important data for future analysis."
  - The last sub-bullet was added: *"Frozen section analysis of the pancreatic neck and bile duct is recommended. 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 to ensure at least 5 mm of clearance."*
- Distal pancreatectomy
  - 1st bullet was revised: "In left-sided resections the peripancreatic soft tissue margins and the pancreatic neck are assessed. Additionally, involvement of the splenic vessels should be documented and invasion of the spleen is important to determine, as direct tumor invasion constitutes a pT4 pathologic stage."

PANC-D (3 of 4)
- Distal Pancreatectomy: "Optional" was added to Anterior (cephalad) peripancreatic (peripheral) surface.
- Footnote "a" was added: Every effort should be made to identify all regional lymph nodes within the pancreatectomy specimen (see Discussion).

PANC-E
- Biliary obstruction, the 1st sub-bullet was revised: "Endoscopic biliary *metal* stent (preferred method)."
- Footnote 1 was modified: "Placement of an enteral stent is particularly important for patients with poor performance status *and should be done after biliary drainage is assured.*"

PANC-F (1 of 3)
- General Principles, the last bullet was modified: "Ideally, patients should be treated on clinical trials when available. Radiation is typically given concurrently with chemotherapy, except in the palliative setting, ~~with intraoperative RT (IORT), or with stereotactic body RT (SBRT).~~"
- Neoadjuvant resectable/borderline resectable, the third sub-bullet was modified: "Induction chemotherapy (2-6 4 cycles) followed by 5-FU- or gemcitabine-based chemoradiation."

PANC-F (2 of 3)
- Adjuvant, the last sentence was modified: "RT 45-48 Gy in 1.8-2 Gy fractions to the tumor bed, surgical anastomoses (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), and adjacent lymph nodes, followed by an additional 5-9 Gy to the tumor bed and anastomoses, *if clinically appropriate*."
- Palliative, the first sub-bullet was modified: "RT alone to the primary tumor plus a margin (Typically 25-36 Gy in 2.4-5 Gy fractions) is reasonable for patients with metastatic disease who require local palliation for obstruction, ~~or~~ pain, *or bleeding*."
- Footnote was added: "Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)"

Continued on next page

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Updates in Version 1.2014 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2013 include:

PANC-F (3 of 6)
- First bullet, the last sentence was revised: "In the neoadjuvant, borderline, and locally advanced settings the pancreatic gross tumor volume (GTV) and pathologic nodes (minimum >1 cm ~~and/or FDG-avid on PET~~) are contoured with assistance from structural (CT/MRI) and functional imaging (PET)."
- Second bullet was modified: "...Further expansion to PTV includes ITV for target/breathing motion and additional margin for patient set-up error (SM). *Image guidance method should be considered when constructing the PTV.* Organs at risk (OARs) should also be contoured and evaluated in the DVH."
- Fourth bullet was modified: "IORT is delivered with electron beam RT (IOERT) or high-dose-rate brachytherapy (HDR-IORT). IORT is generally delivered in a single fraction and in combination with adjuvant or neoadjuvant chemoradiation. The role of IORT for unresectable and resectable cases is controversial *and should only be performed at specialized centers in well selected cases.* ~~but it~~ is ideally used in cases where *surgical* resection may result in close or involved margins.

PANC-F (4 of 6)
- The first bullet was revised: Fractionated RT is typically delivered as 30-~~60~~ *55* Gy over ~3-6 weeks (1.8-3.0 Gy/fraction, *using lower dose per fraction at higher cumulative doses while respecting normal tissue constraints*) with concurrent 5-FU/capecitabine or gemcitabine as a radiosensitizer. *Doses above 55 Gy may be possible in select cases; however, data are limited and normal tissue dose limits (see Table 1) should be maintained.* For resected cases...dose to ~~small~~ bowel *and stomach.* ~~For unresectable disease, 50.4 Gy in 1.8 to 2.8 Gy fractions is recommended. For EBRT it is preferred that high energy photon beams are used.~~ *The use of high-energy photon beams is preferred.* SBRT is often delivered in 1-5 fractions ranging from 5-25 Gy per fraction. IORT can be delivered in a single fraction alone (15-20 Gy) or in combination with EBRT (10-20 Gy).

PANC-G (1 of 3)
- Under Metastatic, the 3rd bullet was revised: "*Second-line chemotherapy may consist of gemcitabine-based therapy for those previously treated with fluoropyrimidine-based therapy, and fluoropyrimidine-based therapy for those previously treated with gemcitabine-based therapy.* Results of the CONKO 003 trial demonstrated a significant improvement in overall survival with the addition of oxaliplatin to 5-FU/leucovorin."
- Footnote was added: "Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)"

PANC-G (2 of 3)
- Neoadjuvant bullet was revised, "Although there is insufficient evidence to recommend specific neoadjuvant regimens, most published neoadjuvant ~~regimens incorporate chemoradiation although chemotherapy alone is currently being evaluated~~ *studies that were done prior to the introduction of more effective combination chemotherapy incorporated chemoradiation. Studies of these more effective regimens (ie, FOLFIRINOX or gemcitabine and albumin-bound paclitaxel) without chemoradiation are in progress.*"

PANC-G (3 of 3)
- References were updated.

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INTRODUCTION

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

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NCCN Guidelines Version 2.2014
Pancreatic Adenocarcinoma

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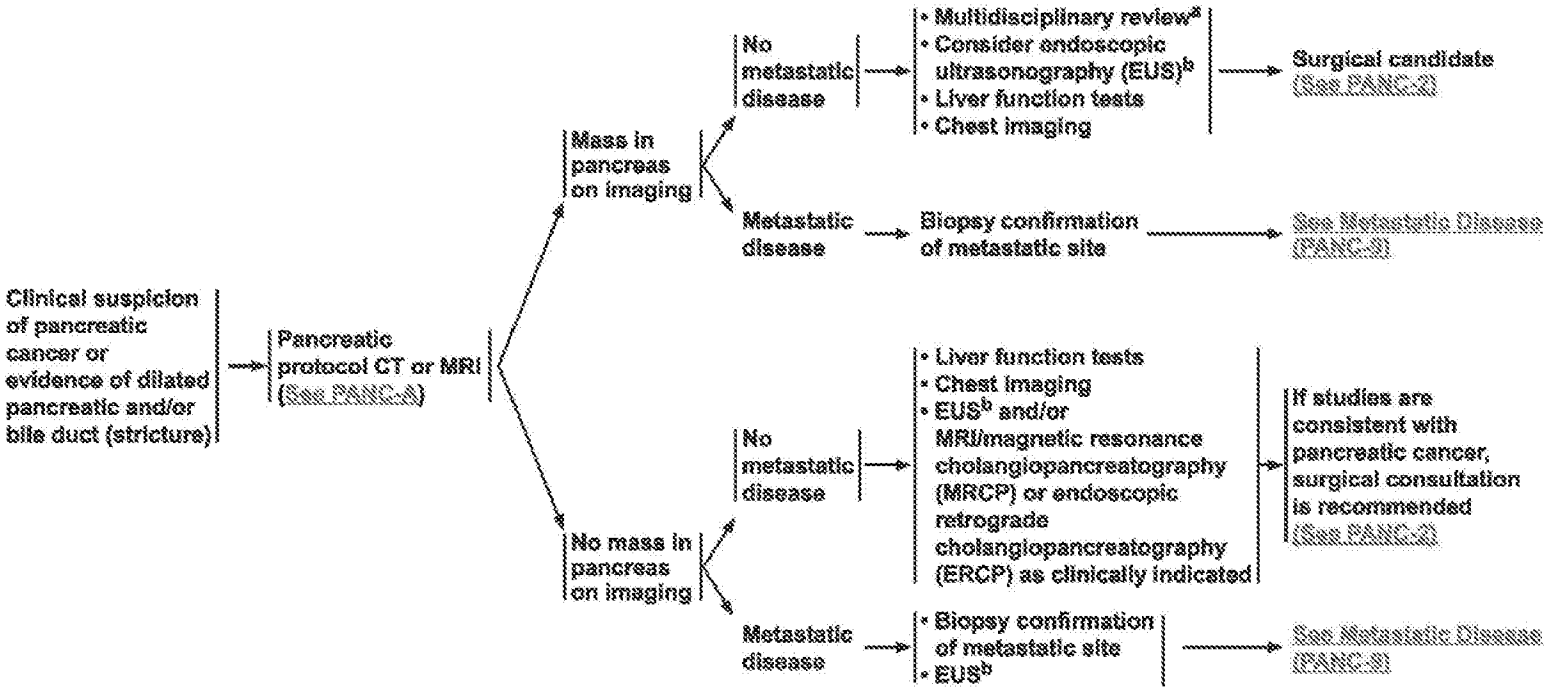
CLINICAL PRESENTATION

WORKUP



[a]Multidisciplinary review should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.
[b]EUS-FNA if clinically indicated.

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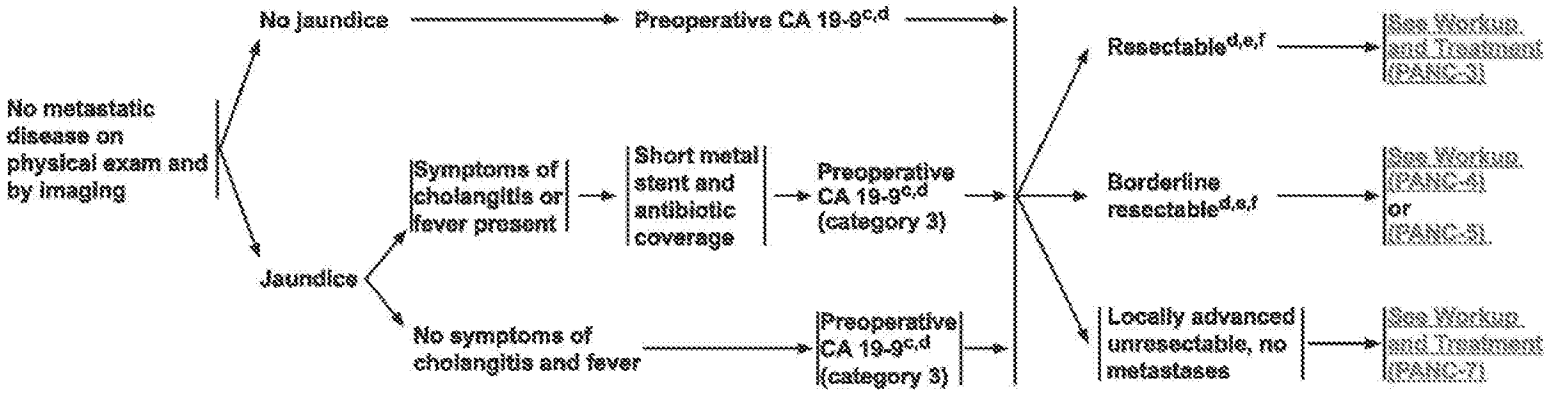

[c]Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary infection (cholangitis), inflammation, or obstruction, benign or malignant. In addition, CA 19-9 may be undetectable in Lewis antigen-negative individuals. (See Discussion)
[d]See Principles of Diagnosis and Staging (PANC-A).
[e]See Criteria Defining Resectability Status (PANC-B).
[f]See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).

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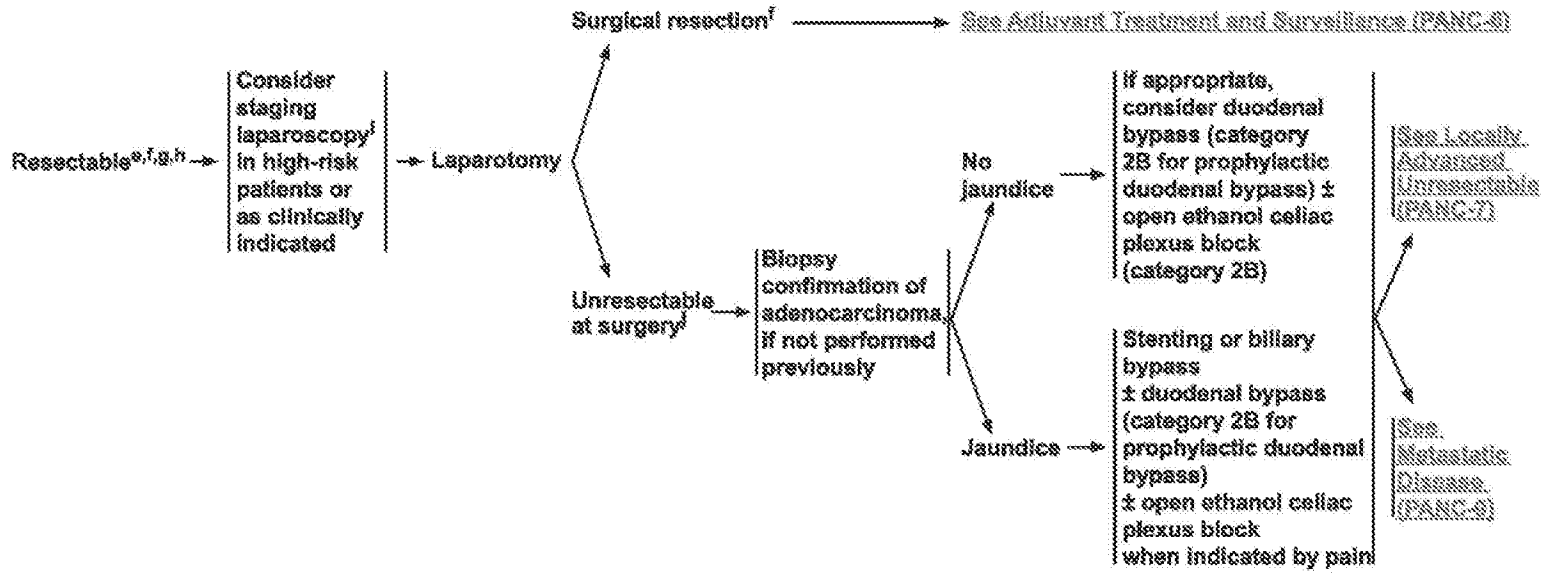
RESECTABLE **WORKUP** **TREATMENT**



[e] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).
[g] In selected patients who appear technically resectable but have poor prognostic features (ie, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, or extreme pain) consider neoadjuvant therapy (clinical trial preferred), which requires biopsy confirmation of adenocarcinoma (see PANC-4). For patients with biliary obstruction, durable biliary decompression is required.
[h] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[i] See Principles of Diagnosis and Staging (PANC-A).
[j] See Principles of Palliation and Supportive Care (PANC-E).

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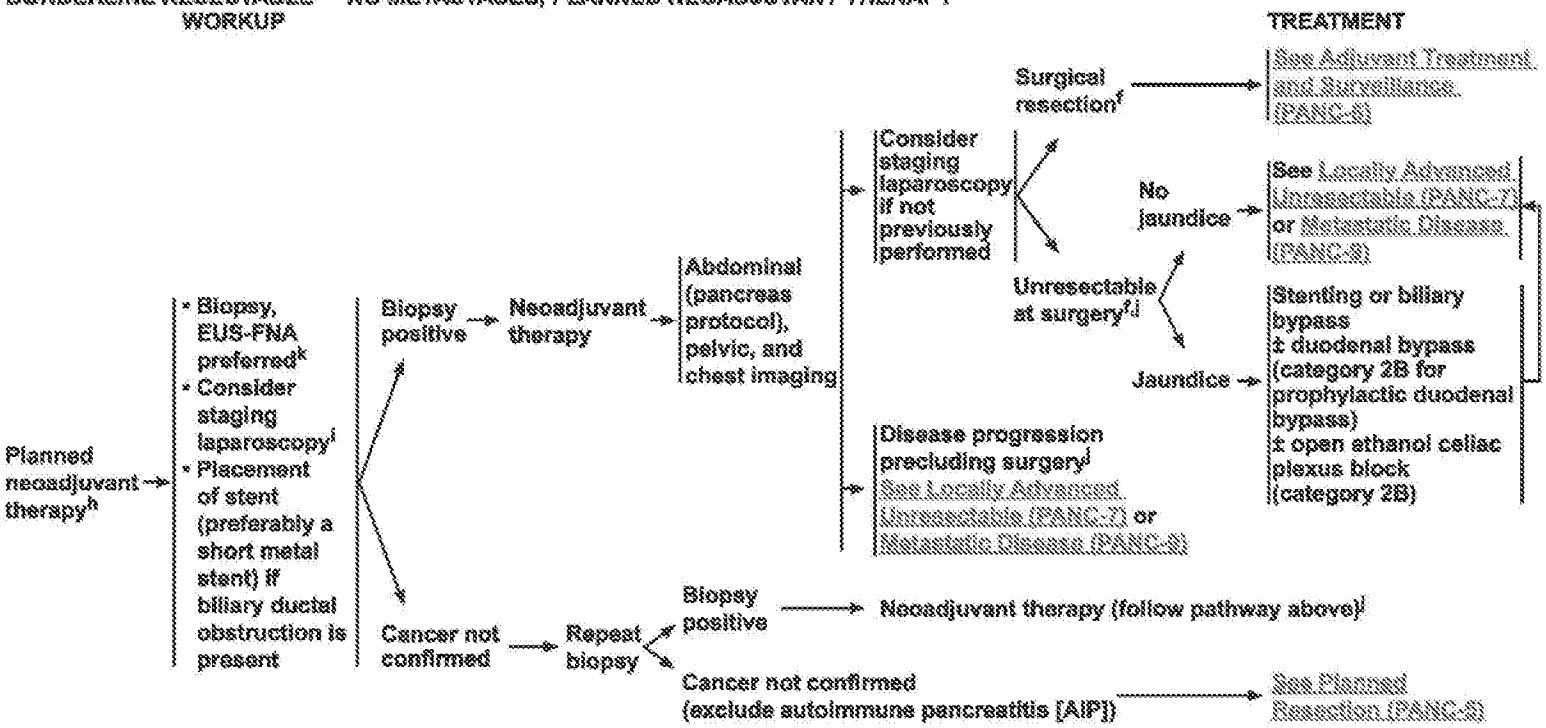
BORDERLINE RESECTABLE[d,e] NO METASTASES, PLANNED NEOADJUVANT THERAPY



[d] See Principles of Diagnosis and Staging (PANC-A).
[e] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Surgical Technique (PANC-C) and Pathologic Analysis, Specimen Orientation, Histologic Sections, and Reporting (PANC-D).
[m] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[i] See Principles of Diagnosis and Staging #9 (PANC-A).
[j] See Principles of Palliation and Supportive Care (PANC-E).
[k] See Principles of Diagnosis and Staging #1 and #8 (PANC-A).

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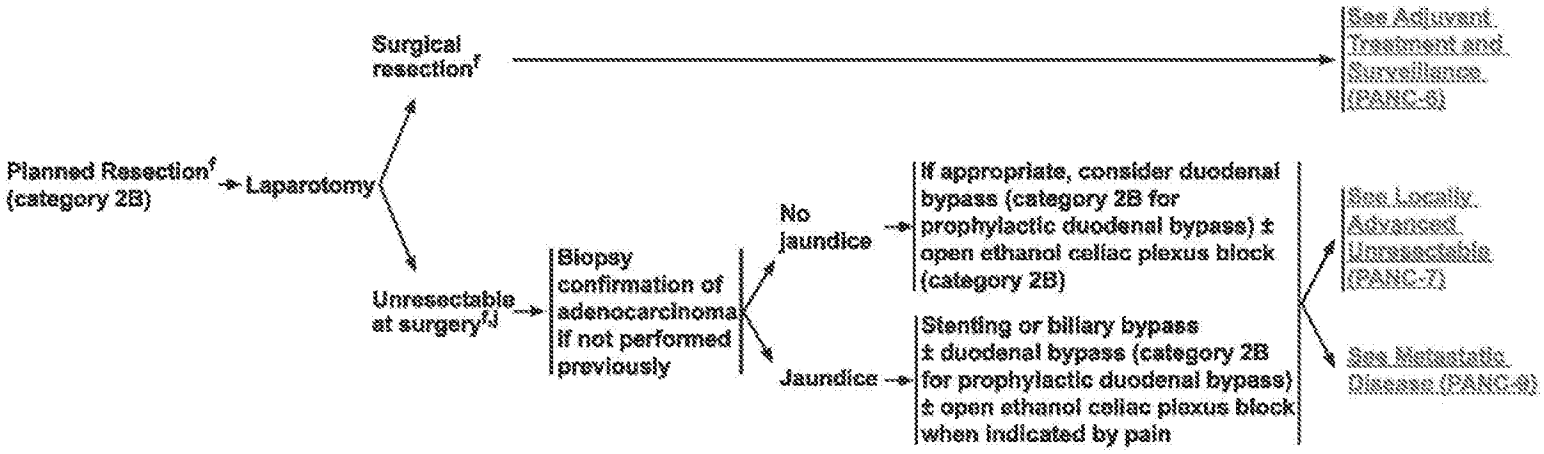
BORDERLINE RESECTABLE[d,e] NO METASTASES, PLANNED RESECTION

WORKUP



[d] See Principles of Diagnosis and Staging (PANC-A).
[e] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).
[i] See Principles of Palliation and Supportive Care (PANC-E).

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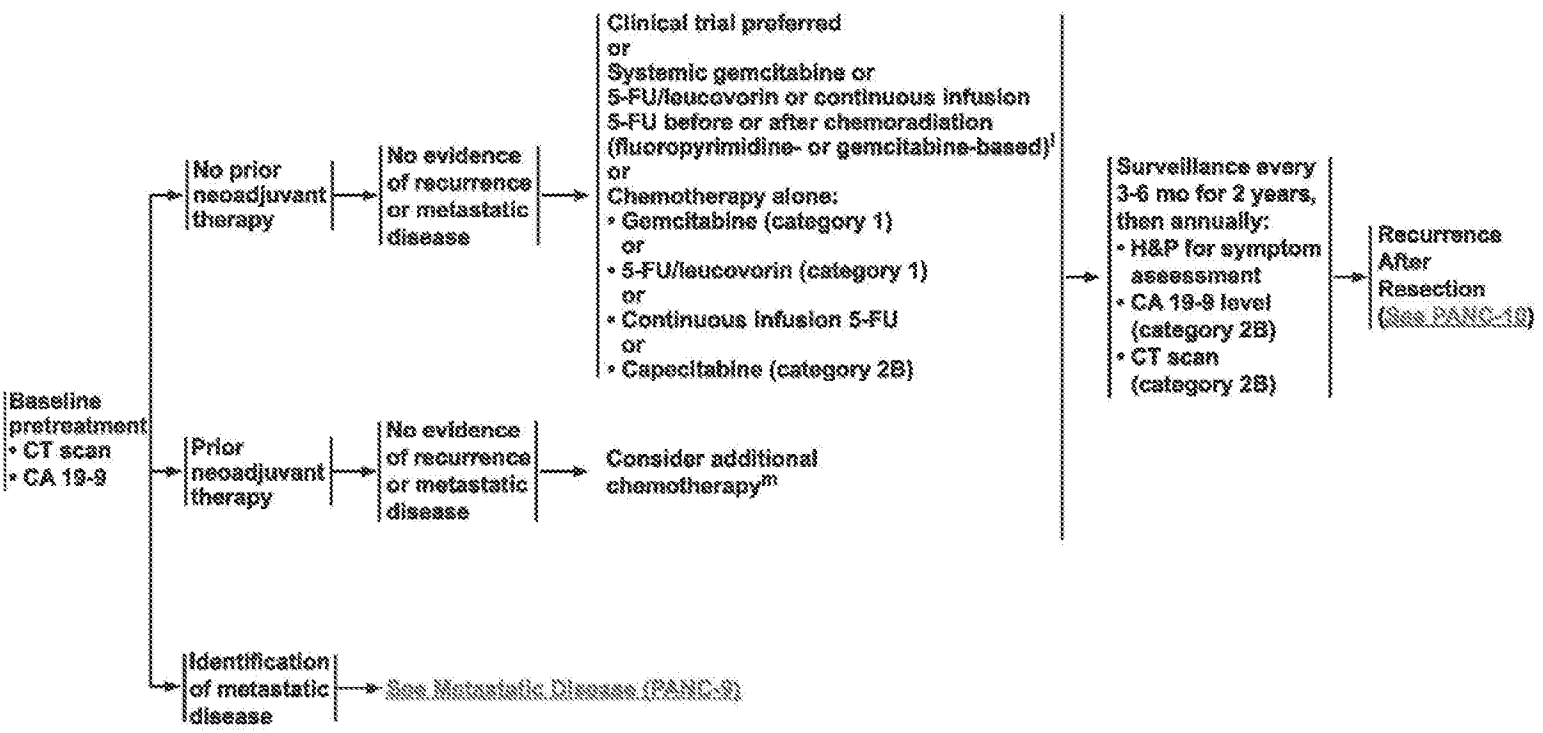

[l] See Principles of Radiation Therapy (PANC-C).

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

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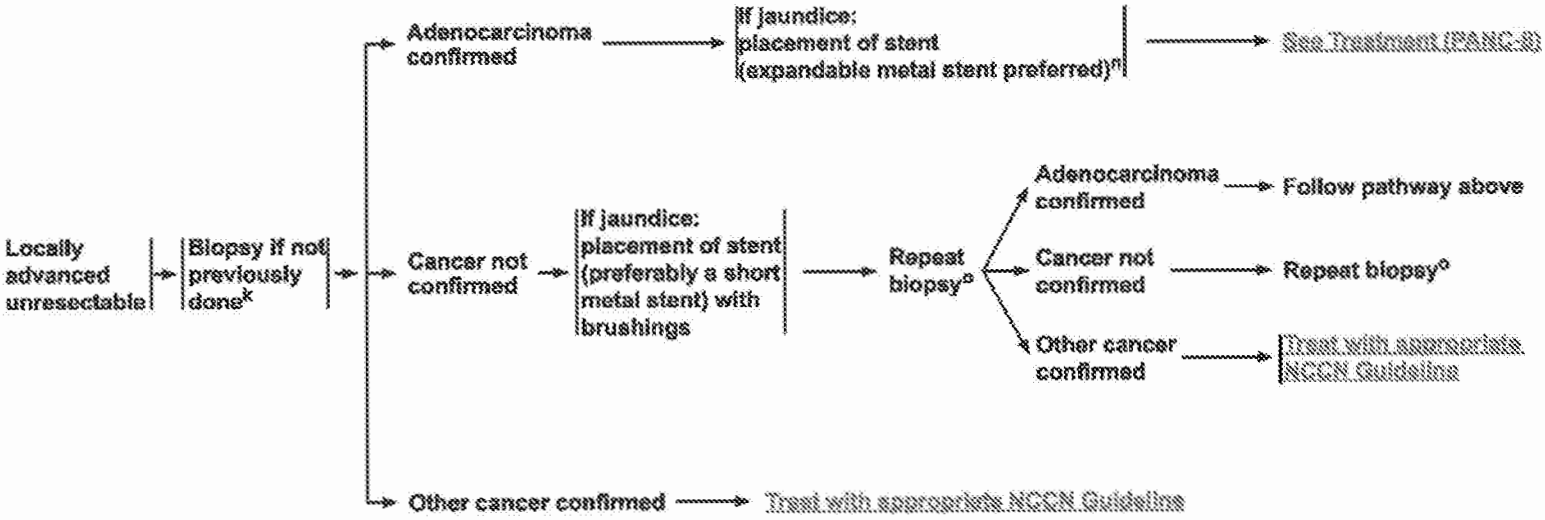
LOCALLY ADVANCED UNRESECTABLE

WORKUP



[k]See Principles of Diagnosis and Staging #1 and #5 (PANC-A).
[l]Unless biliary bypass performed at time of laparoscopy or laparotomy.
[o]EUS-FNA ± core biopsy at a center with multidisciplinary expertise is preferred.

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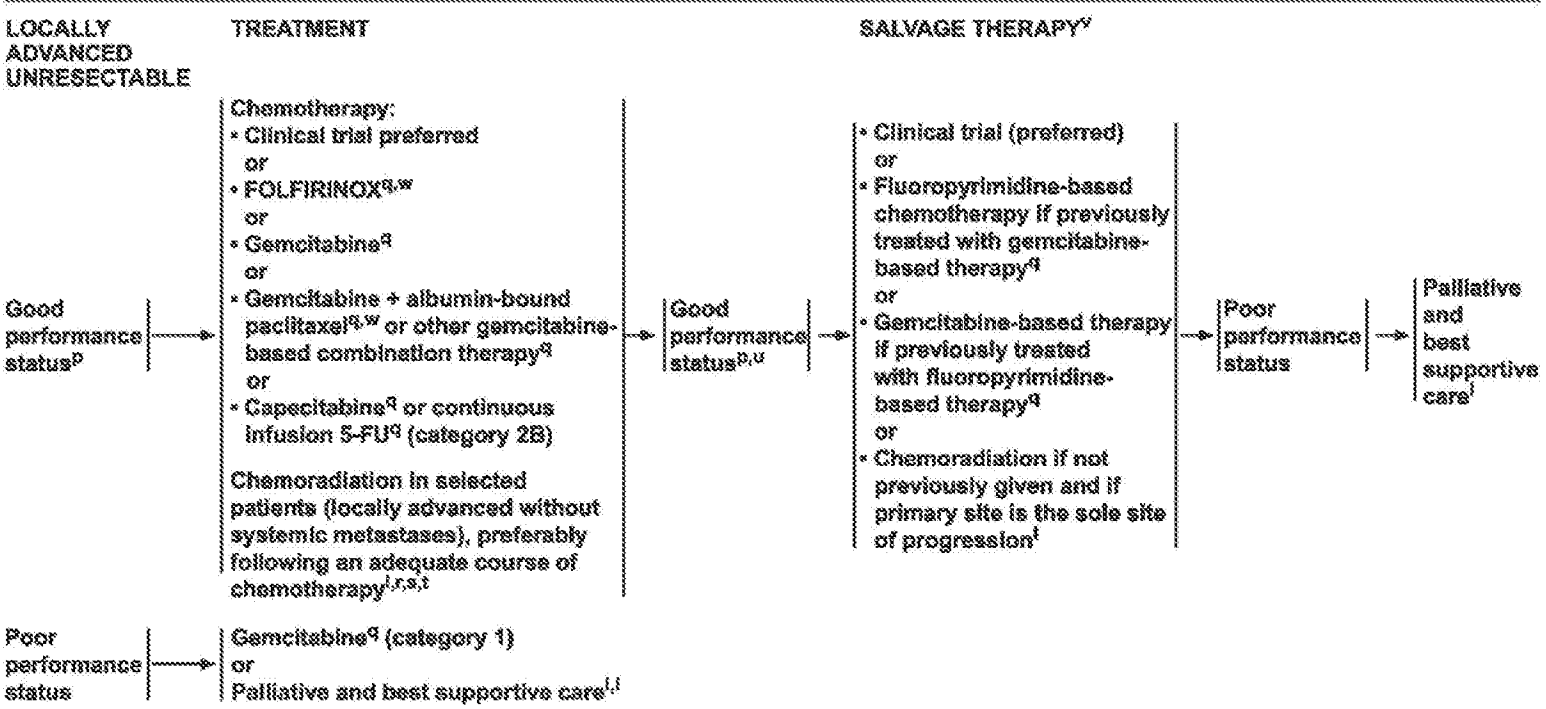

[l] See Principles of Palliative and Supportive Care (PANC-E).
[r] See Principles of Radiation Therapy (PANC-F).
[p] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[q] See Principles of Chemotherapy (PANC-G).
[r] Laparoscopy as indicated to evaluate distant disease.
[s] Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy.
[t] Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)
[u] Patients with a significant response to therapy may be considered for surgical resection.
[v] Best reserved for patients who maintain a good performance status.
[w] 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.

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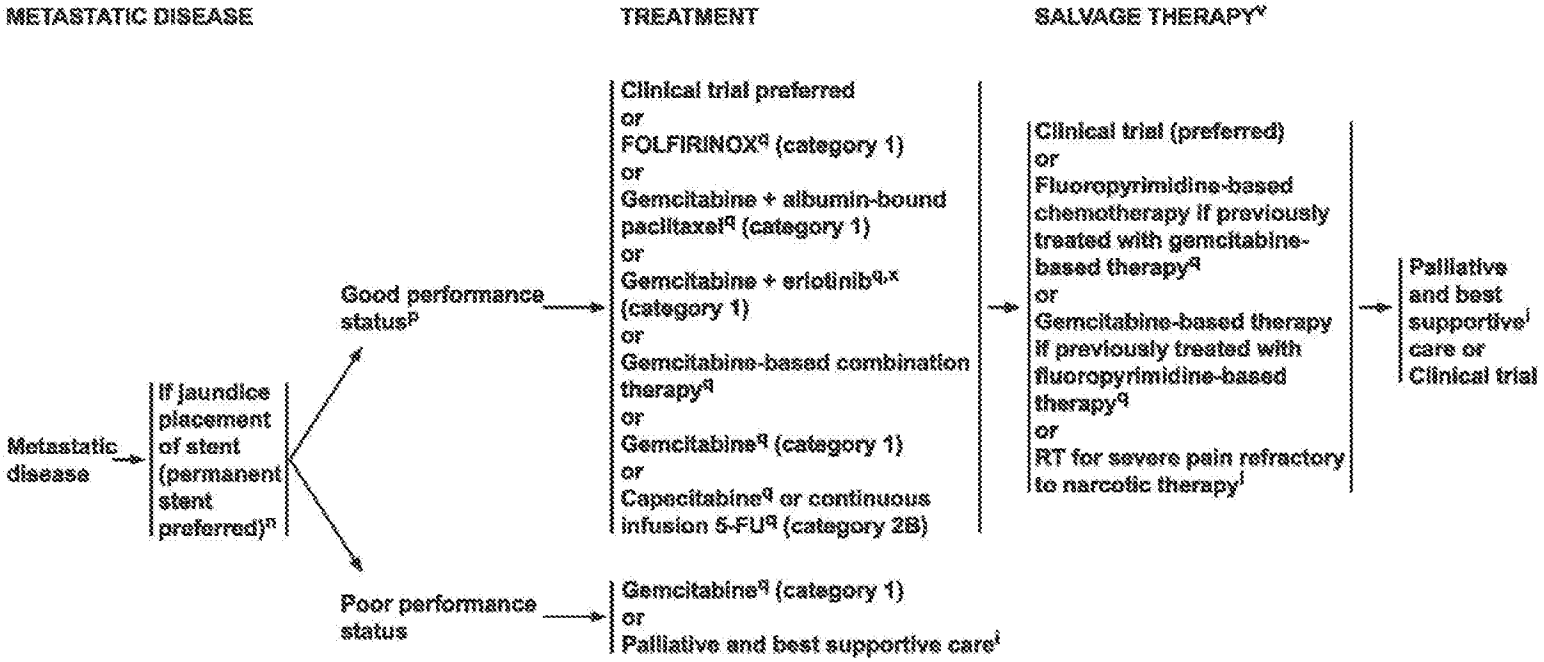

[i] See Principles of Palliation and Supportive Care (PANC-E).
[r] See Principles of Radiation Therapy (PANC-F).
[n] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[P] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[q] See Principles of Chemotherapy (PANC-G).
[V] Best reserved for patients who maintain a good performance status.
[x] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

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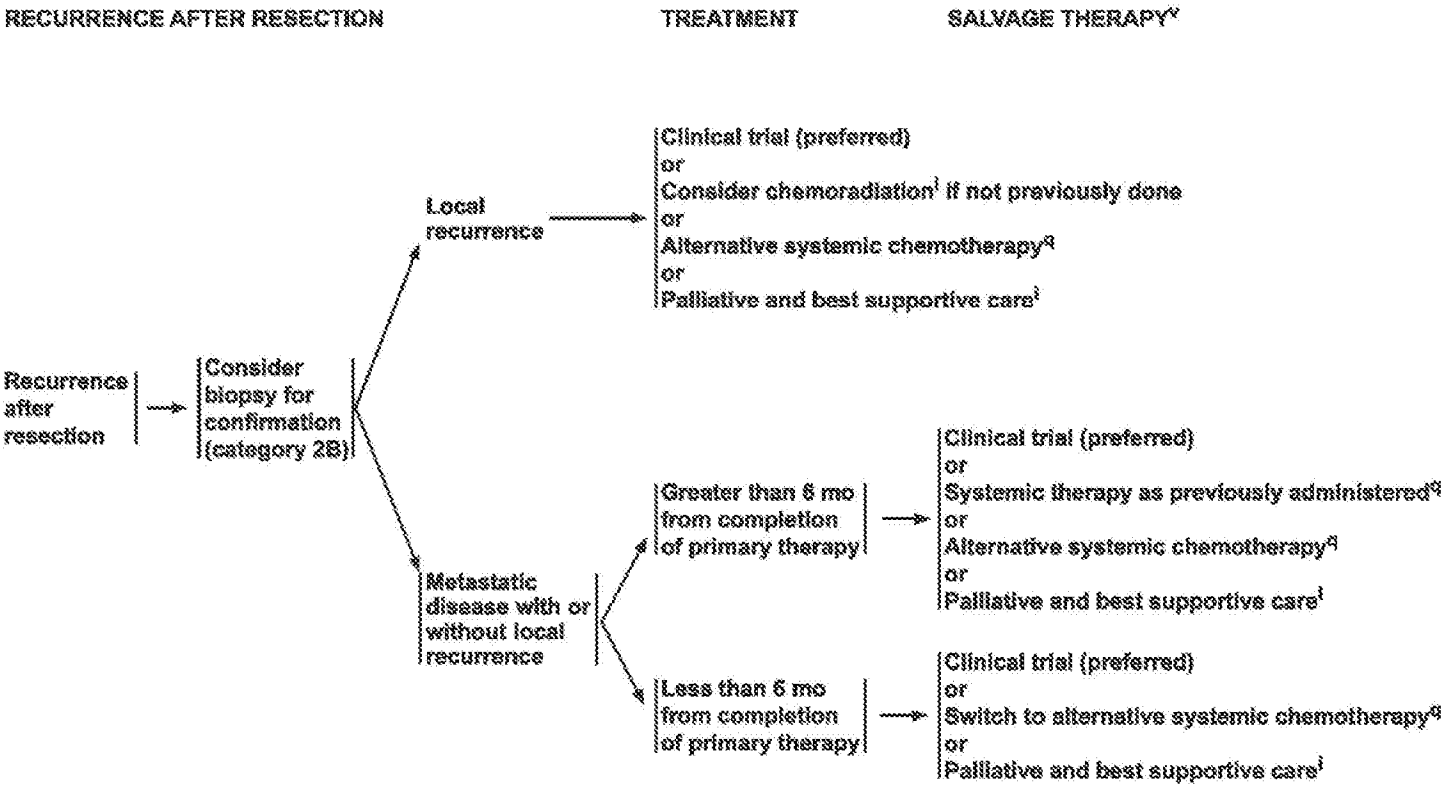

[j]See Principles of Palliation and Supportive Care (PANC-E).
[i]See Principles of Radiation Therapy (PANC-F).
[q]See Principles of Chemotherapy (PANC-G).
[v]Best reserved for patients who maintain a good performance status.

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PRINCIPLES OF DIAGNOSIS AND STAGING

#1 Decisions about diagnostic management and resectability should involve multidisciplinary consultation at 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.

#2 Imaging should include specialized pancreatic CT or MRI. CT should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging and thin slices. Optimal multi-phase imaging technique includes a non-contrast phase plus arterial, pancreatic parenchymal and portal venous phases of contrast enhancement with thin cuts (3 mm or less) through the abdomen. Multiplanar reconstruction is preferred. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3-5 mm. Pancreas protocol MRI is emerging as an alternative to CT for patients.

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

#4 EUS may be complementary to CT for staging.

#5 EUS-FNA is preferable to a CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding with EUS-FNA when compared with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection, and a non-diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.

#6 Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used in some institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk* for disseminated disease.

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

*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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CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and clearly resectable should demonstrate the following:
- **No distant metastases**
- **No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion.**
- **Clear fat planes around the celiac axis, hepatic artery, and SMA.**

Tumors considered borderline resectable[1] include the following:
- **No distant metastases**
- **Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement.**
- **Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.**
- **Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.**

Adapted from: Callery MP, Chang KJ, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol 2009;16:1727-1733.

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

[1]The panel endorses the use of a more restrictive definition of borderline resectable tumors in clinical trials. (Katz M, Marsh R, Herman J, et al. Borderline resectable pancreatic cancer: Need for standardization and methods for optimal clinical trial design. Ann Surg Oncol. 2013 Aug; 20(8):2787-95.)

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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 portal and SMVs 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]
- Utilization of radical resections is associated with an increase in blood loss, transfusion requirements, operating time, length of stay, and whether morbidity/mortality remains acceptable.[5,7]
- Spleen preservation is not indicated in adenocarcinoma.

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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: stitch on posterior margin, safety pin on the retroperitoneal/uncinate margin.**
- **Margins**
  - **Definitions of the margins and uniformity of nomenclature are critical to accurate reporting**
    - **SMA (retroperitoneal/uncinate) Margin: The most important margin is the soft tissue directly adjacent to the proximal 3-4 cm of the superior mesenteric artery. This margin is often referred to as the "retroperitoneal margin" or "posterior margin," but has also been referred to as the "uncinate margin" or "mesenteric margin." More recently, this margin has been referred to as the "SMA margin" to correlate with its location on the specimen. Radial rather than en face sections of this margin will more clearly demonstrate how closely this margin is approached by tumor. The simple step of palpating the specimen can help guide the pathologist as to the best spot along the SMA margin to select for sampling.**
    - **Posterior Margin: This margin is from the posterior caudad aspect of the pancreatic head that merges with the uncinate margin and that appears to be covered by loose connective tissue. Radial rather than en face sections of this margin will more clearly demonstrate whether it is involved by tumor. In some instances this margin can be included in the same section as the SMA margin section.**
    - **Portal Vein Groove Margin: This is the smooth-surfaced groove on the posterior-medial surface of the pancreatic head that rests over the PV. Radial rather than en face sections of this margin will more clearly demonstrate whether it is involved by tumor and also will provide the distance of the tumor from the margin. As is true for the posterior margin, in some instances this margin can be included in the same section as the SMA margin section.**
    - **Portal Vein Margins: If an en bloc partial or complete vein resection is added to the surgical specimen it should be marked separately. En face proximal and distal end margins of the vein should be separately submitted as Proximal Portal Vein Margin and Distal Portal Vein Margin. A section documenting tumor invasion into the vein wall should also be submitted. If feasible, this section should be a full thickness of the vein wall demonstrating the depth of tumor invasion as this has been shown to have prognostic value.[8]**
    - **Pancreatic Neck (transection) Margin: This is the en face section of the transected pancreatic neck. The section should be placed into the cassette with the true margin facing up so that the initial section into the block represents the true surgical margin.**
    - **Bile Duct Margin: This is the en face section of the bile duct end. The section should be removed from the unopened duct and placed into the cassette with the true margin facing up so that the initial section into the block represents the true surgical margin.**
  - **Other margins analyzed in Whipple specimens include the proximal and distal enteric margins (en face sections) and anterior surface (closest representative). The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and therefore should be reported in all cases.[9-12]**
  - **Collectively, these pancreatic tissue surfaces constitute the circumferential transection margin. Designating the various specific margins with different colored inks will allow recognition on microscopy.**

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

- 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 sliding. Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas.
  - Axial slicing provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum, and pancreas, and all of the pancreatic circumferential tissue margins mentioned above.
  - There is no one correct way to dissect a Whipple specimen. The most important aspects of dissection are clear and accurate assessment of the margins.
  - It is currently unknown what constitutes an adequate margin in pancreatic carcinoma resection specimens. A standardized definition of this would allow better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if less than 1 mm clearance is associated with an unacceptably high incidence of local recurrence, then strong consideration for postoperative radiation therapy (RT) might be indicated if not received preoperatively. Tumor clearance should be reported in millimeters for all margins described above to allow prospective accumulation of these important data for future analysis.
  - Attached organs resected with the specimen en bloc require serial sectioning to assess not only direct extension, but metastatic deposits as well. One section that demonstrates direct invasion of the organ and/or a separate metastatic deposit is required.
  - Frozen section analysis of the pancreatic neck and bile duct is recommended. 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 to ensure at least 5 mm of clearance.

Distal Pancreatectomy

- In left-sided resections the peripancreatic soft tissue margins and the pancreatic neck are assessed. Additionally, involvement of the splenic vessels should be documented and invasion of the spleen is important to determine, as direct tumor invasion constitutes a pT3 pathologic stage.
- Margins definitions are as follows:
  - Proximal Pancreatic (transection) Margin: A full en face section of the pancreatic body along the plane of transection. The section should be placed into the cassette with the true margin facing up so that the initial section into the block represents the true surgical margin. More than one block may be needed.
  - Anterior (cephalad) Peripancreatic (peripheral) Surface: This surface demonstrates the relationship between the tumor and the anterior or cephalad peripancreatic soft tissue and can be representative if grossly positive. Several such sections should be taken closest to the tumor to document absence of involvement; the exact number is dependent on the degree of ambiguity of gross involvement.
  - Posterior (caudad) Peripancreatic (peripheral) Margin: This margin 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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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

Reporting

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

Specimen type
- **Tumor size (obtained from careful gross measurement of the largest dimension of the tumor in cm.)**
- **Histologic grade (G (x-4))**
- **Primary tumor extent of invasion (T (x-4))**
- **Regional lymph nodes (N (x-1))[a]**
  - **# Nodes recovered**
  - **# Nodes involved**
- **Metastases (M (0-1))**
- **Margins: [involvement should be defined and surgical clearance measured in mm]**
  - **Whipple Resection:**
    - **SMA (retroperitoneal/uncinate) Margin**
    - **Posterior Margin**
    - **Portal Vein Groove Margin**
    - **Pancreatic Neck (transection) Margin**
    - **Bile Duct Margin**
    - **Enteric Margins**
    - **Anterior Surface**
  - **Distal pancreatectomy:**
    - **Proximal Pancreatic (transection)Margin**
    - **Anterior (cephalad) Peripancreatic (peripheral) Surface (optional)**
    - **Posterior (caudad) Peripancreatic (peripheral) Margin**
- **Lymphatic (small vessel) Invasion (L)**
- **Vascular (large vessel) Invasion (V)**
- **Perineural Invasion (P)**
- **Additional pathologic findings**
  - **Pancreatic Intraepithelial Neoplasia**
  - **Chronic Pancreatitis**

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

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

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE[2]

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

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

- Gastric outlet obstruction
  - Good performance status
    - Gastrojejunostomy (open or laparoscopic) ± J-tube
    - Consider enteral stent[1]
  - Poor performance status
    - Enteral stent[1]
    - Percutaneous endoscopic gastrostomy (PEG) tube

- Severe tumor-associated abdominal pain
  - EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)
  - Consider palliative radiation with or without chemotherapy if not already given as part of primary therapy regimen

- Depression, pain, and malnutrition
  - Formal Palliative Medicine Service evaluation when appropriate (See NCCN Guidelines for Supportive Care)
  - Nutritional evaluation when appropriate.

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

- Thromboembolic disease
  - Low-molecular-weight heparin preferred over warfarin

[1]Placement of an enteral stent is particularly important for patients with poor performance status and should be done after biliary drainage is assured.
[2]Palliative surgical procedures are best reserved for patients with a longer life expectancy.

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PRINCIPLES OF RADIATION THERAPY

General Principles:

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

Standard Recommendations:

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

Neoadjuvant resectable/borderline resectable:

- No standard treatment regimen currently exists for neoadjuvant resectable or borderline resectable pancreatic cancer. Neoadjuvant therapy for patients with resectable tumors should ideally be conducted in a clinical trial. Generally, use similar paradigms as for locally advanced unresectable disease.
  - Upfront fluoropyrimidine (CI-5-FU or capecitabine-based) chemoradiation.[2,3]
  - Upfront gemcitabine-based chemoradiation.[4]
  - Induction chemotherapy (2-6 cycles) followed by 5-FU- or gemcitabine-based chemoradiation.[5]
- Ideally, surgical resection should be attempted 4-8 weeks following chemoradiation. Surgery can be performed >8 weeks following chemoradiation; however, radiation-induced fibrosis may potentially make surgery more difficult.

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PRINCIPLES OF RADIATION THERAPY

Unresectable/Locally advanced (non-metastatic):

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

- Options include:
  - RT 45-54 Gy in 1.8-2.5 Gy fractions (doses higher than 54 Gy may be considered if clinically appropriate) or
  - 36 Gy in 2.4 Gy fractions.[11]
- Following chemoradiation, additional maintenance chemotherapy is sometimes used, especially if tumors are still unresectable.
- In cases where 1) it is highly unlikely that patients will become resectable (complete encasement of superior mesenteric/celiac artsries); 2) there are suspicious metastases; and 3) patients may not be able to tolerate chemoradiation, then it may be reasonable to start with chemotherapy (2-6 cycles) followed by definitive chemoradiation if there is no evidence of metastatic progression.
- If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation.
- No standard total dose or dose per fraction has been established for SBRT; therefore, it should preferably be utilized as part of a clinical trial.[12]

Adjuvant:

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

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

Palliative:

- See Principles of Palliation and Supportive Care (PANC-5).
  - RT alone to the primary tumor plus a margin (Typically 25-36 Gy in 2.4-5 Gy fractions) is reasonable for patients with metastatic disease who require local palliation for obstruction, pain, or bleeding.[18]
  - Palliative RT can also be considered for patients who are elderly and/or not candidates for definitive therapy because of comorbidities.
  - Metastatic sites causing pain may also be palliated with RT.

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*Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)

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PRINCIPLES OF RADIATION THERAPY

Radiation Therapy Treatment Planning Principles

- Patients should undergo a CT simulation (thin slices through the pancreas/bed and locoregional nodal basins) with IV (assuming adequate kidney function) and oral contrast. For resected cases, preoperative CT scans and strategically placed surgical clips are used to determine the tumor bed, ideally with the surgeon's assistance. In the neoadjuvant, borderline, and locally advanced settings the pancreatic gross tumor volume (GTV) and pathologic nodes (minimum >1 cm) are contoured with assistance from structural (CT/MRI) and functional imaging (PET). [19,20]
- The planning target volume (PTV) should be defined per the ICRU-62 guidelines.[21] A GTV should be defined for intact pancreatic tumors. For adjuvant cases, a clinical target volume (CTV) includes high-risk peri-pancreatic lymph nodes, anastomoses (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), pancreatic tumor bed derived from presurgical imaging, and strategically placed surgical clips. CTV expansions are needed to include possible microscopic disease. Further expansion to PTV includes internal target volume (ITV) for target/breathing motion and additional patient set-up error margin (SM).[22-24] Image guidance methods should be considered when constructing the PTV. Organs at risk (OARs) should also be contoured and evaluated in the DVH.
- Elective nodal irradiation (ENI) is commonly used for adjuvant cases but is controversial for unresectable/neoadjuvant/borderline resectable cases.[11] Standard margin expansions for unresectable cases include the gross tumor and any pathologic lymph nodes (GTV) plus a 0.5-1.5 cm margin to target microscopic extension (CTV) and an additional 0.5-2 cm volume to account for tumor/breathing motion and patient set-up errors (PTV). With these expansions, peripancreatic nodes are generally included. 3-D conformal RT (3D-CRT) or intensity modulated RT (IMRT) with breathhold/gating techniques can result in improved PTV coverage with decreased dose to OARs. [25,26] With SBRT, smaller margins are used (0.2-0.5 cm) and the PTV does not cover locoregional elective nodal regions.[27] If small GTV margin expansions are used for CTV and PTV, breathing motion and set-up error should be evaluated or controlled per the AAPM Task Group 76 guidelines.[28]
- IORT is delivered with electron beam RT (IOERT) or high-dose-rate brachytherapy (HDR-IORT). IORT is generally delivered in a single fraction and in combination with adjuvant or neoadjuvant chemoradiation. The role of IORT for unresectable and resectable cases is controversial and should only be performed at specialized centers in well selected cases. It is ideally used in cases where surgical resection may result in close or involved margins.[29]
- It is imperative to evaluate the dose-volume histogram (DVH) of the PTV and critical normal structures such as the liver, kidneys, spinal cord, liver, and bowel.
- (See Table 1, Normal Tissue Dose Volume Recommendations (PANC-F, 4 of 8)) While these examples of limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable). Studies have shown that the tolerability of radiation is largely dependent on PTV size/ENI, types of concurrent systemic/targeted therapy, and whether conformal (3-D, IMRT, SBRT) vs. conventional radiation is used.

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PRINCIPLES OF RADIATION THERAPY

- Fractionated RT is typically delivered as 30-55 Gy over ~3-6 weeks (1.8-3.0 Gy/fraction, using lower dose per fraction at higher cumulative doses while respecting normal tissue constraints) with concurrent 5-FU/capecitabine or gemcitabine as a radiosensitizer. Doses above 55 Gy may be possible in select cases; however, data are limited and normal tissue dose limits (see Table 1) should be maintained. For resected cases, 45 Gy is delivered to the tumor bed, surgical anastomosis (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), and regional lymph nodes. Additional radiation (~5-15 Gy) may be administered to the tumor bed/area of involved margins and anastomoses paying careful attention to dose to bowel and stomach. The use of high-energy photon beams is preferred. SBRT is often delivered in 1-5 fractions ranging from 5-25 Gy per fraction. IORT can be delivered in a single fraction alone (15-20 Gy) or in combination with external beam RT (EBRT) (10-20 Gy).
- Several clinical trials (RTOG) now refer to atlases to assist with contouring and adjuvant RT planning (http://www.rtog.org/CoreLab/ContouringAtlases.aspx).

Table 1: Normal Tissue Dose Volume Recommendations

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

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

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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	Airway Breathing Control
IGRT	Image-Guided Radiation Therapy
4DCT	Four-Dimensional Computerized Tomography
CBCT	Cone Beam Computed Tomography

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Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF CHEMOTHERAPY (1 of 3)

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

- **Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.**

Close follow-up of patients undergoing chemotherapy is indicated.

Metastatic

- **Acceptable chemotherapy combinations for patients with good performance status include:**
  - **FOLFIRINOX[1] (category 1)**
  - **Gemcitabine + albumin-bound paclitaxel[2] (category 1)**
  - **Gemcitabine + erlotinib[3] (category 1)[a]**
  - **Gemcitabine + capecitabine[4]**
  - **Gemcitabine + cisplatin[5] (especially for patients with possible hereditary cancers)**
  - **Fixed-dose rate gemcitabine, docetaxel, capecitabine (GTX regimen)[6] (category 2B)**
  - **Fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin[7] or CapeOx[8])**
- **Acceptable monotherapy options for patients with poor performance status include:**
  - **Gemcitabine at 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1).**
  - **Fixed-dose rate gemcitabine (10 mg/m^2/minute) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B).**
  - **Capecitabine or continuous infusion 5-FU (category 2B)**
- **Second-line chemotherapy may consist of gemcitabine-based therapy for those previously treated with fluoropyrimidine-based therapy, and fluoropyrimidine-based therapy for those previously treated with gemcitabine-based therapy. Results of the CONKO 003 trial demonstrated a significant improvement in overall survival with the addition of oxaliplatin to 5-FU/leucovorin.[7]**

Locally Advanced

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

See Adjuvant and Neoadjuvant PANC-G (2 of 3)

See References on PANC-G (3 of 3)

[a]Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[b]Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)

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PRINCIPLES OF CHEMOTHERAPY (2 of 3)

Adjuvant

- The CONKO 001 trial demonstrated significant improvements in disease-free survival and overall survival with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[9]
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[10]
- The use of gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU-based chemoradiotherapy.
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment.[11]
- For patients who relapse after receiving adjuvant therapy, subsequent therapy may consist of gemcitabine or gemcitabine-based combination therapy for patients previously treated with fluoropyrimidine-based therapy, or fluoropyrimidine-based therapy (eg, 5-FU/leucovorin/oxaliplatin[7] or CapsOx)[8] for patients previously treated with gemcitabine-based therapy.

Neoadjuvant

- Although there is insufficient evidence to recommend specific neoadjuvant regimens, most published neoadjuvant studies that were done prior to the introduction of more effective combination chemotherapy incorporated chemoradiation. Studies of these more effective regimens (ie, FOLFIRINOX or gemcitabine and albumin-bound paclitaxel) without chemoradiation are in progress.

See Metastatic and Locally Advanced PANC-G (1 of 3)

See References on PANC-G (3 of 3)

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PRINCIPLES OF CHEMOTHERAPY (3 of 3)
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Table 1

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

Because only a few patients with pancreatic cancer undergo surgical resection of the pancreas (and adjacent lymph nodes), a single TNM classification must apply to both clinical and pathologic staging.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ*
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

* This also includes the "PanIntIII" classification.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

Stage Grouping

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

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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Overview

During the year 2014 in the United States, an estimated 46,420 people will be diagnosed with pancreatic cancer, and approximately 39,590 people will die of pancreatic cancer.[1] This disease is the fourth most common cause of cancer-related death among U.S. men (after lung, prostate, and colorectal cancer) and women (after lung, breast, and colorectal cancer).[1] Its peak incidence occurs in the seventh and eighth decades of life.[1] Although incidence is roughly equal in both sexes, African Americans have a higher incidence of pancreatic cancer than white Americans.[2,3] Furthermore, the incidence of pancreatic cancer in the United States increased from 1999 to 2008, possibly because of the increasing prevalence of obesity, an aging population, and other unknown factors.[3-5] Mortality rates have remained largely unchanged.[6,7]

In these NCCN Guidelines for Pancreatic Adenocarcinoma, the diagnosis and management of adenocarcinomas of the exocrine pancreas are discussed; neuroendocrine tumors are not included (please see the NCCN Guidelines for Neuroendocrine Tumors, available at www.NCCN.org). These NCCN Guidelines are intended to assist with clinical decision-making, but they cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members during the process of developing and updating these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. A recent study of 3706 patients treated for pancreatic cancer in large California hospitals showed that compliance with these NCCN Guidelines for Pancreatic Adenocarcinoma, defined very permissively, improves survival.[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 reference to appropriate imaging studies. In addition, the panel believes that increasing participation in clinical trials (currently 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.

Risk Factors and Genetic Predisposition

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.[10-15] An increased body mass index (BMI) is also associated with an increased risk for pancreatic cancer.[16-18] There is also some evidence that increased consumption of red/processed meat and dairy products is associated with an elevation in pancreatic cancer risk,[20,21] although other studies have failed to identify dietary risk factors for the disease.[14,22,23] Occupational exposure to chemicals such as beta-naphthylamine and benzidine is associated with increased risk for pancreatic cancer,[24] as is heavy alcohol consumption.[10,12,15,25] Recent data also suggest that low plasma 25-hydroxyvitamin D levels may increase the risk of pancreatic cancer.[26] Chronic pancreatitis has also been identified as a risk factor for pancreatic cancer,[27-30] with one study demonstrating a 7.2-fold increased risk of pancreatic cancer for patients with a history of pancreatitis.[31] Overall, further epidemiologic studies involving careful evaluation of these possible risk factors with adjustments for potential confounders are needed to clarify their impact on pancreatic cancer risk.

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Diabetes and Pancreatic Cancer

The association between diabetes mellitus and pancreatic cancer is particularly complicated. Numerous studies have shown an association between new-onset non-insulin-dependent diabetes and the development of pancreatic cancer,[32-36] especially in those who are elderly, have a lower BMI, experience weight loss, or do not have a family history of diabetes.[37] In these short-onset cases of diabetes diagnoses 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.[38] A population-based study of 2122 patients with diabetes found that approximately 1% of patients diagnosed with diabetes who are age 50 years or younger will be diagnosed with pancreatic cancer within 3 years.[32]

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.[38] However, certain risk factors such as obesity, associated with both diabetes and pancreatic cancer, may confound these analyses.[40] Furthermore, the use of diabetic medications has been reported to alter pancreatic cancer risk. The use of insulin or sulfonylureas has been found to be associated with an increased risk for pancreatic cancer.[41-43] On the other hand, metformin may be associated with a reduced risk for pancreatic and other cancers.[41-44]

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; $P = .009$).[45] The OS difference was significant only in patients without distant metastases and remained significant when insulin users were excluded. In contrast, data from a recent metaanalysis of >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; $P < 0.001$).[35] 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.[46] After multivariable-adjustment, mortality was significantly higher in participants with diabetes compared to those without (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.[14,47-48] The genetic basis of this inherited predisposition is not known in most cases; however, some familial cancer syndromes are associated with an increased risk for pancreatic cancer (see *Table 1*, below).

Germline mutations in the *STK11* gene result in Peutz-Jeghers syndrome, in which individuals have gastrointestinal polyps and a highly elevated risk for colorectal cancer.[50-52] These individuals also have a highly elevated risk for developing pancreatic cancer, reported to be increased by as much as 132-fold.[53,54] Furthermore, *STK11* undergoes somatic mutation in approximately 5% of pancreatic cancers.[55]

As with non-hereditary forms of pancreatitis, familial pancreatitis is also associated with an increased risk for pancreatic cancer.[56] Several genes are associated with the familial form of pancreatitis, including

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PRSS1, *SPINK1*, and *CFTR*.[57] The increased risk for the development of pancreatic cancer in these individuals is estimated to be 26-fold to as high as 87-fold.[26,58-60]

Familial Malignant Melanoma syndrome (also known as Melanoma-Pancreatic Cancer syndrome or Familial Atypical Multiple Mole Melanoma syndrome [FAMMM]) is caused by germline mutation of the *CDKN2A* (p16INK4a/p14ARF) gene.[61] This syndrome is associated with a 20-fold to 47-fold increased risk for pancreatic cancer.[62,63] In addition, patients with Melanoma-Pancreatic Cancer syndrome may experience an earlier onset of pancreatic cancer than the general population.[64] In an unselected series of 225 patients with pancreatic cancer in Italy, 5.7% had mutations in *CDKN2A*.[65]

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*).[66-71] Patients with Lynch syndrome also have an estimated 9- to 11-fold elevated risk for pancreatic cancer.[72,73]

An excess of pancreatic cancer is also seen in families with hereditary Breast-Ovarian Cancer syndrome, harboring *BRCA1* and *BRCA2* (breast cancer susceptibility gene-1 and -2) mutations, although the link with *BRCA2* is better established.[74-78] In a study of 187 Ashkenazi Jewish patients who had resections for pancreatic cancer, mutations in *BRCA1* and *BRCA2* were identified in 5.5% of patients.[78] Other studies of unselected patients with pancreatic cancer have detected *BRCA* mutations at a frequency of 4% to 7%.[80] The risk of pancreatic cancer is elevated 2- to 6-fold in these patients, and the age of onset is younger than average.[74,78,79]

BRCA1 and *BRCA2* are 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.[81-83] Additionally, whole-genome sequencing recently allowed for the identification of germline mutations in *ATM*, a DNA damage response gene, in 2 kindreds with familial pancreatic cancer.[84] Further analyses then revealed *ATM* mutations in 4 of 166 individuals with familial pancreatic cancer.

As many as 80% of patients with a family history of pancreatic cancer have no known genetic cause.[47] 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 of pancreatic cancer by 4.6-fold, whereas having 2 affected first-degree relatives raises risk by about 6.4-fold.[85]

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.[49] 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.

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Pancreatic Cancer Screening

Asymptomatic individuals at high risk for pancreatic cancer (ie, those with first-degree relatives with pancreatic cancer) were assessed using endoscopic ultrasound (EUS) in the Cancer of the Pancreas Screening 2 (CAPS2) project.[86] Preinvasive pancreatic neoplasms were detected in 10% of high-risk patients, suggesting that EUS may have a promising role in screening high-risk patients. The CAPS Consortium recently reported results of their CAPS3 study, in which 225 asymptomatic high-risk individuals were independently (in a blinded manner) screened once with CT, MRI, and EUS.[87] In this study, 42% of individuals were found to have an abnormality; 5 individuals underwent surgical interventions, 3 of whom had high-grade dysplasia in small intraductal papillary mucinous neoplasms and intraepithelial neoplasias. When results of the 3 screening modalities were compared, EUS detected abnormalities in 42% of individuals, versus 33% and 11% for MRI and CT, respectively.

Interestingly, results from a prospective cohort study that followed high-risk individuals for an average of 4.2 years with annual MRI were recently published.[88] Although 32% of 262 participants were found to have pancreatic abnormalities and some intraductal papillary mucinous neoplasms and intraepithelial neoplasias were resected, 3 patients developed pancreatic adenocarcinoma (2 metastatic, 1 recurrent 30 months post-resection) despite screening. These results could be due to rapid malignant progression, but 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,[89] while a German study used EUS plus MRI/magnetic resonance cholangiopancreatography (MRCP) in a similar high-risk population.[90] 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.[91,92] 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%.[93]

An international CAPS Consortium summit with 49 multidisciplinary experts was held in 2011 to develop consensus guidelines for pancreatic cancer screening.[94] 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,

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and depression; however, no early warning signs of pancreatic cancer have been established. As previously noted, sudden onset of adult type 2 diabetes in patients 50 years or older may be linked to a new diagnosis of pancreatic cancer; patients with long-standing diabetes may also develop pancreatic cancer (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.

All patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should undergo initial evaluation by CT or MRI performed according to a defined pancreas protocol.[96,98] Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation, with reference to appropriate studies to evaluate the extent of disease. The Panel recommends that a multidisciplinary review ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, and pathology.

The AJCC has developed staging criteria for adenocarcinoma of the pancreas that follow the tumor/node/metastasis (TNM) system.[97] 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.[97,98] Recent validation of concordance between AJCC stage and OS has been provided through evaluation of 121,713 patients with pancreatic adenocarcinoma included in the National Cancer Data Base (NCDB).[99]

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 (preferred) or MRI (and EUS and/or MRI/MRCP or endoscopic retrograde cholangiopancreatography [ERCP] in some cases), liver function tests, and chest imaging, disease is classified as: 1) resectable; 2) borderline resectable (ie, tumors that are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable with a high chance of a R1 resection); 3) locally advanced unresectable (ie, tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease); or 4) disseminated, and this system is used throughout the guidelines. See *Criteria for Resection* below for more detailed definitions.

Imaging Evaluations

Pancreatic Protocol CT and MRI

Pancreatic protocol CT is the most widely available and best-validated imaging modality for diagnosing and staging patients with pancreatic cancer.[99,100] Studies have shown that 70% to 85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.[99,101-105] However, the sensitivity of CT for small hepatic and peritoneal metastases is limited. Pancreas protocol MRI is emerging as an equivalent alternative to CT, and was added to these guidelines in 2012 as an option for the initial workup of patients for whom pancreatic cancer is suspected. MRI can also be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for detecting the presence of hepatic disease in high-risk patients.[106,107]

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

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disease. The criteria for defining resectable disease favor specificity over sensitivity to avoid denying surgery to patients with a potentially resectable tumor.[99] Optimal multi-phase imaging technique (CT or MRI) includes a non-contrast phase plus arterial, pancreatic parenchymal, and portal venous phases of contrast enhancement with thin cuts (3 mm or less) through the abdomen. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3 to 5 mm.[99,103,107,108] The difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the late arterial phase, thereby providing a clear distinction between a hypodense lesion in the pancreas and the rest of the organ. A multi-phasic pancreatic protocol also allows for selective visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], peripancreatic arteries) and venous structures (eg, superior mesenteric vein [SMV], splenic vein, portal vein [PV]), thereby providing an assessment of vascular invasion by the tumor. All of this information can improve the prediction of resectability. Software allowing for 3-D reconstruction of imaging data can provide additional valuable information on the anatomic relationship between the pancreatic tumor and the surrounding blood vessels and organs, and multiplanar reconstruction is preferred. However, further development of this technology may be needed before it is routinely integrated into clinical practice.[104]

Patients commonly present to the oncologist with a non-pancreas protocol CT already performed. The panel feels that if the CT scan is of high quality, it can be sufficient. If not, a pancreas protocol CT or MRI is recommended. Such selective reimaging was shown to change the staging and management of patients with pancreatic adenocarcinoma in 56% of cases retrospectively reviewed at one institution.[109]

Recently, a multidisciplinary expert consensus group defined standardized language for the reporting of imaging results.[110] 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.

Endoscopic Ultrasound

NCCN Member Institutions vary in the use of additional staging technologies, such as EUS. The role of EUS in staging is felt to be complementary to CT or MRI, providing additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes.[86,111,112] In particular, EUS may provide assessment of certain types of vascular invasion.[113,114] It is the consensus of the panel that while the accuracy of EUS in assessing the involvement of certain veins (eg, PV) is high, this technique is less accurate in imaging tumor invasion of the SMA.[115]

EUS is also used to discriminate between benign and malignant strictures or stenosis, because severe stenosis and marked proximal dilatation most often indicate malignancy.[116] 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 block, removal of ascites). Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

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Endoscopic Retrograde Cholangiopancreatography and MRI/Magnetic Resonance Cholangiopancreatography

ERCP is a technique that combines endoscopic and fluoroscopic procedures and is generally limited to therapeutic interventions.[117] In the guidelines, ERCP with duct brushing cytology is recommended as clinically indicated for patients without a mass in the pancreas and without evidence of metastatic disease who require biliary decompression and who undergo additional imaging with EUS to help establish a diagnosis.[118] MRI/ MRCP is considered to be equivalent to EUS/ERCP in the diagnostic setting. However, 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.

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.[119] The sensitivity of detecting metastatic disease for PET/CT alone, standard CT alone, and the combination of PET/CT and standard CT were 61%, 57%, and 87%, respectively. In this study, the clinical management of 11% of patients with invasive pancreatic cancer was changed as a result of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established. PET/CT is not a substitute for high-quality contrast-enhanced CT or MRI, although it can be considered as an adjunct to a formal pancreatic CT or MRI protocol in high-risk patients. 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.[120-122] 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,[121] although routine use of staging laparoscopy is controversial. The panel does not consider staging laparoscopy to be a substitute for poor-quality preoperative imaging.

Some 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).[123] For example, preoperative serum CA 19-9 levels >100 U/mL (see discussion of *Biomarkers*, below) have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.[124] In a recent prospective review of 838 patients who were diagnosed with resectable pancreatic tumors on imaging evaluation between 1999 and 2005, 14% were found to have unresectable disease (21% yield if only pancreatic adenocarcinoma was considered) following subsequent laparoscopy.[125] Characteristics associated with an increased laparoscopic yield of unresectable disease include the location of the tumor, tumor histology, the presence of weight loss and jaundice, and the facility conducting the imaging evaluation.

Diagnostic staging laparoscopy to rule out sub-radiologic metastases (especially for patients with body and tail lesions) is used routinely in some NCCN Member Institutions prior to surgery or chemoradiation, or

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selectively in patients who are at higher risk for disseminated disease (ie, borderline resectable disease; markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; highly symptomatic). The value of a staging laparoscopy in patients with resectable or borderline resectable disease has been debated by the panel, which believes that it 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 prior to administration of neoadjuvant therapy. The panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[125]

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 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.[127] 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.

In patients without obstructive jaundice at initial presentation, EUS-FNA is highly accurate and reliable for determining malignancy; in patients with obstructive jaundice and biliary stricture, EUS-FNA is less accurate.[85] EUS-FNA of cystic pancreatic lesions can also be useful in the differential diagnosis of non-neoplastic and neoplastic lesions that are difficult to discriminate with imaging studies.[128]

In rare cases when an EUS-FNA cannot be obtained from a borderline resectable or unresectable patient, other acceptable methods of biopsy exist. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy.[129] A percutaneous approach[127] or a laparoscopic biopsy[130] 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-FNA with or without a core biopsy at a center with multidisciplinary expertise is preferred. Alternative diagnoses including autoimmune pancreatitis should be considered (see *Differential Diagnoses*, below). A positive biopsy is required before administration of chemotherapy. However, it is important to reiterate that biopsy proof of malignancy is not required before surgical resection for clearly resectable or borderline resectable patients and that a nondiagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high. The NCCN Pancreatic Adenocarcinoma Panel strongly recommends that all diagnostic and surgical management decisions involve multidisciplinary consultation.

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 samples, including core biopsy, but the panel believes that core biopsies should not replace EUS-FNA, but rather can be done in addition.

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Differential Diagnoses

Chronic pancreatitis and other benign conditions are possible differential diagnoses of patients suspected of having pancreatic cancer.[131-136] 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.[133,136-138] In addition, fine-needle aspirates can be misinterpreted as malignant or suspicious for malignancies.[139,140] 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.[136-142]

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.[143] 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.[137] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis. Jaundiced patients with locally advanced disease should be reviewed for autoimmune pancreatitis, and IgG4 levels should be assessed.

Autoimmune pancreatitis can, however, be negative for IgG4, thus closely mimicking pancreatic adenocarcinoma when there is a large pancreatic mass. For patients with borderline resectable disease and cancer not confirmed after 2 or 3 biopsies, a second opinion is recommended. Alternative diagnoses should be considered, especially autoimmune pancreatitis, and a short course of steroid treatment may be an appropriate first approach. If no response is seen, the patient should undergo laparotomy for removal of the mass.

Biomarkers

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

CA 19-9

The best validated and most clinically useful biomarker is CA 19-9, a sialylated Lewis A blood group antigen. CA 19-9 is commonly expressed and shed in pancreatic and hepatobiliary disease and in many malignancies; thus, it is not tumor-specific. However, the degree of increase in CA 19-9 levels may be useful in differentiating pancreatic adenocarcinoma from inflammatory conditions of the pancreas (see *Differential Diagnoses*, below).[144] 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.[145]

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CA 19-9 is a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 82% to 90% in symptomatic patients, but its low positive predictive value makes it a poor biomarker for screening.[146] 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.[147-149]

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 be prognostic for survival for patients undergoing resection.[146,147,149-155] 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; $P < .0001$).[151]

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.[154] 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 <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.[156] This study found that a normalization of CA 19-9 to <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; $P = .02$) patients.

In the advanced disease setting, data support the role of CA 19-9 as a prognostic marker.[150,157,158] 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.[157] 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.[157-162] For example, a recent study that pooled individual patients' data from 6 prospective trials found that a decline in CA 19-9 levels from baseline to after surgery and 2 rounds of adjuvant therapy were associated with a better outcome.[158] 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.[163] Furthermore, CA 19-9 may be falsely positive in cases of biliary infection (cholangitis), inflammation, or biliary obstruction (regardless of etiology) and do not necessarily indicate cancer or advanced disease.[164,165] 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 jaundiced patient, CA 19-9 levels

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can be assessed (category 3), but they do not represent an accurate baseline.

The panel recommends measurement of serum CA 19-9 levels prior to surgery (category 3), 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. 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.

hENT1

A recent development in the field of advanced pancreatic cancer involves a potential predictive marker. Gemcitabine is a prodrug that must be taken into cells via a nucleoside transporter.[168] Human equilibrative nucleoside transporter 1 (hENT1) is a nucleoside transporter that has been studied as a predictor for response to gemcitabine. Preliminary clinical data have shown that hENT1 expression may in fact predict response to gemcitabine.[167-172]

hENT1 has been validated in 2 retrospective analyses as a predictive biomarker for benefit from gemcitabine. A recent retrospective analysis of core tissue from patients treated on the adjuvant gemcitabine ESPAC-3 trial found that hENT1 expression was predictive of response to gemcitabine but not to 5-FU.[168] Median survival for patients treated with gemcitabine was 17.1 months versus 28.2 months for those with low versus high hENT1 expression, respectively ($P = .002$). In the 5-FU group, median survival was 25.6 months versus 21.9 months for the low and high hENT1 groups, respectively ($P = .36$). A similar analysis was performed on samples of patients treated on RTOG 9704.[167] As with the ESPAC-3 study, hENT1 expression was associated with OS (HR, 0.40; 95% CI, 0.22–0.75; $P = .03$) and DFS (HR, 0.39; 95% CI, 0.21–0.73; $P = .003$) in patients receiving gemcitabine, but hENT1 expression was not associated with OS (HR, 0.78; 95% CI, 0.47–1.27; $P = .31$) and DFS (HR, 0.72; 95% CI, 0.45–1.16; $P = .18$) in the group given 5-FU.

Thus, hENT1 appears to be an excellent predictive biomarker in the adjuvant setting based on the assay used in both of these studies (IHC with the 10D7G2 antibody). Unfortunately, hENT1 could not be validated in the metastatic setting in the LEAP trial, which used a different assay to determine hENT1 expression (IHC with the SP120 antibody). Results from the phase II, randomized, open-label LEAP trial, which compared a lipid-conjugated form of gemcitabine that does not require hENT1 for cell entry (CO-1.01) with gemcitabine in patients with metastatic disease with high versus low expression of hENT1, found that hENT1 expression was not predictive for outcomes in patients treated with gemcitabine.[173] Trial results also found no differences in OS between the 2 treatments in patients with low hENT2 expression (HR, 0.99; 95% CI, 0.75–1.33).

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

Systemic Therapy Approaches

Systemic therapy is used in all settings of pancreatic adenocarcinoma. It is important that biopsy confirmation of pancreatic adenocarcinoma be obtained before treatment in all cases (see Table 2, below). At least 2 or 3 negative or indeterminate biopsies should be obtained before entertaining alternative diagnoses (see *Differential Diagnoses*, above). A second opinion should also be obtained in such a case. Occasionally,

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other cancer types are confirmed, and the patient should be treated according to the appropriate NCCN Guideline. The data supporting the regimens used in pancreatic cancer are described below.

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.[174] The panel recommends gemcitabine monotherapy as one option for front-line therapy for patients with metastatic disease (category 1) or locally advanced 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 option for symptomatic patients with metastatic or locally advanced unresectable 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).[175] 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; $P = .01$).[176] An absolute survival difference of 10.3% was observed between the two groups at 5 years (20.7% vs. 10.4%).[176]

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.[177] In a randomized phase II trial of patients with locally advanced or metastatic pancreatic cancer, the infusion of gemcitabine at a FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.[178] In the phase III randomized ECOG-6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine vs. standard gemcitabine (6.2 months vs. 4.9 months; $P = .04$), although this outcome did not satisfy the protocol-specified criteria for superiority.[179] When gemcitabine is considered for the treatment of advanced pancreatic cancer, the NCCN Panel views FDR gemcitabine (10 mg/m^2/min) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B).

FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX [gemcitabine, oxaliplatin]; GTX [gemcitabine, docetaxel, and capecitabine]). See *Gemcitabine Combinations*, below.[180,181] The combination of FDR gemcitabine and capecitabine has also been found to be active and well tolerated.[182]

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,

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gemcitabine, 5-FU).[179-181,183-185] Two recent meta-analyses of randomized controlled trials both found that gemcitabine combinations give a marginal benefit in OS over gemcitabine monotherapy in the advanced setting, with a significant increase in toxicity.[194,195]

Combinations recommended in the advanced setting are discussed below. The panel does not consider the combination of gemcitabine plus docetaxel[196] or gemcitabine plus irinotecan[193,196,197] to meet the criteria for inclusion in the guidelines. In addition, gemcitabine plus sorafenib is not recommended. The recent multi-center, double-blind, placebo-controlled, randomized phase III BAYPAN trial compared gemcitabine plus either sorafenib or placebo in chemotherapy-naive patients with advanced or metastatic disease.[198] 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 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.[187,188,190]

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 weeks. The median OS at this dose was 12.2 months.[199]

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.[200] Participants were randomized to receive gemcitabine plus albumin-bound paclitaxel or gemcitabine alone. The trial met its primary endpoint of OS (8.5 months vs. 6.7 months; $P < .0001$; HR, 0.72; 95% CI, 0.62–0.83).[200] The addition of albumin-bound paclitaxel also improved other endpoints, including 1-year survival, 2-year survival, response rate, and PFS. The most common grade 3 or higher adverse events attributable to albumin-bound paclitaxel were neutropenia, fatigue, and neuropathy.

For the 2013 guidelines, the panel upgraded the combination of gemcitabine plus albumin-bound paclitaxel from a category 2B to a category 1 recommendation for the treatment of patients with metastatic disease and good performance status based on these results. By extrapolation of the data, the panel recommends this combination in the locally advanced setting as well (category 2A).

Gemcitabine Plus Erlotinib and Other Targeted Therapeutics

Although phase II trial results of gemcitabine combined with new targeted drugs (eg, bevacizumab, cetuximab) were encouraging,[201,202] 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.[203-207] Results of the CALGB phase III trial, which evaluated gemcitabine and bevacizumab (an anti-vascular endothelial growth factor [VEGF] antibody) compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer, and the Southwest Oncology Group (SWOG) phase III randomized trial, which assessed cetuximab (which targets the epidermal growth factor receptor [EGFR]) plus gemcitabine versus gemcitabine alone, did not reveal improvements in survival upon addition of the biologic agent.[204,205] In a phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer, bevacizumab did not improve OS,

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although a significant improvement in PFS was observed with the addition of bevacizumab to the gemcitabine/erlotinib combination.[207] A randomized phase III trial of another VEGF inhibitor, axitinib, in combination with gemcitabine also failed to show any improvement in OS of patients with advanced pancreatic adenocarcinoma.[208]

In contrast, in the phase III, double-blind, placebo-controlled NCIC CTG PA.3 trial of 569 patients with advanced or metastatic pancreatic cancer randomly assigned to receive erlotinib (which is an inhibitor of EGFR tyrosine kinase) plus gemcitabine versus gemcitabine alone, patients in the erlotinib arm showed statistically significant improvements in OS (HR, 0.82; $P = .038$) and PFS (HR, 0.77; $P = .004$) when compared to patients receiving gemcitabine alone.[203] 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.[203] 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.[205,208,209]

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

Gemcitabine Plus Cisplatin

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of randomized controlled trials have not provided support for use of gemcitabine plus cisplatin in the treatment of patients with advanced pancreatic cancer. Three phase III trials evaluating the combination of gemcitabine with cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination over the single agent.[194,195,199]

Nevertheless, selected patients may benefit from this regimen because patients with breast and ovarian cancers who are carriers of a *BRCA* mutation[210,211] and selected patients with inherited forms of pancreatic cancer[78] 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.[212] 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; $P < .01$).[212] Furthermore, in a recent report, 5 of 6 patients with known *BRCA* mutations and metastatic pancreatic adenocarcinoma treated with a platinum-based regimen at Memorial Sloan-Kettering Cancer Center showed a radiographic partial response.[213] 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 disease, especially those with possible hereditary cancers, as a category 2A recommendation.

Gemcitabine Plus Fluoropyrimidine

A number of randomized trials have investigated the combination of gemcitabine with a fluoropyrimidine in patients with advanced pancreatic cancer. The ECOG E2297 trial compared gemcitabine monotherapy with gemcitabine and bolus 5-FU/leucovorin in patients with advanced pancreatic cancer; no statistically significant survival

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advantage was observed for patients receiving the combination regimen.[183] 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.[186] 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.[150] Although there are concerns about dosing and toxicity of capecitabine in a U.S population, results from a recent study suggest that a biweekly regimen of fixed-dose gemcitabine in combination with capecitabine is both effective and well tolerated in patients with advanced disease.[214]

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

GTX Regimen

The panel includes the combination of gemcitabine, docetaxel, and capecitabine (GTX regimen) as a category 2B recommendation for the treatment of patients with advanced disease and good performance status. In a report of 35 patients with metastatic pancreatic cancer treated with this regimen, the authors reported an overall response rate of 29% (all had partial responses), with an additional 31% of patients exhibiting a minor response or stable disease.[181] The median survival was 11.2 months for all patients and 13.5 months for patients exhibiting a partial response. This regimen demonstrated significant toxicities, however, with 14% of patients having grade 3/4 leukopenia, 14% having grade 3/4 thrombocytopenia, and 9% having grade 3/4 anemia. A recent retrospective case-review study at 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.[215]

5-FU/Leucovorin

5-FU with leucovorin is listed in the guidelines as a category 1 option in the adjuvant setting. Results from the European Study Group for Pancreatic Cancer (ESPAC)-1 trial, reported by Neoptolemos and colleagues, suggested that 5-FU/leucovorin is superior to observation.[216] In addition, results from the ESPAC-3 trial of bolus 5-FU/leucovorin versus gemcitabine following surgery showed no difference in median OS between the arms (23.0 months and 23.6 months, respectively).[217]

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.[218] Another study

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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.[218] Also, the Mayo Clinic and North Central Cancer Treatment Group (NCTTG) determined that there was no therapeutic difference between the use of high- (200 mg/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.[220] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

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.[221] 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.[222] A later randomized phase II trial showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.[223]

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.[224] Because of these strong results, the panel added FOLFIRINOX as a category 1 recommendation for first-line treatment of good performance status patients with metastatic pancreatic cancer in 2011. It is listed as a category 2A recommendation for patients with locally advanced unresectable disease by extrapolation.

There are, however, some concerns about the toxicity of the FOLFIRINOX regimen. In the PRODIGE trial, some of the grade 3/4 toxicity rates that were significantly greater in the FOLFIRINOX group than in the gemcitabine group were 45.7% for neutropenia, 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9.0% for sensory neuropathy.[224] Despite the high levels of toxicity, no toxic deaths have been reported.[222-224] 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%, $P < .01$).[224] A more detailed analysis of the quality of life of patients in this trial has been published and shows that FOLFIRINOX maintained and even improved quality of life more than gemcitabine did.[225]

The panel appreciates that 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.[226] Median OS was 12.5 months in the metastatic setting and 13.7 months in patients with locally advanced disease.

Capecitabine and Continuous Infusion 5-FU

The panel lists capecitabine monotherapy and continuous infusion 5-FU as first-line treatment options for patients with locally advanced unresectable or metastatic disease (category 2B). They are also

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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.[227]

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).[228]

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).[229,230] 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).

Possible Role of Maintenance Therapy

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 stopping treatment, dropping the most toxic agents, and using different agents for maintenance therapy.

A recent randomized phase II trial (PACT-12) had intriguing results that suggest maintenance therapy with the angiogenesis inhibitor sunitinib after a full course of first-line treatment may have a benefit in some patients with metastatic disease.[231] Patients without evidence of progression after 6 months of initial therapy (n=55; mostly gemcitabine combinations) were randomized to sunitinib or observation. Median OS was 9.2 months in the observation group versus 10.6 months in the sunitinib group (HR, 0.71; 95% CI, 0.40–1.26; P = .11). The small sample size precludes strong conclusions; however, the 1- and 2-year survival rates were 36% and 7% in the observation arm compared with 41% and 23% in the sunitinib arm, suggesting that a subset of patients derive significant benefit.

Anti-angiogenic agents have not been successful in the treatment of pancreatic cancer to date. Results of the PACT-12 trial suggest that there may in fact be a role for these compounds in this disease. Angiogenesis inhibitors may be more useful after more effective first-line treatments. Clearly additional trials in this important area are needed.

Second-Line Systemic Therapy

For patients who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable second-line options.[229,230,232] The panel includes capecitabine, 5-FU/leucovorin/oxaliplatin,[229] and CapeOx[230] as options. Gemcitabine-based therapy can be given to those previously treated with fluoropyrimidine-based therapy.

Of note, results from the phase III CONKO-003 trial presented in 2008 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,[233,234] making this

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regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy. Published results from this trial demonstrated the superiority of 5-FU/leucovorin/oxaliplatin over best supportive care in both median second-line survival (4.8 months vs. 2.3 months; $P = .008$) and median OS (9.1 months vs.7.9 months; $P = .031$).[229]

The AIO-PK0104 trial also assessed second-line therapy in a randomized cross-over trial and found capecitabine to be efficacious after progression on gemcitabine/erlotinib in patients with advanced disease.[235] In this trial, capecitabine/erlotinib followed by gemcitabine gave similar outcomes to the aforementioned sequence.

A recent systematic review of clinical trials that assessed the efficacy of second-line therapy after gemcitabine in pancreatic cancer concluded that, while data are very limited, evidence suggests an advantage of additional chemotherapy over best supportive care.[236]

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.[237]

Chemoradiation is sometimes used for pancreatic cancer in the adjuvant setting, because of its potential to decrease the likelihood of local recurrence. It is also sometimes used in the locally advanced setting, namely in those patients who do not progress during initial chemotherapy. 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 unresectable disease or in resected patients if it 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 narcotic therapy. Varying levels of evidence support the use of chemoradiation in each setting, as discussed in more detail below.

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.[238,239] 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.[238]

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 radiotherapy and 5-FU versus observation alone after surgery. They found that the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant.[240] At a median follow-up of 11.7 years,

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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.[241]

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.[242] This trial, which utilized daily fractionated radiotherapy, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[243] Results of this study showed that, for patients with tumors of the pancreas head (representing 388 of the 451 patients enrolled in the trial), there was a non-statistically significant increase in OS in the gemcitabine arm compared with the 5-FU arm (median and 3-year survival of 20.5 months and 31% vs. 16.9 months and 22%; P = .09); this benefit became more pronounced on multivariate analysis (HR, 0.80; 95% CI, 0.63–1.00; P = .05). The recently published 5-year analysis of RTOG 9704 showed that there was in fact no difference in OS between the two groups, although patients with tumors in the head of the pancreas showed a trend toward improved OS with gemcitabine (P = .08) upon multivariate analysis.[244]

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),[216] although the ESPAC-1 trial has been criticized for lack of attention to quality control for RT.[245-247] A phase II study by GERCOR randomized patients to adjuvant gemcitabine or adjuvant gemcitabine-based chemoradiation.[248] 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 recently 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.[249]

A 2012 meta-analysis of 15 prospective, randomized trials found that adjuvant chemoradiation did not improve DFS, 2-year survival, or OS (odds ratio, 0.99; P = .93) compared to surgery alone, while adjuvant chemotherapy improved all 3 outcomes (odds ratio for OS, 1.98; P < .001).[250] 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).[251] However, a population-based assessment of outcomes of patients in the NCDB with pancreatic cancer resected from 1998-2002 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).[252]

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

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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.

Benefit of Adjuvant Chemoradiation in Patient Subsets

It has been suggested that subsets of patients (ex, 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.[253] In contrast, results from a prospectively collected database of 816 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.[254] The Mayo Clinic performed a retrospective review of 468 patients who had R0 resections for pancreatic adenocarcinoma, and found an OS benefit of adjuvant chemoradiation over observation.[255] In addition, a retrospective review of resected >1200 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; $P < .001$).[256] A metaanalysis of 4 randomized controlled trials 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).[257]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.[258] 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 metaanalysis of 4 randomized controlled adjuvant trials found that chemoradiation had a similar lack of benefit in lymph node-positive and -negative patients.[259]

Chemoradiation for Locally Advanced Disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer, although the utility of chemoradiation in this population of patients is controversial.[260] It is mainly used in selected patients who do not develop metastatic disease during initial chemotherapy.

The role of chemoradiation in locoregional pancreatic cancer was initially defined in a trial conducted in locally advanced disease by GITSG.[239] 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.[261] Gemcitabine has also been used as a radiation sensitizer in the locally advanced setting.[262-266] 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.[261,265,267,268] The use of capecitabine as a radiosensitizer has also been assessed in this setting and appears to be effective.[269]

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Upfront Chemoradiation in Locally Advanced Disease

Results of 2 early randomized trials comparing upfront chemoradiation to chemotherapy in locally advanced disease were contradictory.[270,271] 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.[262,272-274] Results from small, single-arm trials of upfront chemotherapy followed by chemoradiation in locally advanced disease have been discussed.[275]

The more recent phase III randomized ECOG-4201 trial, which assessed gemcitabine compared with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer, was closed early due to poor accrual. However, an ITT analysis of data for the 74 patients enrolled in this study showed that median OS was significantly longer in the chemoradiation therapy arm of the study (11.1 months vs. 9.2 months; $P = .017$).[276] 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.[277]

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.[278] 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.

Thus the role of upfront chemoradiation in the setting of locally advanced pancreatic cancer is still undefined. The panel points out that if patients present with poorly controlled pain or local invasion with bleeding, it may be preferable to start with upfront chemoradiation therapy.[262,264]

Chemoradiation Following Chemotherapy in Locally Advanced Disease

Starting with 2 to 6 cycles of systemic chemotherapy followed by chemoradiation therapy is an option for selected patients with unresectable disease and good performance status who have not developed metastatic disease.[279-281] 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.[279]

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However, preliminary data from the international phase III LAP 07 trial showed no clear survival benefit (the primary outcome measure) with the addition of conventional chemoradiation following gemcitabine monotherapy.[282] In this study, 269 patients with disease control after induction chemotherapy were randomized to additional chemotherapy or to chemoradiation with capecitabine. Median OS was 16.5 months in the chemotherapy arm versus 15.3 months in the chemoradiation arm (HR, 1.03; 95% CI, 0.79–1.34; $P = .83$). 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

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.[283-287] 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.[287] 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. Results of a recent study demonstrated that 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.[242,288] 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% ($P = .017$),[288] suggesting that IMRT may be well tolerated and allow for higher radiation doses to the tumor.[288] There is no clear consensus on the appropriate maximum dose of radiation when IMRT technique is used.

Stereotactic body radiotherapy (SBRT) is another technique aimed at increasing dose to the gross tumor while sparing radiation to nearby healthy tissue.[289-295] 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.[289] However, another retrospective review of 71 patients reported a median OS of 10.3 months with only 3 patients (4%) experiencing grade 3 toxicity.[291] No standard total dose or dose per fraction has been established for SBRT, and the panel currently recommends that SBRT only be utilized as part of a clinical trial.

Intraoperative radiation therapy (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. 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.[294-297] Some groups, however, believe that IORT can offer benefits in very carefully selected patients with non-metastatic disease.[298-300] Overall, there is no clear established role for IORT in patients with pancreatic cancer.[301]

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

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pain management, patent biliary stent, and adequate nutritional intake). Systemic therapy is therefore recommended for patients with metastatic disease and good performance status, as described in *Systemic Therapy Approaches*, above, and in the guidelines.

Patients who present with poor performance status may benefit from the administration of gemcitabine (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.

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, debilitated patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumor progression may develop quickly, and tumor-related symptoms may be inappropriately attributed to chemotherapy or other causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or in its more subtle form, as abdominal bloating, as decreased oral intake, and as constipation.

For patients who do well on initial therapy, a chemotherapy holiday is appropriate, or maintenance therapy can be considered (see, *Possible Role of Maintenance Therapy*, above). After progression, second-line therapy is possible, especially in patients who maintain a good performance status (see *Second-Line Systemic Therapy*, above).

Management of Locally Advanced Disease

As in the metastatic setting, the primary goals of treatment of patients with unresectable, locoregional 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. Gemcitabine (category 1) and palliative and best supportive care are options for patients with poor performance status, whereas patients with good performance status can be treated with more intensive therapy (ex, FOLFIRINOX [category 2A], gemcitabine/albumin-bound paclitaxel [category 2A]) or with gemcitabine monotherapy (category 2A), as described in *Systemic Therapy Approaches*, 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 locoregional unresectable disease. The experience with FOLFIRINOX in 22 patients with locally advanced pancreatic cancer at the Massachusetts General Hospital Cancer Center through February 2012 was recently reported.[302] 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 ≥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

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occasionally arises.[302-310] 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.[311]

The use of chemoradiation following chemotherapy in locally advanced disease is discussed above (See *Chemoradiation for Locally Advanced Disease*).

Management of Resectable and Borderline Resectable Disease

Surgical Management

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.[312] Early concerns about high mortality associated with various pancreatic resection procedures[313] have now been lessened by studies demonstrating an acceptably low (<5%) mortality in experienced centers (see *Effect of Clinical Volume*, below).[314] Even under the most optimal clinical trial conditions, however, the median survival of resected patients following adjuvant therapy ranges from 20.1 to 23.6 months.[175,216,217,242] Negative margin status (ie, R0 resection), tumor DNA content, tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[315-317] 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.[318-320]

Criteria for Resection

The NCCN Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation at high-volume centers with reference to appropriate high-quality imaging studies to evaluate the extent of disease. Although it is clear that patients with visceral, peritoneal, or pleural metastases or with metastases to nodes beyond the field of resection derive no benefit from resection, institutions differ in their approaches to patients with locoregional disease involvement (pancreas and peripancreatic lymph nodes). Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group developed criteria to define tumor resectability so as to improve patient selection for surgery and increase the likelihood of an R0 resection, and the NCCN Pancreatic Adenocarcinoma panel supports these criteria.[88,321] Other groups have also put forth definitions of resectability of pancreatic cancer.[322,323] Using these criteria, tumors are classified as resectable; borderline resectable; or unresectable (ie, locally advanced or metastatic disease).

By the NCCN definition, the absence of evidence of peritoneal or hepatic metastases following a thorough radiologic assessment is a criterion for both resectable and borderline resectable disease. The panel defines patients with resectable disease as those who have clear fat planes around the celiac axis, hepatic artery, and SMA and no radiologic evidence of SMV or PV distortion. On the other hand, radiologic findings of venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement, characterizes a tumor as borderline resectable. As for arterial involvement, radiologic findings of encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac axis

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and/or tumor abutment of the SMA involving ≤180˚ of the artery circumference, classifies a tumor as borderline resectable.

A more restrictive definition of borderline resectable pancreatic tumors has also been described.[324] This definition uses degrees of contact (eg, interface between tumor and SMA measuring <180˚ of vessel wall circumference) rather than subjective terms such as abutment and impingement. The panel endorses this definition for use in clinical trials.

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.[323,325] 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. Furthermore, the panel recommends that patient factors be considered when deciding whether a patient is a surgical candidate. Age of the patient, comorbidities, performance status, and frailty are all things to be discussed during the multidisciplinary review. Please refer to the NCCN Guidelines for Senior Adult Oncology for further discussion of the treatment of older patients.

Primary Surgery for Pancreatic Cancer

The nature and extent of the surgery for resectable tumors depend on the location and size of the tumor. Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and are rarely resectable. When tumors in the pancreatic tail are resectable, distal pancreatectomy, in which the surgeon removes the tail and body of the pancreas, as well as the spleen, is commonly performed. If the cancer diffusely involves the pancreas or is present at multiple sites within the pancreas, a total pancreatectomy may be required, where the surgeon removes the entire pancreas, part of the small intestine, a portion of the stomach, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes. Patients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with open or laparoscopic pancreatoduodenectomy (ie, the Whipple procedure).[326,327]

If the tumor is found to be unresectable during surgery, the panel recommends biopsy confirmation of adenocarcinoma at this time, if a biopsy was not performed previously. If a patient with jaundice is found to be unresectable at surgery, then the panel recommends stenting or biliary bypass at that time. In addition, duodenal bypass can be considered if appropriate regardless of jaundice (category 2B for prophylactic duodenal bypass). Open ethanol celiac plexus block can also be performed, especially when indicated by pain in a patient with jaundice (category 2B for a non-jaundiced patient). See *Palliation of Locally Advanced and Metastatic Disease*, below, for more details about these procedures.

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

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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).[328,329] Optimal dissection and skeletonization of the SMA can be achieved using ultrasonic or thermal dissectors (Harmonic scalpel or LigaSure). Division of the retroperitoneal tissues between the uncinate process and the SMA with a stapler or a clamp and cut technique may leave up to 43% of the soft tissue between the uncinate process and the SMA in situ and results in suboptimal clearance and increases the risk of an R1 resection.[330,331]

The panel recommends analysis of the pancreatic neck and bile duct at time of surgery by frozen section. Frozen sections should be taken approximately 5 mm from the transection margin, with the clean cut side facing up, 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.

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.[332-334] On evaluation of excised vein specimens, only 60% to 70% had histologic evidence of frank tumor involvement, and R0 resections were still not obtainable in 10% to 30% of patients despite increasing the magnitude of the operative procedure. However, if an R0 resection is obtained with vein excision, longevity appears similar to those with R0 resections without venous involvement, with no significant increase in morbidity and mortality. These data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected, although acceptance of this concept (particularly with respect to vein resection) is not universal.

Although numbers are more limited, similar findings have been noted with respect to hepatic arterial resection and reconstruction.[334,335] Others, however, have noted poor short- and long-term outcomes with arterial resection.[336,337] While further data with respect to arterial resection are clearly needed, judicious utilization of this technique would appear to be reasonable in very select populations.

A recent population-based study of 10,206 patients from the Nationwide Inpatient Sample from years 2000 through 2009 found that vascular reconstruction (about 90% venous and 10% arterial) is associated with a higher risk of intraoperative and postoperative complications.[337] No difference in mortality was seen.

Distal Pancreatectomy

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. 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.[338,339] 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.[339,340] Utilization of these radical resections is associated with

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an increase in blood loss, transfusion requirements, operating time, length of stay, and morbidity, but mortality remains rare.[338-340] 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.[339,340] Local recurrence, however, remains problematic even with pathologically negative margins.[340]

There is an increasing role for laparoscopic distal pancreatectomy. 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.[341] 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.[342] 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.[343]

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.[344] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreatoduodenectomy decreased, a subset of patients was identified who were in need of resection of the SMV wall to achieve negative margins during removal of their tumors. Thus, in the 1990s, there was renewed interest in vein resection for complete resections. The group from the University of Texas MD Anderson Cancer Center has championed this approach, demonstrating that vein resection and reconstruction can allow for complete resection and is not associated with increased morbidity or mortality when compared with patients who did not require vein resection.[345] Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.[346]

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.[347-350] 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.[334] In a more recent 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).[351] 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[352] reported the modern use of pylorus preservation in 1978. The hypothesis was that preservation would improve emptying and provide nutritional benefit, but the benefits have been inconsistent to date. Yeo et al reported no adverse effects of pylorus preservation[353]; however, van Berge Henegouwen et al reported longer nasogastric drainage

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times.[354] In several randomized and nonrandomized studies,[355-358] the pylorus-preserving procedure seemed to be associated with shorter surgical duration. No consistent data suggest that pylorus preservation leads to a better quality of life or nutritional status in patients after resection. Thus, pylorus-preserving pancreatoduodenectomy remains an unproven but certainly acceptable alternative to classic pancreatoduodenectomy performed with antrectomy.

Pancreatic Anastomosis

Efforts in this area have focused on preventing pancreatic leaks and fistulas, which are morbid and potentially lethal complications of pancreatoduodenectomy. 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.[360] However, a more recent multicenter, randomized, superiority trial compared the outcomes of 329 patients undergoing pancreaticoduodenectomy with either pancreaticojejunostomy or pancreaticogastrostomy.[361] 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, 1.36-6.17; $P = .002$). An increase in grade ≥3a postoperative complications was seen, however, in the pancreaticogastrostomy group (24% vs. 21%). Criticisms of this trial have been published,[362] and the optimal approach to anastomosis remains undefined.

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.[363,364] 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.[365] Stents used in the 1930s and 1940s continue to be used today, but data suggest that they do not decrease leak rates.[366]

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).[367,368] Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.[369]

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.[370,371] 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.[372] 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.[373]

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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.[374] A larger randomized prospective trial was performed at Johns Hopkins Hospital from 1996 through 2001 to evaluate the role of extended lymph node dissections.[375] 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.[376-377] Recently, a randomized multicenter trial in Japan came to similar conclusions.[378] Furthermore, a meta-analysis of randomized controlled trials comparing pancreatoduodenectomy with standard versus extended lymphadenectomy supports the conclusion that the extended procedure does not have any impact on survival.[379] In addition, patients undergoing extended lymphadenectomy have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.[380]

The information to date thus does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.[381] 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.[382,383]

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.[384-386] 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.[387-393] 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.[394] 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%; relative risk in the surgery alone group, 0.54; 95% CI, 0.41–0.71; $P < .001$). However, no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.[395]

Based on these reports, most groups who perform resection without neoadjuvant treatment advocate selective use of decompression only in patients who are symptomatic or septic or in whom surgical resection is

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significantly delayed. The panel includes in this group patients who present with jaundice and potentially resectable disease if symptoms of cholangitis or fever are present or if they have significant pruritus and an expected delay to surgery of >1 week. Most panel members endorse use of a plastic stent in these cases, since such patients may undergo surgery shortly thereafter and do not require the longer patency time of a metal stent. If metal stents are used, short metal stents are preferred because they may be less likely to interfere with the subsequent resection yet have a longer patency time. The panel cautions against placement of a metal stent prior to tissue proof of malignancy.

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.[396] 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.[397-400]

The panel notes that stents are an evolving technology. The choice of stents includes plastic and metal; fully covered, partially covered, or uncovered; rigid; or self-expanding (also see the discussion on stents in *Palliation of Locally Advanced and Metastatic Disease*, below). While any stent can become occluded, several groups have reported better patency with metal stents.[398-400] Metal stents are generally viewed as more permanent than plastic stents. Covered metal stents may give more durable patency, since the cover prevents tumor ingrowth,[401] but the reported differences between covered and uncovered stents are not dramatic.[401,402] Furthermore, migration is more of an issue with covered stents.[402] This issue has led to the introduction of partially covered stents,[403] though these stents may still migrate in a substantial number of patients.[404,405] Most metal stents used today are self-expanding. Their small initial diameters make them easy to place, and their placement rarely requires dilation.[403] Several panel members reported that their institutions use plastic stents in patients with short life expectancies (<3 months).[403] The panel could not reach a consensus on which type of stent is best used in each preoperative circumstance, since level 1 evidence is lacking. A clinical trial is currently recruiting patients to compare metal and plastic stents for preoperative biliary decompression in patients with pancreatic cancer (ClinicalTrials.gov NCT01191814).

Effect of Clinical Volume

Several studies have examined the effect of institutional volume on patient outcomes. The fundamental premise was that the decreasing morbidity and mortality seen in the 1980s and 1990s were the direct result of large, single-institution experiences. Moreover, the concern was that if surgeons performed 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% versus 12.3%).[408] 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.[407-411] 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

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centers. Interestingly, this effect was also seen in reports from Canada and the Netherlands.[412-414]

The definitions of high and low volume varied among all these studies. However, a striking difference is seen when the mortality rates from pancreatoduodenectomy in very-low-volume (0–1 procedure/year) and low-volume (1–2 procedures/year) hospitals are compared with rates in higher-volume hospitals (>5 procedures/year).[415] In-hospital mortality rates at these very-low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, versus 4%; $P < .001$). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when 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 >16 procedures per year were classified as "high" and "very-high" volume centers.[416] 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.[417] In addition, a recent systematic review showed that margin status correlates with hospital volume, with negative margin rates ranging from 65% in low-volume centers to 76% for very-high-volume centers ($P = .008$).[418] 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.[419]

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.[420] 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

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(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 October 2013.[421] 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 Guidelines) 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.[422,423]

Lymph Node Counts

The CAP recommendations include a count of the number of lymph nodes recovered and the number of involved nodes.[421] Recent retrospective database analyses have found that patients with N0 disease have a better prognosis with an increasing number of examined lymph nodes.[424-426] 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.[424,426] 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 nodes/nodes examined) appears to be related to prognosis.[424-430] For instance, in one analysis, patients with <15% of examined positive nodes had a 5-year survival rate of 21.7%, while those with >15% positive nodes had a 5.2% 5-year survival rate ($P = .0017$).[428]

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, a stitch can be placed on the posterior margin and a safety pin on the retroperitoneal/uncinate margin.

One of the impediments to comparison of data across institutions is the variability in the names given to various margins. Definitions of the margins and uniformity of nomenclature are critical to accurate reporting. The panel's recommended definitions are included in the *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* section in the guidelines. Margins defined include the SMA (retroperitoneal/uncinate) margin, the posterior margin, the PV groove margin, the proximal and distal PV margins, the pancreatic neck (transection) margin, and the bile duct margin (see Figure 2). Other margins analyzed in Whipple specimens include the proximal and distal enteric margins (en face sections) and the anterior surface (closest representative). The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and so should be reported in all cases.[426,431-433] 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

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

A recent retrospective review compared the outcomes of 169 patients with R0 resections of close margins (within 1 mm) to 170 patients with wider margins (>1 mm) and found an improvement in OS with wider margins (35 months vs. 16 months; $P < .001$).[434] In fact, the close-margin R0 patients had a median survival time similar to that of the R1 population (16 months vs. 14 months; $P = .6$). Consistent with these results, another recent 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 that those with R0 resections (HR, 4.27; 95% CI, 2.07–8.81).[435,436] 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 ($P = .10$).[437] Together, these results suggest that an appropriate definition of a negative margin may be >1 mm.

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

Distal Pancreatectomy Specimen

In left-sided resections, the peripancreatic soft tissue margins and the pancreatic neck are assessed (see Figure 5). Additionally, involvement of the splenic vessels should be documented, and invasion of the spleen is important to determine, because direct tumor invasion constitutes a 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*).

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*

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Approaches 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[176]), 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.

Based on the data discussed above, no definite standard has been established in the adjuvant treatment of pancreatic cancer at this time. Gemcitabine- or fluoropyrimidine-based chemoradiation with additional gemcitabine, continuous infusion 5-FU, or 5-FU/leucovorin chemotherapy and chemotherapy alone with gemcitabine (category 1), 5-FU/leucovorin (category 1), or continuous infusion 5-FU are listed in the guidelines as options for adjuvant treatment. It was the consensus of the panel that when chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over 5-FU/leucovorin for most patients due to its more favorable toxicity profile. In the adjuvant setting, capecitabine monotherapy is also listed in the guidelines (category 2B). The panel 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.

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. While no studies have demonstrated superiority of giving chemoradiation before versus after chemotherapy in the adjuvant setting, when patients have a margin-positive resection, upfront chemoradiation followed by systemic chemotherapy is an appropriate option.

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.[438] These results suggest that delaying chemotherapy until patients adequately recover could possibly improve outcomes.

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

Preoperative (Neoadjuvant) Therapy

Contemporary approaches to perioperative treatment have focused on neoadjuvant therapy for patients with borderline resectable disease with the goal of improving OS.[306,309] Neoadjuvant therapy is also sometimes used in resectable patients, especially in those with high-risk features. The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of resectable patients will receive chemotherapy and/or radiation; the potential to downsize tumors so as to increase the likelihood of a margin-free resection (ie, conversion 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.[308,310,323,439]

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Moreover, surgery following neoadjuvant treatment appears to be safe.[440,441]

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 metal stent) is recommended prior to initiation of neoadjuvant therapy in patients with jaundice.[396-400]

There is insufficient evidence to recommend specific neoadjuvant regimens, and practices vary with regards to chemotherapy and chemoradiation. Neoadjuvant therapy regimens are often similar to those used to treat locally advanced disease (see *Systemic Therapy Approaches*, above), and include upfront continuous infusion 5-FU- or capecitabine-based chemoradiation,[310,442] upfront gemcitabine-based chemoradiation,[443] or induction chemotherapy followed by 5-FU- or gemcitabine-based chemoradiation.[308] Most published neoadjuvant studies that were done prior to the introduction of more effective combination chemotherapy incorporated chemoradiation. Studies of more effective regimens (ie, FOLFIRINOX, gemcitabine/albumin-bound paclitaxel) without chemoradiation are in progress. The role of chemoradiation with more active chemotherapy regimens also needs to be tested.

Abdominal (pancreas protocol), pelvic, and chest imaging 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.

Neoadjuvant Therapy in Borderline Resectable Disease

Patients with borderline resectable disease have the options of upfront resection (category 2B) with adjuvant therapy or 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. In fact, the panel down-graded its recommendation for upfront resection in borderline cases to category 2B in the 2014 version of these guidelines.

Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerated.[444-448] A phase I/II trial of neoadjuvant therapy in borderline resectable disease allowed 4 of 26 patients (15%) to be resected.[446] 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.[447] A recent 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%.[448]

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In 2 retrospective reviews, 31% to 35% of borderline resectable patients who completed neoadjuvant therapy had R0 resections.[450,451] A systematic review and meta-analysis of 19 cohort studies found that unresectable patients (including both borderline and unresectable patients) undergoing neoadjuvant chemoradiation therapy had similar 1-year survival outcomes as patients who were initially deemed resectable.[452] 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.[324] Initial results in patient series suggest that neoadjuvant regimens including FOLFIRINOX are a promising approach in patients with borderline resectable disease.[453,454] Additional randomized trials are needed.

Neoadjuvant Therapy in Resectable Disease

A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[306,309,443,455-462] 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.[458] 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.[458] 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.[458] The MD Anderson group has continued to champion this approach both for its ability to select patients for resection and for cost-effectiveness.[463] Other potential advantages of the neoadjuvant approach in resectable patients have also been described, including sterilization of the field before resection potentially reducing spread during surgery; increased rates of R0 resections; decreased incidence of pancreatic fistulas; prevention of delays or reductions of adjuvant therapy after surgery; and improved delivery of chemotherapy and radiosensitizing oxygenation.[441,464,465]

Although most studies investigating the neoadjuvant experience in patients with resectable pancreatic cancer are retrospective, several small phase II studies have been published.[441,464,466,467] 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.[460]

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.[443] 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

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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.[392] 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.[439] 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,[468] results of randomized trials addressing this issue have yet to be reported. A phase III trial with a PFS endpoint comparing adjuvant therapy with a combination of neoadjuvant and adjuvant therapy is currently recruiting patients (ClinicalTrials.gov NCT01314027).[469] A phase II trial with R0 resection as the primary endpoint is ongoing (ClinicalTrials.gov NCT01389440).

At this time, the panel does not recommend neoadjuvant therapy for most resectable patients, except in a clinical trial. For selected patients who appear technically resectable but have poor prognostic features (ie, borderline resectable disease; markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; highly symptomatic), however, consideration can be given to neoadjuvant therapy after biopsy confirmation, although a clinical trial is still preferred.

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.

Adjuvant chemotherapy or adjuvant chemoradiation should only be considered for pre-treated patients who have adequately recovered from surgery and have no evidence of recurrence or metastatic disease; treatment should ideally be initiated within 4 to 8 weeks. It is recommended that the patient undergo a pretreatment baseline assessment following surgery, including CT scan and CA 19-9 level, to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Further, the panel recommends restaging a patient with imaging following systemic chemotherapy, if it will precede chemoradiation.

Surveillance of Resected Patients

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited,[470-472] recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The panel recommends history and physical examination for symptom assessment every 3 to 6 months for 2 years, then annually. CA 19-9 determinations and follow-up CT scans every 3 to 6 months for 2 years after surgical resection are category 2B recommendations, because data are not available to show that earlier treatment of recurrences, following detection by increased tumor marker levels or CT

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scan, leads to better patient outcomes. In fact, a recent analysis of the SEER-Medicare database showed no significant survival benefit for patients who received regular surveillance CT scans.[473]

Management of Recurrent Disease

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 second-line therapy.[474] 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. Alternatively, chemoradiation can be considered in patients with local disease recurrence only, if not previously administered, or an alternative chemotherapy regimen can be given. For patients for whom there is evidence of metastatic disease (with or without a local recurrence), treatment decisions are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed less than 6 months prior to development of metastatic disease, the panel recommends that an alternative chemotherapy option be administered. When this period is greater than 6 months, systemic therapy as previously administered or an alternative systemic regimen is recommended.

Recommended regimens are as for second-line therapy in metastatic disease (see *Second-Line Therapy*, above), and may consist of gemcitabine or gemcitabine-based combination therapy for patients previously treated with fluoropyrimidine-based therapy or fluoropyrimidine-based therapy for patients previously treated with gemcitabine-based therapy. Examples of appropriate second-line fluoropyrimidine-based therapies recommended by the panel are 5-FU/leucovorin/oxaliplatin or CapeOx.[228,230] Gemcitabine-based therapies include those listed in *Systemic Therapy Approaches*, above.

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.[475] For patients diagnosed with unresectable disease and biliary obstruction upon initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent self-expanding metal stent (SEMS) is recommended unless biliary bypass is performed (also see the discussion on stents in *Preoperative Biliary Drainage*, above). Stent occlusion that causes recurrent cholangitis is a well-known complication of plastic (temporary) biliary stents and typically occurs within 3 months of insertion. Metal stents are wider in diameter than plastic stents (ie, less likelihood of blockage) and become embedded in the bile duct, whereas plastic stents are more likely to become occluded but can be replaced. Results of a randomized,

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controlled trial of 100 patients at a single center randomly assigned to receive either a plastic stent or a covered self-expanding metal stent inserted endoscopically indicated that median patency times were 1.8 and 3.6 months ($P = .002$), respectively.[476] A meta-analysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.[477] 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 recent 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.[478]

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.[479] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.[479]

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors following laparotomy, an open biliary-enteric bypass provides durable palliation of biliary obstruction and can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain. The panel recommends stenting or an open biliary-enteric bypass with or without duodenal bypass (category 2B for prophylactic duodenal bypass[480,481]) and with or without open ethanol celiac plexus block[482-484] (category 2B in non-jaundiced patients). Please see *Gastric Outlet Obstruction* and *Severe Tumor-Associated Abdominal Pain* below for more detailed information on these procedures. Bypass of the common bile duct (choledochojejunostomy) or common hepatic duct (hepaticojejunostomy) to the jejunum is preferred to bypass of the gallbladder (cholecystojejunostomy) since choledochojejunostomy/hepaticojejunostomy provide more durable and reliable palliation of biliary obstruction.[475]

Biliary decompression is also required for jaundiced patients with disease progression precluding surgery with or without neoadjuvant therapy. Here, stenting or biliary bypass is recommended, with or without duodenal bypass (category 2B for prophylactic duodenal bypass[480,481]) and with or without open ethanol celiac plexus block (category 2B). One final circumstance requiring biliary drainage is in jaundiced patients with locally advanced or metastatic disease (those for whom surgical resection will not be attempted). In this situation, a SEMS is preferred unless biliary bypass was performed at the time of laparoscopy or laparotomy. However, several panel members reported that their institutions use plastic stents in patients with short life expectancies because of the lack of concern about long-term patency. If cancer has not been biopsy-confirmed in the setting of locally advanced disease in a jaundiced patient, brushings can be obtained at the time of stent placement (short metal stent preferred in this situation).

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10% to 25% of patients with pancreatic cancer.[475] 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.[479] An alternative for these patients with poor performance status is

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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.[485-487] Nevertheless, placement of an enteral stent is also an option for these patients.

For patients with potentially resectable disease who undergo a laparotomy and are found to have unresectable disease, a prophylactic gastrojejunostomy should be performed for those deemed to be at risk of developing symptomatic gastric outlet obstruction (category 2B). The role of prophylactic gastrojejunostomy in otherwise asymptomatic patients who are found to have unresectable cancers at the time of laparotomy has been evaluated. Two randomized controlled trials have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer, the majority arising from the head of the pancreas.[480,481] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. A recent meta-analysis found similar results, with development of gastric outlet obstruction in 2.5% of patients in the prophylactic gastrojejunostomy group and 27.8% of those not receiving gastrojejunostomy.[488] 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.[484] General principles for cancer-related pain management can be found in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, open ethanol celiac plexus neurolysis should be considered (category 2B, except when indicated by pain in a jaundiced patient who is found unresectable at surgery, for which the recommendation is a category 2A). In 2 randomized controlled trials, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.[482,484] In a recent study of 96 patients with pain related to suspected pancreatic cancer, half were randomized to EUS-guided celiac plexus neurolysis at the time of EUS if unresectable adenocarcinoma was confirmed.[483] These patients reported better pain relief at 3 months ($P = .01$), suggesting that early EUS-guided celiac plexus neurolysis may be beneficial. A recent metaanalysis of 7 randomized controlled trials concluded that celiac plexus block improved pain scores at 4 weeks but not at 8 weeks in patients with pancreatic cancer.[483] Minimally invasive techniques including EUS-guided (preferred if available) and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis are recommended, but laparoscopic, thoracoscopic, and open approaches can also be used.

In selected patients with severe local back pain refractory to narcotic therapy, palliative RT may be considered, even in the setting of metastatic disease, if not already given as part of primary therapy. In such cases, radiation is given with or without concurrent chemotherapy to the primary tumor plus a margin (typically 25–36 Gy in 2.4–5 Gy fractions), or radiation alone is given to the metastatic site.

Pancreatic Insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or blockage of the

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pancreatic duct, or by surgical removal of pancreatic tissue, and results in an inadequate production of digestive enzymes.[490,491] This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.[492] Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency. Because pancreatic insufficiency occurs in up to 94% of patients undergoing pancreatic surgery,[493,494] 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.[492] For patients failing this therapy, doses of the enzyme preparation can be increased, and inhibition of gastric secretion with a proton pump inhibitor can also be considered.[492,493] Patients with a clinical suspicion of pancreatic insufficiency despite appropriate replacement may need a more thorough nutritional evaluation.

Thromboembolic Disease

The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.[495,496] 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.[497] In the CONKO 004 trial, VTE- and chemotherapy-naïve patients with advanced pancreatic cancer were randomized to receive palliative chemotherapy with or without the LMWH, enoxaparin.[498] 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. Please see the NCCN Guidelines for Venous Thromboembolic Disease, available at www.NCCN.org, for more information.

Depression, Pain, and Malnutrition

For many patients, a diagnosis of pancreatic cancer may result in significant psychosocial distress, including anxiety, depression, and sleep disturbances.[499] In fact, the suicide rate in male patients with pancreatic cancer is reportedly 11 times that of the general population.[500] Empathetic discussion about the natural history of this disease and its prognosis and the provision of support and counseling both by the primary oncology team and specialized services may help to alleviate this distress. The panel recommends that patients be screened and evaluated for depression and other psychosocial problems following the NCCN Guidelines for Distress Management (available at www.NCCN.org).

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

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Future Clinical Trials: Recommendations for Design

In 2007, a meeting was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee in recognition of the failure of a number of 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.[501]

- 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.[502] Additionally, the group states that FOLFIRINOX can be considered as a new standard treatment option in selected patients in future clinical trials, but that gemcitabine should remain the standard for most patients. An international expert panel also met recently to discuss current and future pancreatic cancer research and came to similar conclusions.[474] 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.[503] 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.[504] 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-

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bound paclitaxel-eligible patients and a 4- to 5-month improvement in OS for FOLFIRINOX-eligible patients to give results with true clinical impact.

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 a recent Intergroup trial.[324] Endpoints should also be standardized and could include resection rates, R0 resection rates, local recurrence rates, pathologic response rates, DFS, and OS.[305]

Summary

Resection remains the only chance for a cure for pancreatic adenocarcinoma, and most resectable patients should undergo surgery without delay, followed by adjuvant therapy. Borderline resectable patients and select resectable patients can undergo neoadjuvant therapy in the hopes of improving the chances for an R0 resection or can immediately undergo surgery (category 2B). Additional therapy is an option for those patients whose disease recurs following surgery. Patients with locally advanced unresectable disease and good performance status can undergo chemotherapy and chemoradiation with second-line therapy if performance status is maintained after progression. Good performance status patients presenting with metastatic disease can undergo chemotherapy and can undergo second-line therapy if performance status is maintained after progression. Specific palliative measures are recommended for patients with advanced pancreatic adenocarcinoma characterized by biliary or gastric obstruction, severe abdominal pain, or other tumor-associated manifestations of the disease.

Overall, in view of the relatively high likelihood of 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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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% to 36% by age 65–70 years[54]	132-fold[53]
Familial Pancreatitis	*PRSS1, SPINK1, CFTR*	40% to 53% by age 70–75 years[55-60]	26-fold to 87-fold[26,58-60]
Melanoma-Pancreatic Cancer Syndrome	*CDKN2A*	17% by age 75 years[83]	20-fold to 47-fold[82,83]
Lynch Syndrome	*MLH1, MSH2 (MSH6)*	4% by age 70 years[72]	9-fold to 11-fold[72,73]
Hereditary Breast-Ovarian Cancer Syndrome	*BRCA1, BRCA2*	1.4%–1.5% (women) and 2.1%–4.1% (men) by age 70[74,78]	2.4-fold to 6-fold[74,76,78]
Familial Pancreatic Cancer	Unknown in most families (family X is an exception)[*]	≥3 first-degree relatives with pancreatic cancer: 7%–16% by age 70[47] 2 first-degree relatives with pancreatic cancer: 3% by age 70[47]	≥3 first-degree relatives with pancreatic cancer: 32-fold[85] 2 first-degree relatives with pancreatic cancer: 6.4-fold[85] 1 first-degree relative with pancreatic cancer: 4.6-fold[85]

[*]One family (family X) with a mutation in the *palladin* (*PALLD*) gene has been identified.[586]

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

Regimen	Resectable (adjuvant)	Locally Advanced	Metastatic (good performance status)
Gemcitabine	√ (category 1)	√ (category 1 for poor performance status)	√ (category 1 for good and poor performance status)
Gemcitabine/Albumin-Bound Paclitaxel		√	√ (category 1)
Gemcitabine/Erlotinib		√	√ (category 1; survival benefit is small)
Gemcitabine/Cisplatin		√ (especially if possible hereditary cancer)	√ (especially if possible hereditary cancer)
Gemcitabine/Capecitabine		√	√
Fixed-dose-rate gemcitabine		√	√ (category 2B)
GTX [Fixed-dose-rate gemcitabine/docetaxel/capecitabine]		√ (category 2B)	√ (category 2B)
5-FU/Leucovorin	√ (category 1)		
FOLFIRINOX		√	√ (category 1)
Capecitabine	√ (category 2B)	√ (category 2B)	√ (category 2B)
Continuous Infusion 5-FU	√	√ (category 2B)	√ (category 2B)
Fluoropyrimidine/Oxaliplatin (eg, FOLFOX, CapeOx)		√ (category 2B)	√ (category 2B)
Radiation	√ (fluoropyrimidine- or gemcitabine-based)	√ (in select patients without systemic metastases; fluoropyrimidine- or gemcitabine-based)	√ (palliative only)

Note: The panel is undecided about which regimens are best to use in the borderline resectable setting.

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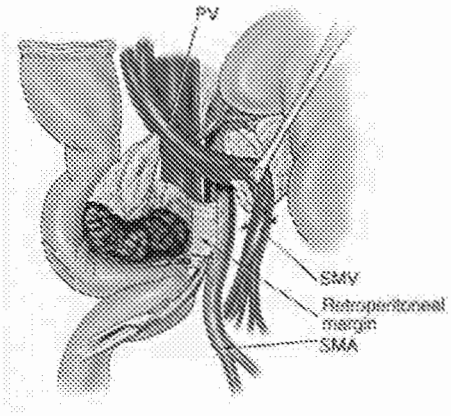

Figure 1. Complete mobilization of the superior mesenteric (SMV) and portal veins, and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA).[507]

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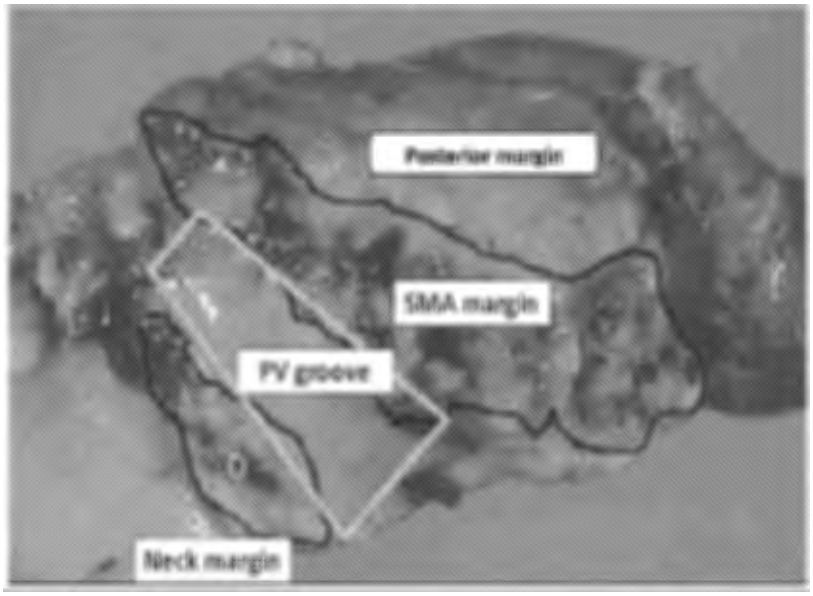

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Figure 2. Whipple specimen with labeled margins.

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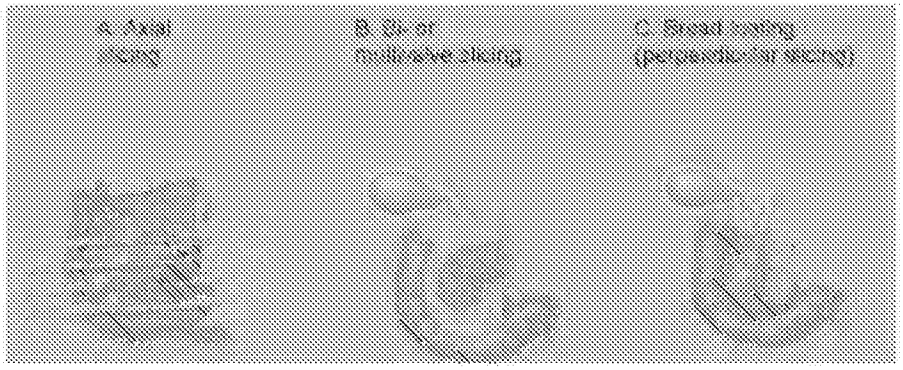

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Figure 3. Slicing of pancreatoduodenectomy specimens.[426]

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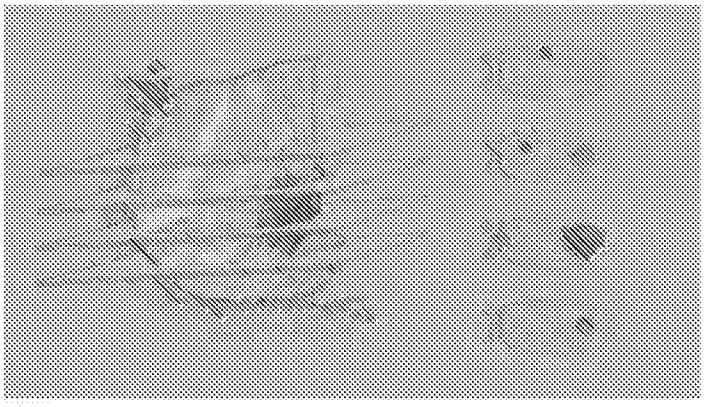

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Figure 4. Slicing of the pancreatoduodenectomy specimen in the axial plane to allow circumferential assessment of tumor.[420]

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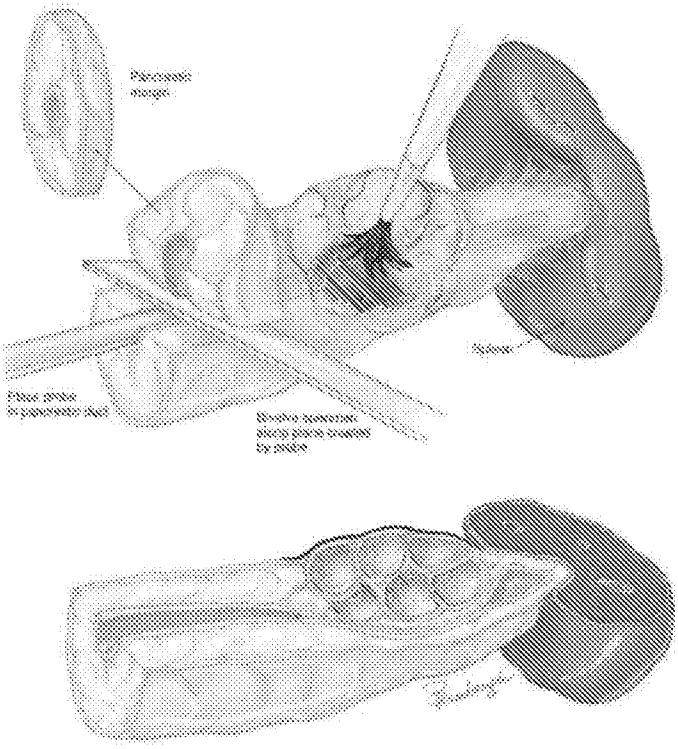

Figure 16-4, from Hruban, Ralph et al. Tumors of the Pancreas: Afip Atlas of Tumor Pathology, American Registry of Pathology, Washington DC 2007

Figure 5. Slicing of the distal pancreatectomy specimen.[433]

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Pancreatic Adenocarcinoma

Clinical Practice Guidelines in Oncology

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Overview

An estimated 36,800 people will die of pancreatic cancer in the United States in 2010.1 This disease is the fourth most common cause of cancer-related death among men and women in the United States.[1] Its peak incidence occurs in the seventh and eighth decades of life. Although incidence is roughly equal for the sexes, African Americans seem to have a higher incidence of pancreatic cancer than white Americans.2 These guidelines only discuss tumors of the exocrine pancreas; neuroendocrine tumors are not included.

NCCN Clinical Practice Guidelines in Oncology on Pancreatic Adenocarcinoma

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, pancreas, adenocarcinoma, ductal carcinoma, endoscopic retrograde cholangiopancreatography, ultrasonography, gemcitabine, (*JNCCN* 2010;8:972–1017)

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

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Disclosures for the NCCN Guidelines Panel for Pancreatic Adenocarcinoma

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines on Pancreatic Adenocarcinoma panel members can be found on page 1017. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the internet. For the latest update, please visit www.NCCN.org.

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By definition, these NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members during development of these guidelines. A 5% rule (omitting clinical scenarios that constitute fewer than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The panel unanimously endorses participation in a clinical trial as the preferred option over standard or accepted therapy.

Risk Factors and Genetic Predisposition

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

The relationship among diabetes mellitus, alcohol intake, and chronic pancreatitis with adenocarcinoma of the pancreas has been a topic of considerable debate. Numerous studies have shown an association between new-onset diabetes and the development of pancreatic cancer.[11-13] However, certain risk factors, such as obesity, and the use of

Text continues on p. 991

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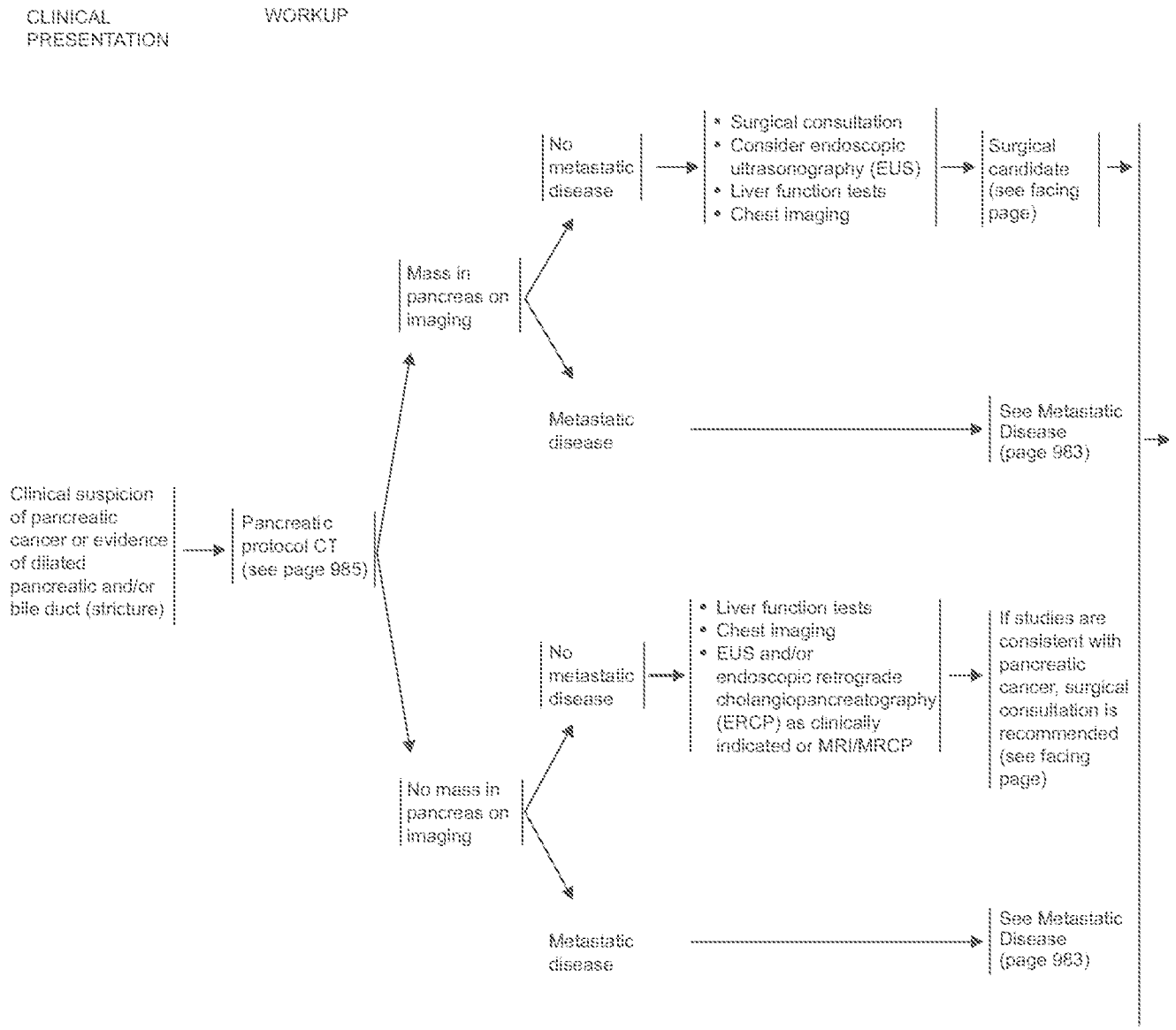

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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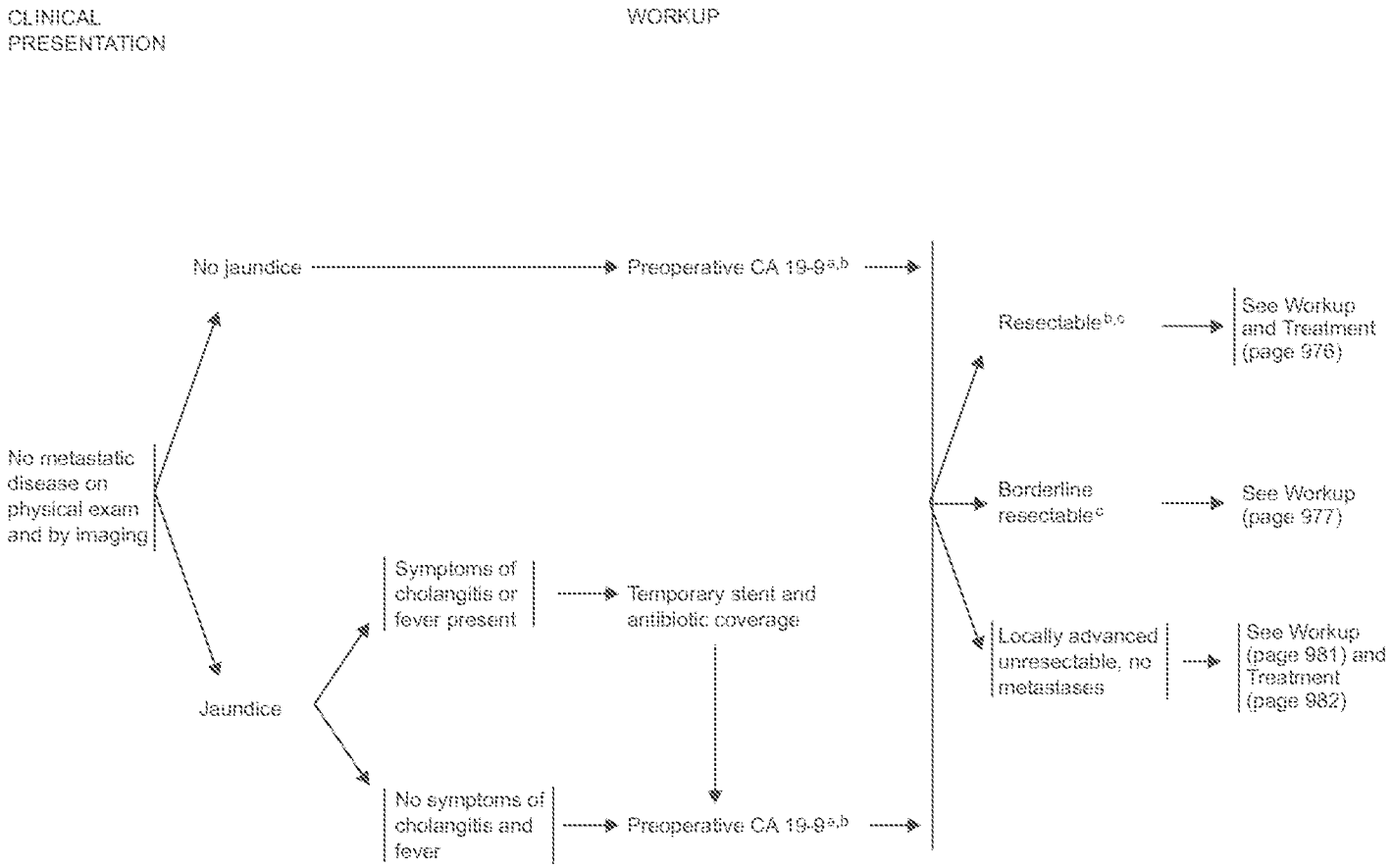

[a]CA 19-9 may be elevated in cases of benign biliary obstruction and does not represent an appropriate baseline until the patient is decompressed. In addition, CA19-9 may be undetectable in Lewis-a negative individuals.
[b]See Principles of Diagnosis and Staging (page 985).
[c]See Criteria Defining Resectability Status (page 986).

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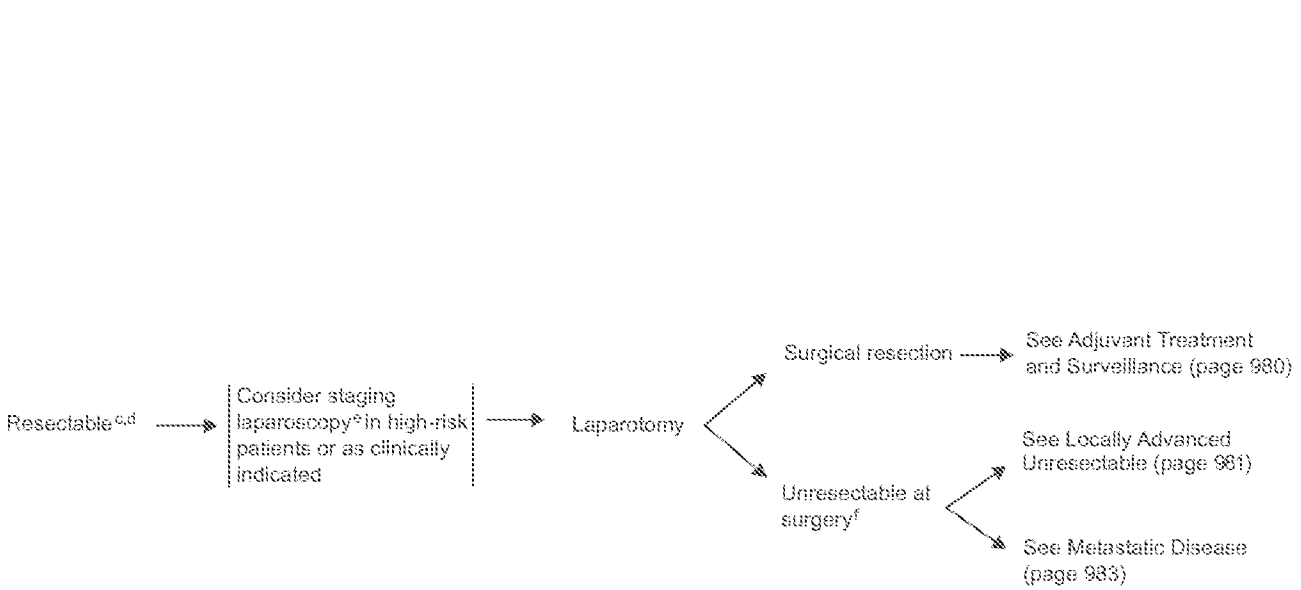

[c]See Criteria Defining Resectability Status (page 986).
[d]Consider neoadjuvant therapy on clinical trial.
[e]See Principles of Diagnosis and Staging (page 985).
[f]See Principles of Palliation and Supportive Care (page 987).

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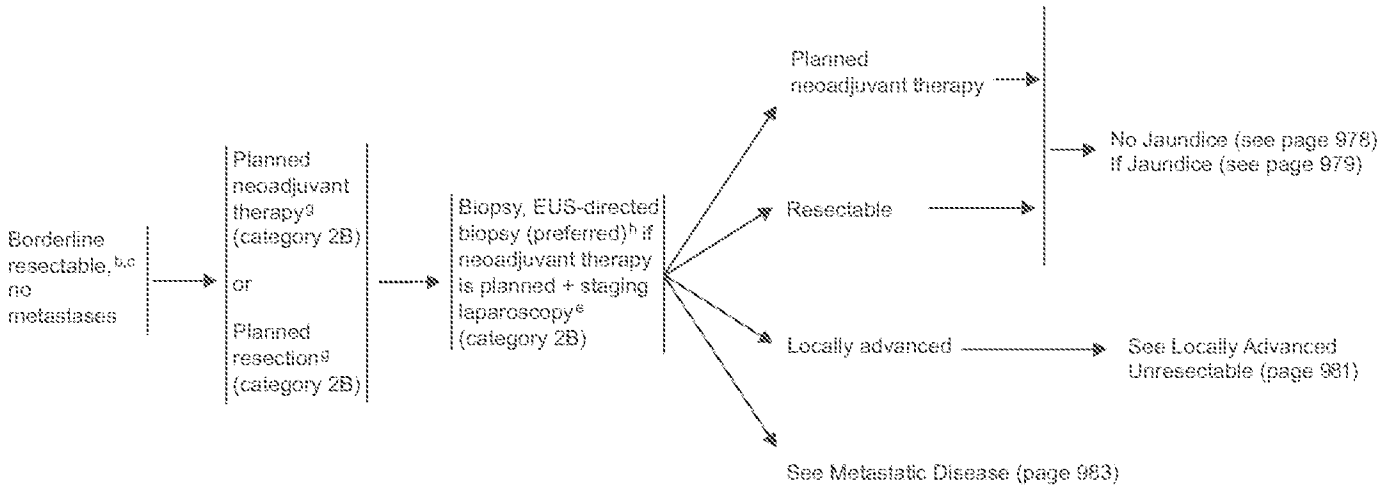
BORDERLINE RESECTABLE, NO METASTASES

WORKUP



[b] See Principles of Diagnosis and Staging (page 985).
[c] See Criteria Defining Resectability Status (page 986).
[e] See Principles of Diagnosis and Staging #6 (page 985).
[g] Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[h] See Principles of Diagnosis and Staging #1 and #5 (page 985).

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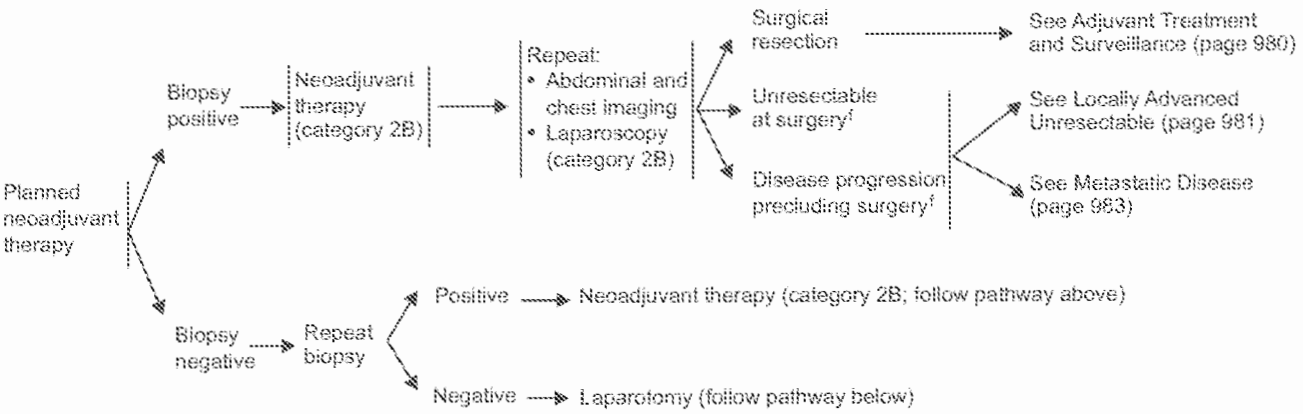
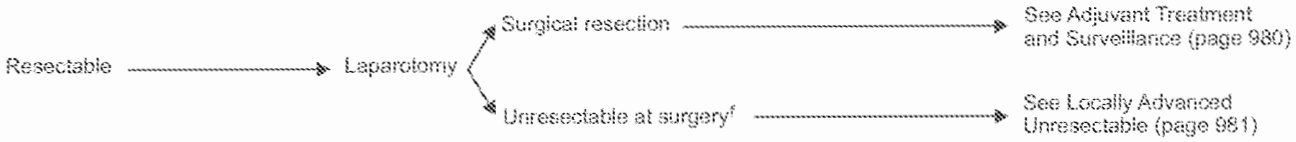
BORDERLINE RESECTABLE
NO METASTASES, NO JAUNDICE

TREATMENT





[f] See Principles of Palliation and Supportive Care (page 987).

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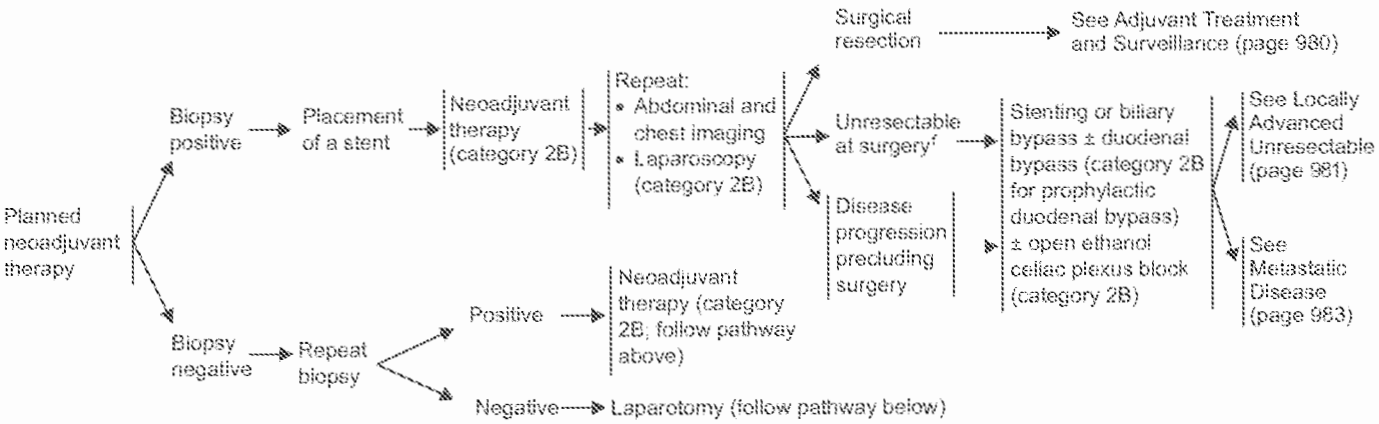
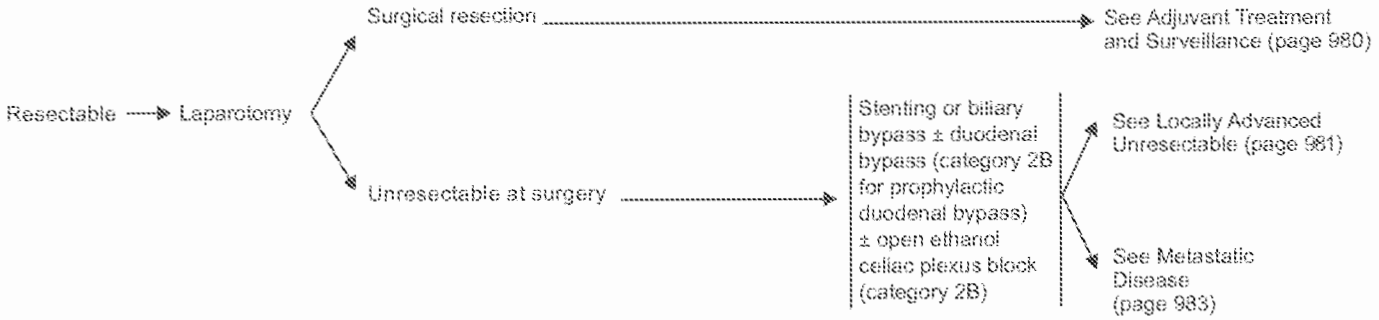
BORDERLINE RESECTABLE
NO METASTASES, JAUNDICE

TREATMENT





See Principles of Palliation and Supportive Care (page 987).

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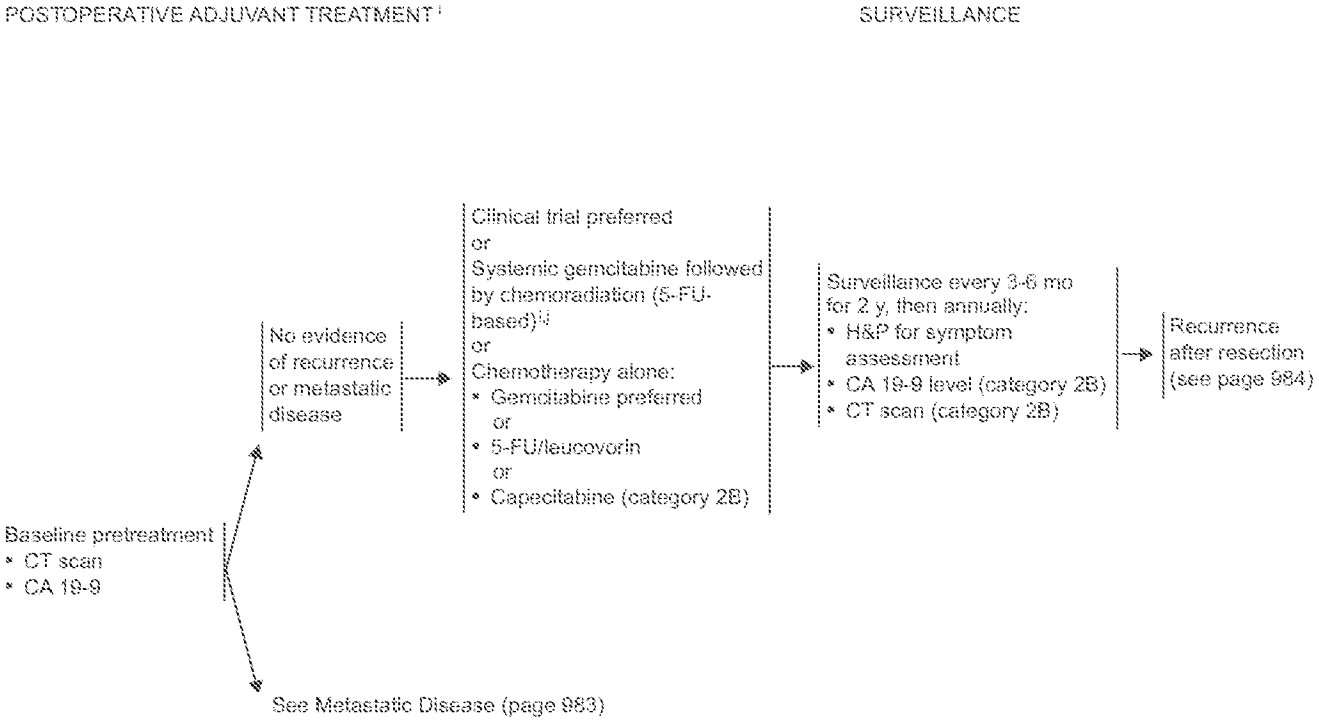

[1]Adjuvant treatment should be administered to patients who have not undergone neoadjuvant therapy and have adequately recovered from surgery; treatment should be initiated within 4 to 8 wk. If systemic chemotherapy precedes chemoradiation, restaging with a CT scan should be performed after each treatment modality. Patients who have undergone neoadjuvant chemoradiation or chemotherapy are candidates for further adjuvant therapy after surgery.
[2]See Principles of Radiation Therapy (page 988).

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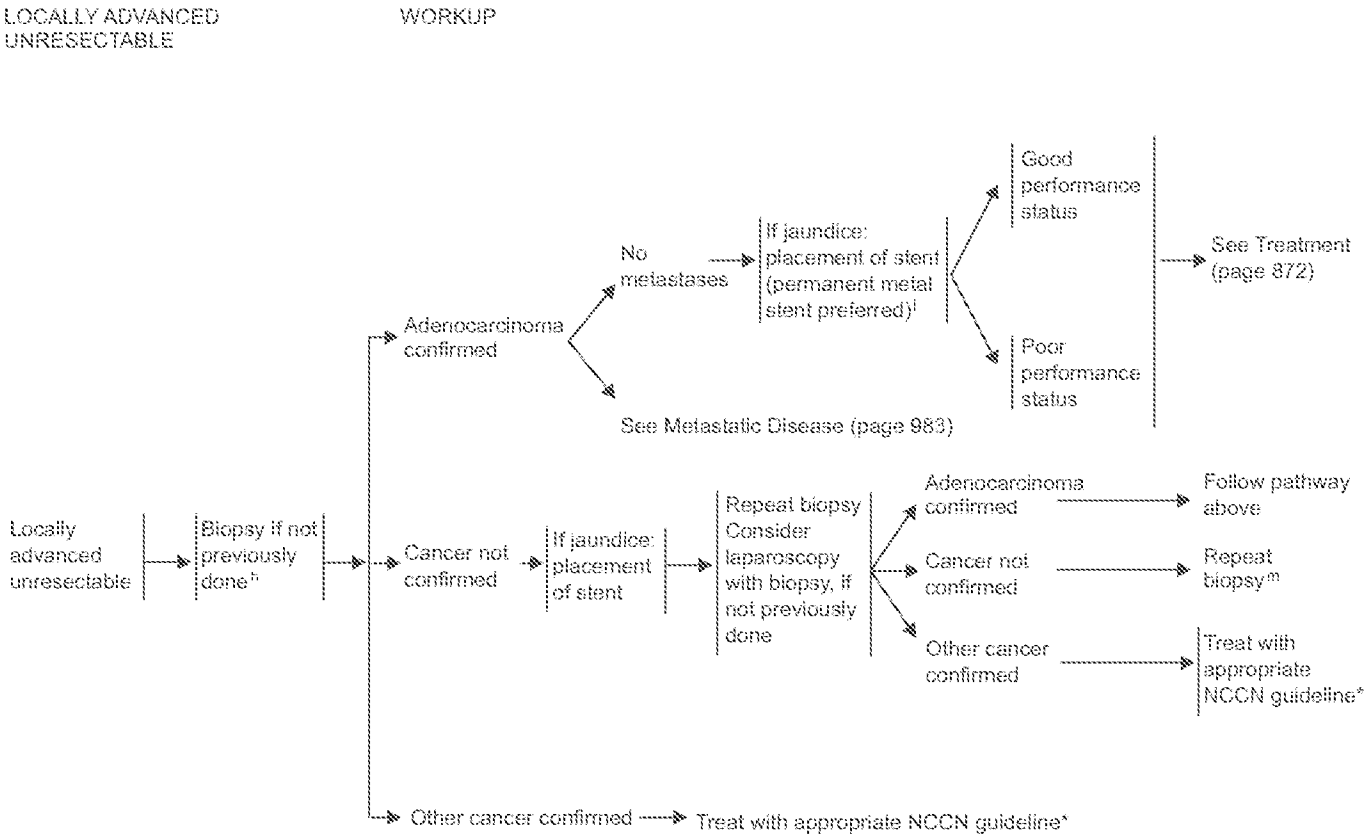

*To view the NCCN Clinical Practice Guidelines in Oncology list of contents, visit the NCCN Web site at www.NCCN.org.

[h] See Principles of Diagnosis and Staging #1 and #5 (page 985).
[i] Unless biliary bypass performed at laparoscopy or laparotomy.
[m] In this situation, a laparscopic-directed biopsy may be useful.

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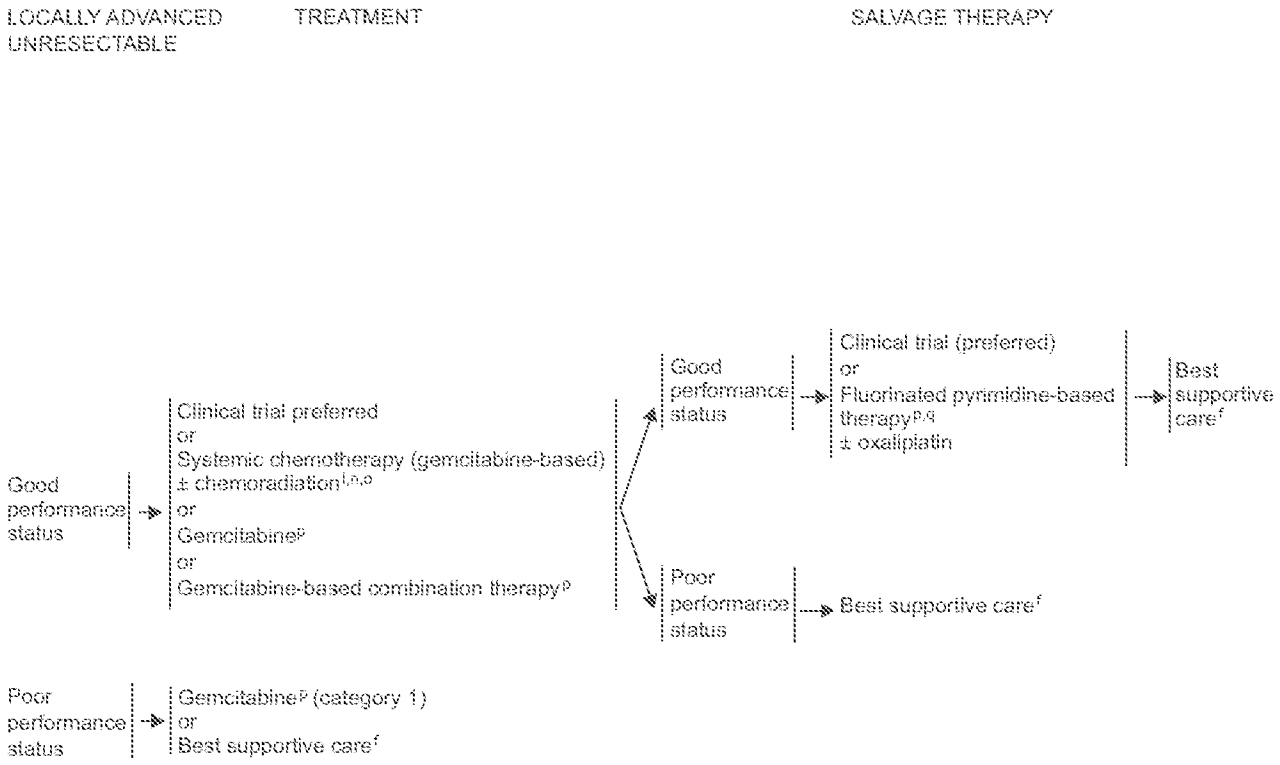

[r] See Principles of Palliation and Supportive Care (page 987).
[l] See Principles of Radiation Therapy (page 986).
[n] Laparoscopy as indicated to evaluate distant disease.
[o] Chemoradiation should be reserved for patients who do not develop metastatic disease while undergoing systemic chemotherapy. Patients with a significant response to chemoradiation may be considered for surgical resection, although no definitive evidence currently supports this intervention.
[p] See Principles of Chemotherapy (pages 989 and 990).
[q] For fluorinated pyrimidine-naive patients. Gemcitabine is also an option for those who received 5-FU chemoradiation and no additional chemotherapy.

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

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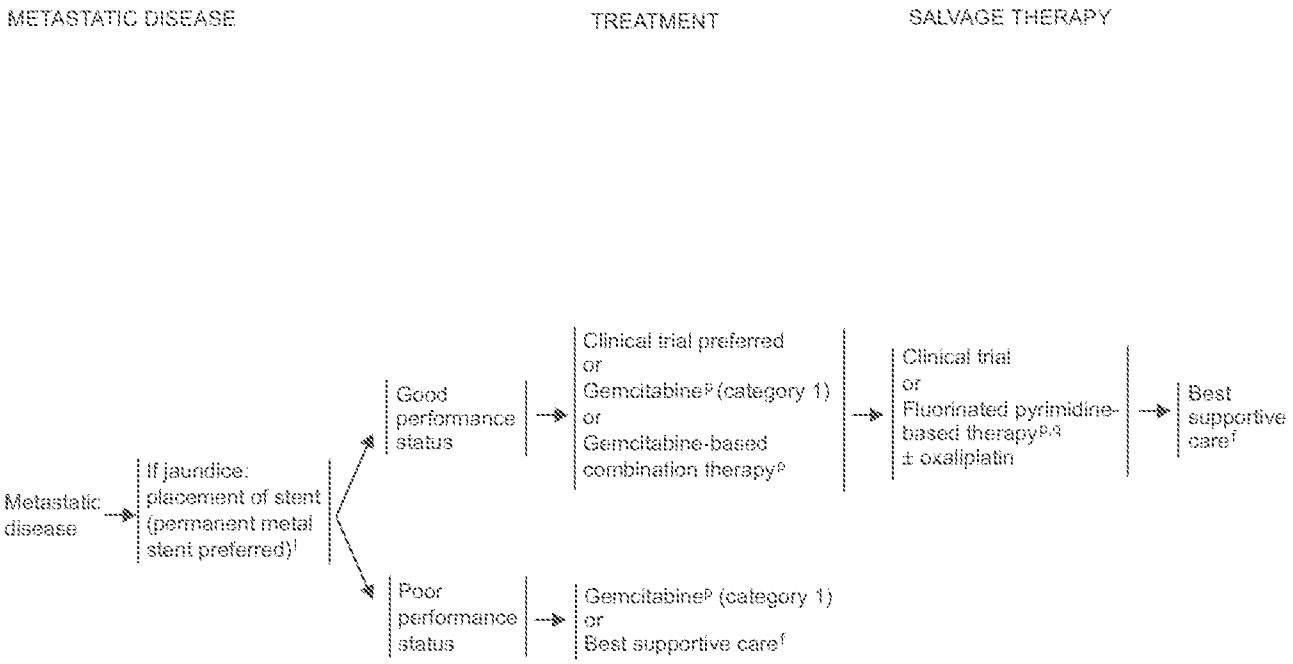

[f] See Principles of Palliation and Supportive Care (page 987).
[l] Unless biliary bypass performed at laparoscopy or laparotomy.
[p] See Principles of Chemotherapy (pages 989 and 990).
[q] For fluorinated pyrimidine-naive patients. Gemcitabine is also an option for those who received 5-FU chemoradiation and no additional chemotherapy.

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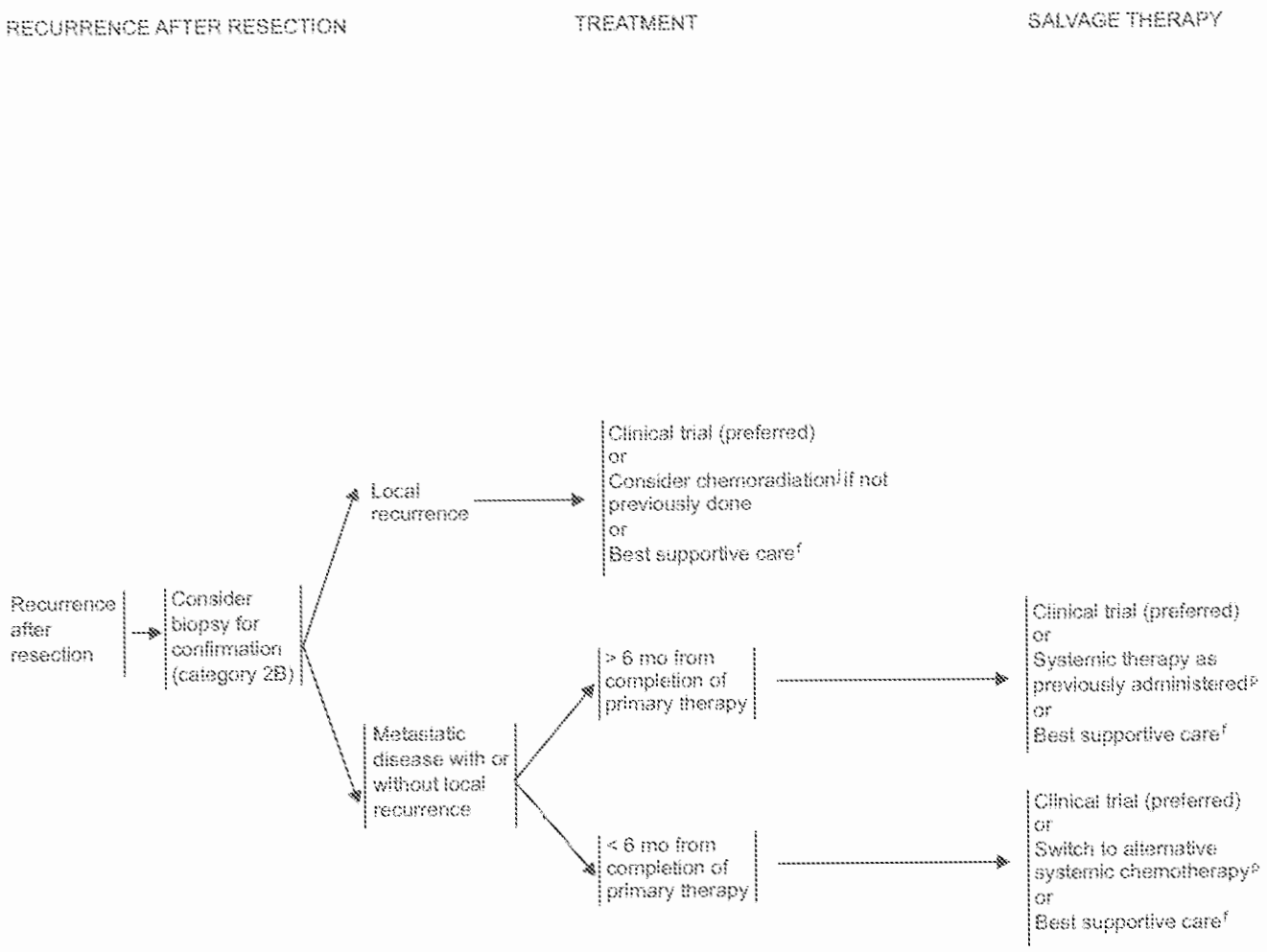

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PRINCIPLES OF DIAGNOSIS AND STAGING

#1: Decisions about diagnostic management and resectability should involve multidisciplinary consultation with reference to appropriate radiographic studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (15-20) of pancreatic resections annually.

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

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

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

#5: EUS-directed FNA biopsy is preferable to a CT-guided FNA in patients with resectable disease because of lower risk of peritoneal seeding with EUS-FNA than with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection, and a nondiagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.

#6. Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is routinely used in some institutions before surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes).

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

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CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and resectable should demonstrate the following:

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

Tumors considered borderline resectable include the following:

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

The NCCN Pancreatic Adenocarcinoma Panel recognizes the work of the experts and adapt their criteria to define resectability status. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 2009;16:1727-1733.

Tumors considered to be unresectable show the following:

- Head
  - Distant metastases
  - > 180° SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion or encasement
- Body
  - Distant metastases
  - SMA or celiac encasement > 180°
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- Tail
  - Distant metastases
  - SMA or celiac encasement > 180°
- Nodal status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable

PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE

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

- Biliary obstruction
  - Endoscopic biliary stent (preferred method)
  - Percutaneous biliary drainage with subsequent internalization
  - Open biliary-enteric bypass
- Gastric outlet obstruction
  - Good performance status
    - Gastrojejunostomy (open or laparoscopic) ± J-tube
    - Consider enteral stent[1]
  - Poor performance status
    - Enteral stent[1]
    - PEG tube
- Severe tumor-associated abdominal pain
  - EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)
  - Consider palliative chemoradiation if not already given as part of primary therapy regimen
- Depression, pain, malnutrition
  - Formal palliative medicine service evaluation when appropriate (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Supportive Care*)
- Pancreatic insufficiency
  - Pancreatic enzyme replacement
- Thromboembolic disease
  - Low-molecular weight heparin preferred over warfarin

*To view the various NCCN Clinical Practice Guidelines in Oncology on Supportive Care, visit the NCCN Web site at www.NCCN.org.

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

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PRINCIPLES OF RADIATION THERAPY

IMRT is being increasingly applied for therapy of pancreatic adenocarcinoma. No clear consensus exists on appropriate maximum dose of radiation in either the adjuvant setting or the setting of locally advanced disease.

Neoadjuvant/Adjuvant RT

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

- Use of CT simulation and 3-dimensional (3-D) treatment planning is strongly encouraged.
- Treatment volumes should be based on preoperative CT scans and surgical clips (when placed).
- Treatment volumes include the location of the primary tumor and regional lymph nodes.
- Dose: 45-54 Gy (1.8-2.0 Gy/d).

Definitive RT for Unresectable Tumors

Radiation is usually given in combination with 5-FU chemotherapy. Recent evidence suggests that concurrent gemcitabine and radiation can yield similar outcomes.

- Use of CT simulation and 3-D treatment planning is strongly encouraged.
- Treatment volumes should be based on CT scans and surgical clips (when placed).
- When 5-FU-based radiochemotherapy is used, treatment volumes include the location of the primary tumor and regional lymph nodes.
- The dose for definitive 5-FU-based radiochemotherapy is 50-60 Gy (1.8-2.0 Gy/d).

ITSG trial: Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil. Cancer 1981;48:1705-1710.
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PRINCIPLES OF CHEMOTHERAPY (1 of 2)

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

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

Metastatic

- Gemcitabine at 1000 mg/m^2 over 30 min, weekly for 3 wk every 28 d, is considered standard front-line therapy for patients with metastatic disease (category 1).
- Fixed-dose rate gemcitabine (10 mg/m^2/min) may substitute for standard infusion of gemcitabine over 30 min (category 2B).
- Gemcitabine combinations have shown a favorable or potentially favorable impact on time to progression or survival (overall or 1 y) for patients with good performance status:
  - Gemcitabine + erlotinib[1]
  - Gemcitabine + cisplatin
  - Fixed-dose rate gemcitabine + oxaliplatin[2]
  - Gemcitabine + fluoropyrimidine[3]
- Second-line therapy may consist of gemcitabine for patients not previously treated with the drug. Other options include capecitabine[4] (1000 mg/m^2 by mouth twice daily, days 1-14 every 21 d), 5-FU/leucovorin,[5] or CapeOx.[6] Results of the CONKO-003 trial showed a significant improvement in overall survival with addition of oxaliplatin to 5-FU/leucovorin.

Locally Advanced

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

Adjuvant

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

See references on page 990

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PRINCIPLES OF CHEMOTHERAPY (2 of 2)

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

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Text continued from p. 973

diabetic medications, can impact insulin resistance and blood glucose levels, thereby confounding these analyses.[14,15] Chronic pancreatitis has also been identified as a risk factor for pancreatic cancer.[16,17] Nevertheless, further epidemiologic studies involving careful evaluation of these possible risk factors, with adjustments for potential confounders, are needed to clarify their impact on pancreatic cancer risk.

True familial pancreatic cancer is rare; however, a genetic predisposition may be present in up to 5% to 10% of patients,[18,19] and familial excess of pancreatic cancer is associated with high risk.[4,19] For example, a germline mutation of the *CDKN2A* (p16) gene has been reported in families with pancreatic cancer and melanoma.[20,21] An excess of pancreatic cancer is also seen in families harboring *BRCA2* (breast cancer susceptibility gene 2) mutations,[22,23] and particular mutations in the *PALB2* gene have recently been identified as possibly increasing pancreatic cancer susceptibility.[24] Asymptomatic individuals at high risk for pancreatic cancer (i.e., those with first-degree relatives with cancer) were assessed using endoscopic ultrasound (EUS) in the Cancer of the Pancreas Screening 2 (CAPS2) project. Preinvasive pancreatic neoplasms were detected, suggesting that EUS may have a promising role in screening high-risk patients.[25] The diagnostic yield of pancreatic cancer screening with EUS or MRI in asymptomatic individuals at high risk of having familial disease has also been investigated in 2 recent studies, although the malignant potential of some preinvasive pancreatic lesions and the impact of screening on survival are currently unclear.[26,27]

Diagnosis and Staging

Ductal adenocarcinoma and its variants account for more than 90% of pancreatic malignancies. The presenting symptoms of this disease can include weight loss, jaundice, floating stools, pain, dyspepsia, nausea, and depression; however, no early warning signs of pancreatic cancer have been established. As previously noted, sudden onset of adult type 2 diabetes in patients 50 years or older may be linked to a new diagnosis of pancreatic cancer; patients with long-standing diabetes may also develop pancreatic cancer.[28,29] Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss. All NCCN Member Institutions represented on the panel agreed that all patients who have clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should undergo initial evaluation with dynamic-phase helical or spiral CT performed according to a defined pancreas protocol (see pages 974 and 975).[30,31]

Imaging Evaluations

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

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

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

When CT is not possible or relatively contraindicated (e.g., allergy to contrast), MRI with gadolinium infusion can be used to diagnose and stage pancreatic cancer,[39,40] although MRI has not been shown

to perform better than CT in this setting. MRI can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for detecting the presence of extrapancreatic disease in high-risk patients.[41]

NCCN Member Institutions vary in the use of additional staging technologies, such as EUS. The role of EUS in staging is believed to be complementary to CT, providing additional information for patients whose CT scans show no lesion or who have questionable involvement of blood vessels or lymph nodes.[30] Because this procedure is operator-dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

The usefulness of PET/CT for upstaging patients with pancreatic cancer has also been evaluated. In one retrospective study, the use of PET/CT following a standard CT protocol showed increased sensitivity for detecting metastatic disease compared with the standard CT protocol or PET/CT alone.[42] The sensitivity of detecting metastatic disease for PET/CT alone, standard CT alone, and the combination of PET/CT and standard CT was 61%, 57%, and 87%, respectively. In this study, the clinical management of 11% of patients with invasive pancreatic cancer was changed as a result of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established. PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered an adjunct to a formal pancreatic CT protocol in high-risk patients. Chest imaging to evaluate for the presence of pulmonary metastases is recommended as part of the preoperative workup for patients with no evidence of abdominal metastases on CT (see page 974).[43]

Patients with a mass in the pancreas on dynamic-phase spiral CT but no evidence of metastatic disease should also have a surgical consultation (see page 974). EUS may provide useful staging information in pancreatic cancer, particularly through assessment of certain types of vascular invasion.[44,45] EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. In addition, EUS may have a role in better characterizing cystic pancreatic lesions. On EUS, malignant cystic lesions may present as a hypoechoic cystic/solid mass or as a complex cyst and are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions can also be performed with EUS (e.g., celiac block, removal of ascites). The panel agreed that, although EUS has a high accuracy in assessing involvement of certain veins (e.g., portal vein), it is less accurate in imaging tumor invasion of the SMA.[45,46]

Patients without a mass in the pancreas on cross-sectional imaging and without evidence of metastatic disease should undergo additional imaging with EUS and/or endoscopic retrograde cholangiopancreatography (ERCP), as clinically indicated (see page 974). Distinguishing between benign and malignant strictures or stenosis can be difficult; however, severe stenosis and marked proximal dilatation more often indicate malignancy.[47] EUS is usually the preferred approach, with ERCP reserved for patients requiring biliary decompression. Stent placement at ERCP can be used to palliate biliary obstruction when surgery is not elected or must be delayed. MRI/magnetic resonance cholangiopancreatography (MRCP) is considered equivalent to EUS/ERCP in this setting. If studies are consistent with pancreatic cancer, then surgical consultation is recommended.

Restaging with high-quality abdominal and chest imaging is also recommended after surgery for resectable disease and before initiation of adjuvant therapy (see page 980). It should also be performed after administration of each treatment modality, when systemic gemcitabine is followed by chemoradiation in the adjuvant setting. In addition, this restaging is also recommended after administration of neoadjuvant therapy and before surgical resection for patients with borderline resectable disease (see pages 978 and 979).

Laparoscopy

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

Some recent evidence provides support for a selective approach to staging laparoscopy (i.e., it is performed if the presence of occult metastatic disease is suggested by high-quality imaging or certain clinical indicators).[50,51] For example, preoperative serum cancer antigen 19-9 (CA 19-9) levels greater than

100 U/mL have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.[52] In a recent prospective review of 838 patients who were diagnosed with resectable pancreatic tumors on imaging evaluation between 1995 and 2005, 8% were found to have unresectable disease (12% yield if only pancreatic adenocarcinoma was considered) after subsequent laparoscopy performed at a single institution.[53] Characteristics associated with an increased laparoscopic yield include the tumor location, tumor histology, presence of weight loss and jaundice, and the facility conducting the imaging evaluation.

Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used routinely in some NCCN institutions before surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (e.g., borderline resectable disease, markedly elevated CA 19-9, large primary tumors).The panel debated the value of a staging laparoscopy in patients with resectable/borderline resectable disease, and it is included as a category 2A recommendation for patients staged with resectable pancreatic cancer considered to be at increased risk of disseminated disease (see pages 976 and 985), and as a category 2B recommendation for patients with borderline resectable disease before and after administration of neoadjuvant therapy, because it is not uniformly performed at all NCCN institutions (see pages 977, 978, and 979). The panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[54]

Tumor-Associated Antigens

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic antioncofetal antigen, tissue polypeptide antigen, CA 125, and CA 19-9. A sialylated Lewis-a blood group antigen, CA 19-9 is commonly expressed and shed in pancreatic and hepatobiliary disease and 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,[55] and CA 19-9 tests may yield false-positive results in cases of benign biliary obstruction[56] or undetectable in Lewis-negative individuals.[57] Preoperative measurement of CA 19-9 levels should be performed after biliary decompression is complete (see page 975).

A low postoperative serum CA 19-9 level, and a decrease in serial CA 19-9 levels following surgery, have been found to correlate with survival for patients undergoing resection for pancreatic cancer.[58–60] In one prospective study of patients undergoing surgery with curative intent, median survival for patients with postresectional CA 19-9 levels of less than 180 U/mL was significantly greater than for the group with higher CA 19-9 levels after surgery (HR, 3.53; $P < .0001$). Similarly, in a prospective study of patients with advanced pancreatic cancer, a dichotomized pretreatment CA 19-9 serum level was shown to be an independent prognostic factor for survival.[61] However, data are conflicting regarding the predictive significance of CA 19-9 response after chemotherapy in patients with advanced disease.[61–65] The panel recommends measuring serum CA 19-9 levels after surgery and before adjuvant therapy is administered (see page 980). Although no FDA-approved testing methodology exists for measuring serum CA 19-9 levels, several different methods are commercially available for quantifying this tumor-associated antigen. Serum CA 19-9 levels measured using one testing method cannot be extrapolated to results obtained using a different procedure.

Differential Diagnoses

Chronic pancreatitis and other benign conditions (e.g., autoimmune pancreatitis) are in the differential diagnosis of patients suspected of having pancreatic cancer.[6–10]

Autoimmune pancreatitis, a rare form of chronic pancreatitis, is a heterogeneous disease that can present with clinical and radiologic characteristics of pancreatic cancer, such as jaundice, weight loss, an elevated CA 19-9 level, and the presence of diffuse pancreatic enlargement, a pancreatic ductal stricture, or a focal pancreatic mass.[71–73] 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.

Increased serum immunoglobulin (Ig) G levels supports a diagnosis of autoimmune pancreatitis, although an elevated serum IgG4 level is the most sensitive and specific laboratory indicator. The classic appearance of the pancreas on abdominal CT in patients with diffuse pancreatic involvement is a sausage-shaped enlargement of the organ surrounded

by a capsule-like peripheral rim, although focal enlargement of the pancreas is observed in some cases.[73] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis.

Pathology

Biopsy: Although a histologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy (see pages 977, 978, and 979), and for patients staged with locally advanced and unresectable pancreatic cancer or metastatic disease (see page 981). A histologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either EUS-guidance (preferred) or CT (see page 977). EUS-directed FNA biopsy is preferable to CT-guided FNA in patients with resectable disease because of the much lower risk for peritoneal seeding with EUS-FNA compared with the percutaneous approach.[74] A negative biopsy should be confirmed by at least 1 repeat EUS biopsy (see pages 978 and 979). However, in some cases (e.g., borderline resectable disease), treatment (i.e., laparotomy) may still be recommended for these patients after 2 negative biopsies, especially if clinical and radiographic evidence strongly suggests pancreatic cancer (see pages 978 and 979).[35]

When clinical and imaging findings indicate that locally advanced disease is present, laparoscopy with biopsy can be considered if repeat FNA biopsy is negative (see page 981). In patients without obstructive jaundice at initial presentation, EUS-FNA is highly accurate and reliable for ruling in malignancy; in patients with obstructive jaundice and biliary stricture, EUS-FNA is less accurate.[30] Non-neoplastic and neoplastic cystic pancreatic lesions can be difficult to discriminate radiographically; however, EUS-guided FNA can be useful in the differential diagnosis of these lesions.[75] Pancreatic ductal brushings or biopsies can also be obtained at ERCP, often revealing malignant cytology consistent with pancreatic adenocarcinoma. It is important to reiterate that proof of malignancy through biopsy is not required before surgical resection and that a nondiagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high. The panel strongly recommends that all diagnostic and surgical management decisions involve multidisciplinary consultation.

Specimen Orientation, Pathologic Analysis, and Reporting: Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The panel supports pathology synoptic reports from the College of American Pathologists (CAP). The CAP protocol information can be accessed at http://www.cap.org/apps/docs/cancer_protocols/2005/pancreasexo05_ckw.doc.

On January 1, 2004, the Commission on Cancer (COC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. CAP protocols comply with COC requirements, and the latest revisions to the CAP pancreatic (exocrine) protocol were issued in January 2005. Pathologists should familiarize themselves with these documents.

The American Joint Committee on Cancer (AJCC) has developed staging criteria for adenocarcinoma of the pancreas (see the staging table, available online, in these guidelines, at www.NCCN.org [ST-1 and ST-2]).[76] Recent validation of concordance between AJCC stage and overall survival has been provided through evaluation of 121,713 patients with pancreatic adenocarcinoma in the National Cancer Database (NCDB).[77] Although the TNM staging criteria for pancreatic cancer in the 7th edition of the AJCC *Cancer Staging Manual* have taken into account the fact that tumors of the pancreas are evaluated preoperatively by CT to determine resectability status, these staging criteria also include information that can be determined only through postsurgical pathologic evaluation of resected tumor.[76] For clinical purposes, most NCCN Member Institutions use a clinical staging system based mainly on results of presurgical imaging studies. After staging with CT (and EUS/ERCP in some cases), preoperative CA 19-9 testing, and evaluation for the presence of jaundice, disease is classified as 1) resectable, 2) borderline resectable (i.e., tumors involved with nearby structures which renders them neither clearly resectable nor clearly unresectable), 3) locally advanced unresectable (i.e., tumors involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease), or 4) disseminated (see Criteria for Resec-

tion, below), and this is the system used throughout the guidelines. Although not part of the TNM staging system criteria, the AJCC recommends that surgeons score the completeness of the resection as 1) R0 for complete tumor resection with all margins negative, 2) R1 for incomplete tumor resection with microscopic involvement of a margin, or 3) R2 for incomplete tumor resection with gross residual tumor that was not resected.[76]

Wide variation exists in the reported R1 rates of pancreaticoduodenectomy specimens.[78] Clear definitions of microscopic margin involvement and a circumferential resection margin are needed. Although several methods of specimen orientation and pathologic analysis have been described, no uniform consensus exists on a standardized protocol for the pathologic examination of these specimens.[78-80]

A pathologic evaluation of the surgical specimen involves both the pathologist and surgeon.[78,80] For example, to evaluate resection margin status, surgical margins must be inked appropriately and the surgeon must specify whether a complete resection was performed to enable the pathologist to distinguish between R1 and R2 resections.[81]

Surgical Management

Criteria for Resection

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

The panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation, with appropriate radiographic studies to evaluate the extent of disease. Although patients with visceral, peritoneal, and pleural metastases, and metastases to nodes beyond the field of resection clearly derive no benefit from resection, institutions seem to differ in their approaches to patients with locoregional (pancreas and peripancreatic lymph node) disease involvement. Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group developed criteria to define tumor resectability to improve patient selection for surgery and increase the likelihood of an R0 resection.[33] Using these criteria, tumors are classified as resectable, borderline resectable, or unresectable (e.g., locally advanced or metastatic disease; see page 986).

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

The likelihood of attaining negative surgical margins (i.e., R0 resection) is a key criterion to consider when determining whether a patient is a potential candidate for resection.[90,91] In this context, a borderline resectable lesion can be defined as one that has a higher likelihood of an incomplete (R1 or R2) resection (see page 986).

Primary Surgery for Pancreatic Cancer

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

Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and uncommonly resectable. Pa-

tients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with pancreaticoduodenectomy. A review of the biomedical literature indicates that no universally accepted surgical techniques exist for performing this procedure. This complex procedure has several controversial issues associated with it that are discussed in more detail in the following sections. Nevertheless, surgery should be performed only by surgeons capable of managing tumor–vessel involvement.

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis and to potentially make surgery less morbid through improving liver function preoperatively. Although controversial, several studies have suggested that pancreaticoduodenectomy is associated with higher perioperative mortality when performed in the setting of hyperbilirubinemia.[92–94] Stenting of the biliary system can improve symptoms and liver function, but whether these changes can decrease the mortality rate of the Whipple procedure is unclear. Several prospective and retrospective studies have failed to show decreased mortality in patients with preoperative biliary drainage.[95–101] In 1999, a retrospective study from Memorial Sloan-Kettering Cancer Center (MSKCC) examined 240 consecutive pancreaticoduodenectomies in which 53% of patients underwent preoperative biliary decompression.[102] This study found a statistical relationship between the use of preoperative drainage (irrespective of the method used) and increased postoperative complications, including death, in patients who went straight to surgery.

In contrast, the University of Texas MD Anderson Cancer Center (MDACC) reported on their experience with more than 300 patients, of whom 57% had preoperative biliary drainage,[103] as part of a neoadjuvant chemoradiation program. Wound complications were significantly increased in the drainage group; however, no other association was found for sepsis, fistulae, or death. In addition, a recent multicenter, randomized trial comparing preoperative biliary drainage with surgery alone for 202 patients with cancer of the pancreatic head characterized by obstructive jaundice showed a nearly 2-fold increase in the rate of serious complications in the former group (74% vs. 39%; relative risk in the early-surgery group, 0.54; 95% CI, 0.41–0.71; $P < .001$), although no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.[104] Based on these reports, most groups who perform resection first advocate selective use of decompression only in patients who are symptomatic or septic, or for whom surgical resection is significantly delayed. For patients with jaundice undergoing neoadjuvant induction therapy before pancreatic resection, biliary decompression is necessary to initiate therapy and seems to be well tolerated, with minimal increase in perioperative morbidity.

Patients who present with jaundice and potentially resectable disease may require placement of a temporary stent (e.g., plastic stent) along with antibiotic coverage if symptoms of cholangitis or fever are present (see page 985). Endoscopic placement of a temporary stent and normalization of bilirubin levels is recommended before CA 19-9 testing during the initial workup of patients with obstructed jaundice characterized by symptoms of cholangitis or fever when no evidence of metastatic disease is present (see page 975). Stent placement is also recommended before neoadjuvant therapy is administered for patients with jaundice and borderline resectable disease that is biopsy-positive (see page 979).

Pylorus Preservation

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

Pancreatic Anastomosis

Efforts in this area have focused on preventing pancreatic leaks and fistulas, which are morbid and po-

tentially lethal complications of pancreaticoduodenectomy. Pancreaticojejunostomy has traditionally been the standard reconstruction and is the major focus of morbidity and mortality after pancreaticoduodenectomy because of leaks, abscess formation, and fistulas from this anastomosis. A randomized study at Johns Hopkins Hospital found no difference in fistula rates after pancreaticojejunostomy and pancreaticogastrostomy.[113] Furthermore, surgeons have examined various other options for the pancreaticojejunal anastomosis; end-to-end, end-to-side, duct-to-mucosa, and invaginating techniques have all proven to be safe and effective.[114,115] Results of a prospective trial show that pancreatic fistula can be almost entirely avoided with a technique that combines placement/tying of sutures under magnification with meticulous attention to blood supply.[116] Stents used in the 1930s and 1940s continue to be used today, but no data suggest that they decrease leak rates.[117] Pancreatic fistula rates are similar (ranging in most studies from 6%–16%),[106,114,118] although the exact way to define a pancreatic leak in terms of volume and duration of drainage remains controversial.[119]

In addition to technical modifications, octreotide has been examined for its ability to decrease postoperative pancreaticojejunal leaks in patients undergoing pancreatic resections. However, octreotide did not decrease fistula rates when assessed in 2 prospective, randomized, double-blind, placebo-controlled studies (from MDACC and Johns Hopkins Hospital).[120,121] Finally, the use of fibrin glue sealant does not seem to decrease the rate of pancreatic fistulas.[122]

Portal Vein Resection

Vascular invasion has been a conventional contraindication to pancreatic resection. Early attempts at resection and reconstruction of the SMA and SMV in the 1970s were associated with poor results in a few patients who underwent "regional" pancreatectomy.[123] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreaticoduodenectomy decreased, a subset of patients was identified who were in need of resection of the SMV wall to achieve negative margins during removal of their tumors. Thus, the 1990s saw a renewed interest in vein resection for complete resections. The group from MDACC championed this approach, arguing that because overall mortality from pancreaticoduodenectomy has decreased, vein resection and reconstruction allow for complete resection and are not associated with increased morbidity or mortality compared with patients who did not require vein resection.[124] Furthermore, long-term outcome is not significantly worse.[125] Although compelling, this approach has not been universally accepted. During 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 undergoing vein resection.[126–129] A recent study found that properly selected patients (n = 141) with adenocarcinoma of the pancreatic head who required vein resection had a median survival of approximately 2 years, which did not differ from that for those undergoing standard pancreaticoduodenectomy and was superior to historical patients believed to have locally advanced disease who did not undergo surgical treatment.[130] Thus, a few groups have recommended caution and only use vein resection for selected patients.

Extended Lymphadenectomy

The role of lymph node dissection as a component of pancreaticoduodenectomy has remained controversial during the past several decades. In patients who undergo pancreaticoduodenectomy, decreased survival led to a hypothesis that a more aggressive lymphadenectomy might improve survival. In the 1970s and 1980s, pathology and autopsy studies showed a high incidence of nodal metastasis (sometimes as high as 80%), leading some groups to propose a more aggressive lymphadenectomy[131,132] to regionally control disease. The definition varies regarding what a regional or extended lymphadenectomy entails in patients undergoing pancreaticoduodenectomy. However, this procedure is most commonly performed in the United States by removing not only the peripancreatic lymph nodes, but also the soft tissue in the retroperitoneum from the hilum of the right kidney to the left lateral border of the aorta in one axis, and from the portal vein to the origin of the inferior mesenteric artery in the other.[133]

Several retrospective or single-institution nonrandomized studies have examined the role of extended lymphadenectomy. The most promising results are from Japan, with a few studies reporting improved survival in patients who underwent more extensive operations, including lymphadenectomy, although these studies included only a few patients.[134,135] In general, these studies had significant

imbalances among patients with regard to disease stage. In contrast, several additional studies from the United States and Europe have failed to show a survival advantage in patients undergoing regional lymphadenectomy.[136,137]

Two prospective randomized trials have tried to address the role of lymphadenectomy in patients undergoing pancreaticoduodenectomy. The Italian Multicenter Lymphadenectomy Group reported on a series of 81 patients randomly assigned to pancreaticoduodenectomy with or without extended lymph node resection. Although the statistical power was low, this study did not support the concept that an extended lymphadenectomy is a good prognostic factor.[138] A larger randomized prospective trial is currently being performed at Johns Hopkins Hospital to evaluate the role of extended lymph node dissections.[139] At last update, 299 patients were entered and no difference had been detected in operative mortality between treatment groups. The group of patients who received the regional lymphadenectomy in addition to pancreaticoduodenectomy had longer operation times, but overall median survival did not differ between the groups at 1, 3, and 5 years.[140]

Current information does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreaticoduodenectomy. Thus, a regional lymphadenectomy should not be considered a routine part of the Whipple procedure. Outside the setting of a clinical trial, the extended node dissection should be reserved for patients with larger tumors or for reoperative patients in whom removing the retroperitoneal nodal tissue can allow dissection in a virgin plane and possibly provide a higher chance of a margin-negative resection. Currently, data suggest that nodal metastases are a marker of systemic disease and that their removal is unlikely to alter overall survival.

Effect of Clinical Volume

Several studies have examined the effect of institutional volume on patient outcomes. The fundamental premise was that the decreasing morbidity and mortality seen in the 1980s and 1990s were the direct result of large single-institution experiences. Moreover, the concern was that if surgeons performed pancreaticoduodenectomy less frequently, patients might have increased morbidity and mortality. In 1993, Edge et al.[141] assessed 223 pancreaticoduodenectomies from 26 United States hospitals, but found that caseload did not correlate with mortality. However, surgeons who performed fewer than 4 resections per year had more complications. The group from MSKCC examined the issue in 1995 and found that in a cohort of 1972 patients, high-volume centers in New York state had significantly less mortality (4% vs. 12.3%) than low-volume centers.[142] High volume was defined as more than 40 cases per year, and this relationship correlated in a regression analysis. Notably, 75% of the cases in New York were performed in low-volume centers. Furthermore, regional outcomes with pancreaticoduodenectomy from United States hospitals were assessed in several other studies that have also reported decreased mortality, hospital length of stay, and overall cost at higher-volume centers compared with low-volume centers.[143-147] Interestingly, this effect was also seen in reports from Canada and the Netherlands.[148,149]

The definitions of high and low volume varied among all these studies. However, a striking difference is seen when the mortality rates from pancreaticoduodenectomy in very–low-volume (0–1 procedure per year) and low-volume (1–2 procedures per year) hospitals are compared with rates in higher-volume hospitals (> 5 procedures per year).[150] In-hospital mortality rates at these very–low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, vs. 4%; $P < .001$). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreaticoduodenectomy is compared with 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 more than 16 procedures per year were classified as "high-" and "very–high-" volume centers, respectively.[151] In this study, 6 or more pancreatic resections were performed at only 6.3% of hospitals. The largest difference in operative mortality between very–low-volume (17.6%) and high-volume (3.8%) centers is seen for pancreaticoduodenectomy compared with major surgery at any other sites, further reinforcing the magnitude of the effect that high-volume centers can specifically have on pancreatic cancer outcomes. The panel recommends that pancreatic resections be performed at institutions that perform a large number (> 15–20) of pancreatic resections annually (see page 985).

A recent study involving 301,033 patients with

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pancreatic adenocarcinoma included in the NCDB evaluated the treatment patterns of 1667 hospitals over a 19-year period.[152] During that time, the pancreatectomy rate and use of multimodality adjuvant therapy (i.e., surgery plus chemoradiation) for patients with stage I and II disease increased significantly (pancreatectomy rate increased from 39.6% to 49.3%; $P < .001$; use of multimodality therapy increased from 26.8% to 38.7%; $P < .001$). Furthermore, patients were more likely to undergo these treatments at academic institutions, particularly those considered to be high-volume hospitals. However, an analysis of 9559 patients diagnosed with early-stage disease from 1995 to 2004 showed that a high percentage (38.2%) of these patients with potentially resectable disease were not treated surgically.[153] Nevertheless, panel consensus is that patients should be selected for surgery based on curative intent as determined by the probability of obtaining R0 resection margins. Patients at high risk for positive surgical margins are not considered good candidates for an up-front resection.

Adjuvant Therapy

Postoperative Therapy

In 1985, the Gastrointestinal Tumor Study Group (GITSG) initially reported that the median survival of patients undergoing pancreaticoduodenectomy could be prolonged almost twofold by postoperative chemoradiation.[154] In this study, patients were randomized to either observation or radiation therapy (RT) combined with an intermittent bolus of 5-fluorouracil (5-FU) after resection. A standard split course of 4000 cGy was used. 5-FU, 500 mg/m^2 daily for 3 days, was given concurrently with each 2000-cGy segment of RT. The 5-FU regimen was then continued weekly for a full 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 43%, compared with 18% in the control group.

In a phase III trial (40891) assessing adjuvant radiotherapy and 5-FU versus observation alone after surgery in patients with both ampullary and pancreatic adenocarcinoma the EORTC found the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant.[155] At a median follow-up of 11.7 years, no statistically significant differences were observed between the study arms with respect to progression-free or overall survival for the subset of patients with pancreatic cancer.[156]

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

An intention to treat analysis of data from the large phase III CONKO-001 trial, which randomized 368 patients without prior chemotherapy or RT to adjuvant gemcitabine versus observation after macroscopically complete resection, showed that the primary end point of increased disease-free survival was met (median disease-free survival, 13.4 vs. 6.9 months; $P < .001$, log rank).[160] Recently, final results from this study showed median overall survival to be improved significantly for patients in the gemcitabine arm (22.8 vs. 20.2 months; $P = .005$).[161] Significant differences in median overall survival only became apparent at 2 years, with an absolute survival difference of 12.0% observed between the groups at 5 years (21% vs. 5%).

The phase II study by the Radiation Therapy Oncology Group (RTOG 97-04) evaluated pre- (3 weeks duration) and postchemoradiation 5-FU (3 months duration) versus pre- and postchemoradiation gemcitabine for postoperative adjuvant treatment of resected pancreatic adenocarcinoma.[162] This trial, which used daily fractionated RT, included prospective quality assurance of all patients and central review of preoperative CT imaging and radiation fields.[163] For patients with tumors of the pancreas head, representing 388 of the 451 patients enrolled in the trial, results showed a nonstatistically significant increase in overall survival in the gemcitabine arm compared with the 5-FU arm (median survival and 3-year survival rate of 20.5 months and 31%, respectively, vs. 16.9 months and 22%, respectively; $P = .09$); this benefit became more pronounced on multivariate analysis. Although results from RTOG 97-04 suggest a possible advantage for adjuvant therapy with gemcitabine over infusional 5-FU, re-

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

Results of RTOG 97-04 cannot be directly compared with the results of the CONKO-001, ESPAC-1, or ESPAC-3 trials because of differences in treatment design and fundamental differences in patient characteristics (e.g., patients enrolled in CONKO-001 were more likely to have negative lymph node status and positive resection margins than those in RTOG 97-04). In addition, limitations of some of these trials include problems with surgery and pathology quality control, and inconsistencies in postoperative restaging with CT.[165] However, median overall survival is remarkably similar among patients in the gemcitabine arm of CONKO-001 (22.8 months), gemcitabine-containing arm of RTOG 9704 (20.5 months), bolus 5-FU/leucovorin arm of ESPAC-1 (20.1 months), and gemcitabine and 5-FU/leucovorin arms of the ESPAC-3 study (23.6 and 23.0 months). Therefore, no definite standard has been established in the adjuvant treatment of pancreatic cancer, and both 5-FU–based chemoradiation with additional gemcitabine-chemotherapy and chemotherapy alone with gemcitabine, 5-FU/leucovorin, or capecitabine are listed in the guidelines as options for adjuvant treatment. All of these adjuvant therapy options are designated as category 2A recommendations, with the exception of capecitabine (category 2B). However, panel consensus was that when chemotherapy alone is chosen as adjuvant therapy, gemcitabine is preferred over either 5-FU/leucovorin or capecitabine for most patients because of its more favorable toxicity profile, and that when chemoradiation is chosen, systemic gemcitabine should be administered before 5-FU–based chemoradiation.

Although the optimal combination and sequencing of RT has yet to be defined, the panel recommends that when postoperative RT is given, it should be administered at a dose of 45 to 54 Gy (1.8–2.0 Gy/d; see page 988).[166] Use of CT simulation and 3-dimensional treatment planning is strongly encouraged. Treatment volumes should be based on preoperative CT scans and surgical clips (when placed). Treatment volumes include the location of the primary tumor and regional lymph nodes. Radiation is usually given in combination with continuous infusion 5-FU or capecitabine; the panel recommends that 5-FU–based chemoradiation be delivered after systemic gemcitabine in the adjuvant setting (see page 980), because emerging data in the study of locally advanced disease suggest that a period of chemotherapy followed by consolidated chemoradiation may be preferable to up-front chemoradiation.[167–169] Therefore, the panel recommends that when chemoradiation is considered as adjuvant therapy, it should be administered after an adequate course (i.e., up to 4 months) of systemic chemotherapy.

Adjuvant chemotherapy or chemoradiation should only be considered for patients who have adequately recovered from surgery; treatment should ideally be initiated within 4 to 8 weeks (see page 980). After surgery, the panel recommends that patients undergo a pretreatment baseline assessment, including CT scan and CA 19-9 level, to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Furthermore, the panel recommends restaging patients with a CT scan after systemic chemotherapy if it will precede chemoradiation (see page 980). Adjuvant therapy is not restricted to patients who have not had neoadjuvant therapy, but adjuvant chemoradiation cannot be administered to patients who have undergone neoadjuvant chemoradiation.

Preoperative (Neoadjuvant) Therapy

Novel contemporary approaches to adjuvant therapy have focused on preoperative (neoadjuvant) therapy with the goal of improving overall survival.[170,171] Although not widely investigated, several studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[37,38,172–174] However, no randomized trials have addressed this issue. A retrospective review of the collective experience at MDACC indicated that the use of preoperative chemoradiation therapy in patients with resectable disease does not seem to be clearly disadvantageous, and that more patients may benefit if the therapy is given preoperatively because the prolonged recovery after pancreaticoduodenectomy prevents the delivery of postoperative therapy in up to 25% of eligible patients.[173]

Other putative advantages to administering neoadjuvant therapy include the potential to select for surgery the patients with more stable disease or disease that is more responsive to therapy; treatment of tissue that has not been subjected to surgery and,

hence, may be more sensitive to chemoradiation; treatment of micrometastases at a earlier stage; and the potential to downsize tumors to increase the likelihood of a margin-free resection.[90,170,175] In an analysis of 132 consecutive patients, the MDACC group reported that combined preoperative chemoradiation and pancreaticoduodenectomy yielded a median survival of 21 months, and 31% of patients were alive without evidence of disease.[173]

Some studies have addressed the use of preoperative chemoradiation to convert selected patients with unresectable disease to a resectable status.[171,172,175–180] Although emerging evidence suggests that preoperative therapy provides a better chance of margin-negative resection,[181] results of randomized trials involving a clinical end point of R0 resection rate have not been reported. Furthermore, the optimal neoadjuvant regimen has not been established.

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

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

Most member institutions prefer an initial approach involving neoadjuvant therapy as opposed to immediate surgery for patients with borderline resectable disease, and the panel recommends neoadjuvant therapy as an alternative to up-front resection after disease is clinically staged as borderline resectable (see page 977). Because most but not all NCCN centers administer neoadjuvant therapy to patients with borderline resectable disease, both of these options are designated as category 2B recommendations. EUS-directed biopsy is the preferred method of obtaining histologic confirmation of disease in these patients, and this confirmation is necessary before administering neoadjuvant therapy. A repeat biopsy should be performed when initial biopsy results are negative. In addition, staging laparoscopy, performed to evaluate for the possible presence of metastatic disease, is also recommended (category 2B) before and after neoadjuvant therapy (see pages 977, 978, and 979). Placement of a stent is recommended before initiation of neoadjuvant therapy in patients with jaundice (see page 979). Neoadjuvant therapy regimens are often similar to those used to treat locally advanced disease (see Chemoradiation for Locally Advanced Disease, below). Abdominal and chest imaging should be repeated after neoadjuvant therapy.

The panel also recommends that neoadjuvant therapy in the context of a clinical trial be considered for patients clinically staged as having resectable disease (see page 976). However, the panel does not support the use of neoadjuvant therapy outside of a clinical trial for patients clinically staged with resectable disease.

Chemoradiation for Locally Advanced Disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer (see pages 981, 982, and 988), although the efficacy of chemoradiation in this population of patients is controversial.[185] The role of chemoradiation was initially defined in a trial conducted by GITSG.[186] This study compared bolus 5-FU and split-course radiation (total dose, 4000 cGy) with

radiation alone or with 6000 cGy combined with 5-FU. A nearly twofold increase in median survival (42.2 vs. 22.9 weeks) was observed in the bolus 5-FU and 4000 cGy arm compared with radiation alone. Subsequent generations of studies have sought to optimize the use of 5-FU, and most contemporary studies no longer use split-course radiation.

For primary definitive chemoradiation therapy, NCCN recommends doses of 50 to 60 Gy (1.8–2.0 Gy/d) with concomitant 5-FU (see page 988).[166,187] Use of CT simulation and 3-dimensional treatment planning is strongly encouraged. Treatment volumes should be based on CT scans and surgical clips (when placed). Radiation is usually given in combination with 5-FU. When 5-FU–based chemoradiation is used, treatment volumes include the location of the primary tumor and regional lymph nodes. Currently, systemic chemotherapy followed by chemoradiation therapy is recommended for patients with unresectable disease, no metastases, and good performance status.

Gemcitabine has also been used as a radiation sensitizer.[183,184,188–190] Evidence suggests that concurrent gemcitabine and radiation can yield similar outcomes compared with 5-FU–based chemoradiation,[190,191] although no randomized trials have directly assessed whether any of these modifications are superior to the original trial results reported by GITSG. Results from a recent phase II study of patients with locally advanced pancreatic adenocarcinoma from the North Central Cancer Treatment Group evaluated the safety and efficacy of RT in combination with gemcitabine and cisplatin. Although this regimen had acceptable toxicity, no survival benefit over other regimens was observed.[192] Chemoradiation is included in the guidelines as an option for patients with locally advanced unresectable disease with no metastases who have a good performance status (category 2A; see pages 981 and 982). The panel recommends that an adequate course (i.e., up to 4 months) of initial systemic chemotherapy (gemcitabine-based) be administered to patients with locally advanced disease for whom chemoradiation therapy is planned, because emerging data suggest that a period of chemotherapy followed by consolidated chemoradiation may be preferable to up-front chemoradiation.[167–169,193] A treatment approach using an initial 3- to 4-month course of chemotherapy may facilitate systemic disease control while simultaneously helping to uncover whether the disease is rapidly progressive. For example, a retrospective analysis of outcomes from the Oncology Multidisciplinary Research Group (GERCOR) studies indicated that first-line treatment with chemotherapy may be a useful strategy for selecting patients with locally advanced disease who are more likely to benefit from subsequent chemoradiation therapy.[167] This approach is currently being evaluated in an ongoing phase III trial (GERCOR-LAP-07-D07-1). When systemic chemotherapy precedes administration of chemoradiation, the panel recommends restaging with a CT scan before RT.

Chemotherapy without RT is also an option for patients with locally advanced pancreatic cancer, especially for those with poor performance status (see pages 981, 982, and 989). Results of 2 early randomized trials comparing chemoradiation with chemotherapy in locally advanced disease were contradictory.[194,195] A phase III randomized trial (ECOG-4201) comparing gemcitabine with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer was closed early because of poor accrual. However, an intent-to-treat analysis of data for the 74 patients enrolled showed that median overall survival was significantly longer in the chemoradiation therapy arm of the study (11.0 vs. 9.2 months; $P = .034$).[196]

The benefit of chemotherapy versus chemoradiation was also addressed in the phase III FFCD-SFRO study from France in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or an intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[197] In this study, gemcitabine alone was associated with a significantly increased overall survival rate at 1 year compared with chemoradiation (53% vs. 32%). Although this study was stopped before the planned inclusion, patients in the chemoradiation arm experienced increased toxicity and were more likely to undergo a shorter course of maintenance therapy with gemcitabine, raising the question of whether the observed differences in survival were more likely attributable to the toxicity of the chemoradiation regimen than the efficacy of the gemcitabine chemotherapy regimen.

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Chemotherapy for Advanced Disease

General Principles

Systemic therapy is used in the adjuvant setting and in the management of locally advanced unresectable and metastatic disease. The primary goals of treatment for advanced pancreatic cancer are palliation and improved survival. Although some effect on survival may be achieved, these benefits are usually limited to patients with an adequate performance status (ECOG 0–2). Patients who present with very poor performance status may benefit from the administration of gemcitabine, but comfort-directed measures are always paramount (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] on Supportive Care; to view the index of supportive care guidelines, visit the NCCN Web site at www.NCCN.org). Before initiating cytotoxic therapy, an open dialogue regarding the goals of treatment should occur, and adjunctive strategies should be discussed (including nonsurgical bypass and celiac block for pain; see Palliation of Locally Advanced and Metastatic Disease, page 1006, and page 987). Notably, debilitated patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumor progression may develop quickly, and tumor-related symptoms may be inappropriately attributed to chemotherapy or other causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or, in its more subtle form, as abdominal bloating, decreased oral intake, and constipation.

Role of Gemcitabine

For patients with locally advanced or metastatic disease, gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU.[198] The panel recommends gemcitabine monotherapy (1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days) as standard front-line therapy for patients with metastatic disease (category 1; see pages 983 and 989).[198] The panel also debated whether gemcitabine monotherapy should be recommended for patients with unresectable, locoregional disease and a poor performance status. Because the approved indications for gemcitabine include symptom relief, the panel recommends gemcitabine as a reasonable option for symptomatic patients (category 1 for patients with poor performance status; category 2A for patients with good performance status). Other options for selected patients include gemcitabine-based combination therapy (category 2A; see Gemcitabine Combinations, below) or best supportive care (see NCCN Guidelines on Supportive Care [to view the index of supportive care guidelines, visit www.NCCN.org] and pages 981 and 982). For patients who derive clinical benefit from initial gemcitabine treatment in the setting of locally advanced disease, without developing distant disease, subsequent chemoradiation may enhance local control. After disease progression, fluorinated pyrimidine-based therapy is an option for some patients (see Second-Line Therapy, page 1005).

Fixed-Dose Rate Gemcitabine: Recent studies have suggested that the infusion rate of gemcitabine may be important for its efficacy. Gemcitabine is a prodrug, which must be phosphorylated for antitumor activity. Clinical studies have shown that administering gemcitabine at a fixed-dose rate ([FDR] 10 mg/m^2/min) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.[199] In a randomized phase II trial, the infusion of gemcitabine at an FDR led to a higher response rate and better survival compared with gemcitabine delivered at a higher dose over 30 minutes.[200] In the phase III randomized ECOG 6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine compared with those receiving standard gemcitabine (6.2 vs. 4.9 months; $P = .04$), although this outcome did not satisfy the protocol-specified criteria for superiority.[201] When gemcitabine is considered for the treatment of advanced pancreatic cancer, the 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 (e.g., GEMOX [gemcitabine, oxaliplatin], GTX [gemcitabine, docetaxel, capecitabine]).[202,203]

Gemcitabine Combinations: The panel also acknowledged that, historically, combination chemotherapy has not appeared to be superior to mono-

therapy in the era of 5-FU–based therapy. However, because gemcitabine is superior to bolus 5-FU when efficacy end points of survival and relief from symptoms are used, it is now often combined with other chemotherapeutic agents for patients with good performance status. Gemcitabine has been investigated in combination with potentially synergistic agents (e.g., cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan) or in a multidrug combination (e.g., cisplatin, epirubicin, gemcitabine, and 5-FU).[201–215]

Data on the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of randomized controlled trials do not support the use of gemcitabine plus cisplatin for treating 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 regimen compared with the single agent.[205,208,214] Similarly, no survival benefit was observed in a phase III trial investigating GEMOX compared with gemcitabine alone, although the combination regimen was superior with respect to response rate, progression-free survival, and clinical benefit.[209] Furthermore, the addition of oxaliplatin to FDR gemcitabine in the ECOG 6201 study did significantly improve survival compared with FDR gemcitabine alone.[201] Nevertheless, selected patients may benefit from this regimen because those with breast and ovarian cancers who have a *BRCA* mutation,[216,217] and some with inherited forms of pancreatic cancer,[218] may have disease that is particularly sensitive to a platinum agent. A retrospective study from Johns Hopkins of patients with metastatic pancreatic cancer and a family history of breast, ovarian, or pancreatic cancer suggested that response to gemcitabine and cisplatin was superior, even in those with one affected relative.[219]

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

The panel considers gemcitabine-based combination therapy with a fluoropyrimidine to be a reasonable option for patients with locally advanced or metastatic disease and a good performance status who are interested in pursuing more aggressive therapy outside a clinical trial (see page 983). Furthermore, gemcitabine plus a platinum agent (i.e., cisplatin or oxaliplatin) may be a good choice in selected patients with disease characterized by hereditary risk factors (e.g., *BRCA* or *PALB2* mutations). However, the panel does not consider the combination of gemcitabine plus docetaxel[222] or gemcitabine plus irinotecan[210,222,223] to meet criteria for inclusion in the guidelines.

Although phase II trial results of gemcitabine combined with new targeted drugs (e.g., bevacizumab, cetuximab) were encouraging,[224,225] results of phase III studies of combinations of gemcitabine with a biologic agent have indicated that only the combination of gemcitabine plus erlotinib is associated with a statistically significant increase in survival compared with gemcitabine alone.[226–228] Results of the CALGB phase III trial evaluating gemcitabine and bevacizumab (an anti–vascular endothelial growth factor antibody) compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer, and the SWOG phase III

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randomized trial assessing cetuximab (which targets the epidermal growth factor receptor [EGFR]) plus gemcitabine versus gemcitabine alone did not show improvements in survival on addition of the biologic agent.[227] However, in a phase III trial of patients (n = 569) with advanced or metastatic pancreatic cancer randomly assigned to receive either erlotinib (an inhibitor of EGFR tyrosine kinase) plus gemcitabine or gemcitabine alone, patients in the combination arm showed statistically significant improvements in overall (HR, 0.82; $P = .038$) and progression-free survival (HR, 0.77; $P = .004$) compared with those receiving gemcitabine alone.[228] Median survival was 6.24 months and 1-year survival was 23%, compared with 5.91 months and 17% in the control arm. Adverse events, such as rash and diarrhea, were increased in the group receiving erlotinib.

A recent phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer did not show improved overall survival in either group, although a significant improvement in progression-free survival was observed with the addition of bevacizumab.[229] The FDA approved erlotinib in combination with gemcitabine for first-line treatment of patients with locally advanced unresectable or metastatic pancreatic cancer. The panel recommends gemcitabine/erlotinib combination therapy as an option for patients with locally advanced or metastatic disease and good performance status (category 2A; see pages 981, 982, and 983).

Results from the recently presented preplanned interim analysis of the phase III Prodige 4 ACCORD 11 trial evaluating the regimen of 5-FU, leucovorin, oxaliplatin, irinotecan (FOLFIRINOX) versus gemcitabine alone in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median progression-free (6.4 vs. 3.3 months; $P < .0001$) and median overall survival (11.1 vs. 6.8 months; $P < .0001$) in favor of the group receiving FOLFIRINOX.[230] However, some concerns exist about the toxicity of the FOLFIRINOX regimen (i.e., approximately one fourth of the patients receiving this regimen experienced grade 3/4 fatigue, 46% experienced grade 3/4 neutropenia, and 5.4% experienced grade 3/4 febrile neutropenia). Furthermore, whether these results can be generalized to the overall population of patients with metastatic pancreatic cancer and good performance status is unclear, because the percentage of patients with tumors of the pancreatic head enrolled in the trial was lower than typically observed in this population, raising the question of whether fewer patients had biliary stents. Nevertheless, further investigation of this very promising regimen is encouraged, particularly in the adjuvant setting.

Emerging data suggest that gemcitabine plus nab-paclitaxel,[231] and GTX[203] are effective and safe for use in the first-line treatment of patients with advanced pancreatic cancer.

Second-Line Therapy

As cross-sectional body imaging has improved, small volume metastatic disease is being detected in patients with pancreatic cancer who are otherwise maintaining good functional status. These patients may initially benefit from either gemcitabine-based or investigational therapy. However, these patients, and those with unresectable disease without detectable metastases, will ultimately progress, although a subset will continue to have sufficiently good performance status for second-line therapy to be considered.

Gemcitabine may offer palliative benefits in the second-line setting if patients have not been previously treated with gemcitabine.[232] For patients who have received prior gemcitabine-based therapy, the panel encourages treatment in a clinical trial. However, when investigational therapy is not available, treatment options for fluorinated pyrimidine–naïve patients include either capecitabine or 5-FU/leucovorin with or without oxaliplatin (see pages 981, 982, 983, and 988).[233–236] The capecitabine dose (1000 mg/m^2 by mouth twice daily) recommended in the algorithms (see page 989) is less than that described by Cartwright et al.,[235] because the higher dose has been associated with increased toxicity (e.g., diarrhea, hand–foot syndrome). Recent results from the phase III CONKO 003 trial showed significant improvements in both median progression-free (13 vs. 9 weeks; $P = .012$) and median overall survival (20 vs. 13 weeks; $P = .014$) when oxaliplatin was added to 5-FU/leucovorin,[233] making this regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy.

Recurrent Disease

For patients experiencing a recurrence following resection (see page 984), the panel recommends con-

sideration of confirmatory biopsy (category 2B). Chemoradiation can be considered if not previously administered in those patients with local disease recurrence only. In patients who have 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 fewer than 6 months before development of metastatic disease, the panel recommends that an alternative chemotherapy option be administered, although systemic therapy as previously administered is recommended when this period is greater than 6 months. In all cases of recurrent disease, a clinical trial is the preferred option and best supportive care should also be administered (see page 987).

Future Clinical Trials: Recommendations for Design

In 2007, a meeting was convened by the NCI's Gastrointestinal Cancer Steering Committee in recognition of the failure of several recent phase III trials to show clinically significant benefit for patients with pancreatic cancer, and to address the importance of integrating basic and clinical knowledge in the design of clinical trials for pancreatic cancer. Meeting participants included representatives from industry, government, and the community, and academic researchers and patient advocates. Several important themes that emerged from this meeting are summarized below, and the recommendations of the committee are endorsed by the panel.[237]

- With the emergence of new agents to treat pancreatic cancer, particularly biologics, clinical trial strategies incorporating principles of molecular biology and new imaging methods and 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 these biomarkers should be well validated.
- Clinical trials should enroll homogeneous patient populations with respect to disease stage (i.e., 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 (i.e., 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 overall survival.
- Quality control standards for preoperative imaging interpretation, pathologic assessment of tumor specimens, and surgical selection criteria are critical when evaluating adjuvant therapies.

Palliation of Locally Advanced and Metastatic Disease

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that, in many respects, are unique to the disease. For patients with locally advanced unresectable and metastatic disease, the multidisciplinary management of symptoms caused by biliary obstruction, gastric outlet obstruction, and cancer-related pain is of primary importance (see page 987).

Biliary Obstruction

Approximately 65% to 75% of patients with pancreatic cancer develop symptomatic biliary obstruction.[238] For patients diagnosed with unresectable disease and biliary obstruction on initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent stent is recommended unless biliary bypass is performed (see pages 979 and 981). Stent occlusion that causes recurrent cholangitis is a well-know complication of plastic biliary stents and typically occurs within 3 months of insertion. Metal stents are wider in diameter than temporary stents (i.e., have less likelihood of blockage) and become embedded in the bile duct, whereas plastic stents are more likely to become occluded but can be replaced. Results of a recent randomized controlled trial of 100 patients at a single center assigned to receive either a plastic stent or an uncovered self-expanding metal stent inserted endoscopically indicated that median patency times were 1.8 and 3.6 months ($P = .002$), respectively.[239] This conclusion is supported by results of a meta-analysis comparing metal and plastic

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biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction, which suggested that the risk of recurrent biliary obstruction was lower for the metal stents (relative risk, 0.52; 95% CI, 0.39–0.69), although no significant differences in technical/therapeutic success, complications, or 30-day mortality rates were found.[240]

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

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors after laparotomy, an open biliary-enteric bypass provides durable palliation of biliary obstruction and can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain (see pages 979 and 987). The panel recommends an open biliary-enteric bypass with or without duodenal bypass (category 2B for prophylactic duodenal bypass) and with or without open ethanol celiac plexus block (category 2B). Bypass of the common bile duct (choledochojejunostomy) or common hepatic duct (hepaticojejunostomy) to the jejunum is preferred to bypass of the gallbladder (cholecystojejunostomy) because choledochojejunostomy/hepaticojejunostomy provides more durable and reliable palliation of biliary obstruction.[238]

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10% to 25% of patients with pancreatic cancer.[238] Patients found to have locally advanced or metastatic disease on evaluation who develop gastric outlet obstruction may be palliated with an endoscopically placed enteral stent, especially if their life expectancy is limited or their performance status is poor.[242] An alternative for these patients is percutaneous endoscopic gastrostomy tube placement. For a fit patient with a life expectancy greater than 3 to 6 months (i.e., locally advanced disease), a laparoscopic gastrojejunostomy with or without a jejunostomy tube should be considered, because it may provide more durable and effective palliation of gastric outlet obstruction than an enteral stent. Nevertheless, placement of an enteral stent is also an option for these patients (see page 987).

In patients with potentially resectable disease who undergo a laparotomy and are found to have unresectable disease, a palliative gastrojejunostomy should be performed for those deemed to be at risk of developing symptomatic gastric outlet obstruction. The role of prophylactic gastrojejunostomy has been evaluated in otherwise asymptomatic patients who are found to be unresectable at laparotomy. Two randomized controlled trials have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer, with most arising from the head of the pancreas.[242,243] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. In both studies, prophylactic retrocolic gastrojejunostomy significantly decreased the incidence of late gastric outlet obstruction but did not extend the length of stay or increase complication rates, such as delayed gastric emptying.

If staging laparoscopy shows unresectable disease, palliation of symptoms may be provided by a laparoscopic gastrojejunostomy, with or without laparoscopic biliary bypass, depending on life expectancy and surgical expertise.

Severe Tumor-Associated Abdominal Pain

Most patients with locally advanced or metastatic pancreatic cancer experience cancer-related pain.[244] General principles for cancer-related pain management can be found in the NCCN Clinical Practice Guidelines (NCCN Guidelines) on Adult Cancer Pain (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, celiac plexus neurolysis should be considered.

In 2 randomized controlled trials, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.[244,245] Minimally invasive techniques include EUS-guided and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis (see page 987), but laparoscopic, thoracoscopic, and open approaches can also be used.

If staging laparoscopy reveals unresectable disease, palliation of tumor-associated abdominal pain may be provided by laparoscopic celiac plexus neurolysis, depending on life expectancy and surgical expertise. In selected patients with severe local back pain, radiation therapy may be considered, even in the setting of metastatic disease.

Additional Palliative Interventions

Pancreatic Insufficiency: Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or pancreatic duct, and surgical removal of pancreatic tissue.[246,247] Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency (e.g., steatorrhea; see page 987).

Treatment of Thromboembolic Disease: The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.[248] The panel recommends low-molecular-weight heparin (LMWH) as preferred therapy over Coumadin for patients with pancreatic cancer who develop a venous thromboembolism (VTE; see page 987). Support for this recommendation comes from results of 2 large prospective randomized clinical trials: CLOT and CONKO 004. In the CLOT study, an approximately twofold decrease in the incidence of recurrent VTE at 6 months was observed in patients with advanced or metastatic cancer diagnosed with a VTE who were treated with the LMWH dalteparin, compared with those treated with an oral anticoagulant.[249] In the CONKO 004 trial, VTE- and chemotherapy-naive patients with advanced pancreatic cancer were randomized to receive palliative chemotherapy either with or without enoxaparin.[250] The risk of developing symptomatic VTE was significantly lower for patients in the LMWH arm of the study, with no significant increase in bleeding observed in this group compared with those not receiving enoxaparin.

Depression, Pain, Malnutrition: The panel recommends that patients with locally advanced or metastatic pancreatic cancer undergo a formal evaluation by a palliative medicine service when appropriate (see page 987). Additional resources are detailed in the NCCN Guidelines on Palliative Care, Adult Cancer Pain, and Distress Management (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Surveillance

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are limited, recommendations were based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The panel recommends a history and physical examination be performed for symptom assessment every 3 to 6 months for 2 years (see page 980). Although the panel discussed the role of CA 19-9 determinations and follow-up CT scans every 3 to 6 months for 2 years after surgical resection, consensus was not uniform on whether this was appropriate (i.e., these recommendations are category 2B), because data are not available to show that earlier treatment of recurrences, after detection through increased tumor marker levels or CT scan, leads to better patient outcomes.

Summary

Overall, in view of the relatively high likelihood of a poor outcome for patients with all stages of pancreatic cancer, the panel recommends that investigational options be considered in all phases of disease management. Specific palliative measures are recommended for patients with advanced pancreatic adenocarcinoma characterized by biliary or gastric obstruction, severe abdominal pain, or other tumor-associated manifestations of the disease.

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NCCN Guidelines Panel Disclosures

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Treatment of Metastatic Pancreatic Adenocarcinoma: A Review

Review Article [1] | January 15, 2014 | Oncology Journal [2], Gastrointestinal Cancer [3], Pancreatic Cancer [4]
By Ramya Thota, MBBS [5], James M. Pauff, MD, PhD [6], and Jordan D. Berlin, MD [7]

Gemcitabine monotherapy has been the standard of care for patients with metastatic pancreatic cancer for several decades. Despite recent advances in various chemotherapeutic regimens and in the development of targeted therapies, metastatic pancreatic cancer remains highly resistant to chemotherapy.

Introduction

Metastatic pancreatic cancer is one of the most aggressive and highly lethal malignancies, with an estimated 5-year survival of less than 5%. In 2013, approximately 45,000 new cases and 38,000 deaths were attributable to pancreatic cancer in the United States alone. The overall median survival is less than 1 year from diagnosis, highlighting the need for the development of newer therapeutic options.[1]

Despite recent advances in chemotherapeutics and in our understanding of the molecular biology of pancreatic cancer, there has been limited progress in therapeutic options for metastatic disease. Over the past 4 decades, studies of several combination therapies have demonstrated minimal or no survival benefit compared with gemcitabine alone. Gemcitabine monotherapy had been the standard of care for patients with metastatic pancreatic cancer for several years, until combination therapy with gemcitabine plus erlotinib was shown to increase median survival by 2 weeks.[2,3] However, the modest survival benefit was tempered by a significant side effect profile and the high cost of treatment. Later, the multidrug combination of leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) was noted to provide an increased median survival of 4.3 months; however, given its side effect profile, it is available only to a select group of patients with advanced pancreatic cancer.[4] Recently, the gemcitabine plus nab-paclitaxel combination was shown to increase median survival by 1.8 months, with increased overall survival at 1 and 2 years; adverse effects were reasonable and included cytopenias and peripheral neuropathy.[5]
The current National Comprehensive Cancer Network recommendations suggest acceptable chemotherapy combinations for patients with good performance status (ie, Eastern Cooperative Oncology Group performance status [ECOG PS] of 0 or 1), good pain management, patent biliary stent, and adequate nutritional intake; these combinations include FOLFIRINOX, gemcitabine plus nab-paclitaxel, and gemcitabine plus erlotinib. The only recommended option for patients with poor performance status is gemcitabine monotherapy.[6] The guidelines for choosing an appropriate treatment regimen for patients with metastatic pancreatic cancer thus remain ambiguous, and in the absence of a randomized trial comparing the combination regimens head to head, the dilemma remains regarding appropriate first-line therapy for these patients. Hence, in this review we discuss in detail the efficacy and toxicities of four treatment choices: gemcitabine alone, gemcitabine plus erlotinib, FOLFIRINOX, and gemcitabine plus nab-paclitaxel.

Gemcitabine Monotherapy

Gemcitabine is a pyrimidine analog that is phosphorylated to diphosphate and triphosphate forms to inhibit both ribonucleotide reductase and DNA polymerase. It was initially approved by the US Food and Drug Administration (FDA) in 1997 for the first-line treatment of pancreatic cancer on the basis of work by Burris et al. In a randomized trial of 126 patients with advanced pancreatic cancer, 63 patients were treated with gemcitabine at 1,000 mg/m^2 weekly for 7 weeks followed by 1 week of rest then weekly for 3 of every 4 weeks thereafter, and 62 patients were treated with fluorouracil, 600 mg/m^2 once weekly. The gemcitabine group showed improved median overall survival (5.6 vs 4.4 months) and 1-year survival (18% vs 2%) and a better overall response rate (24% vs 5%) compared with the fluorouracil group.[2] Gemcitabine monotherapy is generally well tolerated; the most frequent adverse effect is grade 3/4 neutropenia.

Further studies conducted to evaluate any improvement in survival with the fixed-dose-rate infusion regimen did not show any significant difference in survival benefit. The US Intergroup study of 832 patients with advanced pancreatic cancer compared standard-dose gemcitabine (1,000 mg/m^2 over 30 minutes weekly for 7 of 8 weeks, then for 3 of every 4 weeks) vs fixed-dose-rate gemcitabine (1,500 mg/m^2 over 150 minutes weekly for 3 of every 4 weeks) vs combined fixed-dose-rate gemcitabine plus oxaliplatin. Compared with standard-dose gemcitabine alone, there was no significant difference in response rates with the fixed-dose-rate regimen (10% vs 5%, respectively), and there was only a small trend toward improvement in median survival (6.2 vs 4.9 months; hazard ratio = 0.83; P = .05).[7] In the absence of strong evidence for significant improvement in survival with the fixed-dose regimen, standard-dose gemcitabine has been most commonly used in clinical practice.

Since the initial approval of gemcitabine for management of advanced pancreatic cancer, studies of several combination regimens with many other active cytotoxic agents, including fluorouracil, capecitabine, cisplatin, docetaxel, oxaliplatin, irinotecan, cetuximab, and pemetrexed, have shown no significant survival benefit.[7-14]

Gemcitabine Plus Erlotinib

Almost a decade after the initial approval of gemcitabine by the FDA, a Canadian phase III trial compared gemcitabine (1,000 mg/m^2 weekly) with and without erlotinib (100 mg daily) in 569 patients with locally advanced or metastatic pancreatic cancer. This study showed positive results; combination therapy was associated with significantly better overall survival compared with gemcitabine alone (hazard ratio = 0.81; P = .038; median survival, 6.2 vs 5.9 months; 1-year survival, 23% vs 17%, respectively).[3] There was a slight increase in the incidence of grade 3/4 rash and diarrhea (6% vs 1%) in the erlotinib group, but there was no overall difference in quality of life scores between the two groups. Nevertheless, the cost per life year gained was significantly higher than is usually accepted; hence, the modest 2-week improvement in survival remains a source of debate.[15,16]

Recently, Miyabayashi et al found that erlotinib may attenuate mitogen-activated protein kinase signaling induced by gemcitabine.[17] Their results suggest that gemcitabine induces epidermal growth factor receptor (EGFR) ligand expression and that erlotinib inhibits subsequent heterodimerization of EGFR with ERBB2. In a murine model of pancreatic ductal adenocarcinoma, the investigators showed that gemcitabine plus erlotinib was superior to gemcitabine alone, with improved survival and blocked progression of disease.

FOLFIRINOX

The efficacy and safety of the combination chemotherapy regimen FOLFIRINOX were compared with that of gemcitabine alone in a phase III trial (ACCORD 11).[4] A total of 342 chemotherapy-naive patients with metastatic pancreatic cancer, an ECOG PS of 0 or 1, and a serum bilirubin level < 1.5 times the upper limit of normal were randomly assigned to gemcitabine alone (1,000 mg/m^2 weekly for 7 weeks, followed by 1 week of rest, then weekly for 3 of every 4 weeks) or FOLFIRINOX (leucovorin at 400
mg/m^2, fluorouracil at 400 mg/m^2, irinotecan at 180 mg/m^2, and oxaliplatin at 85 mg/m^2 given as a bolus, followed by 2,400 mg/m^2 given as a 46-hour continuous infusion, every 2 weeks). The median overall survival, progression-free survival (PFS), and objective response rate were significantly higher with FOLFIRINOX compared with gemcitabine alone (median overall survival, 11.1 vs 6.8 months; PFS, 6.4 vs 3.3 months; objective response rate, 32% vs 9%). However, treatment-related toxicity was also significantly higher with FOLFIRINOX, including grade 3/4 neutropenia (46% vs 21%), febrile neutropenia (5.4% vs 1.2%), thrombocytopenia (9.1% vs 3.6%), sensory neuropathy (9% vs 0%), vomiting (15% vs 8%), fatigue (23% vs 18%), and diarrhea (13% vs 2%). Still, despite the greater toxicities, FOLFIRINOX significantly improved survival compared with gemcitabine alone, with a median increase in survival of 4.3 months.

Gemcitabine Plus Nab-Paclitaxel

Overexpression of secreted protein acidic and rich in cysteine (SPARC, an albumin-binding protein, also known as osteonectin and basement membrane 40) in stromal fibroblasts within the pancreatic microenvironment is considered an important cause of chemotherapy resistance and is associated with a poor prognosis.[18,19]. SPARC has been suggested to have divergent and even contradictory

roles in various other cancers; it has been implicated in tumor progression, suppression, and metastasis, depending on cancer type. In a detailed review, Tai and Tang proposed that post-translational modifications, including variable proteolysis of the larger SPARC protein, may explain the specific but varying roles suggested by studies that have used different methodologies in assessing or inferring protein function.[20] Targeting SPARC in tumors that overexpress the protein (including pancreatic, breast, and lung cancers, and melanoma) has been shown to have antitumor effects.

Because paclitaxel is a hydrophobic, lipophilic molecule, it is available for parenteral administration in a variety of formulations, including polyoxyethylated castor oil (Cremophor EL, or CreEL), nanoparticle albumin-bound, cationic liposomal, and polymeric micelle formulations.[21-24] The albumin-bound formulation (also known as nab-paclitaxel, or ABI 007) is a solvent-free, colloidal suspension, 130-nm particle form of paclitaxel homogenized with human serum albumin. It has several favorable pharmacokinetic properties, such as larger volume of distribution, higher fraction of unbound drug, and more rapid clearance than other formulations of paclitaxel.[25] In vitro experiments have shown that nab-paclitaxel is four times more efficient than CreEL paclitaxel in crossing layers of endothelial cells.[26]

Nab-paclitaxel binds to albumin receptor binding site gp60 on endothelial cells and activates caveolin-1 and caveolae formation, leading to extracellular transport of drug into the interstitial space, where it binds to SPARC.[26] This gp60/caveolin-1/caveolae/SPARC pathway is a unique mechanism of delivery, enabling higher drug concentrations in close proximity to tumor cells. The favorable pharmacokinetic properties of nab-paclitaxel and receptor-mediated delivery of a higher concentration of drug with rapid clearance contribute to fewer adverse effects than are seen with the CreEL formulation at a similar dose of paclitaxel.[22]

Nab-paclitaxel was initially approved by the FDA in January 2005 for use in metastatic breast cancer after progressive disease following chemotherapy or relapse within 6 months of adjuvant chemotherapy,[27] and in October 2012 it was approved for use in metastatic non–small-cell lung cancer.[28] Preclinical studies have shown that nab-paclitaxel binds to SPARC, causing stromal depletion and an increase in vasculature around the tumor, thereby resulting in higher gemcitabine concentrations within the tumor. The bioavailability and intratumoral concentrations of paclitaxel as nab-paclitaxel have also been shown in preclinical studies to be higher than those achieved with the CreEL formulation. The combination of nab-paclitaxel and gemcitabine resulted in a 2.8-fold increase in gemcitabine concentration compared with gemcitabine alone, and regression occurred in 64% of tumors vs 36% and 18% with nab-paclitaxel and gemcitabine monotherapy, respectively, in primary patient-derived xenograft models.[29] In the phase I/II study conducted in patients with previously untreated metastatic pancreatic cancer, 44 patients who received the maximally tolerated dose (gemcitabine at 1,000 mg/m^2 followed by nab-paclitaxel at 125 mg/m^2 on days 1, 8, and 15 of every 28-day cycle) had a response rate of 48% and a median survival of 12.2 months. At this dose, grade 3/4 toxicities included fatigue in 27% of participants, neuropathy in 20%, and neutropenia in 49%.

The superiority of the combination regimen was later confirmed in the multinational phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) that included 861 patients with previously untreated metastatic pancreatic adenocarcinoma.[5] Combination therapy was associated with a significantly higher objective response rate (23% vs 7%) and significantly longer median overall survival (8.5 vs 6.7 months) and PFS (5.5 vs 3.7 months) compared with gemcitabine monotherapy. Grade 3/4 adverse events that occurred more often with combination therapy than with gemcitabine alone included neutropenia (38% vs 27%), febrile neutropenia (3% vs 1%), fatigue (17% vs 7%), diarrhea (6% vs 1%), and neuropathy (17% vs 1%). In September 2013, nab-paclitaxel in combination with gemcitabine was approved by the FDA for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas.

The synergistic effect of nab-paclitaxel and gemcitabine is attributable to several factors, including its favorable pharmacokinetic properties that enable delivery of a higher dose of paclitaxel, which not only is directly cytotoxic but also raises intratumoral gemcitabine accumulation through the depletion of the stromal matrix and increases in tumor microvasculature. In addition to SPARC-mediated stromal depletion, inactivation of cytidine deaminase (an important enzyme in gemcitabine inactivation) by nab-paclitaxel also potentiates the efficacy of gemcitabine.[30]

Table 1 compares the survival metrics and toxicity profiles of the three major positive trials in advanced pancreatic cancer. Table 2 represents a cost and quality-of-life analysis based on data from Canada's public health-care system, which suggests that FOLFIRINOX is more cost-effective than gemcitabine or gemcitabine plus nab-paclitaxel in patients with metastatic pancreatic cancer.[31] The cross-trial comparisons in Table 1 lack the validity of a randomized trial, although it

is notable that gemcitabine monotherapy is very similar in its response rates (8%, 9.4%, and 7%), median overall survival durations (5.9, 6.8 and 6.7 months), and median PFS durations (3.6, 3.3, and 3.7 months) across the various studies. The median overall survival duration with FOLFIRINOX in the ACCORD 11 trial was 11.1 months, while it was 8.5 months for gemcitabine plus nab-paclitaxel in the MPACT trial and 6.24 months for gemcitabine plus erlotinib. Although this appears to suggest the superiority of FOLFIRINOX over gemcitabine plus nab-paclitaxel in overall survival, the differences in the trials make it impossible to make this claim. Therefore, both FOLFIRINOX and gemcitabine plus nab-paclitaxel are reasonable choices for first-line therapy in patients with good performance status (ECOG PS 0 or 1). The combination of gemcitabine and nab-paclitaxel is an option for those with modest performance status who cannot tolerate a FOLFIRINOX regimen.

Conclusions

In the past few years, two new and more effective chemotherapy regimens (FOLFIRINOX and gemcitabine plus nab-paclitaxel) have demonstrated improved survival over single-agent gemcitabine in patients with metastatic pancreatic adenocarcinoma. However, median survival rates are still < 1 year; thus, more effective therapies are needed. In addition, all advances so far have been with the use of chemotherapy. Molecularly targeted therapies and immune mediators are being tested in pancreatic cancer and may be able to further alter the natural history of this disease.
Financial Disclosure: *The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.*

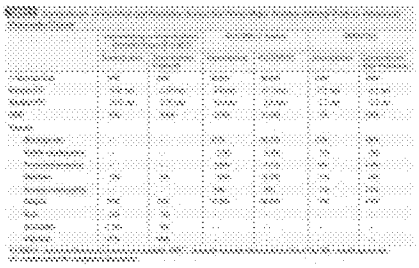

Table 1: Comparison of Survival and Toxicities Across the Three Major ...

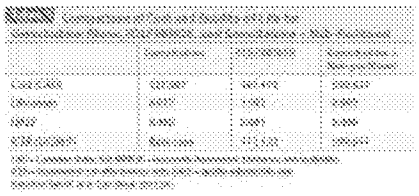

Table 2: Comparison of Cost and Quality-of-Life for Gemcitabine Alone,...

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S-1 Monotherapy as Second-line Treatment for Advanced Pancreatic Cancer after Gemcitabine Failure

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Objective: No standard salvage chemotherapy regimen has been established for patients with advanced pancreatic cancer after failure of gemcitabine-based treatment. Although a Phase II study of S-1 monotherapy was conducted in patients with gemcitabine-refractory advanced pancreatic cancer, the number of patients enrolled was small.

Methods: We retrospectively reviewed 84 consecutive patients who received S-1 monotherapy as a second-line treatment after gemcitabine failure at the Shizuoka Cancer Center between May 2004 and April 2008. The selection criteria in this study were age 20–75 years, ECOG performance status ≤ 2 and preserved organ functions. S-1 was administered orally twice a day at a dose of 40 mg/m^2 for 28 days, followed by 14-day rest.

Results: Fifty-two patients were selected for the analysis. Out of the 47/52 patients with measurable lesions, only 2 patients (4%) showed a partial response and 15 patients (32%) showed stable disease. The median progression-free survival was 2.1 months and the median overall survival was 5.8 months, with a 1-year survival rate of 12%. The common grade 3/4 toxicities were diarrhea (8%), anorexia (6%), fatigue (6%), anemia (6%) and leucopenia (4%).

Conclusions: S-1 monotherapy is marginally effective and well tolerated in the second-line setting in patients with gemcitabine-refractory advanced pancreatic cancer.

Key words: S-1 monotherapy – second line – pancreatic cancer – gemcitabine failure

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INTRODUCTION

Pancreatic cancer is the fifth leading cause of cancer-related death, and the annual mortality is estimated to be more than 20 000 in Japan. The 5-year survival rate of pancreatic cancer is as low as 5.5%, and the poor prognosis is attributed to the difficulty in detection of the disease at an early stage, the high malignant potential and propensity of the cancer to metastasize, and the high resistance level to antitumor agents. Gemcitabine (GEM) showed superiority to 5-fluorouracil (5-FU) as first-line chemotherapy in patients with advanced pancreatic cancer (1). Ever since, monotherapy with GEM has been the standard treatment for advanced pancreatic cancer. However, the median progression-free survival (PFS) time has been reported to be just 2–4 months and the median overall survival time (MST) ranging from 4.9 to 8.2 months (2–18). To improve the prognosis of patients with advanced pancreatic cancer, numerous randomized controlled trials comparing GEM-based combination therapy with GEM monotherapy have been conducted, but only two regimens have shown any significant survival advantage; combined GEM plus capecitabine (13) and combined GEM plus erlotinib (18). However, the efficacy of these regimens has also been only modest, with an MST of around 6 months. It can be said that these clinical trials of new agents in the first-line setting have not led to any remarkable progress in the treatment of pancreatic cancer.

Another possible way to improve the prognosis of patients with pancreatic cancer is the establishment of effective second-line chemotherapy. Until date, numerous Phase II trials have been conducted to evaluate the second-line chemotherapy after GEM failure in pancreatic cancer patients, and the median PFS time in these trials was 1.1–5.5 months and the MST ranged from 2.9–8.3 months (19–38).

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S-1 is an oral agent consisting of a mixture of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate at a molar ratio of 1:0.4:1 (39). In a Phase II study of S-1 for chemonaïve advanced pancreatic cancer, it was reported that 15 (37.5%) of 40 patients showed an objective response, including complete response in 1 patient, and the median PFS time and the MST were 3.7 and 9.2 months (40), respectively. On the basis of these results, S-1 was approved for the treatment of pancreatic cancer in Japan. Furthermore, a Phase II study of this agent in the second-line setting after GEM failure was performed in patients with metastatic pancreatic cancer; among the 40 patients enrolled in this study, the response rate was 16%, the median PFS time and MST were 2.0 and 4.5 months and 1-year survival rate was 14% (19). The toxicity of S-1 was acceptable. Thus, S-1 has been used commonly as a second-line treatment in Japan.

However, this study may have some limitations such as the small number of patients enrolled and selection bias. We performed this retrospective survey because the efficacy and safety of S-1 monotherapy for patients with advanced pancreatic cancer in the second-line setting in clinical practice is still not well known.

PATIENTS AND METHODS

Subjects

The subjects were 84 consecutive patients with advanced pancreatic cancer who received S-1 monotherapy between May 2004 and April 2008 as the second-line treatment after GEM failure, at the Shizuoka Cancer Center, and a retrospective review of their medical records was performed. In most of the patients, the diagnosis of pancreatic cancer was made by computed tomography (CT) and confirmed histologically by EUS-FNA, liver biopsy or cytological examination, where possible. The patient selection criteria for this retrospective study were age 20–74 years, an Eastern Cooperative Oncology Group performance status (PS) of 0–2, good bone marrow function (white blood cell count $\geq$3000/mm^3, neutrophil count $\geq$1500/mm^3, platelet count $\geq$100 000/mm^3 and hemoglobin $\geq$9.0 g/dl), renal function (serum creatinine $\leq$1.5 mg/dl) and liver function (total bilirubin $\leq$2.0 mg/dl and transaminase levels $\leq$2.5 times the upper limit of the respective normal ranges). Patients who had obstructive jaundice were eligible, but only after their serum transaminase levels decreased to within five times the upper normal limit of normal after biliary drainage. Patients who had not received GEM as part of their previous regimen, or with massive pleural effusion or ascites, active concomitant malignancy, brain metastasis, interstitial pneumonia or uncontrolled diabetes mellitus, or regularly using phenytoin, warfarin or fluorouracil were excluded from the study.

Treatment

S-1 was administered orally twice a day at the dose of 40 mg/m^2. The initial doses were determined according to the body surface area (BSA), as follows: BSA $<$ 1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA $\leq$ 1.50 m^2, 100 mg/day; and 1.50 m^2 $\leq$ BSA, 120 mg/day. S-1 was given for 28 days, followed by a rest period of 14 days. This treatment course was repeated until the appearance of disease progression or unacceptable toxicity, or until the patient no longer wished to continue the treatment.

Evaluation

Tumor response was assessed by CT according to the Response Evaluation Criteria in Solid Tumors (RECIST, ver. 1.0). Primary pancreatic lesions were excluded from measurable lesions because of the difficulty in the precise measurement of their sizes. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. PFS was counted from the date of treatment initiation to the date of documentation of disease progression or death, and overall survival was counted from the date of treatment initiation to the date of death or the last follow-up. PFS and overall survival curves were constructed using the Kaplan–Meier method.

RESULTS

Subjects

Of the total of 84 patients registered, 52 were selected for this retrospective study according to the eligibility criteria. The reasons for exclusion of the remaining 32 patients were: age over 75 (10 patients); PS 3 (1 patient), inadequate organ functions (13 patients), massive effusion (2 patients), interstitial pneumonia (2 patients), active concomitant malignancy (3 patients) and regular use of warfarin (1 patient). The patient characteristics of the subjects are shown in Table 1. Of the 52 patients, 29 (56%) were male, 40 (77%) had an ECOG PS of 0–1 and the median age was 64.5 years (range: 42–74). As for the prior treatment, nine patients had undergone curative surgery and received GEM treatment after recurrence. All the subjects had received prior GEM monotherapy, with a median course of GEM administrations of 4 (range: 2–17); disease progression had been confirmed before the second-line therapy in all the subjects. Among the 51 patients who received GEM treatment at our hospital, 4 (7.8%) patients showed a partial response and 28 (55%) showed stable disease. At the start of the second-line chemotherapy, only 1 patient had a locally advanced pancreatic cancer, and 17 (33%) and 3 (6%) patients, respectively, had complicating ascites and pleural effusion.

Treatment Course

A total of 117 courses were administered, with a median of 2 courses per patient (range: 1–10). Reduction of even the initial dose was required in two patients because of renal dysfunction. Dose reductions from the second course were

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Table 1. Patient characteristics at the start of second-line therapy

Characteristic	Patients ($n = 52$)	Percent
Median age (range)	65 (42–74)	
Gender		
Male	29	56
Female	23	44
Prior curative surgery	9	17
Best response of prior GEM treatment ($n = 51$)		
Complete remission	0	0
Partial response	4	7.8
Stable disease	28	55
Progressive disease	19	37
Stage of disease		
Locally advanced	1	2
Metastatic	51	98
Site of metastasis		
Liver	42	81
Lymph node	21	40
Peritoneum	18	35
Lung	10	19
Ascites	17	33
Pleural effusion	3	6
ECOG PS		
0	13	25
1	27	52
2	12	23

GEM, gemcitabine; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Toxicities according to CTCAE v3.0

	Grade							
	1		2		3		4	
	n	Percent	*n*	Percent	*n*	Percent	*n*	Percent
Hematologic								
Leukocytes	9	17	4	8	2	4	0	0
Neutrophils	3	6	4	8	1	2	0	0
Hemoglobin	5	10	11	21	3	6	0	0
Platelets	14	27	1	2	0	0	0	0
Non-hematologic								
AST	3	6	2	4	0	0	0	0
ALT	0	0	2	4	0	0	0	0
Bilirubin	5	10	0	0	1	2	0	0
Creatinine	4	8	0	0	0	0	0	0
Other								
Diarrhea	11	21	2	4	4	8	0	0
Anorexia	12	23	11	21	3	6	0	0
Fatigue	13	25	14	27	3	6	0	0
Stomatitis	6	12	5	10	1	2	0	0
Rash	1	2	1	2	1	2	0	0
Dehydration	0	0	0	0	1	2	0	0
Colitis (CDAD)	0	0	0	0	1	2	0	0
Nausea	13	25	4	8	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDAD, *Clostridium difficile* associated diarrhea.

required in nine patients (17%) and treatment was interrupted during the course in seven patients (13%) due to the development of anorexia, nausea, stomatitis, diarrhea, fatigue, vomiting, cholangitis or rash. S-1 monotherapy was discontinued in 45 patients (87%) because of disease progression and in 7 patients (13%) because of the development of non-hematological toxicities such as grade 3 diarrhea, anorexia or infectious colitis, and grade 2 infection and/or fatigue. The median dose intensity of S-1 was 311.2 mg/m^2/week (range: 69.7–373.3).

Toxicities

The toxicities are summarized in Table 2. No grade 4 toxicity was observed. Hematologic toxicities were generally mild; with grade 3 neutropenia observed in only one patient (1.9%) and grade 3 anemia in three (5.6%). The non-hematologic grade 3 toxicities were diarrhea (four patients, 8%), anorexia (three patients, 6%), fatigue (three patients, 6%), stomatitis (one patient, 2%), rash (one patient, 2%), infectious colitis (one patient, 2%), dehydration (one patient, 2%) and elevation of serum bilirubin (one patient, 2%). All of the adverse events were reversible.

Efficacy

Forty-seven of all the patients had measurable lesions and were evaluable for response. A partial response was obtained in 2 patients (3.7%) and disease stabilization in 17 patients (31%). The median PFS time was 2.1 months (Fig. 1), and the median survival time was 5.8 months, with a 1-year survival rate of 12% (Fig. 2). In the subgroup analysis according to PS, the median survival time was 5.9 months in PS 0–1 and 4.0 months in PS 2. As for tumor markers, the serum CA19-9 level was reduced to less than half in 9 (20%) of 44 evaluable patients.

DISCUSSION

In regard to the treatment for advanced pancreatic cancer after GEM failure in the second-line setting, it is difficult to

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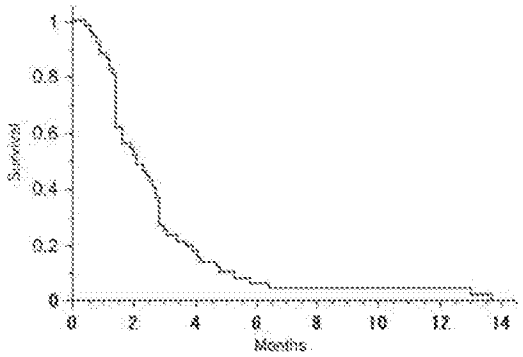

Figure 1. Progression-free survival in the study population.

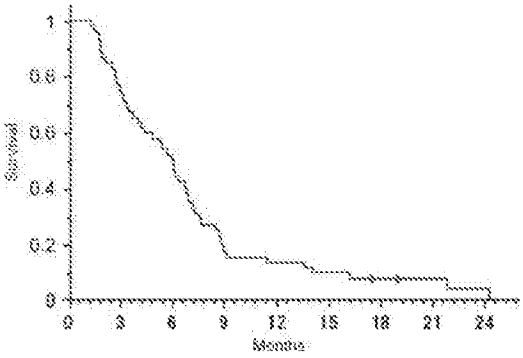

Figure 2. Overall survival in the study population.

compare Phase II trials, because of the varieties of patient backgrounds, such as the PS, the presence of metastatic or locally advanced lesion etc. After 32 of the total of 84 patients were excluded from this study, about a quarter of the subjects showed PS 2 and one-third had ascites. It would seem that the patient backgrounds were rather poor when compared with those in recent Phase II trials, although it is important to exercise caution while interpreting the results of this retrospective study.

The response rate of 4% in this study appears to be inferior to that obtained in a previously conducted Phase II study of S-1 monotherapy, of 16%. As for the median PFS time, it was about 2 months in both this study and the previous Phase II study. The response rate and median PFS time following treatment with 5-FU plus celecoxib were 12.5% and 1.8 months, and those with capecitabine were 0% and 1.7 months, respectively. These results suggest the consistent efficacy of 5-FU derivatives in the second-line setting for pancreatic cancer. Furthermore, in a search of the PubMed database for trials of second-line therapy of pancreatic cancer patients after GEM failure, 20 studies met the following criteria: publication in journal, prospective trial and mentions of PFS or time to progression and MST. Among the 20 trials which evaluated various kinds of chemotherapeutic regimens, including combination chemotherapies, other than S-1 for pancreatic cancer after failure of GEM, the average response rate was 9.9 $\pm$ 9.5%, and the average of median PFS time was 2.8 $\pm$ 1.2 months. Thus, the response rates and PFS following treatment with S-1 in both this study and the previous Phase II study seem to be consistent with the values reported in these trials. As for the overall survival, the MST in this study and the previous Phase II study was 5.8 and 4.5 months, respectively, whereas the results of the aforementioned 20 trials indicated an average MST of 5.7 $\pm$ 1.8 months. From these results, it is considered that S-1 has similar antitumor effects to other chemotherapy regimens, and that there has still been no success at establishing effective chemotherapy in the second-line setting after GEM failure in patients with pancreatic cancer.

As for the toxicities, similar results were obtained in this study and in the previous Phase II study of S-1. Since no grade 4 toxicities were observed and the treatment needed to be discontinued due to the appearance of toxicity(ies) in only seven patients (13%), it is suggested that the use S-1 may be feasible, in terms of its acceptable toxicity, in patients with pancreatic cancer in the second-line setting after GEM failure.

Although there are no established standard regimens for second-line chemotherapy of pancreatic cancer patients, the National Comprehensive Cancer Network guidelines currently recommend fluorinated pyrimidine-based therapy as the second-line chemotherapy after GEM failure in selected patients (41). This study suggests that the use of S-1 may be considered as an option for the treatment of pancreatic cancer in the second-line setting, from the point of view of the efficacy and feasibility in Japan. Furthermore, some patients even with PS 2 can be candidates for the second-line chemotherapy with S-1 if they can take sufficient oral ingestion.

In 2005, a Phase III study compared an oxaliplatin/folinic acid/5-FU (OFF) regimen with best supportive care after confirming first-line GEM failure (42). The study showed that OFF treatment prolonged the MST (the MST was 21 weeks in the treatment group vs. 10 weeks in the BSC group) and improved the overall survival time from the date of initiation of first-line therapy. At the 2008 ASCO annual meeting, the final results of a randomized Phase III study comparing OFF and FF in patients with GEM-refractory advanced pancreatic cancer were reported. A total of 168 patients were enrolled in this study and the results showed significantly improved survival with the OFF regimen than with the FF regimen (MST; 26 vs. 13 weeks, $P = 0.014$) (43). These results suggest that combined chemotherapy with oxaliplatin plus fluorinated pyrimidine therapy offers promise of becoming a new standard for the second-line treatment of pancreatic cancer after GEM failure.

In conclusion, S-1 monotherapy in the second-line setting is only marginally effective but well tolerated in patients with GEM-refractory advanced pancreatic cancer. Further development of second-line chemotherapies is warranted, and now a randomized clinical trial investigating the usefulness of a combined fluorinated pyrimidine, such as S-1, plus oxaliplatin is underway in Japan.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

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Treatment with an oral fluoropyrimidine, S-1, plus cisplatin in patients who failed postoperative gemcitabine treatment for pancreatic cancer: a pilot study

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Abstract
Background. This study set out to evaluate, in patients with gemcitabine-resistant pancreatic cancer, the response rate and toxicity of S-1 plus cisplatin (CDDP).
Methods. Seventeen patients with histologically diagnosed invasive ductal pancreatic cancer were enrolled in this study. All patients had growing recurrent pancreas cancer despite the administration of gemcitabine. Thirteen patients underwent pancreatectomy, and 2 underwent choledocho-jejunostomy and gastrojejunostomy without pancreatectomy. S-1 (80 mg/m^2 per day) was orally administered for 21 consecutive days, followed by a 14-day rest period. CDDP (40 mg/m^2) in 500 ml saline was administered by intravenous drip on day 8. This schedule was repeated every 5 weeks until the occurrence of disease progression, unacceptable toxicities, or the patient's refusal to continue.
Results. Five (29.4%) patients achieved a partial response and 2 (11.8%) had stable disease. In 5 of 15 patients (33.3%) who had elevated serum carbohydrate antigen (CA)19-9 levels at the start of treatment the CA19-9 was reduced by more than 50%. The median survival time was 10 months (range, 20 months), with 63.7% and 31.9% of patients alive at 6 and 12 months, respectively. Major adverse reactions in the 15 patients included gastrointestinal toxicities of grade 1 or 2. Only one patient (5.9%) developed grade 3 leucopenia.
Conclusion. S-1 with CDDP has a promising effect against gemcitabine-resistant pancreatic cancer, with easily manageable toxicities. Further investigation of this regimen is warranted in patients with pancreatic cancer, especially in comparison with gemcitabine.

Key words Pancreatic cancer · Gemcitabine · S-1 · CDDP · Second-line

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Introduction

Patients with advanced pancreatic cancer have an extremely poor prognosis. The reasons for the very high mortality rate of this disease are the difficulty of early diagnosis, low resectability by the time of initial diagnosis, and rapid recurrence after resection. Although surgical resection is the only method of increasing the survival time, there are relatively few patients with resectable pancreatic cancer. Macroscopically "curative" resection has been possible in 10%–15% of all patients.[1–4] Even when so-called curative surgery has been performed, there is usually recurrence shortly thereafter. In addition, no chemotherapy, radiotherapy, immunotherapy, or gene therapy has been established to which pancreatic cancer will respond.[5–9] Fluorouracil (5-FU) has been used as the main agent in most regimens.[10–13] The clinical benefits of chemotherapy for pancreatic cancer have been controversial. Recently, gemcitabine has been developed and it has been rapidly utilized for pancreatic cancer due to improved clinical results. Since Burris et al.[14] reported the clinical benefit of gemcitabine for advanced pancreatic cancer, this agent has been administered to patients with this disease as a first-line drug. Gemcitabine has replaced 5-FU for the treatment of pancreatic cancer. Although the study of Burris et al.[14] was a pivotal one, recent large-scale phase III studies have reported median survival durations in the gemcitabine treatment arm of 7.1[15] and 6.59 months.[16] More effective therapy is required for patients with pancreatic cancer. Since gemcitabine has been employed, no new regimen has been established for patients with recurrent pancreatic cancer. Recently, S-1, an oral drug consisting of the 5-FU prodrug tegafur, combined with two modulators of 5-FU activity, has been developed.[17–19] Several reports have been published regarding the administration of S-1 to patients with solid tumors.[20,21] Hayashi et al.[22] reported the effectiveness of administering S-1 to patients with pancreatic cancer. Also, several reports have been published of results achieved in patients with pancreatic cancer, using cisplatin (CDDP) in combination with gemcitabine.[23–26]

At our department, postoperative adjuvant chemotherapy using gemcitabine has been provided to patients who have undergone pancreatectomy. In the present study, we achieved a high response rate using S-1 plus CDDP as second-line treatment in gemcitabine-tolerant patients with recurrent pancreatic cancer.

Patients and methods

Eligibility criteria

The inclusion criteria were as follows: a histological diagnosis of invasive ductal pancreatic cancer; gemcitabine-resistant disease, defined as recurrent or progressive disease during at least one course of gemcitabine administration (1000 mg/m^2, once weekly for 3 consecutive weeks out of every 4 weeks); normal cardiac, hepatic, and renal function; white blood cell count of more than 3000/mm^3, platelet cell count of more than 10000/mm^3, and hemoglobin level of more than 9.0 g/dl. Patients were required to have a performance status (PS) of 2 or better on the Eastern Cooperative Oncology Group scale. The exclusion criteria were any major organ failure, second tumors, and active infectious disease. All of the patients gave their written informed consent. The age range was from 20 to 75 years.

Treatment schedule

S-1 (80 mg/m^2 per day) was orally administered for 21 consecutive days, followed by a 14-day rest period. CDDP (40 mg/m^2) in 500 ml saline was administered by intravenous drip as a 120-min infusion on day 8. This schedule was repeated every 5 weeks until the occurrence of disease progression, unacceptable toxicities, or the patient's refusal to continue. If grade 3 or higher hematological or grade 2 or higher nonhematological toxicity was observed, the rest period was prolonged until the toxicity had been alleviated.

Evaluation of responses and toxicity

Antitumor responses were evaluated in accordance with the World Health Organization criteria. Briefly, a complete response (CR) was defined as the complete disappearance of all measurable and assessable tumors for a minimum of 4 weeks. A partial response (PR) indicated a 50% or more reduction in the sum of the products of the longest diameters of all measurable disease for at least 4 weeks, without the appearance of any new lesions. Stable disease (SD) corresponded to a decrease of less than 50% in the sum of the products of the greatest perpendicular dimensions of measurable lesions or an increase of less than 25% in the sum of the products of the greatest perpendicular dimensions of measurable disease for a minimum of 3 months. Progressive disease (PD) was defined as a 25% or more increase in the sum of the products of the longest diameters of measurable disease or the appearance of any new lesion. Responses were also assessed according to reductions in serum carbohydrate antigen (CA) 19-9 levels, which were determined before the start of each course.

Survival, which was calculated by Kaplan-Meier method, was measured from the time of initiation of S-1 administration until death. Response duration was defined as the time from the documentation of response to the first observation of disease progression. Toxicity was evaluated according to the toxicity criteria of the National Cancer Institute-Common Toxicity Criteria version 2.0 (1999).

Statistical analysis

All statistical analyses were performed with StatView 5.0 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

From April 2003 to December 2005, 17 eligible patients were registered for this study (Table 1). There were 10 men and 7 women, with an age range of 46–73 years (median, 59.5 years). All patients who had undergone surgery were diagnosed as having invasive ductal pancreatic cancer (pancreatectomy, $n = 15$; biopsy, $n = 2$). Eleven patients had a pancreatoduodenectomy, 3 patients had a distal pancreatectomy, and 1 had a total pancreatectomy. The average operative time and blood loss were 453.2 min (range, 295–614 min) and 1008 ml (range, 310–3125 ml), respectively. The other 2 patients (patients 11 and 16) had a choledochojejunostomy and gastrojejunostomy without pancreatectomy, because of unresectable pancreatic cancer. The pathological stages of the 17 patients were as follows: stage III, $n = 8$; stage IVa, $n = 5$; and stage IVb $n = 4$. The residual tumor scores (R) of the 15 patients in whom pancreatectomy was performed are shown in Table 1. R0 indicates that curative resection was performed. R1 and R2 indicate that pathologically and macroscopically residual tumors were recognized, respectively. The distribution of R scores in the 15 patients who had undergone pancreatectomy were as follows: R0, in 11 patients; R1, in 3; and R2, in 1. All patients treated with gemcitabine (range, 4800–40 500 mg) had experienced recurrence, and were eligible for the assessment of response to S-1 with CDDP. The median disease-free survival of the 14 patients who had undergone macroscopically curative pancreatectomy was 7.8 months (range, 2–26 months). The other 3 patients (patients 11, 15, and 16) were excluded from disease-free survival analysis because of having a residual tumor before starting gemcitabine.

Response and outcome after S-1 plus CDDP

Seventeen patients were treated with S-1 (range, 1800–21 000 mg; mean, 7053.2 mg) and CDDP (range, 60–500 mg;

Table 1. Patients' characteristics

Patient	Age (years)	Sex	Method	Operation data Time (min)	Blood loss (g)	Pathology	Stage	R	GEM (mg)	DFS[a]
1	46	M	DP	426	799	Poor type	IVa	0	28800	7
2	46	F	PD	427	310	Moderate type	III	0	17500	7
3	46	F	PD	544	1994	Moderate type	IVa	0	5400	3
4	51	M	PD	406	725	Moderate type	IVa	0	37800	13
5	52	M	PD	473	530	Poor type	III	0	24000	6
6	54	F	PD	480	1284	Poor type	III	0	4800	4
7	58	M	PD	519	921	Moderate type	III	0	19200	7
8	61	F	PD	512	610	Derived from intraductal tumor	III	0	16500	3
9	62	M	TP	614	3125	Derived from intraductal tumor	III	0	21000	7
10	63	F	PD	518	1558	Moderate type	IVa	1	6200	2
11	64	M	CJ + GJ	295	424	Poor type	IVb	–	24000	–
12	64	M	PD	375	730	Moderate type	III	1	40500	26
13	65	M	PD	407	610	Poor type	III	1	5600	9
14	67	F	DP	500	510	Moderate type	IVa	0	19200	6
15	69	M	DP	446	1785	Moderate type	IVb	2	9600	–
16	72	F	CJ + GJ	340	792	Moderate type	IVb	–	16800	–
17	73	M	PD	422	440	Moderate type	IVb	0	32000	9

DP, distal pancreatectomy; PD, pancreaticoduodenectomy; TP, total pancreatectomy; CJ, choledochojejunostomy; GJ, gastrojejunostomy; R, rresidual tumor; GEM, gemcitabine; DFS, disease-free survival
[a]DFS in months

Table 2. Results of treatment with S-1 plus CDDP

Patient	S-1 (mg)	CDDP (mg)	Survival time (months)	Response	Outcome
1	5040	120	6	SD	Died
2	8240	240	20	PR	Alive
3	6300	150	12	SD	Died
4	4620	110	5	PD	Died
5	14700	350	16	PR	Died
6	7560	180	9	PR	Died
7	3360	80	8	PD	Died
8	4445	120	16	PD	Died
9	5040	120	4	PD	Died
10	21000	500	17	PR	Alive
11	6930	210	4	PD	Died
12	4200	100	4	PD	Alive
13	2730	65	3	PD	Died
14	5040	120	5	PD	Died
15	1890	60	3	PD	Died
16	10080	240	10	PR	Died
17	8820	210	19	PD	Died

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

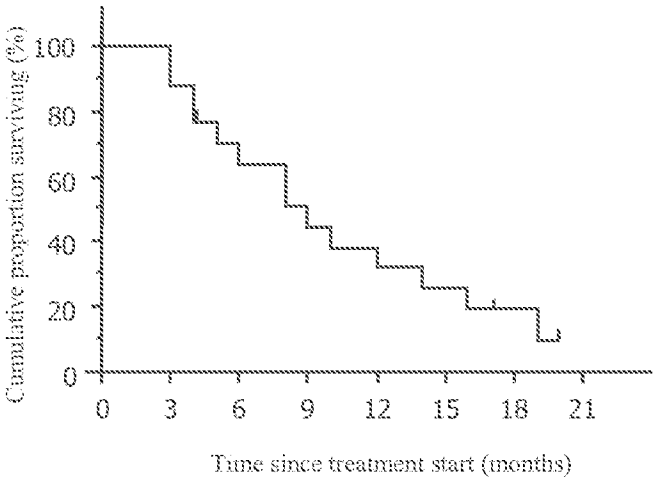

Fig. 1. Survival of the 17 patients with gemcitabine-resistant pancreatic cancer who were treated with S-1 and cisplatin. The median survival was 9 months, with 63.7% and 31.9 % of the patients alive at 6 months and 12 months, respectively. Survival was determined by the Kaplan-Meier product method

mean, 175.6 mg), as shown in Table 2. At the time of the writing of this report, 14 patients with progressive disease had died, and 3 patients were still alive. The average observation period of all 17 patients was 9.5 months (range, 3–20 months). Five of the 17 patients (29.4%; 95% confidence interval, 5.3%–53.6%) had PRs, which were evident on computed tomography (CT). One of these patients (patient 2 in Tables 1 and 2), who had lymph node recurrence around the superior mesenteric artery, showed a PR on CT. The lymph nodes of this patient had disappeared from the positron emission tomography (PET) scans. The median survival of all 17 patients in the study was 9 months, with 63.7% and 31.9% of the patients alive at 6 and 12 months, respectively (Fig. 1). One of the 2 patients (patient 16) who had undergone choledochojejunostomy and gastrojejunostomy had a PR for 5 months, and survived for 10 months. None of the patients had symptomatic pain before S-1 plus CDDP treatment. None underwent secondary surgery. There was no correlation between the disease-free survival time and survival time after this second-line chemotherapy (data not shown). The median survival (14.4 months) of the 5 patients who had a PR was significantly longer than the median survival (7.5 months) of the other 12 patients, who had SD or PD ($P = 0.0197$).

Serum CA19-9 level during the administration of S-1 and CDDP

All patients were evaluated for the serum CA19-9 level at the start of S-1 and CDDP administration; 15 patients (88.2%) had elevated serum CA19-9 levels. Two patients were excluded because of a normal CA 19-9 level at the start of this regimen. One of the 2 patients who had a normal CA 19-9 level had a PR, and the other had PD. In 4 of the 5 patients who achieved a PR (Fig. 2A) and 1 patient with SD (Fig. 2B) the CA19-9 level was reduced by more than 50%. None of the patients who showed a reduction of more than 50% in the serum CA19-9 level were included in the 9 patients with PD (Fig. 2C).

Toxicity

All 17 patients were evaluated for toxicity. There were no episodes of sepsis and no treatment-related fatalities. Myelotoxicity, specifically leucopenia, was the major toxicity observed as a result of this chemotherapy (Table 3). Only one patient (5.9%) developed grade 3 leucopenia. There was no grade 4 toxicity. Nausea was observed in 58.8% of the patients (10/17). Nonhematological toxicity exceeding grade 2 was not observed (Table 3).

Discussion

The long-term effects of adjuvant chemotherapy in pancreatic cancer have been unclear. Recently, the European Study Group for Pancreatic Cancer 1 Trial has reported a survival benefit of adjuvant chemotherapy with leucovorin and 5-FU.[27] Gemcitabine has been used for patients with pancreatic cancer as a first-line drug, since Burris et al.[14] reported its clinical benefit in patients with advanced pancreatic cancer. Although the survival has been prolonged, the median time to progressive disease was only 9 weeks for

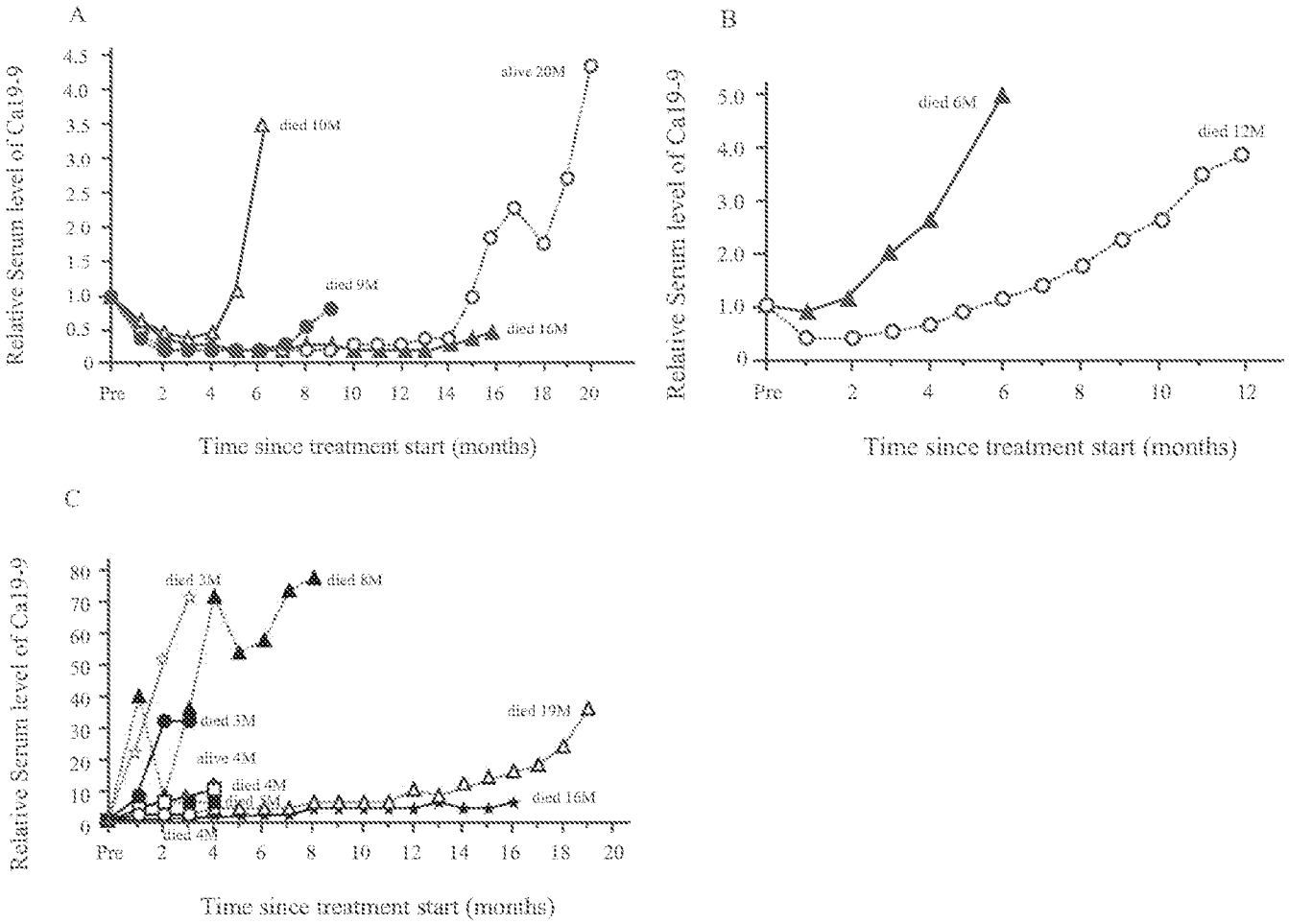

Fig. 2A–C. Relative serum carbohydrate antigen 19-9 (*CA 19-9*) levels in 15 patients whose CA 19-9 levels were elevated at the start of treatment with S-1 and CDDP. From the start of treatment, 4 patients achieved a partial response (**A**), 2 had stable disease (**B**), and 9 had progressive disease (**C**). Two patients were excluded because of a normal level of CA19-9 at treatment start. **A** Three patients died 16, 10, and 9 months, respectively, after the treatment started, and 1 is still alive. **B** The 2 patients died 6 and 12 months, respectively, after the treatment with S-1 and CDDP started. **C** Of the 9 patients with progressive disease, 1 patient is still alive, while 8 patients died

Table 3. Toxicity in 17 patients in whom S-1 plus CDDP was administered

	National Cancer Institute – Common toxicity criteria	
	Grade 1–2 # (%)	Grade 3 # (%)
Leucopenia	4 (23.5)	1 (5.9)
Thrombocytopenia	1 (5.9)	0
Anemia	1 (5.9)	0
Nausea	10 (58.8)	0
Diarrhea	4 (23.5)	0
Anorexia	2 (11.8)	0
Anastomotic ulcer	1 (5.9)	0
Vomiting	1 (5.9)	0
Pigmentation	3 (17.6)	–

gemcitabine. Most patients show cancer progression within 6 months. Recently, large-scale studies in patients with advanced or metastatic pancreas cancer have been reported, although no report has been published that showed the effects of gemcitabine on adjuvant regimens. However, gemcitabine is widely used for adjuvant chemotherapy in patients with pancreatic cancer to improve survival. In fact, there are regional and/or distant recurrences in many patients, even in those who have been treated with gemcitabine. A new regimen, so-called second-line treatment, is needed for patents with gemcitabine-resistant pancreatic cancer.[28]

In the present study, we administered S-1 plus CDDP to patients with invasive ductal pancreatic carcinoma, which had been histologically diagnosed and which was resistant to gemcitabine. Five of the 17 patients (29.4%) achieved PRs as a result. The median survival time after the treatment started was 9 months (Fig. 1). Hayashi et al.[22] used S-1 with CDDP for 16 patients with advanced or recurrent pancreatic cancer as a first-line regimen. Their patients were treated with S-1 for 21 consecutive days plus CDDP 30 mg/m^2 on day 1 and day 8, followed by a 14-day rest period. They reported that 3 patients (18.8%) showed over grade 3 hematological toxicity and 2 (12.5%) showed unacceptable nonhematological toxicity. Recently, Koizumi et al.[29] reported a phase I/II study of S-1 (80 mg/m^2, on 21 consecutive days followed by a 14-day rest) combined with cisplatin (60 mg/m^2 on day 8) in patients with advanced gastric cancer as a first-line regimen. In our study, all patients who were administered S-1 and CDDP had recurrent and progressive pancreas cancer, although they had been treated with gemcitabine. In our study, to avoid severe toxicities, CDDP was administered at 40 mg/m^2 on day 8, 5 weeks after the beginning of S-1 administration.

Interestingly, in our study, there was no correlation between the disease-free survival time, which may indicate the effects of gemcitabine, and the survival time after the administration of S-1 plus CDDP. As noted, S-1 is an oral drug consisting of tegafur, which is a prodrug of 5-FU, combined with two modulators of 5-FU activity. Our data suggest that there are some patients with gemcitabine-resistant disease who respond well to S-1 and CDDP. We have shown that gemcitabine-resistant human pancreatic cancer cells have only partial cross-resistance to 5-FU in vitro.[30] No biomarker has been identified yet that induces resistance to gemcitabine as well as 5-FU does. Further investigations should be carried out to establish the mechanisms of cross-resistance to 5-FU and gemcitabine. Furthermore, a new regimen that includes both S-1 and gemcitabine may have a survival benefit both in patients with resected and in those with nonresectable pancreatic cancer.

Several studies have indicated that the addition of CDDP to gemcitabine significantly improved the response rate in patients with advanced pancreatic cancer, compared to gemcitabine alone.[23–26] In the present study, we used CDDP for all patients, in addition to S-1, because no patient had been administered CDDP at the start of second-line drug administration. In this series, no unacceptable hematological or nonhematological toxicities were observed (Table 3).

In conclusion, in patients with gemcitabine-resistant pancreatic cancer, the combination of S-1 and CDDP was well tolerated, and a high level of response was observed. To clarify the effects of S-1, further studies should be performed; especially important would be a prospective randomized trial of gemcitabine and S-1.

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