



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pancreatic Adenocarcinoma

Version 1.2021 — October 23, 2020

NCCN.org

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

Continue



***Margaret A. Tempero, MD/Chair † ‡**
UCSF Helen Diller Family
Comprehensive Cancer Center

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

Mahmoud Al-Hawary, MD ¶
University of Michigan
Rogel Cancer Center

Stephen W. Behrman, MD ¶
The University of Tennessee
Health Science Center

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

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

Charles Cha, MD ¶
Yale Cancer Center/
Smilow Cancer Hospital

E. Gabriela Chiorean, MD †
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

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 ¶
The Ohio State University
Comprehensive Cancer Center -
James Cancer Hospital and
Solove Research Institute

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

Efrat Dotan, MD †
Fox Chase Cancer Center

Cristina R. Ferrone, MD ¶
Massachusetts General Hospital
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

William G. Hawkins, MD ¶
Siteman Cancer Center
at Barnes-Jewish Hospital
and Washington University
School of Medicine

Kelsey Klute, MD †
Fred & Pamela Buffett
Cancer Center

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

Noelle LoConte, MD †
University of Wisconsin
Carbone Cancer Center

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

Cassadie Moravek ¥
Pancreatic Cancer Action Network

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

Amol K. Narang, MD §
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Jorge Obando, MD ✖
Duke Cancer Institute

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

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

Jeanne Shen, MD ≠
Stanford Cancer Institute

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

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

Brian M. Wolpin, MD, MPH †
Dana-Farber/Brigham and Women's
Cancer Center

NCCN

Beth Lynn RN, BS, CMSRN
Jennifer Burns
Giby George, MD

✖ Gastroenterology
‡ Hematology/Hematology oncology
† Medical oncology
≠ Pathology
¥ Patient advocacy
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
* Discussion section writing committee



[Pancreatic Adenocarcinoma Panel Members](#) [Summary of Guidelines Updates](#)

[Introduction](#)

- [Clinical Suspicion of Pancreatic Cancer/Evidence of Dilated Pancreatic and/or Bile Duct \(PANC-1\)](#)
- [Resectable Disease, Treatment \(PANC-2\)](#)
- [Borderline Resectable Disease, No Metastases \(PANC-3\)](#)
- [Locally Advanced Disease \(PANC-4\)](#)
- [Unresectable Disease at Surgery \(PANC-6\)](#)
- [Postoperative Adjuvant Treatment \(PANC-7\)](#)
- [Metastatic Disease, First-Line Therapy, and Maintenance Therapy \(PANC-8\)](#)
- [Recurrence After Resection \(PANC-10\)](#)
- [Recurrence Therapy for Metastatic Disease \(PANC-11\)](#)

- [Principles of Diagnosis, Imaging, and Staging \(PANC-A\)](#)
- [Pancreatic Cancer Radiology Reporting Template \(PANC-A, 5 of 8\)](#)
- [Principles of Stent Management \(PANC-B\)](#)
- [Criteria Defining Resectability Status at Diagnosis \(PANC-C, 1 of 2\)](#)
- [Criteria for Resection Following Neoadjuvant Therapy \(PANC-C, 2 of 2\)](#)
- [Principles of Surgical Technique \(PANC-D\)](#)
- [Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-E\)](#)
- [Principles of Systemic Therapy \(PANC-F\)](#)
- [Principles of Radiation Therapy \(PANC-G\)](#)
- [Principles of Palliation and Supportive Care \(PANC-H\)](#)

[Staging \(ST-1\)](#)

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

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

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

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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. ©2020.



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

General Changes:

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

[PANC-1](#)

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

[PANC-2](#)

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

[PANC-5](#)

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

[PANC-6](#)

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

[PANC-7](#)

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

[PANC-A 5 of 8](#)

- Location added: Neck (anterior to SMV/PV confluence)
- Footnote added” See Management of Neck Lesions on PANC-D (2 of 2).

[PANC-D 2 of 2](#)

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

[PANC-E](#)

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

[Continued](#)

UPDATES



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

[PANC-F 4 of 8](#)

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

[PANC-F 5 of 8](#)

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

[PANC-F 6 of 8](#)

- Heading modified: ~~Second-line~~ *Subsequent* Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

[PANC-F 8 of 8](#)

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

[PANC-G](#)

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

[PANC-H](#)

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



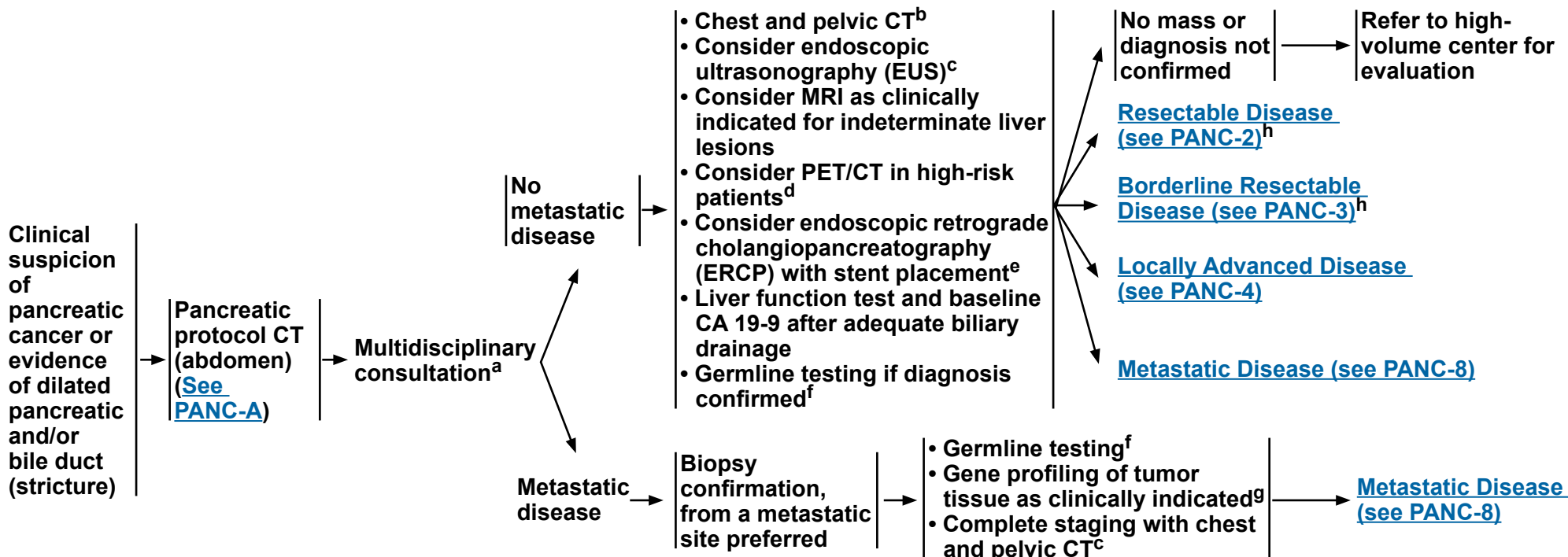
INTRODUCTION

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

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

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

CLINICAL PRESENTATION AND WORKUP



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

^b Imaging with contrast unless contraindicated.

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

^d PET/CT scan may be considered after formal pancreatic CT protocol in high-risk patients to detect extra-pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT. [See Principles of Diagnosis, Imaging, and Staging PANC-A](#).

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

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

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

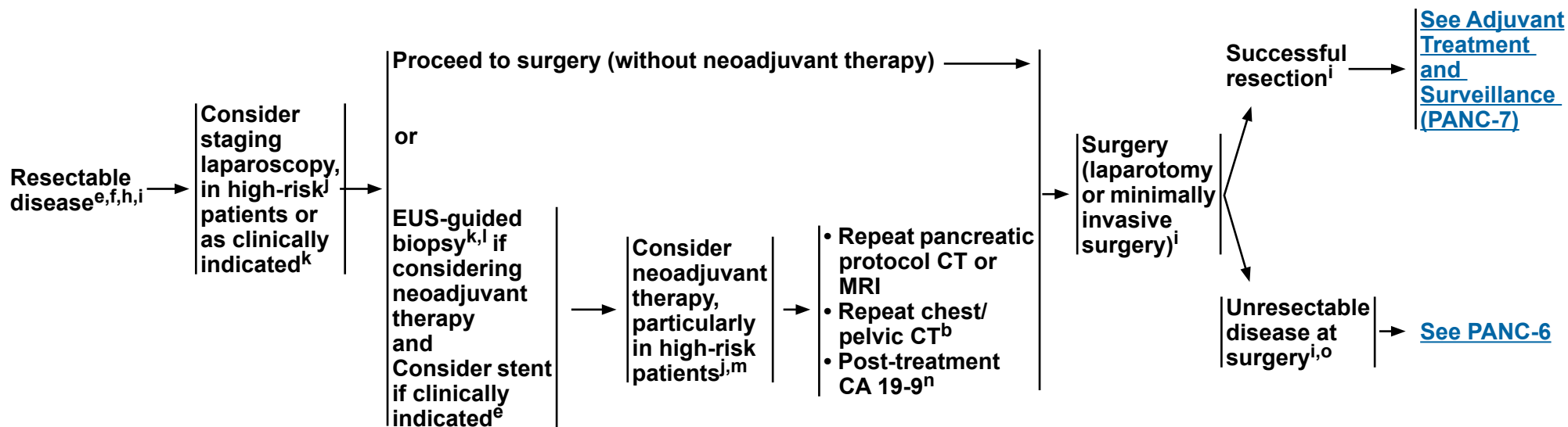
^h [See Criteria Defining Resectability Status at Diagnosis PANC-C](#).

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

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

RESECTABLE DISEASE

TREATMENT



^b Imaging with contrast unless contraindicated.

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

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

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

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

^j High-risk features include imaging findings, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain.

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

^l Core biopsy recommended, if possible, to obtain adequate tissue for possible ancillary studies.

^m There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. See Principles of Systemic Therapy (PANC-F) for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included; see Principles of Radiation Therapy (PANC-G). Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center.

ⁿ Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary infection (cholangitis), inflammation, or obstruction, benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (See Discussion).

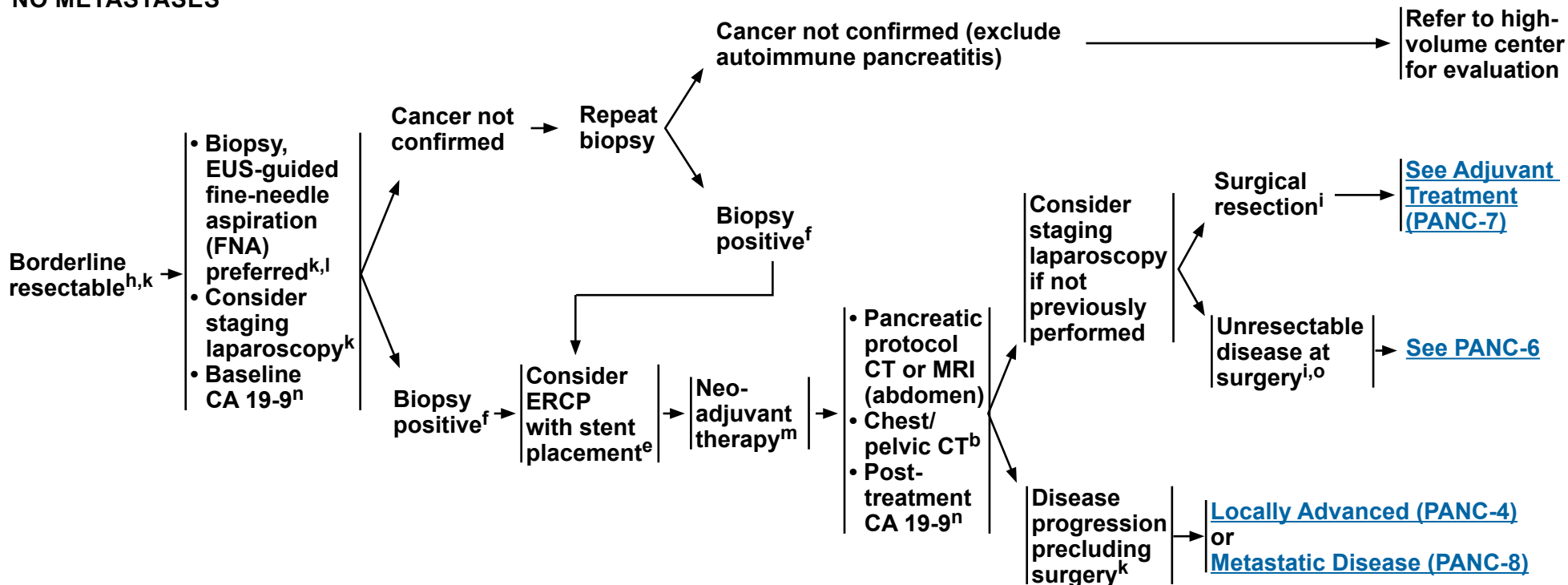
^o See Principles of Palliation and Supportive Care (PANC-H).

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

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

**BORDERLINE RESECTABLE DISEASE
NO METASTASES**

TREATMENT



^b Imaging with contrast unless contraindicated.

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

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

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

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

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

^l Core biopsy recommended, if possible, to obtain adequate tissue for possible ancillary studies.

^m There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. See Principles of Systemic Therapy (PANC-F) for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included; see Principles of Radiation Therapy (PANC-G). Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center.

ⁿ Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary infection (cholangitis), inflammation, or obstruction, benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (See Discussion).

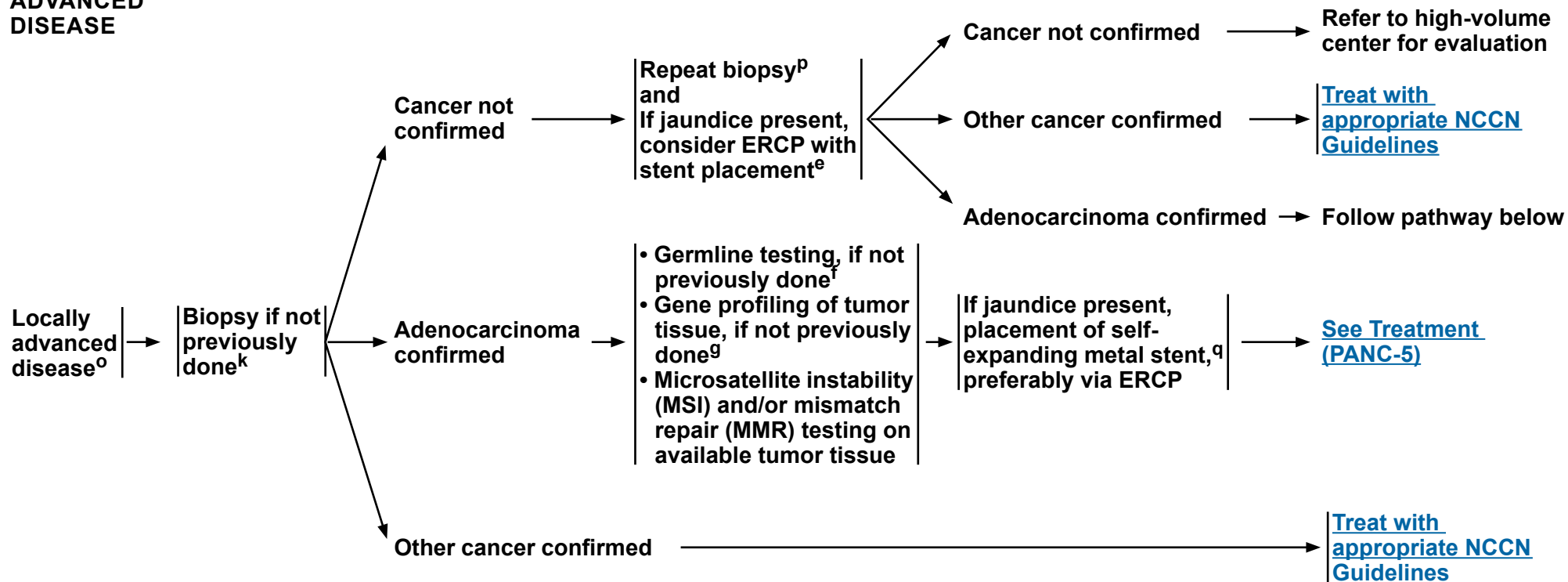
^o See Principles of Palliation and Supportive Care (PANC-H).

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

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

**LOCALLY
ADVANCED
DISEASE**

WORKUP



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

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

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

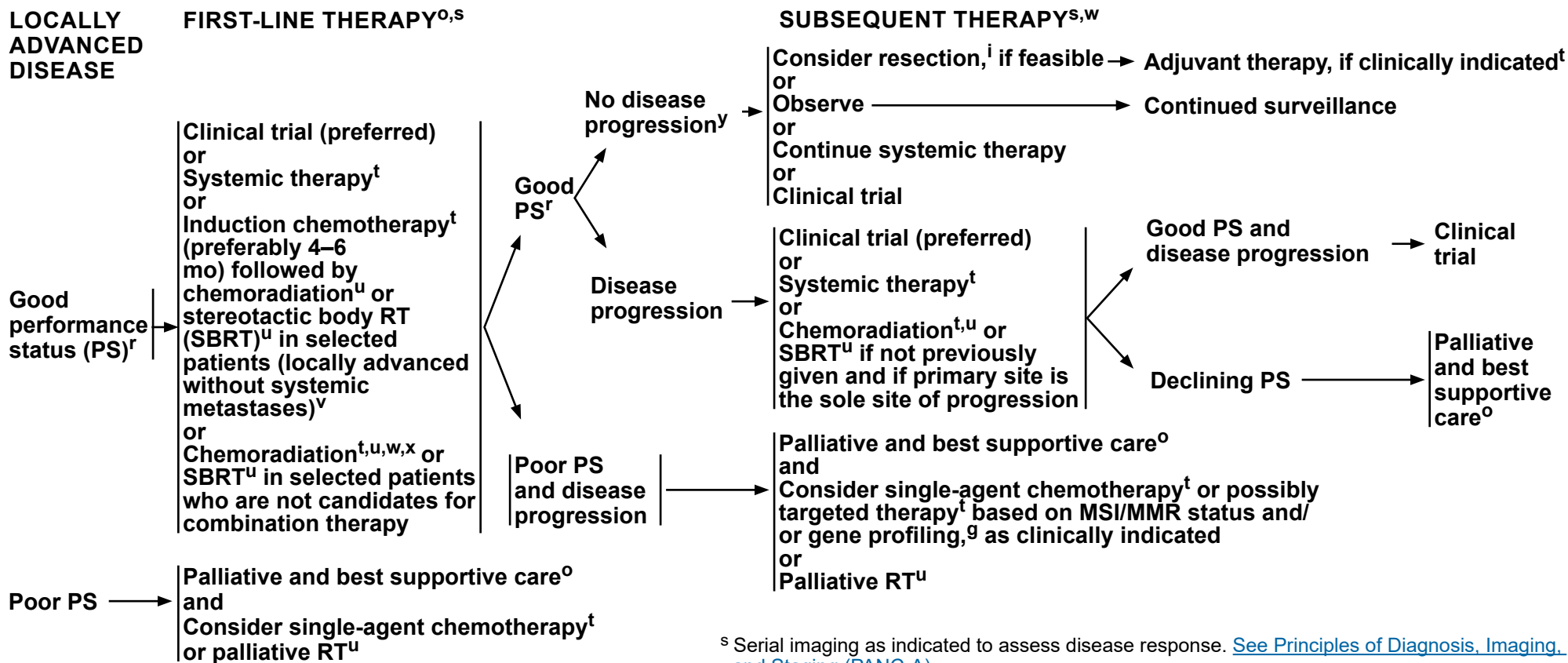
^k See [Principles of Diagnosis, Imaging, and Staging \(PANC-A\)](#).

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

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

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

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



⁹ Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for actionable somatic findings including, but not limited to: fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*), mutations (*BRAF*, *BRCA1/2*, *HER2*, *KRAS*, *PALB2*), and MMR deficiency (detected by tumor IHC, PCR, or NGS). Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. [See Discussion.](#)

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

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

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

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

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

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

^v Laparoscopy as indicated to evaluate distant disease.

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

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

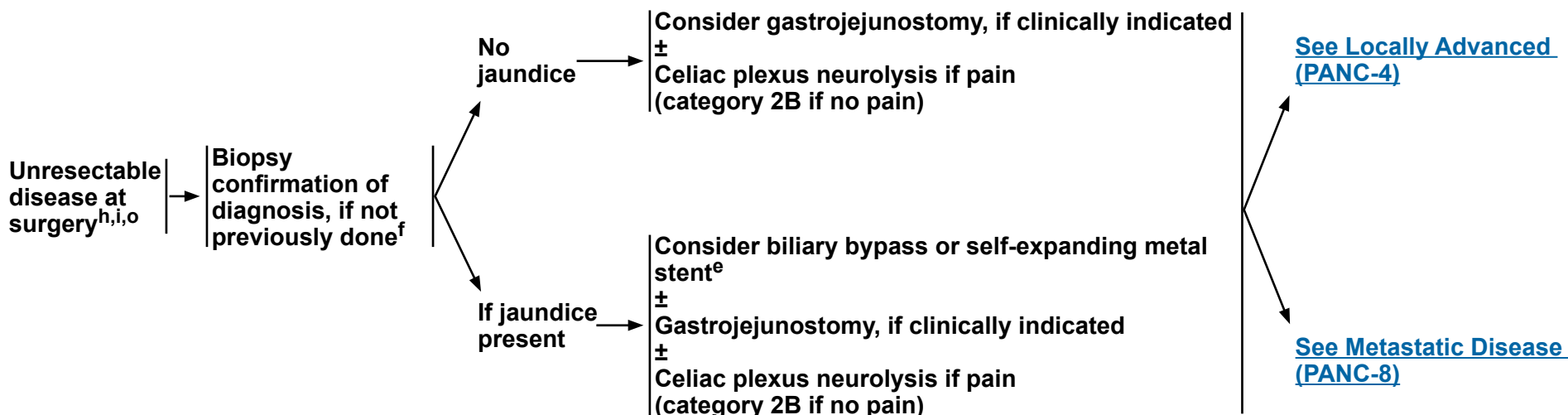
^y In the presence of marked radiographic improvement, the patient should be referred to a high-volume center for consideration of surgery. However, the primary site often does not regress radiographically even in the setting of effective treatment. If there is radiographic stability and marked clinical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

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

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

UNRESECTABLE DISEASE AT SURGERY

TREATMENT



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

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

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

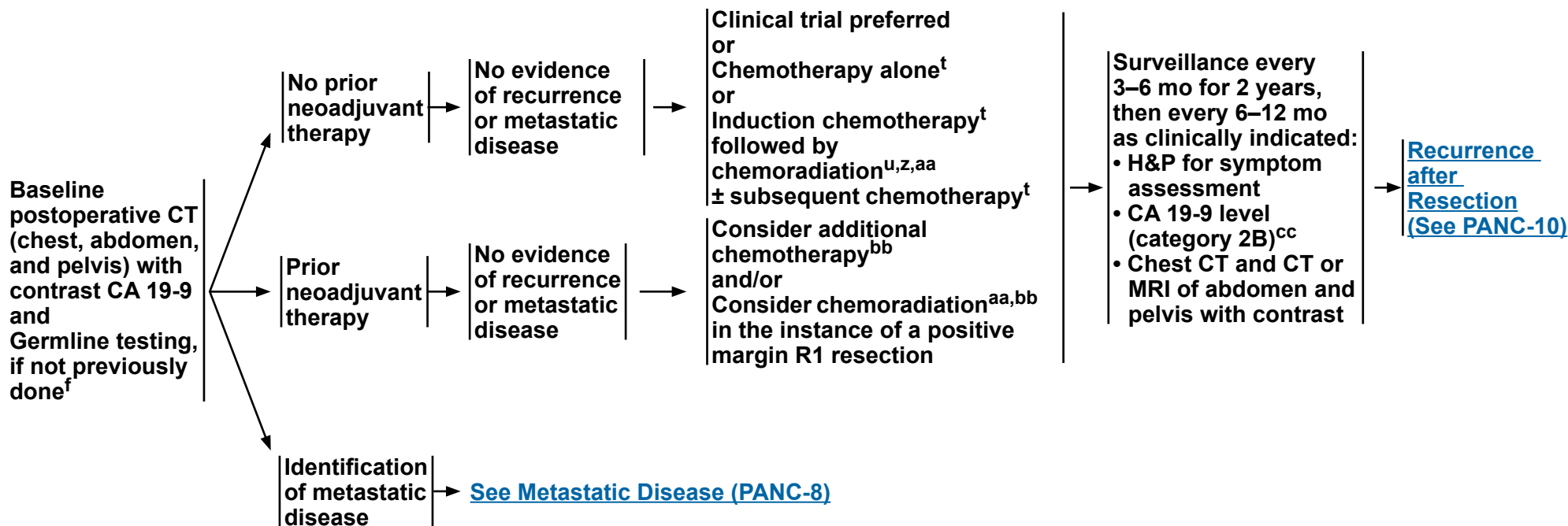
ⁱ See [Principles of Surgical Technique \(PANC-D\)](#) and [Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-E\)](#).

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

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

POSTOPERATIVE ADJUVANT TREATMENT

SURVEILLANCE



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

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

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

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

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

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

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

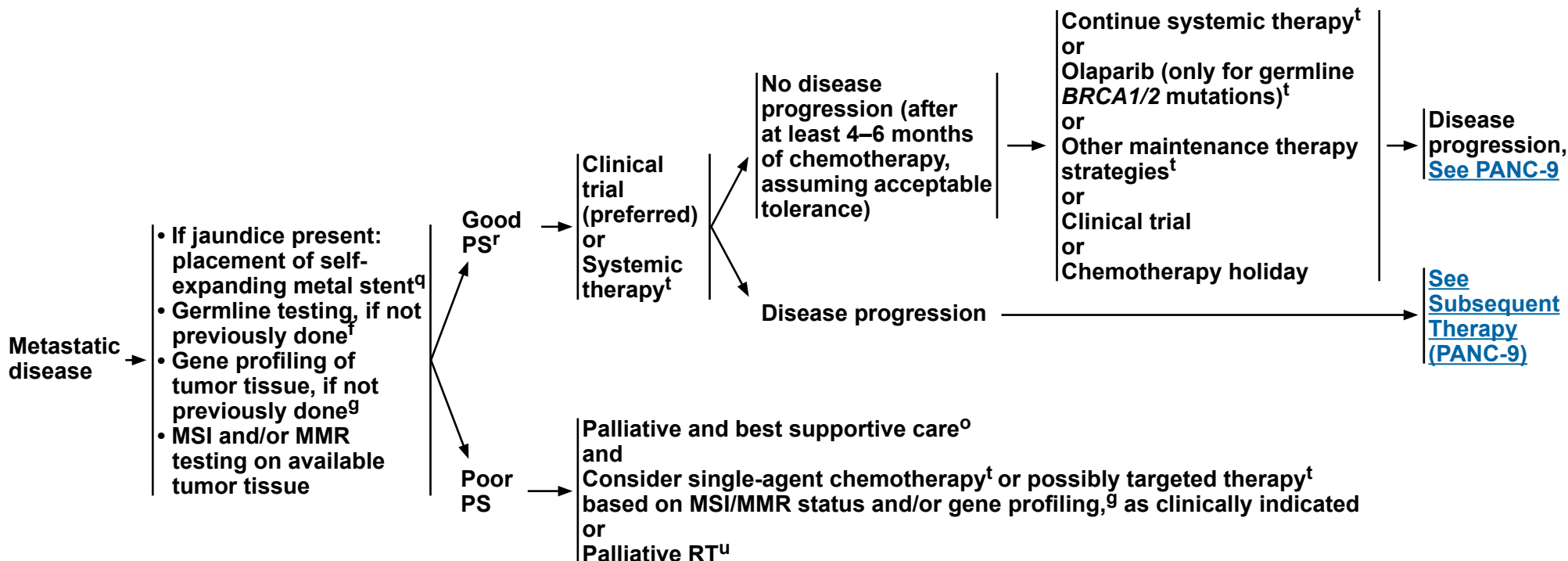
Note: All recommendations are category 2A unless otherwise indicated.

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

METASTATIC DISEASE

FIRST-LINE THERAPY^s

MAINTENANCE THERAPY^s



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

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

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

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

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

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

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

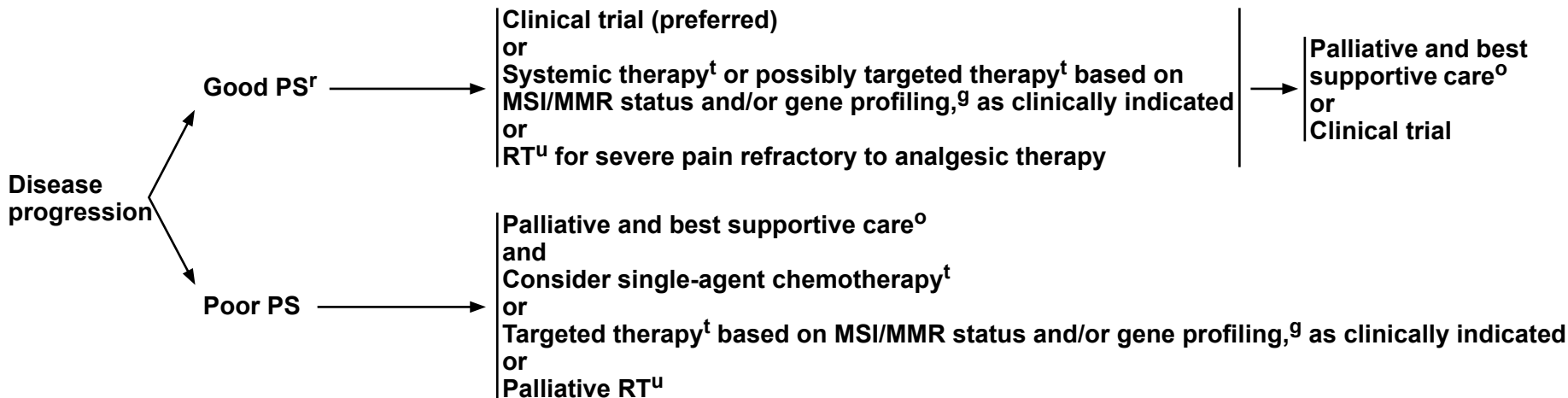
^u [See Principles of Radiation Therapy \(PANC-G\)](#).

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

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

DISEASE PROGRESSION

SUBSEQUENT THERAPY^s



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

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

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

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

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

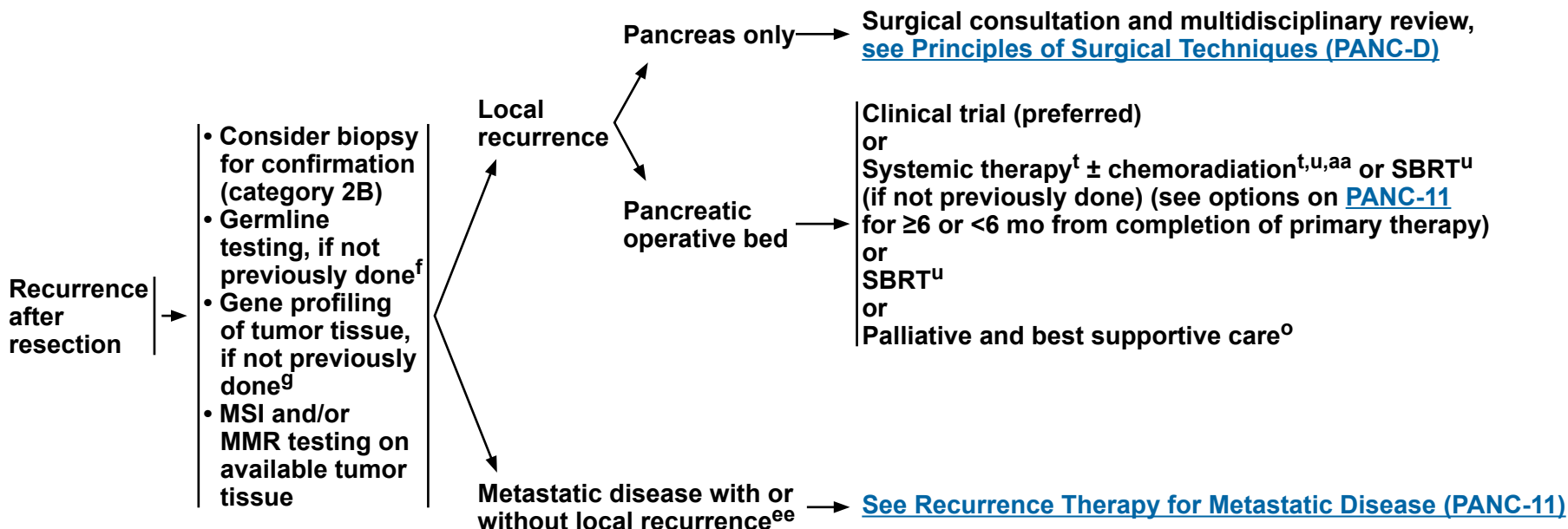
^u [See Principles of Radiation Therapy \(PANC-G\)](#).

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

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

RECURRENCE AFTER RESECTION

RECURRENCE THERAPY^{dd}



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

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

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

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

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

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

^{dd} Best reserved for patients who maintain a good performance status.

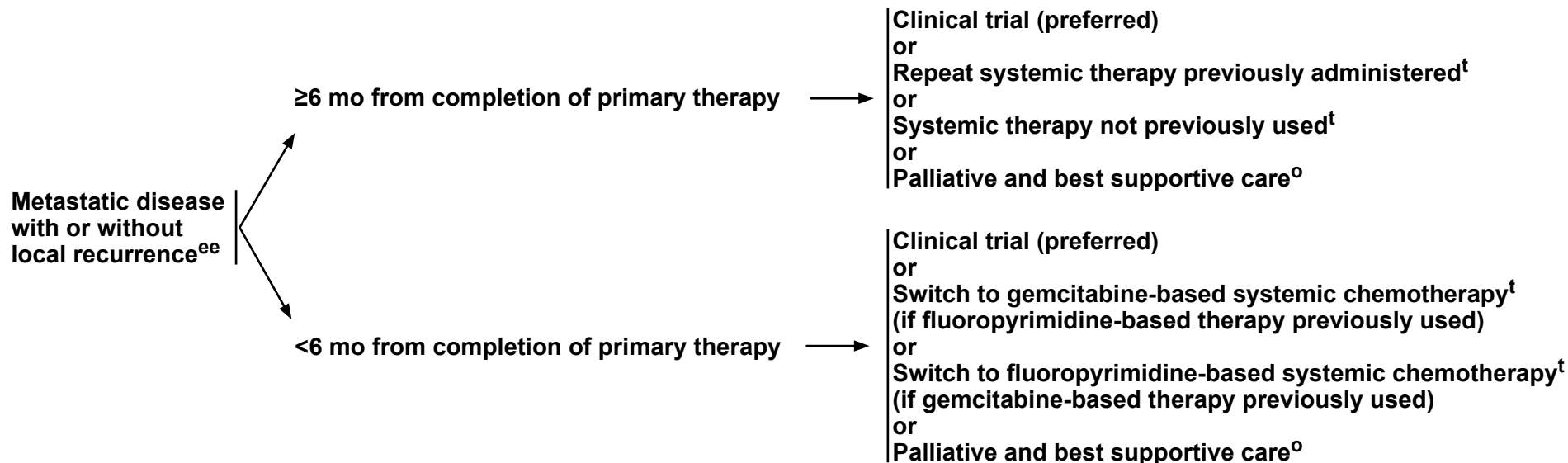
^{ee} For more information about the treatment of isolated pulmonary metastases, [see Discussion](#).

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

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

METASTATIC DISEASE

RECURRENCE THERAPY^{dd}



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

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

^{dd} Best reserved for patients who maintain a good performance status.

^{ee} For more information about the treatment of isolated pulmonary metastases, see Discussion.

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

PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

- Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with reference to appropriate high-quality imaging studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (at least 15–20) of pancreatic resections annually.
- High-quality dedicated imaging of the pancreas should be performed at presentation (even if standard CT imaging is already available), preferably within 4 weeks of surgery, and following neoadjuvant treatment to provide adequate staging and assessment of resectability status. Imaging should be done prior to stenting, when possible.
- Imaging should include dedicated pancreatic CT of abdomen (preferred) or MRI with contrast.
 - ▶ Multidetector computed tomography (MDCT) angiography, performed by acquiring thin, preferably sub-millimeter, axial sections using a dual-phase pancreatic protocol, with images obtained in the pancreatic and portal venous phase of contrast enhancement, is the preferred imaging tool for dedicated pancreatic imaging. Scan coverage can be extended to cover the chest and pelvis for complete staging as per institutional preferences. Multiplanar reconstruction is preferred as it allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits. [See MDCT Pancreatic Adenocarcinoma Protocol, PANC-A \(3 of 8\).](#)
 - ▶ MRI is most commonly used as a problem-solving tool, particularly for characterization of CT-indeterminate liver lesions and when suspected pancreatic tumors are not visible on CT or when contrast-enhanced CT cannot be obtained (as in cases with severe allergy to iodinated intravenous contrast material). This preference for using MDCT as the main imaging tool in many hospitals and imaging centers is mainly due to the higher cost and lack of widespread availability of MRI compared to CT. [See MRI Pancreatic Adenocarcinoma Protocol, PANC-A \(4 of 8\).](#)
- The decision regarding resectability status should be made by consensus at multidisciplinary meetings/discussions following the acquisition of dedicated pancreatic imaging including complete staging. Use of a radiology staging reporting template is preferred to ensure complete assessment and reporting of all imaging criteria essential for optimal staging, which will improve the decision-making process.^a [See Pancreatic Cancer Radiology Reporting Template, PANC-A \(5 of 8\).](#)

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

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

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

PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

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

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

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

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



MDCT Pancreatic Adenocarcinoma Protocol^c

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

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

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

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

PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

MRI Pancreatic Adenocarcinoma Protocol^d

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

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

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

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

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



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

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) ^f	<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	

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

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

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

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

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

Arterial Evaluation				
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		

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

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



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

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	

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

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



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

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

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

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



PRINCIPLES OF STENT MANAGEMENT

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

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

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

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 (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. <p><u>Pancreatic body/tail:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with the CA of $\leq 180^\circ$ • Solid tumor contact with the CA of $>180^\circ$ without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure (some panel members prefer these criteria to be in the locally advanced category). 	<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}	<p><u>Head/uncinate process:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with SMA $>180^\circ$ • Solid tumor contact with the CA $>180^\circ$ <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"> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

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

^b Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans.

^c Distant metastasis (including non-regional lymph node metastasis), regardless of anatomic resectability, implies disease that should not be treated with upfront resection.

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

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

CRITERIA FOR RESECTION FOLLOWING NEOADJUVANT THERAPY^{a-f}

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

Following neoadjuvant therapy:

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

^a Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 2015;261(1):12-7.

^b Macedo FI, Ryon E, Maithel SK, et al. Survival outcomes associated with clinical and pathological response following neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel chemotherapy in resected pancreatic cancer. *Ann Surg* 2019;270(3):400-413.

^c Tsai S, George B, Wittmann D, et al. Importance of normalization of CA19-9 levels following neoadjuvant therapy in patients with localized pancreatic cancer. *Ann Surg* 2020;271:740-747.

^d Michelakos T, Pergolini I, Castillo CF, et al. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. *Ann Surg* 2019;269(4):733-740.

^e Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. *Ann Surg* 2019 Apr 5. [Epub ahead of print]

^f Gilbert JW, Wolpin B, Clancy T, et al. Borderline resectable pancreatic cancer: conceptual evolution and current approach to image-based classification. *Ann Oncol*. 2017;28(9):2067-2076.

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

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

PRINCIPLES OF SURGICAL TECHNIQUE

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

Consider frozen section analysis of the pancreatic neck and bile duct. To avoid cautery artifact that may confound the frozen section, assess the pancreatic neck and bile duct at time of surgery by frozen section approximately 5 mm from the transection margin. If tumor is located within 5 mm of margins, consider further excision of the pancreas and bile duct to ensure at least 5 mm of clearance.

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

Pancreatoduodenectomy (Whipple technique)

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

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

¹ Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. *J Am Coll Surg* 2008;207:510-519.

² Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006;10:1199-1210; discussion 1210-1191.

³ Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. *Curr Probl Cancer* 2002;26:176-275.

⁴ Nakeeb A, Lillemoe KD, Grosfeld JL. Surgical techniques for pancreatic cancer. *Minerva Chir* 2004;59:151-163.

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

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



PRINCIPLES OF SURGICAL TECHNIQUE

Surgery for Locally Recurrent Pancreatic Ductal Adenocarcinoma⁵

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

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

Distal Pancreatectomy with En-bloc Splenectomy

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

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

Management of Neck Lesions

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

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

⁵ Moletta L, Serafini S, Valmasoni M, et al. Surgery for recurrent pancreatic cancer: Is it effective? *Cancers (Basel)* 2019;11(7):991.

⁶ Shoup M, Conlon KC, Klimstra D, et al. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? *J Gastro Surg* 2003;7:946-952; discussion 952.

⁷ Christein JD, Kendrick ML, Iqbal CW, et al. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. *J Gastrointest Surg* 2005;9:922-927.

⁸ Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. *J Am Coll Surg* 2007;204:244-249.

⁹ Hirono S, Kawai M, Okada K, et al. Pancreatic neck cancer has specific and oncologic characteristics regarding portal vein invasion and lymph node metastasis. *Surgery* 2016;159:426-440.

¹⁰ Strasberg SM, Sanchez LA, Hawkins WG, et al. Resection of tumors of the neck of the pancreas with venous invasion: the "Whipple at the Splenic Artery (WATSA)" procedure. *J Gastrointest Surg* 2012;16:1048-1054.

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

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

PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

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

Whipple Specimen

- **Specimen orientation:** Specimen orientation and inking involves both the pathologist and surgeon, as this will help to ensure accurate assessment of the size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method (eg, written on the pathology requisition); for example: the distal and proximal margins of the SMV and SMA and the bile duct margin should be marked.
- **Margins**
 - ▶ **Definitions of the margins and uniformity of nomenclature are critical to accurate reporting.**
 - ◊ **SMA (retroperitoneal/uncinate) Margin:** The most important margin is the soft tissue directly adjacent to the proximal 3–4 cm of the SMA. This margin is often referred to as the “retroperitoneal margin” or “posterior margin,” but has also been referred to as the “uncinate margin” or “mesenteric margin.” More recently, this margin has been referred to as the “SMA margin” to correlate with its location on the specimen. Radial, rather than en face, sections of this margin will more clearly demonstrate how closely this margin is approached by tumor. The uncinata margin should be inked. Rather than being submitted en face, the uncinata margin tissue should be shaved/amputated, then the portion of tissue should be sectioned perpendicular to the ink and submitted entirely for histologic examination.
 - ◊ **Portal Vein Margins:** If an en bloc partial or complete vein resection is added to the surgical specimen, it should be marked separately. En face proximal and distal end margins of the vein should be separately submitted as “Proximal Portal Vein Margin” and “Distal Portal Vein Margin”. A section documenting tumor invasion into the vein wall should also be submitted. If feasible, this section should encompass the full thickness of the vein wall, demonstrating the depth of tumor invasion, as this has been shown to have prognostic value.¹
 - ◊ **Pancreatic Neck (transection) Margin:** This is the en face section of the transected pancreatic neck. Care should be taken when placing the section into the cassette to document the orientation of the section with respect to the true margin (eg, facing down so that the initial section into the block represents the true margin, or facing up so that the initial section represents the surface opposite the true margin).
 - ◊ **Bile Duct Margin:** This is the en face section of the bile duct end. The section should be removed from the unopened duct and care should be taken when placing the section into the cassette to document the orientation of the section with respect to the true margin (eg, facing down so that the initial section into the block represents the true margin, or facing up so that the initial section represents the surface opposite the true margin).
 - ▶ **Other margins analyzed in Whipple specimens include the proximal (gastric or enteric) and distal enteric margins (en face sections).**
 - ▶ **Collectively, these margins and pancreatic tissue surfaces constitute the circumferential surface of the specimen. Designating the various specific margins and surfaces with different colored inks will allow recognition on microscopy.**

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

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

References



PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

• Other Circumferential Surfaces

- ▶ **Posterior (non-SMA margin) Surface:** This surface consists of the posterior caudad aspect of the pancreatic head that is not part of the SMA margin and that appears to be covered by loose connective tissue. Radial, rather than en face, sections of this surface will more clearly demonstrate whether it is involved by tumor. In some instances, this surface may already be included in sections of the SMA margin.
- ▶ **SMV Groove:** Also referred to as the vascular groove surface (and in previous versions of the Guidelines as the Portal Vein Groove Margin), this is the smooth-surfaced groove on the posterior-medial surface of the pancreatic head that rests over the SMV. Radial, rather than en face, sections of this surface will more clearly demonstrate whether it is involved by tumor, and also will provide the distance of the tumor from the surface. As is true for the posterior (non-SMA margin) surface, in some instances, this surface may be included in the same sections as the SMA margin.
- ▶ **Anterior Surface:** The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and is therefore strongly recommended, but not currently required.²⁻⁵ In some cases where the anterior surface is adherent to other structures, from which it is surgically dissected or transected, it should be considered an additional circumferential margin, for which the closest distance from tumor should be reported.

• Histologic Sectioning

- ▶ The approach to histologic sectioning is determined by the unique characteristics of the tumor, but is also influenced by institutional preferences, expertise, and experience. Options include axial, bi- or multi-valve slicing, and perpendicular slicing. Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas.
- ▶ Axial slicing provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum, and pancreas, and all of the pancreatic circumferential tissue margins mentioned above.
- ▶ There is no one correct way to dissect a Whipple specimen. However, knowledge of the clinically suspected lesion is helpful in choosing the best dissection method for examination and appropriate characterization of the lesion. The most important aspects of dissection are clear and accurate assessment of the margins, size of the tumor, and relationship to the relevant structures, such as pancreatic surfaces, margins, bile duct, main pancreatic duct, duodenum, etc.
- ▶ Per the current CAP protocol, the presence of tumor at or within 1 mm of resection margin constitutes a positive margin,^{2,6} although this recommendation is based primarily on extrapolating from data on rectal adenocarcinoma. There is currently a lack of definitive evidence for what constitutes an adequate margin in pancreatic carcinoma resection specimens. A standardized definition of this would allow better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if less than 1-mm clearance is associated with an unacceptably high incidence of local recurrence, then strong consideration for postoperative RT might be indicated if not received preoperatively. Tumor clearance should be reported with millimeter accuracy for all margins where tumor is close (within 1.0 cm or less of the tumor). This may be done using either mm (eg, “2 mm”) or cm (eg, “0.2 cm”). For margins distant from tumor (>1.0 cm from tumor), tumor clearance may be reported with centimeter accuracy.
- ▶ Attached organs resected with the specimen en bloc require serial sectioning to assess not only direct extension, but metastatic deposits as well. One section that demonstrates direct invasion of the organ and/or a separate metastatic deposit is required.

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

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

[References](#)



PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

Distal Pancreatectomy

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

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

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

[References](#)

PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

- The NCCN Pancreatic Cancer Panel currently supports pathology synoptic reports from the College of American Pathologists (CAP). The proposal included herein is an abbreviated minimum analysis of pancreatic cancer specimens from the CAP recommendations. In addition to the standard TNM staging, other variables are included, all of which have prognostic implications in the evolution of this disease.^{7,8}
- Treatment effect should be assessed and reported by the pathologist, as tumor viability may impact postoperative therapy options. For more information about pathologic analysis, refer to the CAP Cancer Protocol Template for carcinoma of the pancreas. (Burgart LJ, Shi C, Adsay VN, et al. Protocol for the Examination of Specimens from Patients with Carcinoma of the Pancreas. College of American Pathologists. Cancer Protocol Templates; 2020.)

Specimen Type

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

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

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

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

[References](#)



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

- ¹ 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.
- ² Verbeke CS, Menon KV. Redefining resection margin status in pancreatic cancer. *HPB (Oxford)* 2009;11(4):282-289.
- ³ 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.
- ⁴ Classification of pancreatic cancer. Japan Pancreas Society. 2nd ed. Tokyo: Kanehara; 2003.
- ⁵ 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.
- ⁶ 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. *Histopathol* 2009;55(3):277-283.
- ⁷ 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.
- ⁸ 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.
- ⁹ 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.

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



PRINCIPLES OF SYSTEMIC THERAPY

General Principles:

- Systemic therapy is used in all stages of pancreatic cancer. This includes neoadjuvant therapy (resectable or borderline resectable), adjuvant therapy, and first-line or subsequent therapy for locally advanced, metastatic, and recurrent disease.
- Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.
- Close follow-up of patients undergoing chemotherapy is indicated.
- For regimens where RT or chemoradiation is included, [see Principles of Radiation Therapy \(PANC-G\)](#) for more details related to radiation delivery, including recommended technique and dose.
- To optimize the care of older adults, see [NCCN Guidelines for Older Adult Oncology](#).

Neoadjuvant Therapy (Resectable/Borderline Resectable Disease)

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

Preferred Regimens

- FOLFIRINOX or modified FOLFIRINOX^a ± subsequent chemoradiation^b
- Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation^b

Only for known BRCA1/2 or PALB2 mutations:

- FOLFIRINOX or modified FOLFIRINOX^a ± subsequent chemoradiation^b
- Gemcitabine + cisplatin (≥2–6 cycles) ± subsequent chemoradiation^b

Other Recommended Regimens

- None

Useful in Certain Circumstances

- None

^a FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1.

^b [See Chemoradiation \(PANC-F, 7 of 8\)](#).

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

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Adjuvant Therapy

- The CONKO 001 trial demonstrated significant improvements in DFS and OS with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.¹
- ESPAC-3 study results showed no significant difference in OS between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.²
- Data from ESPAC-4 support the use of gemcitabine combined with capecitabine (1,660 mg/m²/day days 1–21 every 4 weeks) with superiority demonstrated compared to gemcitabine alone (HR, 0.82; 95% CI, 0.68, 0.98; P = .032).³
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment.⁴
- Recommended adjuvant therapy options apply to patients who did not receive prior neoadjuvant therapy. For those who received prior neoadjuvant therapy, the adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

<u>Preferred Regimens</u>	<u>Other Recommended Regimens</u>	<u>Useful in Certain Circumstances</u>
<ul style="list-style-type: none"> • Modified FOLFIRINOX (category 1)^a • Gemcitabine + capecitabine (category 1) 	<ul style="list-style-type: none"> • Gemcitabine (category 1) • 5-FU + leucovorin (category 1) • Continuous infusion 5-FU • Capecitabine (category 2B) • Induction chemotherapy (gemcitabine, 5-FU + leucovorin, or continuous infusion 5-FU) followed by chemoradiation^{b,c} • Induction chemotherapy (gemcitabine, 5-FU + leucovorin, or continuous infusion 5-FU) followed by chemoradiation^{b,c} followed by subsequent chemotherapy:⁴ <ul style="list-style-type: none"> ▶ Gemcitabine followed by chemoradiation^{b,c} followed by gemcitabine ▶ Bolus 5-FU + leucovorin followed by chemoradiation^{b,c} followed by bolus 5-FU + leucovorin ▶ Continuous infusion 5-FU followed by chemoradiation^{b,c} followed by continuous infusion 5-FU 	<ul style="list-style-type: none"> • None

^a FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1.

^b [See Chemoradiation \(PANC-F, 7 of 8\)](#).

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

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

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

[References](#)



PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced Disease (First-Line Therapy)

	<u>Preferred Regimens</u>	<u>Other Recommended Regimens</u>	<u>Useful in Certain Circumstances</u>
Good PS	<ul style="list-style-type: none"> • FOLFIRINOX or modified FOLFIRINOX^{d,e,f,6} • Gemcitabine + albumin-bound paclitaxel^{d,f,7} <p>Only for known BRCA1/2 or PALB2 mutations:</p> <ul style="list-style-type: none"> • FOLFIRINOX or modified FOLFIRINOX^{d,e,f,6} • Gemcitabine + cisplatin¹⁰ 	<ul style="list-style-type: none"> • Gemcitabine + erlotinib^{9,8} • Gemcitabine + capecitabine⁹ • Gemcitabine • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)¹¹ (category 2B) • Fluoropyrimidine + oxaliplatin (5-FU + leucovorin + oxaliplatin [OFF]¹² or CapeOx¹³) (category 2B) 	<ul style="list-style-type: none"> • Induction chemotherapy with any of the preferred/other regimens (≥4–6 cycles) followed by chemoradiation^{b,h} or SBRT¹⁴ (in selected patients, locally advanced disease without systemic metastases)¹⁵ • Chemoradiation^{b,i} or SBRTⁱ (in select patients who are not candidates for combination therapy)
Poor PS	<ul style="list-style-type: none"> • Gemcitabine <ul style="list-style-type: none"> ▶ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▶ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • None

[See Subsequent Therapy on PANC-F \(6 of 8\)](#)

^b [See Chemoradiation \(PANC-F, 7 of 8\)](#).

^d The recommendations for FOLFIRINOX or modified FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.

^e Due to the high toxicity of this regimen, bolus 5-FU is often omitted.

^f FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.

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

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

ⁱ If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation or SBRT.

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

References

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

PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

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

	<u>Preferred Regimens</u>	<u>Other Recommended Regimens</u>	<u>Useful in Certain Circumstances</u>
Good PS	<ul style="list-style-type: none"> • FOLFIRINOX (category 1) or modified FOLFIRINOX^{e,f,6} • Gemcitabine + albumin-bound paclitaxel^{f,7} (category 1) <p>Only for known BRCA1/2 or PALB2 mutations:</p> <ul style="list-style-type: none"> • FOLFIRINOX (category 1) or modified FOLFIRINOX^{e,f,6} • Gemcitabine + cisplatin¹⁰ 	<ul style="list-style-type: none"> • Gemcitabine + erlotinib^{9,8} (category 1) • Gemcitabine (category 1) • Gemcitabine + capecitabine⁹ • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)¹¹ (category 2B) • Fluoropyrimidine + oxaliplatin (eg, 5-FU + leucovorin + oxaliplatin [OFF]¹² or CapeOx¹³) (category 2B) 	<ul style="list-style-type: none"> • None
Poor PS	<ul style="list-style-type: none"> • Gemcitabine <ul style="list-style-type: none"> ▶ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▶ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Pembrolizumab^{j,16} (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if NTRK gene fusion positive) (category 2B)

[See Maintenance Therapy for Metastatic Disease on PANC-F \(5 of 8\)](#)

[See Subsequent Therapy on PANC-F \(6 of 8\)](#)

^e Due to the high toxicity of this regimen, bolus 5-FU is often omitted.

^f FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.

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

^j See [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

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

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (Maintenance Therapy)

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

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> • If previous platinum-based chemotherapy: <ul style="list-style-type: none"> ▶ Olaparib (only for germline <i>BRCA1/2</i> mutations) 	<ul style="list-style-type: none"> • Clinical trial or • If previous first-line FOLFIRINOX: <ul style="list-style-type: none"> ▶ Capecitabine or • If previous first-line gemcitabine + nab-paclitaxel: <ul style="list-style-type: none"> ▶ Gemcitabine + nab-paclitaxel modified schedule (category 2B) ▶ Gemcitabine single agent (category 2B) 	<ul style="list-style-type: none"> • If previous first-line FOLFIRINOX: <ul style="list-style-type: none"> ▶ 5-FU ± irinotecan^k ▶ FOLFOX^l (category 2B)

[See Subsequent Therapy on PANC-F \(6 of 8\)](#)

^k 5-FU ± irinotecan may be considered for maintenance therapy in the case of oxaliplatin-related progressive neuropathy or allergy to oxaliplatin.

^l While FOLFOX is not commonly used in the maintenance setting, it may be considered as an alternative to irinotecan-based therapy when GI toxicity is a concern.

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

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

References



PRINCIPLES OF SYSTEMIC THERAPY

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

	<u>Preferred Regimens</u>	<u>Other Recommended Regimens</u>	<u>Useful in Certain Circumstances</u>	
Good PS	<ul style="list-style-type: none"> • None 	<p>(If prior gemcitabine-based therapy)</p> <ul style="list-style-type: none"> • 5-FU + leucovorin + liposomal irinotecan^{f,17} (category 1 for metastatic disease) • 5-FU + leucovorin + irinotecan (FOLFIRI)¹⁸⁻²⁰ • FOLFIRINOX or modified FOLFIRINOX^f • Oxaliplatin + 5-FU + leucovorin (OFF) • FOLFOX • Capecitabine + oxaliplatin • Capecitabine • Continuous infusion 5-FU 	<p>(If prior fluoropyrimidine-based therapy)</p> <ul style="list-style-type: none"> • Gemcitabine • Gemcitabine + albumin-bound paclitaxel^f • Gemcitabine + cisplatin (only for known BRCA1/2 or PALB2 mutations) • Gemcitabine + erlotinib • 5-FU + leucovorin + liposomal irinotecan^f (if no prior irinotecan) 	<ul style="list-style-type: none"> • Pembrolizumab^j (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if NTRK gene fusion positive) • Chemoradiation,^{b,c} if not previously given, only an option for: <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
Poor PS	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Gemcitabine <ul style="list-style-type: none"> ▶ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▶ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) 	<ul style="list-style-type: none"> • Pembrolizumab^j (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if NTRK gene fusion positive) (category 2B) 	

^b See Chemoradiation (PANC-F, 7 of 8).

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

^f FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.

^j See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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

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

References



PRINCIPLES OF SYSTEMIC THERAPY

Chemoradiation

Preferred Regimens

- Capecitabine + concurrent RT
- Continuous infusion 5-FU + concurrent RT

Other Recommended Regimens

- Gemcitabine + concurrent RT⁵

Useful in Certain Circumstances

- None

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

[References](#)

PRINCIPLES OF SYSTEMIC THERAPY REFERENCES

- 1 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.
- 2 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.
- 3 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.
- 4 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.
- 5 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.
- 6 Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817-1825.
- 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 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.
- 9 Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. *J Clin Oncol* 2009;27:5513-5518.
- 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 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.
- 12 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.
- 13 Xiong HQ, Varadhachary GR, Blais JC, et al. A phase II trial of oxaliplatin plus capecitabine (xelox) as second-line therapy for patients with advanced pancreatic cancer. *Cancer* 2008;113:2046-2052.
- 14 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.
- 15 Loehrer PJ Sr, Feng Y, Cardenas 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.
- 16 Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase 2 KEYNOTE-158 study. *J Clin Oncol* 2020;38:1-10.
- 17 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.
- 18 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.
- 19 Neuzillet C, Hentic O, Rousseau B, et al. FOLFIRI regimen in metastatic pancreatic adenocarcinoma resistant to gemcitabine and platinum-salts. *World J Gastroenterol* 2012;18:4533-41.
- 20 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;69:1641-5.
- 21 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;101:1658-63.

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

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



PRINCIPLES OF RADIATION THERAPY

General Principles:

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

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

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

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

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

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

[References](#)



PRINCIPLES OF RADIATION THERAPY TREATMENT PLANNING: RADIATION DELIVERY

Simulation:

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

Motion Management:³

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

Planning, Dose and Fractionation:

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

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

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

[References](#)

PRINCIPLES OF RADIATION THERAPY RECOMMENDATIONS BASED ON TREATMENT SETTING

Resectable/Borderline Resectable:

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

Resected (Adjuvant):^a

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

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

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

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



PRINCIPLES OF RADIATION THERAPY RECOMMENDATIONS BASED ON TREATMENT SETTING

Locally Advanced^{14,15}

- The goal of RT is to prevent or delay local progression (that may result in pain or local obstructive symptoms) and facilitate local disease control, and in some instances help facilitate R0 resection in patients considered for surgery.
- Data are limited to support specific RT recommendations for locally advanced disease. Options may include:
 - ▶ Induction chemotherapy followed by chemoradiation or SBRT in select patients (locally advanced without systemic metastases)^{b,c,17-21}
 - ▶ Chemoradiation¹⁶ or SBRT^{b,c} in selected patients who are not candidates for combination chemotherapy.
- RT Dosing/Planning:
 - ▶ For chemoradiation, RT dose generally consists of 45–54 Gy in 1.8–2.0 Gy fractions.
 - ▶ There are limited data to support a specific RT dosing for SBRT; therefore, it should preferably be utilized as part of a clinical trial or at an experienced, high-volume center. SBRT doses of 3 fractions (total dose 30–45 Gy) or 5 fractions (total dose 25–45 Gy) have been reported as have more protracted courses delivering high doses through a hypofractionated approach.²² However, caution is warranted when utilizing higher doses and normal tissue constraints must be respected.²¹ This approach is optimally performed in the setting of a clinical trial.

Recurrent Pancreatic Cancer (pancreatic bed):

- Data are limited to support specific RT recommendations for locally recurrent pancreatic cancer; the options for patients with recurrent, unresectable disease may include:
 - ▶ Induction chemotherapy followed by chemoradiation or SBRT (if not previously performed) ([See Principles of Systemic Therapy \[PANC-F\]](#))
 - ▶ Chemoradiation¹⁶ or SBRT^{b,c} in selected patients who are not candidates for induction chemotherapy.
- RT Dosing/Planning:
 - ▶ For chemoradiation, RT dose generally consists of 45–54 Gy in 1.8–2.0 Gy fractions.
 - ▶ There are limited data to support a specific RT dosing for SBRT; therefore, it should preferably be utilized as part of a clinical trial or at an experienced, high-volume center. SBRT doses of 3 fractions (total dose 30–45 Gy) or 5 fractions (total dose 25–45 Gy) have been reported as have more protracted courses delivering high doses through a hypofractionated approach.
 - ▶ However, caution is warranted when utilizing higher doses and normal tissue constraints must be respected.²¹ This approach is optimally performed in the setting of a clinical trial.

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

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

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

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

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

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

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

^d Adapted from RTOG 1102 (IMRT, 2.2–54 Gy).

^e Adapted from RTOG 0848 (3D or IMRT).

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

[References](#)

PRINCIPLES OF RADIATION THERAPY

Table 2: Commonly Used Radiation Therapy Abbreviations

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

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

[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(10):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 Katz MH, Crane CH, Varadhachary G. Management of borderline resectable pancreatic cancer. *Semin Radiat Oncol* 2014;24:105-112.
- 7 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(8):e161137.
- 8 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(7):963-969.
- 9 White RR, Hurwitz HI, Morse MA, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol* 2001;8:758-765.
- 10 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.
- 11 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 Jul 1;68:801-808.
- 12 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.
- 13 RTOG 0848: <https://clinicaltrials.gov/ct2/show/NCT01013649>
- 14 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(17):1844-1853.
- 15 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(7):1020-1027.
- 16 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.
- 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 Koay EJ, Hanania AN, Hall WA, et al. Dose-escalated radiation therapy for pancreatic cancer: a simultaneous integrated boost approach. *Pract Radiat Oncol* 2020;1879.
- 23 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.
- 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 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.

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

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

PRINCIPLES OF 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"> • Good performance status <ul style="list-style-type: none"> ▶ Gastrojejunostomy (open or laparoscopic) ± J-tube ▶ Consider enteral stent^b • Poor performance status <ul style="list-style-type: none"> ▶ Enteral stent^b ▶ Venting percutaneous endoscopic gastrostomy (PEG) tube for gastric decompression
Severe tumor-associated abdominal pain unresponsive to optimal, around-the-clock analgesic administration, or if patient experiences undesirable analgesic-associated side effects (See NCCN Guidelines for Adult Cancer Pain)	<ul style="list-style-type: none"> • EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable) • Consider palliative radiation with or without chemotherapy if not already given as part of primary therapy regimen. See Principles of Radiation Therapy (PANC-G).
Depression, pain, and malnutrition (See NCCN Guidelines for Supportive Care)	<ul style="list-style-type: none"> • Formal Palliative Medicine Service evaluation when available^d • Nutritional evaluation with a registered dietitian when available
Exocrine pancreatic insufficiency	Pancreatic enzyme replacement
Thromboembolic disease	<ul style="list-style-type: none"> • Low-molecular-weight heparin preferred over warfarin^c • Consider direct oral anticoagulants for select patients
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

^a Palliative surgical procedures are best reserved for patients with a longer life expectancy.

^b Placement of an enteral stent is particularly important for patients with poor performance status and should be done after biliary drainage is assured.

^c A randomized trial 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).

^d Consider encouraging advanced care planning.

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

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

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	<i>Carcinoma 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

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.



NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2021 Pancreatic Adenocarcinoma

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)