National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pancreatic Adenocarcinoma

Version 2.2025 — February 3, 2025

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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Pancreatic Adenocarcinoma Panel Members
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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2025 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2025 include:

PANC-F 8 OF 13
- Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease
  - Good PS 0–1, Useful in Certain Circumstances
    - ◊ 5th bullet added: Zenocutuzumab-zbco (if NRG1 gene fusion-positive) (Also for Intermediate PS 2 on PANC-F 9 of 13)
- Footnote q added: For disease progression on or after prior systemic therapy. (Also for PANC-F 9 of 13)

Updates in Version 1.2025 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 3.2024 include:

General
- References updated across the guidelines.

INTRO
- Opening statement modified: Decisions about *diagnosis, resectability, and* ~~diagnostic~~ management ~~and resectability~~ should involve multidisciplinary consultation at a high-volume center with use of appropriate imaging studies.

PANC-1
- Clinical Presentation And Workup
  - No metastatic disease, 4th bullet modified: Consider PET/CT or PET/MRI in patients with high-risk *features*

PANC-1A
- Footnote e modified: PET/CT *or PET/MRI* scan may be considered after formal pancreatic CT protocol in patients with high risk features to detect extra-pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT.
- Footnote g modified: Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary *obstruction*, infection (cholangitis), or inflammation, ~~or obstruction,~~ benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (*consider obtaining* carcinoembryonic antigen [CEA] and CA-125 in patients who are nonsecreting or those with normal CA 19-9 levels).(Also PANC-2, PANC-3, PANC-4, PANC-8)
- Footnote j modified: Tumor/somatic molecular profiling, *preferably using a next-generation sequencing (NGS) assay,* is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify *clinically actionable and/or emerging alterations* ~~uncommon mutations~~. *These alterations include,* ~~Consider specifically testing for potentially actionable somatic findings including,~~ but are not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), amplifications (HER2), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) *using comprehensive genomic profiling* via an FDA-approved and/or validated ~~next-generation sequencing (~~NGS~~)~~-based assay, and HER2 overexpression via IHC ± *FISH*. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. See Discussion and Principles of Cancer Risk Assessment and Counseling (PANC-I). (Also PANC-5, PANC-6A, PANC-9A, PANC-10, PANC-11)

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Updates in Version 1.2025 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 3.2024 include:

PANC-2
- Resectable disease
  - Neoadjuvant therapy with or without high-risk features (followed by surgery), 2nd bullet modified: ~~Consider~~ Stent *placement* if clinically indicated
  - New pathway added: Medically inoperable
- Footnote l added: Tumor/somatic molecular profiling if clinically indicated.
- Footnote o modified: For neoadjuvant therapy, consider PET/CT *or PET/MRI* scan before and after initiation to assess response to systemic therapy and for restaging. (Also PANC-3)

PANC-6A
- Footnote bb modified: Based on LAP-07 trial data *in locally advanced disease*, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy (Hammel P, et al. JAMA 2016;315:1844-1853).

PANC-8
- Postoperative Adjuvant Treatment
  - No prior neoadjuvant therapy, No evidence of recurrence or metastatic disease
    - ◊ 3rd option modified: Chemotherapy followed by chemoradiation *as clinically indicated*
  - Prior neoadjuvant therapy, No evidence of recurrence or metastatic disease
    - ◊ 2nd option modified: Consider chemoradiation *as clinically indicated* ~~in the instance of a positive margin R1 resection~~
- Footnote ff modified: If considering chemoradiation ~~due to positive margins~~, *neoadjuvant or adjuvant* chemotherapy should be given prior to the administration of chemoradiation.
- Footnote gg modified: *RTOG 0848 showed survival benefit using postoperative RT in patients with node negative disease and who received single agent systemic therapy. Abrams R, et al. J Clin Oncol 2024;42(16 Suppl):Abstract 4005; Herman JM, et al. J Clin Oncol 2008;26:3503-3510; Corsini MM, et al. J Clin Oncol 2008;26:3511-3516; Merchant NB, et al. J Am Coll Surg 2009;208:829-838; Parikh AA, et al. J Am Coll Surg 2016;222:448-456* ~~Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy (Hammel P, et al. JAMA 2016;315:1844-1853)~~.

PANC-9
- Recurrence after resection
  - Local recurrence, Pancreatic operative bed
    - ◊ 2nd option modified: Systemic therapy ± chemoradiation or SBRT (if not previously done) (see options on PANC-12 ~~for ≥6 or <6 mo from completion of primary therapy~~)

PANC-9A
- Footnote removed: Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy (Hammel P, et al. JAMA 2016;315:1844-1853).

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Updates in Version 1.2025 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 3.2024 include:

PANC-10
- Metastatic disease
  - Maintenance Therapy
    - ◊ 1st option modified: Principles of Systemic Therapy (PANC-F 7 of 13) ± *Metastasis-directed therapy at a high-volume center*
- Footnote ll added: In rare circumstances when patients have indolent/oligometastatic disease, they should be referred to a high-volume center to be evaluated for possible metastatic-directed therapy. Ludmir EB, et al. J Clin Oncol 2024;42(3 Suppl):Abstract 603. (Also PANC-12)

PANC-A 2 OF 8
- Principles of Diagnosis, Imaging and Staging
  - 1st bullet modified: PET/CT or PET/MRI scan may be considered after formal pancreatic CT protocol in patients with high-risk *features* to detect extrapancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT.
  - 2nd bullet modified: For neoadjuvant therapy, consider PET/CT *or PET/MRI* scan before and after initiation to assess response to systemic therapy and for restaging.
- Footnote b modified: Indicators of patients with high risk *features* may include equivocal or indeterminate imaging findings, ~~borderline resectable disease,~~ markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes.

PANC-B
- Principles of Obstructive Jaundice and Tissue Acquisition Management
  - Biliary Drainage
    - ◊ 1st bullet modified: Biliary drainage is not routinely recommended prior to planned *upfront* surgery. However, this decision is best made in a multidisciplinary discussion.

PANC-C 1 OF 2
- Criteria Defining Resectability Status At Diagnosis
  - Locally Advanced, Venous
    - ◊ 1st Bullet added: Not currently amenable to resection and primary reconstruction due to complete occlusion of SMV/PV
    - ◊ Bullet removed: Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus).
- Footnote d added: Locally advanced does not imply unresectable tumor.

PANC-C 2 OF 2
- Criteria For Resection Following Neoadjuvant Therapy
  - Following neoadjuvant therapy
    - ◊ 1st bullet added: For neoadjuvant therapy, consider PET/CT or PET/MRI scan before and after initiation to assess response to systemic therapy and for restaging.

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Updates in Version 1.2025 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 3.2024 include:

PANC-F 1 OF 13
- General Principles
  - 3rd bullet modified: Consider testing for potentially actionable somatic findings including, but not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), amplifications (HER2), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) *using comprehensive genomic profiling* via an FDA-approved and/or validated NGS-based assay, and HER2 overexpression via IHC ± *FISH*.
  - 8th bullet added: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

PANC-F 5 OF 13
- Metastatic Disease (First-Line Therapy)
  - 1st bullet added: Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology). (Also PANC-F 6 of 13)
  - Bullet removed: Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes. (Also PANC-F 6 of 13)

PANC-F 6 OF 13
- Metastatic Disease (First-Line Therapy)
  - Intermediate PS 2
    - Preferred Regimens
      - Bullet removed: If unable to tolerate FOLFIRINOX, consider
  - Poor PS 3
    - Preferred Regimens
      - 1st bullet added: Palliative and best supportive care
      - The following regimens moved to Other Recommended Regimens:
        - Capecitabine
        - Continuous infusion 5-FU
        - Gemcitabine
- Footnote k added: Evidence suggest patients with poor PS derive marginal benefit from systemic therapy. See Principles of Palliation and Supportive Care (PANC-H).

PANC-F 8 OF 13
- Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease
  - Good PS 0–1, Useful in Certain Circumstances
    - 3rd bullet added: Erdafitinib (if FGFR genetic alterations)
    - 4th bullet modified: Fam-trastuzumab deruxtecannxki (if HER2 positive [IHC3+ *or IHC2+ with FISH HER2 amplified*])

PANC-F 9 OF 13
- This page was extensively revised.

PANC-F 10 OF 13
- This page was extensively revised.

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Updates in Version 1.2025 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 3.2024 include:

PANC-G 2 OF 6

- Treatment Planning: Radiation Delivery
  - Simulation, 3rd bullet modified: *Unless there is a contraindication to IV contrast,* CT simulation (2- to 3-mm slices) *should be* ~~is often~~ performed with IV contrast *whenever feasible* (assuming adequate kidney function) ~~and oral contrast may also be utilized~~. Multiphase IV contrast delivery *is preferred whenever possible to* ~~may~~ facilitate disease delineation. MRI imaging may be complementary to CT in target delineation. *Neutral oral contrast may also be utilized.*
  - Planning, Dose and Fractionation, 1st bullet modified: 3-D conformal RT (3D-CRT), intensity-modulated RT (IMRT), and SBRT can result in improved planning target volume (PTV) coverage with decreased dose to OARs. *IMRT is preferred over 3D-CRT for conventional or hypofractionated RT, particularly if dose escalation is being considered.* The exact planning strategy used should be individualized to patient anatomy, clinical scenario, treatment goals, and dose goals.

PANC-G 4 OF 6

- Recommendations Based on Treatment Setting
  - Locally Advanced
    - RT Dosing/Planning
      - 1st bullet modified: For chemoradiation, RT dose generally consists of 45–*56* ~~54~~ Gy in 1.8–*2.2* ~~2.0~~ Gy fractions.
  - Recurrent Pancreatic Cancer (pancreatic bed)
    - RT Dosing/Planning
      - 1st bullet modified: For chemoradiation, RT dose generally consists of 45–*56* ~~54~~ Gy in 1.8–*2.2* ~~2.0~~ Gy fractions.

PANC-H 1 OF 2

- Principles Of Palliation And Supportive Care
  - Gastric outlet/duodenal obstruction
    - 3rd bullet added: Endoscopic ultrasound-guided gastrojejunostomy at a high-volume center especially if patient is not a surgical candidate
  - Exocrine pancreatic insufficiency and malnutrition
    - 1st bullet, 1st sub bullet added: Starting dose of at least 48,000 units lipase with meals (preferably 72,000)

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INTRODUCTION

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

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

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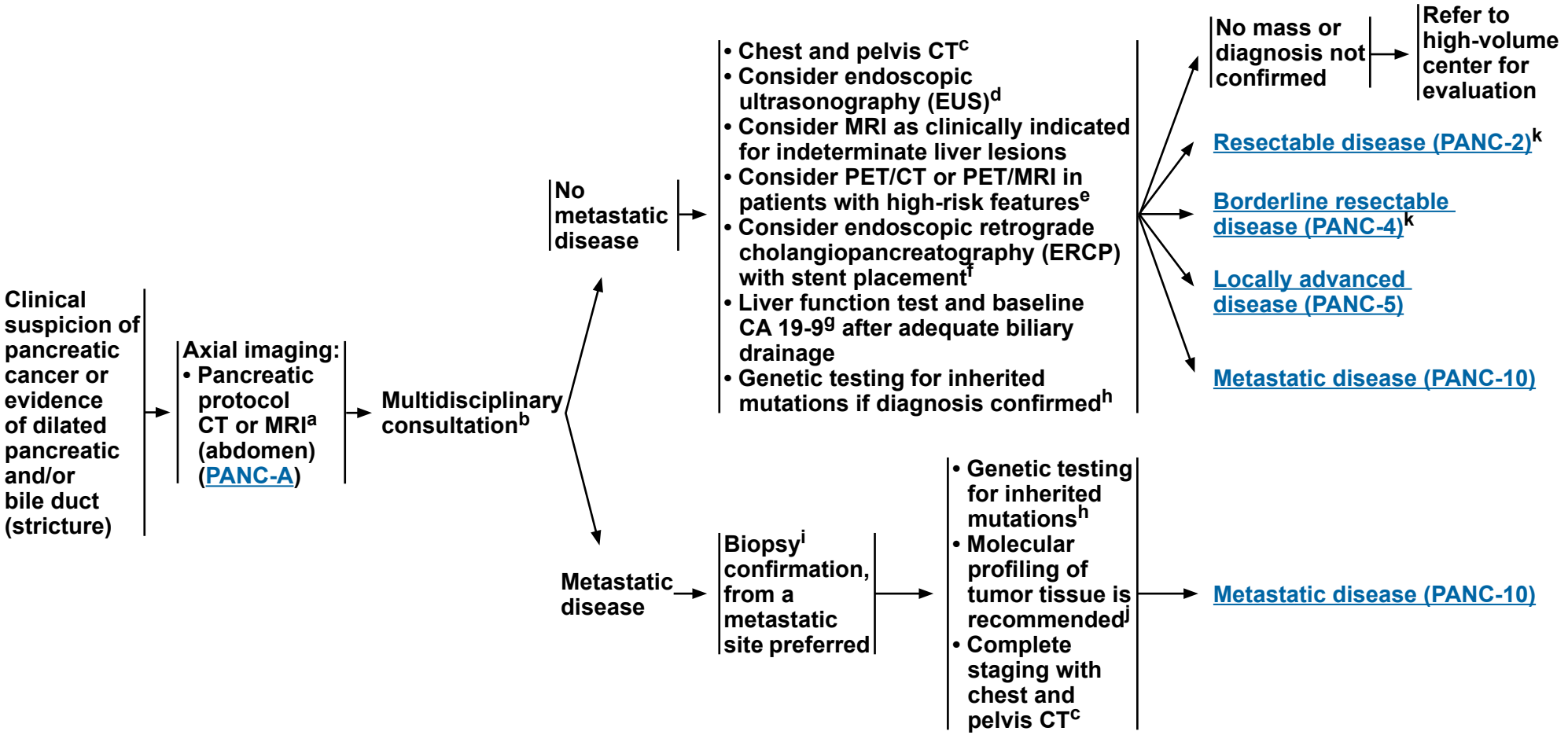
CLINICAL PRESENTATION AND WORKUP



Footnotes on PANC-1A

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FOOTNOTES

[a] MRI of high quality could be substituted.
[b] Multidisciplinary review should consider involving expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, pathology, geriatric medicine, genetic counseling, and palliative care (see Principles of Palliation and Supportive Care [PANC-H]). Consider consultation with a registered dietitian. See NCCN Guidelines for Older Adult Oncology and NCCN Guidelines for Palliative Care.
[c] Imaging with contrast as appropriate for disease management (unless contraindicated).
[d] EUS to confirm primary site of involvement; EUS-guided biopsy if clinically indicated.
[e] PET/CT or PET/MRI scan may be considered after formal pancreatic CT protocol in patients with high risk features to detect extra-pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT.
[f] Principles of Obstructive Jaundice and Tissue Acquisition Management (PANC-B).
[g] Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary obstruction, infection (cholangitis), or inflammation, benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (consider obtaining carcinoembryonic antigen [CEA] and CA-125 in patients who are nonsecreting or those with normal CA 19-9 levels).
[h] Genetic testing for inherited mutations is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2*, *MSH6, PALB2, PMS2, STK11,* and *TP53*) or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. See Discussion and NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[i] Core biopsy is recommended, if possible, to obtain adequate tissue for possible ancillary studies.
[j] Tumor/somatic molecular profiling, preferably using a next-generation sequencing (NGS) assay, is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify clinically actionable and/or emerging alterations. These alterations include, but are not limited to: fusions (*ALK, NRG1, NTRK, ROS1, FGFR2,* and *RET*), mutations (*BRAF, BRCA1/2, KRAS,* and *PALB2*), amplifications (*HER2*), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) using comprehensive genomic profiling via an FDA-approved and/or validated NGS-based assay, and HER2 overexpression via IHC ± FISH. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. See Discussion and Principles of Cancer Risk Assessment and Counseling (PANC-I).
[k] Criteria Defining Resectability Status at Diagnosis (PANC-C).

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

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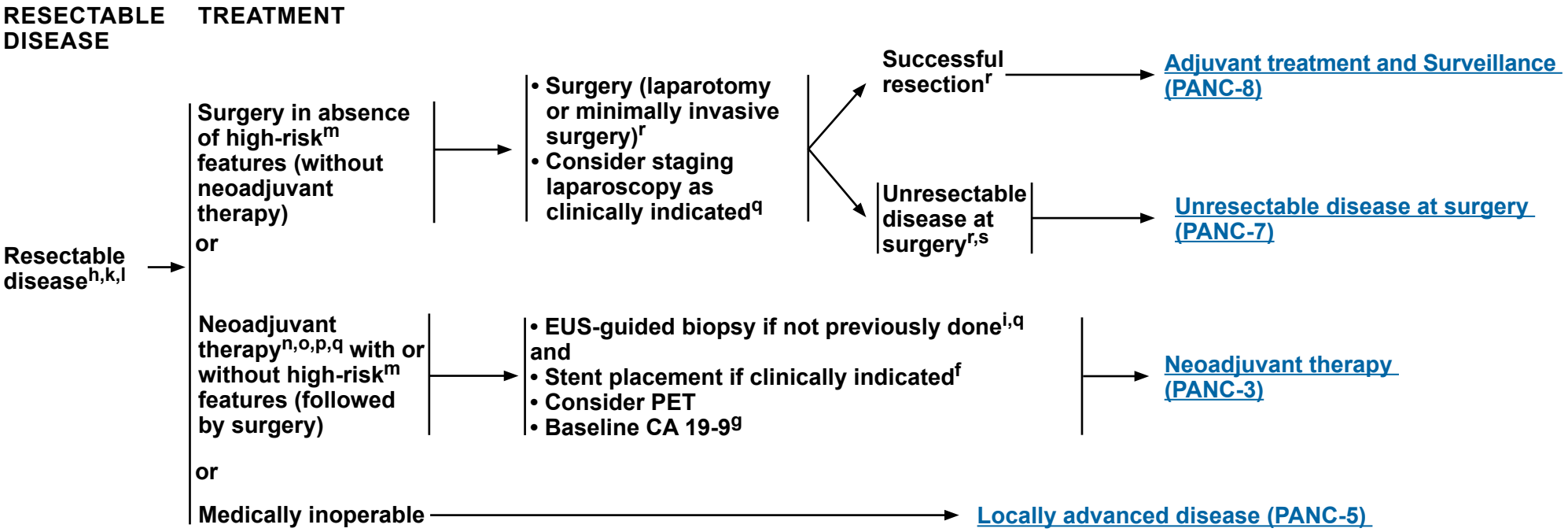

[f] Principles of Obstructive Jaundice and Tissue Acquisition Management (PANC-B).

[g] Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary obstruction, infection (cholangitis), or inflammation, benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (consider obtaining CEA and CA-125 in patients who are nonsecreting or those with normal CA 19-9 levels).

[h] Genetic testing for inherited mutations is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2*, *MSH6, PALB2, PMS2, STK11,* and *TP53*) or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. See Discussion and NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.

[i] Core biopsy is recommended, if possible, to obtain adequate tissue for possible ancillary studies.

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

[l] Tumor/somatic molecular profiling if clinically indicated.

[m] High-risk features include equivocal or indeterminate imaging findings, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, and extreme pain.

[n] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Subsequent chemoradiation is sometimes included. Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center.

[o] For neoadjuvant therapy, consider PET/CT or PET/MRI scan before and after initiation to assess response to systemic therapy and for restaging.

[p] First-line neoadjuvant systemic therapy for up to 6 months pre- or perioperatively.

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

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

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

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

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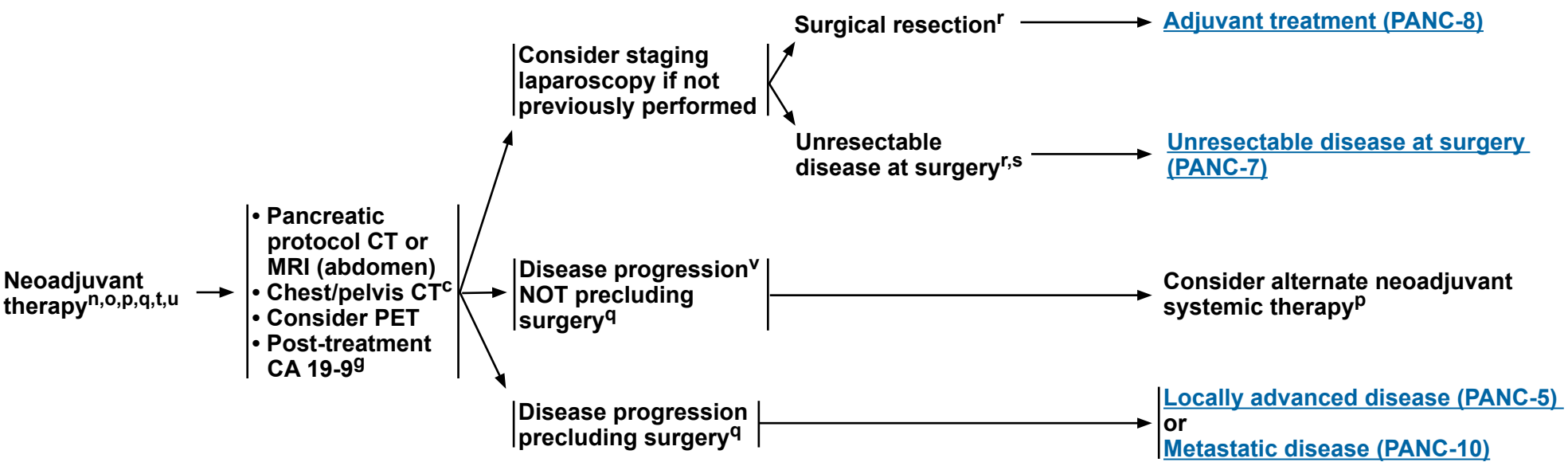
NEOADJUVANT THERAPY



[c] Imaging with contrast as appropriate for disease management (unless contraindicated).
[g] Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary obstruction, infection (cholangitis), or inflammation, benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (consider obtaining CEA and CA-125 in patients who are nonsecreting or those with normal CA 19-9 levels).
[n] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Subsequent chemoradiation is sometimes included. Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center.
[o] For neoadjuvant therapy, consider PET/CT or PET/MRI scan before and after initiation to assess response to systemic therapy and for restaging.
[p] First-line neoadjuvant systemic therapy for up to 6 months pre- or perioperatively.
[q] Principles of Diagnosis, Imaging, and Staging (PANC-A).
[r] Principles of Surgical Technique (PANC-D) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-E).
[s] Principles of Palliation and Supportive Care (PANC-H).
[t] Principles of Systemic Therapy (PANC-F).
[u] Principles of Radiation Therapy (PANC-G).
[v] Disease progression is defined by rising CA 19-9 or enlargement of the mass.

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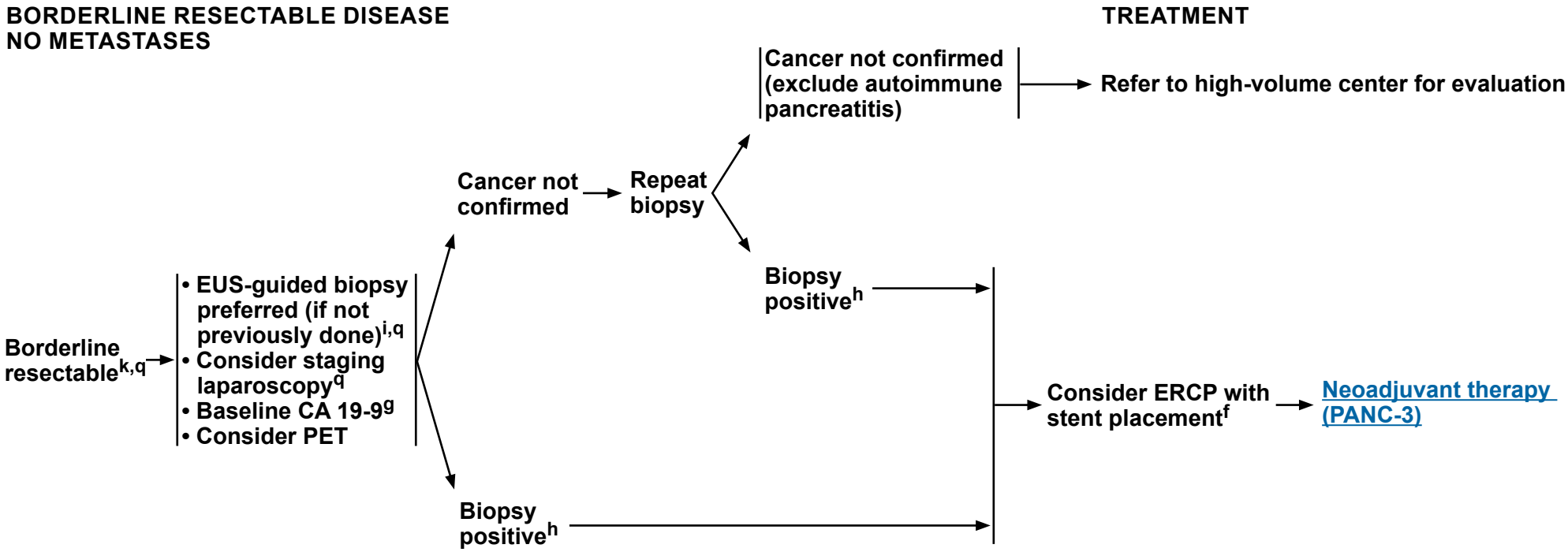

[f] Principles of Obstructive Jaundice and Tissue Acquisition Management (PANC-B).
[g] Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary obstruction, infection (cholangitis), or inflammation, benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (consider obtaining CEA and CA-125 in patients who are nonsecreting or those with normal CA 19-9 levels).
[h] Genetic testing for inherited mutations is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2*, *MSH6, PALB2, PMS2, STK11,* and *TP53*) or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. See Discussion and NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[i] Core biopsy is recommended, if possible, to obtain adequate tissue for possible ancillary studies.
[k] Criteria Defining Resectability Status at Diagnosis (PANC-C).
[q] Principles of Diagnosis, Imaging, and Staging (PANC-A).

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

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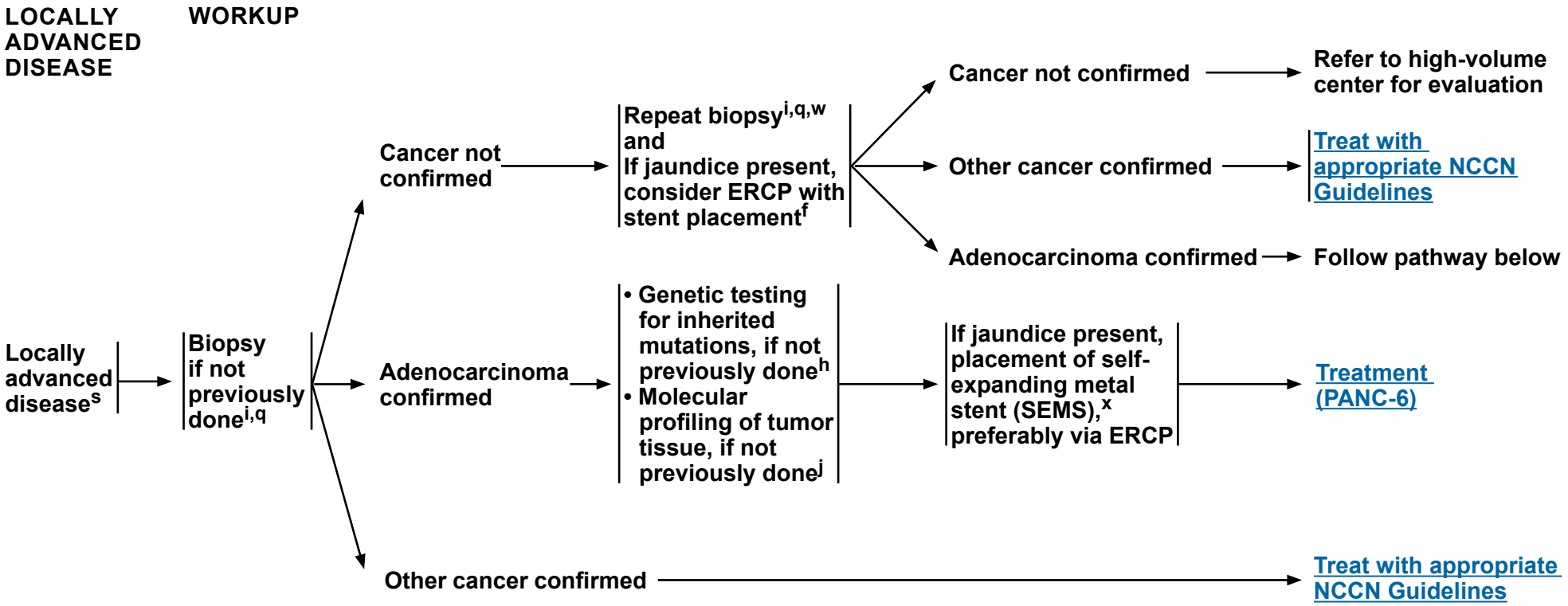

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[j] Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify clinically actionable and/or emerging alterations. These alterations include, but are not limited to: fusions (*ALK, NRG1, NTRK, ROS1, FGFR2,* and *RET*), mutations (*BRAF, BRCA1/2, KRAS,* and *PALB2*), amplifications (*HER2*), MSI, dMMR, or TMB using comprehensive genomic profiling via an FDA-approved and/or validated NGS-based assay, and HER2 overexpression via IHC ± FISH. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. See Discussion and Principles of Cancer Risk Assessment and Counseling (PANC-I).

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

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

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

[x] Unless biliary bypass was performed at the time of laparoscopy or laparotomy.

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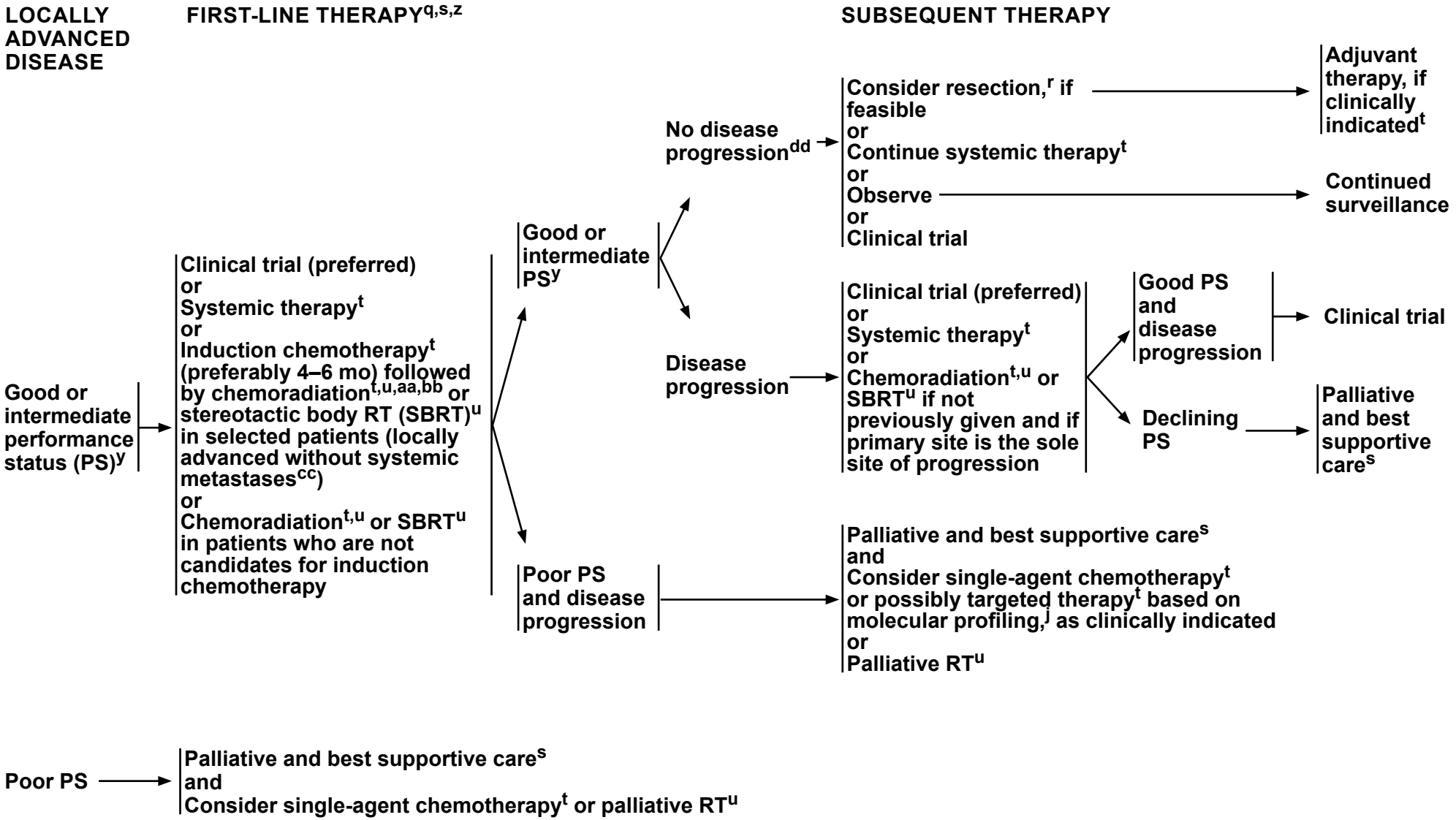

Footnotes on PANC-6A

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FOOTNOTES

[j] Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify clinically actionable and/or emerging alterations. These alterations include, but are not limited to: fusions (*ALK, NRG1, NTRK, ROS1, FGFR2,* and *RET*), mutations (*BRAF, BRCA1/2, KRAS,* and *PALB2*), amplifications (*HER2*), MSI, dMMR, or TMB using comprehensive genomic profiling via an FDA-approved and/or validated NGS-based assay, and HER2 overexpression via IHC ± FISH. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. See Discussion and Principles of Cancer Risk Assessment and Counseling (PANC-I).

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

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

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

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

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

[y] Good PS is defined as ECOG 0–1, with good biliary drainage and adequate nutritional intake, and intermediate PS is defined as ECOG 2.

[z] Serial imaging as indicated to assess disease response.

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

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

[cc] Laparoscopy as indicated to evaluate distant disease.

[dd] In the presence of marked radiographic improvement, the patient should be referred to a high-volume center for consideration of surgery. However, the primary site often does not regress radiographically even in the setting of effective treatment. If there is radiographic stability and marked clinical improvement or decline in CA 19-9, the patient should still be referred for evaluation.

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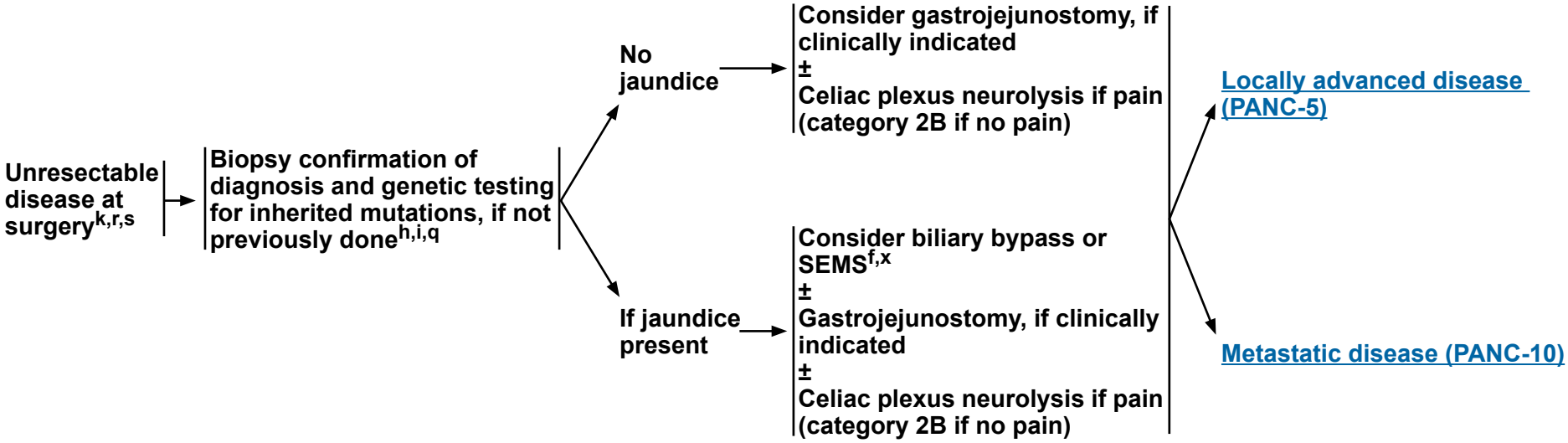
UNRESECTABLE DISEASE AT SURGERY

TREATMENT



[f] Principles of Obstructive Jaundice and Tissue Acquisition Management (PANC-B).
[h] Genetic testing for inherited mutations is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11,* and *TP53*) or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. See Discussion and NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[i] Core biopsy is recommended, if possible, to obtain adequate tissue for possible ancillary studies.
[k] Criteria Defining Resectability Status at Diagnosis (PANC-C).
[q] Principles of Diagnosis, Imaging, and Staging (PANC-A).
[r] Principles of Surgical Technique (PANC-D) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-E).
[s] Principles of Palliation and Supportive Care (PANC-H).
[x] Unless biliary bypass was performed at the time of laparoscopy or laparotomy.

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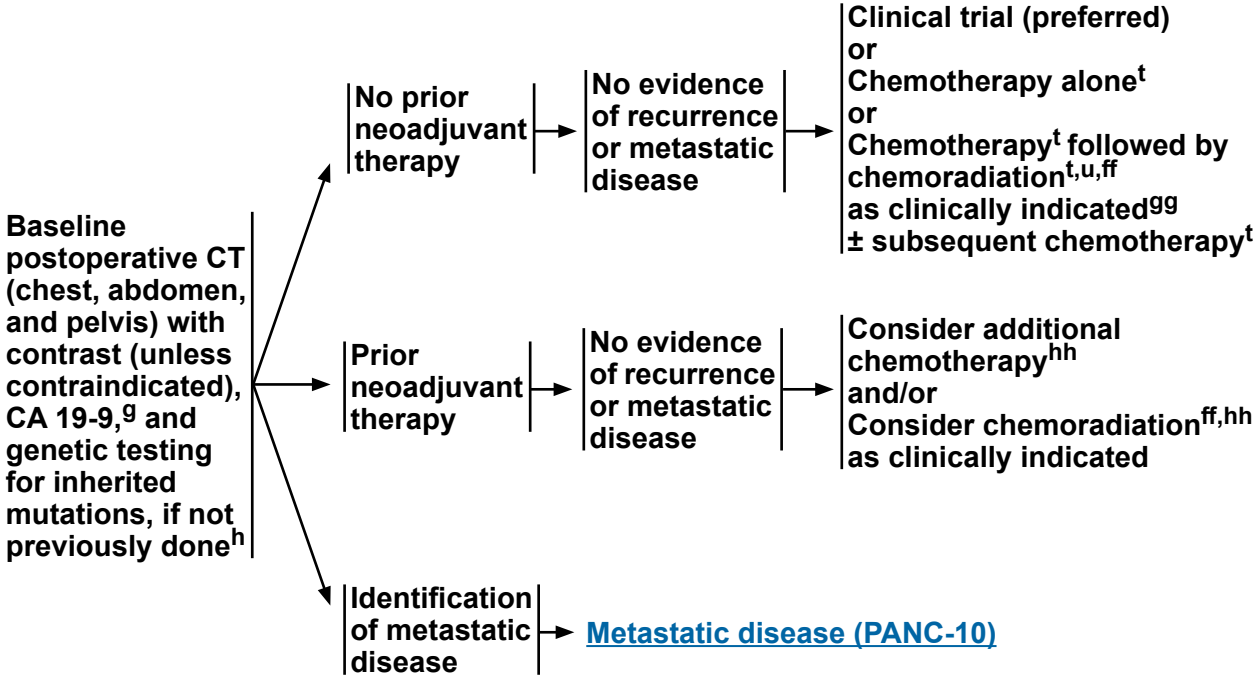
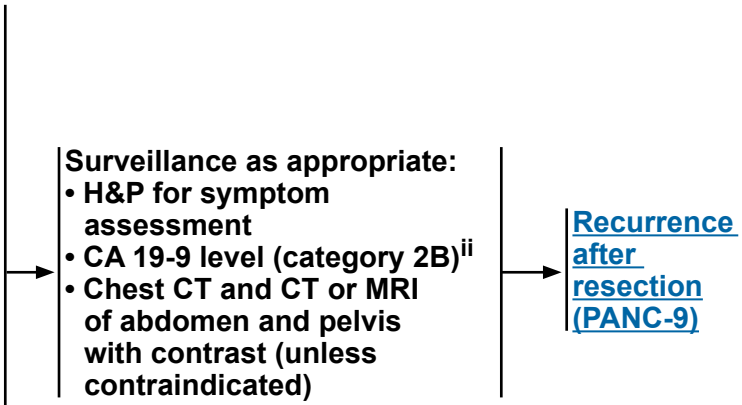
POSTOPERATIVE ADJUVANT TREATMENT[ee]



SURVEILLANCE



[g] Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary obstruction, infection (cholangitis), or inflammation, , benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (consider obtaining CEA and CA-125 in patients who are nonsecreting or those with normal CA 19-9 levels).

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

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

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

[ff] If considering chemoradiation, neoadjuvant or adjuvant chemotherapy should be given prior to the administration of chemoradiation.

[gg] RTOG 0848 showed survival benefit using postoperative RT in patients with node negative disease and who received single agent systemic therapy. Abrams R, et al. J Clin Oncol 2024;42(16 Suppl):Abstract 4005; Herman JM, et al. J Clin Oncol 2008;26:3503-3510; Corsini MM, et al. J Clin Oncol 2008;26:3511-3516; Merchant NB, et al. J Am Coll Surg 2009;208:829-838; Parikh AA, et al. J Am Coll Surg 2016;222:448-456.

[hh] Patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy (or chemoradiation if none was delivered neoadjuvantly) following surgery and multidisciplinary review. The adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations. Total duration of systemic therapy is typically 6 months.

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

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RECURRENCE AFTER RESECTION

Recurrence after resection →
- Consider biopsy for confirmation (category 2B)
- Genetic testing for inherited mutations, if not previously done[h]
- Molecular profiling of tumor tissue[j]

→ Local recurrence
- → Pancreas only → Surgical consultation and multidisciplinary review,[b] Principles of Surgical Techniques (PANC-D)
- → Pancreatic operative bed → Clinical trial (preferred) or Systemic therapy[t] ± chemoradiation[t,u,aa] or SBRT[u] (if not previously done) (see options on PANC-12) or SBRT[u] or Palliative and best supportive care[s]

→ Metastatic disease with or without local recurrence[jj] → Recurrence therapy for metastatic disease (PANC-12)

RECURRENCE THERAPY[kk]

Footnotes on PANC-9A

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FOOTNOTES

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

[h] Genetic testing for inherited mutations is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2*, *MSH6, PALB2, PMS2, STK11,* and *TP53*) or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. See Discussion and NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.

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

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

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

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

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

[kk] Best reserved for patients who maintain a good PS.

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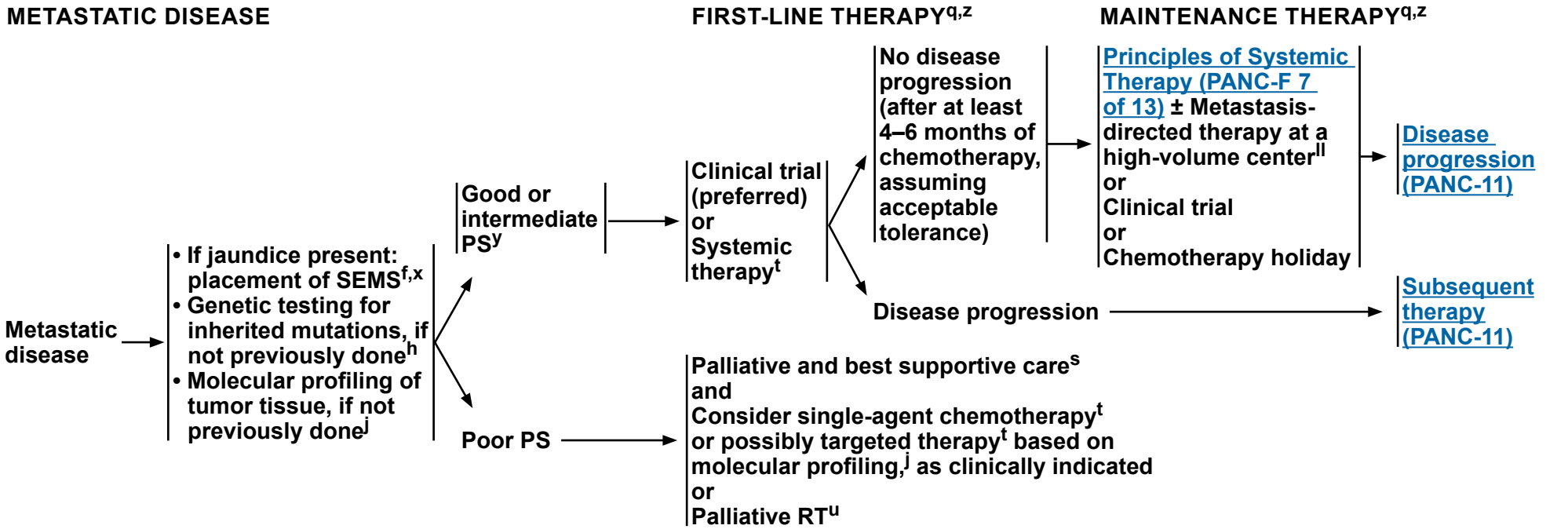

[f] Principles of Obstructive Jaundice and Tissue Acquisition Management (PANC-B).

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

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

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

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

[x] Unless biliary bypass was performed at the time of laparoscopy or laparotomy.

[y] Good PS is defined as ECOG 0–1, with good biliary drainage and adequate nutritional intake, and intermediate PS is defined as ECOG 2.

[z] Serial imaging as indicated to assess disease response.

[ll] In rare circumstances when patients have indolent/oligometastatic disease, they should be referred to a high-volume center to be evaluated for possible metastatic directed therapy. Ludmir EB, et al. J Clin Oncol 2024;42(3 Suppl):Abstract 603.

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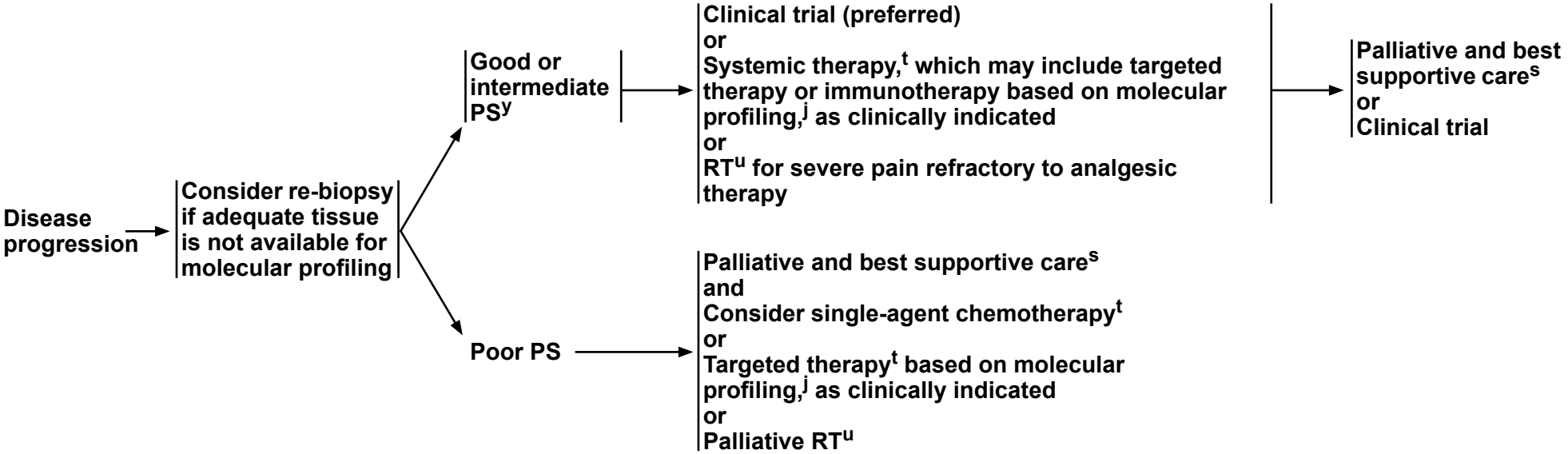
DISEASE PROGRESSION

SUBSEQUENT THERAPY[q,z]



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[q] Principles of Diagnosis, Imaging, and Staging (PANC-A).
[s] Principles of Palliation and Supportive Care (PANC-H).
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[u] Principles of Radiation Therapy (PANC-G).
[y] Good PS is defined as ECOG 0–1, with good biliary drainage and adequate nutritional intake, and intermediate PS is defined as ECOG 2.
[z] Serial imaging as indicated to assess disease response.

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METASTATIC DISEASE FOLLOWING SURGERY

RECURRENCE THERAPY[kk]

Metastatic disease with or without local recurrence[jj,ll]

≥6 mo from completion of primary therapy →

- **Clinical trial (preferred)**
- **or**
- **Repeat systemic therapy previously administered[t]**
- **or**
- **Alternate systemic therapy (not previously used)[t]**
- **or**
- **Palliative and best supportive care[s]**

<6 mo from completion of primary therapy →

- **Clinical trial (preferred)**
- **or**
- **Switch to gemcitabine-based systemic chemotherapy[t] (if fluoropyrimidine-based therapy previously used)**
- **or**
- **Switch to fluoropyrimidine-based systemic chemotherapy[t] (if gemcitabine-based therapy previously used)**
- **or**
- **Alternate systemic therapy (not previously used)[t]**
- **or**
- **Palliative and best supportive care[s]**

[s] Principles of Palliation and Supportive Care (PANC-H).
[t] Principles of Systemic Therapy (PANC-F).
[jj] For more information about the treatment of isolated pulmonary metastases, see Discussion.
[kk] Best reserved for patients who maintain a good PS.
[ll] In rare circumstances when patients have indolent/oligometastatic disease, they should be referred to a high-volume center to be evaluated for possible metastatic directed therapy. Ludmir EB, et al. J Clin Oncol 2024;42(3 Suppl):Abstract 603.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

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

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

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

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

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

Continued

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

- **PET/CT or PET/MRI scan may be considered after formal pancreatic CT protocol in patients with high-risk features[b] to detect extra-pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT.**
- **For neoadjuvant therapy, consider PET/CT or PET/MRI scan before and after initiation to assess response to systemic therapy and for restaging.**
- **EUS is not recommended as a routine staging tool. In select cases, EUS may be complementary to CT for staging.**
- **EUS-guided biopsy is preferable to a CT-guided biopsy in patients with non-metastatic disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding when compared with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection, and a non-diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.**
- **Diagnostic staging laparoscopy to rule out metastases not detected on imaging (especially for body and tail lesions) is used in some institutions prior to surgery or neoadjuvant therapy, or selectively in patients with high-risk features[b] and indicators of disseminated disease. Intraoperative ultrasound can be used as a diagnostic adjunct during staging laparoscopy.**
- **Positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 disease. If resection has been done for such a patient, the patient should be treated for M1 disease.**
- **For locally advanced/metastatic disease, the Panel recommends serial CT with contrast (routine single portal venous phase or dedicated pancreatic protocol if surgery is still contemplated) or MRI with contrast of known sites of disease to determine therapeutic benefit. However, it is recognized that patients can demonstrate progressive disease clinically without objective radiologic evidence of disease progression.**
- **Recent retrospective studies suggest that imaging characteristics may not be a reliable indicator of resectability in patients with borderline resectable or locally advanced disease who have received neoadjuvant therapy. Determinations of resectability and surgical therapy should be made on an individualized basis in a multidisciplinary setting (see Discussion for references).**

[b] Indicators of patients with high risk features may include equivocal or indeterminate imaging findings, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

MDCT Pancreatic Adenocarcinoma Protocol[a]

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

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

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

MRI Pancreatic Adenocarcinoma Protocol[c]

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

[c] Sheridan MB, Ward J, Guthrie JA, et al. Dynamic contrast-enhanced MR imaging and dual-phase helical CT in the preoperative assessment of suspected pancreatic cancer: a comparative study with receiver operating characteristic analysis. AJR Am J Roentgenol 1999;173:583-590.
[d] Unenhanced MRI can be obtained in cases of renal failure or contraindication to gadolinium IV contrast if enhanced CT cannot be obtained due to severe iodinated contrast allergy.

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

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

[a] Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270:248-260.
[e] Principles of Surgical Technique (PANC-D 2 of 3).

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

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

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

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

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

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

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

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

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

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PRINCIPLES OF OBSTRUCTIVE JAUNDICE AND TISSUE ACQUISITION MANAGEMENT

Biliary Drainage

- Biliary drainage is not routinely recommended prior to planned upfront surgery. However, this decision is best made in a multidisciplinary discussion.
- In obstructive jaundice, it is best practice to perform an EUS needle biopsy and ERCP for biliary drainage in the same anesthesia session.
- Biliary drainage before surgery may be considered for:
  - Symptoms of cholangitis/fever
  - Severe symptomatic jaundice (intense pruritus)
  - If surgery is being delayed for any reason, including neoadjuvant therapy
- Biliary drainage is best accomplished with an endoscopically placed biliary stent.
- If ERCP fails, reattempt at a high-volume center should be considered.
- If endoscopic drainage is not possible, a percutaneous biliary drain (PBD) should be considered. Alternatively, EUS-guided biliary drainage may be considered at a high-volume center.
- SEMS are preferable to plastic stents.
- If the tissue diagnosis is not certain, fully covered SEMS should be considered, since these stents can be removed or exchanged.
- If EUS with biopsy is repeated, the fully covered SEMS may be removed for better EUS visualization of the lesion, and biopsy. The SEMS may be replaced after biopsy.
- Once tissue diagnosis is confirmed, a non-removable (partially covered or bare) SEMS may be used, as the migration rate is lower in this type of SEMS.
- Biliary stents should be as short as feasible.
- Stent placement in the pancreatic duct may be indicated in special circumstances where there is persistent pancreatitis secondary to obstruction of the pancreatic duct, which precludes other therapy.
- Plastic biliary stents may be considered for palliation in patients with predicted short survival of less than 3 months.

Tissue Acquisition

- EUS-guided needle biopsy is the preferred mode of obtaining tissue for diagnosis of pancreatic ductal adenocarcinoma (PDAC).
- Preferably, a latest generation ("core") EUS needle should be used.
- Image-guided biopsy methods (CT, ultrasound) are preferred for liver lesions suspicious of metastasis.
- The preferred biopsy target should be the lesion that will provide the highest stage (eg, metastatic lesions).
- In metastatic PDAC, enough tissue should be obtained for next-generation sequencing (NGS) analysis.
- For all needle biopsies, if safe and feasible, two extra needle passes should be performed in addition to the routine diagnostic passes, and stored for future NGS analysis if needed.

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CRITERIA DEFINING RESECTABILITY STATUS AT DIAGNOSIS[a]

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

Resectability Status	Arterial	Venous
Resectable	• No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	• No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180°. • Solid tumor contact with variant arterial anatomy (eg, accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180°.	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced[b,c,d]	Head/uncinate process: • Solid tumor contact >180° with the SMA or CA. Pancreatic body/tail: • Solid tumor contact of >180° with the SMA or CA. • Solid tumor contact with the CA and aortic involvement.	• Not currently amenable to resection and primary reconstruction due to complete occlusion of SMV/PV

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

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CRITERIA FOR RESECTION FOLLOWING NEOADJUVANT THERAPY[e-j]

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

Following neoadjuvant therapy:

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

[e] Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261:12-17.
[f] Macedo FI, Ryon E, Maithel SK, et al. Survival outcomes associated with clinical and pathological response following neoadjuvant FOLFIRINOX or gemcitabine/ nab-paclitaxel chemotherapy in resected pancreatic cancer. Ann Surg 2019;270:400-413.
[g] Tsai S, George B, Wittmann D, et al. Importance of normalization of CA 19-9 levels following neoadjuvant therapy in patients with localized pancreatic cancer. Ann Surg 2020;271:740-747.
[h] Michelakos T, Pergolini I, Castillo CF, et al. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. Ann Surg 2019;269:733-740.
[i] Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. Ann Surg 2021;273:341-349.
[j] Gilbert JW, Wolpin B, Clancy T, et al. Borderline resectable pancreatic cancer: conceptual evolution and current approach to image-based classification. Ann Oncol 2017;28:2067-2076.

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PRINCIPLES OF SURGICAL TECHNIQUE

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

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

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

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

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References on PANC-D 3 of 3

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PRINCIPLES OF SURGICAL TECHNIQUE

Surgery for Locally Recurrent Pancreatic Ductal Adenocarcinoma[5,6]

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

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

Distal Pancreatectomy with En-bloc Splenectomy

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

- **An R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.[7,8]**
- **Similar to the Whipple procedure, lateral venorrhaphy, vein excision and reconstruction, and dissection to the level of the CA and SMA adventitia should be performed if complete tumor clearance can be achieved.[7,9]**
- **Spleen preservation is not indicated in adenocarcinoma.**

Management of Neck Lesions

Pancreas neck adenocarcinomas are especially difficult to manage. Adenocarcinomas in the pancreas neck are located anterior to the superior mesenteric vessels and PV. Depending on the extent of involvement, a pancreaticoduodenectomy extending to the left of the SMV (extended pancreaticoduodenectomy), a distal pancreatectomy extending to the right of the SMV (extended distal pancreatectomy), or a total pancreatectomy may be required to obtain an R0 resection.[10]

The precise extent of involvement often cannot be determined prior to surgery; therefore, complex intraoperative decisions are required, and the surgeon must anticipate this. Complexity of surgery for pancreas neck adenocarcinomas is compounded by the frequent involvement of the SMV/PV.[10,11] Surgeons who operate on pancreas neck adenocarcinomas must anticipate possible SMV/PV involvement and be prepared to manage it.

References on PANC-D 3 of 3

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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[1]

- **Specimen orientation: Specimen orientation and inking involve both the pathologist and surgeon, as this will help to ensure accurate assessment of the size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method (eg, written on the pathology requisition); for example: the distal and proximal margins of the SMV and SMA and the bile duct margin should be marked.**
- **Margins**
  - **Definitions of the margins and uniformity of nomenclature are critical to accurate reporting.**
    - **SMA (retroperitoneal/uncinate) Margin: The most important margin is the soft tissue directly adjacent to the proximal 3–4 cm of the SMA. This margin is often referred to as the "retroperitoneal margin" or "posterior margin," but has also been referred to as the "uncinate margin" or "mesenteric margin." More recently, this margin has been referred to as the "SMA margin" to correlate with its location on the specimen. Radial, rather than en face, sections of this margin will more clearly demonstrate how closely this margin is approached by tumor. The uncinate margin should be inked. Rather than being submitted en face, the uncinate margin tissue should be shaved/amputated, then the portion of tissue should be sectioned perpendicular to the ink and submitted entirely for histologic examination.**
    - **PV Margins: If an en bloc partial or complete vein resection is added to the surgical specimen, it should be marked separately. En face proximal and distal end margins of the vein should be separately submitted as "Proximal Portal Vein Margin" and "Distal Portal Vein Margin." A section documenting tumor invasion into the vein wall should also be submitted. If feasible, this section should encompass the full thickness of the vein wall, demonstrating the depth of tumor invasion, as this has been shown to have prognostic value.[2]**
    - **Pancreatic Neck (transection) Margin: This is the en face section of the transected pancreatic neck. Care should be taken when placing the section into the cassette to document the orientation of the section with respect to the true margin (eg, facing down so that the initial section into the block represents the true margin, or facing up so that the initial section represents the surface opposite the true margin).**
    - **Bile Duct Margin: This is the en face section of the bile duct end. The section should be removed from the unopened duct and care should be taken when placing the section into the cassette to document the orientation of the section with respect to the true margin (eg, facing down so that the initial section into the block represents the true margin, or facing up so that the initial section represents the surface opposite the true margin).**
  - **Other margins analyzed in Whipple specimens include the proximal (gastric or enteric) and distal enteric margins (en face sections).**
  - **Collectively, these margins and pancreatic tissue surfaces constitute the circumferential surface of the specimen. Designating the various specific margins and surfaces with different colored inks will allow recognition on microscopy.**

Continued

References on PANC-E 5 of 5

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

- **Other Circumferential Surfaces**
  - **Posterior (non-SMA margin) Surface: This surface consists of the posterior caudad aspect of the pancreatic head that is not part of the SMA margin and that appears to be covered by loose connective tissue. Radial, rather than en face, sections of this surface will more clearly demonstrate whether it is involved by tumor. In some instances, this surface may already be included in sections of the SMA margin.**
  - **SMV Groove: Also referred to as the vascular groove surface (and in previous versions of the Guidelines as the Portal Vein Groove Margin), this is the smooth-surfaced groove on the posterior-medial surface of the pancreatic head that rests over the SMV. Radial, rather than en face, sections of this surface will more clearly demonstrate whether it is involved by tumor, and also will provide the distance of the tumor from the surface. As is true for the posterior (non-SMA margin) surface, in some instances, this surface may be included in the same sections as the SMA margin.**
  - **Anterior Surface: The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and is therefore strongly recommended, but not currently required.[3-6] In some cases where the anterior surface is adherent to other structures, from which it is surgically dissected or transected, it should be considered an additional circumferential margin, for which the closest distance from tumor should be reported.**
- **Histologic Sectioning**
  - **The approach to histologic sectioning is determined by the unique characteristics of the tumor, but is also influenced by institutional preferences, expertise, and experience. Options include axial, bi- or multi-valve slicing, and perpendicular slicing. Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas.**
  - **Axial slicing provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum, and pancreas, and all of the pancreatic circumferential tissue margins mentioned above.**
  - **There is no one correct way to dissect a Whipple specimen.[7] However, knowledge of the clinically suspected lesion is helpful in choosing the best dissection method for examination and appropriate characterization of the lesion. The most important aspects of dissection are clear and accurate assessment of the margins, size of the tumor, and relationship to the relevant structures, such as pancreatic surfaces, margins, bile duct, main pancreatic duct, and duodenum.**
  - **Per the current CAP protocol, the presence of tumor at or within 1 mm of resection margin constitutes a positive margin,[3,8] although this recommendation is based primarily on extrapolation of data on rectal adenocarcinoma. There is currently a lack of definitive evidence for what constitutes an adequate margin in pancreatic carcinoma resection specimens. A standardized definition of this would allow for better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if less than 1-mm clearance is associated with an unacceptably high incidence of local recurrence, then strong consideration for postoperative RT might be indicated if not received preoperatively. Tumor clearance should be reported with millimeter accuracy for all margins where tumor is close (within ≤1.0 cm of the tumor). This may be done using either mm (eg, 2 mm) or cm (eg, 0.2 cm). For margins distant from tumor (>1.0 cm from tumor), tumor clearance may be reported with centimeter accuracy. Attached organs resected with the specimen en bloc require serial sectioning to assess not only direct extension, but metastatic deposits as well. One section that demonstrates direct invasion of the organ and/or a separate metastatic deposit is required.**

Continued

References on PANC-E 5 of 5

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

Distal Pancreatectomy

- **In left-sided resections, the peripancreatic soft-tissue surfaces and the pancreatic neck are assessed. Additionally, involvement of the splenic vessels should be documented, along with invasion of the spleen. Additionally, the margins of the splenic vein and artery can be shaved and submitted for histologic examination.**
- **Margin and Circumferential Surface Definitions**
  - **Proximal Pancreatic (transection) Margin: A full en face section of the pancreatic body along the plane of transection, if the tumor is grossly >1.0 cm from this margin. Care should be taken when placing the section into the cassette to document the orientation of the section with respect to the true margin (eg, facing down so that the initial section into the block represents the true surgical margin, or facing up so that the initial section represents the surface opposite the true margin). More than one block may be needed. If the tumor is grossly close to the margin (eg, within ≤1.0 cm), the entire margin should be submitted for pathologic evaluation in a manner that allows for millimeter-level accuracy in documenting the distance of tumor from this margin. For example, the margin can be inked and shaved/amputated, followed by perpendicular sectioning with respect to the ink and submission of the entire margin for histologic examination.**
  - **Anterior (cephalad) Peripancreatic (peripheral) Surface: This surface demonstrates the relationship between the tumor and the anterior or cephalad peripancreatic soft tissue and can be representative, if grossly positive. Several such sections should be taken closest to the tumor to document absence of involvement; the exact number is dependent on the degree of ambiguity of gross involvement.**
  - **Posterior (caudad) Peripancreatic (peripheral) Surface: This surface demonstrates the relationship between the tumor and the posterior or caudad peripancreatic soft tissue and can be representative, if grossly positive. Several such sections should be taken closest to the tumor to document absence of involvement; the exact number is dependent on the degree of ambiguity of gross involvement.**

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

- **The NCCN Pancreatic Cancer Panel currently supports pathology synoptic reports from the College of American Pathologists (CAP). The proposal included herein is an abbreviated minimum analysis of pancreatic cancer specimens from the CAP recommendations. In addition to the standard TNM staging, other variables are included, all of which have prognostic implications in the evolution of this disease.[9,10]**
- **Treatment effect should be assessed and reported by the pathologist, as tumor viability may impact postoperative therapy options. For more information about pathologic analysis, refer to the CAP Cancer Protocol Template for carcinoma of the pancreas. (Burgart LJ, Chopp WV, Jain D. Protocol for the Examination of Specimens from Patients with Carcinoma of the Pancreas. College of American Pathologists. Cancer Protocol Templates; 2021.)**

Specimen Type
- **Tumor size (obtained from careful gross measurement of the largest dimension of the tumor in cm, and corroborated on microscopic exam)**
- **Histologic type (H)[11]**
- **Histologic grade [G (x–3)]**
- **Primary tumor stage [T (x–4)]**
- **Regional lymph nodes [N (x–2)][a]**
  - **# nodes recovered**
  - **# nodes involved**
- **Metastases [M (0–1)]**
- **Margins and Other Circumferential Surfaces: Involvement should be defined and surgical clearance measured with mm accuracy for close (within 1.0 cm of tumor) margin**
  - **Whipple resection:**
    - ◊ **SMA (retroperitoneal/uncinate) margin**
    - ◊ **Posterior surface**
    - ◊ **SMV groove**
    - ◊ **Pancreatic neck (transection) margin**
    - ◊ **Bile duct margin**
    - ◊ **Gastric/enteric margins**
    - ◊ **Anterior surface**
  - **Distal pancreatectomy:**
    - ◊ **Proximal pancreatic (transection) margin**
    - ◊ **Anterior (cephalad) peripancreatic (peripheral) surface**
    - ◊ **Posterior (caudad) peripancreatic (peripheral) surface**
- **Lymphovascular invasion (L)**
  - **Lymphatic (small vessel) invasion (optional) and vascular (large vessel) invasion (optional)**
- **Additional pathologic findings**
  - **Pancreatic intraepithelial neoplasia**
  - **Chronic pancreatitis**
- **Tumor regression score following prior chemotherapy and/or RT**

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

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

References on PANC-E 5 of 5

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

General Principles of Systemic Therapy (PANC-F 1 of 13)

Neoadjuvant Therapy (Resectable/Borderline Resectable Disease) (PANC-F 1 of 13)

Adjuvant Therapy (PANC-F 2 of 13)

Locally Advanced Disease (First-Line Therapy) (PANC-F 3 & 4 of 13)

Metastatic Disease (First-Line Therapy) (PANC-F 5 & 6 of 13)

Metastatic Disease (Maintenance Therapy) (PANC-F 7 of 13)

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease (PANC-F 8, 9 of 13 & 10 of 13)

Chemoradiation (PANC-F 11 of 13)

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PRINCIPLES OF SYSTEMIC THERAPY

General Principles:

- **Systemic therapy is used in all stages of pancreatic cancer. This includes neoadjuvant therapy (resectable or borderline resectable), adjuvant therapy, and first-line or subsequent therapy for locally advanced, metastatic, and recurrent disease.**
- **Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.**
- **Consider testing for potentially actionable somatic findings including, but not limited to: fusions (*ALK, NRG1, NTRK, ROS1, FGFR2*, and *RET*), mutations (*BRAF, BRCA1/2, KRAS*, and *PALB2*), amplifications (*HER2*), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) using comprehensive genomic profiling via an FDA-approved and/or validated NGS-based assay, and HER2 overexpression via IHC ± FISH.**
- **Close follow-up of patients undergoing chemotherapy is indicated.**
- **For regimens where RT or chemoradiation is included, Principles of Radiation Therapy (PANC-G) has more details related to radiation delivery, including recommended technique and dose.**
- **To optimize the care of older adults, see NCCN Guidelines for Older Adult Oncology.**
- **Squamous/adenosquamous carcinomas are treated the same as adenocarcinoma. There are no data supporting the efficacy of any of the recommended regimens for squamous/adenosquamous carcinomas.**
- **An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.**

Neoadjuvant Therapy (Resectable/Borderline Resectable Disease)

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

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Fluorouracil (5-FU) + leucovorin + irinotecan + oxaliplatin (FOLFIRINOX) or modified FOLFIRINOX[a] ± subsequent chemoradiation[b] • Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation[b]	• None	• None
Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX or modified FOLFIRINOX[a] ± subsequent chemoradiation[b] • Gemcitabine + cisplatin (≥2 to 6 cycles) ± subsequent chemoradiation[b]		

[a] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0–1.
[b] Chemoradiation (PANC-F 11 of 13)

Continued

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PRINCIPLES OF SYSTEMIC THERAPY

Adjuvant Therapy

- **The CONKO-001 trial demonstrated significant improvements in disease-free survival (DFS) and overall survival (OS) with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[1]**
- **ESPAC-3 study results showed no significant difference in OS between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[2]**
- **Data from ESPAC-4 support the use of gemcitabine combined with capecitabine (1660 mg/m^2/day days 1–21 every 4 weeks) with superiority demonstrated compared to gemcitabine alone (hazard ratio [HR], 0.82; 95% CI, 0.68, 0.98; *P* = .032).[3]**
- **No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment.[4]**
- **Recommended adjuvant therapy options apply to patients who did not receive prior neoadjuvant therapy. For those who received prior neoadjuvant therapy, the adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.**

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

[a] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0–1.
[b] Chemoradiation (PANC-F 11 of 13)
[c] If considering chemoradiation due to positive margins, chemotherapy should be given prior to the administration of chemoradiation.

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References on PANC-F 12 of 13
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PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced Disease (First-Line Therapy)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS 0–1	• FOLFIRINOX or modified FOLFIRINOX[d,e,5] • Gemcitabine + albumin-bound paclitaxel[d,6] • Liposomal irinotecan + 5-FU + leucovorin + oxaliplatin (NALIRIFOX)[f,7] Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX or modified FOLFIRINOX[d,e,5] • Gemcitabine + cisplatin[8,9]	• Gemcitabine • Gemcitabine + capecitabine[10] • Gemcitabine + erlotinib[g,11] • Capecitabine (category 2B) • Fluoropyrimidine + oxaliplatin ▸ Capecitabine + oxaliplatin (CapeOx)[12] (category 2B) ▸ 5-FU + leucovorin + oxaliplatin (OFF)[13] (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15] (category 2B) • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX)[16] (category 2B)	• Induction chemotherapy with any of the preferred/other regimens (≥4 to 6 cycles) followed by chemoradiation[b,h] or SBRT[17] in selected patients (locally advanced disease without systemic metastases)[18] • Chemoradiation[b,i] or SBRT[i] (in patients who are not candidates for induction chemotherapy) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive)[21] • Pembrolizumab[j,22] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if *RET* gene fusion-positive)

Subsequent Therapy on PANC-F (8 & 9 of 13)
References on PANC-F 12 of 13

[b] Chemoradiation (PANC-F 11 of 13)
[d] The recommendations for FOLFIRINOX or modified FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.
[e] Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[f] While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over gemcitabine and albumin-bound paclitaxel, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX and adds considerably more expense compared to FOLFIRINOX.
[g] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[h] Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy.[16]
[i] If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation or SBRT. See Principles of Radiation Therapy (PANC-G).
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced Disease (First-Line Therapy)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Intermediate PS 2	• Capecitabine • Gemcitabine • Gemcitabine + albumin-bound paclitaxel	• None	• Induction chemotherapy with any of the preferred regimens (≥4 to 6 cycles) followed by chemoradiation[b,h] or SBRT[17] in selected patients (locally advanced disease without systemic metastases) • Chemoradiation[b,i] or SBRT[i] (in patients who are not candidates for induction chemotherapy) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive)[21] • Pembrolizumab[j,22] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if *RET* gene fusion-positive)
Poor PS 3	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ▸ 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m^2/min) may be substituted for standard infusion of gemcitabine over 30 minutes (category 2B)	• None	• None

[b] Chemoradiation (PANC-F 11 of 13)

[h] Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy.[16]

[i] If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation or SBRT. See Principles of Radiation Therapy (PANC-G).

[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

Subsequent Therapy on PANC-F (8 & 9 of 13)

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PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

- Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology).

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS 0–1	• FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5] • Gemcitabine + albumin-bound paclitaxel[6] (category 1) • NALIRIFOX[f,7] (category 1) Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5] • Gemcitabine + cisplatin[8,9]	• Gemcitabine (category 1) • Gemcitabine + erlotinib[g,11] (category 1) • Gemcitabine + capecitabine[10] • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15] • Fluoropyrimidine + oxaliplatin ▸ CapeOx[12] (category 2B) ▸ OFF[13] (category 2B) • GTX[16] (category 2B)	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive)[21] • Pembrolizumab[j,22] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if *RET* gene fusion-positive) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive) (category 2B)[19,20]

Maintenance Therapy for Metastatic Disease on PANC-F (7 of 13)

Subsequent Therapy on PANC-F (8 of 13)

[e] Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[f] While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over gemcitabine and albumin-bound paclitaxel, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX and adds considerably more expense compared to FOLFIRINOX.
[g] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

References on PANC-F 12 of 13

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

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PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

- Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology).

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Intermediate PS 2	• Gemcitabine + albumin-bound paclitaxel (category 1) • Capecitabine • Gemcitabine • 5-FU + leucovorin + oxaliplatin (FOLFOX)[23,24] • 5-FU + leucovorin + irinotecan (FOLFIRI)[25,26] • CapeOx[27]	• None	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive)[21] • Pembrolizumab[j,22] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if *RET* gene fusion-positive) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive) (category 2B)[19,20]
Poor PS 3	• Palliative and best supportive care[k]	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ▸ 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m^2/min) may be substituted for standard infusion of gemcitabine over 30 minutes (category 2B)	• Pembrolizumab[j,22] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Larotrectinib (if *NTRK* gene fusion-positive) • Entrectinib (if *NTRK* gene fusion-positive) (category 2B) • Repotrectinib (if *NTRK* gene fusion-positive) (category 2B)[21] • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive) (category 2B)[19,20]

Maintenance Therapy for Metastatic Disease on PANC-F (7 of 13)

[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[k] Evidence suggest patients with poor PS derive marginal benefit from systemic therapy. See Principles of Palliation and Supportive Care (PANC-H).

Subsequent Therapy on PANC-F (8 & 9 of 13)
References on PANC-F 12 of 13

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PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (Maintenance Therapy)

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

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• If previous platinum-based chemotherapy: ▸ Olaparib (only for germline *BRCA1/2* mutations)	• Clinical trial or • If previous first-line FOLFIRINOX: ▸ Capecitabine or • If previous first-line gemcitabine + albumin-bound paclitaxel: ▸ Gemcitabine single agent (category 2B) ▸ Gemcitabine + albumin-bound paclitaxel modified schedule (category 2B)	• If previous first-line FOLFIRINOX: ▸ 5-FU + leucovorin[l,28] ▸ FOLFIRI[l,28] ▸ FOLFOX[m,28] (category 2B) • Prior platinum-based therapy ▸ Rucaparib (for germline or somatic *BRCA1/2* or *PALB2* mutations)[n,o,29]

Subsequent Therapy on PANC-F (8 & 9 of 13)

References on PANC-F 12 of 13

[l] 5-FU ± irinotecan may be considered for maintenance therapy in the case of oxaliplatin-related progressive neuropathy or allergy to oxaliplatin.
[m] While FOLFOX is not commonly used in the maintenance setting, it may be considered as an alternative to irinotecan-based therapy when GI toxicity is a concern.
[n] For patients who did not have disease progression following their most recent platinum-based chemotherapy.
[o] For oncogenic or likely oncogenic mutations in *BRCA1*, *BRCA2*, and *PALB2*, refer to definitions at oncokb.org, cbioportal.org, mycancergenome.org, pmkb.weill.cornell.edu, genie.cbioportal.org, ckb.jax.org, cancer.sanger.ac.uk/cosmic, brcaexchange.org, ncbi.nlm.nih.gov/clinvar or sift.bii.a-star.edu.sg.

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PRINCIPLES OF SYSTEMIC THERAPY

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

	Preferred Regimens	Other Recommended Regimens		Useful in Certain Circumstances
Good PS 0–1	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive)[p,21] If no prior immunotherapy: • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb])	• Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Selpercatinib (if *RET* gene fusion-positive)[30] If no prior immunotherapy: • Dostarlimab-gxly[j] (if MSI-H or dMMR) • Nivolumab + ipilimumab[j] (if TMB-H [≥10 mut/Mb]) (category 2B) If prior gemcitabine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[31] (category 1 for metastatic disease) • Bolus 5-FU + leucovorin • Capecitabine • CapeOx • Continuous infusion 5-FU • FOLFIRI[32-34] • FOLFIRINOX or modified FOLFIRINOX[e,35] • FOLFOX • OFF	If prior fluoropyrimidine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[31] (if no prior irinotecan) • Gemcitabine • Gemcitabine + albumin-bound paclitaxel • Gemcitabine + cisplatin (only for known *BRCA1/2* or *PALB2* mutations) • Gemcitabine + erlotinib[g,36] • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15] (category 2B)	• Adagrasib (if *KRAS G12C* mutation-positive) • Sotorasib (if *KRAS G12C* mutation-positive) • Erdafitinib (if *FGFR* genetic alterations)[37] • Fam-trastuzumab deruxtecan-nxki (if *HER2* positive [IHC3+[38] or IHC2+ with FISH *HER2* amplified]) • Zenocutuzumab-zbco (if *NRG1* gene fusion-positive)[q] • Chemoradiation,[b] if not previously given, only an option for: ▸ Locally advanced disease if primary site is the sole site of progression ▸ Select patients with recurrent disease in combination with systemic therapy

[b] Chemoradiation (PANC-F 11 of 13)
[e] Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[g] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[p] If disease progressed on a prior NTRK targeted agent.
[q] For disease progression on or after prior systemic therapy.

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PRINCIPLES OF SYSTEMIC THERAPY

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

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Intermediate PS 2	**If prior fluoropyrimidine-based therapy:** • 5-FU + leucovorin + liposomal irinotecan[31] (if no prior irinotecan) • Gemcitabine + albumin-bound paclitaxel **If prior gemcitabine-based therapy:** • 5-FU + leucovorin + liposomal irinotecan[31] (category 1 for metastatic disease)	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ▸ 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m^2/min) may be substituted for standard infusion of gemcitabine over 30 minutes (category 2B)	• Adagrasib (if *KRAS* G12C mutation positive) • Sotorasib (if *KRAS* G12C mutation-positive) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Erdafitinib (if *FGFR* genetic alterations)[37] • Fam-trastuzumab deruxtecan-nxki (if *HER2* positive [IHC3+,[38] or IHC2+ with FISH *HER2* amplified]) • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive) (category 2B)[p,21] • Zenocutuzumab-zbco (if *NRG1* gene fusion-positive)[q] • Chemoradiation[b] if not previously given, only an option for: ▸ Locally advanced disease if primary site is the sole site of progression ▸ Selected patients with recurrent disease in combination with systemic therapy **If no prior immunotherapy:** • Dostarlimab-gxly[j] (if MSI-H or dMMR) • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Nivolumab + ipilimumab[j] (if TMB-H [≥10 mut/Mb]) (category 2B)

[b] Chemoradiation (PANC-F 11 of 13)
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[p] If disease progressed on a prior NTRK targeted agent.
[q] For disease progression on or after prior systemic therapy.

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References on PANC-F 12 of 13
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PRINCIPLES OF SYSTEMIC THERAPY

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

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Poor PS 3	• Palliative and best supportive care[k]	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ▸ 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m^2/min) may be substituted for standard infusion of gemcitabine over 30 minutes (category 2B)	• Dabrafenib + trametinib (if *BRAF* V600E mutation positive)[19,20] • Erdafitinib (if *FGFR* genetic alterations)[37] • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive) (category 2B)[p,21] • Adagrasib (if *KRAS* G12C mutation-positive) (category 2B) • Sotorasib (if *KRAS* G12C mutation-positive) (category 2B) If no prior immunotherapy: • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Dostarlimab-gxly[j] (if MSI-H or dMMR) (category 2B)

[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[k] Evidence suggest patients with poor PS derive marginal benefit from systemic therapy. See Principles of Palliation and Supportive Care (PANC-H).
[p] If disease progressed on a prior NTRK targeted agent.

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PRINCIPLES OF SYSTEMIC THERAPY

Chemoradiation

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Capecitabine + concurrent RT • Continuous infusion 5-FU + concurrent RT	• Gemcitabine + concurrent RT[39]	• None

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PRINCIPLES OF RADIATION THERAPY

General Principles:

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

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

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

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PRINCIPLES OF RADIATION THERAPY
TREATMENT PLANNING: RADIATION DELIVERY

Simulation:

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

Motion Management[3]:

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

Planning, Dose and Fractionation:

- 3-D conformal RT (3D-CRT), intensity-modulated RT (IMRT), and SBRT can result in improved planning target volume (PTV) coverage with decreased dose to OARs.[4,5] IMRT is preferred over 3D-CRT for conventional or hypofractionated RT, particularly if dose escalation is being considered. The exact planning strategy used should be individualized to patient anatomy, clinical scenario, treatment goals, and dose goals.
- It is imperative to evaluate the dose-volume histogram (DVH) of the target structures and the critical OARs such as the duodenum, stomach, liver, kidneys, spinal cord, and bowel. See Table 1. Normal Tissue Dose Volume Recommendations for Chemoradiation Utilizing Conventional Fractionation (PANC-G 5 of 6). No definitive dose constraints for SBRT currently exist; however, they are emerging and are dependent on a variety of factors including dose per fraction and total dose.
- While these examples of limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable).

Continued

References on PANC-G 6 of 6

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PRINCIPLES OF RADIATION THERAPY
RECOMMENDATIONS BASED ON TREATMENT SETTING[a]

Resectable/Borderline Resectable:

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

Resected (Adjuvant)[b]:

- In the adjuvant setting, treatment with chemotherapy is recommended; the role of radiation is being evaluated in clinical studies.[12]
- After resection, patients may receive adjuvant RT for features that portend high risk for local recurrence (eg, positive resection margins).
- If no prior neoadjuvant therapy and no evidence of recurrence or metastatic disease after resection, RT is included in the following adjuvant therapy option:
  - Adjuvant chemotherapy followed by chemoradiation ± subsequent chemotherapy (Principles of Systemic Therapy [PANC-F])
- RT Dosing/Planning:
  - For chemoradiation, RT dose generally consists of 45–50.4 Gy in 1.8–2.0 Gy fractions (25–28 fx) to the tumor bed, surgical anastomoses (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), and adjacent lymph node basins, with potential dose escalation to the high-risk regions, if clinically appropriate.[13,14] Careful attention to the bowel and stomach dose is warranted and normal tissue dose constraints should always be considered.
  - Several clinical trials (RTOG) now refer to atlases to assist with contouring and adjuvant RT planning: (https://www.nrgoncology.org/About-Us/Center-for-Innovation-in-Radiation-Oncology).
  - Preoperative CT scans and strategically placed surgical clips may be used to determine the tumor bed, ideally with the surgeon's assistance.

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

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

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PRINCIPLES OF RADIATION THERAPY
RECOMMENDATIONS BASED ON TREATMENT SETTING

Locally Advanced[15,16]

- The goal of RT is to prevent or delay local progression (that may result in pain or local obstructive symptoms) and facilitate local disease control, and in some instances help facilitate R0 resection in patients considered for surgery.
- Data are limited to support specific RT recommendations for locally advanced disease. Options may include:
  - Induction chemotherapy followed by chemoradiation or SBRT in select patients (locally advanced without systemic metastases)[c,d,18-23]
  - Chemoradiation,[17] SBRT,[c,d] or hypofractionated RT in selected patients who are not candidates for combination chemotherapy
- RT Dosing/Planning:
  - For chemoradiation, RT dose generally consists of 45–56 Gy in 1.8–2.2 Gy fractions.
  - There are limited data to support a specific RT dosing for SBRT[24]; therefore, it should preferably be utilized as part of a clinical trial or at an experienced, high-volume center. SBRT doses of 3 fractions (total dose 30–45 Gy) or 5 fractions (total dose 25–50 Gy) have been reported.[25] More protracted courses delivering high doses through a hypofractionated approach (67.5 Gy in 15 fractions or 75 Gy in 25 fractions) are also acceptable.[26] However, caution is warranted when utilizing higher doses and normal tissue constraints must be respected.[22] This approach is optimally performed in the setting of a clinical trial.

Recurrent Pancreatic Cancer (pancreatic bed):

- Data are limited to support specific RT recommendations for locally recurrent pancreatic cancer; the options for patients with recurrent, unresectable disease may include:
  - Induction chemotherapy followed by chemoradiation or SBRT (if not previously performed) (Principles of Systemic Therapy [PANC-F])
  - Chemoradiation[17] or SBRT[c,d] in selected patients who are not candidates for induction chemotherapy
- RT Dosing/Planning:
  - For chemoradiation, RT dose generally consists of 45–56 Gy in 1.8–2.2 Gy fractions.
  - There are limited data to support a specific RT dosing for SBRT; therefore, it should preferably be utilized as part of a clinical trial or at an experienced, high-volume center. SBRT doses of 3 fractions (total dose 30–45 Gy) or 5 fractions (total dose 25–50 Gy) have been reported as having more protracted courses delivering high doses through a hypofractionated approach.
  - However, caution is warranted when utilizing higher doses and normal tissue constraints must be respected.[22] This approach is optimally performed in the setting of a clinical trial.

[c] SBRT should be delivered at an experienced, high-volume center with technology that allows for image-guided RT or in a clinical trial.[24,25] Furthermore, since patients with locally advanced disease are less likely to undergo surgery, every effort should be made to limit dose to the duodenum and stomach in order to limit treatment-related toxicity.

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

Continued

References on PANC-G 6 of 6

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PRINCIPLES OF RADIATION THERAPY

Palliative

- **The goal of palliative RT is often to relieve pain and bleeding and/or ameliorate local obstructive symptoms in patients with non-metastatic or metastatic disease. See Principles of Palliation and Supportive Care (PANC-H).**
  - **Non-Metastatic Disease: Palliative RT can be considered for patients who are older and/or not candidates for definitive therapy due to poor PS or comorbidities.**
  - **Metastatic Disease:**
    - **Metastatic sites causing pain (ie, osseous) may be palliated with a short course of RT.**
    - **RT is reasonable for patients with metastatic disease who require local palliation for symptoms such as obstruction, pain refractory to analgesic therapy, or bleeding.[27]**
- **RT Dosing/Planning:**
  - **Palliative RT is commonly used, although specific dose and fractionation recommendations should take into account burden of metastatic disease, normal tissue tolerance, and expected survival.**

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

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

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

References on PANC-G 6 of 6

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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE[a]

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

Symptom	Therapy
Biliary obstruction	• Endoscopic biliary metal stent (preferred method) • Percutaneous biliary drainage with subsequent internalization • Open biliary-enteric bypass
Gastric outlet/duodenal obstruction	• Gastrojejunostomy (open or laparoscopic) ± G/J-tube • Enteral stent[b] • Endoscopic ultrasound-guided gastrojejunostomy at a high-volume center especially if patient is not a surgical candidate • Venting percutaneous endoscopic gastrostomy (PEG) tube for gastric decompression
Thromboembolic disease[c]	• Low-molecular-weight heparin preferred over warfarin[d] • Consider direct oral anticoagulants for patients without luminal tumors
Bleeding from the primary tumor site	• Therapeutic endoscopy, if clinically indicated • RT, if not previously done • Angiography with embolization, if clinically indicated
Pain (NCCN Guidelines for Adult Cancer Pain)	• Early referral to pain or palliative care specialist to determine the best treatment option • Opioids with or without neurolysis • EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable) • Celiac plexus radiation/radiosurgery[e] • SBRT • Severe tumor-associated abdominal pain unresponsive to optimal, around-the-clock analgesic administration, or if patient experiences undesirable analgesic-associated side effects ▸ High-intensity focused ultrasound ▸ Consider palliative radiation with or without chemotherapy if not already given as part of primary therapy regimen. See Principles of Radiation Therapy (PANC-G). ▸ Intrathecal drug delivery
Anorexia	• Daily low-dose olanzapine[f]
Depression and fatigue (NCCN Guidelines for Supportive Care)	• Formal palliative medicine service evaluation when available[g]
Exocrine pancreatic insufficiency and malnutrition	• Pancreatic enzyme replacement in the case of exocrine pancreatic insufficiency ▸ Starting dose of at least 48,000 units lipase with meals (preferably 72,000) • Nutritional evaluation with a registered dietitian when available

Footnotes on PANC-H 2 of 2

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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE
FOOTNOTES

[a] Palliative surgical procedures are best reserved for patients with a longer life expectancy.
[b] Placement of an enteral stent is particularly important for patients with poor PS and should be done after biliary drainage is assured.
[c] NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease.
[d] A randomized trial examining the effects of prophylactic low-molecular-weight heparin showed a decrease in venous thromboembolism but no effect on survival (Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: Outcomes from the CONKO-004 trial. J Clin Oncol 2015;33:2028-2034).
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[f] Sandhya L, et al. J Clin Oncol 2023;41:2617-2627.
[g] Consider encouraging advance care planning.

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian Pancreatic, and Prostate for the following:
- **Principles of Cancer Risk Assessment and Counseling (EVAL-A)**
- **Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B)**
- **General Testing Criteria (CRIT-1) and Testing Criteria for Pancreatic Cancer Susceptibility Genes (CRIT-5)**
- **Pancreatic Cancer Screening (PANC-A)**

See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric for information on pancreatic cancer in Lynch syndrome.

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

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

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

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

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

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ABBREVIATIONS

3D-CRT	three-dimensional conformal radiation therapy
CA	celiac axis
CAP	College of American Pathologists
CEA	carcinoembryonic antigen
CHA	common hepatic artery
DFS	disease-free survival
dMMR	mismatch repair deficient
DVH	dose-volume histogram
DWI	diffusion-weighted echo
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
FISH	fluorescence in situ hybridization
FRFSE	fast relaxation fast spin-echo sequence
FSE	fast spin echo
G/J-tube	gastrostomy/jejunostomy tube
GDA	gastroduodenal artery
GRE	gradient echo
HR	hazard ratio
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
ITV	internal target volume
IVC	inferior vena cava
MDCT	multi-detector computed tomography
MIP	maximum intensity projection
MPV	main portal vein
MRCP	magnetic resonance cholangiopancreatography
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NGS	next-generation sequencing
NPO	nothing by mouth
OAR	organ at risk
OS	overall survival
PBD	percutaneous biliary drain
PDAC	pancreatic ductal adenocarcinoma
PEG	percutaneous endoscopic gastrostomy
PS	performance status
PTV	planning target volume
PV	portal vein
RHA	right hepatic artery
RTOG	Radiation Therapy Oncology Group
SBRT	stereotactic body radiation therapy
SEMS	self-expanding metal stent
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SSFSE	single-shot fast spin echo
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
TNM	tumor node metastasis

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

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Discussion

This discussion corresponds to the NCCN Guidelines for Pancreatic Adenocarcinoma.
Last updated on: August 2, 2024

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Discussion update in progress

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Overview

In 2023, an estimated 64,050 people were diagnosed with pancreatic cancer, and approximately 50,550 people died from the disease in the United States.[1] Pancreatic cancer is the fourth leading cause of cancer-related death in the United States.[1] In large population studies, pancreatic cancer incidence increased at a greater rate in Black women compared to any other group over almost two decades beginning in 1999; however, pancreatic cancer-related mortality remained unchanged.[2,3]

In the NCCN Clinical Practice Guidelines in Oncology (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 and Adrenal 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 <5% of all cases) was used as a cut-off to exclude rare clinical occurrences or conditions from these guidelines.

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 using appropriate imaging studies. In addition, the Panel believes that increasing participation in clinical trials is critical to making progress in disease outcomes. Thus, the Panel unanimously endorses participation in clinical trials over standard or accepted therapy.

Guidelines Update Methodology

Complete details of the Development and Update of the NCCN Guidelines® are available at www.NCCN.org.

Prior to the update of this version of the NCCN Guidelines for Pancreatic Adenocarcinoma, an electronic search of the PubMed database was performed to obtain key literature in the field of pancreatic cancer using the following search terms: “pancreatic cancer” OR “pancreatic ductal adenocarcinoma” OR “PDAC” OR “ampullary cancer” OR “ampullary adenocarcinoma.” The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[4]

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

Data from key PubMed articles and additional sources deemed as relevant to these guidelines by the Panel during the Guidelines update meeting have been included in this Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel’s review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[5] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate

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and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in ongoing studies and organizations to use more inclusive and accurate language in their future analyses.

Risk Factors

Smoking

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.[6-12] Exposure to chemicals and heavy metals such as beta-naphthylamine, benzidine, pesticides, asbestos, benzene, and chlorinated hydrocarbons is associated with increased risk for pancreatic cancer,[13] as is heavy alcohol consumption.[6,8,14-16] Periodontal disease is associated with pancreatic cancer, even when controlling for other risk factors such as gender, smoking, body mass index (BMI), diabetes, and alcohol consumption.[17]

BMI

Elevated BMI is associated with an increased risk for pancreatic cancer,[14,18-20] with higher BMI during early adulthood associated with increased pancreatic cancer mortality.[21] A meta-analysis including 22 cohort studies of 8,091 patients with pancreatic cancer showed that those who engage in low levels of physical activity have an higher risk for pancreatic cancer, relative to those who engage in high levels of physical activity (relative risk [RR], 0.93; 95% confidence interval [CI], 0.88–0.98).[22] Additionally, there is some evidence that increased consumption of red/processed meat and dairy products is associated with an elevated pancreatic cancer risk,[23,24] although other studies have not identified dietary risk factors for the disease.[10,25,26]

Vitamin D

Studies examining the association between vitamin D and risk for pancreatic cancer show contradictory results. Some data suggest that low plasma 25-hydroxyvitamin D levels may increase the risk for pancreatic cancer.[27] A pooled analysis of nine case-control studies, including 2963 patients with pancreatic cancer and 8,527 control subjects, showed a positive association between vitamin D intake and pancreatic cancer risk (odds ratio [OR], 1.13; 95% CI, 1.07–1.19; $P < .001$).[28] This association may be stronger in those with low retinol/vitamin A intake.

Chronic Pancreatitis

Chronic pancreatitis has been identified as a risk factor for pancreatic cancer,[29-32] with one study demonstrating a 7.2-fold increased risk for pancreatic cancer for patients with a history of pancreatitis.[33] A meta-analysis including two case-control studies and one cohort study (1,636 patients with pancreatic cancer) showed that hepatitis B infection is associated with pancreatic cancer (OR, 1.50; 95% CI, 1.21–1.87).[34] Patients with systemic lupus erythematosus (SLE) may be at an increased risk for pancreatic cancer. In a meta-analysis of 11 cohort studies, patients with SLE were found to be an increased risk for developing pancreatic cancer (CI, 1.32–1.53; hazard ratio [HR], 1.43).[35] However, further epidemiologic studies involving careful evaluation of these possible risk factors with adjustments for potential confounders are needed to clarify their impact on pancreatic cancer risk.

Diabetes

The association between diabetes mellitus and pancreatic cancer is particularly complicated. A population-based study of 2122 patients with

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diabetes found that approximately 1% of patients diagnosed with diabetes who are aged ≤50 years will be diagnosed with pancreatic cancer within 3 years.[36] Prediabetes may also be associated with increased risk for pancreatic cancer.[37] A systematic review and dose-response meta-analysis including nine prospective studies (*N* = 2,408) showed that every 0.56 mmol/L increase in fasting blood glucose is associated with a 14% increase in pancreatic cancer incidence.[38]

Numerous studies have shown an association between new-onset non-insulin–dependent diabetes and the development of pancreatic cancer.[36,39,40] Data from a meta-analysis of >38,000 patients show that those with pancreatic cancer and diabetes have a significantly lower overall survival (OS) than those without diabetes (14.4 vs. 21.7 months; *P* < .001).[40] A similar result was seen in a prospective 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.[41] 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). In acute-onset cases of diabetes prior to pancreatic cancer diagnoses, diabetes is thought to be induced by the cancer.[42] However, the physiologic basis for this effect is not yet completely understood.

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.[43] However, certain risk factors such as obesity, associated with both diabetes and pancreatic cancer, may confound these analyses.[44] A meta-analysis including 44 studies showed that the strength of the association between diabetes and pancreatic cancer risk decreases with duration of diabetes, potentially due to the effects of long-term diabetes treatment.[45]

The use of diabetic medications such as insulin and sulfonylureas is associated with an increased risk for pancreatic cancer.[46-48] However, metformin may be associated with a reduced risk for pancreatic and other cancers,[46-51] though a retrospective cohort study (*N* = 980) showed that metformin did not significantly improve survival in diabetic patients diagnosed with pancreatic cancer.[52] Another retrospective, single-institution study showed that in 302 patients with pancreatic cancer and diabetes, metformin use was associated with increased survival at 2 years (30.1% vs. 15.4%; *P* = .004) and increased OS (15.2 months vs. 11.1 months; *P* = .009).[53] The OS difference was significant only in patients without distant metastases and remained significant when insulin users were excluded.

Genetic Predisposition

The Panel recommends germline testing in any patient with confirmed pancreatic cancer and in those in whom there is a clinical suspicion for inherited susceptibility (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic available at www.NCCN.org). Patients with pancreatic cancer for whom a hereditary cancer syndrome is suspected should be considered for genetic counseling.[54] 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. The Panel recommends using comprehensive gene panels for hereditary cancer syndromes to test for inherited mutations for any patient with confirmed pancreatic cancer. A free online pancreatic cancer risk prediction tool, called PancPRO, is available and may help determine risk.[55] Referral to genetic counseling may be considered for patients diagnosed with pancreatic cancer, especially those who have a family history of cancer or who are young, as well as those of Ashkenazi Jewish ancestry. Genetic counseling is recommended for patients who test positive for a pathogenic

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mutation (*ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *STK11*, and *TP53*) or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. The Panel currently does not identify a specific age to define early-onset pancreatic cancer, though age 50 has been used in previous studies of familial pancreatic cancer.[56] If a cancer syndrome is identified, relatives at risk for disease should be offered genetic counseling. Individuals with a suspicious family history should be advised on risk-reducing strategies including smoking cessation and weight loss, regardless of whether they have a known syndrome. In addition, the possibility of screening for pancreatic and other cancers should be discussed. For patients with locally advanced or metastatic disease who are candidates for anticancer therapy, the NCCN Panel recommends testing for actionable somatic mutations, including but not limited to: fusions (*ALK, NRG1, NTRK, ROS1, FGFR2,* and *RET*), mutations (*BRAF, BRCA1/2, HER2, KRAS,* and *PALB2*), amplifications (*HER2*), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB). These should be tested via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. RNA sequencing assays are preferred for detecting RNA fusions, because gene fusions are better detected by RNA-based NGS. The Panel also recommends testing for HER2 overexpression via immunohistochemistry (IHC).

Premalignant Tumors of the Pancreas

Mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are cystic lesions that can be small and asymptomatic and are often discovered incidentally. MCNs have an ovarian-like stroma[57,58] and IPMNs can occur in the main duct and/or in the branch ducts. Lesions involving the main duct have a higher malignant potential than those in the branches, with the risk of malignancy being around 62%.[59] The risk of malignancy in MCNs is <15%.[59]

An international group of experts has established guidelines for the management of pancreatic IPMNs and MCNs,[60] as has a European group.[61] The international group strongly recommends resection in fit patients with main-duct IPMNs ≥10 mm.[59] For branch-duct IPMNs, surveillance is considered an appropriate option in patients who are older or ineligible for resection or for cysts lacking high-risk stigmata. Branch-duct IPMNs that have an enhancing mural nodule ≥5 mm, or are in the head of the pancreas causing obstructive jaundice should be considered for resection in patients who can undergo surgery.[59,60] Patients with resected IPMNs are followed with imaging studies to identify recurrences. For MCNs, the international group recommends resection for all patients who can undergo surgery.[59] The European group gives similar recommendations.[61] For appropriate management, refer to the most recent available guideline recommendations.

Pancreatic Cancer Risk Assessment, Management, and Screening

Refer to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, available at www.NCCN.org.

Diagnosis and Staging

Ductal adenocarcinoma and its variants account for >90% of pancreatic malignancies. Symptoms can include weight loss, jaundice, floating stools, pain, dyspepsia, nausea, vomiting, and occasionally pancreatitis; however, no early warning signs of pancreatic cancer have been established. Given the association with diabetes (discussed above), a pancreatic cancer diagnosis should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss.

Unlike many other cancers, imaging is the primary means through which pancreatic cancer stage is determined. High-quality multiphase imaging can help to preoperatively distinguish between patients eligible for

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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.[62] All patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should therefore undergo initial evaluation by CT or MRI performed according to a dedicated pancreas protocol of the abdomen.[63] The Panel also recommends imaging after neoadjuvant treatment to provide adequate staging and assessment of resectability status. Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation and use appropriate studies to evaluate the extent of disease. The Panel recommends that a multidisciplinary review ideally involves expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, pathology, geriatric medicine, genetic counseling, and palliative care.

The AJCC has developed staging criteria for adenocarcinoma of the pancreas that follow the tumor, node, metastasis (TNM) system.[64,65] The TNM staging criteria for pancreatic cancer in the 7th edition of the AJCC Cancer Staging Manual accounted for CT or MRI imaging that determined resectability status of pancreatic tumors. These staging criteria also included information determined only through postsurgical pathologic evaluation of resected tumor.[65,66] In the 8th edition of the AJCC Cancer Staging Manual, the definition of N category was revised; N1 was defined as 1–3 metastatic lymph nodes and N2 as >4 metastatic lymph nodes. Additionally, the T category had a size-based definition and the T4 category no longer incorporated resectability.[67] Validation studies of changes to the 8th edition of the AJCC T and N staging found that it better stratifies patients with resected tumors according to their lymph node involvement[68] and retains prognostic accuracy,[69] compared to the 7th edition. Refer to the most recent edition of AJCC Cancer Staging Manual for updated staging information.

For clinical purposes, however, most NCCN Member Institutions use a clinical classification system based mainly on results of presurgical imaging studies. For individuals with no evidence of metastatic disease, the Panel recommends chest and pelvis CT (and endoscopic ultrasound [EUS], and/or MRI if clinically indicated for indeterminate liver lesions, and/or PET/CT or MRI for patients with high risk to detect extra-pancreatic metastases), or endoscopic retrograde cholangiopancreatography (ERCP) to place a stent if jaundiced or undiagnosed on previous placement (or percutaneous transhepatic cholangiography [PTC]) in some cases), liver function tests and baseline CA 19-9 in a decompressed patient, genetic counseling, and germline testing. For patients with confirmed tumors on 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 an R1 resection); 3) locally advanced (ie, tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease); 4) unresectable at surgery; or 5) metastatic, and this classification is used throughout the guidelines. For patients with evidence of metastatic disease, the Panel recommends a biopsy confirmation from preferably a metastatic site followed by genetic testing for inherited mutations, molecular profiling of tumor tissues, and complete staging with chest and pelvis CT.

Imaging Evaluations

Pancreatic Protocol CT and MRI

Multi-detector CT (MDCT) angiography is the preferred imaging tool for dedicated pancreatic imaging. Ideally, MDCT angiography is performed by acquiring thin, preferably sub-millimeter, axial sections using a dual-phase pancreatic protocol with images obtained in the pancreatic and portal venous phase of contrast enhancement. Scans can be extended to cover the chest and pelvis for complete staging as per institutional preferences. Multiplanar reconstruction is preferred as it allows precise visualization of

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the relationship of primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits.[62,63,70] Studies have shown that 70% to 85% of patients were able to undergo resection when CT imaging showed resectable tumors.[62,71-75] However, the sensitivity of CT for small hepatic and peritoneal metastases is limited. Due to the aggressive nature of pancreatic cancer and its ability to rapidly metastasize, the accuracy of MDCT in determining resectability reduces over time.[76] Therefore, high-quality CT imaging should occur no more than 4 weeks before surgery.[76]

The difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the pancreatic phase, thereby providing a clear distinction between a hypodense lesion in the pancreas and the rest of the organ. A multi-phasic pancreatic protocol also allows for enhanced visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], hepatic artery) and venous structures (eg, superior mesenteric vein [SMV], splenic vein, portal vein [PV]), thereby providing an assessment of vascular invasion by the tumor. All this information can improve the prediction of resectability. Software allowing for 3D reconstruction of imaging data can provide additional valuable information on the anatomic relationship between the pancreatic tumor and the surrounding blood vessels and organs. However, further development of this technology may be needed before it is routinely integrated into clinical practice.[74]

Patients commonly present to the oncologist with a non-pancreas protocol CT already performed. The Panel recommends performing high-quality dedicated imaging of the pancreas even if standard CT imaging is already available. Such reimaging changed the staging and management of patients with pancreatic adenocarcinoma in 56% of cases at a single institution.[77] The Panel recommends imaging with contrast, unless contraindicated, for appropriate disease management. PET/CT scan to detect extra-pancreatic metastases may be considered after formal pancreatic CT protocol in patients with high-risk. It is not a substitute for high-quality, contrast-enhanced CT. Pancreas protocol MRI with contrast can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for characterization of CT-indeterminate liver lesions and when suspected pancreatic tumors are not visible on CT or in cases of contrast allergy.[78,79]

A multidisciplinary expert consensus group defined standardized language to report imaging results.[63] Use of the radiology staging reporting template, as put together by the consensus group, is recommended by the Panel. The template includes morphologic, arterial, venous, and extrapancreatic evaluations.[63] Morphologic evaluation includes documentation of tumor appearance, size, and location, as well as the presence of narrowing or abrupt cut-off of pancreatic duct or biliary tree. The arterial evaluation should include celiac axis, SMA, and common hepatic artery assessment. Arterial variations such as vessel contact, solid soft tissue contact, hazy attenuation or stranding contact, and focal vessel narrowing, or contour irregularity should also be noted. Venous evaluation should include an assessment of the main PV (MPV) and SMV. Appearance of thrombus within the vein and venous collaterals should also be documented. The extrapancreatic evaluation should include documentation of liver lesions, peritoneal or omental nodules, ascites, suspicious lymph nodes, and other present extrapancreatic disease sites. Such templates ensure complete assessment and reporting of all imaging criteria essential for optimal staging, can help improve the accuracy and consistency of staging to determine optimal treatment strategies for individual patients, and allow cross-study and cross-institutional comparisons for research purposes.

Endoscopic Ultrasound

NCCN Member Institution practices vary in the use of additional staging technologies, such as EUS. An analysis of 20 studies and 726 cases of

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pancreatic cancer showed that EUS for T1–2 staging has a sensitivity and specificity of 0.72 and 0.90, respectively.[80] Sensitivity and specificity for T3–4 staging is 0.90 and 0.72, respectively.[81-84] EUS may be used to discriminate between benign and malignant strictures or stenosis, because severe stenosis and marked proximal dilatation most often indicate malignancy.[85] EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. 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 that are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions (eg, celiac neurolysis, removal of ascites) can also be done with EUS. Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

The role of EUS in staging is complementary to pancreas CT protocol (which is considered the gold standard). The primary role of EUS is to procure tissue for cytologic diagnosis, but sometimes additional diagnostic information is identified. EUS provides additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes.[81-84] Because variations in hepatic arterial anatomy occur in up to 45% of individuals, and EUS is highly operator dependent, EUS is not recommended as a routine staging tool and should not be used to assess vascular involvement.

Endoscopic Retrograde Cholangiopancreatography and Percutaneous Transhepatic Cholangiography

ERCP is a technique that combines endoscopic and fluoroscopic procedures and is generally limited to therapeutic interventions.[86] ERCP is a preferred recommendation for patients who are jaundiced or diagnosed on previous biopsy and without evidence of metastatic disease who require biliary decompression and who undergo additional imaging with EUS to help establish a diagnosis.[87] Thus, from a therapeutic standpoint ERCP allows for stent placement and can be used to palliate biliary obstruction when surgery is not elected or if surgery must be delayed. However, biliary decompression in those without symptomatic hyperbilirubinemia receiving upfront surgery may be avoided.[88-90] There are occasional anatomic considerations that preclude ERCP stent placement. In these cases, palliation of biliary obstruction can be achieved by placing a stent through the liver using PTC.[91]

PET/CT

The utility of PET/CT for upstaging patients with pancreatic cancer has 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.[92] 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 changed because of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established.[93,94] PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered as an adjunct to a formal pancreatic CT protocol in patients with high risk. Indicators of high risk for metastatic disease may include equivocal or indeterminate imaging findings, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, and extreme pain. In the neoadjuvant setting, PET/CT scan can be considered, before and after therapy initiation, to assess response to systemic therapy and for restaging.

Laparoscopy

Laparoscopy is another potentially valuable diagnostic tool for staging; it can identify peritoneal, capsular, or serosal implants or studding of

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metastatic tumor on the liver that may be missed even with the use of a pancreatic CT protocol.[95-97] 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,[96] although routine use of staging laparoscopy is controversial. There is some concern that laparoscopy may promote trocar-site recurrences and peritoneal disease progression, but these concerns are based on clinical observation and experimental data from animal and in vitro studies, and one retrospective study (*N* = 235) that found no significant association between staging laparoscopy and poor outcomes.[98] The Panel does not consider staging laparoscopy to be a substitute for poor-quality preoperative imaging.

There is some evidence for a selective approach to staging laparoscopy (ie, it is performed if occult metastatic disease is suggested by high-quality imaging or certain clinical indicators).[99] For example, preoperative serum CA 19-9 levels >100 U/mL or >215 U/mL are associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.[100,101] In a prospective review of 838 patients diagnosed with resectable pancreatic tumors via imaging evaluation between 1999 and 2005, 14% were found to have unresectable disease (21% if only pancreatic adenocarcinoma was considered) following subsequent laparoscopy.[102] Characteristics associated with increased laparoscopic yield of unresectable disease include the location of the tumor, tumor histology, the presence of weight loss and jaundice, and the facility conducting the imaging evaluation.

Diagnostic staging laparoscopy to rule out metastases not detected on imaging (especially for patients with body and tail lesions) is used routinely at some NCCN Member Institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (ie, equivocal or indeterminate imaging findings; markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; highly symptomatic; excessive weight loss and extreme pain). Thus, the Panel believes that staging laparoscopy can be considered for patients staged with resectable pancreatic cancer with an increased risk for disseminated disease and for patients with borderline resectable disease prior to and after administration of neoadjuvant therapy. Intraoperative ultrasound may be used as a diagnostic adjunct during staging laparoscopy to further evaluate liver and tumor and vascular involvement. The Panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[103]

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Biopsy

Although a pathologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy and for patients with locally advanced pancreatic cancer, borderline resectable disease, or metastatic disease. A pathologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with EUS guidance (preferred). When EUS-guided biopsy is not feasible, a CT-guided biopsy can be performed. 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.[104-106] Additional risks of CT-directed FNA biopsy include the potential for greater bleeding and infection because of the need to traverse vessels and bowel. EUS-FNA also gives the benefit of additional staging information at the time of biopsy.

EUS-FNA is highly accurate and reliable for determining malignancy. A meta-analysis including 20 studies and 2761 patients showed sensitivity and specificity values of 90.8% and 96.5%, respectively, for diagnosis of solid pancreatic lesions.[107] In rare cases when EUS-FNA cannot be obtained from a patient with borderline resectable or unresectable

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disease, other acceptable methods of biopsy exist. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy.[108] A percutaneous approach[105] or a laparoscopic biopsy[109] are other alternatives. Pancreatic ductal brushings or biopsies can also be obtained at the time of ERCP, which often reveal malignant cytology consistent with pancreatic adenocarcinoma.

If a biopsy does not confirm malignancy, at least one repeat biopsy should be performed; EUS-guided FNA and a core needle biopsy at a high-volume center is preferred. New methods are being developed for diagnosis of pancreatobiliary malignancies (eg, cholangiopancreatoscopy) when repeat biopsy is needed.[110] When cancer is not confirmed after two or three biopsies in patients with borderline resectable disease, the Panel recommends referral to a high-volume center for further evaluation. Core needle biopsy is recommended, if possible, for all patients with locally advanced or metastatic or recurrent disease to obtain adequate tissue for potential ancillary studies, including tumor/somatic molecular profiling. Alternative diagnoses including autoimmune pancreatitis should be considered. A positive biopsy is required before administration of chemotherapy. However, it is important to reiterate that biopsy proof of malignancy is not required before surgical resection for clearly resectable or borderline resectable disease and that a nondiagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high. The NCCN Pancreatic Adenocarcinoma Panel strongly recommends that all diagnostic and surgical management decisions involve multidisciplinary consultation.

Evolving changes in molecular analyses of pancreatic cancer have led some institutions to attempt to procure additional tumor-rich, formalin-fixed, paraffin-embedded tissue to bank for future genomic studies. Several methods can be used to obtain such tissue samples, including core biopsy, but the Panel believes that core biopsies should not replace EUS-guided FNA, but rather can be performed in addition to EUS-guided FNA.

Biomarkers

Association of many tumor-associated antigens, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal antigen, tissue polypeptide antigen, CA 125, and CA 19-9, with pancreatic adenocarcinoma have been investigated. The Panel recognizes the importance of identifying biomarkers for early detection of this difficult disease, and they emphasize the need for collection and sharing of tissue to help accelerate the discovery of prognostic biomarkers. For example, a meta-analysis of eight studies found that S100 calcium-binding protein P (S100P) shows high sensitivity (0.87; 95% CI, 0.83–0.90) and specificity (0.88; 95% CI, 0.82–0.93) for pancreatic cancer diagnosis.[111] A biomarker panel consisting of the immunoassays TIMP1 and LRG1, along with CA 19-9 improved the detection of early-stage pancreatic cancer, relative to CA 19-9 alone.[112]

CA 19-9

The best-validated and most clinically useful biomarker for early detection and surveillance of pancreatic cancer is CA 19-9, a sialylated Lewis A blood group antigen. CA 19-9 is commonly expressed and shed in pancreatic and hepatobiliary disease and other malignancies; thus, it is not tumor-specific. However, the degree of increase in CA 19-9 levels may be useful in differentiating adenocarcinoma from inflammatory conditions of the pancreas.[113] CA 19-9 has potential uses in diagnosis, screening, staging, determining resectability, as a prognostic marker after resection, and as a predictive marker for response to chemotherapy.[114]

CA 19-9 is a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 80% to 90% in symptomatic patients,[115] but its low positive predictive value makes it a poor biomarker for screening.[114] Preoperative

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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.[116-118]

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 is prognostic for survival in patients undergoing resection.[114,116,118-124] In a prospective study of patients undergoing surgery with curative intent, median survival for the group of patients with post-resection 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; $P < .0001$).[120]

Analysis of 260 patients also supports the role of postoperative CA 19-9 levels in predicting the benefit of adjuvant therapy after resection.[123] Patients with CA 19-9 levels of <90 U/mL who received adjuvant therapy (mostly gemcitabine-based) had a longer disease-free survival (DFS) than those who did not receive gemcitabine-based adjuvant therapy (26.0 months vs. 16.7 months; $P = .011$). In contrast, patients with CA 19-9 levels of >90 u/mL did not appear to significantly benefit from adjuvant therapy, with DFS of 16.2 months and 9.0 months for those receiving versus 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 had the best outcome, while the 8 patients with > 37 U/mL CA 19-9 levels had a median DFS of 19.6 months.

In the neoadjuvant/borderline resectable setting, a study of 141 patients found that post-treatment CA 19-9 level was a good prognostic marker in those receiving neoadjuvant therapy with or without subsequent resection.[125] In this study, reduction of CA 19-9 to <40 U/mL was associated with OS improvements in patients with non-resected (15 months vs. 11 months; $P = .02$) and resected (37.9 months vs. 26 months; $P = .02$) disease.

There are data to support the role of CA 19-9 as a prognostic marker in advanced disease.[119,126,127] 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.[126] In addition, change in CA 19-9 levels during chemotherapy in patients with advanced disease can be useful for evaluating the benefit of treatment, although the data are not entirely consistent.[126-130] For example, a study that pooled individual patient data from 6 prospective trials found that a decline in CA 19-9 levels from baseline to after surgery and two rounds of adjuvant therapy were associated with better outcomes.[119] In fact, increases of <5% in CA 19-9 were associated with improved OS compared to patients with a ≥5% increase (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.[131] Furthermore, CA 19-9 may be falsely elevated in cases of biliary infection (cholangitis), inflammation, or biliary obstruction (regardless of etiology) and does not necessarily indicate cancer or advanced disease.[132,133] Measurement of CA 19-9 levels (category 3) is therefore best performed after biliary decompression is complete, and bilirubin is normal. If biliary decompression is not performed in a patient with jaundice, CA 19-9 levels can be assessed (category 3), but they do not represent an accurate baseline.

The Panel recommends measuring serum CA 19-9 levels after neoadjuvant treatment, prior to surgery, following surgery immediately prior to administration of adjuvant therapy, and for surveillance (category 2B). The Panel emphasizes the importance of obtaining a CA 19-9 measurement immediately before therapeutic intervention to get an accurate baseline from which to follow response, for example, before and after neoadjuvant therapy in patients with borderline resectable tumors.

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The Panel recognizes that different commercial methods are available for quantifying this tumor-associated antigen. Measurements of serum levels of CA 19-9 using one testing method cannot be extrapolated to levels obtained using a different procedure.

Differential Diagnoses

Chronic pancreatitis and other benign conditions are possible differential diagnoses of patients suspected of having pancreatic cancer.[134-138] 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, elevated CA 19-9 level, and the presence of diffuse pancreatic enlargement, a pancreatic ductal stricture, or a focal pancreatic mass.[136,139,140] 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.[140] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis. Fine-needle aspirates can also be misinterpreted as malignant or suspicious malignancies.[141] 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.[141-143]

Increased serum immunoglobulin (Ig) G levels are supportive of a diagnosis of autoimmune pancreatitis, although elevated serum levels IgG4 are the most sensitive and specific laboratory indicator.[144] IgG4 levels of >1.0 g/L combined with CA 19-9 levels of <74 U/mL distinguished patients with autoimmune pancreatitis from those with adenocarcinoma with 94% sensitivity and 100% specificity.[145] Autoimmune pancreatitis can, however, be negative for IgG4 when there is a large pancreatic mass, thus closely mimicking pancreatic adenocarcinoma.

Systemic Therapy Approaches for Locally Advanced or Metastatic Disease

Data supporting the regimens recommended in the guidelines for treating patients with pancreatic cancer are described below.

FOLFIRINOX and Modified FOLFIRINOX

A systematic review including 11 studies (*N* = 315) of patients with locally advanced pancreatic cancer treated with fluorouracil (5-FU)/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) showed a pooled median OS of 24.2 months (95% CI, 21.7–26.8).[146] An observational study of 101 patients with locally advanced unresectable disease who were treated with FOLFIRINOX as induction therapy showed that 29% of patients (20% without administration of chemoradiation) had a reduction in tumor size of >30%, and half of these patients underwent resection.[147] Out of the patients who underwent resection, 55% achieved an R0 resection.

In 2003, a French group reported the results from an open phase I study to assess the feasibility of FOLFIRINOX for the treatment of patients with metastatic solid tumors.[148] Their study included 6 patients with pancreatic cancer, of which two patients showed response (complete and partial) to FOLFIRINOX. A subsequent multicenter phase II trial specifically for patients with advanced pancreatic adenocarcinoma demonstrated promising response rates.[149] This was followed by a randomized phase II trial that showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.[150] The larger randomized phase III trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good performance status (PS) showed dramatic improvements in both median progression-free survival (PFS) (6.4 months vs. 3.3 months; *P* < .001) and median OS (11.1 months vs. 6.8 months; *P*

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< .001).[151] The 5-year follow-up showed that DFS was 26.1% vs. 19.0% with median OS of 53.5 months vs. 35.5 months in patients receiving chemotherapy with mFOLFIRINOX compared to gemcitabine.[152] Eligibility criteria for this trial, however, were stringent, limiting real-world generalizability.[153] For example, patients with high bilirubin levels were excluded from participating.

Based on these studies, FOLFIRINOX is included as a preferred, category 1 recommendation for first-line treatment of patients with good PS (ie, ECOG 0–1) with metastatic pancreatic cancer. It is listed as a category 2A recommendation for patients with locally advanced disease by extrapolation. The Panel also recommends this regimen as an acceptable option in the neoadjuvant/borderline resectable setting.

There are some concerns about the toxicity of the FOLFIRINOX regimen. In the phase III trial, some of the grade 3/4 toxicity rates, 45.7% for neutropenia, 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9.0% for sensory neuropathy, were significantly greater in the FOLFIRINOX group than in the gemcitabine group.[151] Despite this toxicity, fewer patients in the FOLFIRINOX group experienced a degradation in their quality of life (QOL) at 6 months compared to those in the gemcitabine group (31% vs. 66%, $P < .01$).[151] A more detailed analysis of patients in this trial was published and showed that FOLFIRINOX maintained and even improved QOL more so than gemcitabine.[154] No toxicity-associated deaths were reported with this regimen.[149-151]

The Panel recognizes the various approaches to manage the toxicity associated with FOLFIRINOX. For example, first-line FOLFIRINOX at 80% dose intensity was associated with good activity and acceptable toxicity when administered with routine growth factor support in carefully selected patients with metastatic or locally advanced disease.[155] Median OS was 12.5 months in the metastatic setting and 13.7 months in patients with locally advanced disease. Another phase II, single-arm, prospective trial (N = 75) assessed the efficacy and toxicity of an mFOLFIRINOX regimen in which the initial dosing of bolus 5-FU and irinotecan were each reduced by 25%.[156] In patients with metastatic disease, the efficacy of the modified regimen was comparable to that of the standard regimen (median OS = 10.2 months).The median OS was 26.6 months in patients with locally advanced disease. Patients who received the modified regimen experienced significantly less neutropenia, fatigue, and vomiting, relative to patients who received the standard FOLFIRINOX regimen (as reported by previous study). An overall response rate (ORR) of 27% was observed in 22 patients with locally advanced pancreatic cancer with a median PFS of 11.7 months.[157] Five patients (23%) were able to undergo R0 resections, although three of these patients experienced distant recurrence by 5 months.[157] Based on these studies, the Panel recommends FOLFIRINOX or mFOLFIRINOX regimen as preferred first-line treatment options for patients with good PS and locally advanced/metastatic disease.

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Gemcitabine-Based Therapy

The NCCN Panel acknowledges that, historically, combination chemotherapy does 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 often combined with other chemotherapeutic agents for patients with good and intermediate PS. Gemcitabine has been investigated in combination with potentially synergistic agents (such as cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan) or in a multidrug combination (eg, cisplatin, epirubicin, gemcitabine, 5-FU).[158-170] Two meta-analyses of randomized controlled trials (RCTs) in the advanced setting found that gemcitabine combinations give a marginal benefit in OS over gemcitabine monotherapy with a significant increase in toxicity.[171,172] Of note, results from several studies have indicated that the benefit of

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gemcitabine combination chemotherapy is predominantly seen in patients with good PS.[164,166]

The Panel does not consider the combination of gemcitabine and docetaxel[173] or irinotecan[170,173,174] to meet the criteria for inclusion in the guidelines. In addition, gemcitabine plus sorafenib is not recommended. The multicenter, double-blind, placebo-controlled, randomized phase III BAYPAN trial comparing gemcitabine plus either sorafenib or placebo in chemotherapy-naïve patients with advanced or metastatic disease did not meet its primary endpoint of PFS in its 104 patients (5.7 months vs. 3.8 months; $P = .90$).[175] Gemcitabine-based therapies recommended in the guidelines are described below.

Gemcitabine Plus Albumin-Bound Paclitaxel

Albumin-bound paclitaxel is a nanoparticle form of paclitaxel. In a phase I/II trial, 67 patients with advanced pancreatic cancer received gemcitabine plus albumin-bound paclitaxel. At the maximum tolerated dose, the partial response rate was 48% and 20% of patients demonstrated stable disease. The median OS at this dose was 12.2 months.[176]

Based on these results, a large, open-label, international, randomized phase III trial was initiated in 861 patients with metastatic pancreatic cancer and no prior cytotoxic chemotherapy.[177] Participants were randomized to receive gemcitabine plus albumin-bound paclitaxel or gemcitabine alone. The primary endpoint for the trial was OS (8.5 months for gemcitabine plus albumin-bound paclitaxel vs. 6.7 months for gemcitabine alone; $P < .001$; HR, 0.72).[177] The addition of albumin-bound paclitaxel also improved other endpoints, including 1- and 2-year survival, response rate, and PFS. In a subsequent analysis, early decrease in CA 19-9 level in both treatment arms was associated with OS improvement.[178] The most common grade 3 or higher adverse events attributable to albumin-bound paclitaxel were neutropenia, fatigue, and neuropathy. Development of peripheral neuropathy was associated with longer treatment duration and improved survival.[179] The MPACT trial showed that at least 3% of patients who received the gemcitabine plus albumin-bound paclitaxel arm were alive at 42 months compared to no patients who received gemcitabine alone.[180] Karnofsky Performance Status (KPS) score and absence of liver metastases were independent prognostic factors for OS and PFS.[181]

Based on these results, gemcitabine plus albumin-bound paclitaxel is a category 1, preferred recommendation option for the treatment of patients with metastatic disease. The clinical trials used KPS ≥70 as an eligibility criterion for gemcitabine plus albumin-bound paclitaxel.[177,180,182,183] By extrapolation of these data, the Panel recommends this combination in the locally advanced setting for patients with ECOG 0–2 (category 2A). The Panel notes that this combination with or without subsequent chemoradiation is an acceptable option in the neoadjuvant setting for resectable/borderline resectable setting. Additionally, gemcitabine plus albumin-bound paclitaxel is an option (other recommended regimens) for subsequent therapy for locally advanced/metastatic disease and therapy for recurrent disease in patients with ECOG 0–2.

Gemcitabine Plus Cisplatin

Data regarding the impact of combining gemcitabine with a platinum agent on survival are conflicting, and results of RCTs have not provided support for use of gemcitabine plus cisplatin in the treatment of patients with advanced pancreatic cancer. Phase III trials evaluating the combination of gemcitabine with cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer did not show a significant survival benefit for the combination over the single agent.[159,160,164]

Nevertheless, gemcitabine plus cisplatin has shown benefit in selected patients with breast and ovarian cancers who are carriers of a *BRCA* mutation.[184-186] A retrospective study of patients with metastatic pancreatic cancer and a family history of breast, ovarian, or pancreatic cancers

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suggested that response to gemcitabine and cisplatin was superior even with one affected relative.[187] 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, 0.76; 95% CI, 0.65–0.89; $P < .001$).[187] Furthermore, a report of five of six patients with known *BRCA* mutations and metastatic pancreatic adenocarcinoma treated with a platinum-based regimen showed a radiographic partial response.[188] Thus, gemcitabine plus cisplatin may be a good choice in selected patients with disease characterized by hereditary risk factors (eg, *BRCA* or *PALB2* mutations). The Panel recommends gemcitabine plus cisplatin for patients with metastatic or locally advanced disease or as a subsequent therapy option for patients with ECOG 0–1 and known *BRCA1/2* or *PALB2* mutations. FOLFIRINOX and modified FOLFIRINOX are also possible treatment options for patients with *BRCA1/2* and *PALB2* mutations.

Gemcitabine Plus Erlotinib and Other Targeted Therapeutics

Phase III studies of gemcitabine combinations with other biologic agents show that only the combination of gemcitabine plus erlotinib is associated with a statistically significant increase in survival compared to gemcitabine alone.[189-193] In the phase III, double-blind, placebo-controlled NCIC CTG PA.3 trial of 569 patients with advanced or metastatic pancreatic cancer randomly assigned to receive erlotinib (an inhibitor of EGFR tyrosine kinase) plus gemcitabine versus gemcitabine alone, data showed statistically significant improvements in OS in patients in the erlotinib arm (HR, 0.82; $P = .038$) and PFS (HR, 0.77; $P = .004$) compared to patients receiving gemcitabine alone.[189] 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 higher in the group receiving erlotinib, but most were grade 1 or 2.[189] This and other trials along with community experience show that occurrence of grade 2 or higher skin rash is associated with better response and OS in patients receiving erlotinib.[189,194,195]

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

Gemcitabine Plus Capecitabine

A number of randomized trials have investigated the combination of gemcitabine with capecitabine, a fluoropyrimidine, in patients with advanced pancreatic cancer. A randomized study in 533 patients with advanced disease found that PFS and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine compared with gemcitabine alone. Although a trend toward an improvement in OS for the combination arm did not reach statistical significance, the authors performed a meta-analysis that included two other studies that showed significant survival benefit.[161] A smaller phase III trial also did not demonstrate an OS advantage for the overall study population receiving the combination of gemcitabine with capecitabine, although a post-hoc analysis showed significantly increased OS in the subgroup of patients with good PS.[166] Despite greater ORR (43.7% vs. 17.6%, respectively; $P = .001$), results from a randomized phase III trial also showed that gemcitabine with capecitabine did not significantly improve OS compared with gemcitabine alone.[196] In a meta-analysis of 8 RCTs, OS was better in patients receiving gemcitabine plus capecitabine than in patients receiving gemcitabine alone (HR, 0.87; $P = .03$).[197] Although there are concerns about dosing and toxicity of capecitabine in the U.S population, a biweekly regimen of fixed-dose gemcitabine in

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combination with capecitabine may be both effective and well-tolerated in patients with advanced disease.[198]

The Panel includes the combination of gemcitabine, docetaxel, and capecitabine (GTX regimen) as a category 2B, first-line therapy for patients with metastatic or locally advanced disease and good PS. In a report of 35 patients with metastatic pancreatic cancer treated with this regimen, the authors reported an ORR in 29% of patients and 31% of patients exhibited a minor response or stable disease.[163] The median survival was 11.2 months for all patients. This regimen was associated with significant toxicities, however, with 14% of patients having grade 3/4 leukopenia, 14% having grade 3/4 thrombocytopenia, and 9% having grade 3/4 anemia. A retrospective case-review study found similar results with a median OS of 11.6 months and grade 3 or higher hematologic and non-hematologic toxicity rates of 41% and 9%, respectively.[199]

Gemcitabine combined with capecitabine and oxaliplatin (GEMOXEL) was assessed in the metastatic setting in a randomized phase II trial (N = 67).[200] Disease control rate (P = .004), PFS (P < .001), and OS (P < .001) were all superior in patients randomized to receive the GEMOXEL regimen, compared to patients randomized to receive gemcitabine alone.

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

Gemcitabine + Albumin-Bound Paclitaxel + Cisplatin

In a single-arm phase Ib/II trial of 25 patients with untreated advanced pancreatic cancer, the addition of cisplatin to gemcitabine and albumin-bound paclitaxel resulted in an ORR of 71%.[201] A phase II trial in an intention-to-treat (ITT) population of 60 patients with advanced biliary tract cancer resulted in a median PFS of 11.8 months and median OS of 19.2 months.[202] Based on these small trials, the Panel recommend this combination as a category 2A (other recommended regimens), first-line therapy for metastatic disease and extrapolating its use as a category 2B option for first-line therapy for locally advanced and subsequent therapy.

Gemcitabine and Other Fluoropyrimidine-Based Therapies

Gemcitabine in combination with other fluoropyrimidine-based therapies has also been examined. A meta-analysis of eight RCTs, including more than 2000 patients, found that OS was significantly improved when a fluoropyrimidine was added to gemcitabine.[197] In a phase II randomized trial, the effects of the FIRGEM regimen (irinotecan delivered before and after infusion of 5-FU/leucovorin [FOLFIRI.3], alternating with fixed-dose-rate [FDR] gemcitabine) were assessed in 98 patients with metastatic pancreatic cancer.[203] Patients were randomized to receive the FIRGEM regimen or FDR gemcitabine monotherapy. The primary objective of a 45% PFS rate at 6 months was reached, and PFS was a median of 5.0 months in those randomized to receive the FIRGEM regimen, while those randomized to receive only gemcitabine had a median PFS of 3.4 months (HR, 0.59; 95% CI, 0.38–0.90). Rates of hematologic toxicity were higher in those who received the FIRGEM regimen, relative to those who received gemcitabine only. Study investigators deemed FIRGEM to be effective and feasible in the metastatic setting.

The ECOG E2297 trial showed no statistically significant survival differences between gemcitabine monotherapy and the combination of gemcitabine and bolus 5-FU/leucovorin in patients with advanced pancreatic cancer.[158] Although results are inconsistent, randomized trials in Asia showed that gemcitabine in combination with the oral fluoropyrimidine S-1 may improve response and survival in patients with locally advanced pancreatic cancer compared with gemcitabine monotherapy.[204-206]

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Gemcitabine Monotherapy

For patients with newly diagnosed locally advanced or metastatic disease, gemcitabine provided a clinical benefit and a modest survival advantage over treatment with bolus 5-FU.[207] The Panel recommends gemcitabine monotherapy as one option for front-line therapy for patients with locally advanced (category 2A) or metastatic disease (category 1) and good PS. Because the approved indications for gemcitabine include relief of symptoms, the Panel also recommends gemcitabine monotherapy as a reasonable first-line and second-line option for symptomatic patients with locally advanced or metastatic disease with intermediate PS.

Gemcitabine monotherapy is also recommended as a category 1 option in the adjuvant setting. In the large phase III CONKO-001 trial, 368 patients without prior chemotherapy or RT were randomly assigned to adjuvant gemcitabine versus observation following macroscopically complete resection. An ITT analysis of the data showed that the study met the primary endpoint of increased DFS (13.4 months vs. 6.9 months; $P < .001$, log rank).[208] Final results from this study showed median OS improved significantly for patients in the gemcitabine arm compared to the observation arm (22.8 months vs. 20.2 months; HR, 0.76; 95% CI, 0.61–0.95; $P = .01$).[209] An absolute survival difference of 10.3% was observed between the two groups at 5 years (20.7% vs. 10.4%).[209]

Gemcitabine Response: hENT1

hENT1 is a nucleoside transporter that has been studied as a predictor for response to gemcitabine.[210] Preliminary clinical data showed that hENT1 expression may in fact predict response to gemcitabine.[211-215]

hENT1 was validated as a predictive biomarker for benefit from gemcitabine in the adjuvant setting. A meta-analysis including 7 studies with 770 patients with resected pancreatic cancer showed that hENT1 expression was associated with DFS (HR, 0.58; 95% CI, 0.42–0.79) and OS (HR, 0.52; 95% CI, 0.38–0.72) in patients who received adjuvant gemcitabine, but not in patients who received adjuvant fluoropyrimidine-based therapy.[216] Two retrospective analyses from ESPAC-3 and RTOG-9704 found the same results, although the adjuvant CONKO-001 and the AIO-PK0104 trials were unable to confirm these results using a different antibody for IHC analysis (SP120).[217,218]

Unfortunately, these results could not be validated in the metastatic setting in the LEAP trial, which also used the SP120 assay to determine hENT1 expression. Further studies based on hENT1 expression using the 10D7G2 assay are limited since a commercial source of the antibody and CLIA-approved testing are not available.

Fixed-Dose-Rate Gemcitabine

Studies have suggested that the infusion rate of gemcitabine may be important for its efficacy. Clinical studies have shown that administering gemcitabine at an FDR maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.[219] In a randomized phase II trial of patients with locally advanced or metastatic pancreatic cancer, the infusion of gemcitabine at an FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.[220] In the phase III randomized ECOG-6201 trial of patients with advanced pancreatic cancer, median survival was higher in the group receiving FDR gemcitabine versus standard gemcitabine (6.2 months vs. 4.9 months; $P = .04$), although this outcome did not satisfy the protocol-specified criteria for superiority.[168] 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) only in patients with poor PS.

FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX [gemcitabine and oxaliplatin]; GTX.[162,163] The combination of FDR gemcitabine and capecitabine has also been found to be active and well-tolerated.[198]

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A systematic review of clinical trials assessing the efficacy of subsequent therapy after gemcitabine in pancreatic cancer concluded that, while data are very limited, evidence suggests an advantage of additional chemotherapy over best supportive care.[221] For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable subsequent options and vice versa.[222-225]

NALIRIFOX

An initial phase I/II trial evaluating the safety and efficacy of NALIRIFOX in the first-line setting for advanced pancreatic cancer showed that this regimen was manageable and tolerated with a median OS of 12.6 months.[226] The follow-up phase III trial showed that first-line NALIRIFOX treatment resulted in a statistically significant improvement in OS and PFS compared with gemcitabine and albumin-bound paclitaxel combination in those patients without prior treatment and metastatic disease.[227] Based on these results and the inclusion of <1% of patients with ECOG ≥2, the Panel recommends NALIRIFOX as first-line therapy for metastatic disease (category 1) and extrapolating its use in locally advanced disease (category 2A). The Panel recognizes that there is high-level evidence supporting NALIRIFOX use over gemcitabine and albumin-bound paclitaxel; however, compared to FOLFIRINOX this regimen does not appear to have an advantage and adds considerably more expense.

Capecitabine-Based Regimens

The Panel lists capecitabine monotherapy as first-line and second-line treatment options for patients with locally advanced disease and metastatic disease (depending on PS). Capecitabine is also recommended as an option in the adjuvant settings (category 2B). The capecitabine recommendation is supported by a randomized phase III crossover 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. [228] 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).[229]

Capecitabine Plus Oxaliplatin

The combination of capecitabine with oxaliplatin is listed as a possible first-line treatment for locally advanced/metastatic disease (category 2B) depending on the PS and as a subsequent therapy option for patients with good PS. These recommendations are based on a phase II study [224] that only enrolled patients who had received one prior chemotherapy regimen, but the Panel feels the extrapolation to first-line therapy is appropriate (category 2B).

5-FU–Based Regimens

Continuous Infusion 5-FU

Continuous infusion 5-FU is a first-line and second-line treatment option for patients with locally advanced disease (category 2B), and for patients with poor PS and metastatic disease (category 2B). It is also recommended as an option in the adjuvant setting (category 2A for continuous infusion 5-FU). [228]

FOLFOX

Results from the open-label phase III PANCREOX trial show that the addition of oxaliplatin to 5-FU/leucovorin (OFF) in subsequent treatment may be detrimental.[230] In this trial, 108 patients with advanced pancreatic cancer who progressed on gemcitabine-based treatment were randomized to receive second-line mFOLFOX6 or infusional 5-FU/ leucovorin. No difference was seen in median PFS (3.1 vs. 2.9 months; *P* = .99), but median OS was worse in those in the FOLFOX arm (6.1 vs. 12.6 months; *P*

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= .02). Furthermore, the addition of oxaliplatin resulted in increased toxicity, with rates of grade 3/4 adverse events of 63% in the FOLFOX arm and of 11% in the 5-FU/ leucovorin arm. However, this trial was limited by imbalances in PS 2 proportion between the study arms and possible crossover in treatment following progression.[231] The randomized phase II SWOG S1115 trial showed that patients with metastatic disease that did not respond to gemcitabine-based therapy (*n* = 62) and who received mFOLFOX (5-FU and oxaliplatin) had a median OS of 6.7 months, which is comparable to the median OS rates found in the CONKO-003 and PANCREOX trials.[232] The Panel therefore recommends FOLFOX as an option for patients with metastatic disease (PS 2) who cannot be administered FOLFIRINOX because of their PS. FOLFOX is also a recommended subsequent therapy option for patients with good PS.

OFF

The Panel bases 5-FU/leucovorin/oxaliplatin (OFF) as a treatment option based on the randomized phase III CONKO study that originally tried to compare OFF to best supportive care.[223] The initial trial was terminated due to insufficient accrual (due to lack of acceptance of best supportive care). The final results of the phase III CONKO-003 trial comparing OFF to 5-FU/folinic acid in patients with metastatic pancreatic cancer and disease progression on first-line gemcitabine therapy showed a median OS in the OFF arm of 5.9 months (95% CI, 4.1–7.4) versus 3.3 months (95% CI, 2.7–4.0) in the 5-FU/leucovorin arm. This translated into a significant improvement in the HR (0.66; 95% CI, 0.48–0.91; *P* = .01).[233] Therefore, the Panel recommends OFF as a category 2A option for subsequent therapy (good PS) and by extrapolation as a category 2B first-line therapy option for both locally advanced and metastatic pancreatic cancer for patients with good PS.

FOLFIRI

The NCCN Panel recommends 5-FU + leucovorin + irinotecan (FOLFIRI) as an option for first-line therapy for patients with metastatic disease who cannot tolerate FOLFIRINOX (intermediate PS-2) and for subsequent therapy (good PS). Toxicity and efficacy studies in small patient cohorts showed that FOLFIRI was tolerable as first-line and subsequent therapies in patients with pancreatic cancer.[234,235] A phase II trial found comparable efficacy and safety for patients treated with mFOLFOX (n = 30, OS: 14.9 weeks) and modified FOLFIRI-3 (n = 31, OS: 16.6 weeks) regimens whose disease had previously not responded to gemcitabine treatment.[236] Another phase II trial investigated FOLFIRI in 63 patients with metastatic disease treated with one to three lines of gemcitabine- and platinum-based chemotherapies (in two different schedules reported together; FOLFIRI-1 and -3).[235] The median OS was 6.6 months (95% CI, 5.3–8.1 months). Patients who had grade 3–4 toxicities (23.8%) experienced mainly hematologic or digestive toxicities. A GISCAD multicenter phase II study of locally advanced or metastatic disease evaluated the FOLFIRI-2 regimen in patients previously treated with gemcitabine with or without platinum-based therapies.[237] OS was 5 months and toxicity such as grade 3–4 neutropenia (20%) and diarrhea (12%) were manageable.

5-FU/Leucovorin/Liposomal Irinotecan

In the NAPOLI-1 phase III randomized trial, effects of nanoliposomal irinotecan were examined in patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy.[238] Patients were randomized to receive nanoliposomal irinotecan monotherapy, 5-FU/leucovorin, or both (*N* = 417). Median PFS (3.1 months vs. 1.5 months; HR, 0.56; 95% CI, 0.41–0.75; *P* < .001) was significantly higher in patients who received nanoliposomal irinotecan with 5-FU/leucovorin compared to patients who did not receive irinotecan. Updated analyses showed that median OS (6.2 months vs. 4.2 months; HR, 0.75; *P* = .042) was significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin compared to patients who received 5-FU/leucovorin without irinotecan. Grade 3 or 4 adverse events that occurred most frequently with this regimen were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).[238] Irinotecan liposomal

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injection, combined with 5-FU/leucovorin, was later approved by the FDA to be used as a subsequent treatment option following gemcitabine-based therapy in patients with metastatic disease. The Panel recommends this regimen as a subsequent treatment option for patients with good/intermediate PS who received prior gemcitabine-based therapy (category 1). It is a category 2A recommendation for patients who received prior fluoropyrimidine-based therapy and for those who did not receive irinotecan.

Targeted Therapy

Larotrectinib, Entrectinib, and Repotrectinib

NTRK gene fusions, although rare, have been implicated in the oncogenesis of pancreatic cancer. The efficacy and safety of larotrectinib, an NTRK inhibitor, was investigated in three multicenter, open-label, single-arm trials (a phase I study in adults, a phase I/II study in children, and a phase II study in adolescents and adults).[239,240] The primary endpoint was set to be ORR and the secondary endpoints were determined to be PFS, duration of response (DOR), and safety. Among 12 tumor types, the ORR during independent review was 75% (95% CI, 61%–85%). After 9.4 months, 86% of participants had either undergone curative surgery or were continuing treatment. At 1 year, 55% of patients were free of disease progression and the toxicity profile of the agent was minimal.[239] Based on these data, larotrectinib was approved by the FDA in 2018 for the treatment of *NTRK* gene fusion-positive solid tumors in adult and pediatric patients with known acquired resistance, with either metastatic disease or in whom surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.[240] Updated data published in 2020 reported that 79% of patients had an objective response (95% CI, 72%–85%) with 16% showing a complete response.[241] Similarly, entrectinib, another NTRK inhibitor, was approved in 2019 by the FDA for adult and pediatric patients (aged ≥12 years) with advanced, morbid, or unresectable *NTRK* gene fusion-positive solid tumors with acquired resistance to standard treatment.[242] Data from three phase I–II trials (ALKA-372-001, STARTRK-1, and STARTRK-2) revealed that entrectinib was associated with an ORR of 75% and a median DOR of 12.9 months. Like its predecessor, it had a tolerable safety profile.[243,244] Thus, the NCCN Panel recommends larotrectinib and entrectinib as first-line and subsequent treatment options for patients with *NTRK* gene fusion-positive locally advanced or metastatic pancreatic adenocarcinoma and for recurrent disease. The only setting in which these NTRK inhibitors are not recommended by the Panel is as first-line therapy for patients with locally advanced disease and poor PS. The FDA issued accelerated approval for repotrectinib, another NTRK-based regimen, for adult and pediatric patients 12 years and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and that have progressed following treatment or have no satisfactory alternative therapy.[245] A small number of patients with pancreatic adenocarcinoma were evaluated in the TRIDENT trial,[246] resulting in a category 2A recommendation as first-line therapy for patients with locally advanced (PS 0-2) or metastatic disease (PS 0-2), and subsequent therapy or therapy for recurrent disease for patients (PS 0-1). Repotrectinib is a category 2B recommendation as first-line for patients with metastatic disease (PS 3) and subsequent therapy or therapy for recurrent disease for patients with intermediate/poor PS (PS 2-3).

Adagrasib and Sotorasib

CodeBreak 100 (NCT03600883) was a phase I/II international, multicenter, open-label, single-arm trial examining sotorasib in patients with advanced solid tumors harboring *KRAS* G12C mutation and with at least one prior therapy.[247] In a subgroup analysis of patients with non-small cell lung cancer (NSCLC) (19/129 patients), 32.2% of the group had confirmed objective responses and 88.1% of patients had disease control (objective response or stable disease). Based on these data, the

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FDA provided accelerated approval for sotorasib in *KRAS* G12C-mutated locally advanced or metastatic NSCLC. This study also included a confirmed partial response in one patient with advanced pancreatic cancer. In 2022, the efficacy of sotorasib was studied in a single-arm phase I/II trial in *KRAS* G12C-mutated advanced pancreatic cancer (n = 38).[248] Eight patients had confirmed objective response, whereas six patients had grade 3 adverse events that confirmed some antitumor activity and an acceptable safety profile of sotorasib in patients with advanced pancreatic cancer. Sotorasib is recommended as a subsequent therapy option as useful under certain circumstances for patients whose tumors have *KRAS* G12C mutations.

Around a similar time, adagrasib received accelerated approval for adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC with at least one prior therapy. A multicohort phase I/II study evaluating adagrasib showed partial responses in 50% of patients with advanced pancreatic adenocarcinoma who received prior therapy.[249] Based on these data and nearly all pancreatic tumors having *KRAS* mutations,[250] both adagrasib and sotorasib are recommended as subsequent therapy options for patients with any PS (category 2B for poor PS).

Dabrafenib/Trametinib

A subprotocol of the NCI-MATCH platform trial and the ROAR basket trial studied the efficacy of BRAF/MEK inhibitor combination of dabrafenib/trametinib in solid tumors with *BRAF* V600E mutations and biliary tract cancer, respectively.[251,252] Both of these trials showed efficacy and acceptable toxicity profiles. In 2022, the FDA provided accelerated approval for the treatment of adult and pediatric patients ≥6 years of age with unresectable or metastatic solid tumors with *BRAF* V600E mutation with progression on prior treatment and no satisfactory alternate treatments. In lieu of this, the Panel recommends dabrafenib/trametinib for first-line metastatic disease (category 2B) and as subsequent line options (category 2A) for patients with good/poor PS and with tumors that have *BRAF* V600E mutations.

Selpercatinib

Selpercatinib, a kinase inhibitor, received accelerated approval from the FDA based on treatment of *RET* fusion-positive non-small cell lung, medullary thyroid, and thyroid cancers. The trial included 11 patients with pancreatic adenocarcinoma, at least 50% of whom had objective response rates.[253] Based on these observations, selpercatinib is a recommended first-line therapy for patients with locally advanced/metastatic disease (PS 0–2) and as an subsequent therapy option for those with good PS (0–1).

Fam-trastuzumab Deruxtecan-nxki

In 2024, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. The DESTINY-PanTumor2 trial included a total of 25 patients (all good PS) with advanced or metastatic pancreatic cancer, with <20% of patients having tumors that expressed IHC 3+ HER2.[254] Based on this the Panel recommends fam-trastuzumab as a subsequent therapy option only for patients with good PS and HER2 IHC 3+ expression.

Immunotherapy

Pembrolizumab

Advances in research have revealed that human immune checkpoint inhibitor antibodies that prevent the interactions between immune cells and antigen-presenting cells may also have a similar role in tumor cells.[255] There is evidence that programmed cell death protein 1 (PD-1) blockade with pembrolizumab may be effective in tumors with dMMR.[256] Pembrolizumab is an anti-PD-1 receptor antibody and blocks its interaction with programmed death ligand 1 (PD-L1) and PD-L2, releasing

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PD-1–mediated inhibition of the immune response and improving antitumor immunity. The results of a phase II study in patients with 12 different dMMR advanced cancers, including pancreas (*N* = 6), found that treatment with pembrolizumab resulted in durable responses (ORR in 53% of patients, with 21% complete response).[257] Sixty-two percent of patients had an ORR, with two patients showing complete response and three patients showing progressive disease. Adverse events were experienced by 74% of all patients receiving pembrolizumab; most were low grade (20% experienced grade 3 or 4 adverse events, such as diarrhea/colitis, pancreatitis/hyperamylasemia, fatigue, arthritis/arthralgias, or anemia).[257] Adverse events for immune checkpoint inhibitors can be significant; please refer to the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org.

Based on these data, pembrolizumab was granted accelerated FDA approval in 2017 followed by full approval for patients with unresectable or metastatic MSI-high (MSI-H) or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Similar results were reported from the phase II KEYNOTE-158 study. Among 27 noncolorectal tumor types, including pancreatic cancer, with a median follow-up of 13.4 months; the ORR was reported to be 34.3% (95% CI, 28.3%–40.8%), the median PFS was 4.1 months (95% CI, 2.4–4.9 months), and the median OS was 23.5 months.[258,259] Results from KEYNOTE-164 and 051 showed similar durable antitumor activity, prolonged OS, and manageable safety in certain pediatric tumors and in patients with previously treated MSI-H/dMMR colorectal cancer.[260,261] These results led the FDA to grant full approval for the use of pembrolizumab for patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed on prior treatment and who have no satisfactory alternative treatment options. Pembrolizumab is a recommended option by the NCCN Panel for the advanced disease setting for first-line and subsequent treatment (if no prior immunotherapy).

Dostarlimab-gxly

Dostarlimab-gxly was active across multiple tumor types, with an ORR of 44.1% overall and 41.7% for 11 patients with pancreatic adenocarcinoma.[262] The safety profile of dostarlimab-gxly across different tumor types was acceptable with manageable toxicities. Dostarlimab-gxly received an accelerated approval for the treatment of adult patients with dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment with no satisfactory alternative treatments. The Panel consensus was to include dostarlimab-gxly as a subsequent treatment option (if no prior immunotherapy) for patients with MSI-H or dMMR locally advanced, metastatic, or recurrent pancreatic adenocarcinoma and any PS.

Nivolumab/Ipilimumab

Checkmate 848, a randomized, open-label, phase II study, was conducted in patients with advanced or metastatic solid tumors of TMB-high (TMB-H) and who were immunotherapy naïve.[263] ORR and survival outcomes with the combination improved in patients with TMB-H and who had manageable safety profiles. With limited data on pancreatic cancer, the Panel consensus resulted in nivolumab/ipilimumab being rated a category 2B, subsequent therapy option for patients with good or intermediate PS and those who did not receive prior immunotherapy.

Maintenance Therapy in Advanced Disease

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

BRCA genes encode for proteins involved in homologous recombination repair and cells with *BRCA* mutations are sensitive to PARP inhibitors; the efficacy of olaparib, a PARP inhibitor, was investigated. In a phase II trial

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assessing its efficacy and safety, the tumor response rate for patients with metastatic pancreatic cancer and germline *BRCA1/2* mutations (*n* = 23) was 21.7% (95% CI, 7.5–43.7).[264] Following this, a randomized, double-blind, placebo-controlled, phase 3 POLO trial showed that olaparib was an effective maintenance therapy agent for patients with metastatic pancreatic cancer and germline *BRCA1/2* mutations with no disease progression following at least 16 weeks of first-line platinum-based therapy. A total of 154 patients were randomized to receive either olaparib or placebo. In the olaparib arm, median PFS was 7.4 months compared to 3.8 months in the placebo arm (95% CI, 0.35–0.82, *P* = .004). At the interim analysis, however, there was no difference in OS between olaparib and placebo groups (18.9 months vs. 16.1 months, 95% CI, 0.56–1.46; *P* = .68). Adverse events, such as grade 3 or higher, were found to be higher in the olaparib arm than in the placebo arm (40% vs. 23%).[265] Based on these data, the Panel recommends olaparib as a preferred targeted maintenance therapy for patients with germline *BRCA*-mutated metastatic disease and no disease progression after 4 to 6 months of first-line platinum-based therapy. Other maintenance therapy options for patients include clinical trial enrollment; gemcitabine-based therapy for patients who received previous first-line gemcitabine and nab-paclitaxel; or capecitabine, 5-FU with or without irinotecan, or FOLFOX for patients who received previous FOLFIRINOX. The Panel included 5-FU with or without irinotecan for patients who exhibited oxaliplatin-related progressive neuropathy or allergy. Finally, if irinotecan-related gastrointestinal (GI) toxicity is of concern, then FOLFOX may be a suitable maintenance therapy.

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 several phase III trials failing 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.[266]

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

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A 2011 consensus report from a group of European experts came to many of the same conclusions.[267] Additionally, the group states that FOLFIRINOX can be considered as a new standard treatment option in selected patients in future clinical trials; however, gemcitabine should remain the standard for most patients. An international expert panel also met to discuss current and future pancreatic cancer research and came to similar conclusions.[268] 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.[269] 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 convened a working group to discuss designs for pancreatic cancer clinical trials that would accomplish meaningful clinical improvements.[270] This group concluded OS should be the primary endpoint of first-line, metastatic pancreatic cancer trials. They also concluded that trials should aspire to a 3- to 4-month improvement in OS in gemcitabine-eligible and gemcitabine/albumin-bound paclitaxel-eligible patients and a 4- to 5-month improvement in OS for FOLFIRINOX-eligible patients to have endpoints with true clinical impact.

A systematic review including 32 phase III trials showed that the following benchmarks for phase II trials were most predictive of a clinically meaningful phase III trial: 50% improvement in OS, 90% increase in 1-year survival, or 80% to 100% increase in PFS.[271] Furthermore, an algorithm, based on an analysis of a database of cooperative group trials, has been developed to calculate historic benchmarks for OS and PFS for single-arm phase II trials based on gemcitabine.[272]

Radiation and Chemoradiation Approaches

Radiation is usually given concurrently with gemcitabine- or fluoropyrimidine-based chemotherapy in patients with pancreatic cancer. Although the mechanism of radiosensitization is unclear, it is postulated that gemcitabine and fluoropyrimidines decrease the number of tumor cells in S phase of the cell cycle during which cells are resistant to radiation damage.[273]

Radiation and chemoradiation are sometimes used for pancreatic cancer in the resectable and adjuvant settings, because these treatment methods could potentially decrease local recurrence.[274] A major goal of radiation therapy (RT) in these settings is to sterilize vessel margins and increase the likelihood of margin-negative resection. It may also be used to enhance local control and prevent disease progression, while minimizing the risk of RT exposure to surrounding organs at risk. Chemoradiation is often incorporated into neoadjuvant regimens, although randomized trials demonstrating the role of chemoradiation in this setting have not been performed. The Panel notes that practices vary with regard to chemoradiation in the neoadjuvant setting, and when feasible should be coordinated through a high-volume center when neoadjuvant therapy is being considered or recommended. Chemoradiation can also be given as second-line therapy in patients with locally advanced disease following induction chemotherapy if the primary site is the sole site of progression or in patients who are not candidates for induction chemotherapy. Finally, radiation without chemotherapy is used in the metastatic or non-metastatic setting as a palliative measure.

Stereotactic body RT (SBRT), another technique aimed at increasing dose to the gross tumor while sparing radiation to nearby healthy tissue, has been studied in various stages of pancreatic cancer.[275-279] Retrospective analyses from the National Cancer Database (NCDB) including patients with locally advanced pancreatic cancer (*N* = 988, propensity matched

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groups) showed that patients treated with SBRT had better median OS (13.9 vs. 11.6 months, respectively; $P < .001$) and 2-year OS (21.7% vs. 16.5%, respectively; $P = .001$), compared to patients treated with conventionally fractionated RT.[280] Analyses of patient-reported outcomes from a phase II trial in which patients with locally advanced pancreatic cancer received SBRT either upfront or following gemcitabine showed that SBRT did not significantly impact global QOL and improved pancreatic pain ($P = .001$) and body image ($P = .007$), based on assessment at 4 to 6 weeks following treatment.[281] However, 4 months after treatment, role functioning was negatively impacted ($P = .002$). Results from a prospective trial showed that SBRT was associated with less severe radiation-induced lymphopenia 1 month after beginning treatment, relative to conventional chemoradiation (13.8% vs. 71.7%, respectively; $P < .001$).[282] SBRT should not be used if direct invasion of the bowel or stomach is observed on imaging, and care should be taken to limit dose to these areas to reduce treatment-related toxicity. SBRT delivered in 3 to 5 fractions may reduce toxicity, though longer follow-up may then be needed.[283] Since the data regarding appropriate use of SBRT are evolving, the Panel recommends that SBRT should preferably be used in the context of a clinical trial and at an experienced high-volume center.

Adjuvant Chemoradiation

In the 1980s, 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.[284,285] 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 prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 42%, compared with 15% in the control group.[284]

Other studies have also shown an advantage to adjuvant chemoradiation over observation after resection. EORTC conducted a phase III trial (40891) in patients with adenocarcinoma, in the pancreatic head and periampullary regions, assessing adjuvant RT and 5-FU versus observation alone after surgery. They found that the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant.[286] At a median follow-up of 11.7 years, no statistically significant differences were observed in PFS or OS in the different study arms.[287]

More contemporary studies have compared different regimens incorporating chemoradiation. The phase III Radiation Therapy Oncology Group study, RTOG 9704, evaluated the addition of gemcitabine to adjuvant 5-FU-based chemoradiation in patients with resected pancreatic adenocarcinoma.[288] Results of this study showed that, for patients with tumors of the pancreatic head (n = 388), there was a non-statistically significant increase in OS in the gemcitabine arm compared with the 5-FU arm (20.5 vs. 16.9 months median survival; $P = .09$). This benefit became more pronounced on multivariate analysis (HR, 0.80; 95% CI, 0.63–1.00; $P = .05$). The 5-year analysis of RTOG 9704 showed that there was in fact no OS difference between the two groups, although multivariate analysis showed that patients with tumors in the head of the pancreas trended towards improved OS with gemcitabine ($P = .08$).[289]

The Role of Radiation in Adjuvant Regimens

The majority of data comparing chemotherapy to chemoradiation in the adjuvant setting does not generally show an advantage to the addition of radiation. Results of ESPAC-1 suggested that 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,

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chemotherapy, and chemotherapy plus chemoradiation, respectively),[290] although the ESPAC-1 trial has been criticized for lack of attention to quality control for RT.[291-293] A phase II study by GERCOR randomized patients to adjuvant gemcitabine or adjuvant gemcitabine-based chemoradiation.[294] No differences were seen in OS (24.4 months vs. 24.3 months) or DFS (10.9 months vs. 11.8 months) between the groups, but with only 45 patients in each arm no *P* values were reported. In addition, the multicenter, open-label, randomized phase III CapRI trial found that adjuvant chemoradiation with 5-FU, cisplatin, and interferon alfa-2b followed by 5-FU chemotherapy resulted in no better outcomes than adjuvant treatment with 5-FU alone.[295]

A meta-analysis of 15 prospective, randomized trials found that adjuvant chemoradiation did not improve DFS, 2-year survival, or OS (OR, 0.99; $P = .93$) compared to surgery alone, while adjuvant chemotherapy improved DFS, 2-and 5-year survival, and OS (OR for OS, 1.98; $P < .001$).[296] Another meta-analysis of 9 trials found similar results, with HRs 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) compared to no adjuvant treatment.[297]

However, a population-based assessment of patient outcomes in the NCDB for those undergoing pancreatic cancer resections between 1998 to 2002 found the opposite result: chemoradiation was associated with 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).[298] A multi-institutional pooled analysis of 955 consecutive patients with pancreatic cancer who had R0-1 resections also showed that adjuvant chemoradiation improved survival compared to chemotherapy alone (OS, 39.9 months vs. 27.8 months; $P < .001$).[299]

To definitively clarify the role of chemoradiation following gemcitabine monotherapy in the adjuvant setting, RTOG is conducting trial 0848 (NCT01013649). In step 1 of this protocol (the chemotherapy comparison arm), patients were randomized to adjuvant gemcitabine versus the combination of gemcitabine and erlotinib; however, there was no OS differences between the two groups.[300] Similarly, adjuvant SBRT did not provide survival benefit or improved local disease control for resected stage II pancreatic ductal adenocarcinoma (PDAC) in a single-center randomized control trial.[301]

Benefit of Adjuvant Chemoradiation in Patient Subsets

Studies that have looked at subsets of patients with R0 or R1 resections 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.[302] In contrast, results from a prospective database with 616 patients who had resected pancreatic cancer found that adjuvant chemoradiation benefited both the R0 and R1 subsets compared to observation alone.[303] A retrospective review of patients who had R0 resections for pancreatic adenocarcinoma found an OS benefit in those receiving adjuvant chemoradiation over observation.[304] In addition, a retrospective review of >1200 resected patients 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; $P < .001$).[305] A meta-analysis of four RCTs found evidence of increased survival benefit with 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).[306]

Fewer analyses have looked at the role of chemoradiation in resected patients with positive lymph nodes. One retrospective review compared patients who received adjuvant chemoradiation to those who were

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observed after distal pancreatectomy and found higher survival in the patients who received adjuvant chemoradiation.[307]

Chemoradiation and SBRT for Locally Advanced Disease

A meta-analysis of 15 RCTs in the locally advanced setting showed that chemoradiation improved survival compared to radiation alone but not to chemotherapy.[308] Chemoradiation was also significantly associated with higher hematologic and non-hematologic toxicities compared to radiation and chemotherapy groups.

Multiple regimens have been tested in the chemoradiation setting for locally advanced disease. An initial study by GITSG showed that the combination of bolus 5-FU and split-course radiation (total dose, 4000 cGy) resulted in a nearly 2-fold increase in median survival (42.2 vs. 22.9 weeks) compared with radiation alone.[285] Subsequent studies have sought to optimize the use of 5-FU, and most contemporary studies no longer use split-course radiation. Multiple studies studied the utility of gemcitabine as part of chemoradiation.[309-313] Some evidence even 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.[311,314-316] Capecitabine was also assessed in a small number of patients.[317] Health-related QOL scores (ie, cognitive functioning, fatigue, bloating, dry mouth, body image, future health concerns) of this trial favored capecitabine-based chemoradiation, compared to gemcitabine-based chemoradiation.[318] Therefore, the Panel lists 5-FU- and capecitabine-based chemoradiation as preferred regimens and gemcitabine as an other recommended chemoradiation-based regimen.

Upfront Chemoradiation or SBRT in Locally Advanced Disease

Results of two early randomized trials comparing upfront chemoradiation to chemotherapy in locally advanced disease showed contradictory results and were not able to confirm superiority of upfront chemoradiation.[319,320] Additional phase II trials assessed the upfront chemoradiation approach in locally advanced PDAC, with median survival rates ranging from 8.2 to 9 months.[309,321-323] Results from small, single-arm trials of induction chemotherapy followed by chemoradiation in locally advanced disease show median survival between 12 to 19 months.[324]

The phase III randomized ECOG-4201 trial that assessed the addition of radiation to gemcitabine chemotherapy compared with gemcitabine alone in patients with locally advanced pancreatic cancer was closed early due to poor accrual. However, an ITT analysis of data for the 74 patients enrolled in this study showed that median OS was significantly longer in the chemoradiation therapy arm of the study (11.1 months vs. 9.2 months; one-sided $P = .017$ by stratified log-rank test).[313] However, the poor accrual rate decreased its statistical power resulting in no difference in PFS and the CIs for OS overlapped between the two groups of patients[325]

The benefit of chemotherapy versus chemoradiation was also addressed in the phase III FFCD-SFRO study from France that showed 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; $P = .006$) in patients with locally advanced pancreatic cancer.[326] This study was stopped before the planned accrual, because an interim analysis revealed that patients in the chemoradiation arm had a lower survival rate. Patients in the chemoradiation arm also 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 toxicity associated with the chemoradiation regimen.

Upfront SBRT may be used in patients with locally advanced disease who are not candidates for combination systemic treatment. A retrospective analysis of 77 patients with unresectable disease demonstrated that while

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SBRT gave effective local control it was associated with significant toxicities.[275] However, another retrospective study of 71 patients reported a median OS of 10.3 months with only three patients experiencing grade 3 toxicity.[277] Another study showed that hypofractionated dosing may also be used in these patients, with acceptable toxicity.[327] The incorporation of simultaneous integrated boost is being investigated to develop SBRT use for downstaging.[328]

The role of upfront chemoradiation in the setting of locally advanced pancreatic cancer is still undefined. If patients present with poorly controlled pain or local invasion with bleeding, then starting with upfront chemoradiation therapy or SBRT is an option.[309,313]

Chemoradiation or SBRT Following Chemotherapy in Locally Advanced Disease

Based on certain study results, starting with 2 to 6 cycles of systemic chemotherapy followed by chemoradiation or SBRT is an option under useful in certain circumstances for selected patients with locally advanced disease and good/intermediate PS who have not developed systemic metastatic disease.[329-331] SBRT or chemoradiation may delay time to disease progression. Employing an initial course of chemotherapy may improve systemic disease control. In addition, the natural history of the disease can become apparent during initial chemotherapy allowing for selection of patients most likely to benefit from subsequent chemoradiation. For example, a retrospective analysis of outcomes from the GERCOR studies indicate that first-line treatment with chemotherapy may be a useful strategy for selecting patients, with locally advanced disease and no rapid progression, who are more likely to benefit from subsequent chemoradiation therapy.[329]

In the randomized phase II SCALOP trial, patients with locally advanced pancreatic cancer received gemcitabine and capecitabine combination chemotherapy, followed by either gemcitabine- or capecitabine-based chemoradiation (n = 74).[317,332] Though OS and PFS did not significantly differ between the two treatment arms, results favored capecitabine-based chemoradiation, with a median OS of 17.6 vs. 14.6 months and a median PFS of 12 vs. 10.5 months compared to gemcitabine-based chemoradiation.[332]

In the international phase III LAP-07 RCT, patients with locally advanced pancreatic cancer (n = 269 after second randomization) received chemoradiation with capecitabine following 4 months of induction chemotherapy with either gemcitabine monotherapy or gemcitabine and erlotinib.[333] Chemoradiation in this setting provided no survival benefit, compared to chemotherapy only (HR, 1.03; 95% CI, 0.79–1.34; P = .83). SBRT following gemcitabine monotherapy was associated with low toxicity and favorable freedom from local disease progression in patients with locally advanced pancreatic cancer has also been examined in phase II trials.[334,335]

Advanced Radiation Techniques

Intensity-modulated RT (IMRT) is increasingly being applied for therapy of locally advanced pancreatic adenocarcinoma and in the adjuvant setting with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues.[336-340] A retrospective treatment planning study that evaluated whether dose escalation might have been possible in 15 patients with locally advanced, unresectable pancreatic adenocarcinoma if IMRT had been used instead of 3D conformal planning concluded that IMRT would have allowed for a significant increase in target dose volume.[340] However, there is no clear consensus on the appropriate maximum dose of radiation when IMRT is used. A systematic review including 13 IMRT studies showed that IMRT does not improve survival outcomes, compared to 3D conformal RT (CRT).[341] However, toxicities grade 3 or greater, mainly GI, specifically nausea/vomiting and diarrhea, were more numerous in 3D-CRT, relative to IMRT (P = .017).

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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 3D-CRT in the RTOG 9704 trial.[288,342] Comparing the two 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),[342] suggesting that IMRT may be well-tolerated and allow for higher radiation doses to the tumor.[342]

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 PS (ECOG 0-1, with good biliary drainage, and adequate nutritional intake). Systemic therapy is therefore recommended for patients with metastatic disease and good PS, as described in *Systemic Therapy Approaches for Locally Advanced or Metastatic Disease*, above, and in the algorithm.

Patients who present with poor PS may benefit from single-agent chemotherapy (gemcitabine, standard infusion, is a category 1 recommendation). Alternative options for patients with poor PS include targeted therapy based on molecular profiling and as clinically indicated, palliative RT, and palliative and best supportive care. Patients with metastatic disease are generally not candidates for RT. However, palliative RT may be administered to patients who present with poor PS (ie, patients who are older and/or not candidates for definitive treatment), instead of single-agent chemotherapy. A short course of RT may be administered to metastatic sites that cause pain (eg, osseous pain).[343] For patients with metastatic disease who do well on initial therapy, a chemotherapy holiday is appropriate, or maintenance therapy can be considered. In case of disease progression, subsequent therapy can be considered. But comfort-directed measures are always paramount (see *Palliative and Supportive Care*, below, and the various NCCN Guidelines for Supportive Care, available at www.NCCN.org).

Before initiating therapy, an open dialogue regarding the goals and side effects of treatment should take place and, if needed, adjunctive strategies can be used. Of note, patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is initiated, it should proceed with close monitoring and follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumors may develop quickly, and new tumor-related symptoms may be inappropriately attributed to chemotherapy or other causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or in its more subtle form, as abdominal bloating, as decreased oral intake, and/or as constipation.

Management of Locally Advanced Disease

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

Historically, most studies in the locally advanced setting use gemcitabine monotherapy. However, there is an increasing emphasis on understanding the role of modern, more active regimens in locoregionally advanced disease. Other studies and case reports addressing the use of

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chemotherapy with or without chemoradiation in patients with locally unresectable disease have noted that the opportunity for curative intent resection occasionally arises.[344-349] The Panel believes that patients with no disease progression when treated with chemotherapy and/or chemoradiation may be considered for surgical resection, but acknowledges that such conversions are rare in patients with true locally advanced disease.

Upfront chemoradiation or SBRT may be used in select patients. If disease progression occurs in patients with locally advanced disease, clinical trial (preferred) or systemic therapy or chemoradiation or SBRT are treatment options. However, chemoradiation or SBRT is only recommended for those who maintain good PS, if chemoradiation or SBRT were not previously given, and the primary site is the sole site of progression.

Irreversible electroporation (IRE) is an ablative technique in which electric pulses are used to create nanopores to induce cell death. This technique has been used in patients with locally advanced pancreatic cancer and may be safe and feasible and improve survival.[350-352] However, due to concerns about complications and technical expertise,[353] the Panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer.

Management of Resectable and Borderline Resectable Disease

Surgical Management

The goals of surgery for adenocarcinoma of the pancreas include an oncologic resection of the primary tumor and regional lymph nodes. Surgical resection is the only potentially curative technique for managing pancreatic cancer. However, >80% of patients present with disease that is not resectable.[354] Surgery should be done efficiently, optimizing QOL and cost. Early concerns about high mortality associated with various pancreatic resection procedures[355] were lessened by studies demonstrating an acceptably low (<5%) mortality in experienced centers.[356] Even under the most optimal clinical trial conditions, the median survival of resected patients following adjuvant therapy ranges from 20.1 to 28.0 months.[208,288,290,357,358] Negative margin status (ie, R0 resection), tumor DNA content, small tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[359-361]

Criteria for Resection

The Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation at high-volume centers with use of appropriate high-quality imaging studies. Although it is clear that patients with visceral, peritoneal, or pleural metastases or with metastases to nodes beyond the field of resection derive no benefit from resection, institutions differ in their approaches to patients with locoregional disease involvement (pancreas and peripancreatic lymph nodes).

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

The Panel recommends considering frozen section analysis of the pancreatic neck and bile duct at the time of surgery. Frozen sections should be taken approximately 5 mm from the transection margin, with the clean-cut side facing down, to avoid cautery artifact that may confound analysis and result in false negatives. If tumor is located within 5 mm of margins, further excision of the pancreas should be considered to ensure

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at least 5 mm of clearance. A review of four studies with 2580 patients showed that additional resection to achieve a negative surgical margin was not associated with improved survival.[362] For cancers involving head and uncinate of the pancreas, a pancreatoduodenectomy (Whipple procedure) is performed. For cancers involving body and tail of the pancreas, a distal pancreatectomy with en-bloc splenectomy is performed.

Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus and other groups developed criteria to define tumor resectability to improve patient selection for surgery and increase the likelihood of an R0 resection.[62,363-365] A more restrictive definition of borderline resectable pancreatic tumors has also been described.[366] This definition uses degrees of contact (eg, interface between tumor and SMA measuring ≤180˚ of vessel wall circumference) and contour deformity/narrowing (eg, tear drop deformity in the MPV or SMV) to ascribe likelihood of vascular invasion rather than subjective terms such as abutment and impingement. The Panel endorses this definition for use in clinical trials. Degree of contact and deformity are much more objective and are more easily communicated. Deformity, in particular, is extremely accurate in predicting vascular invasion and the need for resection/reconstruction. Using a combination of these sets of criteria, tumors are classified as resectable, borderline resectable, locally advanced, or metastatic disease.

The Panel has adapted the criteria put forth by other groups and lists its recommended criteria for defining resectability status in the guidelines. The consensus of the Panel is that patients should be selected for surgery on the basis of curative intent as determined by the probability of obtaining negative (R0) resection margins. The likelihood of attaining negative margins is the key criterion for consideration when determining whether a patient is a potential candidate for resection.[365,367] Therefore, a borderline resectable lesion can be defined as one in which there is a higher probability of an incomplete resection. Patients at high risk for positive surgical margins are not considered to be good candidates for upfront resection but may be potentially down staged and safely resected following neoadjuvant therapy. The Panel recommends that patient factors be considered when deciding whether a patient is a surgical candidate and decisions about resectability status be made in consensus in multidisciplinary meetings/discussions. Comorbidities, PS, and frailty are all things to be discussed during the multidisciplinary review. Please refer to the NCCN Guidelines for Older Adult Oncology (available at www.NCCN.org) for further discussion of the treatment of older patients.

Primary Surgery for Pancreatic Cancer

The nature and extent of surgery for resectable tumors depend on the location and size of the tumor. Because tumors of the pancreatic body and tail cause symptoms late in their development, they are usually advanced at diagnosis and are rarely resectable. When tumors in the pancreatic tail are resectable, distal pancreatectomy, in which the surgeon removes the tail and body of the pancreas, as well as the spleen, is commonly performed. If the cancer diffusely involves the pancreas or is present at multiple sites within the pancreas, a total pancreatectomy may be required where the surgeon removes the entire pancreas, part of the small intestine, a portion of the stomach, the common bile duct, gallbladder, spleen, and nearby lymph nodes. Patients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with open or minimally invasive pancreaticoduodenectomy (ie, the Whipple procedure).[368,369]

In patients with suspected borderline resectable disease for whom cancer is not confirmed following repeated biopsy with EUS-FNA, referral to a high-volume center for further evaluation is recommended. If biopsy is positive, the Panel recommends considering ERCP with stent placement followed by neoadjuvant therapy. If the tumor is found to be unresectable

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during surgery, the Panel recommends biopsy confirmation of adenocarcinoma and genetic testing for inherited mutations, if not previously performed. If a patient with jaundice is found to be unresectable at surgery, then the Panel recommends surgical biliary bypass at that time, unless biliary bypass was performed at the time of laparoscopy or laparotomy. If a stent has been previously placed, then surgical biliary bypass could be considered. In addition, gastrojejunostomy can be considered if appropriate regardless of jaundice. Celiac plexus neurolysis can also be performed, especially when indicated by pain in a patient with jaundice (category 2B if no pain).

Pancreatoduodenectomy (Whipple Procedure)
Achieving a margin-negative dissection requires focusing on meticulous perivascular dissection of the lesion, recognizing the need for vascular resection and/or reconstruction, and the potential need for extra-pancreatic organ resection. However, 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 there is no evidence of tumor infiltration). Further, skeletonization of the lateral, posterior, and anterior borders of the SMA down to the level of the adventitia will maximize uncinate yield and radial margin (see Figure 1).[370,371] Optimal dissection and skeletonization of the SMA can be achieved using ultrasonic or thermal dissectors. Division of the retroperitoneal tissues between the uncinate process and SMA with a stapler or a clamp and cut technique may leave up to 43% of the soft tissue in situ and result in suboptimal clearance and increase the risk of an R1 resection.[372,373]

In the absence of frank venous occlusion noted on preoperative imaging, the need for lateral venorrhaphy or complete PV/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 carcinoma to the lateral wall of the PV is not uncommon and, if at all possible, requires careful dissection to free the vein from the pancreatic head. It is frequently impossible to differentiate tumor infiltration into the vein wall from tumor-related desmoplasia. Liberal use of partial or complete vein resection when vein infiltration is suspected during Whipple procedures has been studied.[374-376] 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 operative procedure. However, if an R0 resection is obtained with vein excision, longevity appears similar to those with R0 resections without venous involvement, with no significant increase in morbidity and mortality. These data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected.

Although numbers are more limited, similar findings have been noted in cases of hepatic arterial resection and reconstruction.[376,377] A population-based study of 10,206 patients from the Nationwide Inpatient Sample from years 2000 through 2009 found that although no differences in mortality were observed, vascular reconstruction (about 90% venous and 10% arterial) is associated with a higher risk of intraoperative and postoperative complications.[378] Others have noted poor short- and long-term outcomes with arterial resection.[378,379] 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 with En-bloc Splenectomy
The goals of left-sided resection are similar to those of pancreatoduodenectomy, although they are often more difficult to achieve because of the advanced stage at which most of these cancers are discovered. Plane of dissection anterior to adrenal gland or en bloc

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resection of left adrenal gland with plane of dissection posterior to Gerota's fascia as clinically indicated is recommended. 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 ≤40% of patients.[380,381] 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.[381,382] 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.[380-382] 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.[381,382] Local recurrence, however, remains problematic even with pathologically negative margins.[382]

There is an increasing role for laparoscopic distal pancreatectomy. A meta-analysis including 29 observational studies with 3701 patients showed that laparoscopic distal pancreatectomy may decrease intraoperative blood loss ($P < .01$), time to first oral intake ($P < .01$), and length of hospital stay ($P < .01$), as compared to open distal pancreatectomy.[383] Similarly, other studies found significant benefits in patients ($N = 172$) who had laparoscopic versus open distal pancreatectomy with reductions in blood loss, need for blood transfusions, and length of hospital or intensive care unit stays without any difference in oncologic outcomes.[384,385 386]

Management of Neck Lesions

Pancreas neck adenocarcinomas are especially difficult to manage since these tumors are located anterior to the superior mesenteric vessels and PV. The precise extent of involvement often cannot be determined prior to surgery; therefore, complex intraoperative decisions are required, and the surgeon must anticipate this. Complexity of surgery for pancreas neck cancers is compounded by the frequent involvement of the SMV/PV.[387,388] Surgeons who operate on pancreas neck cancers must anticipate possible SMV/PV involvement and be prepared to manage it. Depending on the extent of involvement, a pancreaticoduodenectomy extending to the left of the SMV (extended pancreaticoduodenectomy), a distal pancreatectomy extending to the right of the SMV (extended distal pancreatectomy), or a total pancreatectomy may be required to obtain an R0 resection.[388]

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.[389] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreatoduodenectomy decreased, a subset of patients in need of resection of the SMV wall to achieve negative margins during removal of their tumors were identified. Thus, in the 1990s, there was renewed interest in vein resection for complete resection. A single-institution experience has demonstrated that vein resection and reconstruction can allow for complete resection and is not associated with increased morbidity or mortality in comparison to cases where vein resection was not required.[390] Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.[391]

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.[392-395] One study found that properly selected patients with adenocarcinoma of the pancreatic head who required vein resection (n = 141) had a median

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survival of approximately 2 years that statistically did not differ from those having standard pancreatoduodenectomy and was superior to historical controls in which patients believed to have locally advanced disease did not receive surgical treatment.[376] A meta-analysis of 22 retrospective studies (*N* = 2890) found that, although R0 resection rates were lower, vein resection resulted in perioperative morbidity and mortality equal to that of standard resection.[396] In a multi-institutional database analysis of 492 patients undergoing pancreaticoduodenectomy, R0 resection rates were no different between those who had vein resection compared to those without venous involvement (66% vs. 75%; *P* = NS).[397] Nevertheless, a few groups have recommended caution and use vein resection only for selected patients.

Pylorus Preservation

Stomach reconstruction options after pancreatoduodenectomy center on preservation of the pylorus. Traverso and Longmire[398] reported on the modern use of pylorus preservation in 1978. The hypothesis was that preservation would improve emptying and provide nutritional benefit, but the advantages have been inconsistent to date. A systematic review (including eight RCTs with 512 patients) showed no significant differences for mortality, morbidity, and survival, but some perioperative measures (ie, operating time, intraoperative blood loss, red blood cell transfusion) were better in patients who received pylorus-preserving pancreaticoduodenectomy, relative to those who received a classic Whipple procedure.[399] Though more data from high-quality RCTs are needed, pylorus-preserving pancreatoduodenectomy is an acceptable alternative to classic pancreatoduodenectomy performed with antrectomy.

Pancreatic Anastomosis

Efforts have focused on preventing pancreatic leaks and fistulas, which are morbid and potential lethal complications of pancreatoduodenectomy. Pancreaticojejunostomy has traditionally been the standard reconstruction method and is the major focus of morbidity and mortality after pancreatoduodenectomy because of leaks, abscess formation, and fistulas from this anastomosis. A randomized study found no difference in fistula rates after pancreaticojejunostomy and pancreaticogastrostomy.[400] However, a multicenter, randomized superiority trial (*N* = 329) showed a significant difference in postoperative fistulas, which occurred in 19.8% of patients in the pancreaticojejunostomy group vs. 8.0% of patients in the pancreaticogastrostomy group (OR, 2.86; 95% CI, 1.38–6.17; *P* = .002).[401] An increase in grade ≥3a postoperative complications was seen, however, in the pancreaticogastrostomy group (39 vs. 35 patients). Although a meta-analysis of four RCTs (676 patients) concluded that pancreaticogastrostomy is associated with a lower risk of fistula formation than pancreaticojejunostomy (RR, 0.41; 95% CI, 0.21–0.62),[402] the optimal approach to anastomosis remains based on the surgeons experience, preference, and adherence to principles including good exposure and visualization.[403]

Surgeons have also examined various other options, including end-to-end, end-to-side, duct-to-mucosa, and invaginating techniques, for pancreaticojejunal anastomosis, which have all proven to be safe and effective.[404,405] Results of a prospective trial show that pancreatic fistula can be almost entirely avoided by combining placement/tying of sutures under magnification with meticulous attention to blood supply.[406] Stents used in the 1930s/1940s continue to be used today with data suggesting that they do not decrease leak rates.[407]

Technical modifications, such as octreotide, have been examined for their ability to decrease postoperative pancreaticojejunal leaks in patients undergoing pancreatic resections. However, octreotide did not decrease fistula rates when assessed in two prospective, randomized, double-blind, placebo-controlled studies.[408,409] The use of fibrin glue sealant also does not appear to decrease the rate of pancreatic fistulas.[410] Pasireotide, in

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contrast, significantly decreased the rate of grade ≥3 fistula, leak, or abscess in a single-center, double-blind RCT of 300 patients (9% in pasireotide group vs. 21% in placebo group; RR, 0.24; 95% CI, 0.24–0.78; *P* = .006).[411]

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.[412,413] An extended lymphadenectomy in patients undergoing pancreatoduodenectomy entails removal of nodes at the duodenum and pancreas, on the right side of the hepatoduodenal ligament and SMA, and the anterior and posterior pancreatoduodenal lymph nodes.[414] An extended lymphadenectomy is most commonly performed in the United States by removing not only the nodes removed in the standard procedure, but also soft tissue in the retroperitoneum from hilum of the right kidney to the left lateral border of the aorta on the right side, and from PV to origin of the inferior mesenteric artery on the left.[415]

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 (with low statistical power) and did not support the concept that an extended lymphadenectomy was a good prognostic factor.[416] A larger, randomized, prospective, single-institution trial was performed from 1996 to 2001 to evaluate the role of extended lymph node dissections.[417] The group of patients who received regional lymphadenectomy in addition to pancreatoduodenectomy had longer operation times, but overall median survival did not differ between the two groups at 1, 3, and 5 years.[417-419] A randomized multicenter trial in Japan came to similar conclusions.[420] Furthermore, multiple systematic literature reviews and meta-analyses of RCTs comparing pancreatoduodenectomy with standard versus extended lymphadenectomy support the conclusion that the extended procedure does not have any impact on survival.[421-423] In fact, a review of four prospective randomized trials and a meta-analysis inferred that patients undergoing extended lymphadenectomy may have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.[424]

No survival advantage has been found when performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.[425] Data suggest that nodal metastases is 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 sites have inferior prognoses.[426,427]

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis and potentially make surgery less morbid by improving liver function preoperatively. Although controversial, several studies suggest that pancreatoduodenectomy is associated with higher perioperative mortality when performed in the setting of hyperbilirubinemia.[428-430] Stenting of the biliary system can improve symptoms and liver function, but it is not clear whether these changes can decrease the mortality rate associated with the Whipple procedure. Several prospective and retrospective studies have not shown decreased mortality in patients with preoperative biliary drainage.[431-437] A

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retrospective analysis of 593 patients treated with pancreatoduodenectomy 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.[438] In contrast, a multicenter, randomized trial in 202 patients with cancer of the pancreatic head characterized by obstructive jaundice and comparing preoperative biliary drainage with surgery alone, showed a nearly 2-fold increase in the rate of serious complications in the stented group (74% vs. 39%; RR in the surgery alone group, 0.54; 95% CI, 0.41–0.71; $P < .001$). However, no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.[90]

Based on these reports, most groups who perform resection without neoadjuvant treatment advocate selective use of decompression only in patients who are symptomatic, septic, coagulopathic, have renal insufficiency, or in whom surgical resection is significantly delayed. The Panel includes in this group patients who present with jaundice and potentially resectable disease if symptoms of cholangitis or fever are present, or if they have significant pruritus with an expected delay to surgery of >1 week.

For patients with jaundice undergoing neoadjuvant therapy, biliary decompression is necessary before initiation of therapy and appears to be well-tolerated with minimal increase in perioperative morbidity. A single-institute experience with more than 300 patients, 57% of whom had preoperative biliary drainage as part of a neoadjuvant chemoradiation program, found that wound complications were significantly increased in the drainage group; however, no other association was found for sepsis, fistulae, or death.[439] Stent placement is thus required prior to administration of neoadjuvant therapy for patients with jaundice.[440-443]

The Panel notes that stents are an evolving technology. The choice of stents includes plastic and self-expanding metal (fully covered, partially covered, or uncovered). While any stent can become occluded, several groups have reported better patency with metal stents.[441,442] Since covered metal stents prevent tumor ingrowth, they may give more durable patency however migration may be an issue with these stents.[444,445] However, there are no obvious differences between covered and uncovered stents.[444,445] This issue has led to the introduction of partially covered stents, but these stents may still migrate in a substantial number of patients.[446,447] Most metal stents used today are self-expanding. Their small initial diameters make them easy to place and their placement rarely requires dilation.[448] Several institutions use plastic stents in patients with short life expectancies (<3 months).[449] In the absence of level 1 data, the Panel consensus is that short, self-expanding metal stents (SEMS) are preferred because they are easy to place without dilation, unlikely to interfere with the subsequent resection, and have a significantly longer patency rate than plastic stents. The Panel recommends that a fully covered self-expandable metal stent be placed if tissue diagnosis has not been confirmed, as fully covered metal stents can be removed or exchanged.

Effect of Clinical Volume

The fundamental premise of several studies that examined the effect of institutional volume on patient outcomes 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 1995 study that included a cohort of almost 2000 patients showed that two high-volume centers in New York State had significantly less perioperative mortality than low-volume centers (4% vs. 12.3%).[450] High volume, defined as >81 cases per year, correlated to perioperative mortality in a regression analysis. Of note, 75% of the

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cases in New York State were performed in low-/minimal-volume centers. Several other studies that assessed regional outcomes with pancreatoduodenectomy from U.S. and international hospitals have reported decreased mortality, hospital length of stay, and overall cost at high-volume centers (or with surgeons who perform the resections frequently) when compared with low-volume centers. [451-458]

The definitions of high and low volume varied among all these studies. However, a striking difference was seen when the mortality rates from pancreatoduodenectomy in very-low-volume (0–1 procedure/year) and low-volume (1–2 procedures/year) hospitals were compared with rates in high-volume hospitals (>5 procedures/year).[459] The association of hospital volume and improved 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 pancreatic resections per year were classified as “high” and “very-high” volume centers.[460] In this study, ≥6 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 specifically observed for pancreatic resections. These results further reinforced the magnitude of effect that high-volume centers can specifically have on outcomes in patients with pancreatic cancer.

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 high-volume centers.[461] In addition, a systematic review showed that margin status correlates with hospital volume, with negative margin rates ranging from 55% in low-volume centers to 75.7% for very-high-volume centers (P = .008).[462] This review also found that 5-year survival rates were superior 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.[463] The Panel recommends that pancreatic resections should be conducted at institutions that perform a large number (at least 15–20) of pancreatic resections annually.

Pathology

Making progress in pancreatic adenocarcinoma treatments is encumbered due to variations, such as pathologic analysis and reporting, among different members involved in diagnosing and treating this disease.[464] A standardized approach could maximize the likelihood of more complete and consistent reports 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 the pathology report will provide better communication among the various members of the patient care team, including physicians. It will also provide a clear and specific understanding of the individual tumor characteristics, including critical margin status, allowing for a more accurate assessment 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 are useful for reporting results from examinations of surgical specimens and assist pathologists in providing clinically useful and relevant information. In 2004, the Commission on Cancer (CoC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. The pathology synoptic reports from the College of American Pathologists

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(CAP) comply with the CoC requirements, and are updated and revised regularly.[465] The Panel currently supports the CAP pathology synoptic reports and includes in the guidelines an abbreviated *minimum* analysis of pancreatic cancer specimens from the CAP recommendations. Attached organs resected with the specimen en bloc require serial sectioning to assess not only direct extension, but metastatic deposits as well. In addition to the standard TNM staging, other variables are included, all of which have prognostic implications in disease evolution.[466,467]

Lymph Node Counts and Lymph Node Ratio

A systematic review showed that the number of positive lymph nodes and lymph node ratio are associated with OS in patients with pancreatic cancer.[468] The CAP recommendations include a count of the number of lymph nodes recovered and the number of involved nodes.[465] Retrospective analyses show that patients with N0 disease have a better prognosis with an increasing number of examined lymph nodes.[469-471] These results suggest that a significant portion of patients with N0 disease might be under staged. 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.[469,471,472] For patients with N1 disease, lymph node ratio (positive node/nodes examined) appears to be related to prognosis.[469-476] 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).[474] The Panel believes that every effort should be made to identify all regional lymph nodes within the pancreatectomy specimen.

Whipple Specimen

Specimen orientation and inking involves both a pathologist and surgeon, as this will help to ensure accurate assessment of size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method (ie, written on the pathology requisition). For example, the distal and proximal margins of SMV and SMA, as well as the bile duct margin, should be marked.

One of the impediments to comparison of data across institutions is the variability in the names given to various margins. Definitions of the margins and uniformity of nomenclature are critical to accurate reporting. The Panel's recommended definitions are included in the *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* section of the algorithm. Margins defined include the SMA (retroperitoneal/uncinate) margin, posterior surface, SMA groove margin, gastric/enteric margins, 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 is therefore strongly recommended but not required to be reported in all cases.[464,477-479] 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 also influenced by institutional preferences, expertise, and experience. There is no one correct way to dissect a Whipple specimen. Options include axial, bi- or multi-valve slicing, and perpendicular slicing (see Figure 3). Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas. Axial slicing provides an overall assessment of the epicenter of tumor

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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 would allow better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if <1-mm clearance is associated with an unacceptably high incidence of local recurrence, then strong consideration for postoperative RT, if not received preoperatively, might be indicated. The Panel strongly recommends reporting tumor clearance in mm for all margins (within 1.0 cm of tumor) to allow prospective accumulation of these important data for future analysis.

A retrospective review found that patients with R0 resections of close margins (within 1 mm) had an improvement in OS (35 months vs. 16 months; $P < .001$) compared with patients with wider margins (>1 mm).[480] In fact, patients with close-margin R0 resections had a median survival time similar to that of the R1 population (16 months vs. 14 months; $P = .6$). Consistent with these results, another retrospective review of 285 patients found that those with R1 resections, defined as tumor ≤1 mm from the margin, had a significantly worse local recurrence-free survival than those with R0 resections (HR, 4.27; 95% CI, 2.07–8.81).[481] Additionally, a study using a standardized pathologic protocol that involved multicolor inking and careful evaluation of multiple margins distances found that patients with at least one positive inked margin had a median survival of 17.7 months versus a median survival of 32.9 months in patients with R0 resections ($P = .10$).[482] Together, these results suggest that an appropriate definition of a negative margin may be >1 mm.

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 because direct tumor invasion of the spleen constitutes a pT3 pathologic stage. Frozen section analysis of the pancreatic neck is a recommended option. Definitions of the proximal pancreatic (transection) margin, anterior (cephalad) peripancreatic (peripheral) surface, and posterior (caudad) peripancreatic (peripheral) margin are included in the guidelines.

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. 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. For example, patients enrolled in CONKO-001 were more likely to have negative lymph nodes and positive resection margins than those in RTOG 9704, whereas CONKO-001 excluded patients with high postoperative CA 19-9 or CEA levels.[208,289] Despite these differences, the median OS for patients in the gemcitabine arm of CONKO-001 (22.8 months), the gemcitabine-containing arm of RTOG 9704 (20.5 months), the bolus 5-FU/leucovorin arm of ESPAC-1 (20.1 months), and the gemcitabine and 5-FU/leucovorin arms of the ESPAC-3 study (23.6 and 23.0 months) are remarkably similar. Results of the ESPAC-4 phase III randomized trial ($N = 730$) showed that median survival was greater for participants randomized to receive the adjuvant gemcitabine/capecitabine combination regimen (28.0 months) relative to patients randomized to receive adjuvant gemcitabine monotherapy (25.5 months) (HR, 0.82; 95% CI, 0.68–0.98; $P = .032$).[358] In the CONKO-005 phase III randomized trial, gemcitabine

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administered with erlotinib did not significantly improve OS or DFS compared to gemcitabine administered alone in the adjuvant setting.[483] A phase II prospective trial with 22 patients with resected pancreatic cancer showed that gemcitabine/cisplatin is feasible, with a median OS of 35.5 months and median recurrence-free survival of 16.7 months.[484]

Based on the data discussed above, no definite standard has been established in the adjuvant treatment of pancreatic cancer at this time. The Panel-recommended adjuvant options (for patients who did not receive prior neoadjuvant therapy) for chemotherapy alone include gemcitabine/capecitabine (category 1, preferred), modified FOLFIRINOX (category 1, preferred), gemcitabine (category 1, other recommended), 5-FU/leucovorin (category 1, other recommended), or continuous infusion 5-FU (other recommended). Capecitabine monotherapy is also a treatment option for the adjuvant setting (category 2B). Gemcitabine, bolus 5-FU/leucovorin, or continuous infusion 5-FU before gemcitabine- or fluoropyrimidine-based chemoradiation with subsequent chemotherapy are also recommended as adjuvant treatment options. To date, no studies have demonstrated superiority of giving chemoradiation before versus after chemotherapy in the adjuvant setting. For those who received prior neoadjuvant therapy, the options for adjuvant therapy depend on the response to neoadjuvant therapy and other clinical factors. Regardless of the therapy being considered it is important to evaluate the patient for extent of disease prior to therapy, because some patients have early recurrence within the first few weeks following surgery. In addition, the Panel recommends restaging a patient with imaging following systemic chemotherapy if chemoradiation is planned.

A retrospective analysis of data from patients in the ESPAC-3 trial found that completion, but not the time to initiate treatment, of the six-course chemotherapy was an independent prognostic factor for survival.[485] These results suggest that delaying chemotherapy until patients fully recover after surgery could possibly allow for completion of the full chemotherapy course and improve outcomes. The Panel therefore recommends that adjuvant treatment should ideally be initiated within 12 weeks, to allow for adequate recovery from surgery.

Results of the phase III RCT JASPAC-01 trial (*N* = 385), in which S-1, an oral chemotherapy drug used in Japan, used in the adjuvant setting showed greater median OS (46.5 months; 95% CI, 37.8–63.7) compared to gemcitabine (25.5 months; 95% CI, 22.5–29.6).[486] Three- and 5-year survival rates were 59.7% and 44.1%, respectively, for S-1, and 38.8% and 24.4%, respectively, for gemcitabine. S-1 was generally well-tolerated, and patients were less likely to discontinue treatment compared to patients randomized to receive gemcitabine (*P* = .005). Grade 3 or 4 adverse events that were more likely to be reported in patients receiving gemcitabine included leucopenia, neutropenia, aspartate aminotransferase, and alanine aminotransferase, while stomatitis and diarrhea were more common in patients receiving S-1.

Results of the PRODIGE 24/CCTG PA.6 phase III trial (n = 493) comparing adjuvant chemotherapy with gemcitabine versus mFOLFIRINOX to treat resected pancreatic adenocarcinoma in patients with good PS have been published.[487] The median follow-up was 69.7 months (95% CI, 67.0–73.9). The 5-year DFS rate was greater for mFOLFIRINOX (26.1%; 95% CI, 20.5–32.1) compared to gemcitabine (19.0%; 95% CI, 14.3–24.3). The median OS (53.5 vs. 35.5 months, respectively) and metastasis-free survival (29.4 months vs. 17.7 months, respectively) were also greater for mFOLFIRINOX compared to gemcitabine. An ongoing clinical trial in the adjuvant setting includes RTOG 0848 (NCT01013649), which is assessing gemcitabine with or without subsequent chemoradiation.

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In the Event of Leucovorin Shortage

There is 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 levoleucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levoleucovorin 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, based on several studies, that lower doses are likely to be as efficacious as higher doses. The QUASAR study, in patients with colorectal cancer, 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.[488] Another study in patients with metastatic colorectal cancer showed no difference in response rate or survival between those who received bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) leucovorin.[489] Although 5-FU doses were different in the two arms, a study in the 1980s 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.[490] Finally, if none of the above options is available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

Preoperative (Neoadjuvant) Therapy

The standard approach to therapy in patients with resectable disease has been postoperative treatment, with median survivals in the range of 20.1 to 23.6 months under the most optimal clinical trial conditions.[208,288,290,357] However, it is becoming increasingly apparent that patients with borderline resectable disease, at a higher risk for R1 resections, potentially need a different management approach. Contemporary approaches to perioperative treatment have focused on neoadjuvant therapy for patients with borderline resectable disease with the goal of improving OS.[348] Neoadjuvant therapy is also sometimes used in patients with resectable disease, especially in those with high-risk features. The putative benefits of neoadjuvant therapy include: 1) increasing the likelihood that a higher proportion of patients with resectable disease will receive chemotherapy and/or radiation; 2) increasing the likelihood of a margin-free resection by downstaging tumors (ie, conversion to resectable status); 3) selecting patients with disease that is more stable or responsive to therapy for surgery; and 4) treating micrometastases at an earlier stage.[365,491-493] Moreover, surgery following neoadjuvant treatment appears to be safe.[494,495]

Retrospective analyses showed that relative to neoadjuvant chemotherapy, neoadjuvant chemoradiation is associated with better local control, with no significant differences in survival.[496] Chemoradiation following chemotherapy is sometimes included in the neoadjuvant setting. Doses for neoadjuvant chemoradiation that have been reported include 36 Gy in 2.4 Gy/fraction, or 45 to 54 Gy in 1.8 to 2.0 Gy/fraction.[493,497] The role of chemoradiation with more active chemotherapy regimens needs to be tested. Practices vary with regard to neoadjuvant chemotherapy and chemoradiation, and when feasible, treatment should be performed at or coordinated through a high-volume center. The Panel strongly encourages participation in clinical trials.

Pancreatic protocol CT or MRI of the abdomen, and chest/pelvis CT should be repeated following neoadjuvant therapy. Retrospective studies suggest that imaging characteristics may not be a reliable indicator of resectability in borderline resectable and locally advanced patients who have received neoadjuvant therapy.[498,499] Determinations of resectability and surgical therapy should be made on an individualized basis in a multidisciplinary setting. Surgical resection should only be attempted if

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there is a high likelihood of achieving an R0 resection. Surgery is ideally performed 4 to 8 weeks after therapy. Surgery can be performed more than 8 weeks following therapy, but radiation-induced fibrosis may potentially make surgery more difficult. Importantly, results from retrospective studies suggest that radiographic response does not correlate with pathologic response in patients with borderline resectable disease.[500,501] Therefore, if no apparent tumor shrinkage is observed after neoadjuvant treatment and no extrapancreatic progressive disease is evident, surgery should still be attempted.

Neoadjuvant Therapy in Borderline Resectable Disease
Patients with borderline resectable disease and no metastatic disease should be considered for neoadjuvant therapy followed by restaging and resection in patients without disease progression that precludes surgery. Use of neoadjuvant therapy in the setting of borderline resectable disease has been a highly debated topic. 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. Upfront resection in patients with borderline resectable disease is no longer recommended.

Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerated.[502-507] Most of these were phase II trials and showed that neoadjuvant therapy in a small percentage of patients with borderline resectable disease allowed for tumor resection and in one study R0 resection.[503-505] In two retrospective studies, 31% to 35% of patients with borderline resectable disease who completed neoadjuvant therapy had R0 resections.[508,509] A systematic review and meta-analysis of 19 cohort studies found that patients with unresectable disease (including both borderline resectable and unresectable) undergoing neoadjuvant chemoradiation therapy had similar 1-year survival outcomes as patients who were initially deemed resectable, although there was an increased risk of perioperative death.[510]

It is important to note that no randomized phase III trials have compared neoadjuvant therapy in borderline resectable disease versus surgery without initial therapy. Although not yet published, the results of NCT00557492, studying neoadjuvant chemoradiation, are posted on clinicaltrials.gov. In addition, the Alliance A021101 trial (NCT01821612), a single-arm pilot study, evaluated the safety and efficacy of FOLFIRINOX before capecitabine-based chemoradiation and surgery. [507] Preliminary results including 22 patients, with borderline resectable disease, from multiple centers showed that median OS was 21.7 months, and 68% of patients underwent resection.[507] Out of the 15 patients who underwent resection, all but one had microscopically negative margins, and two had a complete response. However, the number of grade 3 or higher adverse events was considerable, with 64% of patients experiencing one of these events. Other results with small patient cohorts suggest that FOLFIRINOX, as a neoadjuvant regimen, is a promising approach in patients with borderline resectable disease.[511-513] Chemotherapy followed by SBRT may also be safe and feasible in the neoadjuvant setting, and improve the potential for resection in patients with borderline resectable or locally advanced disease.[283,514] However, further studies are needed before SBRT is recommended as a treatment option for patients with borderline resectable disease.

Neoadjuvant Therapy in Resectable Disease
A retrospective study showed that patients who received neoadjuvant therapy followed by resection had better OS than those with the same propensity score and received upfront resection (median survival 26 months vs. 21 months, respectively; HR, 0.72; 95% CI, 0.68–0.78; $P < .01$).[515] A number of studies, trials, and retrospective analyses have evaluated the use of neoadjuvant chemoradiation in patients with

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resectable disease.[516-524] A retrospective review of the collective single-institution experience suggested that preoperative chemoradiation therapy in patients with resectable disease provides an survival advantage.[517] 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.[517] In this analysis of 132 consecutive patients, the authors reported that combined preoperative chemoradiation and pancreatoduodenectomy yielded a median survival of 21 months, and 31% of patients were alive without evidence of disease at a median follow-up of 14 months.[517]

Other potential advantages of the neoadjuvant approach in patients with resectable disease have also been described, including sterilization of the field before resection potentially reducing spread during surgery, increased rates of R0 resections, decreased incidence of pancreatic fistulas, prevention of delays or reductions of adjuvant therapy after surgery, and improved delivery of chemotherapy and radiosensitizing oxygenation.[495,525]

Although most studies investigating the neoadjuvant experience in patients with resectable pancreatic cancer are retrospective, several small phase II studies have been published.[495,526,527] A randomized phase II trial evaluating the safety and efficacy of gemcitabine-based neoadjuvant therapy for patients with resectable pancreatic cancer found that more patients receiving gemcitabine with cisplatin were able to undergo resection compared with those who received gemcitabine only.[522]

In a prospective trial, preoperative radiation with concurrent gemcitabine was administered to 86 patients with resectable disease, and patients were restaged and evaluated for surgery 4 to 6 weeks following completion of neoadjuvant treatment.[519] Although all patients were able to complete neoadjuvant therapy, only 73 (85%) patients were able to undergo surgery at the time of restaging; the majority of the remaining patients were precluded from undergoing a pancreatoduodenectomy due to disease progression. Similar results were observed in another phase II trial with 90 enrolled patients (n = 79 who completed chemo-chemoradiation); 52 out of 79 patients were able to complete neoadjuvant gemcitabine/cisplatin followed by gemcitabine-based chemoradiation therapy underwent surgery.[442] Most patients precluded from surgery had advanced disease at restaging. These results provide support for restaging patients with abdominal (pancreas protocol), pelvis, and chest imaging; measuring CA 19-9 levels; and staging laparoscopy, if not done previously, 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,[528] randomized trials testing this association are needed. A randomized phase II trial, terminated early because of slow accrual, compared gemcitabine/cisplatin neoadjuvant chemoradiation followed by surgery with upfront surgery; both arms received adjuvant chemotherapy.[529] With only 66 patients eligible for analysis, no significant differences were seen in R0 resection rate (52% vs. 48%, $P = 0.81$), (y)pN0 rate (39% vs. 30%, $P = 0.44$), or OS (25.0 months vs. 18.9 months, $P = 0.79$). All comparisons favored the neoadjuvant arm, and no safety issues were noted. The phase III NEOPA trial, with OS as the primary endpoint, was set to study patients with resectable pancreatic cancer and compared neoadjuvant gemcitabine chemoradiation therapy to upfront surgery in this population and was terminated early due to lack of recruitment.[530,531] A randomized phase II study comparing mFOLFIRINOX and gemcitabine/nab-paclitaxel as neoadjuvant regimens following surgery showed that 76% completed perioperative therapy and of these 33% had a complete or major pathologic response following surgery. Although the trial demonstrated safety and high resectability rate, the 2-year survival rate for patients who

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received any neoadjuvant therapy was not significantly different from historical data of patients with resectable disease receiving adjuvant therapy.[532,533] The GEMCAD 10-03 trial enrolled a small number of patients and showed promising results in those who received neoadjuvant gemcitabine and erlotinib followed by chemoradiation and then surgery.[534]

There is limited evidence to recommend specific neoadjuvant regimens that are not investigated as part of a clinical trial, and practices vary among the Panel with regard to the use of chemotherapy and chemoradiation.

Adjuvant Treatment After Neoadjuvant Therapy

For patients who received neoadjuvant treatment, data supporting additional therapy after surgery are lacking. The consensus of the Panel is that patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. When chemotherapy is given, the choice of regimen may be based on response seen to neoadjuvant therapy and other clinical considerations, such as PS and patient tolerability.

Adjuvant chemotherapy or adjuvant chemoradiation, ideally initiated within 12 weeks, should only be considered for patients who have adequately recovered from surgery and have no evidence of recurrence or metastatic disease. It is recommended that the patient undergo a pretreatment baseline assessment following surgery, including pancreas protocol CT scan (abdomen) and chest/pelvis CT with contrast, CA 19-9 level, and genetic testing if not previously performed, to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Further, the Panel recommends restaging a patient with imaging after each treatment modality, if it will precede chemoradiation.

Neoadjuvant Clinical Trials

For neoadjuvant trials, study populations should be well-defined and standardized. The Panel endorses use of a restrictive definition of borderline resectable disease in clinical trials, such as that defined in an Intergroup trial.[366] Endpoints should also be standardized by including resection rates, R0 resection rates, local recurrence rates, pathologic response rates, DFS, and OS.[535]

Surveillance of Patients with Resected Disease

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited,[536,537] recommendations are based on the consensus that earlier identification of disease may allow patients to enroll in investigational studies or other forms of treatment. The Panel recommends history and physical examination for symptom assessment and chest CT and CT or MRI of abdomen and pelvis with contrast (unless contraindicated) as appropriate. An analysis of the SEER-Medicare database showed no significant survival benefit for patients who received regular surveillance CT scans.[538] CA 19-9 determination is a category 2B recommendation because there are no data on early treatment of recurrences due to increased tumor marker levels leading to better patient outcomes.

Management of Recurrent Disease After Resection

As cross-sectional body imaging has improved, small-volume metastatic disease or local recurrences are being detected in patients with resected pancreatic cancer who otherwise maintain good functional status. These patients will, however, ultimately progress.

For patients experiencing a recurrence of disease following resection, the Panel recommends consideration of confirmatory biopsy (category 2B), genetic testing for hereditary mutations (if not previously done), or molecular profiling of tumor tissues. In cases of recurrent disease, except

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in cases of pancreas only, clinical trial is an option; palliative and best supportive care without additional therapy is also an option, especially for patients with metastatic disease and poor PS. In a pooled analysis of 55 patients (from 19 studies) who underwent pancreatectomy for recurrent pancreatic cancer, 1-, 3-, and 5-year survival rates were 82.2%, 49.2%, and 40.6%, respectively.[539] Therefore, for patients with local disease recurrence, surgical resection may be considered in select cases (ie, location of recurrence is in the pancreas only). Chemoradiation can be considered in patients with local disease recurrence in the pancreatic bed, if radiation has not been previously administered, or a systemic chemotherapy regimen can be given. However, there are limited data to support specific RT recommendations for recurrent disease. For patients for whom there is evidence of metastatic disease (with or without a local recurrence), systemic therapy options are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed <6 months prior to development of metastatic disease, the Panel recommends that an alternative chemotherapy option be administered (eg, switching to a gemcitabine-based regimen if fluoropyrimidine-based therapy was previously used, or vice versa). When this period is ≥6 months, repeating systemic therapy as previously administered or switching to any other systemic regimen are recommended options.

Management of Isolated Pulmonary Metastases

Some patients have isolated lung metastases after resection of localized pancreatic adenocarcinoma. A growing body of evidence in this population suggests that the lung is the most common site of recurrence in patients who are followed 5 years after their first diagnosis.[540] Preliminary retrospective data suggest that resections of isolated pulmonary metastasis may be advantageous in this population.[541] More data are needed before recommendations can be made regarding the management of pulmonary metastases of pancreatic cancers.

Palliative and Supportive Care

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that are, in many respects, unique to the disease. The multidisciplinary management of symptoms due to biliary obstruction, gastric outlet obstruction, and cancer-related pain is of primary importance. The main objective of palliative care is to prevent and ameliorate suffering while ensuring optimal QOL. 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.[542] For patients diagnosed with unresectable disease and biliary obstruction upon initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent SEMS is recommended unless biliary bypass was performed at the time of laparoscopy or laparotomy. Stent occlusion that causes recurrent cholangitis is a well-known complication of plastic (temporary) biliary stents and typically occurs within 3 months of insertion. Metal stents are wider in diameter than plastic stents (ie, less likelihood of blockage) and become embedded in the bile duct, whereas plastic stents are more likely to become occluded but can be replaced. Results of an RCT of 100 patients at a single center randomly assigned to receive either a plastic stent or a covered SEMS inserted endoscopically indicated that median patency times were 1.8 and 3.6 months (P = .002), respectively.[543] A meta-analysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.[544] 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); however, no significant differences in technical/therapeutic success, complications, or 30-day mortality were found. Another randomized trial studying biliary obstruction due to

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pancreatic cancer showed that covered SEMS, with an anti-migration system, had longer patency than uncovered SEMS due to prevention of tumor ingrowth.[545]

When a biliary stent cannot be placed (often because the endoscope cannot be advanced past the tumor 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, which has been shown to be safe and effective in the long term.[546] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.[546]

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, which can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain. The Panel recommends stenting or an open biliary-enteric bypass with or without gastrojejunostomy (category 2B for prophylactic gastrojejunostomy[547,548]) and with or without celiac plexus neurolysis [549-551] (category 2B in patients without pain).

Biliary decompression is also required for jaundiced patients with disease progression precluding surgery with or without neoadjuvant therapy. Here, stenting or biliary bypass is recommended, with or without gastrojejunostomy, if clinically indicated, and with or without celiac plexus neurolysis (category 2B in patients without pain). One final circumstance requiring biliary drainage is in jaundiced patients with locally advanced or metastatic disease (those for whom surgical resection will not be attempted). In this situation, a SEMS is preferred unless biliary bypass was performed at the time of laparoscopy or laparotomy. If cancer has not been biopsy-confirmed in the setting of locally advanced disease in a patient with jaundice, biopsy can be repeated at the time of stent placement.

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10% to 25% of patients with pancreatic cancer.[542] Patients with locally advanced or metastatic disease and a short life expectancy or poor PS who develop gastric outlet obstruction may be palliated with an endoscopically placed enteral stent after biliary drainage is assured.[546] An alternative for these patients with poor PS is percutaneous endoscopic gastrostomy (PEG) tube placement. For a fit patient with a life expectancy >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.[552-554] Placement of an enteral stent is particularly important in patients with poor PS and should be done after biliary drainage is assured.

For patients with potentially resectable disease who undergo a laparotomy and are found to have unresectable disease, a gastrojejunostomy should be performed as clinically indicated. The role of prophylactic gastrojejunostomy in otherwise asymptomatic patients, with unresectable cancers found at the time of laparotomy, has been evaluated. Two RCTs have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer, the majority arising from the head of the pancreas.[547,548] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. A meta-analysis found similar results, with development of gastric outlet obstruction in 2.5% of patients in the prophylactic gastrojejunostomy group and 27.8% of those not receiving gastrojejunostomy.[555] In both studies, prophylactic retrocolic

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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.[551] General principles for cancer-related pain management can be found in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). Patients with severe tumor-associated abdominal pain should be treated with around-the-clock analgesics. However, some patients will be unresponsive to analgesics or will experience undesirable side effects. Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, celiac plexus neurolysis should be considered (category 2A only when indicated by pain in a patient with jaundice with unresectable disease found at surgery). In several RCTs, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.[549,551,556] In a study of 96 individuals with pain related to suspected pancreatic cancer, patients (n = 48) randomized to EUS-guided celiac plexus neurolysis at the time of EUS with confirmed unresectable adenocarcinoma reported better pain relief at 3 months (P = .01).[550] These results suggest that early EUS-guided celiac plexus neurolysis may be beneficial. A meta-analysis of seven RCTs in patients with pancreatic cancer concluded that celiac plexus neurolysis significantly improved pain scores at 4 weeks, which was not maintained at 8 weeks.[557] Another RCT measuring the effectiveness of ethanol celiac plexus neurolysis for pain in resectable pancreatic and periampullary adenocarcinoma found no significant impact on postoperative pain (N = 467).[558] Minimally invasive techniques including EUS-guided (preferred if available) and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis are recommended, but laparoscopic, thoracoscopic, and open approaches can also be used.

In selected patients with severe local back pain refractory to analgesic therapy, palliative RT may be considered to ameliorate pain, bleeding, and/or local obstructive symptoms, in the settings of both metastatic and non-metastatic disease, if not already given as part of primary therapy. In such cases, radiation is given with or without concurrent chemotherapy to the primary tumor plus a margin, or radiation alone is given to the metastatic site. The dose used should take into account the burden of disease, normal tissue tolerance, and expected survival.

Pancreatic Exocrine Insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or blockage of the pancreatic duct, or by surgical removal of pancreatic tissue, and results in an inadequate production of digestive enzymes.[559,560] This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.[561] Pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency. Because pancreatic exocrine insufficiency occurs in >80% of patients undergoing pancreatic surgery,[562,563] enzyme replacement 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.[561] A prospective, double-blind, phase II RCT including 67 patients with unresectable pancreatic cancer showed no significant difference in weight loss between patients randomized to receive pancreatic exocrine replacement therapy or placebo.[564] For patients with disease that does not respond to this therapy, doses of the enzyme preparation can be increased, and inhibition of gastric secretion with a proton pump inhibitor can also be considered.[561,562] Patients with a

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clinical suspicion of pancreatic exocrine insufficiency despite appropriate replacement may need a more thorough nutritional evaluation with a registered dietitian when available.

Thromboembolic Disease

The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.[565,566] 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 two large, prospective, randomized clinical trials: CLOT and CONKO-004. In CLOT, investigation of patients with advanced or metastatic cancer and VTE over a period of 6 months showed a 2-fold decrease in the incidence of recurrent VTE in patients treated with the LMWH, dalteparin, compared with those treated with an oral anticoagulant.[567]

Results from the CONKO-004 trial showed that the cumulative incidence rates of symptomatic VTEs were lower in patients randomized to receive enoxaparin (n = 160) relative to patients receiving chemotherapy only (n = 152) (HR, 0.40; 95% CI, 0.19–0.83; P = .01).[568] PFS and OS did not significantly differ between the two groups. In a pilot trial conducted in preparation for the CONKO-004 trial, the risk of developing symptomatic VTE was significantly lower for patients in the LMWH arm of the study with no significant increase in bleeding observed in this group compared to those not receiving enoxaparin.[568] The Panel does not recommend prophylactic LMWH at this time, due to the lack of evidence regarding impact on survival. Please see the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease for more information (available at www.NCCN.org).

Bleeding From the Primary Tumor Site

GI bleeding in patients with pancreatic adenocarcinoma is hard to study because it is uncommon, but can carry a serious prognosis.[569] Various causes of GI bleeding include segmental portal hypertension,[570] gastric or duodenal ulcer erosion, and radiation-induced gastritis.[569] Treatment options for GI bleeding should be used according to clinical judgment regarding the specifics of the patient's case. Endoscopic techniques[571] or RT,[572] when other options are not feasible, may be an effective treatment for GI bleeding. As a final attempt, upper GI bleeding may be stopped with angiography with embolization.[573,574]

One study of 246 eligible patients with pancreatic cancer included 32 patients with GI bleeding of varying grade.[569] The median OS of patients with GI bleeding was 9 months and in patients without GI bleeding was 14.5 months. Conservative care was given to patients with bad physical state (N = 11), endoscopic hemostasis was given to 20 patients, and angiography and embolization were given to 1 patient. Therapeutic endoscopy was successful in 37.5% of patients and angiography with embolization was successful in 1 patient. Overall, 10.2% (25 patients) succumbed due to bleeding. The average time from GI bleeding to death was 31.5 days and the average OS rate was 10 months.

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

Depression, Pain, and Malnutrition

For many patients, a diagnosis of pancreatic cancer may result in significant psychosocial distress, including anxiety, depression, and sleep disturbances.[575] In fact, the suicide rate in male patients with pancreatic cancer is reportedly about 11 times that of the general population.[576]

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Empathetic discussion about the natural history of this disease and its prognosis and the provision of support and counseling both by the primary oncology team and specialized services may help to alleviate this distress. The Panel recommends that patients be screened and evaluated for depression and other psychosocial problems following the NCCN Guidelines for Distress Management (available at www.NCCN.org).

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

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Summary

Patients with borderline resectable disease and select patients with resectable disease can undergo neoadjuvant therapy in the hopes of improving the chances for an R0 resection. Patients with locally advanced disease and good PS can undergo chemotherapy and chemoradiation or SBRT with second-line therapy if PS is maintained after progression. Patients with good PS presenting with metastatic disease can undergo chemotherapy and second-line therapy if PS is maintained after progression. Specific palliative measures are recommended for patients with advanced pancreatic adenocarcinoma characterized by biliary or gastric obstruction, severe abdominal pain, or other tumor-associated manifestations of the disease. Overall, in view of the relatively high likelihood of poor outcomes for patients with all stages of pancreatic cancer, the NCCN Panel recommends that investigational options be considered in all phases of disease management.

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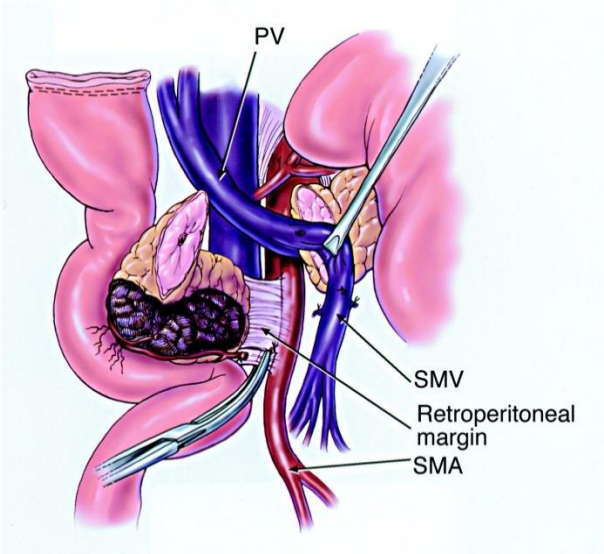

Figure 1. Complete mobilization of the superior mesenteric (SMV) and portal vein (PV), and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA).[577]

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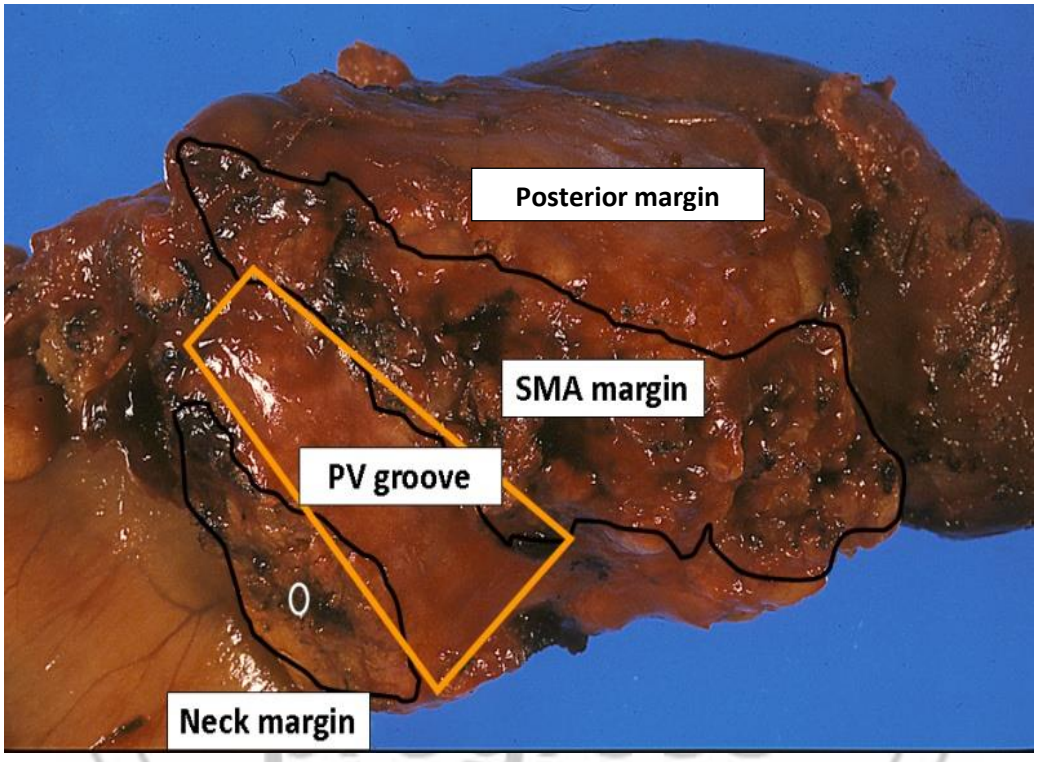

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Figure 2. Whipple specimen with labeled margins.

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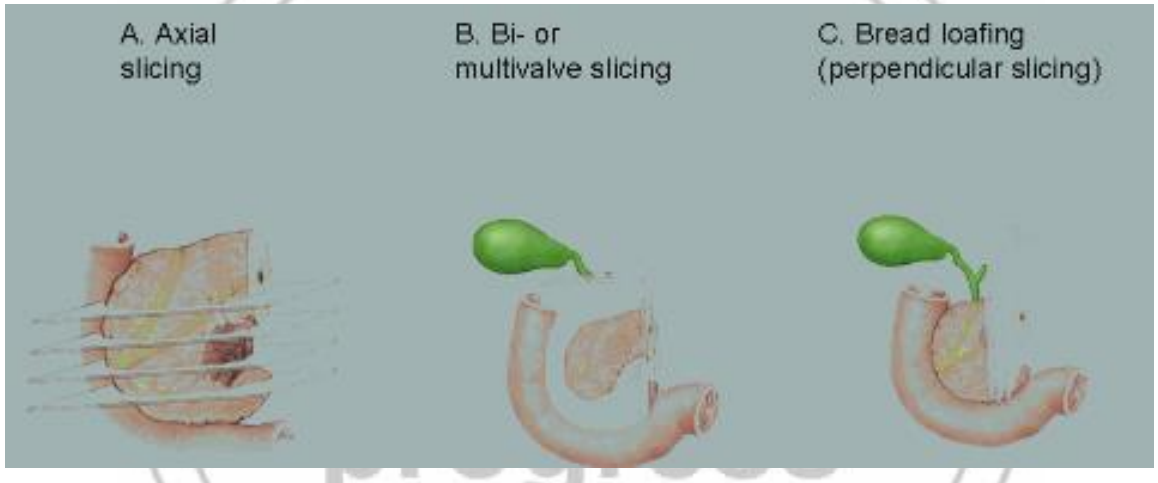

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Figure 3. Slicing of pancreatoduodenectomy specimens.[464]

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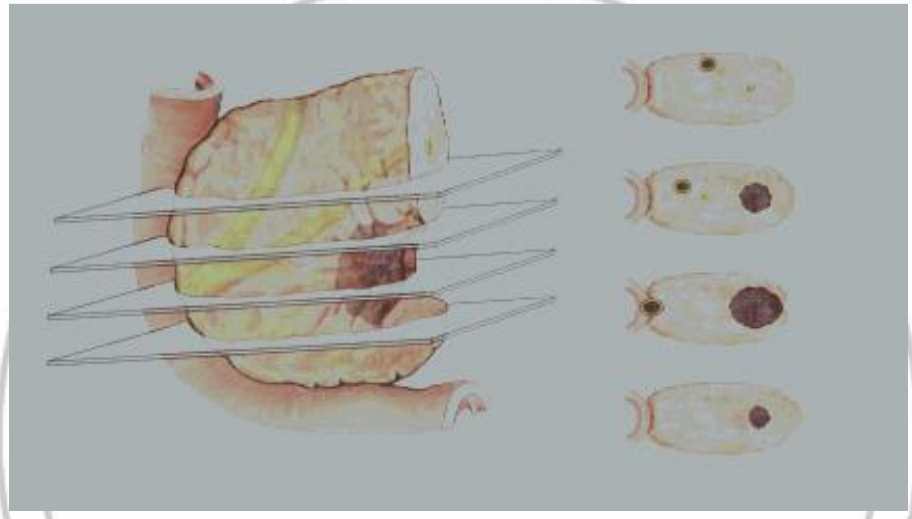

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Figure 4. Slicing of the pancreatoduodenectomy specimen in the axial plane to allow circumferential assessment of tumor.[464]

progress

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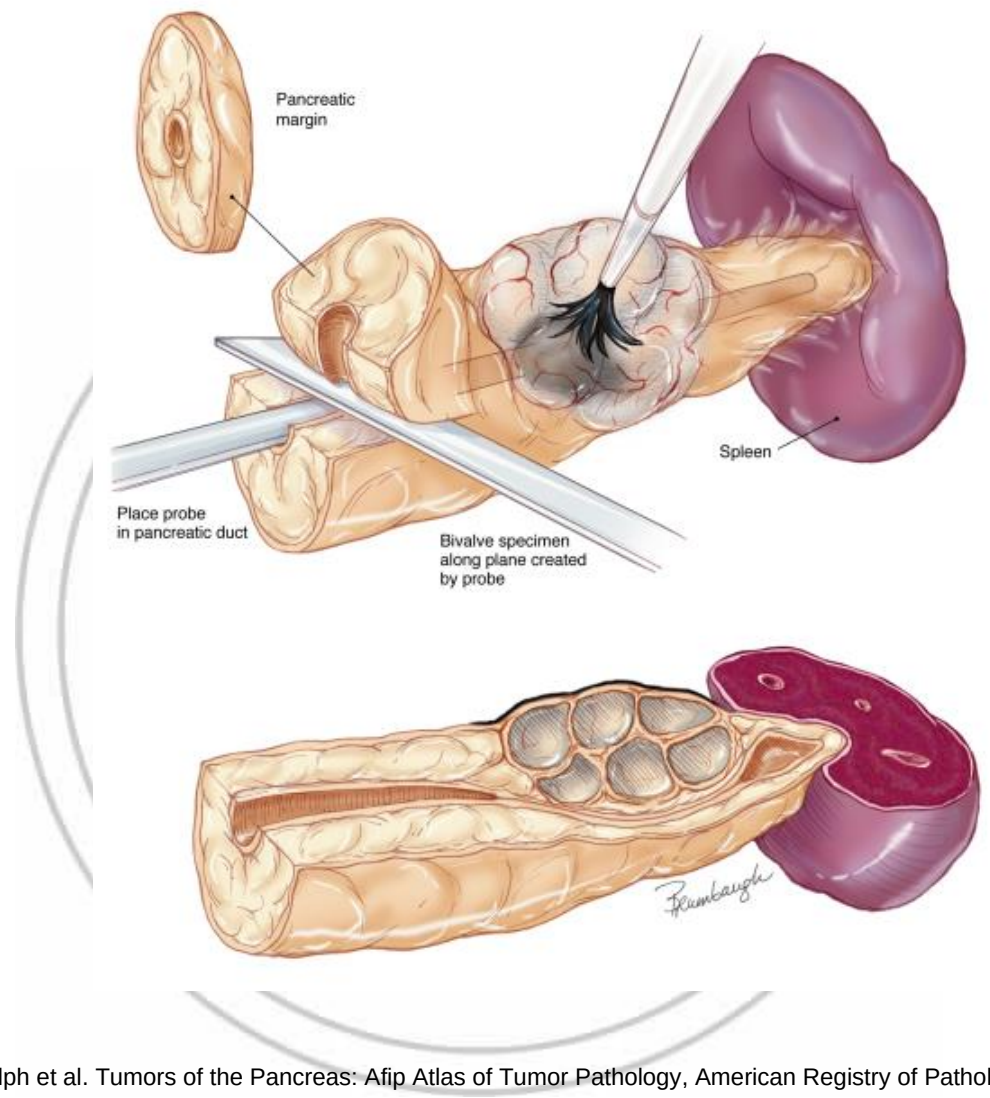

Figure 16-4, from Hruban, Ralph et al. Tumors of the Pancreas: Afip Atlas of Tumor Pathology, American Registry of Pathology, Washington DC 2007

Figure 5. Slicing of the distal pancreatectomy specimen.[479]

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