



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pancreatic Adenocarcinoma

Version 2.2026 — April 22, 2026

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.

NCCN Guidelines for Patients® available at www.nccn.org/patients



***Andrew H. Ko, MD/Chair †**
UCSF Helen Diller Family
Comprehensive Cancer Center

***Mokenge P. Malafa, MD/Vice Chair ¶**
Moffitt Cancer Center

Olca Basturk, MD ≠
Memorial Sloan Kettering Cancer Center

Al B. Benson III, MD †
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Dana B. Cardin, MD †
Vanderbilt-Ingram Cancer Center

E. Gabriela Chiorean, MD †
Fred Hutchinson Cancer Center

Jared A. Christensen, MD ϕ
University of Michigan Rogel Cancer Center

Vincent Chung, MD †
City of Hope National Medical Center

Brian Czito, MD §
Duke Cancer Institute

Marco Del Chiaro, MD, PhD ¶
University of Colorado Cancer Center

Mary Dillhoff, MD, MS ¶
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Timothy R. Donahue, MD ¶
UCLA Jonsson Comprehensive Cancer Center

Christos Fountzilas, MD † ‡
Roswell Park Comprehensive Cancer Center

Jeffrey Hardacre, MD ¶
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute

Kelsey Klute, MD †
Fred & Pamela Buffett Cancer Center

John W. Kunstman, MD, MHS ¶
Yale Cancer Center/Smilow Cancer Hospital

Kian-Huat Lim, MD, PhD †
Siteman Cancer Center at Barnes-Jewish Hospital
and WashU Medicine

Noelle LoConte, MD †
University of Wisconsin Carbone Cancer Center

Andrew M. Lowy, MD ¶
UC San Diego Moores Cancer Center

Ashiq Masood, MD ‡
Indiana University Melvin and Bren Simon
Comprehensive Cancer Center

Cassadie Moravek, BS ¥
Pancreatic Cancer Action Network

Eric K. Nakakura, MD ¶
UCSF Helen Diller Family
Comprehensive Cancer Center

Amol K. Narang, MD §
Johns Hopkins Kimmel Cancer Center

Lorenzo Nardo, MD, PhD ϕ ϕ
UC Davis Comprehensive Cancer Center

Jorge Obando, MD ≠
Duke Cancer Institute

Patricio M. Polanco, MD ¶
UT Southwestern Simmons
Comprehensive Cancer Center

George Poultsides, MD, MS ¶
Stanford Cancer Institute

Sushanth Reddy, MD ¶
O'Neal Comprehensive Cancer Center at UAB

Marsha Reyngold, MD, PhD §
Memorial Sloan Kettering Cancer Center

Courtney Scaife, MD ¶
Huntsman Cancer Institute
at the University of Utah

Ardaman Shergill, MD †
The UChicago Medicine
Comprehensive Cancer Center

Mark J. Truty, MD, MS ¶
Mayo Clinic Comprehensive Cancer Center

Charles Vollmer Jr, MD ¶
Abramson Cancer Center
at the University of Pennsylvania

David Weinberg, MD, MSc ≠
Fox Chase Cancer Center

Robert A. Wolff, MD †
The University of Texas
MD Anderson Cancer Center

Brian M. Wolpin, MD, MPH †
Dana-Farber Cancer Institute

NCCN

Beth McCullough, RN, BS
Swathi Ramakrishnan, PhD
Sydney L. Roth, BS

ϕ Diagnostic/Interventional radiology	≠ Pathology
≠ Gastroenterology	¥ Patient advocacy
‡ Hematology/Hematology oncology	§ Radiotherapy/Radiation oncology
† Medical oncology	¶ Surgery/Surgical oncology
ϕ Nuclear medicine	* Discussion section writing committee

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Find an NCCN Member Institution:
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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](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2026.



Updates in Version 2.2026 of the NCCN Guidelines for Pancreatic Adenocarcinoma include:

[MS-1](#)

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

Updates in Version 1.2026 of the NCCN Guidelines for Pancreatic Adenocarcinoma include:

General

- References were updated throughout the guidelines.
- The algorithm pages were rearranged.
- The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities name changed to *NCCN Guidelines for the Management of Immune Checkpoint Inhibitor-Related Toxicities*.

[PANC-1A](#)

- Footnote i revised: Core biopsy is recommended, if possible, to obtain adequate tissue for ~~possible~~ *molecular profiling or other* ancillary studies. (Also PANC-2A, PANC-3, PANC-8, and PANC-9)
- Footnote j revised: Tumor/somatic molecular profiling, preferably using a next-generation sequencing (NGS) assay, is recommended for ~~all 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...fluorescence in situ hybridization (FISH). *In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting* ~~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 circulating tumor DNA (ctDNA) testing can be considered if tumor tissue testing is not feasible. See Discussion and Principles of Cancer Risk Assessment and Counseling (PANC-J).~~ (Also PANC-6A, PANC-9, PANC-10A, PANC-11, and PANC-12)

[PANC-2](#)

- Revised: Treatment *Decision*.
- Added: Pre-Treatment Workup
 - ▶ 5th bullet added: Staging laparoscopy as clinically indicated
- Added: Treatment
 - ▶ Revised: Unresectable disease at surgery (*PANC-8*)

[PANC-2A](#)

- Footnote n revised: *Neoadjuvant Therapy (Resectable/Borderline Resectable Disease) (PANC-G, 1 of 13)*. There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. ~~Subsequent Consolidative~~ chemoradiation is sometimes included. Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center. (Also PANC-4A)
- Footnote r added: Exploratory laparoscopy could be indicated in select cases, especially in those with high risk for metastatic disease. (Also PANC-4A and PANC-9A)

[PANC-3](#)

- Footnote l added: Tumor/somatic molecular profiling if clinically indicated. (Also PANC-5A, PANC-6A, PANC-7, PANC-8, and PANC-9)

[PANC-4](#)

- This page was extensively revised.

[PANC-4A](#)

- Footnote w added: Consider staging laparoscopy as clinically indicated. (Also PANC-9A)
- Footnote x added: Criteria for Resection following Neoadjuvant Therapy (PANC-D).

[Continued](#)

UPDATES



Updates in Version 1.2026 of the NCCN Guidelines for Pancreatic Adenocarcinoma include:

PANC-5

- Postoperative Adjuvant Treatment separated into bullets:
 - ▶ 1st bullet: Baseline postoperative CT (chest, abdomen, and pelvis) with contrast (unless contraindicated)
 - ▶ 2nd bullet: CA 19-9
 - ▶ 3rd bullet, If not previously done, separated into sub-bullets:
 - ◊ 1st sub-bullet: Genetic testing for inherited mutations
 - ◊ 2nd sub-bullet added: Biopsy confirmation
 - ◊ 3rd sub-bullet added: Molecular profiling

PANC-5A

- Footnote i added: Core biopsy is recommended, if possible, to obtain adequate tissue for molecular profiling or other ancillary studies. (Also PANC-6A and PANC-12)
- Footnote j added: Tumor/somatic molecular profiling, preferably using a next-generation sequencing (NGS) assay, is recommended for all patients 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See Discussion and Principles of Cancer Risk Assessment and Counseling (PANC-J). (Also PANC-7 and PANC-8)
- Footnote z added: The NCCN Panel recognizes the emerging use of ctDNA to assess minimal residual disease (MRD) in the postoperative setting and for surveillance purposes. However, while a positive ctDNA test appears to be prognostic for disease recurrence, the Panel cannot offer a consensus recommendation regarding its use due to limited data as to how ctDNA results would guide treatment decision-making for patients with pancreatic cancer.

PANC-6

- This page was extensively revised.

PANC-6A

- Footnote ii added: 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 to undergo a detailed restaging assessment followed by the formulation of a multimodal therapy care plan, which may include neoadjuvant chemotherapy, possible RT, and possible surgical resection.

PANC-7

- This page was extensively revised.

PANC-8

- Unresectable Disease at Surgery
 - ▶ If not previously done separated into bullets:
 - ◊ 1st bullet: Biopsy confirmation of diagnosis
 - ◊ 2nd bullet: Genetic testing for inherited mutations
 - ◊ 3rd bullet added: Molecular profiling of tumor tissue
- Footnote kk added: Refer to tertiary cancer center for second opinion about unresectability.

PANC-9A

- Footnote nn added: Less common variants, such as squamous/adenosquamous carcinomas, are treated similarly to adenocarcinoma. There are insufficient data supporting the efficacy of any of the recommended regimens for these rare subtypes. For mixed histologies, the Panel recommends treating the more aggressive histology.

[Continued](#)

UPDATES



Updates in Version 1.2026 of the NCCN Guidelines for Pancreatic Adenocarcinoma include:

[PANC-10](#)

- Revised: Locally Advanced Disease *Treatment*
- Subsequent Therapy, Disease Progression: ...Systemic therapy (See *PANC-G, 8 of 13* or *PANC-G, 9 of 13*)...

[PANC-10A](#)

- Footnote oo revised: Good PS is defined as ECOG 0–1; with good biliary drainage and adequate nutritional intake, and intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care. (Also PANC-11 and PANC-12)

[PANC-11](#)

This page was extensively revised.

[PANC-12](#)

- Disease Progression, Good or intermediate PS, Subsequent Therapy revised: ...Systemic therapy, which may include targeted therapy or immunotherapy based on molecular profiling, ± *Metastasis-directed therapy at a high-volume center*, as clinically indicated...
- Footnote jj added: In rare circumstances when patients have indolent/oligometastatic disease, they should be referred to a high-volume center to be evaluated for possible metastasis-directed therapy. Ludmir EB, et al. J Clin Oncol 2024;42(3 Suppl):Abstract 603.

[PANC-D](#)

- Section added: Criteria for Resection Following Neoadjuvant Therapy

[PANC-E 1 of 3](#)

- Principles of Surgical Technique, 2nd paragraph revised: Consider frozen section analysis of the pancreatic neck and bile duct. *Avoid cautery at margins sent for frozen section.* 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...

[PANC-E 2 of 3](#)

- Principles of Surgical Technique, Surgery for Locally Recurrent Pancreatic Ductal Adenocarcinoma revised: ...These patients should be carefully evaluated in the multidisciplinary clinic where following a detailed restaging assessment, a multimodal therapy care plan, ~~consisting of~~ *which may include* neoadjuvant chemotherapy, possible RT, and possible surgical resection can be formulated.

[PANC-F 1 of 5](#)

- Pathologic Analysis: Specimen Orientation, Histological Sections, and Reporting, Whipple Specimen
 - ▶ 1st bullet revised: ...There should either be 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 and, if present, the proximal and distal margins of the PV~~ should be marked.
 - ▶ Margins, 1st sub-bullet, 1st sub-sub-bullet revised: ...~~The uncinate margin should be inked. Rather than being submitted en face, the uncinate margin tissue should be~~ *Therefore, the margin should be inked*, shaved/amputated, then ~~the portion of tissue~~ sectioned perpendicular to the ink and submitted entirely for histologic examination.
 - ▶ 3rd bullet revised: Every effort should be made to identify all regional lymph nodes within the pancreatoduodenectomy specimen. ~~For optimal staging, a minimum of 17 lymph nodes in pancreatoduodenectomy specimens is recommended.~~ *Adequate lymph node assessment may be more challenging after neoadjuvant therapy, but the Panel consensus is an assessment of at least 12 lymph nodes.*

[Continued](#)

UPDATES



Updates in Version 1.2026 of the NCCN Guidelines for Pancreatic Adenocarcinoma include:

[PANC-F 2 of 5](#)

- Pathologic Analysis: Specimen Orientation, Histological Sections, and Reporting, Whipple Specimen
 - ▶ Other Circumferential Surfaces, 2nd sub-bullet revised: ...Also referred to as the vascular groove/*vascular bed* 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...
 - ▶ Histologic sectioning, 1st sub-bullet revised: 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 *the axial, bi- or multi-valve slicing, and perpendicular slicing* and bivalve methods. ~~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. In the axial method, the pancreas is sectioned perpendicular to its long axis at regular intervals. In the bivalve method, the pancreas is bisected along probes placed within the bile and pancreatic ducts, and each half is then sectioned perpendicularly to the inked anterior and posterior surfaces. Axial slicing helps preserve spatial relationships, making it especially useful for radiologic-pathologic correlation. The bivalve method is particularly advantageous for localizing tumors—especially small lesions near the ampulla or ducts—and for assessing ductal involvement and surgical margins.~~
 - ▶ Histologic sectioning, 2nd sub-bullet removed: 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.

[PANC-G](#)

- Principles of Systemic Therapy, General Principles
 - ▶ 4th bullet added: If BRCA1/2 status is unknown, then treat with systemic therapy as clinically indicated.
 - ▶ 8th bullet revised: ~~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. Less common variants, such as squamous/adenosquamous carcinomas, are treated similarly to adenocarcinoma. There are insufficient data supporting the efficacy of any of the recommended regimens for these rare subtypes. For mixed histologies, the Panel recommends treating the more aggressive histology.~~
 - ▶ 10th bullet added: For information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer.
 - ▶ 11th bullet added: Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV Pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV Pembrolizumab.

[PANC-G 1 of 13](#)

- Principles of Systemic Therapy, Neoadjuvant Therapy
 - ▶ Bullet revised: There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and radiation. ~~Subsequent Consolidative~~ chemoradiation is sometimes included (*PANC-4 and PANC-D*). 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.
 - ▶ Resectable/Borderline Resectable Disease
 - ◊ Preferred, 2nd, 4th, 6th, and 8th bullets revised: ...with ~~subsequent consolidative~~ chemoradiation
 - ◊ Useful in Certain Circumstances added: PAXG (Cisplatin/Albumin-bound Paclitaxel/Capecitabine/Gemcitabine)
- Footnote c added: Due to the high toxicity of this regimen, bolus fluorouracil is often omitted. (Also PANC-G 2 of 13)

[PANC-G 3 of 13](#)

- Footnote e added: Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care. (Also PANC-G 4 of 13, PANC-G 5 of 13, PANC-G 6 of 13, PANC-G 7 of 13, PANC-G 8 of 13, PANC-G 9 of 13, and PANC-G 10 of 13)
- Footnote g revised: While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over Albumin-bound Paclitaxel/Gemcitabine, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX. ~~and adds considerably more expense compared to FOLFIRINOX.~~ (Also PANC-G 5 of 13)
- Footnote i revised: 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*). (Also PANC-G 4 of 13)



Updates in Version 1.2026 of the NCCN Guidelines for Pancreatic Adenocarcinoma include:

[PANC-G 5 of 13](#)

- Principles of Systemic Therapy, Metastatic Disease (First-Line Therapy), Good PS 0-1, Useful in Certain Circumstances: Dabrafenib/Trametinib (if BRAF V600E mutation-positive) was changed to a category 2A recommendation from a category 2B.

[PANC-G 6 of 13](#)

- Principles of Systemic Therapy, Metastatic Disease (First-Line Therapy), Intermediate PS 2, Useful in Certain Circumstances: Dabrafenib/Trametinib (if BRAF V600E mutation-positive) was changed to a category 2A recommendation from a category 2B.

[PANC-G 7 of 13](#)

- Principles of Systemic Therapy, Metastatic Disease revised: Metastatic Disease (Maintenance Therapy for Good/Intermediate PS)
- Footnote q revised: 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.

[PANC-G 8 of 13](#)

- This page was extensively revised.

[PANC-G 9 of 13](#)

- Principles of Systemic Therapy, Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease
 - ▶ Intermediate PS 2, Preferred regimen added: FOLFOX (if prior Gemcitabine-based therapy).
- Footnote q added: For locally advanced disease progression (good/intermediate PS), local recurrence after resection, and recurrent metastatic disease after resection. If ≥6 months from completion of primary therapy, may repeat systemic therapy previously administered or may use alternate systemic therapy (not previously used). If <6 months from completion of primary therapy, switching drug class or using alternate systemic therapy (not previously used) is recommended. (Also PANC-G 10 of 13)

[PANC-H 2 of 7](#)

- Principles of Radiation Therapy, Treatment Planning: Radiation Delivery, Planning, Dose and Fractionation, 4th bullet added: The role and definition of elective target volume irradiation remain unclear. However, emerging data has increasingly suggested value to elective targeting of at-risk anatomic sites defined by extra-pancreatic neural tract anatomy (ie, the “Triangle Volume”) and/or regional nodal basins. More prospective data is needed to further refine target volume definition recommendations across stages of disease.

[PANC-H 3 of 7](#)

- Principles of Radiation Therapy, Recommendations Based on Treatment Setting, Resectable/Borderline Resectable
 - ▶ 3rd bullet revised: ~~Subsequent Consolidative~~ chemoradiation is sometimes an option following neoadjuvant chemotherapy^{9,10} (Principles of Systemic Therapy [PANC-G]).
 - ▶ 5th bullet, 2nd sub-bullet removed: Optimal elective irradiation target remains undefined, but broad coverage of mesenteric vasculature ± nodal regions should be considered when feasible.

[PANC-H 5 of 7](#)

- Principles of Radiation Therapy, Palliative, 2nd bullet, 2nd sub-bullet added: Single fraction SBRT can be used for celiac axis pain relief.

[PANC-I 2 of 2](#)

- Footnote e revised: ~~Yaacov YR, et al. J Clin Oncol 2023;41(4_suppl):Abstract 662; Jacobson G, et al. BMJ Open 2022;12:e050169. Lawrence YR, Miszczyk M, Dawson LA, et al. Celiac plexus radiosurgery for pain management in advanced cancer: A multicentre, single-arm, phase 2 trial. Lancet Oncol 2024;25:1070-1079.~~

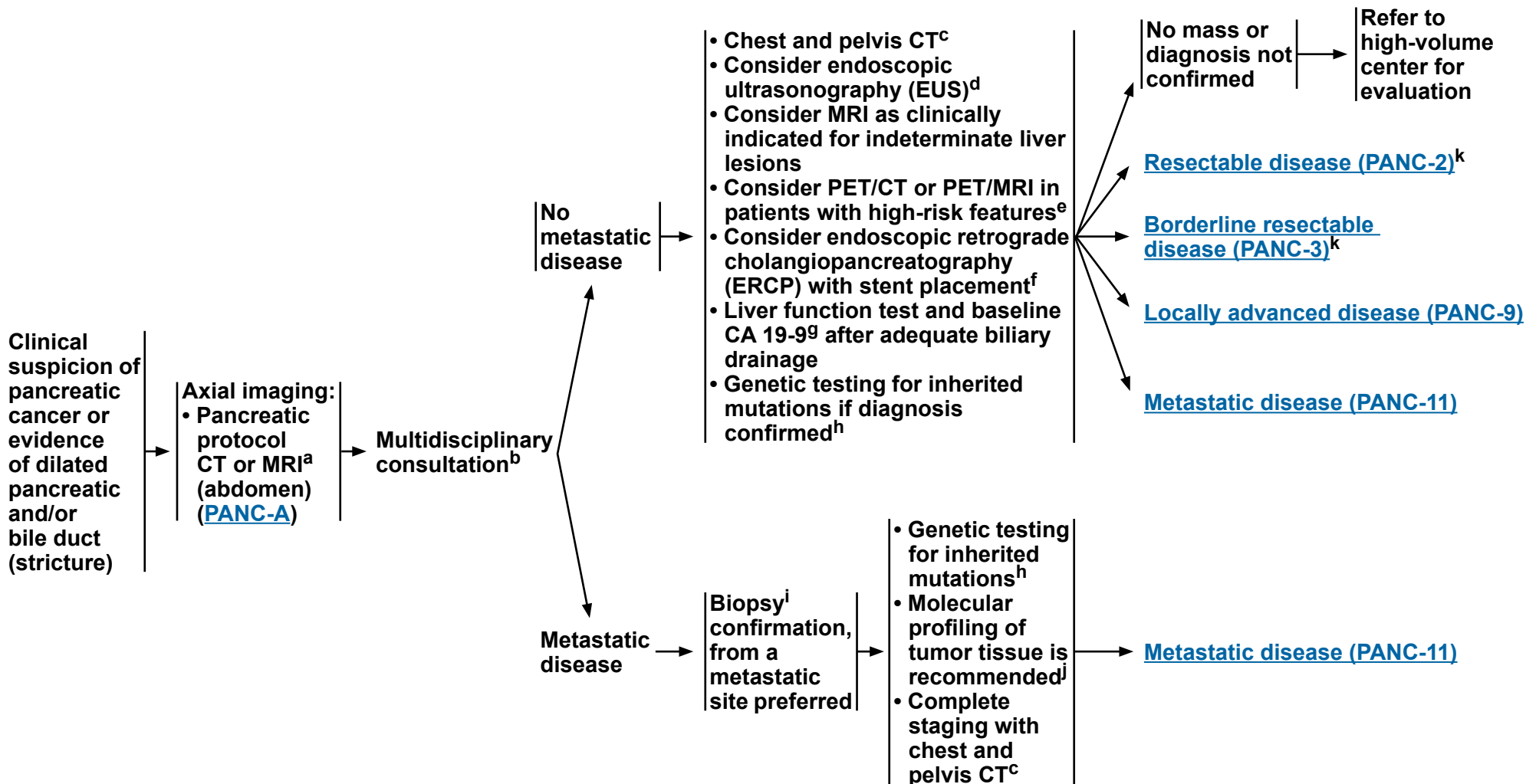


INTRODUCTION

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.

CLINICAL PRESENTATION AND WORKUP



Footnotes

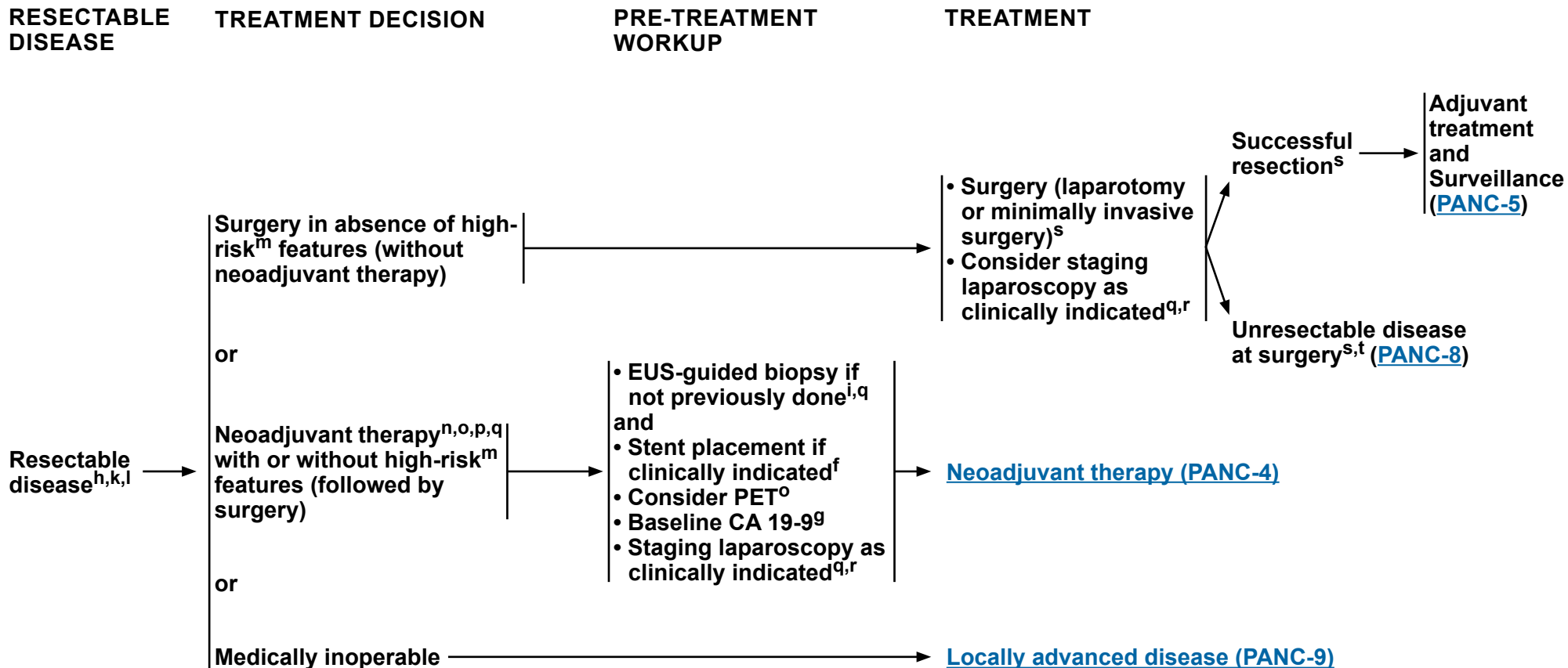
Note: All recommendations are category 2A unless otherwise indicated.



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 \[PANC-I\]](#)). 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 individuals who are Lewis antigen-negative (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 molecular profiling or other ancillary studies.
- ^j Tumor/somatic molecular profiling, preferably using a next-generation sequencing (NGS) assay, is recommended for all patients 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 immunohistochemistry (IHC) ± fluorescence in situ hybridization (FISH). In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, circulating tumor DNA (ctDNA) testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).
- ^k [Criteria Defining Resectability Status at Diagnosis \(PANC-C\)](#).

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



Footnotes

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



FOOTNOTES

^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 individuals who are Lewis antigen-negative (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 molecular profiling or other 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 [Neoadjuvant Therapy \(Resectable/Borderline Resectable Disease\) \(PANC-G 1 of 13\)](#). There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Consolidative 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 Exploratory laparoscopy could be indicated in select cases, especially in those with high risk for metastatic disease.

^s [Principles of Surgical Technique \(PANC-E\)](#) and [Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-F\)](#).

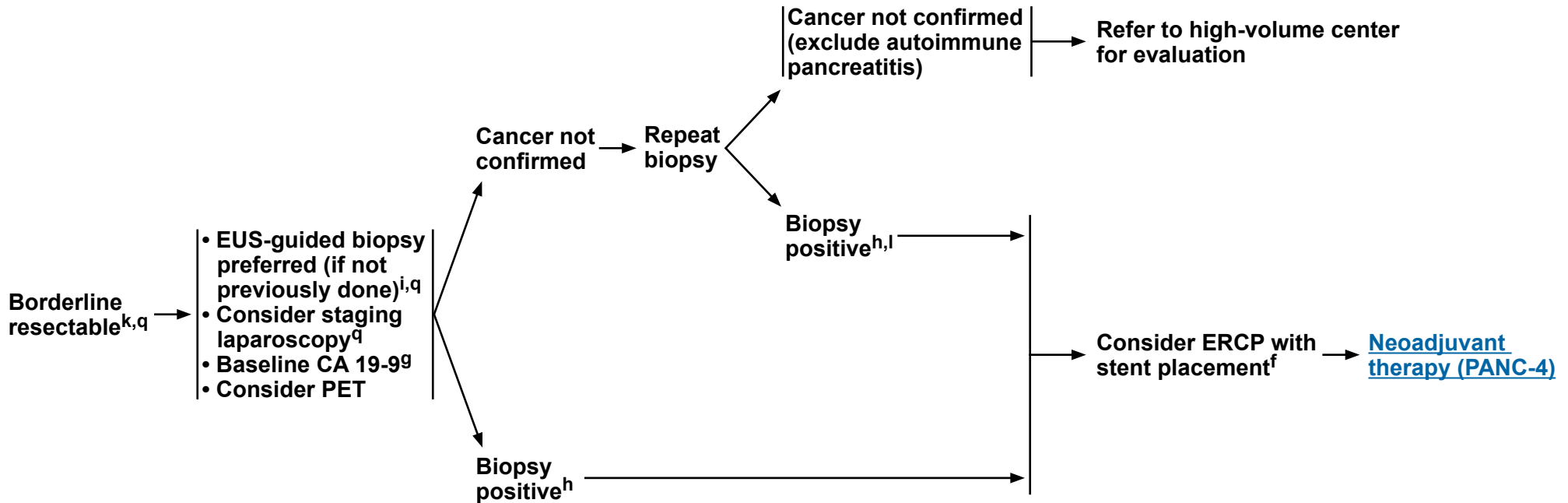
^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).

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



BORDERLINE RESECTABLE DISEASE, NO METASTASES

TREATMENT



^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 individuals who are Lewis antigen-negative (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 molecular profiling or other ancillary studies.

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

^l Tumor/somatic molecular profiling if clinically indicated.

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

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



NEOADJUVANT THERAPY

RESTAGING WORKUP

RESPONSE

TREATMENT

Adjuvant treatment and Surveillance ([PANC-5](#))

Adjuvant treatment and Surveillance ([PANC-5](#))

Reassess response

Reassess response

[Locally advanced disease \(PANC-9\)](#) or [Metastatic disease \(PANC-11\)](#)

- Pancreatic protocol CT or MRI (abdomen)
- Chest/pelvis CT^c
- Consider PET
- Post-treatment CA 19-99
- Consider staging laparoscopy as clinically indicated^q

Significant^x

Surgical resection^s

Unresectable disease at surgery^{s,t} ([PANC-8](#))

Minimal^x

Surgical resection^s

- Consider alternate neoadjuvant chemotherapy^{p,u}
- ▶ Consider chemoradiation (if not previously used) or radiation ([PANC-G](#) and [PANC-H](#))

Significant response^x (see top pathway)

No progression^y → Surgical resection^s

Consider chemoradiation (if not previously used) or radiation if no metastatic disease ([PANC-G](#) and [PANC-H](#))

Disease progression^y not precluding surgery^{q,x}

Consider alternate neoadjuvant chemotherapy^{p,u}

Disease progression precluding surgery^{q,x}

Neoadjuvant therapy^{n,o,p,q,r,u,v,w}

Footnotes

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



FOOTNOTES

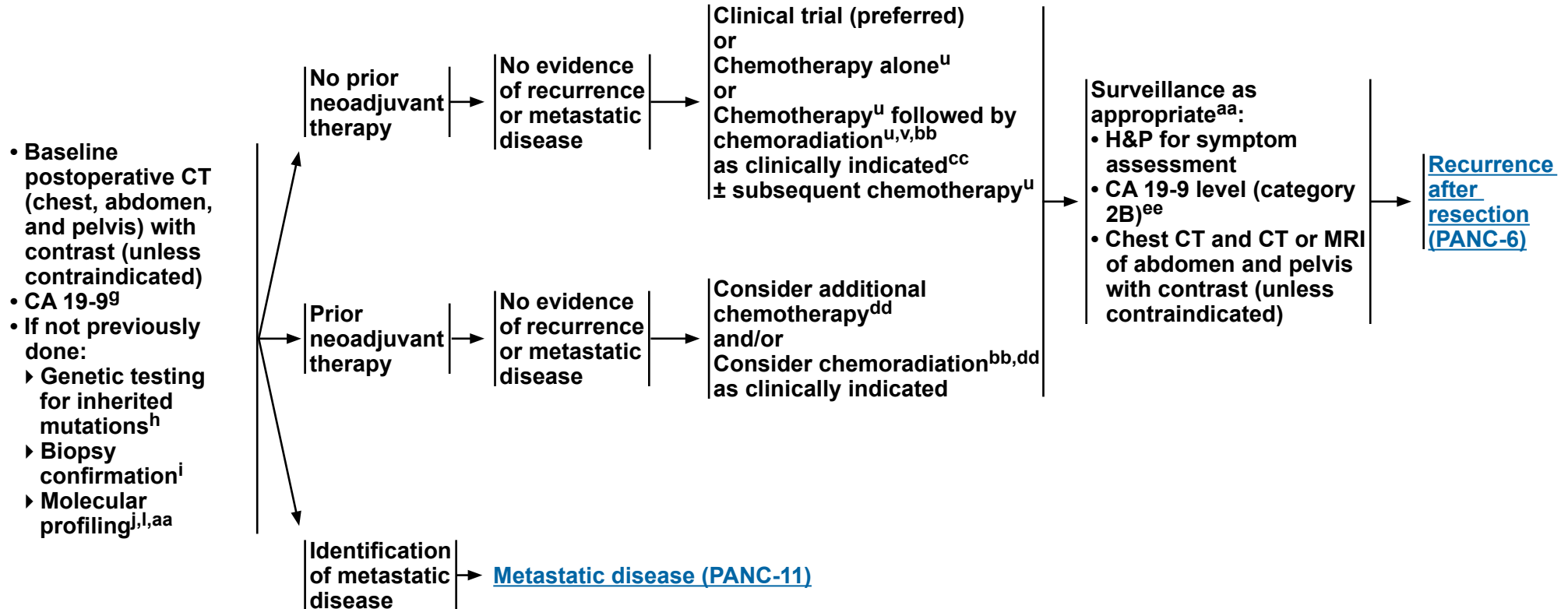
- ^c Imaging with contrast as appropriate for disease management (unless contraindicated).
- ^g Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary obstruction, infection (cholangitis), or inflammation, benign or malignant. In addition, CA 19-9 will be undetectable in individuals who are Lewis antigen-negative (consider obtaining CEA and CA-125 in patients who are nonsecreting or those with normal CA 19-9 levels).
- ⁿ [Neoadjuvant Therapy \(Resectable/Borderline Resectable Disease\) \(PANC-G 1 of 13\)](#). There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Consolidative 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 Exploratory laparoscopy could be indicated in select cases, especially in those with high risk for metastatic disease.
- ^s [Principles of Surgical Technique \(PANC-E\)](#) and [Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-F\)](#).
- ^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).
- ^u [Principles of Systemic Therapy \(PANC-G\)](#).
- ^v [Principles of Radiation Therapy \(PANC-H\)](#).
- ^w Consider staging laparoscopy as clinically indicated.
- ^x [Criteria for Resection following Neoadjuvant Therapy \(PANC-D\)](#).
- ^y Disease progression is defined by rising CA 19-9 or enlargement of the mass.

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



POSTOPERATIVE ADJUVANT TREATMENT^z

SURVEILLANCE



Footnotes

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



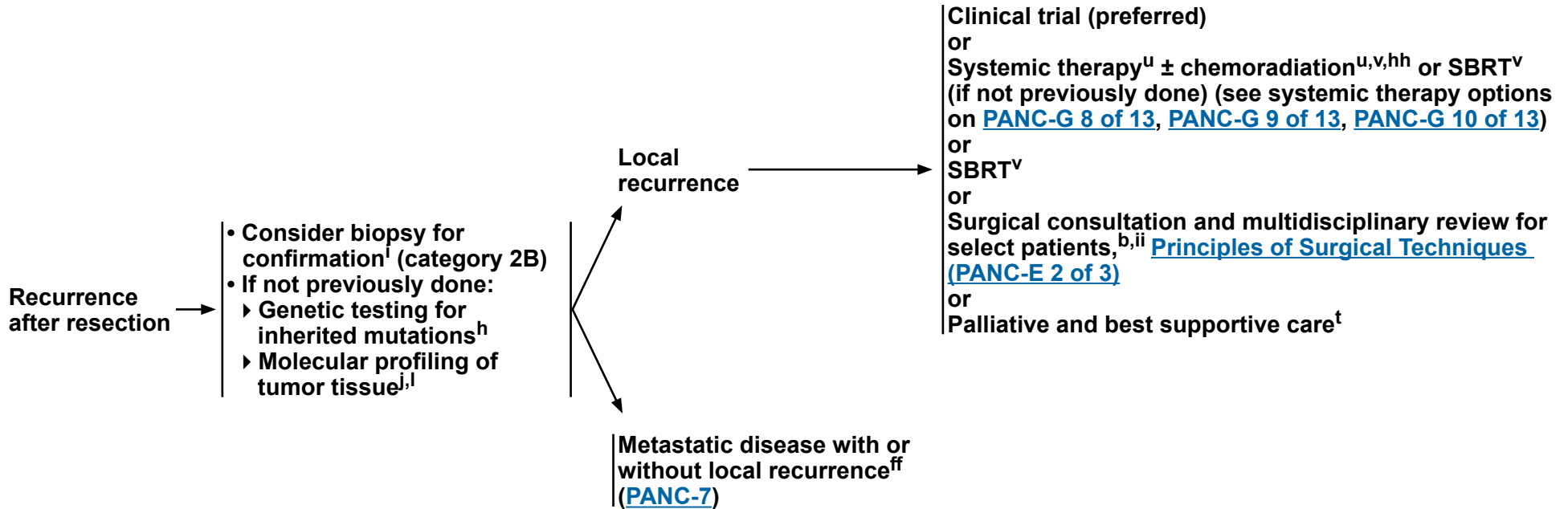
FOOTNOTES

- ^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 individuals who are Lewis antigen-negative (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 molecular profiling or other ancillary studies.
- ^j Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for all patients 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).
- ^l Tumor/somatic molecular profiling if clinically indicated.
- ^u [Principles of Systemic Therapy \(PANC-G\)](#).
- ^v [Principles of Radiation Therapy \(PANC-H\)](#).
- ^z 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.
- ^{aa} The NCCN Panel recognizes the emerging use of ctDNA to assess minimal residual disease (MRD) in the postoperative setting and for surveillance purposes. However, while a positive ctDNA test appears to be prognostic for disease recurrence, the Panel cannot offer a consensus recommendation regarding its use due to limited data as to how ctDNA results would guide treatment decision-making for patients with pancreatic cancer.
- ^{bb} If considering chemoradiation, neoadjuvant or adjuvant chemotherapy should be given prior to the administration of chemoradiation.
- ^{cc} 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.
- ^{dd} 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.
- ^{ee} CA 19-9 elevation, without other evidence of disease recurrence, is not a clear indication for treatment.

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

RECURRENCE AFTER RESECTION

RECURRENCE THERAPY⁹⁹



Footnotes

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



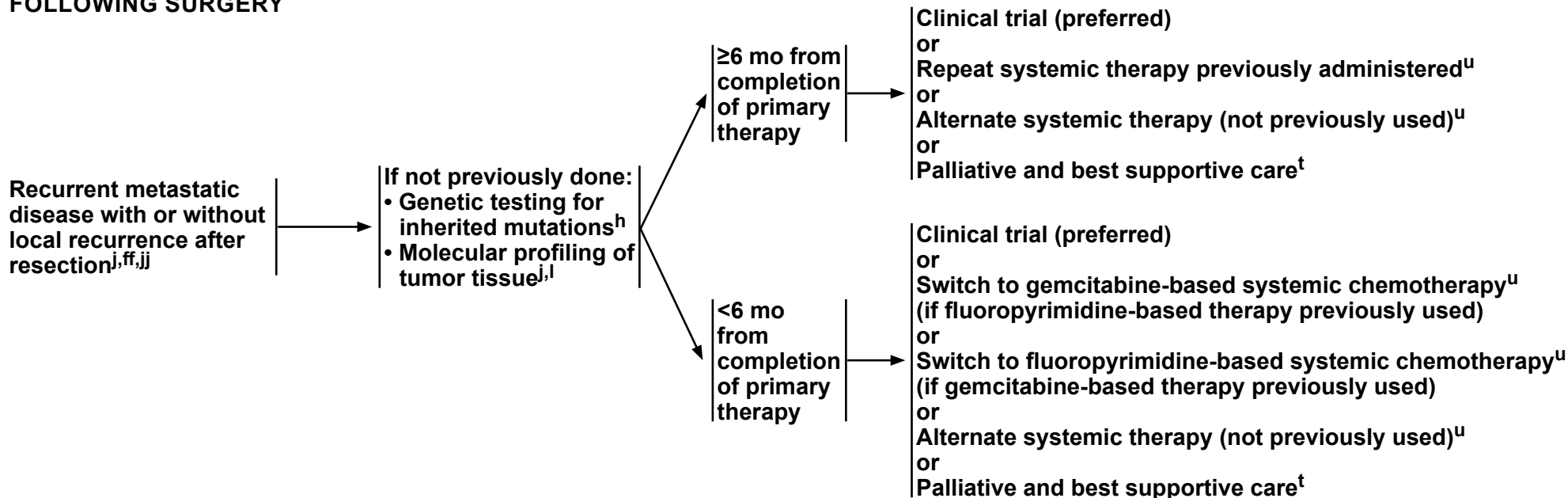
FOOTNOTES

- ^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 \[PANC-I\]](#)). 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](#).
- ⁱ Core biopsy is recommended, if possible, to obtain adequate tissue for possible molecular profiling or other ancillary studies.
- ^j Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for all patients 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).
- ^l Tumor/somatic molecular profiling if clinically indicated.
- ^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).
- ^u [Principles of Systemic Therapy \(PANC-G\)](#).
- ^v [Principles of Radiation Therapy \(PANC-H\)](#).
- ^{ff} For more information about the treatment of isolated pulmonary metastases, see [Discussion](#).
- ^{gg} Best reserved for patients who maintain a good PS.
- ^{hh} Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy.
- ⁱⁱ 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 to undergo a detailed restaging assessment followed by the formulation of a multimodal therapy care plan, which may include neoadjuvant chemotherapy, RT, and possible surgical resection.

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



METASTATIC RECURRENT DISEASE FOLLOWING SURGERY



^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](#).

^j Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for all patients 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).

^l Tumor/somatic molecular profiling if clinically indicated.

^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).

^u [Principles of Systemic Therapy \(PANC-G\)](#).

^{ff} For more information about the treatment of isolated pulmonary metastases, see [Discussion](#).

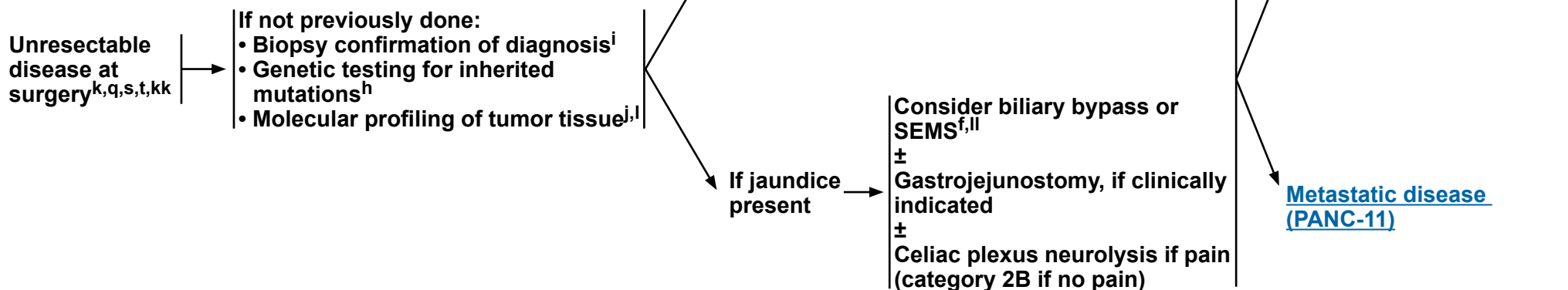
⁹⁹ Best reserved for patients who maintain a good performance status (PS).

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

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

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 molecular profiling or other ancillary studies.

^j Tumor/somatic molecular profiling, preferably using a next-generation sequencing (NGS) assay, is recommended for all patients 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).

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

^l Tumor/somatic molecular profiling if clinically indicated.

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

^s [Principles of Surgical Technique \(PANC-E\)](#) and [Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-F\)](#).

^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).

^{kk} Refer to tertiary cancer center for second opinion about unresectability.

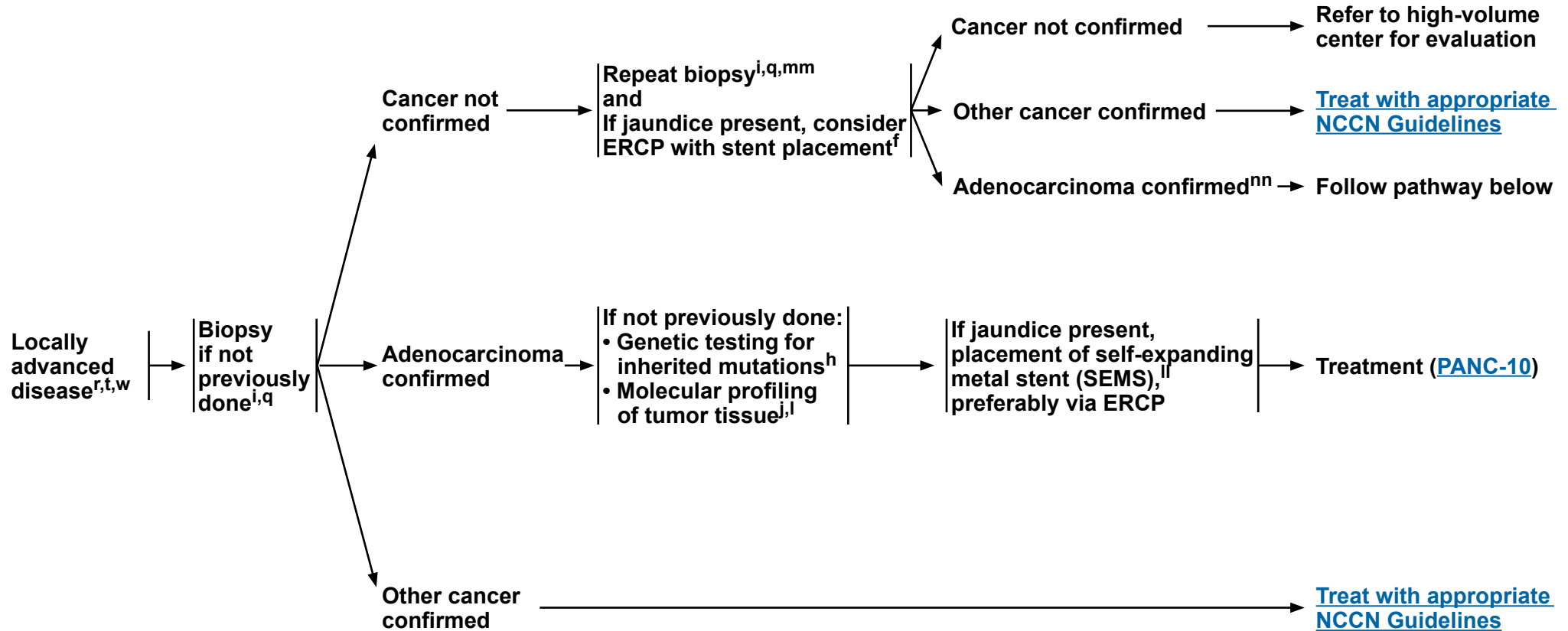
^{ll} Unless biliary bypass was performed at the time of laparoscopy or laparotomy.

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



LOCALLY ADVANCED DISEASE

WORKUP



Footnotes

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



FOOTNOTES

^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 molecular profiling or other ancillary studies.

^j Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for all patients 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).

^l Tumor/somatic molecular profiling if clinically indicated.

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

^r Exploratory laparoscopy could be indicated in select cases, especially in those with high risk for metastatic disease.

^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).

^w Consider staging laparoscopy as clinically indicated.

^{ll} Unless biliary bypass was performed at the time of laparoscopy or laparotomy.

^{mmm} EUS-guided biopsy at a center with multidisciplinary expertise is preferred. When EUS-guided biopsy is not feasible, CT-guided biopsy can be done.

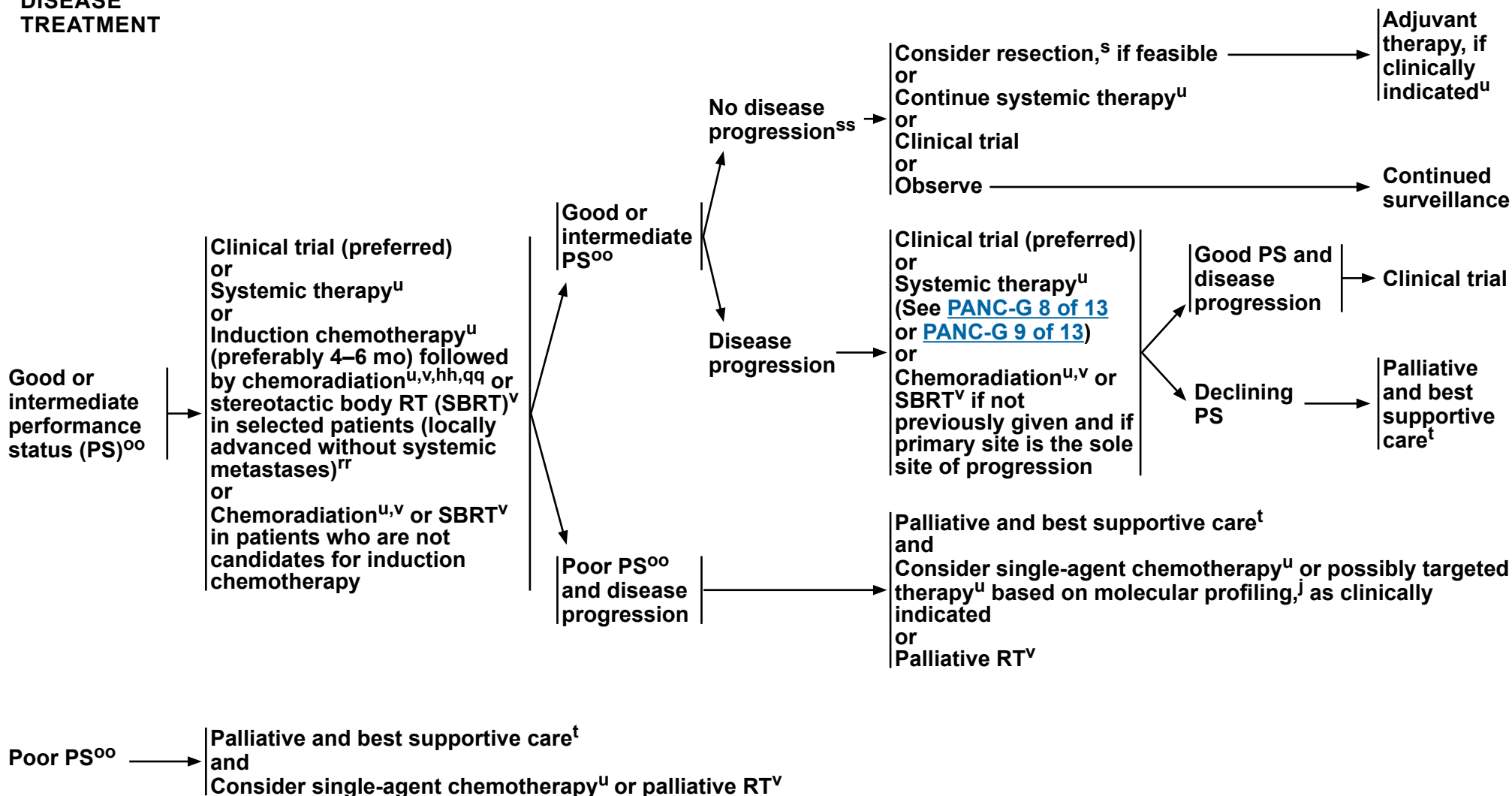
ⁿⁿ Less common variants, such as squamous/adenosquamous carcinomas, are treated similarly to adenocarcinoma. There are insufficient data supporting the efficacy of any of the recommended regimens for these rare subtypes. For mixed histologies, the Panel recommends treating the more aggressive histology.

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

**LOCALLY
ADVANCED
DISEASE
TREATMENT**

FIRST-LINE THERAPY^{q,s,pp}

SUBSEQUENT THERAPY



Footnotes

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



FOOTNOTES

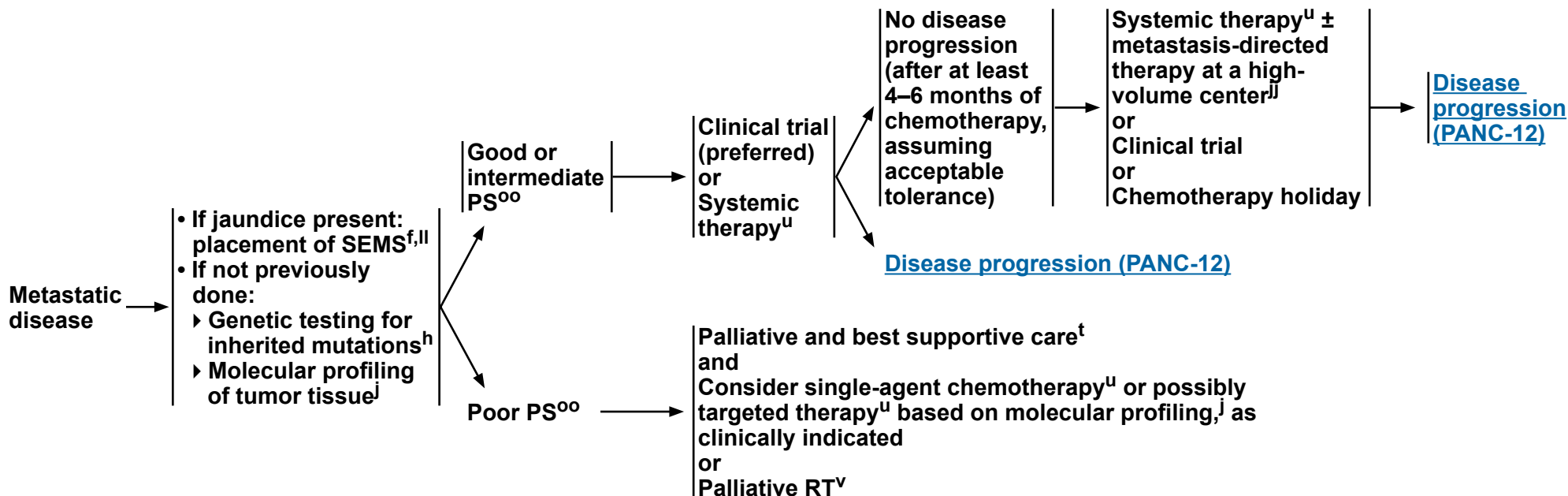
- ^j Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for all patients who are candidates for anti-cancer therapy to identify clinically actionable and/or emerging alterations. These alterations include, but are not limited to: fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).
- ^q [Principles of Diagnosis, Imaging, and Staging \(PANC-A\)](#).
- ^s [Principles of Surgical Technique \(PANC-E\)](#) and [Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-F\)](#).
- ^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).
- ^u [Principles of Systemic Therapy \(PANC-G\)](#).
- ^v [Principles of Radiation Therapy \(PANC-H\)](#).
- ^{hh} Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy.
- ^{oo} Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.
- ^{pp} Serial imaging as indicated to assess disease response.
- ^{qq} 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).
- ^{rr} Laparoscopy as indicated to evaluate distant disease.
- ^{ss} 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.

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

METASTATIC DISEASE

FIRST-LINE THERAPY^{q,pp}

MAINTENANCE THERAPY^{q,pp}



^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](#).

^j Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for all patients 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).

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

^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).

^u [Principles of Systemic Therapy \(PANC-G\)](#).

^v [Principles of Radiation Therapy \(PANC-H\)](#).

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

^{ll} Unless biliary bypass was performed at the time of laparoscopy or laparotomy.

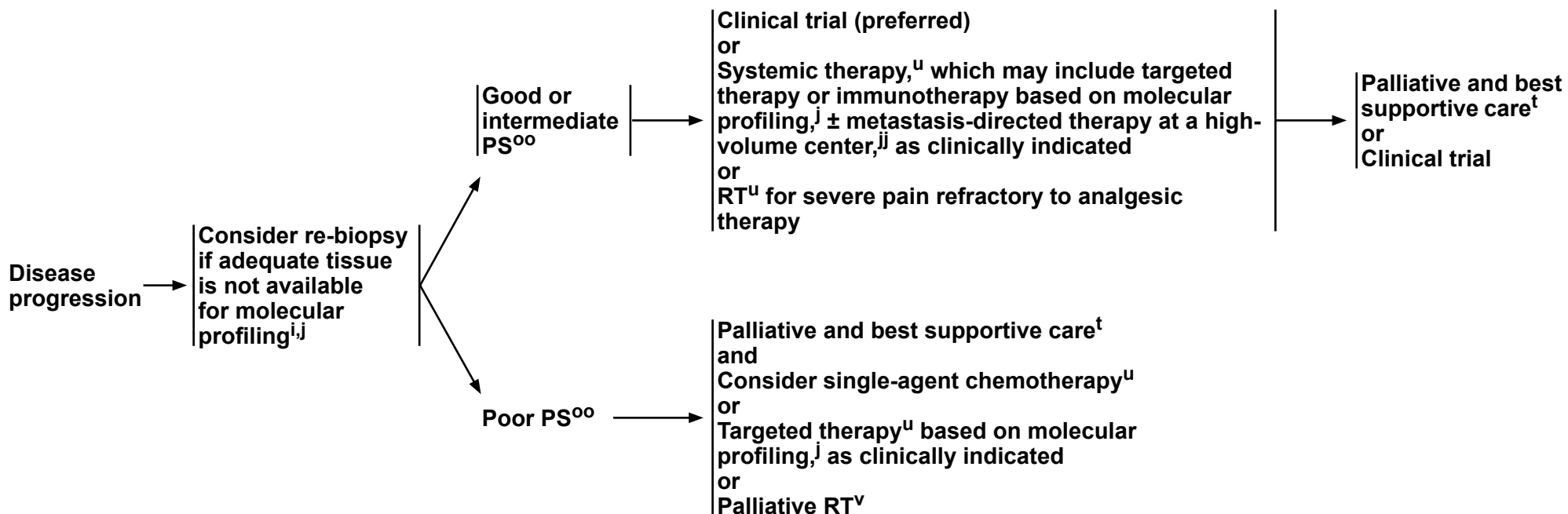
^{oo} Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

^{pp} Serial imaging as indicated to assess disease response.

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

DISEASE PROGRESSION

SUBSEQUENT THERAPY^{q,pp}



ⁱ Core biopsy is recommended, if possible, to obtain adequate tissue for molecular profiling or other ancillary studies.

^j Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for all patients 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. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. Testing on tumor tissue is preferred; however, ctDNA testing can be considered if tumor tissue testing is not feasible. See [Discussion](#) and [Principles of Cancer Risk Assessment and Counseling \(PANC-J\)](#).

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

^t [Principles of Palliation and Supportive Care \(PANC-I\)](#).

^u [Principles of Systemic Therapy \(PANC-G\)](#).

^v [Principles of Radiation Therapy \(PANC-H\)](#).

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

^{oo} Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

^{pp} Serial imaging as indicated to assess disease response.

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

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.

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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.

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



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	<ul style="list-style-type: none"> - 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)	<input type="checkbox"/> Hypoattenuating	<input type="checkbox"/> Isoattenuating	<input type="checkbox"/> Hyperattenuating
Size (maximal axial dimension in centimeters)	<input type="checkbox"/> Measurable	<input type="checkbox"/> Nonmeasurable (isoattenuating tumors)	
Location	<input type="checkbox"/> Head/uncinate (right of SMV)	<input type="checkbox"/> Neck (anterior to SMV/PV confluence) ^e	<input type="checkbox"/> Body/tail (left of SMV)
Pancreatic duct narrowing/abrupt cutoff with or without upstream dilatation	<input type="checkbox"/> Present	<input type="checkbox"/> Absent	
Biliary tree abrupt cutoff with or without upstream dilatation	<input type="checkbox"/> Present	<input type="checkbox"/> 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 \(PANC-E, 2 of 3\)](#).

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

Arterial Evaluation				
Superior mesenteric artery (SMA) Contact	<input type="checkbox"/> Present	<input type="checkbox"/> Absent		
Degree of solid soft-tissue contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180		
Degree of increased hazy attenuation/stranding contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180		
Focal vessel narrowing or contour irregularity	<input type="checkbox"/> Present	<input type="checkbox"/> Absent		
Extension to first SMA branch	<input type="checkbox"/> Present	<input type="checkbox"/> Absent		
Celiac Axis Contact				
Degree of solid soft-tissue contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180		
Degree of increased hazy attenuation/stranding contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180		
Focal vessel narrowing or contour irregularity	<input type="checkbox"/> Present	<input type="checkbox"/> Absent		
CHA Contact				
Degree of solid soft-tissue contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180		
Degree of increased hazy attenuation/stranding contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180		
Focal vessel narrowing or contour irregularity	<input type="checkbox"/> Present	<input type="checkbox"/> Absent		
Extension to celiac axis	<input type="checkbox"/> Present	<input type="checkbox"/> Absent		
Extension to bifurcation of right/left hepatic artery	<input type="checkbox"/> Present	<input type="checkbox"/> Absent		
Arterial Variant				
Variant anatomy	<input type="checkbox"/> Accessory right hepatic artery	<input type="checkbox"/> Replaced right hepatic artery	<input type="checkbox"/> Replaced common hepatic artery	<input type="checkbox"/> Others (origin of replaced or accessory artery) _____
Variant vessel contact	<input type="checkbox"/> Present	<input type="checkbox"/> Absent		
Degree of solid soft-tissue contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180		
Degree of increased hazy attenuation/stranding contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180		
Focal vessel narrowing or contour irregularity	<input type="checkbox"/> Present	<input type="checkbox"/> 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	<input type="checkbox"/> Present	<input type="checkbox"/> Absent	<input type="checkbox"/> Complete occlusion
Degree of solid soft-tissue contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180	
Degree of increased hazy attenuation/stranding contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180	
Focal vessel narrowing or contour irregularity (tethering or tear drop)	<input type="checkbox"/> Present	<input type="checkbox"/> Absent	
SMV Contact			
SMV Contact	<input type="checkbox"/> Present	<input type="checkbox"/> Absent	<input type="checkbox"/> Complete occlusion
Degree of solid soft-tissue contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180	
Degree of increased hazy attenuation/stranding contact	<input type="checkbox"/> ≤180	<input type="checkbox"/> >180	
Focal vessel narrowing or contour irregularity (tethering or tear drop)	<input type="checkbox"/> Present	<input type="checkbox"/> Absent	
Extension	<input type="checkbox"/> Present	<input type="checkbox"/> Absent	
Other			
Thrombus within vein (tumor, bland)	<input type="checkbox"/> Present <input type="checkbox"/> MPV <input type="checkbox"/> SMV <input type="checkbox"/> Splenic vein	<input type="checkbox"/> Absent	
Venous collaterals	<input type="checkbox"/> Present <input type="checkbox"/> Around pancreatic head <input type="checkbox"/> Porta hepatis <input type="checkbox"/> Root of the mesentery <input type="checkbox"/> Left upper quadrant	<input type="checkbox"/> 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	<input type="checkbox"/> Present <input type="checkbox"/> Suspicious <input type="checkbox"/> Indeterminate <input type="checkbox"/> Likely benign	<input type="checkbox"/> Absent
Peritoneal or omental nodules	<input type="checkbox"/> Present	<input type="checkbox"/> Absent
Ascites	<input type="checkbox"/> Present	<input type="checkbox"/> Absent
Suspicious lymph nodes	<input type="checkbox"/> Present <input type="checkbox"/> Porta hepatis <input type="checkbox"/> Celiac <input type="checkbox"/> Splenic hilum <input type="checkbox"/> Paraaortic <input type="checkbox"/> Aortocaval <input type="checkbox"/> Other _____	<input type="checkbox"/> Absent
Other extrapancreatic disease (invasion of adjacent structures)	<input type="checkbox"/> Present • Organs involved: _____	<input type="checkbox"/> Absent
Impression		
	Tumor size: _____	Tumor location: _____
Vascular contact	<input type="checkbox"/> Present • Vessel involved: _____ • Extent: _____	<input type="checkbox"/> Absent
Metastasis	<input type="checkbox"/> Present (Location _____)	<input type="checkbox"/> 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	<ul style="list-style-type: none"> • No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). 	<ul style="list-style-type: none"> • No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or $\leq 180^\circ$ contact without vein contour irregularity.
Borderline Resectable^b	<p><u>Pancreatic head/uncinate process:</u></p> <ul style="list-style-type: none"> • 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 $\leq 180^\circ$. • 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. <p><u>Pancreatic body/tail:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with the CA of $\leq 180^\circ$. 	<ul style="list-style-type: none"> • Solid tumor contact with the SMV or PV of $> 180^\circ$, contact of $\leq 180^\circ$ 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}	<p><u>Head/uncinate process:</u></p> <ul style="list-style-type: none"> • Solid tumor contact $> 180^\circ$ with the SMA or CA. <p><u>Pancreatic body/tail:</u></p> <ul style="list-style-type: none"> • Solid tumor contact of $> 180^\circ$ with the SMA or CA. • Solid tumor contact with the CA and aortic involvement. 	<ul style="list-style-type: none"> • 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

- Decisions about responses to neoadjuvant therapy and 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.
- The purpose of neoadjuvant therapy is to improve outcomes for patients compared to an upfront surgical approach. This includes: increasing the probability of a negative (R0) resection, allowing systemic treatment exposure for treatment of occult metastatic disease as well as identifying those patients with surgical futility, and allowing time for preoperative optimization of patients prior to an operation.
- The following guidelines and principles should be utilized for patients being considered for potential surgical resection after neoadjuvant therapy:
 - ▶ Curative-intent resection should only be considered in the absence of metastatic disease.
 - ▶ Objective response criteria and metrics are necessary to determine suitability of resection after neoadjuvant therapy (See Table 1). In general, the more complex the resection (greater risk) that is required, the greater the need for objective response to neoadjuvant therapy (to justify those risks).
 - ▶ In addition to standard response modalities (eg, CT/MRI, CA 19-9) that have limited utility in determining treatment responses in a significant proportion of patients, consider metabolic (FDG-PET) imaging (PET/CT or PET/MRI) before and after initiation of neoadjuvant chemotherapy to assess metabolic response and for restaging. Clinical improvements (eg, performance status, pain, satiety, weight/nutritional status, diabetes control) are other possible metrics of response to treatment.
 - ▶ For patients with anatomically advanced tumors (borderline resectable/locally advanced) with radiologic vascular involvement that achieve objective responses to neoadjuvant therapy, the criteria for resection include the following surgical principles to be considered: en bloc resection of tumor and “at-risk” tissues in order to achieve complete tumor excision with negative margins (R0), re-establishment of end-organ arterial inflow and venous outflow, restoration of GI continuity, and biliary drainage. This may be assessed intraoperatively, considering the low accuracy of traditional cross-sectional imaging in differentiating viable tumor tissue from scar tissue.
 - ▶ Venous resection (portal/SMV axis) is supported by evidence if complete tumor excision (R0) is technically feasible with reasonably limited risks; however, it is associated with higher complexity and potential for increased blood loss and postoperative morbidity/mortality and a higher likelihood of a positive margin.
 - ▶ Arterial resection (hepatic artery, celiac axis, superior mesenteric artery) is often associated with multivisceral resection and potential for significantly greater morbidity/mortality and should be limited to centers with experienced surgical and multidisciplinary teams (proven experience in pancreatectomies with vascular resections and reconstructions) and considered only in highly selected patients after extensive neoadjuvant therapy with objective responses.
 - ▶ Patients who are technical candidates for vascular resection/reconstruction (vs arterial divestment) after neoadjuvant therapy should be counseled about the operative morbidity and mortality risks, the potential effects on their quality of life, and that the long-term benefit (ie, chance for cure) is currently unknown. These patients should always be handled in highly specialized centers.

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

References



NCCN Guidelines Version 2.2026

Pancreatic Adenocarcinoma

TABLE 1: CRITERIA FOR RESECTION FOLLOWING NEOADJUVANT THERAPY

Response Category ^a	Response Metrics ^c	Response Recommendation
Significant^b	<p><u>RADIOLOGIC^d</u> Significant reduction (RECIST) of tumor size/volume (does not require decrease in degree of any vascular involvement) and/or</p> <p><u>BIOCHEMICAL^e</u> Significant reduction of CA19-9/CEA and/or</p> <p><u>METABOLIC^f</u> Significant reduction of PET SUV/metabolic tumor volume</p>	<ul style="list-style-type: none"> • Surgical resection recommended (independent of degree of vascular involvement) in majority of cases if R0 resection is technically feasible. • If response warrants surgical resection but technically unfeasible locally, then second opinion at center with expertise with vascular resections is recommended. • Consolidative chemoradiation may be considered after chemotherapy and prior to surgical resection.
Minimal	<p><u>RADIOLOGIC^d</u> Stable or minimal reduction (RECIST) of tumor size/volume and/or</p> <p><u>BIOCHEMICAL^e</u> Stable or minimal reduction of CA19-9/CEA and/or</p> <p><u>METABOLIC^f</u> Stable or minimal reduction of PET SUV/metabolic tumor volume</p>	<ul style="list-style-type: none"> • Surgical resection considered in select cases in tumors without or with limited vascular involvement (without significant increased surgical risk). • Otherwise, switching to a different neoadjuvant therapy should be considered with response re-evaluation after second-line chemotherapy. <ul style="list-style-type: none"> ▶ Surgical resection may be considered after switching to a different neoadjuvant therapy as long as no progression, if R0 resection is technically feasible. ▶ If subsequent response after switching to a different neoadjuvant therapy warrants possible surgical resection but technically unfeasible locally, then second opinion at center with expertise with vascular resections is recommended. • Consolidative chemoradiation may be considered with minimal response after first-line chemotherapy versus switching to a different neoadjuvant therapy.
Progression	<p><u>RADIOLOGIC^d</u> Increase (RECIST) of tumor size/volume or degree of vascular involvement (no metastatic progression) and/or</p> <p><u>BIOCHEMICAL^e</u> Increase of CA19-9/CEA and/or</p> <p><u>METABOLIC^f</u> Increase of PET SUV/metabolic tumor volume</p>	<ul style="list-style-type: none"> • Switching to a different neoadjuvant therapy is recommended with response re-evaluation of second-line chemotherapy. <ul style="list-style-type: none"> ▶ Surgical resection may be considered after switching to a different neoadjuvant therapy as long as no progression in select cases in tumors without or with limited vascular involvement (without significant increased surgical risk), if R0 resection is technically feasible. ▶ Surgical resection in tumors with vascular involvement may be considered only with significant response after switching to a different neoadjuvant therapy, if R0 resection is technically feasible. ▶ If subsequent response after switching to a different neoadjuvant therapy warrants possible surgical resection but technically unfeasible locally, then second opinion at center with expertise with vascular resections is recommended. • Consolidative chemoradiation may be considered without metastatic disease after switching to a different neoadjuvant therapy.

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



CRITERIA FOR RESECTION FOLLOWING NEOADJUVANT THERAPY

FOOTNOTES

- ^a Responses measured are specifically for neoadjuvant systemic therapy and not from neoadjuvant (chemo)radiation therapy alone. The duration of neoadjuvant systemic therapy is determined by the local treatment team.
- ^b Degree of “significance” is determined by local treatment team; however, examples of optimal response metrics include CA19-9 normalization (or near-normalization or at least 50% decrease) and complete (or near-complete) metabolic response on PET.
- ^c In case of mixed responses (ie, reduction in tumor size on CT but increase in CA19-9), a third response metric (ie, PET response) and multidisciplinary tumor board discussion may assist in determining response category (ie, 2 out of 3 metrics).
- ^d Radiologic response on high quality triple phase CT or contrast enhanced MRI. Mild increases in perivascular soft tissue can be observed, but alone do not represent progression.
- ^e In those patients with an elevated tumor marker at baseline and normalization of liver function tests.
- ^f Metabolic responses assessed on FDG-PET (either PET/CT or PET/MRI) compared to baseline treatment naïve PET scan if baseline study revealed an avid tumor.

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



CRITERIA FOR RESECTION FOLLOWING NEOADJUVANT THERAPY REFERENCES

- Abdelrahman AM, Goenka AH, Alva-Ruiz R, et al. FDG-PET predicts neoadjuvant therapy response and survival in borderline resectable/locally advanced pancreatic adenocarcinoma. *J Natl Compr Canc Netw* 2022;20:1023-1032.e3.
- Al Abbas AI, Zenati M, Reiser CJ, et al. Serum CA19-9 response to neoadjuvant therapy predicts tumor size reduction and survival in pancreatic adenocarcinoma. *Ann Surg Oncol* 2020;27:2007-2014.
- Alva-Ruiz R, Truty MJ. ASO author reflections: Neoadjuvant chemotherapy switch: Optimizing neoadjuvant treatment sequencing in pancreas cancer. *Ann Surg Oncol* 2022;29:1592-1593.
- Ashitomi Y, Motoi F, Oba A, et al. Favorable response defined by CA19-9 reduction after neoadjuvant treatment for pancreatic cancer. *Ann Surg Oncol* Published online September 1, 2025.
- Barreto SG, Loveday B, Windsor JA, et al. Detecting tumour response and predicting resectability after neoadjuvant therapy for borderline resectable and locally advanced pancreatic cancer. *ANZ J Surg* 2019;89:481-487.
- Cassinotto C, Sa-Cunha A, Trillaud H. Radiological evaluation of response to neoadjuvant treatment in pancreatic cancer. *Diagn Interv Imaging* 2016;97:1225-1232.
- Cloyd JM, Ejaz A, Shen C, et al. Pathologic complete response following neoadjuvant therapy for pancreatic ductal adenocarcinoma: defining the incidence, predictors, and outcomes. *HPB (Oxford)* 2020;22:1569-1576.
- Dekker EN, Narayan RR, Ahmami MA, et al. Chemotherapy switch for localized pancreatic cancer: a systematic review and meta-analysis. *Br J Surg* 2024;111:znae244.
- Fong ZV, Verdugo FL, Fernandez-Del Castillo C, et al. Tolerability, attrition rates, and survival outcomes of neoadjuvant FOLFIRINOX for nonmetastatic pancreatic adenocarcinoma: Intent-to-treat analysis. *J Am Coll Surg* 2023;236:1126-1136.
- Gillson JE, Byeon S, Chou A, et al. Promising biomarker panel to monitor therapeutic efficacy of neoadjuvant chemotherapy in pancreatic cancer patients. *Eur J Clin Invest* 2025;55:e14341.
- Heger U, Sun H, Hinz U, et al. Induction chemotherapy in pancreatic cancer: CA 19-9 may predict resectability and survival. *HPB (Oxford)* 2020;22:224-232.
- Kato H, Kishiwada M, Hayasaki A, et al. Role of serum carcinoma embryonic antigen (CEA) level in localized pancreatic adenocarcinoma: CEA level before operation is a significant prognostic indicator in patients with locally advanced pancreatic cancer treated with neoadjuvant therapy followed by surgical resection: A retrospective analysis. *Ann Surg* 2022;275:e698-e707.
- Kim KS, Kwon J, Kim K, Chie EK. Impact of resection margin distance on survival of pancreatic cancer: A Systematic review and meta-analysis. *Cancer Res Treat* 2017;49:824-833.
- Kim S, Lee S, Lee HS, et al. Retrospective evaluation of treatment response in patients with nonmetastatic pancreatic cancer using CT and CA 19-9. *Radiology* 2022;303:548-556.
- Kobayashi K, Ono Y, Sato S, et al. Evaluation of local recurrence after pancreaticoduodenectomy for borderline resectable pancreatic head cancer with neoadjuvant chemotherapy: Can the resection level change after chemotherapy?. *Surgery* 2023;173:1220-1228.
- Panda A, Garg I, Truty MJ, et al. Borderline resectable and locally advanced pancreatic cancer: FDG PET/MRI and CT tumor metrics for assessment of pathologic response to neoadjuvant therapy and prediction of survival. *AJR Am J Roentgenol* 2021;217:730-740.
- Perri G, Prakash L, Wang H, et al. Radiographic and serologic predictors of pathologic major response to preoperative therapy for pancreatic cancer. *Ann Surg* 2021;273:806-813.
- Qiao G, Li X, Mohamed M, et al. Efficacy of neoadjuvant therapy and the prognostic significance of serum carcinoembryonic antigen level in patients with localized pancreatic adenocarcinoma with non-elevated carbohydrate antigen 19-9 Levels. *Ann Surg* Published online April 8, 2025.
- Rose JB, Edwards AM, Rocha FG, et al. Sustained carbohydrate antigen 19-9 response to neoadjuvant chemotherapy in borderline resectable pancreatic cancer predicts progression and survival. *Oncologist* 2020;25:859-866.
- Soloff EV, Al-Hawary MM, Desser TS, et al. Imaging assessment of pancreatic cancer resectability after neoadjuvant therapy: AJR expert panel narrative review. *AJR Am J Roentgenol* 2022;218:570-581.
- Tee MC, Krajewski AC, Groeschl RT, et al. Indications and perioperative outcomes for pancreatotomy with arterial resection. *J Am Coll Surg* 2018;227:255-269.
- Thalji SZ, Kamgar M, George B, et al. CA19-9 response to first-line neoadjuvant FOLFIRINOX and second-line Gemcitabine/Nab-Paclitaxel for patients with operable pancreatic cancer. *Ann Surg Oncol* 2023;30:3013-3021.
- 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.
- van Veldhuisen E, Vogel JA, Klomp maker S, et al. Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. *HPB (Oxford)* 2018;20:605-611.

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



CRITERIA FOR RESECTION FOLLOWING NEOADJUVANT THERAPY REFERENCES

Vreeland TJ, McAllister F, Javadi S, et al. Benefit of Gemcitabine/Nab-Paclitaxel rescue of patients with borderline resectable or locally advanced pancreatic adenocarcinoma after early failure of FOLFIRINOX. *Pancreas* 2019;48:837-843.

Wagner M, Antunes C, Pietrasz D, et al. CT evaluation after neoadjuvant FOLFIRINOX chemotherapy for borderline and locally advanced pancreatic adenocarcinoma. *Eur Radiol* 2017;27:3104-3116.

Ye C, Sadula A, Ren S, et al. The prognostic value of CA19-9 response after neoadjuvant therapy in patients with pancreatic cancer: a systematic review and pooled analysis. *Cancer Chemother Pharmacol* 2020;86:731-740.

Yokose T, Kitago M, Matsusaka Y, et al. Usefulness of 18 F-fluorodeoxyglucose positron emission tomography/computed tomography for predicting the prognosis and treatment response of neoadjuvant therapy for pancreatic ductal adenocarcinoma. *Cancer Med* 2020;9:4059-4068.

Zhang Y, Huang ZX, Song B. Role of imaging in evaluating the response after neoadjuvant treatment for pancreatic ductal adenocarcinoma. *World J Gastroenterol* 2021;27:3037-3049.

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



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. Avoid cautery at margins sent for frozen section. To avoid cautery artifact that may confound the frozen section, assess the pancreatic neck and bile duct at time of surgery by frozen section. 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.

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

[References](#)

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, which may include neoadjuvant chemotherapy, 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.

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

[References](#)



PRINCIPLES OF SURGICAL TECHNIQUE REFERENCES

- ¹ Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. *J Am Coll Surg* 2008;207:510-519.
- ² Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006;10:1199-1210.
- ³ Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. *Curr Probl Cancer* 2002;26:176-275.
- ⁴ Nakeeb A, Lillemoe KD, Grosfeld JL. Surgical techniques for pancreatic cancer. *Minerva Chir* 2004;59:151-163.
- ⁵ Moletta L, Serafini S, Valmasoni M, et al. Surgery for recurrent pancreatic cancer: Is it effective? *Cancers (Basel)* 2019;11:991.
- ⁶ Serafini S, Sperti C, Friziero A, et al. Systematic review and meta-analysis of surgical treatment for isolated local recurrence of pancreatic cancer. *Cancers (Basel)* 2021;13:1277.
- ⁷ Shoup M, Conlon KC, Klimstra D, Brennan MF. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? *J Gastro Surg* 2003;7:946-952; discussion 952.
- ⁸ Christein JD, Kendrick ML, Iqbal CW, et al. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. *J Gastrointest Surg* 2005;9:922-927.
- ⁹ Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. *J Am Coll Surg* 2007;204:244-249.
- ¹⁰ Hirono S, Kawai M, Okada K, et al. Pancreatic neck cancer has specific and oncologic characteristics regarding portal vein invasion and lymph node metastasis. *Surgery* 2016;159:426-440.
- ¹¹ Strasberg SM, Sanchez LA, Hawkins WG, et al. Resection of tumors of the neck of the pancreas with venous invasion: the “Whipple at the Splenic Artery (WATSA)” procedure. *J Gastrointest Surg* 2012;16:1048-1054.

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

PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING¹

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 Specimen²

- 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 either be 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 bile duct margin and, if present, the proximal and distal margins of the PV 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. Therefore, the margin should be inked, shaved/amputated, then 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.³
 - ◇ 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.
- Every effort should be made to identify all regional lymph nodes within the pancreatoduodenectomy specimen. Adequate lymph node assessment may be more challenging after neoadjuvant therapy, but the Panel consensus is an assessment of at least 12 lymph nodes.²⁻⁴

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



PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING¹

- 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/vascular bed 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.⁴⁻⁷ 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 the axial and bivalve methods. In the axial method, the pancreas is sectioned perpendicular to its long axis at regular intervals. In the bivalve method, the pancreas is bisected along probes placed within the bile and pancreatic ducts, and each half is then sectioned perpendicularly to the inked anterior and posterior surfaces.⁸ Axial slicing helps preserve spatial relationships, making it especially useful for radiologic-pathologic correlation. The bivalve method is particularly advantageous for localizing tumors—especially small lesions near the ampulla or ducts—and for assessing ductal involvement and surgical margins.⁹⁻¹¹
 - ▶ There is no one correct way to dissect a Whipple specimen.⁸ 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,^{4,12} 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.

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

References



PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING¹

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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References



PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING¹

- The NCCN Pancreatic Cancer Panel currently supports pathology synoptic reports from the College of American Pathologists (CAP). The proposal included herein is an abbreviated minimum analysis of pancreatic cancer specimens from the CAP recommendations. In addition to the standard TNM staging, other variables are included, all of which have prognostic implications in the evolution of this disease.^{13,14}
- 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)¹⁵
 - 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](#)).

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

References



PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING REFERENCES

- ¹ Wang H, Chetty R, Hosseini M, et al. Pathologic examination of pancreatic specimens resected for treated pancreatic ductal adenocarcinoma: Recommendations from the pancreatobiliary pathology society. *Am J Surg Pathol* 2022;46:754-764.
- ² Dhall D, Shi J, Allende DS, et al. Towards a more standardized approach to pathologic reporting of pancreatoduodenectomy specimens for pancreatic ductal adenocarcinoma: Cross-continental and cross-specialty survey from the Pancreatobiliary Pathology Society Grossing Working Group. *Am J Surg Pathol* 2021;45:1364-1373.
- ³ Fukuda S, Oussoultzoglou E, Bachellier P, et al. Significance of the depth of portal vein wall invasion after curative resection for pancreatic adenocarcinoma. *Arch Surg* 2007;142:172-179; discussion 180.
- ⁴ Verbeke CS, Menon KV. Redefining resection margin status in pancreatic cancer. *HPB (Oxford)* 2009;11:282-289.
- ⁵ The Royal College of Pathologists. Standards and minimum datasets for reporting cancers. Minimum dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma. The Royal College of Pathologists. 2002.
- ⁶ Classification of pancreatic cancer. Japan Pancreas Society. 2nd ed. Tokyo: Kanehara; 2003.
- ⁷ Hruban RH, Pitman MB, Klimstra DS. Tumors of the Pancreas. Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, D.C.: American Registry of Pathology; Armed Forces Institutes of Pathology; 2007.
- ⁸ Adsay NV, Basturk O, Saka B, et al. Whipple made simple for surgical pathologists: orientation, dissection, and sampling of pancreaticoduodenectomy specimens for a more practical and accurate evaluation of pancreatic, distal common bile duct, and ampullary tumors. *Am J Surg Pathol* 2014;38:480-493.
- ⁹ Adsay V, Ohike N, Tajiri T, et al. Ampullary region carcinomas: definition and site specific classification with delineation of four clinicopathologically and prognostically distinct subsets in an analysis of 249 cases. *Am J Surg Pathol* 2012;36:1592-1608.
- ¹⁰ Ohike N, Kim GE, Tajiri T, et al. Intra-ampullary papillary-tubular neoplasm (IAPN): characterization of tumoral intraepithelial neoplasia occurring within the ampulla: a clinicopathologic analysis of 82 cases. *Am J Surg Pathol* 2010;34:1731-1748.
- ¹¹ Tarcan ZC, Esmer R, Akar KE, et al. Intra-ampullary papillary tubular neoplasm (IAPN): Clinicopathologic analysis of 72 cases highlights the distinctive characteristics of a poorly recognized entity. *Am J Surg Pathol* 2024;48:1093-1107.
- ¹² Campbell F, Smith RA, Whelan P, et al. Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. *Histopathology* 2009;55:277-283.
- ¹³ Mitsunaga S, Hasebe T, Iwasaki M, et al. Important prognostic histological parameters for patients with invasive ductal carcinoma of the pancreas. *Cancer Sci* 2005;96:858-865.
- ¹⁴ Gebhardt C, Meyer W, Reichel M, Wunsch PH. Prognostic factors in the operative treatment of ductal pancreatic carcinoma. *Langenbecks Arch Surg Jan* 2000;385:14-20.
- ¹⁵ Gill AJ, Klimstra DS, Lam AK, Washington MK, eds. Tumours of the pancreas. In: WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon, France; 2019:295-371.

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

PRINCIPLES OF SYSTEMIC THERAPY

Neoadjuvant Therapy (Resectable/Borderline Resectable Disease) ([PANC-G 1 of 13](#))

Adjuvant Therapy ([PANC-G 2 of 13](#))

Locally Advanced Disease (First-Line Therapy) ([PANC-G 3 & 4 of 13](#))

Metastatic Disease (First-Line Therapy) ([PANC-G 5 & 6 of 13](#))

Metastatic Disease (Maintenance Therapy) ([PANC-G 7 of 13](#))

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

Chemoradiation ([PANC-G 11 of 13](#))

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.
- If *BRCA1/2* status is unknown, then treat with systemic therapy as clinically indicated.
- Close follow-up of patients undergoing chemotherapy is indicated.
- For regimens where RT or chemoradiation is included, [Principles of Radiation Therapy \(PANC-H\)](#) 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](#).
- Less common variants, such as squamous/adenosquamous carcinomas, are treated similarly to adenocarcinoma. There are insufficient data supporting the efficacy of any of the recommended regimens for these rare subtypes. For mixed histologies, the Panel recommends treating the more aggressive histology.
- An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
- For information regarding *DPYD* testing, see the [NCCN Guidelines for Colon Cancer](#).
- Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV Pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV Pembrolizumab.

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

PRINCIPLES OF SYSTEMIC THERAPY

Neoadjuvant Therapy		
<p>• There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and radiation. Consolidative chemoradiation is sometimes included (PANC-4 and PANC-D). 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.</p>		
	Preferred	Useful in Certain Circumstances
Resectable/ Borderline Resectable Disease	<ul style="list-style-type: none"> • Albumin-bound Paclitaxel/Gemcitabine • Albumin-bound Paclitaxel/Gemcitabine with consolidative chemoradiation^a • FOLFIRINOX (Leucovorin/Fluorouracil/Irinotecan/Oxaliplatin) or modified FOLFIRINOX^{b,c,1} • FOLFIRINOX or modified FOLFIRINOX^{b,c,1} with consolidative chemoradiation^a <p><u>Only for known <i>BRCA1/2</i> or <i>PALB2</i> mutations:</u></p> <ul style="list-style-type: none"> • Cisplatin/Gemcitabine (≥2 to 6 cycles) • Cisplatin/Gemcitabine (≥2 to 6 cycles) with consolidative chemoradiation^a • FOLFIRINOX or modified FOLFIRINOX^{b,c,1} • FOLFIRINOX or modified FOLFIRINOX^{b,c,1} with consolidative chemoradiation^a 	<ul style="list-style-type: none"> • PAXG (Cisplatin/Albumin-bound Paclitaxel/Capecitabine/Gemcitabine)²

^a [Chemoradiation \(PANC-G 11 of 13\)](#).

^b FOLFIRINOX or Modified FOLFIRINOX should be limited to those with ECOG 0–1.

^c Due to the high toxicity of this regimen, bolus fluorouracil is often omitted.

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

References

PRINCIPLES OF SYSTEMIC THERAPY

Adjuvant Therapy	
<ul style="list-style-type: none"> • 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.³ • ESPAC-3 study results showed no significant difference in OS between Fluorouracil/Leucovorin versus Gemcitabine following surgery. When the groups receiving adjuvant Fluorouracil/Leucovorin and adjuvant Gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.⁴ • Data from ESPAC-4 support the use of Gemcitabine combined with Capecitabine (1660 mg/m²/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; <i>P</i> = .032).⁵ • No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation Fluorouracil with pre- and post-chemoradiation Gemcitabine for postoperative adjuvant treatment.⁶ • 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	Other Recommended
<ul style="list-style-type: none"> • Capecitabine/Gemcitabine (category 1) • Modified FOLFIRINOX (category 1)^{b,c} 	<ul style="list-style-type: none"> • Bolus Fluorouracil/Leucovorin (category 1) • Gemcitabine (category 1) • Continuous infusion Fluorouracil • Chemotherapy followed by chemoradiation^{a,d}: <ul style="list-style-type: none"> ▶ Bolus Fluorouracil/Leucovorin ▶ Continuous infusion Fluorouracil ▶ Gemcitabine • Chemotherapy followed by chemoradiation^{a,d} with subsequent chemotherapy⁶: <ul style="list-style-type: none"> ▶ Bolus Fluorouracil/Leucovorin followed by chemoradiation^{a,d} with subsequent bolus Fluorouracil/Leucovorin ▶ Continuous infusion Fluorouracil followed by chemoradiation^{a,d} with subsequent continuous infusion Fluorouracil ▶ Gemcitabine followed by chemoradiation^{a,d} with subsequent Gemcitabine • Capecitabine (category 2B)

^a [Chemoradiation \(PANC-G 11 of 13\)](#).

^b FOLFIRINOX or Modified FOLFIRINOX should be limited to those with ECOG 0–1.

^c Due to the high toxicity of this regimen, bolus fluorouracil is often omitted.

^d If considering chemoradiation due to positive margins, chemotherapy should be given prior to the administration of chemoradiation.

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced Disease (First-Line Therapy) ^e			
	Preferred	Other Recommended	Useful in Certain Circumstances
Good PS 0–1	<ul style="list-style-type: none"> Albumin-bound Paclitaxel/Gemcitabine^{f,7} FOLFIRINOX or modified FOLFIRINOX^{c,f,1,8} NALIRIFOX (Liposomal Irinotecan/Fluorouracil/Leucovorin/Oxaliplatin)^{g,9} <p><u>Only for known <i>BRCA1/2</i> or <i>PALB2</i> mutations:</u></p> <ul style="list-style-type: none"> Cisplatin/Gemcitabine^{10,11} FOLFIRINOX or modified FOLFIRINOX^{c,f,1,8} 	<ul style="list-style-type: none"> Capecitabine/Gemcitabine¹² Erlotinib/Gemcitabine^{h,13} Gemcitabine Albumin-bound Paclitaxel/Cisplatin/Gemcitabine^{14,15} (category 2B) Capecitabine (category 2B) CAPEOX (Capecitabine/Oxaliplatin)¹⁶ (category 2B) Continuous infusion Fluorouracil (category 2B) GTX (Gemcitabine fixed-dose-rate/Docetaxel/Capecitabine)¹⁷ (category 2B) OFF (Oxaliplatin/Fluorouracil/Leucovorin)¹⁸ (category 2B) 	<ul style="list-style-type: none"> Induction chemotherapy with any of the preferred/other regimens (≥4 to 6 cycles) followed by chemoradiation^{a,i} or SBRT¹⁹ in selected patients (locally advanced disease without systemic metastases)²⁰ Chemoradiation^{a,j} or SBRT^j (in patients who are not candidates for induction chemotherapy) Dabrafenib/Trametinib (if <i>BRAF</i> V600E mutation-positive)^{21,22} Entrectinib or Larotrectinib or Repotrectinib²³ (if <i>NTRK</i> gene fusion-positive) Pembrolizumab^{k,24} (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) Selpercatinib (if <i>RET</i> gene fusion-positive)

^a [Chemoradiation \(PANC-G 11 of 13\)](#).

^c Due to the high toxicity of this regimen, bolus fluorouracil is often omitted.

^e Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

^f The recommendations for FOLFIRINOX or modified FOLFIRINOX and Albumin-bound Paclitaxel/Gemcitabine in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.

^g While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over Albumin-bound Paclitaxel/Gemcitabine, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX.

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

ⁱ 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).

^j 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 \(PANC-H\)](#).

^k [NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities](#).

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

References

PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced Disease (First-Line Therapy)^e		
• Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology).		
	Preferred	Useful in Certain Circumstances
Intermediate PS 2	<ul style="list-style-type: none"> • Albumin-bound Paclitaxel/Gemcitabine • Capecitabine • Gemcitabine 	<ul style="list-style-type: none"> • Induction chemotherapy with any of the preferred regimens (≥4 to 6 cycles) followed by chemoradiation^{a,i} or SBRT¹⁹ in selected patients (locally advanced disease without systemic metastases) • Chemoradiation^{a,j} or SBRT^j (in patients who are not candidates for induction chemotherapy) • Dabrafenib/Trametinib (if <i>BRAF</i> V600E mutation-positive)^{21,22} • Entrectinib or Larotrectinib or Repotrectinib²³ (if <i>NTRK</i> gene fusion-positive) • Pembrolizumab^{k,24} (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if <i>RET</i> gene fusion-positive)

Locally Advanced Disease (First-Line Therapy)^e		
• Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology).		
	Preferred	
Poor PS 3	<ul style="list-style-type: none"> • Gemcitabine 1000 mg/m² over 30 Minutes, Weekly for 3 Weeks every 28 Days (category 1) • Capecitabine (category 2B) • Continuous infusion Fluorouracil (category 2B) • Gemcitabine fixed-dose-rate (10 mg/m²/min) may be substituted for standard infusion of Gemcitabine over 30 Minutes (category 2B) 	

^a [Chemoradiation \(PANC-G 11 of 13\)](#).

^e Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

ⁱ 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).

^j 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 \(PANC-H\)](#).

^k [NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities](#).

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

References

PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)^e			
• Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology).			
	Preferred	Other Recommended	Useful in Certain Circumstances
Good PS 0–1	<ul style="list-style-type: none"> • Albumin-bound Paclitaxel/Gemcitabine (category 1)⁷ • FOLFIRINOX⁸ (category 1) • NALIRIFOX^{9,9} (category 1) • Modified FOLFIRINOX^c <p><u>Only for known <i>BRCA1/2</i> or <i>PALB2</i> mutations:</u></p> <ul style="list-style-type: none"> • FOLFIRINOX⁸ (category 1) • Cisplatin/Gemcitabine^{10,11} • Modified FOLFIRINOX^{c,1,8} 	<ul style="list-style-type: none"> • Erlotinib/Gemcitabine^{h,13} (category 1) • Gemcitabine (category 1) • Albumin-bound Paclitaxel/Cisplatin/Gemcitabine^{14,15} • Capecitabine/Gemcitabine¹² • CAPEOX¹⁶ (category 2B) • GTX¹⁷ (category 2B) • OFF¹⁸ (category 2B) 	<ul style="list-style-type: none"> • Dabrafenib/Trametinib (if <i>BRAF</i> V600E mutation-positive)^{21,22} • Entrectinib or Larotrectinib or Repotrectinib²³ (if <i>NTRK</i> gene fusion-positive) • Pembrolizumab^{k,24} (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if <i>RET</i> gene fusion-positive)

^c Due to the high toxicity of this regimen, bolus fluorouracil is often omitted.

^e Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

^g While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over Albumin-bound Paclitaxel/Gemcitabine, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX.

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

^k [NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities](#).

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy) ^e		
• Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology).		
	Preferred	Useful in Certain Circumstances
Intermediate PS 2	<ul style="list-style-type: none"> Albumin-bound Paclitaxel/Gemcitabine (category 1) Capecitabine CAPEOX²⁵ FOLFIRI (Leucovorin/Fluorouracil/Irinotecan)^{26,27} FOLFOX (Leucovorin/Fluorouracil/Oxaliplatin)^{28,29} Gemcitabine 	<ul style="list-style-type: none"> Dabrafenib/Trametinib (if <i>BRAF</i> V600E mutation-positive)^{21,22} Entrectinib or Larotrectinib or Repotrectinib²³ (if <i>NTRK</i> gene fusion-positive) Pembrolizumab^{k,24} (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) Selpercatinib (if <i>RET</i> gene fusion-positive)

Metastatic Disease (First-Line Therapy) ^e			
• Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology).			
	Preferred	Other Recommended	Useful in Certain Circumstances
Poor PS 3	<ul style="list-style-type: none"> Palliative and best supportive care^l 	<ul style="list-style-type: none"> Gemcitabine 1000 mg/m² over 30 Minutes, Weekly for 3 Weeks every 28 Days (category 1) Capecitabine (category 2B) Continuous infusion Fluorouracil (category 2B) Gemcitabine fixed-dose-rate (10 mg/m²/min) may be substituted for standard infusion of Gemcitabine over 30 Minutes (category 2B) 	<ul style="list-style-type: none"> Larotrectinib (if <i>NTRK</i> gene fusion-positive) Pembrolizumab^{k,24} (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) Dabrafenib/Trametinib (if <i>BRAF</i> V600E mutation-positive) (category 2B)^{21,22} Entrectinib or Repotrectinib²³ (if <i>NTRK</i> gene fusion-positive) (category 2B)

^e Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

^k [NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities](#).

^l Evidence suggest patients with poor PS derive marginal benefit from systemic therapy. See [Principles of Palliation and Supportive Care \(PANC-I\)](#).

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (Maintenance Therapy for Good/Intermediate PS)^e		
<ul style="list-style-type: none"> • Patients who have response or stable disease after 4–6 months of chemotherapy may undergo a chemotherapy holiday or maintenance therapy. 		
Preferred	Other Recommended	Useful in Certain Circumstances
<p><u>If previous platinum-based chemotherapy:</u></p> <ul style="list-style-type: none"> • Olaparib (only for germline <i>BRCA1/2</i> mutations) 	<ul style="list-style-type: none"> • Clinical trial <p><u>If previous first-line FOLFIRINOX:</u></p> <ul style="list-style-type: none"> • Capecitabine <p><u>If previous first-line Albumin-bound Paclitaxel/ Gemcitabine:</u></p> <ul style="list-style-type: none"> • Modified Albumin-bound Paclitaxel/Gemcitabine (category 2B) • Gemcitabine (category 2B) 	<p><u>If previous first-line FOLFIRINOX:</u></p> <ul style="list-style-type: none"> • FOLFIRI^{m,30} • Fluorouracil/Leucovorin^{m,30} • FOLFOX^{n,30} (category 2B) <p><u>Prior platinum-based therapy:</u></p> <ul style="list-style-type: none"> • Rucaparib (for germline or somatic <i>BRCA1/2</i> or <i>PALB2</i> mutations)^{o,p,31}

^e Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

^m Fluorouracil ± Irinotecan may be considered for maintenance therapy in the case of Oxaliplatin-related progressive neuropathy or allergy to Oxaliplatin.

ⁿ 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.

^o For patients who did not have disease progression following their most recent platinum-based chemotherapy.

^p For oncogenic or likely oncogenic mutations in *BRCA1*, *BRCA2*, and *PALB2*, refer to definitions at oncokb.org, cbiportal.org, mycancergenome.org, pmkb.weill.cornell.edu, genie.cbiportal.org, ckb.jax.org, cancer.sanger.ac.uk/cosmic, brcaexchange.org, ncbi.nlm.nih.gov/clinvar or sift.bii.a-star.edu.sg.

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease ^{e,q}			
	Preferred	Useful in Certain Circumstances	
Good PS 0–1	<p><u>If prior Gemcitabine-based therapy:</u></p> <ul style="list-style-type: none"> Fluorouracil/Leucovorin/Liposomal Irinotecan³² (category 1 for metastatic disease) Capecitabine CAPEOX Continuous infusion Fluorouracil Bolus Fluorouracil/Leucovorin FOLFIRI³³⁻³⁵ FOLFIRINOX or modified FOLFIRINOX^{c,1,36} FOLFOX OFF 	<p><u>If prior Fluoropyrimidine-based therapy:</u></p> <ul style="list-style-type: none"> Albumin-bound Paclitaxel/Gemcitabine Cisplatin/Gemcitabine (only for known <i>BRCA1/2</i> or <i>PALB2</i> mutations) Erlotinib/Gemcitabine^{h,37} Fluorouracil/Leucovorin/Liposomal Irinotecan³² (if no prior Irinotecan) Gemcitabine Albumin-bound Paclitaxel/Cisplatin/Gemcitabine^{14,15} (category 2B) 	<ul style="list-style-type: none"> Adagrasib or Sotorasib (if <i>KRAS G12C</i> mutation-positive) Dabrafenib/Trametinib (if <i>BRAF V600E</i> mutation-positive)^{21,22} Entrectinib or Larotrectinib or Repotrectinib^{r,23} (if <i>NTRK</i> gene fusion-positive) Erdafitinib (if <i>FGFR</i> genetic alterations)³⁸ Fam-trastuzumab deruxtecan-nxki (if HER2 positive [IHC3+³⁹ or IHC2+ with FISH <i>HER2</i> amplified]) Selpercatinib (if <i>RET</i> gene fusion-positive)³⁹ Zenocutuzumab-zbco (if <i>NRG1</i> gene fusion-positive)^s Chemoradiation,^a if not previously given, only an option for: <ul style="list-style-type: none"> Locally advanced disease if primary site is the sole site of progression Select patients with recurrent disease in combination with systemic therapy <p><u>If no prior immunotherapy:</u></p> <ul style="list-style-type: none"> Dostarlimab-gxly^k (if MSI-H or dMMR) Pembrolizumab^k (if MSI-H, dMMR, or TMB-H ≥ 10 mut/Mb) Ipilimumab + Nivolumab^k (if TMB-H ≥ 10 mut/Mb) (category 2B)

^a [Chemoradiation \(PANC-G 11 of 13\)](#).

^c Due to the high toxicity of this regimen, bolus Fluorouracil is often omitted.

^e Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

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

^k [NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities](#).

^q For locally advanced disease progression (good/intermediate PS), local recurrence after resection, and recurrent metastatic disease after resection. If ≥ 6 months from completion of primary therapy, may repeat systemic therapy previously administered or may use alternate systemic therapy (not previously used). If < 6 months from completion of primary therapy, switching drug class or using alternate systemic therapy (not previously used) is recommended.

^r If disease progressed on a prior NTRK targeted agent.

^s For disease progression on or after prior systemic therapy.

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease ^{e,q}			
	<u>Preferred</u>	<u>Other Recommended</u>	<u>Useful in Certain Circumstances</u>
Intermediate PS 2	<p><u>If prior Fluoropyrimidine-based therapy:</u></p> <ul style="list-style-type: none"> Albumin-bound Paclitaxel/ Gemcitabine Fluorouracil/Leucovorin/ Liposomal Irinotecan³² (if no prior Irinotecan) <p><u>If prior Gemcitabine-based therapy:</u></p> <ul style="list-style-type: none"> Fluorouracil/Leucovorin/ Liposomal Irinotecan³² (category 1 for metastatic disease) FOLFOX 	<p><u>If prior Fluoropyrimidine-based therapy:</u></p> <ul style="list-style-type: none"> Gemcitabine 1000 mg/m² over 30 Minutes, Weekly for 3 Weeks every 28 Days (category 1) Gemcitabine fixed-dose-rate (10 mg/m²/min) may be substituted for standard infusion of Gemcitabine over 30 Minutes (category 2B) <p><u>If prior Gemcitabine-based therapy:</u></p> <ul style="list-style-type: none"> Capecitabine (category 2B) Continuous infusion Fluorouracil (category 2B) 	<ul style="list-style-type: none"> Adagrasib or Sotorasib (if <i>KRAS G12C</i> mutation positive) Dabrafenib/Trametinib (if <i>BRAF V600E</i> mutation-positive)^{20,21} Entrectinib or Larotrectinib (if <i>NTRK</i> gene fusion-positive) Erdafitinib (if <i>FGFR</i> genetic alterations)³⁸ Fam-trastuzumab deruxtecan-nxki (if HER2 positive [IHC3+,⁴⁰ or IHC2+ with FISH <i>HER2</i> amplified]) Zenocutuzumab-zbco (if <i>NRG1</i> gene fusion-positive)^s Repotrectinib (if <i>NTRK</i> gene fusion-positive) (category 2B)^{r,23} Chemoradiation^a if not previously given, only an option for: <ul style="list-style-type: none"> Locally advanced disease if primary site is the sole site of progression Selected patients with recurrent disease in combination with systemic therapy <p><u>If no prior immunotherapy:</u></p> <ul style="list-style-type: none"> Dostarlimab-gxly^k (if MSI-H or dMMR) Pembrolizumab^k (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) Ipilimumab + Nivolumab^k (if TMB-H [≥10 mut/Mb]) (category 2B)

^a [Chemoradiation \(PANC-G 11 of 13\)](#).

^e Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

^k [NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities](#).

^q For locally advanced disease progression (good/intermediate PS), local recurrence after resection, and recurrent metastatic disease after resection. If ≥6 months from completion of primary therapy, may repeat systemic therapy previously administered or may use alternate systemic therapy (not previously used). If <6 months from completion of primary therapy, switching drug class or using alternate systemic therapy (not previously used) is recommended.

^r If disease progressed on a prior NTRK targeted agent.

^s For disease progression on or after prior systemic therapy.

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease ^{e,9}			
	Preferred	Other Recommended	Useful in Certain Circumstances
Poor PS 3	<ul style="list-style-type: none"> Palliative and best supportive care^l 	<p><u>If prior Fluoropyrimidine-based therapy:</u></p> <ul style="list-style-type: none"> Gemcitabine 1000 mg/m² over 30 Minutes, Weekly for 3 Weeks every 28 Days (category 1) Gemcitabine fixed-dose-rate (10 mg/m²/min) may be substituted for standard infusion of Gemcitabine over 30 Minutes (category 2B) <p><u>If prior Gemcitabine-based therapy:</u></p> <ul style="list-style-type: none"> Capecitabine (category 2B) Continuous infusion Fluorouracil (category 2B) 	<p><u>If no prior immunotherapy:</u></p> <ul style="list-style-type: none"> Dabrafenib/Trametinib (if <i>BRAF</i> V600E mutation positive)^{21,22} Entrectinib or Larotrectinib (if <i>NTRK</i> gene fusion-positive) Erdafitinib (if <i>FGFR</i> genetic alterations)³⁸ Adagrasib or Sotorasib (if <i>KRAS G12C</i> mutation-positive) (category 2B) Repotrectinib (if <i>NTRK</i> gene fusion-positive) (category 2B)^{r,23} Pembrolizumab^k (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) Dostarlimab-gxly^k (if MSI-H or dMMR) (category 2B)

^e Good PS is defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake, intermediate PS is defined as ECOG 2, and poor PS is defined as ECOG 3. Patients with ECOG 4 should be exclusively supported by palliative and best supportive care.

^k [NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities](#).

^l Evidence suggest patients with poor PS derive marginal benefit from systemic therapy. See [Principles of Palliation and Supportive Care \(PANC-I\)](#).

⁹ For locally advanced disease progression (good/intermediate PS), local recurrence after resection, and recurrent metastatic disease after resection. If ≥6 months from completion of primary therapy, may repeat systemic therapy previously administered or may use alternate systemic therapy (not previously used). If <6 months from completion of primary therapy, switching drug class or using alternate systemic therapy (not previously used) is recommended.

^r If disease progressed on a prior *NTRK* targeted agent.

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Chemoradiation	
Preferred	Other Recommended
<ul style="list-style-type: none"> • Capecitabine with concurrent RT • Continuous infusion Fluorouracil with concurrent RT 	<ul style="list-style-type: none"> • Gemcitabine with concurrent RT⁴¹

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

References



PRINCIPLES OF SYSTEMIC THERAPY REFERENCES

- ¹ Conroy T, Castan F, Lopez A, et al. Five-year outcomes of FOLFIRINOX vs gemcitabine as adjuvant therapy for pancreatic cancer: A randomized clinical trial. *JAMA Oncol* 2022;8:1571-1578.
- ² Reni M, Macchini M, Orsi G, et al. Preoperative mFOLFIRINOX versus PAXG for stage I-III resectable and borderline resectable pancreatic ductal adenocarcinoma (PACT-21 CASSANDRA): results of the first randomisation analysis of a randomised, open-label, 2 × 2 factorial phase 3 trial. *Lancet* 2025;406:2945-2956.
- ³ Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013;310:1473-1481.
- ⁴ Neoptolemos J, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010;304:1073-1081.
- ⁵ Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017;389:1011-1024.
- ⁶ Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma. A randomized controlled trial. *JAMA* 2008;299:1019-1026.
- ⁷ Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691-1703.
- ⁸ Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817-1825.
- ⁹ Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. *Lancet* 2023;402:1272-1281.
- ¹⁰ Oliver GR, Sugar E, Laheru D, et al. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma [abstract]. Presented at: 2010 ASCO Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, Florida. Abstract 180.
- ¹¹ O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline *BRCA/PALB2* mutation. *J Clin Oncol* 2020;38:1378-1388.
- ¹² Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009;27:5513-5518.
- ¹³ Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25:1960-1966.
- ¹⁴ Jameson GS, Borazanci E, Babiker HM, et al. Response rate following albumin-bound paclitaxel plus gemcitabine plus cisplatin treatment among patients with advanced pancreatic cancer: A phase 1b/2 pilot clinical trial [published online ahead of print, 2019 Oct 3] [published correction appears in *JAMA Oncol* 2019;5:1643]. *JAMA Oncol* 2019;6:125-132.
- ¹⁵ Shroff RT, Javle MM, Xiao L, et al. Gemcitabine, cisplatin, and nab-paclitaxel for the treatment of advanced biliary tract cancers: A phase 2 clinical trial. *JAMA Oncol* 2019;5:824-830.
- ¹⁶ Xiong HQ, Varadhachary GR, Blais JC, et al. A phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. *Cancer* 2008;113:2046-2052.
- ¹⁷ Fine RL, Fogelman DR, Schreiber SM, et al. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. *Cancer Chemother Pharmacol* 2008;61:167-175.
- ¹⁸ Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011;47:1676-1681.
- ¹⁹ Schellenberg D, Kim J, Christman-Skieller C, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2011;81:181-188.
- ²⁰ Loehrer PJ Sr, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2011;29:4105-4112.

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

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PRINCIPLES OF SYSTEMIC THERAPY REFERENCES

- ²¹ Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAF V600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol* 2020;38:3895-3904.
- ²² Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol* 2020;21:1234-1243.
- ²³ Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusion-positive advanced solid tumors, including non-small cell lung cancer: update from the phase 1/2 TRIDENT-1 trial. *Ann Oncol* 2023;34:S787-S788.
- ²⁴ Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol* 2020;38:1-10.
- ²⁵ Bullock A, Stuart K, Jacobus S, et al. Capecitabine and oxaliplatin as first and second line treatment for locally advanced and metastatic pancreatic ductal adenocarcinoma. *J Gastrointest Oncol* 2017;8:945-952.
- ²⁶ Moretto R, Raimondo L, De Stefano A, et al. FOLFIRI in patients with locally advanced or metastatic pancreatic or biliary tract carcinoma: a monoinstitutional experience. *Anticancer Drugs* 2013;24:980-5.
- ²⁷ Taïeb J, Lecomte T, Aparicio T, et al. FOLFIRI.3, a new regimen combining 5-fluorouracil, folinic acid and irinotecan, for advanced pancreatic cancer: results of an Association des Gastro-Enterologues Oncologues (Gastroenterologist Oncologist Association) multicenter phase II study. *Ann Oncol* 2007;18:498-503.
- ²⁸ Ghosn M, Farhat F, Kattan J, et al. FOLFOX-6 combination as the first-line treatment of locally advanced and/or metastatic pancreatic cancer. *Am J Clin Oncol* 2007;30:15-20.
- ²⁹ Pishvaian MJ, Wang H, He AR, et al. A phase I/II study of veliparib (ABT-888) in combination with 5-fluorouracil and oxaliplatin in patients with metastatic pancreatic cancer. *Clin Cancer Res* 2020;26:5092-5101.
- ³⁰ Hammel P, Vitellius C, Boisteau E, et al. Maintenance therapies in metastatic pancreatic cancer: present and future with a focus on PARP inhibitors. *Ther Adv Med Oncol* 2020;12:1758835920937949.
- ³¹ Reiss KA, Mick R, O'Hara MH, et al. Phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in *BRCA1*, *BRCA2*, or *PALB2*. *J Clin Oncol* 2021;39:2497-2505.
- ³² Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016;387:545-557.
- ³³ Neuzillet C, Hentic O, Rousseau B, et al. FOLFIRI regimen in metastatic pancreatic adenocarcinoma resistant to gemcitabine and platinum-salts. *World J Gastroenterol* 2012;18:4533-4541.
- ³⁴ Zaniboni A, Aitini E, Barni S, et al. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. *Cancer Chemother Pharmacol* 2012;69:1641-1645.
- ³⁵ Chiorean EG, Guthrie KA, Philip PA, et al. Randomized phase II study of PARP inhibitor ABT-888 (veliparib) with modified FOLFIRI versus FOLFIRI as second-line treatment of metastatic pancreatic cancer: SWOG S1513. *Clin Cancer Res* 2021;27:6314-6322.
- ³⁶ Yoo C, Hwang JY, Kim JE, et al. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Br J Cancer* 2009;101:1658-1663.
- ³⁷ Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The LAP07 randomized clinical trial. *JAMA* 2016;315:1844-1853.
- ³⁸ Pant S, Schuler M, Iyer G, et al. Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): an international, single-arm, phase 2 study. *Lancet Oncol* 2023;24:925-935.
- ³⁹ Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selipercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol* 2022;23:1261-1273.
- ⁴⁰ Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol* 2024;42:47-58.
- ⁴¹ Hurt CN, Mukherjee S, Bridgewater J, et al. Health-related quality of life in SCALOP, a randomized phase 2 trial comparing chemoradiation therapy regimens in locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2015;93:810-818.

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



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.

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

[References](#)



PRINCIPLES OF RADIATION THERAPY TREATMENT PLANNING: RADIATION DELIVERY

Simulation:

- For localized, intact pancreatic cancer (resectable, borderline, and locally advanced), placement of 1–5 (preferably ≥ 3) fiducial markers may be useful for targeting purposes. Placement of fiducial markers directly into the tumor and/or periphery under EUS is preferred. Stents can assist with targeting; however, they can shift and are therefore less reliable than fiducials.
- Position patient supine with arms up in an immobilization device that will be custom-made for each patient. The simulation scan range should include the target structures and OARs.
- 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 Management³:

- 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 \(PANC-H 5 of 7\)](#). No definitive dose constraints for SBRT currently exist; however, they are emerging and are dependent on a variety of factors including dose per fraction and total dose.
- While these examples of limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs unresectable).
- The role and definition of elective target volume irradiation remain unclear. However, emerging data has increasingly suggested value to elective targeting of at-risk anatomic sites defined by extra-pancreatic neural tract anatomy (ie, the “Triangle Volume”) and/or regional nodal basins. More prospective data is needed to further refine target volume definition recommendations across stages of disease.⁶

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

[References](#)



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.^{2,7,8,9} 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 \[PANC-G\]](#)).
- Neoadjuvant therapy for patients with resectable tumors should ideally be conducted in a clinical trial.
- Consolidative chemoradiation is sometimes an option following neoadjuvant chemotherapy^{10,11} ([Principles of Systemic Therapy \[PANC-G\]](#)).
- 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).

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 \[PANC-G\]](#))
- 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 \(PANC-G\)](#) 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.

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

References



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,17-22}
 - ▶ Chemoradiation,²³ 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 SBRT²⁴; 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 \[PANC-G\]](#))
 - ▶ Chemoradiation¹⁷ 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.

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

[References](#)



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 \(PANC-I\)](#).
 - ▶ 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.
 - ▶ Single fraction SBRT can be used for celiac axis pain relief.²⁸

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).

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

References



**PRINCIPLES OF RADIATION THERAPY
REFERENCES**

- 1 Pawlik TM, Laheru D, Hruban RH, et al; Johns Hopkins Multidisciplinary Pancreas Clinic Team. Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. *Ann Surg Oncol* 2008;15:2081-2088.
- 2 Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020;38:1763-1773.
- 3 Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM task group 76. *Med Phys* 2006;33:3874-3900.
- 4 Spalding AC, Jee KW, Vineberg K, et al. Potential for dose-escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions. *Med Phys* 2007;34:521-529.
- 5 Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys* 2011;79:158-162.
- 6 Sanford NN, Narang AK, Aguilera TA, et al. NRG Oncology International Consensus Contouring Atlas on target volumes and dosing strategies for dose-escalated pancreatic cancer radiation therapy. *Int J Radiat Oncol Biol Phys* 2025;121:918-929.
- 7 Katz MH, Crane CH, Varadhachary G. Management of borderline resectable pancreatic cancer. *Semin Radiat Oncol* 2014;24:105-112.
- 8 Katz MHG, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg* 2016;151:e161137.
- 9 Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: A phase 2 clinical trial. *JAMA Oncol* 2018;4:963-969.
- 10 White RR, Hurwitz HI, Morse MA, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol* 2001;8:758-765.
- 11 Le Scodan R, Mornex F, Girard N, et al. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: Feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. *Ann Oncol* 2009;20:1387-1396.
- 12 Abrams R, et al. *J Clin Oncol* 2024;42(16 Suppl):Abstract 4005.
- 13 Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol* 2008;26:3503-3510.
- 14 Gemcitabine Hydrochloride With or Without Erlotinib Hydrochloride Followed by the Same Chemotherapy Regimen With or Without Radiation Therapy and Capecitabine or Fluorouracil in Treating Patients With Pancreatic Cancer That Has Been Removed by Surgery. *ClinicalTrials.gov* Identifier NCT01013649. Updated October 24, 2024. <https://clinicaltrials.gov/ct2/show/NCT01013649>
- 15 Hammel P, Huguet F, van Laethem J, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The LAP07 Randomized Clinical Trial. *JAMA* 2016;315:1844-1853.
- 16 Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: A phase 2 clinical trial. *JAMA Oncol* 2019;5:1020-1027.
- 17 Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer* 2007;110:47-55.
- 18 Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007;25:326-331.
- 19 Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer* 2015;121:1128-1137.
- 20 Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;78:735-742.
- 21 Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* 2009;115:665-672.
- 22 Mellon EA, Hoffs SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol* 2015;54:979-985.

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

Continued



PRINCIPLES OF RADIATION THERAPY REFERENCES

- ²³ Huguet F, Girard N, Guerche CS, et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: A qualitative systematic review. *J Clin Oncol* 2009;27:2269-2277.
- ²⁴ Yang W, Reznik R, Fraass BA, et al. Dosimetric evaluation of simultaneous integrated boost during stereotactic body radiation therapy for pancreatic cancer. *Med Dosim* 2015;40:47-52.
- ²⁵ Koay EJ, Hanania AN, Hall WA, et al. Dose-escalated radiation therapy for pancreatic cancer: a simultaneous integrated boost approach. *Pract Radiat Oncol* 2020;10:e495-e507.
- ²⁶ Reyngold M, O'Reilly EM, Varghese AM, et al. Association of ablative radiation therapy with survival among patients with inoperable pancreatic cancer. *JAMA Oncol* 2021;7:735-738.
- ²⁷ Zimmermann FB, Jeremic B, Lersch C, et al. Dose escalation of concurrent hypofractionated radiotherapy and continuous infusion 5-FU-chemotherapy in advanced adenocarcinoma of the pancreas. *Hepatogastroenterology* 2005;52:246-250.
- ²⁸ Lawrence YR, Miszczyk M, Dawson LA, et al. Celiac plexus radiosurgery for pain management in advanced cancer: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2024;25:1070-1079.

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

PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE^a

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

Symptom	Therapy
Biliary obstruction	<ul style="list-style-type: none"> • Endoscopic biliary metal stent (preferred method) • Percutaneous biliary drainage with subsequent internalization • Open biliary-enteric bypass
Gastric outlet/duodenal obstruction	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Low-molecular-weight heparin preferred over warfarin^d • Consider direct oral anticoagulants for patients without luminal tumors
Bleeding from the primary tumor site	<ul style="list-style-type: none"> • Therapeutic endoscopy, if clinically indicated • RT, if not previously done • Angiography with embolization, if clinically indicated
Pain (NCCN Guidelines for Adult Cancer Pain)	<ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> ▶ 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-H). ▶ Intrathecal drug delivery
Anorexia	<ul style="list-style-type: none"> • Daily low-dose olanzapine^f
Depression and fatigue (NCCN Guidelines for Supportive Care)	<ul style="list-style-type: none"> • Formal palliative medicine service evaluation when available^g
Exocrine pancreatic insufficiency and malnutrition	<ul style="list-style-type: none"> • Pancreatic enzyme replacement in the case of exocrine pancreatic insufficiency <ul style="list-style-type: none"> ▶ Starting dose of at least 48,000 units lipase with meals (preferably 72,000) • Nutritional evaluation with a registered dietitian when available

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

Footnotes



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, Deuschinoff 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).
- ^e Lawrence YR, Mischczyk M, Dawson LA, et al. Celiac plexus radiosurgery for pain management in advanced cancer: A multicentre, single-arm, phase 2 trial. Lancet Oncol 2024;25:1070-1079.
- ^f Sandhya L, Devi Sreenivasan N, Goenka L, et al. Randomized double-blind placebo-controlled study of olanzapine for chemotherapy-related anorexia in patients with locally advanced or metastatic gastric, hepatopancreaticobiliary, and lung cancer. J Clin Oncol 2023;41:2617-2627.
- ^g Consider encouraging advance care planning.

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



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.

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

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

T	Primary Tumor	N	Regional Lymph Nodes
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastases
Tis	Carcinoma <i>in situ</i> 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	N1	Metastasis in one to three regional lymph nodes
T1	Tumor ≤2 cm in greatest dimension	N2	Metastasis in four or more regional lymph nodes
T1a	Tumor ≤0.5 cm in greatest dimension	M	Distant Metastasis
T1b	Tumor >0.5 cm and <1 cm in greatest dimension	M0	No distant metastasis
T1c	Tumor 1–2 cm in greatest dimension	M1	Distant metastasis
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		

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



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	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended	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: April 22, 2026

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Overview

In 2026, an estimated 67,530 people will be diagnosed with pancreatic cancer, and approximately 52,740 people will die 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 diagnosis, resectability, and management of pancreatic cancer should involve multidisciplinary consultation at high-volume centers using appropriate imaging studies. In addition, the Panel believes that increased 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; Multicenter Study; 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.⁶⁻⁸ 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,⁹ as is heavy alcohol consumption.^{6,10,11} 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.¹²

BMI

Elevated BMI is associated with an increased risk for pancreatic cancer,^{13,14} with higher BMI during early adulthood associated with increased pancreatic cancer mortality.¹⁵ A meta-analysis including 22 cohort studies of 8091 patients with pancreatic cancer showed that those who engage in low levels of physical activity have a higher risk for pancreatic cancer, relative to those who engage in high levels of physical activity (relative risk [RR], 0.93; 95% CI, 0.88–0.98).¹⁶ Additionally, there is some evidence that increased consumption of red/processed meat and

dairy products is associated with an elevated pancreatic cancer risk,^{17,18} although other studies have not identified dietary risk factors for the disease.^{19,20}

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.²¹ A pooled analysis of nine case-control studies, including 2963 patients with pancreatic cancer and 8527 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; $P < .001$).²² 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,^{23,24} with one study demonstrating a 7.2-fold increased risk for pancreatic cancer for patients with a history of pancreatitis.²⁵ A meta-analysis including two case-control studies and one cohort study (1636 patients with pancreatic cancer) showed that hepatitis B infection is associated with pancreatic cancer (OR, 1.50; 95% CI, 1.21–1.87).²⁶ 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 at an increased risk for developing pancreatic cancer (CI, 1.32–1.53; hazard ratio [HR], 1.43).²⁷ 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.²⁸ Prediabetes may also be associated with increased risk for pancreatic cancer.²⁹ A systematic review and dose-response meta-analysis including nine prospective studies ($N = 2408$) showed that every 0.56 mmol/L increase in fasting blood glucose is associated with a 14% increase in pancreatic cancer incidence.³⁰

Numerous studies have shown an association between new-onset non-insulin-dependent diabetes and the development of pancreatic cancer.^{28,31,32} 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; $P < .001$).³² 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.³³ 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.³⁴ 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.³⁵ However, certain risk factors such as obesity, associated with both diabetes and pancreatic cancer, may confound these analyses.³⁶ 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.³⁷

The use of diabetic medications such as insulin and sulfonylureas is associated with an increased risk for pancreatic cancer.^{38,39} However, metformin may be associated with a reduced risk for pancreatic and other cancers,³⁸⁻⁴⁰ though a retrospective cohort study ($N = 980$) showed that metformin did not significantly improve survival in patients with diabetes diagnosed with pancreatic cancer.⁴¹ 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 vs 11.1 months; $P = .009$).⁴² 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, Pancreatic, and Prostate available at www.NCCN.org). Patients with pancreatic cancer for whom a hereditary cancer syndrome is suspected should be considered for genetic counseling.⁴³ 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.⁴⁴ 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 mutation (*ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*,



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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.⁴⁵ 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 all patients who are candidates for anticancer therapy, the Panel recommends testing for clinically actionable and/or emerging alterations, 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), and tumor mutational burden (TMB). These should be tested via an U.S. Food and Drug (FDA)-approved and/or validated next-generation sequencing (NGS)-based assay. In addition to DNA sequencing, RNA sequencing is recommended since it is better at detecting gene fusions. The Panel also recommends testing for HER2 overexpression via immunohistochemistry (IHC) ± fluorescence in situ hybridization (FISH).

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 that are often discovered incidentally. MCNs have an ovarian-like stroma^{46,47} 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%.^{48,49} The risk of malignancy in MCNs is <15%.^{48,49}

An international group of experts has established guidelines for the management of pancreatic IPMNs and MCNs,⁴⁹ as has a European group.⁵⁰ The international group strongly recommends resection in patients who can undergo surgery and with main-duct IPMNs ≥ 10 mm.⁴⁹ 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.⁴⁹ 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.⁴⁹ The European group gives similar recommendations.⁵⁰ 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, Pancreatic, and Prostate (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, a pancreatic cancer diagnosis should be considered in patients with diabetes 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



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can help to preoperatively distinguish between patients eligible for resection with curative intent and those with unresectable disease. The criteria for defining resectable disease favor specificity over sensitivity to avoid denying surgery to patients with a potentially resectable tumor.⁵¹ 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.⁵² 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.^{53,54} The TNM staging criteria for pancreatic cancer in the 7th edition of the AJCC Cancer Staging Manual accounted for CT or MRI scans, which determined resectability status of pancreatic tumors. These staging criteria also included information determined only through postsurgical pathologic evaluation of resected tumor.^{54,55} 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.⁵⁶ 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 involvement⁵⁷ and retains prognostic accuracy,⁵⁸ 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 PET/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 such that there would be a high chance of an R1 resection if surgery were performed up-front); 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); the Panel recommends that the patient be referred to a tertiary cancer center for second opinion about unresectability; or 4) metastatic. This classification is used throughout the guidelines. For patients with evidence of metastatic disease, the Panel recommends a biopsy confirmation preferably from 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



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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 the relationship of primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits.^{51,52,59} Studies have shown that 70% to 85% of patients were able to undergo resection when CT imaging showed resectable tumors.^{51,60-63} 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.⁶⁴ Therefore, high-quality CT imaging should occur no more than 4 weeks before surgery.⁶⁴

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 surrounding blood vessels and organs. However, further development of this technology may be needed before it is routinely integrated into clinical practice.⁶²

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.⁶⁵ 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 features. 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.^{66,67}

A multidisciplinary expert consensus group defined standardized language to report imaging results.⁵² The Panel recommends using the radiology staging reporting template as put together by the consensus group. The template includes morphologic, arterial, venous, and extrapancreatic evaluations.⁵² 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



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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 pancreatic cancer showed that EUS for T1–2 staging has a sensitivity and specificity of 0.72 and 0.90, respectively.⁶⁸ Sensitivity and specificity for T3–4 staging is 0.90 and 0.72, respectively.^{69–72} EUS may be used to discriminate between benign and malignant strictures or stenosis, because severe stenosis and marked proximal dilatation most often indicate malignancy.⁷³ 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.^{69–72} 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.⁷⁴ ERCP is a preferred recommendation for patients who present with jaundice or have been diagnosed on previous biopsy with no evidence of metastatic disease, requiring biliary decompression and undergo additional EUS imaging to help establish a diagnosis.⁷⁵ 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 may be avoided in those without symptomatic hyperbilirubinemia receiving upfront surgery.^{76–78} 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.⁷⁹

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.⁸⁰ 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.^{81,82} 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,



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and extreme pain. In the neoadjuvant setting, PET/CT or PET/MRI 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 metastatic tumor on the liver that may be missed even with the use of a pancreatic CT protocol.⁸³⁻⁸⁵ 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,⁸⁴ 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.⁸⁶ 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).⁸⁷ 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.^{88,89} 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.⁹⁰ 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, especially 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). The Panel believes that staging laparoscopy should be considered for patients with resectable, borderline resectable, or locally advanced pancreatic cancer. This can be performed both at time of original diagnosis, and for patients receiving neoadjuvant chemotherapy, also following completion of neoadjuvant chemotherapy prior to planned chemoradiation or surgery. Intraoperative ultrasound may be used as a diagnostic adjunct during staging laparoscopy to further evaluate liver, tumor and vascular involvement. The Panel considers positive cytology from washings, obtained at laparoscopy or laparotomy, to be equivalent to M1 disease.⁹¹

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.⁹²⁻⁹⁴ 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



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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.⁹⁵ In rare cases when EUS-FNA cannot be obtained from a patient with borderline resectable or unresectable disease, other acceptable methods of biopsy exist. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy.⁹⁶ A percutaneous approach⁹³ or a laparoscopic biopsy⁹⁷ 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, cholangiopancreatography) when repeat biopsy is needed.⁹⁸ 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 molecular profiling or other ancillary studies. 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 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, cancer antigen 125 (CA 125), and cancer antigen 19-9 (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.⁹⁹ 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.¹⁰⁰

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



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tumor-specific. However, the degree of increase in CA 19-9 levels may be useful in differentiating adenocarcinoma from inflammatory conditions of the pancreas.¹⁰¹ 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.¹⁰²

CA 19-9 is a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 80% to 90% in symptomatic patients,¹⁰³ but its low positive predictive value makes it a poor biomarker for screening.¹⁰² Preoperative CA 19-9 levels correlate with both AJCC staging and resectability and thus can provide additional information for staging and determining resectability, along with information from imaging, laparoscopy, and biopsy.¹⁰⁴⁻¹⁰⁶

CA 19-9 also seems to have value as a prognostic 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.^{102,104,106-108} 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; $P < .0001$).¹⁰⁹

Analysis of 260 patients also supports the role of postoperative CA 19-9 levels in predicting the benefit of adjuvant therapy after resection.¹¹⁰ 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 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.¹¹¹ In this study, reduction of CA 19-9 to <40 U/mL was associated with OS improvements in patients with non-resected (15 vs 11 months; $P = .02$) and resected (37.9 vs 26 months; $P = .02$) disease.

There are data to support the role of CA 19-9 as a prognostic marker in advanced disease.^{107,112} 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.¹¹² 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.¹¹²⁻¹¹⁴ 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.¹⁰⁷ In fact, increases of <5% in CA 19-9 were associated with improved OS compared to patients with a $\geq 5\%$ increase (10.3 vs 5.1 months; $P = .002$).

It is important to note that CA 19-9 may be undetectable in individuals who are negative for Lewis antigen.¹¹⁵ 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.^{116,117} 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.



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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. 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.¹¹⁸⁻¹²¹ 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.^{119,122,123} 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.¹²³ 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.¹²⁴ 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.¹²⁴⁻¹²⁶

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.¹²⁷ 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.¹²⁸ Autoimmune pancreatitis can, however, be negative for IgG4 when there is a large pancreatic mass, thus closely mimicking pancreatic adenocarcinoma.

Management of Resectable and Borderline Resectable Disease

Preoperative (Neoadjuvant) Therapy

The standard approach to therapy in patients with resectable disease has been postoperative treatment, with median survival ranging from 20.1 to 23.6 months under the most optimal clinical trial conditions.¹²⁹⁻¹³² 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 have focused on neoadjuvant therapy for patients with borderline resectable disease with the goal of improving OS.¹³³ 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.¹³⁴⁻¹³⁷ Moreover, surgery following neoadjuvant treatment appears to be safe.^{138,139}

Retrospective analyses showed that relative to neoadjuvant chemotherapy, neoadjuvant chemoradiation is associated with better local



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control, with no significant differences in survival.¹⁴⁰ 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 56 Gy in 1.8 to 2.2 Gy/fraction.^{137,141} 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 patients with borderline resectable and locally advanced disease who have received neoadjuvant therapy.^{142,143} Determinations of resectability and surgical therapy should be made on an individual basis in a multidisciplinary setting. Surgical resection should only be attempted if there is a high likelihood of achieving an R0 resection. Surgery is ideally performed 4 to 8 weeks after therapy. Surgery can be performed >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.^{144,145} 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.¹⁴⁶⁻¹⁴⁹ 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.¹⁴⁶⁻¹⁴⁸ In two retrospective studies, 31% to 35% of patients with borderline resectable disease who completed neoadjuvant therapy had R0 resections.^{150,151} 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.¹⁵²

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 leucovorin/fluorouracil/irinotecan/oxaliplatin (FOLFIRINOX) before capecitabine-based chemoradiation and surgery.¹⁴⁹ 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.¹⁴⁹ Out of the 15 patients who underwent resection, all but one had microscopically negative margins, and two had a complete



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response. However, the number of \geq grade 3 adverse events (AEs) 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.¹⁵³⁻¹⁵⁵ Chemotherapy followed by stereotactic body radiation therapy (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.^{156,157} 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 who received upfront resection (median survival, 26 months vs 21 months, respectively; HR, 0.72; 95% CI, 0.68–0.78; $P < .01$).¹⁵⁸ A number of studies, trials, and retrospective analyses have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.¹⁵⁹⁻¹⁶⁴ A retrospective review of the collective single-institution experience suggested that preoperative chemoradiation therapy in patients with resectable disease provides a survival advantage.¹⁶⁵ The authors suggest that preoperative therapy gives a selection advantage because approximately 25% of patients who are re-staged after therapy are found to have progressive disease and are therefore spared the morbidity of a surgical procedure that would not benefit them.¹⁶⁵ 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.¹⁶⁵

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.^{139,166}

Although most studies investigating the neoadjuvant experience in patients with resectable pancreatic cancer are retrospective, several small phase II studies have been published.^{139,167,168} 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.¹⁶²

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.¹⁶⁰ Although all patients were able to complete neoadjuvant therapy, 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 completed neoadjuvant cisplatin/gemcitabine followed by gemcitabine-based chemoradiation therapy and underwent surgery.¹⁶⁹ 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. After neoadjuvant therapy, the Panel recommends explorative



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laparoscopy in select cases, especially in the ones with high risk for metastatic disease.

Although evidence suggests that there may be a better chance of margin-negative resection with preoperative therapy,¹⁷⁰ randomized trials testing this association are needed. A randomized phase II trial, terminated early because of slow accrual, compared cisplatin/gemcitabine neoadjuvant chemoradiation followed by surgery with upfront surgery; both arms received adjuvant chemotherapy.¹⁷¹ With only 66 patients eligible for analysis, no significant differences were seen in R0 resection rate (52% vs 48%; $P = 0.81$), pN0 rate (39% vs 30%; $P = .44$), or OS (25.0 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 compare neoadjuvant gemcitabine chemoradiation therapy to upfront surgery in this population but was terminated early due to lack of recruitment.^{172,173} A randomized phase II study comparing modified FOLFIRINOX (mFOLFIRINOX) and albumin-bound paclitaxel/gemcitabine 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 received any neoadjuvant therapy was not significantly different from historical data of patients with resectable disease receiving adjuvant therapy.^{174,175} 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.¹⁷⁶

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.

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.¹⁷⁷ Endpoints should also be standardized by including resection rates, R0 resection rates, local recurrence rates, pathologic response rates, DFS, and OS.¹⁷⁸

Treatment Based on Response to Neoadjuvant Therapy

For V.1.2026, the Panel updated the guidelines to include treatment options based on initial response to neoadjuvant therapy. The Panel added four response categories: significant, minimal, disease progression not precluding surgery, and disease progression precluding surgery. Responses can be determined by imaging and/or other clinical parameters (eg, change in performance status, pain, satiety, weight/nutritional status, diabetes control). Those patients who are not eligible for surgery will be treated based on whether their disease is now locally advanced or metastatic. For all others, the following treatment strategies are options.

Switching to an Alternate Neoadjuvant Therapy

In a review of 468 patients with borderline resectable/locally advanced disease in a single institution, 30% of patients switched neoadjuvant regimens while 70% continued the same neoadjuvant chemotherapy regimen.¹⁷⁹ Of the patients who switched therapies, 72% of patients went on to receive curative-intent surgery. OS was not significantly different between those who received first-line neoadjuvant therapy and those who switched therapies. This study concluded that switching to alternate neoadjuvant therapy may allow a greater proportion of patients to proceed to curative-intent surgery. The study notes that OS was significantly worse in those who switched therapies but did not undergo subsequent resection (41.4 vs 36.4 months; $P = .94$, respectively; 19 months; $P < .0001$). In another study, 25 patients who switched early



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from FOLFIRINOX to albumin-bound paclitaxel/gemcitabine were identified.¹⁸⁰ About half of these patients responded to the switch, especially in those with head or uncinate tumors or lower stage and were able to undergo resection. This study also demonstrated the usefulness of switching to an alternate neoadjuvant therapy in select patients.

In cases of minimal response or disease progression (which does not preclude surgery), the Panel recommends to consider switching to alternate neoadjuvant therapy. This may be followed by chemoradiation or radiation (if the disease has not metastasized), after which the disease can again be reassessed for response.

Surgery After Neoadjuvant Therapy

Curative-intent resection should only be considered in the absence of metastatic disease. In general, the more complex the resection (greater risk) that is required, the greater the need for objective response to neoadjuvant therapy (to justify those risks). However, even with any objective response to neoadjuvant therapy, the disease may still be unresectable. In this case, the Panel recommends getting a second opinion at a center with expertise with vascular resections. If it is still deemed unresectable, then appropriate treatment options should be followed based on the presence (treated as metastatic disease) or absence (treated as locally advanced disease) of jaundice.

For patients who received neoadjuvant treatment, data supporting additional therapy after surgery are lacking. The consensus of the Panel is that patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. When chemotherapy is given, the choice of regimen may be based on response seen to neoadjuvant therapy and other clinical considerations, such as performance status (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. Additionally, the Panel recognizes the emerging use of ctDNA to assess minimal residual disease (MRD) in the postoperative setting and for surveillance purposes. However, while a positive ctDNA test appears to be prognostic for disease recurrence, the Panel cannot offer a consensus recommendation regarding its use due to limited data as to how ctDNA results would guide treatment decision-making for patients with pancreatic cancer.

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.¹⁸¹ Surgery should be done efficiently, optimizing quality of life (QOL) and cost. Early concerns about high mortality associated with various pancreatic resection procedures¹⁸² were lessened by studies demonstrating an acceptably low (<5%) mortality in experienced centers.¹⁸³ 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.^{130-132,184} 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.¹⁸⁵⁻¹⁸⁷



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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 with the clean-cut side facing down and with an effort to avoid cautery artifact at margins that may confound analysis and result in false negatives. If tumor is located within 5 mm of margins, further excision of the pancreas should be considered to ensure at least 5 mm of clearance. A review of four studies with 2580 patients showed that additional resection to achieve a negative surgical margin was not associated with improved survival.¹⁸⁸ 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.^{51,136,189,190} A more restrictive definition of borderline resectable pancreatic tumors has also been described.¹⁷⁷ This definition uses degrees of contact (eg, interface between tumor and SMA measuring $\leq 180^\circ$ 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 based on 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.^{136,191} 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.



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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.¹⁹²⁻¹⁹⁴ 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 shown no decrease in mortality rates in patients with preoperative biliary drainage.¹⁹⁵⁻¹⁹⁸ A 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.¹⁹⁹ 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.⁷⁸

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 also recommends decompression in 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 >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.²⁰⁰ Stent placement is thus required prior to administration of neoadjuvant therapy for patients with jaundice.²⁰¹⁻²⁰³

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.^{169,202} Since covered metal stents prevent tumor ingrowth, they may give more durable patency however migration may be an issue with these stents.^{204,205} However, there are no obvious differences between covered and uncovered stents.^{204,205} This issue has led to the introduction of partially covered stents, but these stents may still migrate in a substantial number of patients.^{206,207} Most metal stents used today are self-expanding. Their small initial diameters make them easy to place and their placement rarely requires dilation.²⁰⁸ Several institutions use plastic stents in patients with short life expectancies (<3 months).²⁰⁹ 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



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been confirmed, as fully covered metal stents can be removed or exchanged.

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).^{210,211}

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 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 ([Figure 1](#)).^{212,213} 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.^{214,215}

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.²¹⁶⁻²¹⁸ 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



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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.^{218,219} A population-based study of 10,206 patients from the Nationwide Inpatient Sample from 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.²²⁰ Others have noted poor short- and long-term outcomes with arterial resection.^{220,221} While further data with respect to arterial resection are clearly needed, judicious utilization of this technique 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 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.^{222,223} 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.^{223,224} 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.²²²⁻²²⁴ 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.^{223,224} Local recurrence, however, remains problematic even with pathologically negative margins.²²⁴

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.²²⁵ 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.²²⁶⁻²²⁸

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.^{229,230} 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.²³⁰



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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.²³¹ 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.²³² Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.²³³

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.^{234–237} One study found that properly selected patients with adenocarcinoma of the pancreatic head who required vein resection ($n = 141$) had a median survival of approximately 2 years that 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.²¹⁸ 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.²³⁸ 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%; $P = NS$).²³⁹ 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 Longmire²⁴⁰ 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 randomized controlled trials [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.²⁴¹ 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.²⁴² 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 versus 8.0% of patients in the pancreaticogastrostomy group (OR, 2.86; 95% CI, 1.38–6.17; $P =$



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.002).²⁴³ An increase in grade $\geq 3a$ postoperative complications was seen 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),²⁴⁴ the optimal approach to anastomosis remains based on the surgeons experience, preference, and adherence to principles including good exposure and visualization.²⁴⁵

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.^{246,247} 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.²⁴⁸ Stents used in the 1930s/1940s continue to be used today with data suggesting that they do not decrease leak rates.²⁴⁹

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.^{250,251} The use of fibrin glue sealant also does not appear to decrease the rate of pancreatic fistulas.²⁵² Pasireotide, in contrast, significantly decreased the rate of grade ≥ 3 fistula, leak, or abscess in a single-center, double-blind RCT of 300 patients (9% in pasireotide group vs 21% in placebo group; RR, 0.24; 95% CI, 0.24–0.78; $P = .006$).²⁵³

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.^{254,255} 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.²⁵⁶ 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.²⁵⁷

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.²⁵⁸ A larger, randomized, prospective, single-institution trial was performed from 1996 to 2001 to evaluate the role of extended lymph node dissections.²⁵⁹ The group of patients who received regional lymphadenectomy in addition to pancreatoduodenectomy had longer operation times, but median OS did not differ between the two groups at 1, 3, and 5 years.²⁵⁹⁻²⁶¹ A randomized multicenter trial in Japan came to similar conclusions.²⁶² 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.²⁶³⁻²⁶⁵ 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.²⁶⁶



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No survival advantage has been found when performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.²⁶⁷ 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.^{268,269}

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%).²⁷⁰ High volume, defined as >81 cases per year, correlated to perioperative mortality in a regression analysis. Of note, 75% of the 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.²⁷¹⁻²⁷⁵

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).²⁷⁶ 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.²⁷⁷ 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 National Cancer Database (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.²⁷⁸ 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 ($P = .008$).²⁷⁹ 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.²⁸⁰ The Panel recommends that pancreatic resections should be conducted at institutions that perform a large number (at least 15–20) of pancreatic resections annually.



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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.²⁸¹ 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 (CAP) comply with the CoC requirements, and are updated and revised regularly.²⁸² 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.^{283,284}

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.²⁸⁵ The CAP recommendations include a count of the number of lymph nodes recovered and the number of involved nodes.²⁸² Retrospective analyses show that patients with N0 disease have a better prognosis with an increasing number of examined lymph nodes.²⁸⁶⁻²⁸⁸ 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.^{286,288,289} For patients with N1 disease, lymph node ratio (positive node/nodes examined) appears to be related to prognosis.^{286,288-290} 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 ($P = .0017$).²⁹¹ Adequate lymph node assessment may be more challenging after neoadjuvant therapy, but the Panel consensus is that at least 12 lymph nodes should be assessed.

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 bile duct margin and if present, the proximal and distal margins of the PV should be marked.



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One of the impediments to data comparison 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 ([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.^{281,292,293} 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 and bi-valve slicing ([Figure 3](#)). In the axial method, the pancreas is sectioned perpendicular to its long axis at regular intervals. In the bi-valve method, the pancreas is bisected along probes placed within the bile and pancreatic ducts, and each half is then sectioned perpendicularly to the inked anterior and posterior surfaces.²⁹⁴ Axial slicing helps preserve spatial relationships, making it especially useful for radiologic-pathologic correlation. The bi-valve method is particularly advantageous for localizing tumors—especially small lesions near the ampulla or ducts—and for assessing ductal involvement and surgical margins.²⁹⁵⁻²⁹⁷ 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 ([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 radiation therapy (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 (≤ 1 mm) had an improvement in OS (35 vs 16 months; $P < .001$) compared with patients with wider margins (> 1 mm).²⁹⁸ In fact, patients with close-margin R0 resections had a median survival time similar to that of the R1 population (16 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).²⁹⁹ 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 ($P = .10$).³⁰⁰ Together, these results suggest that an appropriate definition of a negative margin may be > 1 mm.



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Distal Pancreatectomy Specimen

In left-sided resections, the peripancreatic soft tissue margins and the pancreatic neck are assessed ([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.

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.^{131,301} 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 fluorouracil/leucovorin arm of ESPAC-1 (20.1 months), and the gemcitabine and fluorouracil/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 capecitabine/gemcitabine (28.0 months) relative to patients randomized to receive adjuvant gemcitabine monotherapy (25.5 months) (HR, 0.82; 95% CI, 0.68–0.98; $P = .032$).¹⁸⁴ In the CONKO-005 phase III randomized trial, gemcitabine administered with erlotinib did not significantly improve OS or DFS compared to gemcitabine administered alone in the adjuvant setting.³⁰² A

phase II prospective trial with 22 patients with resected pancreatic cancer showed that cisplatin/gemcitabine is feasible, with a median OS of 35.5 months and median recurrence-free survival of 16.7 months.³⁰³

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 capecitabine/gemcitabine (category 1, preferred), mFOLFIRINOX (category 1, preferred), gemcitabine (category 1, other recommended), fluorouracil/leucovorin (category 1, other recommended), or continuous infusion fluorouracil (other recommended). Capecitabine monotherapy is also a treatment option for the adjuvant setting (category 2B). Gemcitabine, bolus fluorouracil/leucovorin, or continuous infusion fluorouracil 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.³⁰⁴ These results suggest that delaying chemotherapy until patients fully recover after surgery could possibly allow for completion of the full chemotherapy



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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 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.³⁰⁵ 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) and metastasis-free survival (29.4 vs 17.7 months) were also greater for mFOLFIRINOX compared to gemcitabine.

RTOG 0848 was a randomized trial assessing the benefit of fluoropyrimidine (capecitabine or fluorouracil)-based chemoradiation following adjuvant gemcitabine-based chemotherapy in patients with resected adenocarcinoma of the pancreatic head.³⁰⁶ Patients with node negative disease showed longer OS and DFS with the addition of chemoradiation to adjuvant chemotherapy, compared to those receiving chemotherapy alone. On the other hand, chemoradiation did not improve OS or DFS in patients with node positive disease.

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/m² of levoleucovorin is equivalent to 400 mg/m² of standard leucovorin. Another option is 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 found that 175 mg

leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus fluorouracil as adjuvant therapy to patients following R0 resections for colorectal cancer.³⁰⁷ Another study in patients with metastatic colorectal cancer showed no difference in response rate or survival between those who received bolus fluorouracil with either high-dose (500 mg/m²) or low-dose (20 mg/m²) leucovorin.³⁰⁸ Although fluorouracil 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/m²) or low- (20 mg/m²) dose leucovorin with bolus fluorouracil in the treatment of advanced colorectal cancer.³⁰⁹ Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in fluorouracil dose (in the range of 10%) may be considered.

Surveillance of Patients with Resected Disease

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited,^{310,311} 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.³¹² CA 19-9 determination is a category 2B recommendation because there are no data that suggest increased tumor marker levels led early treatment measurements for potential recurrences lead 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



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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) and if not previously done, genetic testing for hereditary mutations, or molecular profiling of tumor tissues. Chemoradiation can be considered in patients with local disease recurrence, 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.

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.³¹³ Therefore, for patients with local disease recurrence, surgical resection may be considered in select cases (ie, location of recurrence is in the pancreas only). There is a potential benefit of re-resection for pancreatic ductal adenocarcinoma recurrences in selected patients. These patients should be carefully evaluated in a multidisciplinary clinic where following detailed restaging assessment, a multimodal therapy care plan that may include neoadjuvant chemotherapy +/- RT and possible surgical resection can be formulated.

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. Clinical trials or palliative and best supportive care are also options for patients with local or metastatic recurrence after resection.

Management of Isolated Pulmonary Metastases

Some patients have isolated lung metastases after resection of localized pancreatic adenocarcinoma. A growing body of evidence suggests that the lung is the most common site of recurrence in patients who are followed for 5 years after their first diagnosis.³¹⁴ Preliminary retrospective data suggest that resections of isolated pulmonary metastasis may be advantageous in this population.³¹⁵ More data are needed before recommendations can be made regarding additional options for managing pulmonary metastases of pancreatic cancers.

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.

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 chemotherapy with or without chemoradiation in patients with locally unresectable disease have noted that the opportunity for curative intent resection occasionally arises.^{133,316-318} The Panel believes that patients with no disease progression when treated with chemotherapy and/or chemoradiation may be considered for surgical resection, but



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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.^{319,320} However, due to concerns about complications and technical expertise,³²¹ the Panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer.

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 or intermediate PS.

Palliative and best supportive care including palliative RT are the preferred options for patients with poor PS. 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).³²² However, some

patients who present with poor PS may benefit from single-agent chemotherapy. 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). Alternative options for patients with poor PS include targeted therapy based on molecular profiling and as clinically indicated. The Panel also recommends considering geriatric assessment in appropriate patients.

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.

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. Less common variants, such as squamous/adenosquamous carcinomas, are treated similar to adenocarcinoma. There are insufficient data supporting the



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efficacy of any of the recommended regimens for these rare subtypes. For mixed histologies, the Panel recommends treating the more aggressive histology.

For information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer (available at www.NCCN.org).

Cisplatin/Albumin-bound Paclitaxel/Capecitabine/

Gemcitabine (PAXG)

A randomized, phase 3 trial involving 17 Italian academic hospitals ($n = 260$) investigated the efficacy of PAXG (cisplatin, albumin-bound paclitaxel, capecitabine, and gemcitabine) compared to mFOLFIRINOX in patients with pathologically confirmed resectable or borderline resectable disease.³²³ Median event-free survival (EFS) was higher with PAXG compared to mFOLFIRINOX (16.0 vs 10.2 months; HR, 0.63 [0.47–0.84]; $P = .0018$). The Panel acknowledges the study but notes that not all the centers have experience with this regimen and therefore added it as an useful in certain circumstances option.

FOLFIRINOX and mFOLFIRINOX

A systematic review including 11 studies ($N = 315$) of patients with locally advanced pancreatic cancer treated with FOLFIRINOX showed a pooled median OS of 24.2 months (95% CI, 21.7–26.8).³²⁴ 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.³²⁵ 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.³²⁶ Their study included six 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.³²⁷ This was followed by a randomized phase II trial that showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.³²⁸ The larger randomized phase III trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good PS showed dramatic improvements in both median progression-free survival (PFS) (6.4 vs 3.3 months; $P < .001$) and median OS (11.1 vs 6.8 months; $P < .001$).³²⁹ The 5-year follow-up showed that DFS was 26.1% versus 19.0% with median OS of 53.5 months versus 35.5 months in patients receiving chemotherapy with mFOLFIRINOX compared to gemcitabine.³³⁰ Eligibility criteria for this trial, however, were stringent, limiting real-world generalizability.³³¹ 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.³²⁹ Despite this toxicity, fewer patients in the FOLFIRINOX group experienced a degradation in their QOL at 6 months compared to those in the gemcitabine group (31% vs 66%; $P < .01$).³²⁹ A more detailed analysis of patients in this trial was published and showed



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that FOLFIRINOX maintained and even improved QOL more so than gemcitabine.³³² No toxicity-associated deaths were reported with this regimen.³²⁷⁻³²⁹

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.³³³ 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 fluorouracil and irinotecan were each reduced by 25%.³³⁴ 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.³³⁵ Five patients (23%) were able to undergo R0 resections, although three of these patients experienced distant recurrence by 5 months.³³⁵ 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 or metastatic disease or as subsequent therapy. FOLFIRINOX and mFOLFIRINOX are also possible treatment options for patients with *BRCA1/2* and *PALB2* mutations.

Gemcitabine-Based Therapy

The Panel acknowledges that, historically, combination chemotherapy does not appear to be superior to monotherapy in the era of fluorouracil-based therapy. However, because gemcitabine is superior to bolus fluorouracil 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, fluorouracil, and irinotecan) or in a multidrug combination (eg, cisplatin, epirubicin, gemcitabine, fluorouracil).³³⁶⁻³⁴⁵ Two meta-analyses of RCTs in the advanced setting found that gemcitabine combinations give a marginal benefit in OS over gemcitabine monotherapy with a significant increase in toxicity.^{346,347} Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good PS.^{340,341}

The Panel does not consider the combination of gemcitabine and docetaxel or irinotecan^{345,348,349} 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 vs 3.8 months; $P = .90$).³⁵⁰

Gemcitabine-based therapies that are recommended in the guidelines are described below.

Albumin-bound Paclitaxel/Gemcitabine

Albumin-bound paclitaxel is a nanoparticle form of paclitaxel. In a phase I/II trial, 67 patients with advanced pancreatic cancers received albumin-



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bound paclitaxel/gemcitabine. 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.³⁵¹

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.³⁵² Participants were randomized to receive albumin-bound paclitaxel/gemcitabine or gemcitabine alone. The primary endpoint for the trial was OS (8.5 months for albumin-bound paclitaxel/gemcitabine vs 6.7 months for gemcitabine alone; $P < .001$; HR, 0.72).³⁵² 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.³⁵³ The most common grade ≥ 3 AEs attributable to albumin-bound paclitaxel were neutropenia, fatigue, and neuropathy. Development of peripheral neuropathy was associated with longer treatment duration and improved survival.³⁵⁴ The MPACT trial showed that at least 3% of patients who received the albumin-bound paclitaxel/gemcitabine arm were alive at 42 months compared to no patients who received gemcitabine alone.³⁵⁵ Karnofsky Performance Status (KPS) score and absence of liver metastases were independent prognostic factors for OS and PFS.³⁵⁶

Based on these results, albumin-bound paclitaxel/gemcitabine 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 albumin-bound paclitaxel/gemcitabine.^{352,355,357} 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, albumin-bound

paclitaxel/gemcitabine 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.

Cisplatin/Gemcitabine

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 cisplatin/gemcitabine in the treatment of patients with advanced pancreatic cancer. Phase III trials evaluating the combination of cisplatin/gemcitabine versus gemcitabine alone in patients with advanced pancreatic cancer did not show a significant survival benefit for the combination over the single agent.^{337,340}

Nevertheless, cisplatin/gemcitabine has shown benefit in selected patients with breast and ovarian cancers who are carriers of a *BRCA* mutation.³⁵⁸⁻³⁶⁰ A retrospective study of patients with metastatic pancreatic cancer and a family history of breast, ovarian, or pancreatic cancers suggested that response to gemcitabine and cisplatin was superior even with one affected relative.³⁶¹ 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; $P < .001$).³⁶¹ 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.³⁶² Thus, cisplatin/gemcitabine may be a good choice in selected patients with disease characterized by hereditary risk factors (eg, *BRCA* or *PALB2* mutations). The Panel recommends cisplatin/gemcitabine 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.



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Erlotinib/Gemcitabine and Other Targeted Therapeutics

Phase III studies of gemcitabine combinations with other biologic agents show that only the combination of erlotinib/gemcitabine is associated with a statistically significant increase in survival compared to gemcitabine alone.³⁶³⁻³⁶⁷ 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)/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.³⁶³ Median survival was 6.24 months and 1-year survival was 23%, compared with 5.91 months and 17% in the control arm. AEs, such as rash and diarrhea, were higher in the group receiving erlotinib, but most were grade 1 or 2.³⁶³ This and other trials along with community experience show that occurrence of grade ≥ 2 skin rash is associated with better response and OS in patients receiving erlotinib.^{363,368,369}

The Panel recommends the erlotinib/gemcitabine 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. It is also a preferred subsequent therapy option. The Panel notes that although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

Capecitabine/Gemcitabine

A number of randomized trials have investigated the combination of capecitabine/gemcitabine 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 capecitabine/gemcitabine 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.³⁷⁰ A smaller phase III trial also did not demonstrate an OS advantage for the overall study population receiving the combination of capecitabine/gemcitabine, although a post-hoc analysis showed significantly increased OS in the subgroup of patients with good PS.³⁴¹ Despite greater ORR (43.7% vs 17.6%, respectively; $P = .001$), results from a randomized phase III trial also showed that capecitabine/gemcitabine did not significantly improve OS compared with gemcitabine alone.³⁷¹ In a meta-analysis of eight RCTs, OS was better in patients receiving capecitabine/gemcitabine than in patients receiving gemcitabine alone (HR, 0.87; $P = .03$).³⁷² Although there are concerns about dosing and toxicity of capecitabine in the U.S population, a biweekly regimen of fixed-dose capecitabine/gemcitabine may be both effective and well-tolerated in patients with advanced disease.³⁷³

The Panel considers capecitabine/gemcitabine 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.

Albumin-bound Paclitaxel/Cisplatin/Gemcitabine

In a single-arm phase Ib/II trial of 25 patients with untreated advanced pancreatic cancer, the addition of cisplatin to albumin-bound paclitaxel/gemcitabine resulted in an ORR of 71%.³⁷⁴ A phase II trial in the intent-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.³⁷⁵ 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.



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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 >2000 patients, found that OS was significantly improved when a fluoropyrimidine was added to gemcitabine.³⁷² In a phase II randomized trial, the effects of the FIRGEM regimen (irinotecan delivered before and after infusion of fluorouracil/leucovorin [FOLFIRI.3], alternating with fixed-dose-rate [FDR] gemcitabine) were assessed in 98 patients with metastatic pancreatic cancer.³⁷⁶ 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 fluorouracil/leucovorin in patients with advanced pancreatic cancer.³³⁶

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 fluorouracil.³⁷⁷ 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 vs 6.9 months; $P < .001$, log rank).¹³¹ Final results from this study showed median OS improved significantly for patients in the gemcitabine arm compared to the observation arm (22.8 vs 20.2 months; HR, 0.76; 95% CI, 0.61–0.95; $P = .01$).³⁷⁸ An absolute survival difference of 10.3% was observed between the two groups at 5 years (20.7% vs 10.4%).³⁷⁸

Gemcitabine Response: hENT1

hENT1 is a nucleoside transporter that has been studied as a predictor for response to gemcitabine.³⁷⁹ Preliminary clinical data showed that hENT1 expression may in fact predict response to gemcitabine.³⁸⁰⁻³⁸²

hENT1 was validated as a predictive biomarker for benefit from gemcitabine in the adjuvant setting. A meta-analysis including seven 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.³⁸³ 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).^{384,385}

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



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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.

Gemcitabine Fixed-Dose-Rate

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.³⁸⁶ 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.³⁸⁷ 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 vs 4.9 months; $P = .04$), although this outcome did not satisfy the protocol-specified criteria for superiority.³⁴³ When gemcitabine is considered for the treatment of advanced pancreatic cancer, the Panel views FDR gemcitabine (10 mg/m²/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, GTX.^{338,339} The combination of FDR gemcitabine and capecitabine has also been found to be active and well-tolerated.³⁷³ The Panel includes the combination of gemcitabine FDR, docetaxel, and capecitabine (GTX) 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.³³⁹ 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 hematologic and non-hematologic toxicity rates of 41% and 9%, respectively.³⁸⁸

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.³⁸⁹ For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable subsequent options and vice versa.³⁹⁰

Liposomal Irinotecan/Fluorouracil/Leucovorin/Oxaliplatin (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.³⁹¹ The follow-up phase III trial showed that first-line NALIRIFOX treatment resulted in a statistically significant improvement in OS and PFS compared with albumin-bound paclitaxel/gemcitabine in those patients without prior treatment and metastatic disease.³⁹² 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 albumin-bound paclitaxel/gemcitabine; however, this regimen does not appear to have an advantage compared to FOLFIRINOX.

Capecitabine-Based Regimens

The Panel lists capecitabine monotherapy as first and second-line treatment options for patients with locally advanced disease and



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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/erlotinib followed by gemcitabine monotherapy or erlotinib/gemcitabine followed by capecitabine monotherapy.³⁹³ Note that the capecitabine dose recommended by the Panel (1000 mg/m² 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).³⁹⁴

Capecitabine/Oxaliplatin (CAPEOX)

CAPEOX 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 study³⁹⁵ 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).

Fluorouracil–Based Regimens

Continuous Infusion Fluorouracil

Continuous infusion fluorouracil is a first 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 fluorouracil).³⁹³

Leucovorin/Fluorouracil/Oxaliplatin (FOLFOLX)

Results from the open-label phase III PANCREOX trial show that the addition of oxaliplatin to fluorouracil/leucovorin (OFF) in subsequent treatment may be detrimental.³⁹⁶ In this trial, 108 patients with advanced pancreatic cancer who progressed on gemcitabine-based treatment were

randomized to receive second-line modified mFOLFOX6 or infusional fluorouracil/leucovorin. No difference was seen in median PFS (3.1 vs 2.9 months; $P = .99$), but median OS was worse in those in the FOLFOX arm (6.1 vs 9.9 months; $P = .02$). Furthermore, the addition of oxaliplatin resulted in increased toxicity, with rates of grade 3/4 AEs of 63% in the FOLFOX arm and of 11% in the fluorouracil/leucovorin arm. However, this trial was limited by imbalances in PS 2 proportion between the study arms and possible crossover in treatment following progression.³⁹⁷ 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 had a median OS of 6.7 months, which is comparable to the median OS rates found in the CONKO-003 and PANCREOX trials.³⁹⁸ 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 and intermediate PS.

OFF

Based on the randomized phase III CONKO study that compared OFF to best supportive care, the Panel included OFF as a treatment option.³⁹⁹ 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 fluorouracil/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 fluorouracil/leucovorin arm. This translated into a significant improvement in the HR (0.66; 95% CI, 0.48–0.91; $P = .01$).⁴⁰⁰ 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 in patients with good PS.



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Leucovorin/Fluorouracil/Irinotecan (FOLFIRI)

The Panel recommends 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.^{401,402} 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.⁴⁰³ 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).⁴⁰² 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.⁴⁰⁴ OS was 5 months and toxicity such as grade 3–4 neutropenia (20%) and diarrhea (12%) were manageable.

Fluorouracil/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.⁴⁰⁵ Patients were randomized to receive nanoliposomal irinotecan monotherapy, fluorouracil/leucovorin, or both (N = 417). Median PFS (3.1 vs 1.5 months; HR, 0.56; 95% CI, 0.41–0.75; $P < .001$) was significantly higher in patients who received nanoliposomal irinotecan with fluorouracil/leucovorin compared to patients who did not receive irinotecan. Updated analyses showed that median OS (6.2 vs 4.2 months; HR, 0.75; $P = .042$) was significantly greater for patients who received nanoliposomal irinotecan with fluorouracil/leucovorin compared to patients who received

fluorouracil/leucovorin without irinotecan. Grade 3 or 4 AEs that occurred most frequently with this regimen were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).⁴⁰⁵ Irinotecan liposomal injection, combined with fluorouracil/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

Neurotrophic tyrosine receptor kinase (*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).⁴⁰⁶ 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 (with 1 patient with pancreatic cancer), 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.⁴⁰⁶ 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. Updated data published in 2020 reported that 79% of patients had an objective response (95% CI,



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72%–85%) with 16% showing a complete response.⁴⁰⁷ 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.⁴⁰⁸ 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.^{409,410} Thus, the 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 of age with solid tumors that have a *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.⁴¹¹ A small number of patients with pancreatic adenocarcinoma were evaluated in the TRIDENT trial,⁴¹² 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.⁴¹³ 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 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).⁴¹⁴ Eight patients had confirmed objective response, whereas six patients had grade 3 AEs 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.⁴¹⁵ Based on these data and nearly all pancreatic tumors having *KRAS* mutations,⁴¹⁶ both adagrasib and sotorasib are recommended as subsequent therapy options for patients with any PS (category 2B for poor PS).

Erdafitinib

Primary analysis of a phase 2 trial studied the efficacy of erdafitinib in previously treated patients with *FGFR*-altered advanced solid tumors.⁴¹⁷ In the pancreatic cancer subgroup (n = 18), objective response was observed in 10 of 18 patients (56%). Although *FGFR* alterations are rare in pancreatic cancer,⁴¹⁸ based on the observed results in the RAGNAR study, the Panel added erdafitinib as a subsequent therapy option for patients with *FGFR* alterations.



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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.^{419,420} 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 as first-line therapy for metastatic disease and as a subsequent line option for tumors with *BRAF* V600E mutations. The only setting in which it is a category 2B recommendation is in the first-line metastatic disease setting for patients with poor PS.

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 ORR.⁴²¹ 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+ or IHC2+ with FISH HER2 amplified) 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+ HER2.⁴²² Based on this the Panel recommends fam-trastuzumab as a

subsequent therapy option only for patients with good PS and HER2 IHC 3+ or IHC2+ with FISH HER2 amplified.

Zenocutuzumab-zbco

Emerging studies show that pancreatic adenocarcinoma with *NRG1* fusions are enriched in younger patients with *KRAS* wild-type disease and may present with a unique biology. In a single institution series, the median age of patients with a detectable *NRG1* fusion (n=10) was 48.5 years.⁴²³ Zenocutuzumab-zbco, a HER2/HER3 bispecific antibody, was investigated in a phase 2 study that included patients with advanced *NRG1+* solid tumors. Most patients in this trial had a PS 0–1 status. This study included 36 patients with pancreatic ductal adenocarcinoma, 97% of whom had received prior systemic therapy (FOLFIRINOX and/or gemcitabine-paclitaxel). ORR was observed in 15/36 patients, with a median DOR of 7.4 months (95% CI, 4.0 to 11.2). Primarily grade 1 or 2 AEs were observed, and investigators did not identify any grade ≥ 3 AEs in $> 5\%$ of patients. Following FDA approval, the Panel added zenocutuzumab-zbco as subsequent therapy option for patients whose disease progressed on or after prior systemic therapy and PS 0–2.

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.⁴²⁴ There is evidence that programmed cell death protein 1 (PD-1) blockade with pembrolizumab may be effective in tumors with dMMR.⁴²⁵ Pembrolizumab is an anti-PD-1 receptor antibody and blocks its interaction with programmed death ligand 1 (PD-L1) and PD-L2, releasing 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%



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of patients, with 21% complete response).⁴²⁶ Sixty-two percent of patients had an ORR, with two patients showing complete response and three patients showing progressive disease. AEs were experienced by 74% of all patients receiving pembrolizumab; most were low grade (20% experienced grade 3 or 4 AEs, such as diarrhea/colitis, pancreatitis/hyperamylasemia, fatigue, arthritis/arthritis, or anemia).⁴²⁶ AEs for immune checkpoint inhibitors can be significant; please refer to the NCCN Guidelines for the Management of Immune Checkpoint Inhibitor-Related Toxicities (available at www.NCCN.org).

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.^{427,428} 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 microsatellite instability-high (MSI-H)/dMMR colorectal cancer.^{429,430} 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 recommended as an option by the 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.⁴³¹ 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.

Ipilimumab + Nivolumab

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.⁴³² 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 ipilimumab + nivolumab 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. A randomized phase II basket trial (EXTEND) tested the addition of metastasis-directed therapy (MDT) to chemotherapy in patients with ≤5 metastases (n = 81).⁴³³ Approximately, 60% of patients had liver metastases, with other sites including lung, lymph nodes, and bone. MDT consisted of definitive local therapy, most commonly stereotactic radiotherapy. After a median follow-up of 17.3 months, the median PFS in the MDT arm was 10.3 months versus 2.5 months in the control arm ($P = .03$). Based on these data, the Panel added that maintenance therapy could include MDT as an option for appropriately selected patients with indolent oligometastatic disease, typically following systemic therapy. This is recommended to be performed at a high-volume center.



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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 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).⁴³⁴ 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 vs 16.1 months, 95% CI, 0.56–1.46; $P = .68$). AEs, such as grade ≥ 3 , were found to be higher in the olaparib arm than in the placebo arm (40% vs. 23%).⁴³⁵ 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 albumin-bound paclitaxel/gemcitabine; or capecitabine, fluorouracil with or without irinotecan, or FOLFOX for patients who received previous FOLFIRINOX. The Panel included fluorouracil 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.⁴³⁶

- 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.



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

A 2011 consensus report from a group of European experts came to many of the same conclusions.⁴³⁷ 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.⁴³⁸ 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.⁴³⁹ 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.⁴⁴⁰ 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 patients eligible for gemcitabine and albumin-bound paclitaxel/gemcitabine and a 4- to 5-month improvement in OS in patients eligible for FOLFIRINOX 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.⁴⁴¹

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.⁴⁴²

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.⁴⁴³

Radiation and chemoradiation are sometimes used for pancreatic cancer in the resectable and adjuvant settings, because these treatment methods could potentially decrease local recurrence.⁴⁴⁴ A major goal of 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 metastatic or non-metastatic settings as a palliative measure.



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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.⁴⁴⁵⁻⁴⁴⁸ Retrospective analyses from the NCDB including patients with locally advanced pancreatic cancer ($N = 988$, propensity matched groups) showed that patients treated with SBRT had better median OS (13.9 vs 11.6 months; $P < .001$) and 2-year OS (21.7% vs 16.5%; $P = .001$), compared to patients treated with conventionally fractionated RT.⁴⁴⁹ Analyses of patient-reported outcomes, 4 to 6 weeks following treatment, 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 ($P = .007$).⁴⁵⁰ 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; $P < .001$).⁴⁵¹ 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.¹⁵⁷ Since the data regarding appropriate use of SBRT are evolving, the Panel recommends that SBRT should be delivered at an experienced, high-volume center with technology that allows for image-guided RT or in a clinical trial.

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.^{452,453} In this study, patients were randomly assigned to either observation or RT combined with an intermittent bolus fluorouracil after resection. A standard split course of 4,000 cGy was used.

Fluorouracil, 500 mg/m² daily for 3 days, was given concurrently with each 2,000-cGy segment of RT. The fluorouracil 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.⁴⁵²

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 fluorouracil 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.⁴⁵⁴ At a median follow-up of 11.7 years, no statistically significant differences were observed in PFS or OS in the different study arms.⁴⁵⁵

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 fluorouracil-based chemoradiation in patients with resected pancreatic adenocarcinoma.¹³² 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 fluorouracil arm (median survival, 20.5 vs 16.9 months; $P = .09$). 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 ($P = .08$).³⁰¹



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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 fluorouracil chemotherapy may be unnecessary and perhaps even harmful (OS, 13.9, 21.6, and 19.9 months for chemoradiation, chemotherapy, and chemotherapy plus chemoradiation, respectively),¹²⁹ although the ESPAC-1 trial has been criticized for lack of attention to quality control for RT.⁴⁵⁶⁻⁴⁵⁸ A phase II study by GERCOR randomized patients to adjuvant gemcitabine or adjuvant gemcitabine-based chemoradiation.⁴⁵⁹ No differences were seen in OS (24.4 vs 24.3 months) or DFS (10.9 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 either with fluorouracil, cisplatin, and interferon alfa-2b followed by fluorouracil chemotherapy resulted in no better outcomes than adjuvant treatment with fluorouracil alone.⁴⁶⁰

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).⁴⁶¹ Another meta-analysis of nine trials found similar results, with HRs of 0.62 for fluorouracil (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 fluorouracil (95% CI, 0.15–1.80), and 0.44 for chemoradiation plus gemcitabine (95% CI, 0.10–1.81) compared to no adjuvant treatment.⁴⁶²

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).⁴⁶³ 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 vs 27.8 months; *P* < .001).⁴⁶⁴

To definitively clarify the role of chemoradiation following gemcitabine monotherapy in the adjuvant setting, RTOG conducted a two-step randomized trial (RTOG0848 (NCT01013649)). In step 1 of this protocol (the chemotherapy comparison arm), patients were randomized to adjuvant gemcitabine versus the combination of erlotinib/gemcitabine; however, there was no OS differences between the two groups.⁴⁶⁵ Step 2 involved a randomization to fluoropyrimidine-based (capecitabine or fluorouracil) chemoradiation versus no chemoradiation. In the entire study cohort, a DFS but not OS benefit was observed with the addition of chemoradiation to gemcitabine-based chemotherapy. By subgroup analysis, a survival benefit with postoperative RT was seen in patients with node negative disease, but not node positive disease.³⁰⁶ Importantly, because most patients on this study only received gemcitabine-based chemotherapy (the majority of whom received gemcitabine monotherapy), the role and benefit of chemoradiation remains unclear in patients who receive adjuvant mFOLFIRINOX, the contemporary standard of care.

Adjuvant SBRT did not provide survival benefit or improved local disease control for resected stage II pancreatic ductal adenocarcinoma in a single-center randomized control trial.⁴⁶⁶

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.⁴⁶⁷ 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.⁴⁶⁸ A retrospective review of patients who had R0 resections for pancreatic adenocarcinoma found an OS benefit in those receiving adjuvant chemoradiation over observation.⁴⁶⁹ In addition, a retrospective review of >1200 resected patients who received adjuvant fluorouracil-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; $P < .001$).⁴⁷⁰ 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).⁴⁷¹ However, in the aforementioned RTOG 0848 trial, no significant survival benefit was observed from the addition of chemoradiation to chemotherapy even in patients who underwent an R1 resection.

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 observed after distal pancreatectomy and found higher survival in the patients who received adjuvant chemoradiation.⁴⁷²

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.⁴⁷³ 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 fluorouracil 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.⁴⁵³ Subsequent studies have sought to optimize the use of fluorouracil, and most contemporary studies no longer use split-course radiation. Multiple studies studied the utility of gemcitabine as part of chemoradiation.^{474–477} Some evidence even suggests that concurrent gemcitabine and radiation can yield similar or better outcomes when compared with fluorouracil-based chemoradiation in the setting of locally advanced disease.^{475,478} Capecitabine was also assessed in a small number of patients.⁴⁷⁹ 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.⁴⁸⁰ Therefore, the Panel lists fluorouracil- 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.^{481,482} Additional phase II trials assessed the upfront chemoradiation approach in locally advanced pancreatic ductal adenocarcinoma, with median survival rates ranging from 8.2 to 9 months.^{474,483,484} Results from small, single-arm trials of induction chemotherapy followed by chemoradiation in locally advanced disease show median survival between 12 to 19 months.⁴⁸⁵

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



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the chemoradiation therapy arm of the study (11.1 vs 9.2 months; one-sided $P = .017$ by stratified log-rank test).⁴⁷⁷ 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.⁴⁸⁶

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.⁴⁸⁷ 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 SBRT gave effective local control it was associated with significant toxicities.⁴⁸⁸ However, another retrospective study of 71 patients reported a median OS of 10.3 months with only three patients experiencing grade 3 toxicity.⁴⁴⁶ Another study showed that hypofractionated dosing may also be used in these patients, with acceptable toxicity.⁴⁸⁹ The incorporation of simultaneous integrated boost is being investigated to develop SBRT use for downstaging.⁴⁹⁰

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.^{474,477}

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.^{491,492} SBRT or chemoradiation may delay time to disease progression. Using 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.⁴⁹¹

In the randomized phase II SCALOP trial, patients with locally advanced pancreatic cancer received capecitabine/gemcitabine, followed by either gemcitabine- or capecitabine-based chemoradiation ($n = 74$).^{479,493} 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 versus 14.6 months and a median PFS of 12 versus 10.5 months compared to gemcitabine-based chemoradiation.⁴⁹³

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 erlotinib/gemcitabine.⁴⁹⁴ 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 has also been examined in phase II trials and was found to be associated with low



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toxicity and favorable freedom from local disease progression in patients with locally advanced pancreatic cancer.^{495,496}

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.⁴⁹⁷⁻⁵⁰⁰ IMRT is preferred over 3D-conformal RT (CRT) for conventional or hypofractionated RT, particularly if dose escalation is being considered. 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.⁵⁰⁰ 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-CRT.⁵⁰¹ However, toxicities grade ≥ 3 , mainly GI, specifically nausea/vomiting and diarrhea, were more numerous in 3D-CRT, relative to IMRT ($P = .017$). IMRT resulted in reduced grade 3/4 toxicities when the authors made a cross-study comparison of toxicities in patients who received a similar fluorouracil-based regimen with 3D-CRT in the RTOG 9704 trial.^{132,502} Comparing the two trials, rates of grade 3/4 nausea and vomiting were 0% versus 11% ($P = .024$), and rates of grade 3/4 diarrhea were 3% versus 18% ($P = .017$),⁵⁰² suggesting that IMRT may be well-tolerated and allow for higher radiation doses to the tumor.⁵⁰²

The role and definition of elective target volume irradiation remain unclear. However, emerging data has increasingly suggested value to elective targeting of at-risk anatomic sites defined by extra-pancreatic neural tract anatomy (ie, the “Triangle Volume”) and/or regional nodal basins. More

prospective data is needed to further refine target volume definition recommendations across stages of disease.⁵⁰³

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.⁵⁰⁴ 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.⁵⁰⁵ A meta-analysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.⁵⁰⁶ This study suggested that the risk of recurrent biliary obstruction was lower for the metal stents (RR,

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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 pancreatic cancer showed that covered SEMs, with an anti-migration system, had longer patency than uncovered SEMs due to prevention of tumor ingrowth.⁵⁰⁷

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.⁵⁰⁸ Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis in this situation.⁵⁰⁸

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^{509,510}) and with or without celiac plexus neurolysis^{511,512} (category 2B in patients without pain).

Biliary decompression is also required for patients with jaundice 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.⁵⁰⁴ 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.⁵⁰⁸ 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.⁵¹³⁻⁵¹⁵ 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 or if a patient is not a surgical candidate, 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.^{509,510} 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



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outlet obstruction in 2.5% of patients in the prophylactic gastrojejunostomy group and 27.8% of those not receiving gastrojejunostomy.⁵¹⁶ In both studies, prophylactic retrocolic gastrojejunostomy significantly decreased the incidence of late gastric outlet obstruction but did not extend the length of stay or increase complication rates, such as delayed gastric emptying.

Severe Tumor-Associated Abdominal Pain

Most patients with locally advanced or metastatic pancreatic cancer experience cancer-related pain.⁵¹² 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.^{512,517,518} 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 ($P = .01$).⁵¹¹ 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.⁵¹⁹ 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 ($N = 467$).⁵²⁰ 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.^{521,522} This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.⁵²³ 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,^{524,525} enzyme replacement therapy may be initiated without diagnostic tests. The Panel recommends a starting dose of at least 48,000 units lipase with meals (preferably 72,000). 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.⁵²³ A prospective, double-blind, phase II RCT including 67 patients with unresectable pancreatic cancer showed no significant difference in



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weight loss between patients randomized to receive pancreatic exocrine replacement therapy or placebo.⁵²⁶ 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.^{523,524} Patients with a 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.^{527,528} 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.⁵²⁹

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; $P = .01$).⁵³⁰ 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.⁵³⁰ 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.⁵³¹ Various causes of GI bleeding include segmental portal hypertension,⁵³² gastric or duodenal ulcer erosion, and radiation-induced gastritis.⁵³¹ Treatment options for GI bleeding should be used according to clinical judgment regarding the specifics of the patient's case. Endoscopic techniques⁵³³ or RT,⁵³⁴ 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.^{535,536}

One study of 246 eligible patients with pancreatic cancer included 32 patients with GI bleeding of varying grade.⁵³¹ 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.



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Depression, Pain, and Malnutrition

For many patients, a diagnosis of pancreatic cancer may result in significant psychosocial distress, including anxiety, depression, and sleep disturbances.⁵³⁷ In fact, the suicide rate in male patients with pancreatic cancer is reportedly about 11 times that of the general population.⁵³⁸ 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).

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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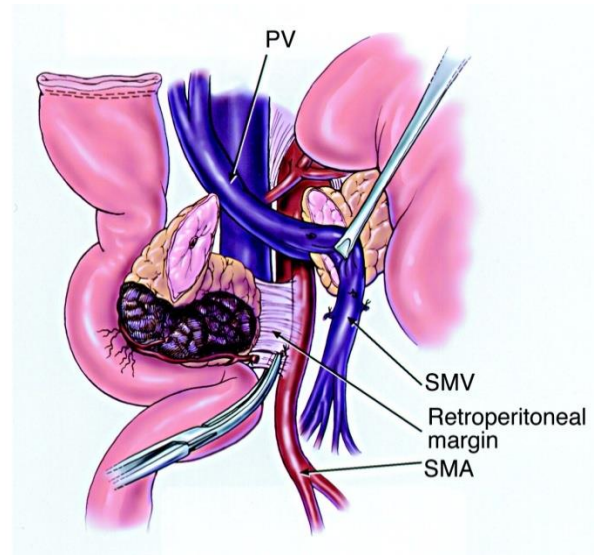


Figure 1. Complete mobilization of the superior mesenteric (SMV) and portal vein (PV), and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA).⁵³⁹

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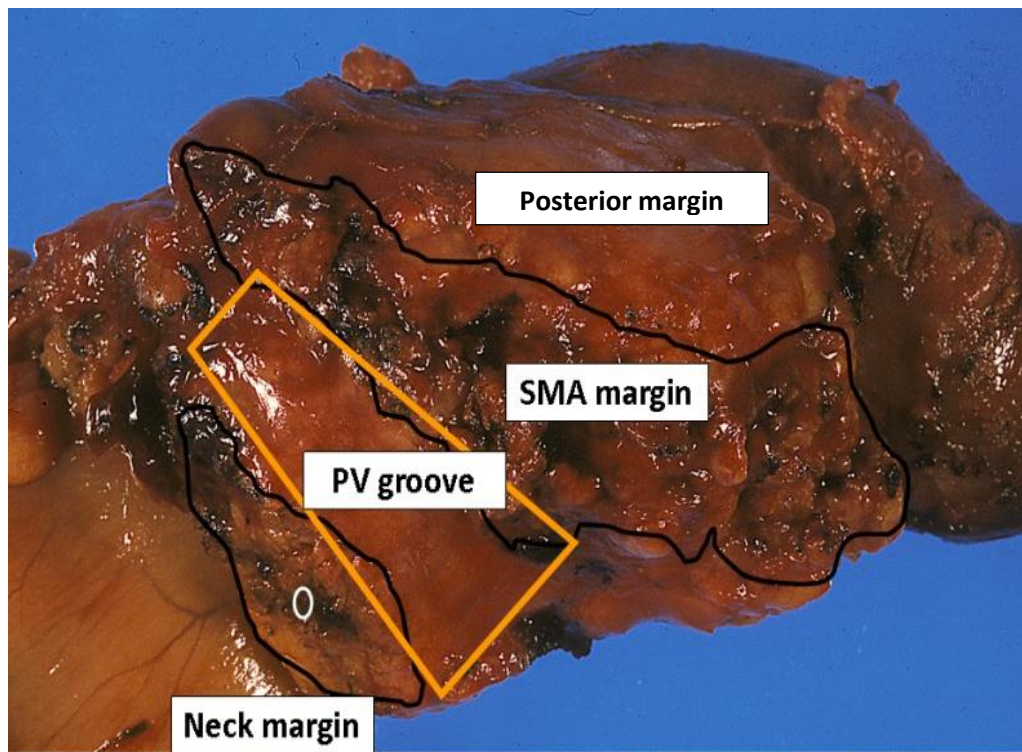
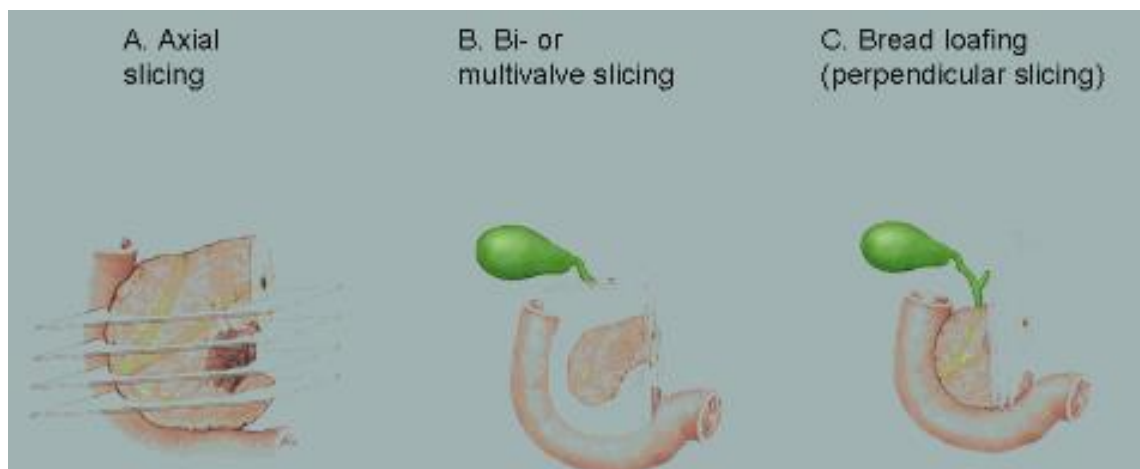


Image courtesy of Dr. N. Volkan Adsay

Figure 2. Whipple specimen with labeled margins.

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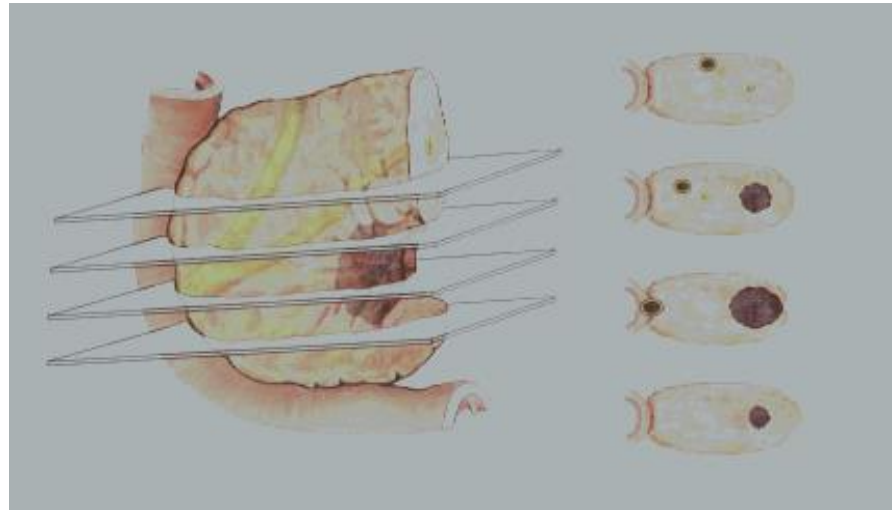


Courtesy of Mr. Paul Brown, Specialist Medical Illustrator, St James's University Hospital Leeds

Figure 3. Slicing of pancreatoduodenectomy specimens.²⁸¹

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

Figure 4. Slicing of the pancreatoduodenectomy specimen in the axial plane to allow circumferential assessment of tumor.²⁸¹

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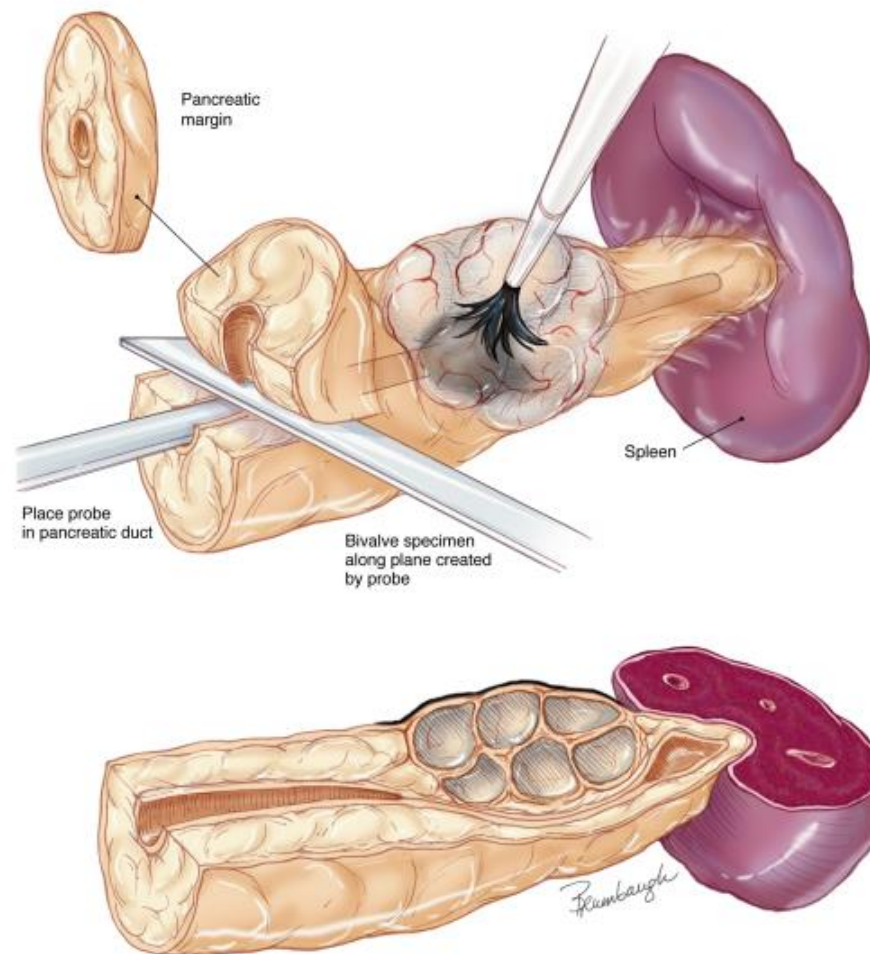


Figure 16-4, from Hruban, Ralph et al. Tumors of the Pancreas: Afip Atlas of Tumor Pathology, American Registry of Pathology, Washington DC 2007

Figure 5. Slicing of the distal pancreatectomy specimen.²⁹³



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References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin* 2023;73:17–48. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36633525>.
2. Abboud Y, Samaan JS, Oh J, et al. Increasing Pancreatic Cancer Incidence in Young Women in the United States: A Population-Based Time-Trend Analysis, 2001–2018. *Gastroenterology* 2023;164:978–989 e976. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36775072>.
3. Ward EM, Sherman RL, Henley SJ, et al. Annual Report to the Nation on the Status of Cancer, Featuring Cancer in Men and Women Age 20–49 Years. *J Natl Cancer Inst* 2019;111:1279–1297. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31145458>.
4. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed July 24, 2014.
5. Freedman-Cass DA, Fischer T, Alpert AB, et al. The Value and Process of Inclusion: Using Sensitive, Respectful, and Inclusive Language and Images in NCCN Content. *J Natl Compr Canc Netw* 2023;21:434–441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37156485>.
6. Anderson MA, Zolotarevsky E, Cooper KL, et al. Alcohol and tobacco lower the age of presentation in sporadic pancreatic cancer in a dose-dependent manner: a multicenter study. *Am J Gastroenterol* 2012;107:1730–1739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22929760>.
7. Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol* 2012;23:1880–1888. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22104574>.
8. Park JH, Hong JY, Shen JJ, et al. Smoking Cessation and Pancreatic Cancer Risk in Individuals With Prediabetes and Diabetes: A Nationwide Cohort Study. *J Natl Compr Canc Netw* 2023;21:1149–1155 e1143. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37935099>.
9. Antwi SO, Eckert EC, Sabaque CV, et al. Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer. *Cancer Causes Control* 2015;26:1583–1591. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26293241>.
10. Lucenteforte E, La Vecchia C, Silverman D, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol* 2012;23:374–382. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21536662>.
11. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer* 2015;112:580–593. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25422909>.
12. Maisonneuve P, Amar S, Lowenfels AB. Periodontal disease, edentulism, and pancreatic cancer: a meta-analysis. *Ann Oncol* 2017;28:985–995. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28453689>.
13. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA* 2009;301:2553–2562. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19549972>.
14. Patel AV, Rodriguez C, Bernstein L, et al. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. *Cancer Epidemiol Biomarkers Prev* 2005;14:459–466. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15734973>.
15. Genkinger JM, Kitahara CM, Bernstein L, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. *Ann Oncol* 2015;26:2257–2266. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26347100>.
16. Behrens G, Jochem C, Schmid D, et al. Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. *Eur J Epidemiol* 2015;30:279–298. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25773752>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

17. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. *Br J Cancer* 2012;106:603–607. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22240790>.
18. Thiebaut AC, Jiao L, Silverman DT, et al. Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. *J Natl Cancer Inst* 2009;101:1001–1011. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19561318>.
19. Genkinger JM, Wang M, Li R, et al. Dairy products and pancreatic cancer risk: a pooled analysis of 14 cohort studies. *Ann Oncol* 2014;25:1106–1115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24631943>.
20. Rohrmann S, Linseisen J, Nothlings U, et al. Meat and fish consumption and risk of pancreatic cancer: results from the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2013;132:617–624. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22610753>.
21. Wolpin BM, Ng K, Bao Y, et al. Plasma 25-hydroxyvitamin D and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2012;21:82–91. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22086883>.
22. Waterhouse M, Risch HA, Bosetti C, et al. Vitamin D and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Case-Control Consortium. *Ann Oncol* 2015;26:1776–1783. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25977560>.
23. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012;23:2964–2970. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22767586>.
24. Munigala S, Kanwal F, Xian H, et al. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. *Clin Gastroenterol Hepatol* 2014;12:1143–1150 e1141. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24440214>.
25. Bracci PM, Wang F, Hassan MM, et al. Pancreatitis and pancreatic cancer in two large pooled case-control studies. *Cancer Causes Control* 2009;20:1723–1731. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19760029>.
26. Majumder S, Bockorny B, Baker WL, Dasanu CA. Association between HBsAg positivity and pancreatic cancer: a meta-analysis. *J Gastrointest Cancer* 2014;45:347–352. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24788082>.
27. Seo MS, Yeo J, Hwang IC, Shim JY. Risk of pancreatic cancer in patients with systemic lupus erythematosus: a meta-analysis. *Clin Rheumatol* 2019;38:3109–3116. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31270697>.
28. Chari S, Leibson C, Rabe K, et al. Probability of Pancreatic Cancer Following Diabetes: A Population-Based Study. *Gastroenterology* 2005;129:504–511. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16083707>.
29. Huang Y, Cai X, Qiu M, et al. Prediabetes and the risk of cancer: a meta-analysis. *Diabetologia* 2014;57:2261–2269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25208757>.
30. Liao WC, Tu YK, Wu MS, et al. Blood glucose concentration and risk of pancreatic cancer: systematic review and dose-response meta-analysis. *BMJ* 2015;350:g7371. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25556126>.
31. Gupta S, Vittinghoff E, Bertenthal D, et al. New-onset diabetes and pancreatic cancer. *Clin Gastroenterol Hepatol* 2006;4:1366–1372; quiz 1301. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16945591>.
32. Raghavan SR, Ballehaninna UK, Chamberlain RS. The impact of perioperative blood glucose levels on pancreatic cancer prognosis and surgical outcomes: an evidence-based review. *Pancreas* 2013;42:1210–1217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24152946>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

33. Toriola AT, Stolzenberg-Solomon R, Dalidowitz L, et al. Diabetes and pancreatic cancer survival: a prospective cohort-based study. *Br J Cancer* 2014;111:181–185. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24786605>.
34. Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat Rev Gastroenterol Hepatol* 2013;10:423–433. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23528347>.
35. Elena JW, Stepilowski E, Yu K, et al. Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *Cancer Causes Control* 2013;24:13–25. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23112111>.
36. Pezzilli R, Casadei R, Morselli-Labate AM. Is type 2 diabetes a risk factor for pancreatic cancer? *JOP* 2009;10:705–706. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19890202>.
37. Song S, Wang B, Zhang X, et al. Long-Term Diabetes Mellitus Is Associated with an Increased Risk of Pancreatic Cancer: A Meta-Analysis. *PLoS One* 2015;10:e0134321. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26222906>.
38. Bodmer M, Becker C, Meier C, et al. Use of antidiabetic agents and the risk of pancreatic cancer: a case-control analysis. *Am J Gastroenterol* 2012;107:620–626. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22290402>.
39. Li D, Yeung SC, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009;137:482–488. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19375425>.
40. Soranna D, Scotti L, Zambon A, et al. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist* 2012;17:813–822. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22643536>.
41. Chaiteerakij R, Petersen GM, Bamlet WR, et al. Metformin Use and Survival of Patients With Pancreatic Cancer: A Cautionary Lesson. *Journal of Clinical Oncology* 2016;34:1898–1904. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27069086>.
42. Sadeghi N, Abbruzzese JL, Yeung SC, et al. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. *Clin Cancer Res* 2012;18:2905–2912. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22465831>.
43. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 2015;110:223–262; quiz 263. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25645574>.
44. Wang W, Chen S, Brune KA, et al. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. *J Clin Oncol* 2007;25:1417–1422. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17416862>.
45. Brune KA, Lau B, Palmisano E, et al. Importance of age of onset in pancreatic cancer kindreds. *J Natl Cancer Inst* 2010;102:119–126. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20068195>.
46. Clores MJ, Thosani A, Buscaglia JM. Multidisciplinary diagnostic and therapeutic approaches to pancreatic cystic lesions. *J Multidiscip Healthc* 2014;7:81–91. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24520195>.
47. Farrell JJ, Fernandez-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. *Gastroenterology* 2013;144:1303–1315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23622140>.
48. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatol* 2012;12:183–197. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22687371>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

49. Ohtsuka T, Fernandez-Del Castillo C, Furukawa T, et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. *Pancreatology* 2024;24:255–270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38182527>.
50. Del Chiaro M, Verbeke C, Salvia R, et al. European experts consensus statement on cystic tumours of the pancreas. *Dig Liver Dis* 2013;45:703–711. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23415799>.
51. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009;16:1727–1733. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19396496>.
52. 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. *Gastroenterology* 2014;146:291–304 e291. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24355035>.
53. Amin MB, Edge SB, Greene FL, et al. *AJCC Cancer Staging Manual*, 8th edition. New York: Springer; 2017.
54. Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual* (ed 7th). New York: Springer; 2010.
55. Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer* 2007;110:738–744. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17580363>.
56. Chun YS, Pawlik TM, Vauthey JN. 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers. *Ann Surg Oncol* 2018;25:845–847. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28752469>.
57. Kamarajah SK, Burns WR, Frankel TL, et al. Validation of the American Joint Commission on Cancer (AJCC) 8th Edition Staging System for Patients with Pancreatic Adenocarcinoma: A Surveillance, Epidemiology and End Results (SEER) Analysis. *Ann Surg Oncol* 2017;24:2023–2030. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28213792>.
58. Allen PJ, Kuk D, Castillo CF, et al. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. *Ann Surg* 2017;265:185–191. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27163957>.
59. Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. *Clin Gastroenterol Hepatol* 2008;6:1301–1308. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18948228>.
60. Fuhrman GM, Charnsangavej C, Abbruzzese JL, et al. Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. *Am J Surg* 1994;167:104–111; discussion 111–103. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7906097>.
61. House MG, Yeo CJ, Cameron JL, et al. Predicting resectability of periampullary cancer with three-dimensional computed tomography. *J Gastrointest Surg* 2004;8:280–288. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15019924>.
62. Klauss M, Schobinger M, Wolf I, et al. Value of three-dimensional reconstructions in pancreatic carcinoma using multidetector CT: initial results. *World J Gastroenterol* 2009;15:5827–5832. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19998504>.
63. McNulty NJ, Francis IR, Platt JF, et al. Multi--detector row helical CT of the pancreas: effect of contrast-enhanced multiphasic imaging on enhancement of the pancreas, peripancreatic vasculature, and pancreatic adenocarcinoma. *Radiology* 2001;220:97–102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11425979>.
64. Raman SP, Reddy S, Weiss MJ, et al. Impact of the time interval between MDCT imaging and surgery on the accuracy of identifying



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

metastatic disease in patients with pancreatic cancer. *AJR Am J Roentgenol* 2015;204:W37–42. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25539271>.

65. Walters DM, Lapar DJ, de Lange EE, et al. Pancreas-protocol imaging at a high-volume center leads to improved preoperative staging of pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2011;18:2764–2771. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21484522>.

66. Schima W, Ba-Ssalamah A, Goetzinger P, et al. State-of-the-art magnetic resonance imaging of pancreatic cancer. *Top Magn Reson Imaging* 2007;18:421–429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18303400>.

67. Vachiranubhap B, Kim YH, Balci NC, Semelka RC. Magnetic resonance imaging of adenocarcinoma of the pancreas. *Top Magn Reson Imaging* 2009;20:3–9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19687720>.

68. Li JH, He R, Li YM, et al. Endoscopic ultrasonography for tumor node staging and vascular invasion in pancreatic cancer: a meta-analysis. *Dig Surg* 2014;31:297–305. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25376486>.

69. Agarwal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol* 2004;99:844–850. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15128348>.

70. Deerenberg EB, Poley JW, Hermans JJ, et al. Role of endoscopic ultrasonography in patients suspected of pancreatic cancer with negative helical MDCT scan. *Dig Surg* 2011;28:398–403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22188923>.

71. Nawaz H, Fan CY, Kloke J, et al. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. *JOP* 2013;14:484–497. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24018593>.

72. Wang W, Shpaner A, Krishna SG, et al. Use of EUS-FNA in diagnosing pancreatic neoplasm without a definitive mass on CT. *Gastrointest Endosc* 2013;78:73–80. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23523302>.

73. Inoue K, Ohuchida J, Ohtsuka T, et al. Severe localized stenosis and marked dilatation of the main pancreatic duct are indicators of pancreatic cancer instead of chronic pancreatitis on endoscopic retrograde balloon pancreatography. *Gastrointest Endosc* 2003;58:510–515. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14520282>.

74. Nallamothe G, Hilden K, Adler DG. Endoscopic retrograde cholangiopancreatography for non-gastroenterologists: what you need to know. *Hosp Pract (1995)* 2011;39:70–80. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21576899>.

75. Pavey DA, Gress FG. The role of EUS-guided FNA for the evaluation of biliary strictures. *Gastrointest Endosc* 2006;64:334–337. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16923478>.

76. Dolejs S, Zarzaur BL, Zyromski NJ, et al. Does Hyperbilirubinemia Contribute to Adverse Patient Outcomes Following Pancreatoduodenectomy? *J Gastrointest Surg* 2017;21:647–656. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28205125>.

77. Mezhir JJ, Brennan MF, Baser RE, et al. A matched case-control study of preoperative biliary drainage in patients with pancreatic adenocarcinoma: routine drainage is not justified. *J Gastrointest Surg* 2009;13:2163–2169. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19774424>.

78. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010;362:129–137. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20071702>.

79. Sut M, Kennedy R, McNamee J, et al. Long-term results of percutaneous transhepatic cholangiographic drainage for palliation of



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

malignant biliary obstruction. *J Palliat Med* 2010;13:1311–1313. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20958250>.

80. Farma JM, Santillan AA, Melis M, et al. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. *Ann Surg Oncol* 2008;15:2465–2471. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18551347>.

81. Rijkers AP, Valkema R, Duivenvoorden HJ, van Eijck CH. Usefulness of F-18-fluorodeoxyglucose positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. *Eur J Surg Oncol* 2014;40:794–804. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24755095>.

82. Wang Z, Chen JQ, Liu JL, et al. FDG-PET in diagnosis, staging and prognosis of pancreatic carcinoma: a meta-analysis. *World J Gastroenterol* 2013;19:4808–4817. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23922481>.

83. Ahmed SI, Bochkarev V, Oleynikov D, Sasson AR. Patients with pancreatic adenocarcinoma benefit from staging laparoscopy. *J Laparoendosc Adv Surg Tech A* 2006;16:458–463. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17004868>.

84. Allen VB, Gurusamy KS, Takwoingi Y, et al. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. *Cochrane Database Syst Rev* 2013;11:CD009323. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24272022>.

85. Warshaw AL, Gu ZY, Wittenberg J, Waltman AC. Preoperative staging and assessment of resectability of pancreatic cancer. *Arch Surg* 1990;125:230–233. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2154172>.

86. Velanovich V. The effects of staging laparoscopy on trocar site and peritoneal recurrence of pancreatic cancer. *Surg Endosc* 2004;18:310–313. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14691701>.

87. Andersson R, Vagianos CE, Williamson RC. Preoperative staging and evaluation of resectability in pancreatic ductal adenocarcinoma. *HPB (Oxford)* 2004;6:5–12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18333037>.

88. Alexakis N, Gomatos IP, Sbarounis S, et al. High serum CA 19-9 but not tumor size should select patients for staging laparoscopy in radiological resectable pancreas head and peri-ampullary cancer. *Eur J Surg Oncol* 2015;41:265–269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25266999>.

89. Karachristos A, Scarmeas N, Hoffman JP. CA 19-9 levels predict results of staging laparoscopy in pancreatic cancer. *J Gastrointest Surg* 2005;9:1286–1292. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16332484>.

90. White R, Winston C, Gonen M, et al. Current utility of staging laparoscopy for pancreatic and peripancreatic neoplasms. *J Am Coll Surg* 2008;206:445–450. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18308214>.

91. Ferrone CR, Haas B, Tang L, et al. The influence of positive peritoneal cytology on survival in patients with pancreatic adenocarcinoma. *J Gastrointest Surg* 2006;10:1347–1353. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17175453>.

92. Brugge WR, De Witt J, Klapman JB, et al. Techniques for cytologic sampling of pancreatic and bile duct lesions: The Papanicolaou Society of Cytopathology Guidelines. *Cytojournal* 2014;11:2. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25191516>.

93. Micames C, Jowell PS, White R, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. *Gastrointest Endosc* 2003;58:690–695. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14595302>.

94. Okasha HH, Naga MI, Esmat S, et al. Endoscopic Ultrasound-Guided Fine Needle Aspiration versus Percutaneous Ultrasound-Guided Fine Needle Aspiration in Diagnosis of Focal Pancreatic Masses. *Endosc*



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

Ultrasound 2013;2:190–193. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24949394>.

95. Banafea O, Mghanga FP, Zhao J, et al. Endoscopic ultrasonography with fine-needle aspiration for histological diagnosis of solid pancreatic masses: a meta-analysis of diagnostic accuracy studies. *BMC Gastroenterol* 2016;16:108. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27580856>.

96. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatography system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). *Gastrointest Endosc* 2007;65:832–841. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17466202>.

97. Strasberg SM, Middleton WD, Teefey SA, et al. Management of diagnostic dilemmas of the pancreas by ultrasonographically guided laparoscopic biopsy. *Surgery* 1999;126:736–741; discussion 741–733. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10520923>.

98. Ramchandani M, Reddy DN, Lakhtakia S, et al. Per oral cholangiopancreatography in pancreatic biliary diseases--expert consensus statements. *World J Gastroenterol* 2015;21:4722–4734. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25914484>.

99. Hu H, Zhang Q, Huang C, et al. Diagnostic value of S100P for pancreatic cancer: a meta-analysis. *Tumour Biol* 2014;35:9479–9485. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25123266>.

100. Capello M, Bantis LE, Scelo G, et al. Sequential Validation of Blood-Based Protein Biomarker Candidates for Early-Stage Pancreatic Cancer. *J Natl Cancer Inst* 2017;109. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28376157>.

101. Safi F, Roscher R, Bittner R, et al. High sensitivity and specificity of CA 19-9 for pancreatic carcinoma in comparison to chronic pancreatitis. Serological and immunohistochemical findings. *Pancreas* 1987;2:398–403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3306667>.

102. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol* 2012;3:105–119. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22811878>.

103. Huang Z, Liu F. Diagnostic value of serum carbohydrate antigen 19-9 in pancreatic cancer: a meta-analysis. *Tumour Biol* 2014;35:7459–7465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24789274>.

104. Hartwig W, Strobel O, Hinz U, et al. CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy. *Ann Surg Oncol* 2013;20:2188–2196. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23247983>.

105. Kim YC, Kim HJ, Park JH, et al. Can preoperative CA19-9 and CEA levels predict the resectability of patients with pancreatic adenocarcinoma? *J Gastroenterol Hepatol* 2009;24:1869–1875. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19686409>.

106. Kondo N, Murakami Y, Uemura K, et al. Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer. *Ann Surg Oncol* 2010;17:2321–2329. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20336387>.

107. Bauer TM, El-Rayes BF, Li X, et al. Carbohydrate antigen 19-9 is a prognostic and predictive biomarker in patients with advanced pancreatic cancer who receive gemcitabine-containing chemotherapy: a pooled analysis of 6 prospective trials. *Cancer* 2013;119:285–292. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22786786>.

108. Berger AC, Winter K, Hoffman JP, et al. Five year results of US intergroup/RTOG 9704 with postoperative CA 19-9 \leq 90 U/mL and comparison to the CONKO-001 trial. *Int J Radiat Oncol Biol Phys* 2012;84:e291–297. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22682806>.

109. Berger AC, Garcia M, Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

adjuvant chemoradiation: a prospective validation by RTOG 9704. *J Clin Oncol* 2008;26:5918–5922. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19029412>.

110. Humphris JL, Chang DK, Johns AL, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. *Ann Oncol* 2012;23:1713–1722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22241899>.

111. Tzeng CW, Balachandran A, Ahmad M, et al. Serum carbohydrate antigen 19-9 represents a marker of response to neoadjuvant therapy in patients with borderline resectable pancreatic cancer. *HPB (Oxford)* 2014;16:430–438. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23991810>.

112. Hess V, Glimelius B, Grawe P, et al. CA 19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomised controlled trial. *Lancet Oncol* 2008;9:132–138. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18249033>.

113. Ko AH, Hwang J, Venook AP, et al. Serum CA19-9 response as a surrogate for clinical outcome in patients receiving fixed-dose rate gemcitabine for advanced pancreatic cancer. *Br J Cancer* 2005;93:195–199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15999098>.

114. Wong D, Ko AH, Hwang J, et al. Serum CA19-9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving chemotherapy. *Pancreas* 2008;37:269–274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18815548>.

115. Tempero MA, Uchida E, Takasaki H, et al. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res* 1987;47:5501–5503. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3308077>.

116. Mann DV, Edwards R, Ho S, et al. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. *Eur J Surg*

Oncol 2000;26:474–479. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11016469>.

117. Marrelli D, Caruso S, Pedrazzani C, et al. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. *Am J Surg* 2009;198:333–339. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19375064>.

118. NIH state-of-the-science statement on endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy. *NIH Consens State Sci Statements* 2002;19:1–26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14768653>.

119. Kajiwarra M, Kojima M, Konishi M, et al. Autoimmune pancreatitis with multifocal lesions. *J Hepatobiliary Pancreat Surg* 2008;15:449–452. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18670850>.

120. Kalady MF, Peterson B, Baillie J, et al. Pancreatic duct strictures: identifying risk of malignancy. *Ann Surg Oncol* 2004;11:581–588. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15150064>.

121. Menges M, Lerch MM, Zeitz M. The double duct sign in patients with malignant and benign pancreatic lesions. *Gastrointest Endosc* 2000;52:74–77. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10882966>.

122. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. *N Engl J Med* 2006;355:2670–2676. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17182992>.

123. Law R, Bronner M, Vogt D, Stevens T. Autoimmune pancreatitis: a mimic of pancreatic cancer. *Cleve Clin J Med* 2009;76:607–615. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19797461>.

124. Holmes BJ, Hruban RH, Wolfgang CL, Ali SZ. Fine needle aspirate of autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis): cytomorphologic characteristics and clinical correlates. *Acta Cytol* 2012;56:228–232. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22555522>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

125. Learn PA, Grossman EB, Do RK, et al. Pitfalls in avoiding operation for autoimmune pancreatitis. *Surgery* 2011;150:968–974. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21893326>.

126. Sah RP, Chari ST. Autoimmune pancreatitis: an update on classification, diagnosis, natural history and management. *Curr Gastroenterol Rep* 2012;14:95–105. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22350841>.

127. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732–738. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11236777>.

128. van Heerde MJ, Buijs J, Hansen BE, et al. Serum level of Ca 19-9 increases ability of IgG4 test to distinguish patients with autoimmune pancreatitis from those with pancreatic carcinoma. *Dig Dis Sci* 2014;59:1322–1329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24385012>.

129. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004;350:1200–1210. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15028824>.

130. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010;304:1073–1081. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20823433>.

131. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007;297:267–277. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17227978>.

132. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a

randomized controlled trial. *JAMA* 2008;299:1019–1026. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18319412>.

133. Massucco P, Capussotti L, Magnino A, et al. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. *Ann Surg Oncol* 2006;13:1201–1208. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16955382>.

134. Mornex F, Girard N, Delpero JR, Partensky C. Radiochemotherapy in the management of pancreatic cancer--part I: neoadjuvant treatment. *Semin Radiat Oncol* 2005;15:226–234. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16183476>.

135. Reni M. Neoadjuvant treatment for resectable pancreatic cancer: time for phase III testing? *World J Gastroenterol* 2010;16:4883–4887. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20954273>.

136. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006;13:1035–1046. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16865597>.

137. White RR, Hurwitz HI, Morse MA, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol* 2001;8:758–765. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11776488>.

138. Araujo RL, Gaujoux S, Huguet F, et al. Does pre-operative chemoradiation for initially unresectable or borderline resectable pancreatic adenocarcinoma increase post-operative morbidity? A case-matched analysis. *HPB (Oxford)* 2013;15:574–580. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23458208>.

139. Lim KH, Chung E, Khan A, et al. Neoadjuvant therapy of pancreatic cancer: the emerging paradigm? *Oncologist* 2012;17:192–200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22250057>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

140. Cloyd JM, Crane CH, Koay EJ, et al. Impact of hypofractionated and standard fractionated chemoradiation before pancreatoduodenectomy for pancreatic ductal adenocarcinoma. *Cancer* 2016;122:2671–2679. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27243381>.
141. Le Scodan R, Mornex F, Girard N, et al. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. *Ann Oncol* 2009;20:1387–1396. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19502533>.
142. Cassinotto C, Cortade J, Belleanne G, et al. An evaluation of the accuracy of CT when determining resectability of pancreatic head adenocarcinoma after neoadjuvant treatment. *Eur J Radiol* 2013;82:589–593. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23287712>.
143. Marchegiani G, Todaro V, Boninsegna E, et al. Surgery after FOLFIRINOX treatment for locally advanced and borderline resectable pancreatic cancer: increase in tumour attenuation on CT correlates with R0 resection. *Eur Radiol* 2018;28:4265–4273. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29679211>.
144. Dholakia AS, Hacker-Prietz A, Wild AT, et al. Resection of borderline resectable pancreatic cancer after neoadjuvant chemoradiation does not depend on improved radiographic appearance of tumor–vessel relationships. *J Radiat Oncol* 2013;2:413–425. Available at: <http://citations.springer.com/item?doi=10.1007/s13566-013-0115-6>.
145. Katz MH, Fleming JB, Bhosale P, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer* 2012;118:5749–5756. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22605518>.
146. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer* 2013;119:2692–2700. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23720019>.
147. Landry J, Catalano PJ, Staley C, et al. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. *J Surg Oncol* 2010;101:587–592. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20461765>.
148. Marti JL, Hochster HS, Hiotis SP, et al. Phase I/II trial of induction chemotherapy followed by concurrent chemoradiotherapy and surgery for locoregionally advanced pancreatic cancer. *Ann Surg Oncol* 2008;15:3521–3531. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18830756>.
149. Katz MH, Shi Q, Ahmad SA, et al. Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg* 2016;151:e161137. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27275632>.
150. McClaine RJ, Lowy AM, Sussman JJ, et al. Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer. *HPB (Oxford)* 2010;12:73–79. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20495649>.
151. Stokes JB, Nolan NJ, Stelow EB, et al. Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. *Ann Surg Oncol* 2011;18:619–627. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21213060>.
152. Laurence JM, Tran PD, Morarji K, et al. A systematic review and meta-analysis of survival and surgical outcomes following neoadjuvant chemoradiotherapy for pancreatic cancer. *J Gastrointest Surg* 2011;15:2059–2069. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21913045>.
153. Christians KK, Tsai S, Mahmoud A, et al. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? *Oncologist* 2014;19:266–274. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24569947>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

154. Tinchon C, Hubmann E, Pichler A, et al. Safety and efficacy of neoadjuvant FOLFIRINOX treatment in a series of patients with borderline resectable pancreatic ductal adenocarcinoma. *Acta Oncol* 2013;52:1231–1233. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23445338>.

155. Kim SS, Nakakura EK, Wang ZJ, et al. Preoperative FOLFIRINOX for borderline resectable pancreatic cancer: Is radiation necessary in the modern era of chemotherapy? *J Surg Oncol* 2016;114:587–596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27444658>.

156. Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol* 2015;54:979–985. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25734581>.

157. Moningi S, Marciscano AE, Rosati LM, et al. Stereotactic body radiation therapy in pancreatic cancer: the new frontier. *Expert Rev Anticancer Ther* 2014;14:1461–1475. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25183386>.

158. Mokdad AA, Minter RM, Zhu H, et al. Neoadjuvant Therapy Followed by Resection Versus Upfront Resection for Resectable Pancreatic Cancer: A Propensity Score Matched Analysis. *J Clin Oncol* 2017;35:515–522. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27621388>.

159. Artinyan A, Anaya DA, McKenzie S, et al. Neoadjuvant therapy is associated with improved survival in resectable pancreatic adenocarcinoma. *Cancer* 2011;117:2044–2049. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21523715>.

160. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3496–3502. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18640930>.

161. Hoffman JP, Lipsitz S, Pisansky T, et al. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology

Group Study. *J Clin Oncol* 1998;16:317–323. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9440759>.

162. Palmer DH, Stocken DD, Hewitt H, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. *Ann Surg Oncol* 2007;14:2088–2096. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17453298>.

163. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol* 1997;15:928–937. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9060530>.

164. Talamonti MS, Small W, Jr., Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. *Ann Surg Oncol* 2006;13:150–158. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16418882>.

165. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. *Ann Surg Oncol* 2001;8:123–132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11258776>.

166. Takahashi H, Ogawa H, Ohigashi H, et al. Preoperative chemoradiation reduces the risk of pancreatic fistula after distal pancreatectomy for pancreatic adenocarcinoma. *Surgery* 2011;150:547–556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21621236>.

167. Andriulli A, Festa V, Botteri E, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. *Ann Surg Oncol* 2012;19:1644–1662. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22012027>.

168. Chua TC, Saxena A. Preoperative chemoradiation followed by surgical resection for resectable pancreatic cancer: a review of current



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

results. *Surg Oncol* 2011;20:e161–168. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21704510>.

169. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3487–3495. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18640929>.

170. Pingpank JF, Hoffman JP, Ross EA, et al. Effect of preoperative chemoradiotherapy on surgical margin status of resected adenocarcinoma of the head of the pancreas. *J Gastrointest Surg* 2001;5:121–130. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11331473>.

171. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol* 2015;191:7–16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25252602>.

172. Tachezy M, Gebauer F, Petersen C, et al. Sequential neoadjuvant chemoradiotherapy (CRT) followed by curative surgery vs. primary surgery alone for resectable, non-metastasized pancreatic adenocarcinoma: NEOPA- a randomized multicenter phase III study (NCT01900327, DRKS00003893, ISRCTN82191749). *BMC Cancer* 2014;14:411. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24906700>.

173. Tachezy M, Gebauer F, Yekebas E, Izbicki JR. Failure of a Multi-Centric Clinical Trial Investigating Neoadjuvant Radio-Chemotherapy in Resectable Pancreatic Carcinoma (NEOPA-NCT01900327)—Which Lessons Are Learnt? *Cancers* 2023;15:4262. Available at: <https://www.mdpi.com/2072-6694/15/17/4262>.

174. Ahmad SA, Duong M, Sohal DPS, et al. Surgical Outcome Results From SWOG S1505: A Randomized Clinical Trial of mFOLFIRINOX Versus Gemcitabine/Nab-paclitaxel for Perioperative Treatment of Resectable Pancreatic Ductal Adenocarcinoma. *Ann Surg* 2020;272:481–486. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32740235>.

175. Sohal DPS, Duong M, Ahmad SA, et al. Efficacy of Perioperative Chemotherapy for Resectable Pancreatic Adenocarcinoma: A Phase 2 Randomized Clinical Trial. *JAMA Oncol* 2021;7:421–427. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33475684>.

176. Maurel J, Sanchez-Cabus S, Laquente B, et al. Outcomes after neoadjuvant treatment with gemcitabine and erlotinib followed by gemcitabine-erlotinib and radiotherapy for resectable pancreatic cancer (GEMCAD 10-03 trial). *Cancer Chemother Pharmacol* 2018;82:935–943. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30225601>.

177. Katz MH, Marsh R, Herman JM, et al. Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol* 2013;20:2787–2795. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23435609>.

178. Varadhachary GR, Evans DB. Rational study endpoint(s) for preoperative trials in pancreatic cancer: pathologic response rate, margin negative resection, overall survival or 'all of the above'? *Ann Surg Oncol* 2013;20:3712–3714. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23943023>.

179. Alva-Ruiz R, Yohanathan L, Yonkus JA, et al. Neoadjuvant Chemotherapy Switch in Borderline Resectable/Locally Advanced Pancreatic Cancer. *Ann Surg Oncol* 2022;29:1579–1591. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34724125>.

180. Vreeland TJ, McAllister F, Javadi S, et al. Benefit of Gemcitabine/Nab-Paclitaxel Rescue of Patients With Borderline Resectable or Locally Advanced Pancreatic Adenocarcinoma After Early Failure of FOLFIRINOX. *Pancreas* 2019;48:837–843. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31210666>.

181. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet* 2004;363:1049–1057. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15051286>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

182. Gudjonsson B. Cancer of the pancreas. 50 years of surgery. *Cancer* 1987;60:2284–2303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3326653>.

183. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. *Ann Surg* 1987;206:358–365. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3632096>.

184. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017;389:1011–1024. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28129987>.

185. Allison DC, Piantadosi S, Hruban RH, et al. DNA content and other factors associated with ten-year survival after resection of pancreatic carcinoma. *J Surg Oncol* 1998;67:151–159. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9530884>.

186. Howard TJ, Krug JE, Yu J, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. *J Gastrointest Surg* 2006;10:1338–1345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17175452>.

187. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000;4:567–579. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11307091>.

188. Petrucciani N, Nigri G, Debs T, et al. Frozen section analysis of the pancreatic margin during pancreaticoduodenectomy for cancer: Does extending the resection to obtain a secondary R0 provide a survival benefit? Results of a systematic review. *Pancreatology* 2016;16:1037–1043. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27697467>.

189. Abrams RA, Lowy AM, O'Reilly EM, et al. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert

consensus statement. *Ann Surg Oncol* 2009;16:1751–1756. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19390900>.

190. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014;155:977–988. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24856119>.

191. Talamonti M. Borderline resectable pancreatic cancer: a new classification for an old challenge. *Ann Surg Oncol* 2006;13:1019–1020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16865593>.

192. Bottger TC, Junginger T. Factors influencing morbidity and mortality after pancreaticoduodenectomy: critical analysis of 221 resections. *World J Surg* 1999;23:164–171; discussion 171–162. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9880426>.

193. Braasch JW, Gray BN. Considerations that lower pancreatoduodenectomy mortality. *Am J Surg* 1977;133:480–484. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/848682>.

194. Lerut JP, Gianello PR, Otte JB, Kestens PJ. Pancreaticoduodenal resection. Surgical experience and evaluation of risk factors in 103 patients. *Ann Surg* 1984;199:432–437. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6712319>.

195. Hatfield AR, Tobias R, Terblanche J, et al. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. *Lancet* 1982;2:896–899. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6126752>.

196. Lai EC, Mok FP, Fan ST, et al. Preoperative endoscopic drainage for malignant obstructive jaundice. *Br J Surg* 1994;81:1195–1198. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7741850>.

197. McPherson GA, Benjamin IS, Hodgson HJ, et al. Pre-operative percutaneous transhepatic biliary drainage: the results of a controlled trial. *Br J Surg* 1984;71:371–375. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6372935>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

198. Thomas JH, Connor CS, Pierce GE, et al. Effect of biliary decompression on morbidity and mortality of pancreatoduodenectomy. *Am J Surg* 1984;148:727–731. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6439064>.

199. Cavell LK, Allen PJ, Vinoya C, et al. Biliary self-expandable metal stents do not adversely affect pancreatoduodenectomy. *Am J Gastroenterol* 2013;108:1168–1173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23545711>.

200. Pisters PW, Hudec WA, Hess KR, et al. Effect of preoperative biliary decompression on pancreatoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 2001;234:47–55. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11420482>.

201. Aadam AA, Evans DB, Khan A, et al. Efficacy and safety of self-expandable metal stents for biliary decompression in patients receiving neoadjuvant therapy for pancreatic cancer: a prospective study. *Gastrointest Endosc* 2012;76:67–75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22483859>.

202. Mullen JT, Lee JH, Gomez HF, et al. Pancreatoduodenectomy after placement of endobiliary metal stents. *J Gastrointest Surg* 2005;9:1094–1104; discussion 1104–1095. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16269380>.

203. Varadhachary GR, Wolff RA. The war on pancreatic cancer: are we gaining ground? *Oncology* 2011;24:1335–1336. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21294479>.

204. Krokidis M, Fanelli F, Orgera G, et al. Percutaneous palliation of pancreatic head cancer: randomized comparison of ePTFE/FEP-covered versus uncovered nitinol biliary stents. *Cardiovasc Intervent Radiol* 2011;34:352–361. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20467870>.

205. Kullman E, Frozanpor F, Soderlund C, et al. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter

study. *Gastrointest Endosc* 2010;72:915–923. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21034892>.

206. Ho H, Mahajan A, Gosain S, et al. Management of complications associated with partially covered biliary metal stents. *Dig Dis Sci* 2010;55:516–522. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19267200>.

207. Telford JJ, Carr-Locke DL, Baron TH, et al. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. *Gastrointest Endosc* 2010;72:907–914. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21034891>.

208. Han S, Obando JV, Bhatt A, et al. Biliary and pancreatic stents. *Gastrointest Endosc* 2023;97:1003–1004. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37115164>.

209. Chun HJ, Kim ES, Hyun JJ, et al. Gastrointestinal and biliary stents. *J Gastroenterol Hepatol* 2010;25:234–243. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20136988>.

210. Gumbs AA, Rodriguez Rivera AM, Milone L, Hoffman JP. Laparoscopic pancreatoduodenectomy: a review of 285 published cases. *Ann Surg Oncol* 2011;18:1335–1341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21207166>.

211. Venkat R, Edil BH, Schulick RD, et al. Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. *Ann Surg* 2012;255:1048–1059. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22511003>.

212. Nakeeb A, Lillemoe KD, Grosfeld JL. Surgical techniques for pancreatic cancer. *Minerva Chir* 2004;59:151–163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15238889>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

213. Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. *Curr Probl Cancer* 2002;26:176–275. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12399802>.

214. Baque P, Iannelli A, Delotte J, et al. Division of the right posterior attachments of the head of the pancreas with a linear stapler during pancreaticoduodenectomy: vascular and oncological considerations based on an anatomical cadaver-based study. *Surg Radiol Anat* 2009;31:13–17. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18712270>.

215. Evans DB, Pisters PW. Novel applications of endo GIA linear staplers during pancreaticoduodenectomy and total pancreatectomy. *Am J Surg* 2003;185:606–607. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12781900>.

216. Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection? *Ann Surg* 1996;224:342–347; discussion 347–349. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8813262>.

217. Riediger H, Makowiec F, Fischer E, et al. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. *J Gastrointest Surg* 2006;10:1106–1115. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16966029>.

218. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg* 2004;8:935–949; discussion 949–950. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15585381>.

219. Stitzenberg KB, Watson JC, Roberts A, et al. Survival after pancreatectomy with major arterial resection and reconstruction. *Ann Surg Oncol* 2008;15:1399–1406. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18320285>.

220. Worni M, Castleberry AW, Clary BM, et al. Concomitant vascular reconstruction during pancreatectomy for malignant disease: a propensity score-adjusted, population-based trend analysis involving 10,206 patients.

JAMA Surg 2013;148:331–338. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23715922>.

221. Mollberg N, Rahbari NN, Koch M, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011;254:882–893. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22064622>.

222. Christein JD, Kendrick ML, Iqbal CW, et al. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. *J Gastrointest Surg* 2005;9:922–927. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16137585>.

223. Shoup M, Conlon KC, Klimstra D, Brennan MF. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? *J Gastrointest Surg* 2003;7:946–952; discussion 952. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14675703>.

224. Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. *J Am Coll Surg* 2007;204:244–249. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17254928>.

225. Mehrabi A, Hafezi M, Arvin J, et al. A systematic review and meta-analysis of laparoscopic versus open distal pancreatectomy for benign and malignant lesions of the pancreas: it's time to randomize. *Surgery* 2015;157:45–55. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25482464>.

226. Stauffer JA, Rosales-Velderrain A, Goldberg RF, et al. Comparison of open with laparoscopic distal pancreatectomy: a single institution's transition over a 7-year period. *HPB (Oxford)* 2013;15:149–155. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23297726>.

227. Tran Cao HS, Lopez N, Chang DC, et al. Improved perioperative outcomes with minimally invasive distal pancreatectomy: results from a population-based analysis. *JAMA Surg* 2014;149:237–243. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24402232>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

228. Bruna CL, van Hilst J, Korrel M, et al. Minimally Invasive vs Open Left Pancreatectomy for Resectable Pancreatic Cancer: Long-Term Results of the Randomized DIPLOMA Trial. *JAMA Surg* 2025;160:1299–1307. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/41060640>.

229. Strasberg SM, Sanchez LA, Hawkins WG, et al. Resection of tumors of the neck of the pancreas with venous invasion: the "Whipple at the Splenic Artery (WATSA)" procedure. *J Gastrointest Surg* 2012;16:1048–1054. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22399270>.

230. Hirono S, Kawai M, Okada K, et al. Pancreatic neck cancer has specific and oncologic characteristics regarding portal vein invasion and lymph node metastasis. *Surgery* 2016;159:426–440. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26253244>.

231. Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Tumor staging and results. *Ann Surg* 1984;199:418–425. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6712317>.

232. Fuhrman GM, Leach SD, Staley CA, et al. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. *Ann Surg* 1996;223:154–162. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8597509>.

233. Leach SD, Lee JE, Charnsangavej C, et al. Survival following pancreaticoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. *Br J Surg* 1998;85:611–617. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9635805>.

234. Clavien PA, Rudiger HA. A simple technique of portal vein resection and reconstruction during pancreaticoduodenectomy. *J Am Coll Surg* 1999;189:629–634. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10589601>.

235. Launois B, Stasik C, Bardaxoglou E, et al. Who benefits from portal vein resection during pancreaticoduodenectomy for pancreatic cancer?

World J Surg 1999;23:926–929. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10449822>.

236. Taschieri AM, Elli M, Rovati M, et al. Surgical treatment of pancreatic tumors invading the spleno-mesenteric-portal vessels. An Italian Multicenter Survey. *Hepatogastroenterology* 1999;46:492–497. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10228849>.

237. van Geenen RC, ten Kate FJ, de Wit LT, et al. Segmental resection and wedge excision of the portal or superior mesenteric vein during pancreaticoduodenectomy. *Surgery* 2001;129:158–163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11174708>.

238. Yu XZ, Li J, Fu DL, et al. Benefit from synchronous portal-superior mesenteric vein resection during pancreaticoduodenectomy for cancer: a meta-analysis. *Eur J Surg Oncol* 2014;40:371–378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24560302>.

239. Kelly KJ, Winslow E, Kooby D, et al. Vein involvement during pancreaticoduodenectomy: is there a need for redefinition of "borderline resectable disease"? *J Gastrointest Surg* 2013;17:1209–1217; discussion 1217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23620151>.

240. Traverso LW, Longmire WP, Jr. Preservation of the pylorus in pancreaticoduodenectomy. *Surg Gynecol Obstet* 1978;146:959–962. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/653575>.

241. Huttner FJ, Fitzmaurice C, Schwarzer G, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database Syst Rev* 2016;2:CD006053. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26905229>.

242. Yeo CJ, Cameron JL, Maher MM, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. *Ann Surg* 1995;222:580–588; discussion 588–592. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7574936>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

243. Topal B, Fieuws S, Aerts R, et al. Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial. *Lancet Oncol* 2013;14:655–662. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23643139>.

244. Hallet J, Zih FS, Deobald RG, et al. The impact of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction on pancreatic fistula after pancreaticoduodenectomy: meta-analysis of randomized controlled trials. *HPB (Oxford)* 2015;17:113–122. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25040921>.

245. Gomez T, Palomares A, Serradilla M, Tejedor L. Reconstruction after pancreatoduodenectomy: Pancreatojejunostomy vs pancreaticogastrostomy. *World J Gastrointest Oncol* 2014;6:369–376. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25232462>.

246. Bassi C, Falconi M, Molinari E, et al. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. *Surgery* 2003;134:766–771. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14639354>.

247. Sikora SS, Posner MC. Management of the pancreatic stump following pancreaticoduodenectomy. *Br J Surg* 1995;82:1590–1597. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8548218>.

248. Strasberg SM, Drebin JA, Mokadam NA, et al. Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. *J Am Coll Surg* 2002;194:746–758; discussion 759–760. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12081065>.

249. Winter JM, Cameron JL, Campbell KA, et al. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. *J Gastrointest Surg* 2006;10:1280–1290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17114014>.

250. Lowy AM, Lee JE, Pisters PW, et al. Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. *Ann Surg* 1997;226:632–641. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9389397>.

251. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. *Ann Surg* 2000;232:419–429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10973392>.

252. Lillemoe KD, Cameron JL, Kim MP, et al. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. *J Gastrointest Surg* 2004;8:766–772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15531229>.

253. Allen PJ, Gonen M, Brennan MF, et al. Pasireotide for postoperative pancreatic fistula. *N Engl J Med* 2014;370:2014–2022. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24849084>.

254. Cubilla AL, Fortner J, Fitzgerald PJ. Lymph node involvement in carcinoma of the head of the pancreas area. *Cancer* 1978;41:880–887. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/638975>.

255. Nagai H, Kuroda A, Morioka Y. Lymphatic and local spread of T1 and T2 pancreatic cancer. A study of autopsy material. *Ann Surg* 1986;204:65–71. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3015059>.

256. Glanemann M, Shi B, Liang F, et al. Surgical strategies for treatment of malignant pancreatic tumors: extended, standard or local surgery? *World J Surg Oncol* 2008;6:123. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19014474>.

257. Pisters P, Brennan M. Regional lymph node dissection for pancreatic adenocarcinoma. In: Evans D, Pisters P, Abbruzzese J, eds., eds. *Pancreatic Cancer*. New York: Springer-Verlag; 2002:139–151.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

258. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. *Ann Surg* 1998;228:508–517. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9790340>.

259. Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. *Ann Surg* 1999;229:613–622; discussion 622–614. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10235519>.

260. Riall TS, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma--part 3: update on 5-year survival. *J Gastrointest Surg* 2005;9:1191–1204; discussion 1204–1196. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16332474>.

261. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. *Ann Surg* 2002;236:355–366; discussion 366–358. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12192322>.

262. Nimura Y, Nagino M, Takao S, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. *J Hepatobiliary Pancreat Sci* 2012;19:230–241. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22038501>.

263. Michalski CW, Kleeff J, Wente MN, et al. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. *Br J Surg* 2007;94:265–273. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17318801>.

264. Sun J, Yang Y, Wang X, et al. Meta-analysis of the efficacies of extended and standard pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas. *World J Surg* 2014;38:2708–2715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24912627>.

265. Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). *Surgery* 2014;156:591–600. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25061003>.

266. Farnell MB, Aranha GV, Nimura Y, Michelassi F. The role of extended lymphadenectomy for adenocarcinoma of the head of the pancreas: strength of the evidence. *J Gastrointest Surg* 2008;12:651–656. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18085343>.

267. Shrikhande SV, Barreto SG. Extended pancreatic resections and lymphadenectomy: An appraisal of the current evidence. *World J Gastrointest Surg* 2010;2:39–46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21160848>.

268. Cordera F, Arciero CA, Li T, et al. Significance of common hepatic artery lymph node metastases during pancreaticoduodenectomy for pancreatic head adenocarcinoma. *Ann Surg Oncol* 2007;14:2330–2336. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17492334>.

269. Shimada K, Sakamoto Y, Sano T, Kosuge T. The role of paraaortic lymph node involvement on early recurrence and survival after macroscopic curative resection with extended lymphadenectomy for pancreatic carcinoma. *J Am Coll Surg* 2006;203:345–352. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16931307>.

270. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. *Ann Surg* 1995;222:638–645. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7487211>.



NCCN Guidelines Version 2.2026

Pancreatic Adenocarcinoma

271. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. *Ann Surg* 2003;237:509–514. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12677147>.

272. Imperato PJ, Nenner RP, Starr HA, et al. The effects of regionalization on clinical outcomes for a high risk surgical procedure: a study of the Whipple procedure in New York State. *Am J Med Qual* 1996;11:193–197. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8972936>.

273. Rosemurgy AS, Bloomston M, Serafini FM, et al. Frequency with which surgeons undertake pancreaticoduodenectomy determines length of stay, hospital charges, and in-hospital mortality. *J Gastrointest Surg* 2001;5:21–26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11309644>.

274. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. *Ann Surg* 1998;228:429–438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9742926>.

275. Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Ann Surg* 2000;232:786–795. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11088073>.

276. Birkmeyer JD, Finlayson SR, Tosteson AN, et al. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. *Surgery* 1999;125:250–256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10076608>.

277. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–1137. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11948273>.

278. Bilimoria KY, Bentrem DJ, Ko CY, et al. Multimodality therapy for pancreatic cancer in the U.S. : utilization, outcomes, and the effect of hospital volume. *Cancer* 2007;110:1227–1234. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17654662>.

279. La Torre M, Nigri G, Ferrari L, et al. Hospital volume, margin status, and long-term survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am Surg* 2012;78:225–229. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22369834>.

280. Hyder O, Dodson RM, Nathan H, et al. Influence of patient, physician, and hospital factors on 30-day readmission following pancreatoduodenectomy in the United States. *JAMA Surg* 2013;148:1095–1102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24108580>.

281. Verbeke CS. Resection margins and R1 rates in pancreatic cancer--are we there yet? *Histopathology* 2008;52:787–796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18081813>.

282. College of American Pathologists. <https://www.cap.org>: Available at: Accessed 7/16/2024.

283. Gebhardt C, Meyer W, Reichel M, Wunsch PH. Prognostic factors in the operative treatment of ductal pancreatic carcinoma. *Langenbecks Arch Surg* 2000;385:14–20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10664114>.

284. Mitsunaga S, Hasebe T, Iwasaki M, et al. Important prognostic histological parameters for patients with invasive ductal carcinoma of the pancreas. *Cancer Sci* 2005;96:858–865. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16367904>.

285. Elshaer M, Gravante G, Kosmin M, et al. A systematic review of the prognostic value of lymph node ratio, number of positive nodes and total nodes examined in pancreatic ductal adenocarcinoma. *Ann R Coll Surg Engl* 2017;99:101–106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27869496>.

286. Huebner M, Kendrick M, Reid-Lombardo KM, et al. Number of lymph nodes evaluated: prognostic value in pancreatic adenocarcinoma. *J Gastrointest Surg* 2012;16:920–926. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22421988>.



NCCN Guidelines Version 2.2026

Pancreatic Adenocarcinoma

287. Opfermann KJ, Wahlquist AE, Garrett-Mayer E, et al. Adjuvant radiotherapy and lymph node status for pancreatic cancer: results of a study from the Surveillance, Epidemiology, and End Results (SEER) Registry Data. *Am J Clin Oncol* 2014;37:112–116. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23211221>.

288. Valsangkar NP, Bush DM, Michaelson JS, et al. N0/N1, PNL, or LNR? The effect of lymph node number on accurate survival prediction in pancreatic ductal adenocarcinoma. *J Gastrointest Surg* 2013;17:257–266. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23229885>.

289. Ashfaq A, Pockaj BA, Gray RJ, et al. Nodal counts and lymph node ratio impact survival after distal pancreatectomy for pancreatic adenocarcinoma. *J Gastrointest Surg* 2014;18:1929–1935. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24916590>.

290. John BJ, Naik P, Ironside A, et al. Redefining the R1 resection for pancreatic ductal adenocarcinoma: tumour lymph nodal burden and lymph node ratio are the only prognostic factors associated with survival. *HPB (Oxford)* 2013;15:674–680. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23458477>.

291. Robinson SM, Rahman A, Haugk B, et al. Metastatic lymph node ratio as an important prognostic factor in pancreatic ductal adenocarcinoma. *Eur J Surg Oncol* 2012;38:333–339. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22317758>.

292. Campbell F, Cairns A, Duthie F, Feakins R. Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct. The Royal College of Pathologists 2019. Available at: <http://www.rcpath.org/Resources/RCPPath/Migrated%20Resources/Documents/D/datasethistopathologicalreportingcarcinomasmay10.pdf>.

293. Klimstra DS, Hruban RH, Sigel C, Kloppel G. Tumors of the Pancreas: Afip Atlas of Tumor Pathology; 5th Series: American Registry of Pathology; Armed Forces Institutes of Pathology; 2023.

294. Adsay NV, Basturk O, Saka B, et al. Whipple made simple for surgical pathologists: orientation, dissection, and sampling of pancreaticoduodenectomy specimens for a more practical and accurate evaluation of pancreatic, distal common bile duct, and ampullary tumors. *Am J Surg Pathol* 2014;38:480–493. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24451278>.

295. Adsay V, Ohike N, Tajiri T, et al. Ampullary region carcinomas: definition and site specific classification with delineation of four clinicopathologically and prognostically distinct subsets in an analysis of 249 cases. *Am J Surg Pathol* 2012;36:1592–1608. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23026934>.

296. Ohike N, Kim GE, Tajiri T, et al. Intra-ampullary papillary-tubular neoplasm (IAPN): characterization of tumoral intraepithelial neoplasia occurring within the ampulla: a clinicopathologic analysis of 82 cases. *Am J Surg Pathol* 2010;34:1731–1748. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21084962>.

297. Tarcan ZC, Esmer R, Akar KE, et al. Intra-ampullary Papillary Tubular Neoplasm (IAPN): Clinicopathologic Analysis of 72 Cases Highlights the Distinctive Characteristics of a Poorly Recognized Entity. *Am J Surg Pathol* 2024;48:1093–1107. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38938087>.

298. Konstantinidis IT, Warshaw AL, Allen JN, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? *Ann Surg* 2013;257:731–736. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22968073>.

299. Gnerlich JL, Luka SR, Deshpande AD, et al. Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. *Arch Surg* 2012;147:753–760. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22911074>.

300. Delpero JR, Bachellier P, Regenet N, et al. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in 150



NCCN Guidelines Version 2.2026

Pancreatic Adenocarcinoma

evaluable specimens. HPB (Oxford) 2014;16:20–33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23464850>.

301. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol* 2011;18:1319–1326. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21499862>.

302. Sinn M, Bahra M, Liersch T, et al. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. *J Clin Oncol* 2017;35:3330–3337. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28817370>.

303. Postlewait LM, Ethun CG, Kooby DA, et al. Combination gemcitabine/cisplatin therapy and ERCC1 expression for resected pancreatic adenocarcinoma: Results of a Phase II prospective trial. *J Surg Oncol* 2016;114:336–341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27501338>.

304. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol* 2014;32:504–512. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24419109>.

305. Conroy T, Hammel P, Turpin A, et al. LBA57 Unicancer PRODIGE 24/CCTG PA6 trial: Updated results of a multicenter international randomized phase III trial of adjuvant mFOLFIRINOX (mFFX) versus gemcitabine (gem) in patients (pts) with resected pancreatic ductal adenocarcinomas (PDAC). *Ann Oncol* 2021;32:S1334. Available at: <https://doi.org/10.1016/j.annonc.2021.08.2137>.

306. Abrams RA, Winter KA, Goodman KA, et al. NRG Oncology/RTOG 0848: Results after adjuvant chemotherapy +/- chemoradiation for patients with resected periampullary pancreatic adenocarcinoma (PA). *J Clin Oncol* 2024;42:4005–4005. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2024.42.16_suppl.4005.

307. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. *Lancet* 2000;355:1588–1596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10821362>.

308. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. *J Clin Oncol* 1996;14:2274–2279. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8708717>.

309. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study. *Cancer* 1989;63:1026–1030. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2465076>.

310. Tzeng CW, Fleming JB, Lee JE, et al. Yield of clinical and radiographic surveillance in patients with resected pancreatic adenocarcinoma following multimodal therapy. *HPB (Oxford)* 2012;14:365–372. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22568412>.

311. Tzeng CW, Abbott DE, Cantor SB, et al. Frequency and intensity of postoperative surveillance after curative treatment of pancreatic cancer: a cost-effectiveness analysis. *Ann Surg Oncol* 2013;20:2197–2203. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23408126>.

312. Witkowski ER, Smith JK, Ragulin-Coyne E, et al. Is it worth looking? Abdominal imaging after pancreatic cancer resection: a national study. *J Gastrointest Surg* 2012;16:121–128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21972054>.

313. Zhou Y, Song A, Wu L, et al. Second pancreatectomy for recurrent pancreatic ductal adenocarcinoma in the remnant pancreas: A pooled analysis. *Pancreatology* 2016;16:1124–1128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27717684>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

314. Katz MH, Wang H, Fleming JB, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. *Ann Surg Oncol* 2009;16:836–847. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19194760>.

315. Arnaoutakis GJ, Rangachari D, Laheru DA, et al. Pulmonary resection for isolated pancreatic adenocarcinoma metastasis: an analysis of outcomes and survival. *J Gastrointest Surg* 2011;15:1611–1617. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21725701>.

316. Ammori JB, Colletti LM, Zalupski MM, et al. Surgical resection following radiation therapy with concurrent gemcitabine in patients with previously unresectable adenocarcinoma of the pancreas. *J Gastrointest Surg* 2003;7:766–772. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/13129554>.

317. Bickenbach KA, Gonen M, Tang LH, et al. Downstaging in pancreatic cancer: a matched analysis of patients resected following systemic treatment of initially locally unresectable disease. *Ann Surg Oncol* 2012;19:1663–1669. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22130621>.

318. Mondo EL, Noel MS, Katz AW, et al. Unresectable locally advanced pancreatic cancer: treatment with neoadjuvant leucovorin, fluorouracil, irinotecan, and oxaliplatin and assessment of surgical resectability. *J Clin Oncol* 2013;31:e37–39. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23233707>.

319. Martin RC, 2nd, Kwon D, Chalikhonda S, et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. *Ann Surg* 2015;262:486–494; discussion 492–484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26258317>.

320. Martin RC, 2nd, McFarland K, Ellis S, Velanovich V. Irreversible electroporation therapy in the management of locally advanced pancreatic adenocarcinoma. *J Am Coll Surg* 2012;215:361–369. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22726894>.

321. Jenks S. Shock Therapy for Late-Stage Pancreatic Cancer Gets Closer Look. *J Natl Cancer Inst* 2016;108:djw159. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27257026>.

322. Zimmermann FB, Jeremic B, Lersch C, et al. Dose escalation of concurrent hypofractionated radiotherapy and continuous infusion 5-FU-chemotherapy in advanced adenocarcinoma of the pancreas. *Hepatogastroenterology* 2005;52:246–250. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15783041>.

323. Reni M, Macchini M, Orsi G, et al. Preoperative mFOLFIRINOX versus PAXG for stage I-III resectable and borderline resectable pancreatic ductal adenocarcinoma (PACT-21 CASSANDRA): results of the first randomisation analysis of a randomised, open-label, 2 x 2 factorial phase 3 trial. *Lancet* 2026;406:2945–2956. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/41275879>.

324. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 2016;17:801–810. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27160474>.

325. Sadot E, Doussot A, O'Reilly EM, et al. FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma. *Ann Surg Oncol* 2015;22:3512–3521. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26065868>.

326. Ychou M, Conroy T, Seitz JF, et al. An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/ 5-fluorouracil every 2 weeks in patients with advanced solid tumors. *Ann Oncol* 2003;14:481–489. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12598357>.

327. Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol* 2005;23:1228–1236. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15718320>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

328. Ychou M, Desseigne F, Guimbaud R, et al. Randomized phase II trial comparing folfirinox (5FU/leucovorin [LV], irinotecan [I] and oxaliplatin [O]) vs gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA). First results of the ACCORD 11 trial [abstract]. *J Clin Oncol* 2007;25 (June 20 Suppl):4516. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.4516.

329. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21561347>.

330. Conroy T, Castan F, Lopez A, et al. Five-Year Outcomes of FOLFIRINOX vs Gemcitabine as Adjuvant Therapy for Pancreatic Cancer: A Randomized Clinical Trial. *JAMA Oncol* 2022;8:1571–1578. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36048453>.

331. Peixoto RD, Ho M, Renouf DJ, et al. Eligibility of Metastatic Pancreatic Cancer Patients for First-Line Palliative Intent nab-Paclitaxel Plus Gemcitabine Versus FOLFIRINOX. *Am J Clin Oncol* 2017;40:507–511. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25844823>.

332. Gourgou-Bourgade S, Bascoul-Mollevis C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013;31:23–29. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23213101>.

333. Lowery MA, Yu KH, Adel NG, et al. Activity of front-line FOLFIRINOX (FFX) in stage III/IV pancreatic adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC) [abstract]. *ASCO Meeting Abstracts* 2012;30:4057. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2012.30.15_suppl.4057.

334. Stein SM, James ES, Deng Y, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer* 2016;114:737–743. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27022826>.

335. Faris JE, Blaszkowsky LS, McDermott S, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist* 2013;18:543–548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23657686>.

336. Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002;20:3270–3275. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12149301>.

337. Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol* 2010;28:1645–1651. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20194854>.

338. Demols A, Peeters M, Polus M, et al. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. *Br J Cancer* 2006;94:481–485. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16434988>.

339. Fine RL, Fogelman DR, Schreiber SM, et al. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. *Cancer Chemother Pharmacol* 2008;61:167–175. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17440727>.

340. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006;24:3946–3952. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16921047>.

341. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 2007;25:2212–2217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17538165>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

342. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005;23:3509–3516. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15908661>.

343. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009;27:3778–3785. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19581537>.

344. Reni M, Cordio S, Milandri C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005;6:369–376. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15925814>.

345. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004;22:3776–3783. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15365074>.

346. Ciliberto D, Botta C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. *Eur J Cancer* 2013;49:593–603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22989511>.

347. Sun C, Ansari D, Andersson R, Wu DQ. Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer? *World J Gastroenterol* 2012;18:4944–4958. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23002368>.

348. Kulke MH, Tempero MA, Niedzwiecki D, et al. Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic

pancreatic cancer: CALGB 89904. *J Clin Oncol* 2009;27:5506–5512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19858396>.

349. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer* 2006;95:587–592. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16909140>.

350. Goncalves A, Gilabert M, Francois E, et al. BAYPAN study: a double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. *Ann Oncol* 2012;23:2799–2805. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22771827>.

351. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* 2011;29:4548–4554. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21969517>.

352. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–1703. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24131140>.

353. Chiorean EG, Von Hoff DD, Reni M, et al. CA19-9 decrease at 8 weeks as a predictor of overall survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer. *Ann Oncol* 2016;27:654–660. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26802160>.

354. Goldstein D, Von Hoff DD, Moore M, et al. Development of peripheral neuropathy and its association with survival during treatment with nab-paclitaxel plus gemcitabine for patients with metastatic adenocarcinoma of the pancreas: A subset analysis from a randomised phase III trial (MPACT). *Eur J Cancer* 2016;52:85–91. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26655559>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

355. Goldstein D, El-Maraghi RH, Hammel P, et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. *J Natl Cancer Inst* 2015;107. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25638248>.

356. Taberero J, Chiorean EG, Infante JR, et al. Prognostic factors of survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer. *Oncologist* 2015;20:143–150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25582141>.

357. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer* 1996;32A:1135–1141. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8758243>.

358. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. *Br J Cancer* 2014;111:1132–1138. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25072261>.

359. Majdak EJ, Debniak J, Milczek T, et al. Prognostic impact of BRCA1 pathogenic and BRCA1/BRCA2 unclassified variant mutations in patients with ovarian carcinoma. *Cancer* 2005;104:1004–1012. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16047333>.

360. Stefansson OA, Jonasson JG, Johannsson OT, et al. Genomic profiling of breast tumours in relation to BRCA abnormalities and phenotypes. *Breast Cancer Res* 2009;11:R47. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19589159>.

361. Fogelman D, Sugar EA, Oliver G, et al. Family history as a marker of platinum sensitivity in pancreatic adenocarcinoma. *Cancer Chemother Pharmacol* 2015;76:489–498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26126726>.

362. Lowery MA, Kelsen DP, Stadler ZK, et al. An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation:

clinical descriptors, treatment implications, and future directions. *Oncologist* 2011;16:1397–1402. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21934105>.

363. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25:1960–1966. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17452677>.

364. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol* 2010;28:3605–3610. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20606093>.

365. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010;28:3617–3622. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20606091>.

366. Kindler HL, Ioka T, Richel DJ, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol* 2011;12:256–262. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21306953>.

367. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol* 2009;27:2231–2237. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19307500>.

368. Aranda E, Manzano JL, Rivera F, et al. Phase II open-label study of erlotinib in combination with gemcitabine in unresectable and/or metastatic adenocarcinoma of the pancreas: relationship between skin rash and survival (Pantar study). *Ann Oncol* 2012;23:1919–1925. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22156621>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

369. Stepanski EJ, Reyes C, Walker MS, et al. The association of rash severity with overall survival: findings from patients receiving erlotinib for pancreatic cancer in the community setting. *Pancreas* 2013;42:32–36. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22699203>.

370. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009;27:5513–5518. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19858379>.

371. Lee HS, Chung MJ, Park JY, et al. A randomized, multicenter, phase III study of gemcitabine combined with capecitabine versus gemcitabine alone as first-line chemotherapy for advanced pancreatic cancer in South Korea. *Medicine (Baltimore)* 2017;96:e5702. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28072706>.

372. Li Q, Yan H, Liu W, et al. Efficacy and safety of gemcitabine-fluorouracil combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomized controlled trials. *PLoS One* 2014;9:e104346. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25093849>.

373. Ko AH, Espinoza AM, Jones KA, et al. Optimizing the administration of fixed-dose rate gemcitabine plus capecitabine using an alternating-week schedule: a dose finding and early efficacy study in advanced pancreatic and biliary carcinomas. *Am J Clin Oncol* 2012;35:411–417. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21552099>.

374. Jameson GS, Borazanci E, Babiker HM, et al. Response Rate Following Albumin-Bound Paclitaxel Plus Gemcitabine Plus Cisplatin Treatment Among Patients With Advanced Pancreatic Cancer: A Phase 1b/2 Pilot Clinical Trial. *JAMA Oncol* 2020;6:125–132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31580386>.

375. Shroff RT, Javle MM, Xiao L, et al. Gemcitabine, Cisplatin, and nab-Paclitaxel for the Treatment of Advanced Biliary Tract Cancers: A Phase 2 Clinical Trial. *JAMA Oncol* 2019;5:824–830. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30998813>.

376. Trouilloud I, Dupont-Gossard AC, Malka D, et al. Fixed-dose rate gemcitabine alone or alternating with FOLFIRI.3 (irinotecan, leucovorin and fluorouracil) in the first-line treatment of patients with metastatic pancreatic adenocarcinoma: an AGEO randomised phase II study (FIRGEM). *Eur J Cancer* 2014;50:3116–3124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25454414>.

377. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–2413. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9196156>.

378. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013;310:1473–1481. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24104372>.

379. Mackey JR, Mani RS, Selner M, et al. Functional nucleoside transporters are required for gemcitabine influx and manifestation of toxicity in cancer cell lines. *Cancer Res* 1998;58:4349–4357. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9766663>.

380. Farrell JJ, Elsaleh H, Garcia M, et al. Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. *Gastroenterology* 2009;136:187–195. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18992248>.

381. Greenhalf W, Ghaneh P, Neoptolemos JP, et al. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. *J Natl Cancer Inst* 2014;106:djt347. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24301456>.

382. Marechal R, Bachet JB, Mackey JR, et al. Levels of gemcitabine transport and metabolism proteins predict survival times of patients treated with gemcitabine for pancreatic adenocarcinoma. *Gastroenterology* 2012;143:664–674 e666. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22705007>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

383. Bird NT, Elmasry M, Jones R, et al. Immunohistochemical hENT1 expression as a prognostic biomarker in patients with resected pancreatic ductal adenocarcinoma undergoing adjuvant gemcitabine-based chemotherapy. *Br J Surg* 2017;104:328–336. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28199010>.

384. Ormanns S, Heinemann V, Raponi M, et al. Human equilibrative nucleoside transporter 1 is not predictive for gemcitabine efficacy in advanced pancreatic cancer: translational results from the AIO-PK0104 phase III study with the clone SP120 rabbit antibody. *Eur J Cancer* 2014;50:1891–1899. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24857044>.

385. Sinn M, Riess H, Sinn BV, et al. Human equilibrative nucleoside transporter 1 expression analysed by the clone SP 120 rabbit antibody is not predictive in patients with pancreatic cancer treated with adjuvant gemcitabine - Results from the CONKO-001 trial. *Eur J Cancer* 2015;51:1546–1554. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26049689>.

386. Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W. Saturation of 2',2'-difluorodeoxycytidine 5'-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. *Cancer Chemother Pharmacol* 1991;27:258–262. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1998982>.

387. Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol* 2003;21:3402–3408. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12885837>.

388. De Jesus-Acosta A, Oliver GR, Blackford A, et al. A multicenter analysis of GTX chemotherapy in patients with locally advanced and metastatic pancreatic adenocarcinoma. *Cancer Chemother Pharmacol* 2012;69:415–424. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21800112>.

389. Rahma OE, Duffy A, Liewehr DJ, et al. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. *Ann Oncol* 2013;24:1972–1979. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23670093>.

390. Chiorean EG, Von Hoff DD, Tabernero J, et al. Second-line therapy after nab-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. *Br J Cancer* 2016;115:e13. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27657342>.

391. Wainberg ZA, Bekaii-Saab T, Boland PM, et al. First-line liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study. *Eur J Cancer* 2021;151:14–24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33957442>.

392. Wainberg ZA, Melisi D, Macarulla T, et al. NAPOLI-3: A randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). *J Clin Oncol* 2023;41:LBA661–LBA661. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.4_suppl.LBA661.

393. Heinemann V, Vehling-Kaiser U, Waldschmidt D, et al. Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104). *Gut* 2013;62:751–759. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22773551>.

394. Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. *J Clin Oncol* 2002;20:160–164. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11773165>.

395. Xiong HQ, Varadhachary GR, Blais JC, et al. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

with advanced pancreatic cancer. *Cancer* 2008;113:2046–2052. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18756532>.

396. Gill S, Ko YJ, Cripps C, et al. PANCREOX: A Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. *J Clin Oncol* 2016;34:3914–3920. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27621395>.

397. Uccello M, Moschetta M, Arkenau HT. Second-Line Combination Therapies in Pancreatic Cancer: Where Are We Now? *J Clin Oncol* 2017;35:1370–1371. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28113022>.

398. Chung V, McDonough S, Philip PA, et al. Effect of Selumetinib and MK-2206 vs Oxaliplatin and Fluorouracil in Patients With Metastatic Pancreatic Cancer After Prior Therapy: SWOG S1115 Study Randomized Clinical Trial. *JAMA Oncol* 2017;3:516–522. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27978579>.

399. Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011;47:1676–1681. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21565490>.

400. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014;32:2423–2429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24982456>.

401. Moretto R, Raimondo L, De Stefano A, et al. FOLFIRI in patients with locally advanced or metastatic pancreatic or biliary tract carcinoma: a monoinstitutional experience. *Anticancer Drugs* 2013;24:980–985. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23928570>.

402. Neuzillet C, Hentic O, Rousseau B, et al. FOLFIRI regimen in metastatic pancreatic adenocarcinoma resistant to gemcitabine and

platinum-salts. *World J Gastroenterol* 2012;18:4533–4541. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22969226>.

403. Yoo C, Hwang JY, Kim JE, et al. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Br J Cancer* 2009;101:1658–1663. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19826418>.

404. Zaniboni A, Aitini E, Barni S, et al. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. *Cancer Chemother Pharmacol* 2012;69:1641–1645. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22576338>.

405. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016;387:545–557. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26615328>.

406. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018;378:731–739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29466156>.

407. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol* 2020;21:531–540. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32105622>.

408. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. 2019. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntkr-solid-tumors-and-ros-1-nsclc>. Accessed July 16, 2024.

409. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21:271–282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31838007>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

410. Demetri GD, De Braud F, Drilon A, et al. Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Patients With NTRK Fusion-Positive Solid Tumors. *Clin Cancer Res* 2022;28:1302–1312. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35144967>.

411. FDA grants accelerated approval to repotrectinib for adult and pediatric patients with NTRK gene fusion-positive solid tumors. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-repotrectinib-adult-and-pediatric-patients-ntrk-gene-fusion-positive>. Accessed July 12, 2024.

412. Solomon BJ, Drilon A, Lin JJ, et al. 1372P Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial. *Ann Oncol* 2023;34:S787–S788. Available at: <https://doi.org/10.1016/j.annonc.2023.09.2405>.

413. Hong DS, Fakih MG, Strickler JH, et al. KRAS(G12C) Inhibition with Sotorasib in Advanced Solid Tumors. *N Engl J Med* 2020;383:1207–1217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32955176>.

414. Strickler JH, Satake H, George TJ, et al. Sotorasib in KRAS p.G12C-Mutated Advanced Pancreatic Cancer. *N Engl J Med* 2023;388:33–43. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36546651>.

415. Bekaii-Saab TS, Spira AI, Yaeger R, et al. KRYSTAL-1: Updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a KRASG12C mutation. *J Clin Oncol* 2022;40:519–519. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.4_suppl.519.

416. Waters AM, Der CJ. KRAS: The Critical Driver and Therapeutic Target for Pancreatic Cancer. *Cold Spring Harb Perspect Med* 2018;8. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29229669>.

417. Pant S, Schuler M, Iyer G, et al. Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): an international, single-

arm, phase 2 study. *Lancet Oncol* 2023;24:925–935. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37541273>.

418. Stein L, Murugesan K, Reeser JW, et al. FGFR2-fusions define a clinically actionable molecular subset of pancreatic cancer. *NPJ Precis Oncol* 2024;8:207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/39289482>.

419. Subbiah V, Lassen U, Elez E, et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol* 2020;21:1234–1243. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32818466>.

420. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAF(V600E) Mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol* 2020;38:3895–3904. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32758030>.

421. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol* 2022;23:1261–1273. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36108661>.

422. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. *J Clin Oncol* 2024;42:47–58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37870536>.

423. Schram AM, Yang SR, Kahn G, et al. NRG1 fusion-positive solid tumors: clinical detection, genomic landscape, and real-world data in pancreatic cancer. *J Natl Cancer Inst* 2025. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/41390931>.

424. Ribas A. Releasing the Brakes on Cancer Immunotherapy. *N Engl J Med* 2015;373:1490–1492. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26348216>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

425. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015;372:2509–2520. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26028255>.

426. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409–413. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28596308>.

427. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol* 2020;38:1–10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31682550>.

428. Maio M, Ascierto PA, Manzyuk L, et al. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. *Ann Oncol* 2022;33:929–938. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35680043>.

429. Le DT, Diaz LA, Jr., Kim TW, et al. Pembrolizumab for previously treated, microsatellite instability-high/mismatch repair-deficient advanced colorectal cancer: final analysis of KEYNOTE-164. *Eur J Cancer* 2023;186:185–195. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37141828>.

430. Georger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. *Lancet Oncol* 2020;21:121–133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31812554>.

431. Andre T, Berton D, Curigliano G, et al. Antitumor Activity and Safety of Dostarlimab Monotherapy in Patients With Mismatch Repair Deficient Solid Tumors: A Nonrandomized Controlled Trial. *JAMA Netw Open* 2023;6:e2341165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37917058>.

432. Schenker M, Burotto M, Richardet M, et al. Abstract CT022: CheckMate 848: A randomized, open-label, phase 2 study of nivolumab in combination with ipilimumab or nivolumab monotherapy in patients with advanced or metastatic solid tumors of high tumor mutational burden. *Cancer Research* 2022;82:CT022–CT022. Available at: <https://doi.org/10.1158/1538-7445.AM2022-CT022>.

433. Ludmir EB, Sherry AD, Fellman BM, et al. Addition of Metastasis-Directed Therapy to Systemic Therapy for Oligometastatic Pancreatic Ductal Adenocarcinoma (EXTEND): A Multicenter, Randomized Phase II Trial. *J Clin Oncol* 2024;42:3795–3805. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/39102622>.

434. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015;33:244–250. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25366685>.

435. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *N Engl J Med* 2019;381:317–327. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31157963>.

436. Philip PA, Mooney M, Jaffe D, et al. Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment. *J Clin Oncol* 2009;27:5660–5669. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19858397>.

437. Van Laethem JL, Verslype C, Iovanna JL, et al. New strategies and designs in pancreatic cancer research: consensus guidelines report from a European expert panel. *Ann Oncol* 2012;23:570–576. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21810728>.

438. Tempero MA, Berlin J, Ducreux M, et al. Pancreatic cancer treatment and research: an international expert panel discussion. *Ann Oncol* 2011;22:1500–1506. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21199884>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

439. Tempero MA, Klimstra D, Berlin J, et al. Changing the way we do business: recommendations to accelerate biomarker development in pancreatic cancer. *Clin Cancer Res* 2013;19:538–540. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23344262>.

440. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014;32:1277–1280. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24638016>.

441. Rahib L, Fleshman JM, Matrisian LM, Berlin JD. Evaluation of Pancreatic Cancer Clinical Trials and Benchmarks for Clinically Meaningful Future Trials: A Systematic Review. *JAMA Oncol* 2016;2:1209–1216. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27270617>.

442. Philip PA, Chansky K, LeBlanc M, et al. Historical controls for metastatic pancreatic cancer: benchmarks for planning and analyzing single-arm phase II trials. *Clin Cancer Res* 2014;20:4176–4185. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24914040>.

443. Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm—general principles. *Nat Clin Pract Oncol* 2007;4:86–100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17259930>.

444. Boyle J, Czito B, Willett C, Palta M. Adjuvant radiation therapy for pancreatic cancer: a review of the old and the new. *J Gastrointest Oncol* 2015;6:436–444. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26261730>.

445. Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol Phys* 2013;86:516–522. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23562768>.

446. Rwigema JC, Parikh SD, Heron DE, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the

pancreas. *Am J Clin Oncol* 2011;34:63–69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20308870>.

447. Tozzi A, Comito T, Alongi F, et al. SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience. *Radiat Oncol* 2013;8:148. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23799996>.

448. Wild AT, Hiniker SM, Chang DT, et al. Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions. *J Gastrointest Oncol* 2013;4:343–351. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24294505>.

449. Zhong J, Patel K, Switchenko J, et al. Outcomes for patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiation therapy versus conventionally fractionated radiation. *Cancer* 2017;123:3486–3493. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28493288>.

450. Rao AD, Sugar EA, Chang DT, et al. Patient-reported outcomes of a multicenter phase 2 study investigating gemcitabine and stereotactic body radiation therapy in locally advanced pancreatic cancer. *Pract Radiat Oncol* 2016;6:417–424. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27552809>.

451. Wild AT, Herman JM, Dholakia AS, et al. Lymphocyte-Sparing Effect of Stereotactic Body Radiation Therapy in Patients With Unresectable Pancreatic Cancer. *Int J Radiat Oncol Biol Phys* 2016;94:571–579. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26867885>.

452. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985;120:899–903. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/4015380>.

453. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-



NCCN Guidelines Version 2.2026

Pancreatic Adenocarcinoma

fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer* 1981;48:1705–1710. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7284971>.

454. Klinkenbijn JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999;230:776–782; discussion 782–774. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10615932>.

455. Smeenk HG, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Ann Surg* 2007;246:734–740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17968163>.

456. Crane CH, Ben-Josef E, Small W, Jr. Chemotherapy for pancreatic cancer. *N Engl J Med* 2004;350:2713–2715; author reply 2713–2715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15218575>.

457. Koshy MC, Landry JC, Cavanaugh SX, et al. A challenge to the therapeutic nihilism of ESPAC-1. *Int J Radiat Oncol Biol Phys* 2005;61:965–966. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15752874>.

458. Morris SL, Beasley M, Leslie M. Chemotherapy for pancreatic cancer. *N Engl J Med* 2004;350:2713–2715; author reply 2713–2715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15215490>.

459. Van Laethem JL, Hammel P, Mornex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol* 2010;28:4450–4456. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20837948>.

460. Schmidt J, Abel U, Debus J, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic

adenocarcinoma. *J Clin Oncol* 2012;30:4077–4083. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23008325>.

461. Ren F, Xu YC, Wang HX, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, for resectable advanced pancreatic adenocarcinoma: continue or stop? *Pancreatol* 2012;12:162–169. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22487527>.

462. Liao WC, Chien KL, Lin YL, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Lancet Oncol* 2013;14:1095–1103. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24035532>.

463. Kooby DA, Gillespie TW, Liu Y, et al. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: an appraisal of data from the national cancer data base. *Ann Surg Oncol* 2013;20:3634–3642. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23771249>.

464. Morganti AG, Falconi M, van Stiphout RG, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2014;90:911–917. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25220717>.

465. Abrams RA, Winter KA, Safran H, et al. Results of the NRG Oncology/RTOG 0848 Adjuvant Chemotherapy Question-Erlotinib+Gemcitabine for Resected Cancer of the Pancreatic Head: A Phase II Randomized Clinical Trial. *Am J Clin Oncol* 2020;43:173–179. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31985516>.

466. Ma T, Bai X, Wei Q, et al. Adjuvant therapy with gemcitabine and stereotactic body radiation therapy versus gemcitabine alone for resected stage II pancreatic cancer: a prospective, randomized, open-label, single center trial. *BMC Cancer* 2022;22:865. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35941566>.

467. Neoptolemos JP, Stocken DD, Dunn JA, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

controlled trial. *Ann Surg* 2001;234:758–768. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/11729382>.

468. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol* 2008;26:3503–3510. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18640931>.

469. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975–2005). *J Clin Oncol* 2008;26:3511–3516. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/18640932>.

470. Hsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Ann Surg Oncol* 2010;17:981–990. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/20087786>.

471. Butturini G, Stocken DD, Wente MN, et al. Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. *Arch Surg* 2008;143:75–83; discussion 83. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/18209156>.

472. Redmond KJ, Wolfgang CL, Sugar EA, et al. Adjuvant chemoradiation therapy for adenocarcinoma of the distal pancreas. *Ann Surg Oncol* 2010;17:3112–3119. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/20680697>.

473. Chen Y, Sun XJ, Jiang TH, Mao AW. Combined radiochemotherapy in patients with locally advanced pancreatic cancer: a meta-analysis. *World J Gastroenterol* 2013;19:7461–7471. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/24259979>.

474. Blackstock AW, Tepper JE, Niedwiecki D, et al. Cancer and leukemia group B (CALGB) 89805: phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas. *Int J*

Gastrointest Cancer 2003;34:107–116. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/15361643>.

475. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2007;68:801–808. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/17379445>.

476. Shibuya K, Oya N, Fujii T, et al. Phase II study of radiation therapy combined with weekly low-dose gemcitabine for locally advanced, unresectable pancreatic cancer. *Am J Clin Oncol* 2010;34:115–119. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20065850>.

477. Loehrer PJ, Sr., Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2011;29:4105–4112. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/21969502>.

478. Huang J, Robertson JM, Margolis J, et al. Long-term results of full-dose gemcitabine with radiation therapy compared to 5-fluorouracil with radiation therapy for locally advanced pancreas cancer. *Radiother Oncol* 2011;99:114–119. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/21621866>.

479. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* 2013;14:317–326. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/23474363>.

480. Hurt CN, Mukherjee S, Bridgewater J, et al. Health-Related Quality of Life in SCALOP, a Randomized Phase 2 Trial Comparing Chemoradiation Therapy Regimens in Locally Advanced Pancreatic Cancer. *Int J Radiat Oncol Biol Phys* 2015;93:810–818. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/26530749>.

481. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst* 1988;80:751–755. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2898536>.

482. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1985;3:373–378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3973648>.

483. Brunner TB, Grabenbauer GG, Kastl S, et al. Preoperative Chemoradiation in Locally Advanced Pancreatic Carcinoma: A Phase II Study. *Onkologie* 2000;23:436–442. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11441238>.

484. Thomas CR, Jr., Weiden PL, Traverso LW, Thompson T. Concomitant intraarterial cisplatin, intravenous 5-fluorouracil, and split-course radiation therapy for locally advanced unresectable pancreatic adenocarcinoma: a phase II study of the Puget Sound Oncology Consortium (PSOC-703). *Am J Clin Oncol* 1997;20:161–165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9124192>.

485. Cinar P, Ko AH. Evolving treatment options for locally advanced unresectable pancreatic ductal adenocarcinoma. *J Natl Compr Canc Netw* 2014;12:167–172. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24586078>.

486. Philip PA. Locally advanced pancreatic cancer: where should we go from here? *J Clin Oncol* 2011;29:4066–4068. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21969514>.

487. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 2008;19:1592–1599. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18467316>.

488. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* 2009;115:665–672. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19117351>.

489. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;78:735–742. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20171803>.

490. Yang W, Reznik R, Fraass BA, et al. Dosimetric evaluation of simultaneous integrated boost during stereotactic body radiation therapy for pancreatic cancer. *Med Dosim* 2015;40:47–52. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25445989>.

491. Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007;25:326–331. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17235048>.

492. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer* 2007;110:47–55. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17538975>.

493. Hurt CN, Falk S, Crosby T, et al. Long-term results and recurrence patterns from SCALOP: a phase II randomised trial of gemcitabine- or capecitabine-based chemoradiation for locally advanced pancreatic cancer. *Br J Cancer* 2017;116:1264–1270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28376080>.

494. Hammel P, Huguet F, van Laethem JL, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA* 2016;315:1844–1853. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27139057>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

495. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer* 2015;121:1128–1137. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25538019>.

496. Schellenberg D, Kim J, Christman-Skieller C, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2011;81:181–188. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21549517>.

497. Bai YR, Wu GH, Guo WJ, et al. Intensity modulated radiation therapy and chemotherapy for locally advanced pancreatic cancer: results of feasibility study. *World J Gastroenterol* 2003;9:2561–2564. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14606097>.

498. Combs SE, Habermehl D, Kessel K, et al. Intensity modulated radiotherapy as neoadjuvant chemoradiation for the treatment of patients with locally advanced pancreatic cancer. Outcome analysis and comparison with a 3D-treated patient cohort. *Strahlenther Onkol* 2013;189:738–744. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23896630>.

499. Crane CH, Antolak JA, Rosen, II, et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. *Int J Gastrointest Cancer* 2001;30:123–132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12540024>.

500. Spalding AC, Jee KW, Vineberg K, et al. Potential for dose-escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions. *Med Phys* 2007;34:521–529. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17388169>.

501. Bittner MI, Grosu AL, Brunner TB. Comparison of toxicity after IMRT and 3D-conformal radiotherapy for patients with pancreatic cancer - a systematic review. *Radiother Oncol* 2015;114:117–121. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25497876>.

502. Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys* 2011;79:158–162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20399035>.

503. Sanford NN, Narang AK, Aguilera TA, et al. NRG Oncology International Consensus Contouring Atlas on Target Volumes and Dosing Strategies for Dose-Escalated Pancreatic Cancer Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2025;121:918–929. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/39510320>.

504. House MG, Choti MA. Palliative therapy for pancreatic/biliary cancer. *Surg Clin North Am* 2005;85:359–371. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15833477>.

505. Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. *Gastrointest Endosc* 2006;63:986–995. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16733114>.

506. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. *Cochrane Database Syst Rev* 2006;2006:CD004200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16625598>.

507. Kitano M, Yamashita Y, Tanaka K, et al. Covered self-expandable metal stents with an anti-migration system improve patency duration without increased complications compared with uncovered stents for distal biliary obstruction caused by pancreatic carcinoma: a randomized multicenter trial. *Am J Gastroenterol* 2013;108:1713–1722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24042190>.

508. Maire F, Hammel P, Ponsot P, et al. Long-term outcome of biliary and duodenal stents in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas. *Am J Gastroenterol* 2006;101:735–742. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16635221>.



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509. Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. *Ann Surg* 1999;230:322–328. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10493479>.

510. Van Heek NT, De Castro SM, van Eijck CH, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. *Ann Surg* 2003;238:894–902; discussion 902–895. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14631226>.

511. Wyse JM, Carone M, Paquin SC, et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol* 2011;29:3541–3546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21844506>.

512. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. *JAMA* 2004;291:1092–1099. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14996778>.

513. Jeurnink SM, Polinder S, Steyerberg EW, et al. Cost comparison of gastrojejunostomy versus duodenal stent placement for malignant gastric outlet obstruction. *J Gastroenterol* 2010;45:537–543. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20033227>.

514. Jeurnink SM, Steyerberg EW, Hof G, et al. Gastrojejunostomy versus stent placement in patients with malignant gastric outlet obstruction: a comparison in 95 patients. *J Surg Oncol* 2007;96:389–396. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17474082>.

515. Jeurnink SM, van Eijck CH, Steyerberg EW, et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol* 2007;7:18. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17559659>.

516. Gurusamy KS, Kumar S, Davidson BR. Prophylactic gastrojejunostomy for unresectable periampullary carcinoma. *Cochrane Database Syst Rev* 2013;2013:CD008533. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23450583>.

517. Gao L, Yang YJ, Xu HY, et al. A randomized clinical trial of nerve block to manage end-stage pancreatic cancerous pain. *Tumour Biol* 2014;35:2297–2301. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24163058>.

518. Lillemoe KD, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. *Ann Surg* 1993;217:447–455; discussion 456–447. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7683868>.

519. Zhong W, Yu Z, Zeng JX, et al. Celiac plexus block for treatment of pain associated with pancreatic cancer: a meta-analysis. *Pain Pract* 2014;14:43–51. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23682788>.

520. Lavu H, Lengel HB, Sell NM, et al. A prospective, randomized, double-blind, placebo controlled trial on the efficacy of ethanol celiac plexus neurolysis in patients with operable pancreatic and periampullary adenocarcinoma. *J Am Coll Surg* 2015;220:497–508. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25667135>.

521. Dominguez-Munoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Curr Gastroenterol Rep* 2007;9:116–122. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17418056>.

522. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut* 2005;54 Suppl 6:vi1–28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15951527>.

523. Sikkens EC, Cahen DL, Kuipers EJ, Bruno MJ. Pancreatic enzyme replacement therapy in chronic pancreatitis. *Best Pract Res Clin Gastroenterol* 2010;24:337–347. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20510833>.



NCCN Guidelines Version 2.2026 Pancreatic Adenocarcinoma

524. Dominguez-Munoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol* 2011;26 Suppl 2:12–16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21323992>.

525. Lemaire E, O'Toole D, Sauvanet A, et al. Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis. *Br J Surg* 2000;87:434–438. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10759738>.

526. Woo SM, Joo J, Kim SY, et al. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. *Pancreatol* 2016;16:1099–1105. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27618657>.

527. Epstein AS, O'Reilly EM. Exocrine pancreas cancer and thromboembolic events: a systematic literature review. *J Natl Compr Canc Netw* 2012;10:835–846. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22773799>.

528. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism in hospitalized neutropenic cancer patients. *J Clin Oncol* 2006;24:484–490. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16421425>.

529. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349:146–153. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12853587>.

530. Pelzer U, Opitz B, Deuschinoff 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25987694>.

531. Wang YU, Yuan C, Liu X. Characteristics of gastrointestinal hemorrhage associated with pancreatic cancer: A retrospective review of 246 cases. *Mol Clin Oncol* 2015;3:902–908. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26171204>.

532. Revel-Mouroz P, Mokrane FZ, Collot S, et al. Hemostatic embolization in oncology. *Diagn Interv Imaging* 2015;96:807–821. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26188637>.

533. Imbesi JJ, Kurtz RC. A multidisciplinary approach to gastrointestinal bleeding in cancer patients. *J Support Oncol* 2005;3:101–110. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15796441>.

534. Lee JA, Lim DH, Park W, et al. Radiation therapy for gastric cancer bleeding. *Tumori* 2009;95:726–730. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20210237>.

535. Thacker PG, Friese JL, Loe M, et al. Embolization of nonliver visceral tumors. *Semin Intervent Radiol* 2009;26:262–269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21326571>.

536. Homma H, Doi T, Mezawa S, et al. A novel arterial infusion chemotherapy for the treatment of patients with advanced pancreatic carcinoma after vascular supply distribution via superselective embolization. *Cancer* 2000;89:303–313. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10918160>.

537. Boyd AD, Brown D, Henrickson C, et al. Screening for depression, sleep-related disturbances, and anxiety in patients with adenocarcinoma of the pancreas: a preliminary study. *ScientificWorldJournal* 2012;2012:650707. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22666142>.

538. Turaga KK, Malafa MP, Jacobsen PB, et al. Suicide in patients with pancreatic cancer. *Cancer* 2011;117:642–647. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20824626>.

539. Wayne JD, Abdalla EK, Wolff RA, et al. Localized adenocarcinoma of the pancreas: the rationale for preoperative chemoradiation. *Oncologist* 2002;7:34–45. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11854545>.