

American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Adjuvant Therapy for Resected Adenocarcinoma of the Pancreas

Expert Panel Adjuvant Therapy for Resected Adenocarcinoma of the Pancreas:

Krishan R. Jethwa, MD, MPH¹; Neil B. Newman, MD, MS²; J. Eva Selfridge, MD³; Christopher Anker, MD⁴; Gerard Abood, MD⁵; Dmitriy Akselrod, MD⁶; Joseph Attallah, MD⁷; Christopher L. Hallemeier, MD⁸; Leslie C. Hassett, M.L.S., AHIP⁹; Zhaohui Jin, MD¹⁰; Ed Kim, MD¹¹; Timothy Kennedy, MD¹²; Percy Lee, MD¹³; Diane C. Ling, MD¹⁴; Eric D. Miller, MD, PhD¹⁵; Navesh Sharma, DO¹⁶; William Small, Jr, MD¹⁷; Leila Tchelebi, MD¹⁸; Suzanne Russo, MD¹⁹

¹Principal Author, Department of Radiation Oncology, Mayo Clinic College of Medicine, Rochester, MN

²Department of Radiation Oncology, University of Texas San Antonio Health Science Center, San Antonio, TX

³Department of Medical Oncology, University Hospitals Cleveland, Case Western Reserve University School of Medicine, Cleveland OH

⁴Division of Radiation Oncology, University of Vermont Larner College of Medicine, Burlington, VT

⁵Department of Surgery, Loyola University Stritch School of Medicine, Maywood, IL

⁶Department of Radiology, University of Vermont Larner College of Medicine, Burlington, VT

⁷Department of Medicine, Division of Medical Oncology, MetroHealth, Case Western Reserve University School of Medicine, Cleveland OH

⁸Department of Radiation Oncology, Mayo Clinic College of Medicine, Rochester, MN

⁹Mayo Clinic Libraries, Mayo Clinic, Rochester, MN

¹⁰Department of Medical Oncology, Mayo Clinic College of Medicine, Rochester, MN

¹¹Department of Radiation Oncology, University of Washington, Seattle, WA

¹²Department of Surgery, Division of Surgical Oncology, Georgetown University, Washington DC

¹³Department of Radiation Oncology, City of Hope National Medical Center, Los Angeles, CA

¹⁴Department of Radiation Oncology, Keck School of Medicine, University of Southern California, Los Angeles, CA

¹⁵Department of Radiation Oncology, The James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH

¹⁶Department of Radiation Oncology, WellSpan Cancer Center, York PA

¹⁷Department of Radiation Oncology, Loyola University Stritch School of Medicine, Maywood, IL

¹⁸Department of Radiation Oncology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY

¹⁹Department of Radiation Oncology, MetroHealth, Case Western Reserve University School of Medicine, Cleveland OH

Conflict of Interest Disclosure Statement

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity. The ARS Appropriate Use Criteria Steering Committee reviewed the disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work. Disclosures potentially relevant to the content of this guideline are provided:

¹Dr. Jethwa reports honoraria from RadOncQuestions.com, LLC.

³Dr. Selfridge reports drug support for clinical trials from Medpacto, Inc and Clinigen, Inc. and Industry sponsored studies from BioAtla, Arcus Biosciences, AvEO, Cue Biopharma, and Pfizer.

⁶Dr. Akselrod reports consulting fees from Otsuka America Pharmaceutical

⁷Dr. Attallah reports consulting fees from Aptitude Health, Curio Science, GLG, Targeted Oncology and ZoomRx.

¹⁰Dr. Jin reports grants from Lilly, GlaxoSmithKline, Daiichi Sankyo/Astra Zeneca, Exelis, Elvar

¹³Dr. Lee reports honoraria from Varian, ViewRay, AstraZeneca; consulting fees from Varian, ViewRay, AstraZeneca, Genentech, Johnson & Johnson, Roche, RTOG foundation, and meeting and travel support from Radiosurgery Society.

¹⁶Dr. Small reports personal fees from Carl Zeiss.; and meeting and travel support for ACR, NRG Oncology and Carl Zeiss.

Acknowledgements

Ellie See, Talley Management Group for her attention to detail and diligence in this project.

The ARS Appropriate Use Criteria seek and encourage collaboration with other organizations on the development of the Criteria through representation on expert panels. Participation by representatives from collaborating organizations on the expert panel does not necessarily imply individual or society endorsement of the final document.

*The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Uniformed Services University of the Health Sciences or the Department of Defense or the National Institutes of Health. Reprint requests to: auc@americanradiumsociety.org

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the 10th most commonly diagnosed cancer in the U.S. and it is the third leading cause of cancer-related deaths.¹ Approximately 67,530 Americans will be diagnosed with PDAC and 52,740 are expected to die from the disease in 2024.¹ Surgical treatment with the goal of resection with tumor-free margins (R0) is considered an essential component of curative treatment for PDAC. Despite this, only 15-20% of patients are found to have localized and potentially resectable disease at diagnosis.² Even with curative-intent resection, the rates of locoregional recurrence (LRR) and distant metastases (DM) are high, with 2-year disease-free survival (DFS) of 20-25%, and 5-year overall survival (OS) of 10% following surgery alone.³ Both adjuvant chemotherapy and chemoradiation (CRT) for resected PDAC have been investigated with the intent to reduce the risk of recurrence and improve OS. This systematic literature search and review summarizes the current evidence for adjuvant therapy following surgical resection for non-metastatic PDAC with a focus on high-level evidence and randomized controlled trials.

In 2017 the American College of Radiology® (ACR) published Appropriate Use Criteria (AUC) for the treatment of Resectable Pancreatic Cancer⁴. In 2017 the ACR AUC committees transitioned to the American Radium Society® (ARS) for oversight. In 2024 the ARS AUC published Executive Summary of the American Radium Society Appropriate Use Criteria for *Neoadjuvant Therapy* for Nonmetastatic Pancreatic Adenocarcinoma: Systematic Review and Guidelines⁵. The present systematic review and guidelines provides an update to the original 2017 ACR Resectable Pancreatic Cancer AUC and is intended to guide adjuvant treatment decisions for patients with resected PDAC based on the available evidence. The Population, Intervention, Comparator, and Outcome (PICO) questions included (1) What is the role of adjuvant chemotherapy for initially resected PDAC?, (2) What is the role of adjuvant CRT following initially resected PDAC?, (3) What is the role of adjuvant radiation (RT) (with or without chemotherapy) for patients with resected PDAC who have received neoadjuvant chemotherapy?, and (4) What is the optimal adjuvant therapy for initially resected PDAC?

This update incorporates recent advancements for adjuvant treatment of resected PDAC using modern systemic therapy regimens and selective use of radiotherapy using modern techniques.

METHODS

Using the Population, Intervention, Comparator, Outcome, Timing and Study Design (PICOTS) framework, the evidence regarding treatment outcomes was assessed using Cochrane and PRISMA 2020 methodology.^{6,7} Eligible studies included prospective observational or phase II-III trials which were identified by a comprehensive search published between 1/1/2014 to July 11, 2024, and updated on February 13, 2026. Results were limited by study design, English Language, and date from January 1, 2014 forward. Databases searched were Ovid MEDLINE(R) (1946+ including epub ahead of print, in-process, and other nonindexed citations), Ovid Embase (1974+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), and Scopus via Elsevier (1970+). The search strategies were designed and conducted by a medical librarian with input from the study investigators. Controlled vocabulary supplemented with keywords was used. The actual strategies listing all search terms used and how they are combined is available in the supplemental material. Trial size required for inclusion was > 25 patients. **Appendix A** contains the database search strategy designed by a librarian. Two authors independently screened the comprehensive list of articles, and one assessed the full text articles to determine the final studies included in the Summary of the Literature Review which advised our recommendations (**Appendix B**). Discrepancies between the reviewers were resolved by consensus. Of the 1217 articles identified using the search strategy, 37 were selected for inclusion that met all inclusion criteria. 19 additional studies were included through backward citation searching that were identified from the reference lists of articles found from the search strategy, were published prior to 1/1/2014, and significantly contributed to the literature. Of the 78 citations in the original bibliography, 18 citations were retained in the final document. Articles were removed from the original bibliography if they were more than 10 years old and did not contribute to the evidence or they were no longer cited in the revised narrative text. Fourteen additional studies referenced outside the “Summary of Literature Review” are included to provide context, but unless they are also cited within the “Summary of Literature Review” they were not used by the committee to guide recommendations. In total, 74 references were selected for inclusion (**Appendix C**). Study type and quality for the references were assessed via ARS AUC methodology (**Appendix C**). The

systematic review PRISMA 2020 checklist confirms the completion of essential elements (**Appendix D**). Well-established RAND-UCLA consensus methodology (modified Delphi) was used by the expert panel to rate the appropriateness of the treatment options⁸, with a total of 1 round of voting employed by the group. Categories included (1) usually not appropriate (U, score 1-3); (2) may be appropriate (M, score 4-6); and (3) usually appropriate (A, score 7-9). Studies referenced outside the “Summary of Literature Review” are included to provide context, but unless they are also cited within the “Summary of Literature Review” they were not used by the committee to guide recommendations. The project proposal as well as this executive summary were reviewed and approved by the ARS AUC steering committee, which includes a librarian with expertise in systematic reviews. For further details on ARS AUC methodology guidelines. See <https://www.americanradiumsociety.org/page/aucmethodology>.

STAGING AND PATIENT SELECTION

Patients with histologically-confirmed PDAC undergo initial staging prior to resection. Computed tomography (CT) with intravenous contrast of the chest, abdomen and pelvis is used for assessment of regional or distant metastasis (staging), and to assess locoregional extent of disease, such as degree of vascular involvement, to identify patients who are surgical candidates. CT imaging is also used to identify those patients who are at risk of incomplete resection (R1, microscopic or R2, macroscopic disease). In addition, clinical and/or biological factors such as large tumor size⁹, presence of vascular involvement¹⁰, high preoperative CA 19-9⁹, lymph node involvement¹¹, and high tumor grade¹² are considered prior to surgical recommendations as these prognostic features have been associated with higher risk of early relapse after surgery. For those patients who are not able to safely receive iodinated contrast, MRI without and with contrast has been shown to be equivalent to multiphase contrast-enhanced CT scan for abdominal staging¹³, which would also require non-contrast chest CT, and non-contrast pelvis CT or pelvis MRI with and without contrast. Positron emission tomography/computed tomography (PET-CT) has demonstrated limited utility for local staging, however PET combined with contrast-enhanced CT has been shown to be superior to contrast-enhanced CT for evaluating distant metastatic disease.¹⁴ A preoperative multidisciplinary evaluation is recommended to identify patients who should be considered for initial resection followed by adjuvant therapy, keeping in mind that many patients ultimately do not receive adjuvant therapy because of the development of comorbidities, the worsening of performance status (PS), post-operative complications, or early recurrence.¹⁵ Pathologic findings, postoperative restaging imaging, postoperative CA 19-9, and patient performance status following surgery should be considered prior to adjuvant therapy recommendations.

Herein we describe the data in support of various adjuvant treatment strategies and provide ARS AUC for Adjuvant Therapy for Resected PDAC.

RESULTS/SUMMARY OF LITERATURE REVIEW

Topic 1/Adjuvant Chemotherapy

Adjuvant chemotherapy in patients who undergo upfront resection for PDAC is considered a standard of care for patients with good performance status following resection. Four randomized controlled studies have compared adjuvant chemotherapy to observation: European Study Group for Pancreatic Cancer (ESPAC)-1¹⁶, ESPAC composite¹⁷, Charité Onkologie (CONKO)-001^{3,18}, and Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP)-02¹⁹. At least seven randomized controlled trials compared specific adjuvant chemotherapy regimens: ESPAC-3²⁰, Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC)-01²¹, Radiation Therapy Oncology Group (RTOG) 9704^{22,23}, ESPAC-4²⁴, CONKO-005²⁵, Adjuvant Pancreatic Adenocarcinoma Trial (APACT)²⁶, and Partenariat de Recherche en Oncologie Digestive (PRODIGE) 24/ Canadian Cancer Trials Group (CCTG) PA.6^{27,28}.

In patients who receive upfront resection, adjuvant chemotherapy improves survival compared to observation. The ESPAC-1 trial randomized patients to one of four arms: observation, CRT, chemotherapy (fluorouracil (5-FU) with leucovorin (LV)) and CRT followed by chemotherapy, and showed that chemotherapy improved median survival from 15.5 months to 20.1 months¹⁶. The trial was not powered to compare the chemotherapy only subgroup to observation only, thus a separate arm (ESPAC-1 plus) randomized patients to chemotherapy only vs observation. Data from ESPAC-1, ESPAC-1 plus and ESPAC-3 (which randomized patients to observation vs chemotherapy with gemcitabine alone vs

5FU/LV) were pooled in a composite analysis, which showed improved OS of 23.2 months with adjuvant chemotherapy vs 16.8 months with observation alone¹⁷. Subsequently, the CONKO-001 trial demonstrated an improvement in DFS with adjuvant gemcitabine monotherapy compared to observation following resection of PDAC (13.4 vs 6.9 months, respectively). Long-term follow-up showed that this translated into improvement in OS with 5-year OS rates of 21% (gemcitabine) vs 10% (observation).^{3,18} Similarly, the JSAP-02 demonstrated longer DFS with the use of adjuvant gemcitabine compared to observation (11.4 months vs 5.0 months, respectively; hazard ratio (HR) 0.60, $p=0.01$)¹⁹, but no difference in OS.¹⁹ Of those studies that reported QOL endpoints, chemotherapy was not associated with worse QOL.^{3,16}

While data strongly supports a survival benefit with adjuvant chemotherapy after resected PDAC, the choice of which chemotherapy is optimal has been the topic of several studies. ESPAC-3 compared bolus 5FU/LV with gemcitabine, and found no difference in OS between the two regimens.²⁰ Additional analysis of ESPAC-3 showed that completion of 6 months' adjuvant chemotherapy was more important than timing of initiation of adjuvant therapy, and demonstrated that chemotherapy could safely be postponed for up to 12 weeks after surgery.²⁹ Gemcitabine was associated with fewer Grade 3-4 toxicities than bolus 5FU/LV.²⁰ Relatedly, RTOG 9704 compared regimens of 5FU versus gemcitabine preceeding and following 5FU-based CRT and found a non-significant trend towards improved median (20.5 months vs 16.9 months) and 3-year OS (31% vs 22%) with gemcitabine.²² Thus, gemcitabine was considered standard of care until the results of the Japanese randomized, non-inferiority trial JASPAC 01 compared adjuvant S-1 to gemcitabine and showed a 5-year OS rate of 24% for the gemcitabine group vs 44% for the S-1 group, which was associated with less toxicity.²¹ The applicability of S-1 in European and North American patients has not been established.

Seeking to improve upon single-agent chemotherapy, several studies explored the use of multiagent chemotherapy in the adjuvant setting. ESPAC-4 randomized patients to the combination of gemcitabine and capecitabine vs gemcitabine alone. This trial demonstrated no difference in RFS between the two arms, but did show improved median OS for the gemcitabine plus capecitabine arm (31.6 months vs 28.4 months; HR 0.83, $p=0.031$).^{24,30} Long-term results of ESPAC-4 subgroup analyses demonstrated similar improved median survival for gemcitabine plus capecitabine in patients with R0 resection (49.9 months vs 32.2 months; HR 0.62, $p=0.002$), and improved 5-year survival for patients with uninvolved lymph nodes (59% vs 53%; HR 0.63, $p=0.04$), but not for those with involved lymph nodes ($p=0.23$).³⁰ The addition of erlotinib to adjuvant gemcitabine failed to demonstrate improvement in DFS or OS in CONKO-005.²⁵ The APACT trial compared nab-paclitaxel plus gemcitabine with gemcitabine alone and did not meet its primary endpoint of improvement in independently-assessed DFS, but did show an improvement in median OS of 41.8 months vs 37.7 months (HR, 0.80, 95% CI 0.678 to 0.947, $p=0.0091$).²⁶

The PRODIGE 24/CCTG PA.6 trial compared an intensified adjuvant chemotherapy regimen consisting of modified 5FU/LV/irinotecan/oxaliplatin (mFOLFIRINOX) with gemcitabine alone. Improvements in median OS were observed with the use of mFOLFIRINOX compared to gemcitabine 54.4 months vs 35 months, respectively (HR 0.64; $p=0.003$).^{27,28} Median DFS was also improved by mFOLFIRINOX (21.6 months mFOLFIRINOX vs 12.8 months gemcitabine; HR 0.58; $p<0.001$). Long-term follow-up confirmed sustained benefit to mFOLFIRINOX, with similar median OS and DFS as in the initial analysis.^{27,28} It is important to note that mFOLFIRINOX was associated with significantly higher rates of grade 3-4 toxicities (76% vs 51%), and that the patients included in this trial were highly selected (adequate surgical recovery with ECOG performance status 0-1, post-operative CT scan negative for residual or recurrence, and post-operative CA19-9 serum levels < 180 U/ml). Only 66% of patients in the mFOLFIRINOX arm received all the planned cycles of chemotherapy compared to 79% in the gemcitabine arm.^{27,28} Because dose intensity and receipt of 6 months of systemic therapy is associated with improved survival, neoadjuvant chemotherapy has been proposed as an option for resectable pancreas cancer. The ongoing multicenter, randomized, phase III PREOPANC-3 trial is designed to compare perioperative mFOLFIRINOX (8 cycles neoadjuvant + 4 cycles adjuvant) with adjuvant mFOLFIRINOX (12 cycles) in patients with resectable pancreatic cancer.³¹ Similarly, the Alliance for Clinical Trials in Oncology (Alliance) A021806 randomized trial is currently accruing patients and is designed to compare 8 cycles of neoadjuvant mFOLFIRINOX followed by 4 cycles of adjuvant mFOLFIRINOX to includes upfront surgery followed by 12 cycles of adjuvant mFOLFIRINOX.³²

In summary, mFOLFIRINOX is considered an appropriate adjuvant chemotherapy for fit patients following surgery for resectable PDAC. In patients for whom mFOLFIRINOX would be deemed poorly tolerated, gemcitabine plus capecitabine is considered the preferred option as there was a survival advantage for gemcitabine plus capecitabine over gemcitabine alone demonstrated in the ESPAC-4 trial. Single agent gemcitabine should be reserved for patients who are not able to tolerate combination chemotherapy. Notably, in all but one of these trials, the majority of patients (55% to 88%) had R0 resections, whereas only 40% of patients in ESPAC-4 had R0 resection.²⁴ It is important to consider patient characteristics including functional status, patient goals and quality of life, R0 resection, nodal status, and baseline CA19-9 when selecting the best adjuvant therapy for resected pancreas cancer.

Topic 2/Adjuvant (Chemo)Radiation

Since the 1970s, multiple prospective clinical trials have evaluated if postoperative CRT offers benefit to patients with resected PDAC. The Gastrointestinal Tumor Study Group (GITSG) 9173 study included 43 patients with R0 resected PDAC from 1974-1982.^{33,34} Patients were randomized to no adjuvant treatment vs adjuvant split-course RT with 40-Gy in 20 fractions delivered using anterior-posterior/posterior-anterior (AP/PA) fields concurrently with 5-FU–based chemotherapy, followed by maintenance 5-FU for a total of 2 years. Adjuvant CRT with maintenance 5-FU was associated with an improvement in median OS of 20 months vs 11 months and 5-year survival was 19% vs 5%.

The follow-up European Organisation for Research and Treatment of Cancer (EORTC) 40891 trial included 218 patients with PDAC or perampullary adenocarcinoma with either R0 or R1 resection (22%), and similarly randomized patients to no adjuvant therapy vs split-course 40-Gy in 20 fractions concurrently with 5-FU–based chemotherapy without any additional maintenance 5-FU.³⁵ In the adjuvant therapy arm, 20% of patients did not receive adjuvant RT and 44% did not receive chemotherapy per protocol. Overall, the use of adjuvant CRT, compared with no adjuvant therapy, was not associated with an improvement in median OS (24.5 months vs 19 months) or 2-year survival (51% vs 41%, $p=0.208$). On subset analysis inclusive of only patients with PDAC, there was no difference in median OS (17 months vs 13 months) or 2-year survival (34% vs 26%, 2-sided $p=0.099$). A subsequent re-analysis of the EORTC data utilizing a 1-sided log rank test was performed and suggested an OS benefit ($p<0.04$) with the use of adjuvant CRT.

Topic 3/Optimal Adjuvant Therapy: Adjuvant Chemotherapy vs Adjuvant Chemoradiation

Multiple studies have explored the optimal adjuvant therapy for resected PDAC, including whether the addition of CRT to systemic therapy improves outcomes when compared with systemic therapy alone.

The ESPAC-1 phase 3 randomized trial demonstrated that CRT, with a regimen of split course 40 Gy in 20 fractions, was not associated with improvement in OS (median OS 15.9 months with CRT vs 17.9 months with no CRT) or local control. The validity of the results, however, was questioned due to several methodologic limitations, including sub-optimal RT regimens and techniques, lack of RT quality assurance, and significant background therapy with inadequate adjustment.^{16,36} Similarly, the Taiwan Cooperative Oncology Group performed an exploratory prospective randomized study evaluating regimens of six cycles of adjuvant gemcitabine or three cycles of gemcitabine followed by CRT, 50.4 Gy in 28 fractions with concurrent gemcitabine, and three additional cycles of gemcitabine.³⁷ There were no significant differences in recurrence rates (82% vs 82%), median relapse-free survival (RFS) (11.6 vs 13.2 months, $p = 0.56$) or OS (23.5 vs 22.2 months, $p = 0.96$) between chemotherapy alone vs CRT. CRT was associated with a reduced risk of locoregional progression, 41% vs 11%, however, there was an increase in distant metastatic progression (41% vs 61%). Post-operative CA 19-9 and CA 19-9 response to chemotherapy were correlated with OS, however, CA 19-9 did not demonstrate prognostic or predictive associations with benefit from CRT.

A metanalysis of 12 prospective phase 3 randomized trials evaluating post-operative chemotherapy alone or CRT, suggested that CRT was associated with improved DFS but no significant difference in OS.³⁸ The regimens associated with the best OS were either FOLFIRINOX or S1-based chemotherapy.

Subtopic 1/Adjuvant Radiation +/- Chemotherapy for Adverse Pathologic Features

Several prognostic pathologic risk factors have been identified. Pathologic lymph node involvement is identified in approximately 50-80% of patients following resection for anatomically resectable disease and has been strongly associated with poorer locoregional control, distant metastasis, and OS.³⁹⁻⁴⁵ Microscopic (R1) or grossly (R2) positive resection margins are similarly associated with poorer outcomes.^{39,41,42,44,46,47} The presence of lymphovascular invasion (LVI) or perineural invasion (PNI) have each demonstrated prognostic associations, however, these associations have generally been less strong potentially attributable to the near universal presence of either of these features in patients with PDAC and confounding with other known risk factors such as lymph node involvement or positive margins.⁴⁰⁻⁴² That said, PNI has been further differentiated to include categories such as intratumoral intrapancreatic, extratumoral intrapancreatic, or extratumoral extrapancreatic. Extratumoral extrapancreatic PNI is the highest risk entity as it includes disease spread along perineural tracks along vasculature and is very challenging to curatively resect thus leading to higher risks of microscopic residual disease and subsequent locoregional recurrence and/or distant disease spread.

An elevated postoperative CA 19-9 has also demonstrated prognostic significance with higher rates of locoregional recurrence, distant metastasis, and poorer survival identified in those with a post-operative CA 19-9 ≥ 90 .^{48,49}

In general, while these features have demonstrated prognostic significance, there are not strong data guiding how they should direct postoperative treatment decision-making. Post-operative chemotherapy is generally indicated even in the absence of other adverse risk factors, although, some do consider a more nuanced approach to the use of post-operative RT.

A retrospective review from Mayo Clinic compared outcomes for 472 consecutively treated patients who underwent margin negative resection for PDAC and subsequently were treated with or without postoperative RT.⁴³ The subset that received RT had higher risk features with a greater proportion having lymph node involvement or high-grade disease. Despite this imbalance, postoperative RT was associated with improved median survival, 25.2 vs 19.2 months, and improved 2-year OS (50% vs 39%), and 5-year OS (28% vs 17%). A similar study from Johns Hopkins Hospital, inclusive of high-risk patients with lymph node involvement (82%) or positive margins (48%), found that the addition of 5FU-based CRT improved survival vs surgery alone.⁴⁴ A subsequent combined analysis from Johns Hopkins Hospital and Mayo Clinic including 794 patients similarly demonstrated improved median survival, 21.1 vs 15.5 months, 2- and 5-year OS 44.7% vs 34.6% and 22.3% vs 16.1%, with postoperative CRT vs surgery alone, and these findings were further strengthened in a matched pair analysis.⁵⁰ Elamir et al. performed a retrospective analysis of 467 patients with resected PDAC.⁴² Amongst those treated with surgery, without post-operative RT, risk factors for locoregional recurrence included lymph node involvement, R1 resection, moderately or poorly differentiated tumors, or LVI. Amongst those who had high risk features, the risk of locoregional recurrence was 32% vs 57% for those treated with vs without post-operative RT. Taken together, these retrospective data suggest that the addition of post-operative RT may overcome some of these adverse risk factors thus offering improved locoregional disease control and survival, even amongst those with higher risk disease features.

In summary, the addition of adjuvant CRT appears to provide a DFS benefit and possible OS benefit in a select group of patients with resected PDAC without causing an increase in toxicity. While multiple factors such as margin status, lymph node status, tumor grade, perineural invasion, or lymphovascular invasion have demonstrated prognostic associations, the available data do not provide definitive guidance on how they should be utilized to guide clinical decision making, however, the available retrospective data suggest it would be reasonable to selectively consider the addition of CRT in such patients.

Subtopic 2/Choice of Concurrent Chemotherapy

The majority of prospective trials evaluating postoperative CRT for resected PDAC have utilized either concurrent 5-FU/capecitabine or gemcitabine. The GITSG 9173, EORTC 40891, ESPAC-1, and RTOG 9704 utilized concurrent 5-

5-FU/capecitabine and each suggest safety and efficacy with that strategy.^{16,22,23,33,35,36,51} Similarly, the EORTC-40013-22012/FFCD-9203/GERCOR, amongst others, utilized concurrent weekly gemcitabine and also demonstrated safety and efficacy.^{52,53}

Various experimental concurrent regimens have been explored including 3- or 4-drug combinations of 5-FU, leucovorin, mitomycin-C, dipyrindamole, cisplatin, or interferon alpha.^{54,55} Combinations of cytotoxic chemotherapy and targeted agents, such as cetuximab and bevacizumab, have also been explored.⁵⁶ Unfortunately, these combinations did not demonstrate compelling evidence to support subsequent randomized phase 3 trials or compelling evidence to incorporate as standard of care. For patients with locally advanced disease, the SCALOP trial investigated definitive CRT with concurrent capecitabine (830 mg/m² twice daily on days of RT) vs gemcitabine (300 mg/m² once weekly).⁵⁷ The primary endpoint was 9-month progression-free survival (PFS), and 63% and 51% had not progressed in the capecitabine and gemcitabine cohorts, although, there were no significant differences in PFS at 12 months. The median OS was slightly improved with capecitabine (15.2 months vs 13.4 months, p= 0.012). The conclusion of the study was that capecitabine may be preferable to gemcitabine, however, caution was warranted considering the small sample size and lack of improvement in the study primary endpoint.

Taken together, these data suggest that continuous infusion 5-FU/capecitabine or weekly gemcitabine are suitable concurrent chemotherapy approaches for patients receiving CRT.

Subtopic 3/ Timing of Therapies

Strong data guiding the timing and sequencing of postoperative therapy is relatively lacking and is predominately limited to retrospective data and population-based registry studies. A retrospective study by Patel et al suggested that there were no differences in OS, PFS, or local control with the early use of CRT within 1-2 cycles of systemic therapy vs CRT sequenced after 3 cycles of chemotherapy.⁵⁸ In contrast, a National Cancer Center Database (NCDB) analysis stratified patients into those that had stage 1-2 disease and stage 3 disease.⁵⁹ Early vs late use of CRT was further dichotomized by a median chemotherapy duration of less than 70 days in those with stage 1-2 disease or 90 days in those with stage III disease. The study demonstrated that a longer duration of systemic therapy prior to CRT was associated with improved OS and this difference persisted after propensity matching.

Despite the limited data, contemporary postoperative management for patients with resected PDAC generally incorporates initial systemic therapy followed by interval imaging reassessment.^{52,53,60} Postoperative CRT is selectively considered in those that do not have distant metastatic disease progression on interval imaging. The use of initial systemic therapy allows for biologic selection to assist with identification of patients who may derive greater benefit from CRT. This approach has been adopted on most recent prospective clinical trials including RTOG 0848^{45,60} and EORTC-40013-22012/FFCD-9203/GERCOR.⁵² For example, RTOG 0848^{45,60} used 6 months of systemic therapy prior to transitioning to CRT, where-as the EORTC-40013-22012/FFCD-9203/GERCOR⁵² phase 2 trial used 2 months of systemic therapy prior to CRT.

Subtopic 4/Radiation Technique

Simulation

Patients are typically instructed to limit oral intake for 2-3 hours prior to CT simulation. Patients are positioned supine with arms raised using a custom immobilization device (eg. Vac-Lok). Respiratory motion should be assessed, typically with a 4-dimensional CT. If excessive target motion is observed (eg. greater than 1 cm), respiratory motion management strategies should be considered. Intravenous contrast assists in accurately delineating the resection bed and/or any sites of gross residual disease and regional vasculature. Oral contrast administered approximately 30 minutes before simulation may be helpful in delineating small bowel for avoidance.

Radiation Dose

Historical trials evaluating the use of postoperative CRT for patients with resected PDAC used split-course 40-60 Gy RT, however, this strategy is considered inferior to conventionally fractionated continuous courses of treatment.^{16,33-35} Most recent prospective trials have treated patients to a dose of 50-54 Gy in 1.8-2.0 Gy fractions.^{23,37,45,52,53} Although, no prospective trial has clearly established the optimal postoperative RT dose for R0 resected PDAC, an analysis of data from the NCDB for all patients treated with adjuvant RT from 1998–2002 suggested the optimal dose was in the range of 50-55 Gy.⁶¹

There is also a lack of consensus on optimal RT dose for patients treated following R1 or R2 resection, however, most patients are still treated to a dose of 50-54 Gy in 1.8-2.0 Gy fractions. There has been some consideration of RT dose intensification, analogous to that used in locally advanced, unresectable, disease for patients with grossly residual disease if it can be delivered safely without excessive risk to adjacent organs at risk, although, comparative data supporting the strategy are limited.

There has also been investigation of alternative fractionation schemes, including both stereotactic body radiotherapy (SBRT) and hypofractionated approaches, with data suggesting relatively favorable outcomes with each strategy albeit limited by small sample sizes and lack of direct comparisons with conventional regimens. Bernard et al. reported a prospective phase 2 trial of patients with resected PDAC with either involved or close margins treated with postoperative SBRT to a dose of 36 Gy in 3 fractions.⁶² They reported a 2-year local PFS of 77% and regional PFS of 73%, respectively. Grade 3 or higher toxicities occurred in 4% of patients. Ma et al. and Weinberg et al. each reported early phase prospective trials evaluating post-operative 25 Gy in 5 fractions with photon⁶³ or proton-based techniques⁶⁴. Weinberg et al. included 9 patients and reported no local progression events or grade 3+ GI toxicity.⁶⁴ Ma et al. included 40 patients randomized to gemcitabine +/- post-operative 25 Gy in 5 fractions RT, and demonstrated no differences in local control or toxicity rates with the addition of RT.⁶³ At present, there is insufficient data to provide strong support of post-operative SBRT or alternative fractionation schemes, and therefore, conventional fractionation to doses of 50-54 Gy in 1.8-2.0 Gy fractions is preferred.

Treatment Volumes

PDAC is a highly infiltrative disease with high rates of occult regional lymph node involvement, peri-neural or vascular disease spread, and extra-pancreatic tumor extension. Pathologic analysis of patients with anatomically resectable disease who undergo up-front surgery suggest approximately a 50-80% risk of regional lymph node involvement and > 90% risk of peri-neural invasion. The most common sites of lymph node involvement for patients with pancreatic head, neck, or uncinate process tumors include the pancreaticoduodenal, superior mesenteric, common hepatic, and para-aortic regions. For pancreatic body or tail tumors, common sites of lymph node involvement include splenic artery, inferior margin of pancreas, para-aortic, common hepatic, celiac, and superior mesenteric. Furthermore, a study by Dholakia et al. evaluating patterns of disease recurrence after curative intent surgery for PDAC suggested that 90% of locoregional recurrences occurred within a 3.0-cm right-lateral, 2.0-cm left-lateral, 1.5-cm anterior, 1.0-cm posterior, 1.0-cm superior, and 2.0-cm inferior margin of the most proximal 1 cm of the celiac artery and 3 cm of the SMA.⁶⁵ These data have been informative in generating consensus guidelines for post-operative RT target volume delineation for PDAC, and in general, consensus is to utilize post-operative volumes as described in the RTOG 0848 contouring atlas.⁶⁶

The RTOG 0848 atlas suggests identifying the most proximal 1.0-1.5 cm of the celiac artery including up to the 1st branches, the most proximal 2.5-3.0 cm of the superior mesenteric artery, and the portal vein extending inferiorly from just above the junction with the superior mesenteric vein to superiorly up to the bifurcation into the right and left portal veins. A 1.0-1.5 cm margin should be applied to each of the structures. The preoperative tumor volume should be delineated with the assistance of a registered preoperative diagnostic CT and should include any surgical clips, if any, that were placed to delineate areas of particular concern such as close margin. The pancreaticojejunostomy should be included with a 0.5-1 cm margin. The aorta should be contoured from the most cephalad contour of the celiac artery, portal vein, or pancreaticojejunostomy and extended inferiorly to the level of L2. An asymmetric margin should be added

to include the prevertebral nodal regions. This includes approximate expansions of 2.5-3 cm to the right, 1.0 cm to the left, 2.0-2.5 cm anteriorly, and 0.2 cm posteriorly, anatomically constrained such that they do not extend into the kidneys, liver, stomach, or vertebral bodies.

The postoperative pancreas bed and adjacent regions at risk are susceptible to both intrafraction and interfraction motion, and bony landmarks are relatively poor surrogates for the pancreas target. This motion is attributable to respiration but also variability in adjacent organs at risk (OARs), such as gastric filling. To account for these uncertainties, daily image guidance is recommended. Additionally, a 4-dimensional CT should be acquired for treatment planning to allow generation of an iGTV or ITV that accounts for target motion throughout the respiratory cycle. If excessive motion is observed, motion management strategies should be utilized to mitigate motion. Utilizing these strategies, a PTV margin of 0.5-1 cm is sufficient.

Treatment Modality

Most recent prospective trials evaluating postoperative CRT for patients with resected PDAC have utilized either 3D-conformal RT or intensity-modulated radiotherapy (IMRT) and both are considered appropriate options.^{23,45}

Data comparing treatment techniques are relatively limited and there are no prospective randomized trials to provide high level evidence of superiority of one technique vs an alternative. Retrospective data have suggested that the use of IMRT can offer dosimetric benefits with improved conformality and a reduction of high-dose exposure to adjacent OARs including the stomach, bowel, kidneys, and liver. Retrospective data have also suggested that IMRT is associated with a lower risk of gastrointestinal toxicities including grade 3+ nausea, vomiting, and diarrhea.⁶⁷ Furthermore, a retrospective study by Lee et al. which performed routine posttreatment endoscopic assessment demonstrated that 3D conformal RT, compared with IMRT, was associated with a higher risk of post-treatment gastroduodenal ulcer.⁶⁸ Improved high dose conformality is of even greater importance when considering dose escalated RT, for example in cases where there is an identifiable positive margin in which focal RT boost is considered.

The use of proton beam therapy (PBT) has also been explored, and in general the available data suggest significant dosimetric benefits when compared with IMRT with improved sparing of low-intermediate and mean RT doses to adjacent OARs including small bowel, stomach, liver, and kidneys.⁶⁹⁻⁷¹ There are limited data comparing clinical outcomes of patients treated with postoperative PBT vs photon CRT, however, Nichols et al. have reported an institutional retrospective series suggesting a 0% risk of grade 3 acute GI toxicity in patients treated with PBT.⁶⁹ Weinberg et al. reported a prospective phase 1 study including 9 patients who previously underwent R0 or R1 resection of PDAC.⁶⁴ Patients were planned to receive 12 cycles of postoperative modified FOLFIRINOX and 25 Gy in 5 fractions, utilizing PBT, was delivered between cycles 6 and 7. No patient experienced local recurrence and there was only 1 dose limiting toxicity of prolonged grade 3 neutropenia that limited future receipt of systemic therapy. Available studies utilizing PBT have suggested favorable outcomes, although further data are needed to clarify if there are any significant benefits when compared with photon-based techniques.

There are limited data and no prospective randomized trials evaluating SBRT for postoperative management of patients with resected PDAC. Bernard et al. reported a prospective phase 2 study including patients with a positive or close margin after curative-intent resection of PDAC.⁶² Patients were treated with postoperative SBRT, 36 Gy in 3 fractions. The median OS is 23.7 months, 2-year locoregional PFS was 77%, and the rate of grade 3 or higher toxicity was 4.1%. Further data are needed to clarify the role of postoperative SBRT for patients with resected pancreas cancer.

Topic 4/Adjuvant Treatment for Patients who Received Neoadjuvant Therapy

The role of postoperative chemotherapy or RT in patients who received neoadjuvant therapy has not been defined. Multiple clinical trials have incorporated postoperative chemotherapy following surgery in patients with PDAC who received neoadjuvant chemotherapy⁷²⁻⁷⁴ or CRT⁷⁵⁻⁷⁷. However, no randomized trials have demonstrated improvement in

outcomes with addition of adjuvant chemotherapy after having received neoadjuvant therapy nor is their guidance from prospective trials on the optimal post-operative chemotherapy regimen in such a scenario. An NCDB analysis including 1247 patients with PDAC who received neoadjuvant therapy followed by surgery compared outcomes amongst those who were subsequently observed or received post-operative chemotherapy.⁷⁸ The study demonstrated improved OS with the use of post-operative chemotherapy in the overall cohort and also after propensity matching for known risk factors. Another NCDB analysis evaluated the use of post-operative chemotherapy in patients who received preoperative CRT and subsequent surgery and did not demonstrate a significant difference in OS with post-operative chemotherapy compared with observation.⁷⁹ Extrapolating primarily from prior clinical trials in the post-operative setting and the limited retrospective data available, the current standard is to complete a total of 6 months of chemotherapy if less than 6 months were administered in the neoadjuvant setting.

Similarly, there are limited data guiding the use of post-operative CRT in patients who received neoadjuvant chemotherapy. Considering this paucity of literature, the indications and use of post-operative CRT is based on expert opinion and are extrapolations primarily from the aforementioned data for post-operative CRT following up-front surgical resection.

Variant Cases and Treatment Algorithm

Variant cases were developed as examples for these guidelines to illustrate practical applications of consensus recommendations. A **treatment algorithm** is also provided to assist in selection of therapies for Adjuvant Therapy for Resected Adenocarcinoma of the Pancreas.

CONCLUSIONS/SUMMARY OF RECOMMENDATIONS

1. The panel strongly recommends that adjuvant chemotherapy alone is usually appropriate for the typical case with resected node-negative PDAC in the absence of adverse pathologic features such as positive surgical margin, high grade tumors, and presence of LVI or PNI. The panel also recommends that addition of chemoradiation following initial systemic therapy may be appropriate if there is no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9 in the setting of resected PDAC [**Variant 1**].
2. The panel strongly recommends that adjuvant chemotherapy alone is usually appropriate for the typical case with resected node-positive PDAC in the absence of adverse pathologic features such as positive surgical margin, high grade tumors, and presence of LVI or PNI. The panel also recommends that addition of chemoradiation following initial systemic therapy may be appropriate if there is no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9 in the setting of resected PDAC, especially in the setting of high-risk pathologic features including node-positive disease [**Variant 2**].
3. The panel strongly recommends that adjuvant chemotherapy alone is usually appropriate for the typical case with resected node-negative PDAC with positive surgical positive margin. The panel also strongly recommends that chemoradiation following initial systemic therapy is usually appropriate if there is no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9 in the setting of resected PDAC with positive surgical margin [**Variant 3**].
4. The panel strongly recommends that adjuvant chemotherapy alone is usually appropriate for the typical case with resected node-negative PDAC in the absence of adverse pathologic features such as positive surgical margin, node-positive disease, and presence of LVI or PNI in patients who received neoadjuvant chemotherapy. Completion of at least 6 months of systemic therapy is recommended if not administered preoperatively. The panel also recommends that addition of chemoradiation following initial systemic therapy may be appropriate if there is no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9 in the setting of resected PDAC following neoadjuvant chemotherapy [**Variant 4**].
5. The panel strongly recommends that adjuvant chemotherapy alone is usually appropriate for the typical case with resected node-positive PDAC in patients who received neoadjuvant chemotherapy. Completion of at least 6 months of systemic therapy is recommended if not administered preoperatively. The panel also recommends that chemoradiation following initial systemic therapy may be appropriate if there is no evidence of distant metastasis

upon interval imaging assessment in the setting of resected PDAC with presence of adverse pathologic features such as node-positive disease and presence of LVI or PNI [Variant 5].

6. The panel strongly recommends that observation is usually appropriate for the typical case with resected PDAC in the in a patient with poor postoperative performance status with the goal of supportive care and optimization of performance status. The panel also strongly recommends that adjuvant single agent chemotherapy may be appropriate in patients with borderline poor performance status deemed able to tolerate [Variant 6].

DISCUSSION/FUTURE DIRECTIONS

We await the publication of the final results of RTOG 0848, which was designed to more definitively address if the addition of CRT to systemic therapy improves outcomes for patients with resected PDAC. The study was a prospective phase 3 randomized trial with a 2-step design inclusive of patients with CA 19-9 up to 180 resected with positive or negative margins. In the first step, patients were randomized to treatment with 6 cycles of chemotherapy (primarily gemcitabine; no patients received FOLFIRINOX) with or without erlotinib, and the study did not demonstrate improvement in OS with the addition of erlotinib.⁶⁰ In phase 2, patients without progression after 5 cycles of chemotherapy were randomized to a sixth cycle of chemotherapy with or without the addition of RT to 50.4 Gy in 28 fractions concurrently with 5-FU. Preliminary analysis reported that the vast majority of patients underwent resection with negative margins (83%), had lymph node involvement (74%), and post-operative CA19-9 <90 (96%).⁴⁵ The protocol required real time quality assurance and RT treatment plan review to ensure standardization. Amongst the overall cohort, there was no difference in toxicity rates or median OS, 31 months vs 27 months ($p=0.38$), for the chemotherapy vs CRT cohort, however, CRT was associated with improved median DFS, 12 months vs 16 months ($p=0.045$). The majority of recurrences were distant (31%) as opposed to local (19%). On prespecified subgroup analysis of patients with node-negative disease, CRT was associated with improvement in OS, 47 months vs 36 months ($p=0.03$), and 5-year OS, 48% vs 29%. While only 17% of patients were margin positive, there was no benefit to the addition of CRT in this subgroup. The data as preliminarily presented suggest that the benefit of CRT may be most pronounced in a biologically favorable subset of patients with pathologically node-negative disease, with the caveat that patients with margin-positive disease were not well represented and patients were not treated with FOLFIRINOX chemotherapy.

Despite the notable advancements seen, outcomes for patients with resectable PDAC remain suboptimal and further investigation is needed of treatment sequencing (neoadjuvant vs adjuvant; PREOPANC-3, NCT04927780³¹ and Alliance A021806, NCT04340141³²), prognostic/predictive biomarkers, and optimal use of peri-operative interventions.

Presently, patients remain at significant risk of disease progression despite margin negative resection, normal postoperative CA 19-9, and standard of care post-operative therapy, thus suggesting that currently available prognostic indices are insufficient. Further work is needed to identify prognostic and/or predictive biomarkers to inform prognosis and guide optimal post-operative intervention.⁸⁰

There is active investigation of the role adjuvant therapies based on germline mutations. ASCO guidelines for advanced PDAC recommend early testing for actionable genomic alteration for patients who are potential candidates for additional treatment after first-line.⁸¹ Germline and tumor (somatic) testing are recommended, and testing should look for microsatellite instability/mismatch repair deficiency, BRCA mutations, and neurotrophic tyrosine receptor kinase (NTRK) gene fusions.⁸¹

For example, in metastatic germline-mutated PDAC, maintenance olaparib (the poly adenosine diphosphate-ribose polymerase (PARP) inhibition for DNA damage repair mutations) is associated with improvements in PFS compared to placebo.⁸² Other examples include the HER2-directed antibody-drug conjugate fam-trastuzumab deruxtecan which has demonstrated benefit in unresectable or metastatic HER2-positive (IHC 3+) PDACs that occurs in approximately 2% of patients⁸³, dabrafenib plus trametinib for patients with PDAC with BRAF gene V600E alterations (approximately 2.2%)⁸⁴, and larotrectinib or entrectinib for patients with PDAC with an NTRK gene fusion (approximately 0.5%)⁸⁵. Pembrolizumab,

an immune checkpoint inhibitor, has shown benefit in PDAC patients that harbor microsatellite unstable genotype (MSI-H) and/or a mismatch repair deficient phenotype (dMMR)⁸⁶ (approximately 0.8% and 1.3%), often seen in people with Lynch syndrome⁸⁷.

Although targetable genomic therapies will impact a minority of patients with PDAC, data suggest that patients with PDAC with actionable molecular alterations who receive a matched therapy had a significantly longer OS rate than patients who only received unmatched therapies (2.58 years vs 1.32 years).⁸⁸ As we continue to investigate genomic variants of PDAC, these and other targeted therapeutics may provide future options for patients in the adjuvant setting.

For patients with resected PDAC, the addition of postoperative CRT to combination chemotherapy has not yet been investigated. However, the patterns of recurrence and available data have supported the influence of pre- or post-operative RT on reducing locoregional recurrence and improving pathologic surrogates for survival such as R0 resection, lymph node clearance, and clearance of PNI or LVI. Further work is needed to clarify if there are specific genomic, biochemical, radiographic, or pathologic factors that better identify subsets of patients who may be at higher risk of locoregional recurrence with a comparatively lower competing risk of distant metastasis or have a locoregionally predominant disease phenotype (i.e. SMAD4) in whom locoregional RT may be associated with improved survival.

Further work, in tandem, is needed in each of these realms harnessing the mechanistically distinct roles of all forms of peri-operative interventions to further improve outcomes for patients.

SUMMARY OF EVIDENCE

Of the 88 references cited in the American Radium Society® Appropriate Use Criteria for Adjuvant Therapy for Resected Adenocarcinoma of the Pancreas, 37 were identified through the search strategy, with 19 additional studies included through backward citation searching identified by examining the reference lists of articles directly found through the search strategy. Of the 78 citations in the original bibliography, 18 citations were retained in the final document. Articles were removed from the original bibliography if they were more than 10 years old and did not contribute to the evidence or they were no longer cited in the revised narrative text. Fourteen additional studies referenced outside the “Summary of Literature Review” are included to provide context, but unless they are also cited within the “Summary of Literature Review” they were not used by the committee to guide recommendations. In sum the authors added 51 citations from bibliographies, websites, or books not found in the literature search. Of the 74 references used as evidence, 74 are categorized as therapeutic references including 31 well-designed studies (Phase II randomized and Phase III), 14 moderately well- designed studies that account for most common biases (matched cohort and Phase II studies), 28 studies with design limitations (retrospective reviews), and 1 reference that is a meta-analysis.

SUPPORTING DOCUMENTS

For additional information on the ARS Appropriate Use Criteria methodology and other supporting documents go to <http://www.americanradiumsociety.org/page/aucmethodology>.

The American Radium Society™ Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient’s condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.

REFERENCES

1. Siegel RL, Kratzer TB, Wagle NS, Sung H, Jemal A. Cancer statistics, 2026. *CA Cancer J Clin.* Jan-Feb 2026;76(1):e70043. doi:10.3322/caac.70043
2. Katz MH, Marsh R, Herman JM, et al. Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol.* Aug 2013;20(8):2787-95. doi:10.1245/s10434-013-2886-9
3. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA.* Jan 17 2007;297(3):267-77. doi:10.1001/jama.297.3.267
4. Jones WE, 3rd, Suh WW, Abdel-Wahab M, et al. ACR Appropriateness Criteria(R) Resectable Pancreatic Cancer. *Am J Clin Oncol.* Apr 2017;40(2):109-117. doi:10.1097/COC.0000000000000370
5. Jethwa KR, Kim E, Berlin J, et al. Executive Summary of the American Radium Society Appropriate Use Criteria for Neoadjuvant Therapy for Nonmetastatic Pancreatic Adenocarcinoma: Systematic Review and Guidelines. *Am J Clin Oncol.* Apr 1 2024;47(4):185-199. doi:10.1097/COC.0000000000001076
6. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ.* Mar 29 2021;372:n160. doi:10.1136/bmj.n160
7. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* Mar 29 2021;372:n71. doi:10.1136/bmj.n71
8. Fitch K, Bernsein S, Aguilar M, et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica: Rand Corporation. 2001
9. Matsumoto I, Murakami Y, Shinzeki M, et al. Proposed preoperative risk factors for early recurrence in patients with resectable pancreatic ductal adenocarcinoma after surgical resection: A multi-center retrospective study. *Pancreatology.* Nov-Dec 2015;15(6):674-80. doi:10.1016/j.pan.2015.09.008
10. Liu L, Katz MH, Lee SM, et al. Superior Mesenteric Artery Margin of Posttherapy Pancreaticoduodenectomy and Prognosis in Patients With Pancreatic Ductal Adenocarcinoma. *Am J Surg Pathol.* Oct 2015;39(10):1395-403. doi:10.1097/PAS.0000000000000491
11. Sho M, Murakami Y, Motoi F, et al. Postoperative prognosis of pancreatic cancer with para-aortic lymph node metastasis: a multicenter study on 822 patients. *J Gastroenterol.* Jun 2015;50(6):694-702. doi:10.1007/s00535-014-1005-4
12. Wasif N, Ko CY, Farrell J, et al. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging? *Ann Surg Oncol.* Sep 2010;17(9):2312-20. doi:10.1245/s10434-010-1071-7
13. Koelblinger C, Ba-Ssalamah A, Goetzing P, et al. Gadobenate dimeglumine-enhanced 3.0-T MR imaging versus multiphasic 64-detector row CT: prospective evaluation in patients suspected of having pancreatic cancer. *Radiology.* Jun 2011;259(3):757-66. doi:10.1148/radiol.11101189
14. Asagi A, Ohta K, Nasu J, et al. Utility of contrast-enhanced FDG-PET/CT in the clinical management of pancreatic cancer: impact on diagnosis, staging, evaluation of treatment response, and detection of recurrence. *Pancreas.* Jan 2013;42(1):11-9. doi:10.1097/MPA.0b013e3182550d77
15. DePeralta DK, Ogami T, Zhou JM, et al. Completion of adjuvant therapy in patients with resected pancreatic cancer. *HPB (Oxford).* Feb 2020;22(2):241-248. doi:10.1016/j.hpb.2019.07.008
16. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med.* Mar 18 2004;350(12):1200-10. doi:10.1056/NEJMoa032295
17. Neoptolemos JP, Stocken DD, Tudur Smith C, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. *Br J Cancer.* Jan 27 2009;100(2):246-50. doi:10.1038/sj.bjc.6604838
18. 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.* Oct 9 2013;310(14):1473-81. doi:10.1001/jama.2013.279201
19. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. *Br J Cancer.* Sep 15 2009;101(6):908-15. doi:10.1038/sj.bjc.6605256

20. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA*. Sep 8 2010;304(10):1073-81. doi:10.1001/jama.2010.1275
21. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. Jul 16 2016;388(10041):248-57. doi:10.1016/S0140-6736(16)30583-9
22. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol*. May 2011;18(5):1319-26. doi:10.1245/s10434-011-1630-6
23. 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*. Mar 5 2008;299(9):1019-26. doi:10.1001/jama.299.9.1019
24. 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*. Mar 11 2017;389(10073):1011-1024. doi:10.1016/S0140-6736(16)32409-6
25. Sinn M, Bahra M, Liersch T, et al. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. *J Clin Oncol*. Oct 10 2017;35(29):3330-3337. doi:10.1200/JCO.2017.72.6463
26. Tempero MA, Pelzer U, O'Reilly EM, et al. Adjuvant nab-Paclitaxel + Gemcitabine in Resected Pancreatic Ductal Adenocarcinoma: Results From a Randomized, Open-Label, Phase III Trial. *J Clin Oncol*. Apr 10 2023;41(11):2007-2019. doi:10.1200/JCO.22.01134
27. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N Engl J Med*. Dec 20 2018;379(25):2395-2406. doi:10.1056/NEJMoa1809775
28. Conroy T, Castan F, Lopez A, et al. Five-Year Outcomes of FOLFIRINOX vs Gemcitabine as Adjuvant Therapy for Pancreatic Cancer: A Randomized Clinical Trial. *JAMA Oncol*. Nov 1 2022;8(11):1571-1578. doi:10.1001/jamaoncol.2022.3829
29. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol*. Feb 20 2014;32(6):504-12. doi:10.1200/JCO.2013.50.7657
30. Palmer DH, Jackson R, Springfield C, et al. Pancreatic Adenocarcinoma: Long-Term Outcomes of Adjuvant Therapy in the ESPAC4 Phase III Trial. *J Clin Oncol*. Apr 2025;43(10):1240-1253. doi:10.1200/JCO.24.01118
31. van Dam JL, Verkolf EMM, Dekker EN, et al. Perioperative or adjuvant mFOLFIRINOX for resectable pancreatic cancer (PREOPANC-3): study protocol for a multicenter randomized controlled trial. *BMC Cancer*. Aug 7 2023;23(1):728. doi:10.1186/s12885-023-11141-5
32. Eade AV, Friedman LR, Larrain C, et al. ALLIANCE A021806: A Phase III Trial of Perioperative Versus Adjuvant Chemotherapy for Resectable Pancreatic Cancer. *Ann Surg Oncol*. Jul 24 2024;doi:10.1245/s10434-024-15817-5
33. Kaiser M. Pancreatic Cancer. *Archives of Surgery*. 1985;120(8):899.
34. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer*. 1987;59(12):2006-2010. doi:10.1002/1097-0142(19870615)59:12<2006::aid-cncr2820591206>3.0.co;2-b
35. Klinkenbijnl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. Dec 1999;230(6):776-82; discussion 782-4. doi:10.1097/00000658-199912000-00006
36. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet*. Nov 10 2001;358(9293):1576-85. doi:10.1016/S0140-6736(01)06651-x
37. Chiu YF, Liu TW, Shan YS, et al. Carbohydrate Antigen 19-9 Response to Initial Adjuvant Chemotherapy Predicts Survival and Failure Pattern of Resected Pancreatic Adenocarcinoma but Not Which Patients Are Suited for Additional Adjuvant Chemoradiation Therapy: From a Prospective Randomized Study. *Int J Radiat Oncol Biol Phys*. Sep 1 2023;117(1):74-86. doi:10.1016/j.ijrobp.2023.02.061

38. Kamarajah SK, Bundred JR, Alrawashdeh W, Manas D, White SA. A systematic review and network meta-analysis of phase III randomised controlled trials for adjuvant therapy following resection of pancreatic ductal adenocarcinoma (PDAC). *HPB (Oxford)*. May 2020;22(5):649-659. doi:10.1016/j.hpb.2019.12.001
39. Ghaneh P, Kleeff J, Halloran CM, et al. The Impact of Positive Resection Margins on Survival and Recurrence Following Resection and Adjuvant Chemotherapy for Pancreatic Ductal Adenocarcinoma. *Ann Surg*. Mar 2019;269(3):520-529. doi:10.1097/SLA.0000000000002557
40. Schiavo Lena M, Gasparini G, Crippa S, et al. Quantification of perineural invasion in pancreatic ductal adenocarcinoma: proposal of a severity score system. *Virchows Arch*. Aug 2023;483(2):225-235. doi:10.1007/s00428-023-03574-x
41. Di Martino M, Ielpo B, de Nova JLM, et al. Lymph Node Ratio, Perineural Invasion and R1 Resection as Independent Prognostic Factors in Pancreatic Adenocarcinoma: A Retrospective Cohort Study. *Surg Technol Int*. May 28 2020;36:82-88.
42. Elamir AM, Hutchinson S, Albaba H, et al. A Risk Score Model for Locoregional Recurrence Following Upfront Surgery for Pancreatic Adenocarcinoma: Implications for Adjuvant Therapy. *Clin Oncol (R Coll Radiol)*. Aug 2021;33(8):527-535. doi:10.1016/j.clon.2021.03.007
43. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). *J Clin Oncol*. Jul 20 2008;26(21):3511-6. doi:10.1200/JCO.2007.15.8782
44. 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*. Jul 20 2008;26(21):3503-10. doi:10.1200/JCO.2007.15.8469
45. Abrams R, Winter K, Goodman K, et al. NRG Oncology/RTOG 0848: Results after adjuvant chemotherapy +/- chemoradiation for patients with resected periampullary pancreatic adenocarcinoma (PA). *Journal of Clinical Oncology*. 2024;32(Number16_suppl)doi:https://doi.org/10.1200/JCO.2024.42.16_suppl.4005
46. Delpero JR, Bachellier P, Regenet N, et al. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in 150 evaluable specimens. *HPB (Oxford)*. Jan 2014;16(1):20-33. doi:10.1111/hpb.12061
47. Daamen LA, van Goor I, Schouten TJ, et al. Microscopic resection margin status in pancreatic ductal adenocarcinoma - A nationwide analysis. *Eur J Surg Oncol*. Mar 2021;47(3 Pt B):708-716. doi:10.1016/j.ejso.2020.11.145
48. Regine WF, Winter K, Abrams RA, et al. Postresection CA19-9 and margin status as predictors of recurrence after adjuvant treatment for pancreatic carcinoma: Analysis of NRG oncology RTOG trial 9704. *Adv Radiat Oncol*. Apr-Jun 2018;3(2):154-162. doi:10.1016/j.adro.2018.01.003
49. Berger AC, Winter K, Hoffman JP, et al. Five year results of US intergroup/RTOG 9704 with postoperative CA 19-9 </=90 U/mL and comparison to the CONKO-001 trial. *Int J Radiat Oncol Biol Phys*. Nov 1 2012;84(3):e291-7. doi:10.1016/j.ijrobp.2012.04.035
50. Hsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Ann Surg Oncol*. Apr 2010;17(4):981-90. doi:10.1245/s10434-009-0743-7
51. Cho M, Wang-Gillam A, Myerson R, et al. A phase II study of adjuvant gemcitabine plus docetaxel followed by concurrent chemoradiation in resected pancreaticobiliary carcinoma. *HPB (Oxford)*. Jul 2015;17(7):587-93. doi:10.1111/hpb.12413
52. Van Laethem JL, Hammel P, Mornex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol*. Oct 10 2010;28(29):4450-6. doi:10.1200/JCO.2010.30.3446
53. Lee KH, Chie EK, Im SA, et al. Phase II Trial of Postoperative Adjuvant Gemcitabine and Cisplatin Chemotherapy Followed by Chemoradiotherapy with Gemcitabine in Patients with Resected Pancreatic Cancer. *Cancer Res Treat*. Oct 2021;53(4):1096-1103. doi:10.4143/crt.2020.928
54. Schunke KJ, Rosati LM, Zahurak M, et al. Long-term analysis of 2 prospective studies that incorporate mitomycin C into an adjuvant chemoradiation regimen for pancreatic and periampullary cancers. *Adv Radiat Oncol*. Jan-Mar 2018;3(1):42-51. doi:10.1016/j.adro.2017.07.008
55. Ohman KA, Liu J, Linehan DC, et al. Interferon-based chemoradiation followed by gemcitabine for resected pancreatic adenocarcinoma: long-term follow-up. *HPB (Oxford)*. May 2017;19(5):449-457. doi:10.1016/j.hpb.2017.01.012

56. Berlin JD, Feng Y, Catalano P, et al. An Intergroup Randomized Phase II Study of Bevacizumab or Cetuximab in Combination with Gemcitabine and in Combination with Chemoradiation in Patients with Resected Pancreatic Carcinoma: A Trial of the ECOG-ACRIN Cancer Research Group (E2204). *Oncology*. 2018;94(1):39-46. doi:10.1159/000480295
57. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol*. Apr 2013;14(4):317-26. doi:10.1016/S1470-2045(13)70021-4
58. Patel AA, Nagarajan S, Scher ED, et al. Early vs. Late Chemoradiation Therapy and the Postoperative Interval to Adjuvant Therapy Do Not Correspond to Local Recurrence in Resected Pancreatic Cancer. *Pancreat Disord Ther*. Jun 2015;5(2)doi:10.4172/2165-7092.1000151
59. Ma SJ, Iovoli AJ, Hermann GM, Prezzano KM, Singh AK. Duration of chemotherapy prior to chemoradiation affects survival outcomes for resected stage I-II or unresected stage III pancreatic cancer. *Cancer Med*. Aug 2019;8(9):4110-4123. doi:10.1002/cam4.2326
60. Abrams RA, Winter KA, Safran H, et al. Results of the NRG Oncology/RTOG 0848 Adjuvant Chemotherapy Question-Erlotinib+Gemcitabine for Resected Cancer of the Pancreatic Head: A Phase II Randomized Clinical Trial. *Am J Clin Oncol*. Mar 2020;43(3):173-179. doi:10.1097/COC.0000000000000633
61. Hall WA, Colbert LE, Liu Y, et al. The influence of adjuvant radiotherapy dose on overall survival in patients with resected pancreatic adenocarcinoma. *Cancer*. Jun 15 2013;119(12):2350-7. doi:10.1002/cncr.28047
62. Bernard ME, Sutera PA, Iarrobino NA, et al. Initial Results of a Prospective Study of Adjuvant Pancreatic Stereotactic Body Radiation Therapy for Close or Positive Margins. *Adv Radiat Oncol*. Apr-Jun 2019;4(2):294-301. doi:10.1016/j.adro.2018.11.007
63. Ma T, Bai X, Wei Q, et al. Adjuvant therapy with gemcitabine and stereotactic body radiation therapy versus gemcitabine alone for resected stage II pancreatic cancer: a prospective, randomized, open-label, single center trial. *BMC Cancer*. Aug 8 2022;22(1):865. doi:10.1186/s12885-022-09974-7
64. Weinberg BA, Wang H, Noel MS, et al. Phase 1 Study of Hypofractionated Proton Beam Radiation Therapy in Adjuvant Pancreatic Cancer (PROTON-PANC). *Int J Radiat Oncol Biol Phys*. Feb 1 2024;118(2):362-367. doi:10.1016/j.ijrobp.2023.09.015
65. Dholakia AS, Kumar R, Raman SP, et al. Mapping patterns of local recurrence after pancreaticoduodenectomy for pancreatic adenocarcinoma: a new approach to adjuvant radiation field design. *Int J Radiat Oncol Biol Phys*. Dec 1 2013;87(5):1007-15. doi:10.1016/j.ijrobp.2013.09.005
66. Goodman KA, Regine WF, Dawson LA, et al. Radiation Therapy Oncology Group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer. *Int J Radiat Oncol Biol Phys*. Jul 1 2012;83(3):901-8. doi:10.1016/j.ijrobp.2012.01.022
67. 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*. Jan 1 2011;79(1):158-62. doi:10.1016/j.ijrobp.2009.10.043
68. Lee KJ, Yoon HI, Chung MJ, et al. A Comparison of Gastrointestinal Toxicities between Intensity-Modulated Radiotherapy and Three-Dimensional Conformal Radiotherapy for Pancreatic Cancer. *Gut Liver*. Mar 2016;10(2):303-9. doi:10.5009/gnl15186
69. Nichols RC, Jr., George TJ, Zaiden RA, Jr., et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. *Acta Oncol*. Apr 2013;52(3):498-505. doi:10.3109/0284186X.2012.762997
70. Nichols RC, Jr., Huh SN, Prado KL, et al. Protons offer reduced normal-tissue exposure for patients receiving postoperative radiotherapy for resected pancreatic head cancer. *Int J Radiat Oncol Biol Phys*. May 1 2012;83(1):158-63. doi:10.1016/j.ijrobp.2011.05.045
71. Ding X, Dionisi F, Tang S, et al. A comprehensive dosimetric study of pancreatic cancer treatment using three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated radiation therapy (VMAT), and passive-scattering and modulated-scanning proton therapy (PT). *Med Dosim*. Summer 2014;39(2):139-45. doi:10.1016/j.meddos.2013.11.005
72. Seufferlein T, Uhl W, Kornmann M, et al. Perioperative or only adjuvant gemcitabine plus nab-paclitaxel for resectable pancreatic cancer (NEONAX)-a randomized phase II trial of the AIO pancreatic cancer group. *Ann Oncol*. Jan 2023;34(1):91-100. doi:10.1016/j.annonc.2022.09.161

73. Cecchini M, Salem RR, Robert M, et al. Perioperative Modified FOLFIRINOX for Resectable Pancreatic Cancer: A Nonrandomized Controlled Trial. *JAMA Oncol.* Aug 1 2024;10(8):1027-1035. doi:10.1001/jamaoncol.2024.1575
74. Ahmad SA, Duong M, Sohal DPS, et al. Surgical Outcome Results From SWOG S1505: A Randomized Clinical Trial of mFOLFIRINOX Versus Gemcitabine/Nab-paclitaxel for Perioperative Treatment of Resectable Pancreatic Ductal Adenocarcinoma. *Ann Surg.* Sep 1 2020;272(3):481-486. doi:10.1097/SLA.0000000000004155
75. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol.* Jan 2015;191(1):7-16. doi:10.1007/s00066-014-0737-7
76. Coveler AL, Pillarisetty VG, Koh WJ, et al. Perioperative Chemotherapy and Chemoradiotherapy for Patients With Resectable and Borderline Resectable Pancreatic Adenocarcinoma. *Pancreas.* May 1 2023;52(5):e282-e287. doi:10.1097/MPA.0000000000002253
77. Versteijne E, van Dam JL, Suker M, et al. Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial. *J Clin Oncol.* Apr 10 2022;40(11):1220-1230. doi:10.1200/JCO.21.02233
78. Ma SJ, Serra LM, Bartl AJ, et al. Adjuvant chemotherapy versus observation following neoadjuvant therapy and surgery for resectable stage I-II pancreatic cancer. *J Radiother Pract.* Sep 2022;21(3):383-392. doi:10.1017/s1460396921000194
79. de Geus SWL, Kasumova GG, Eskander MF, et al. Is Neoadjuvant Therapy Sufficient in Resected Pancreatic Cancer Patients? A National Study. *J Gastrointest Surg.* Feb 2018;22(2):214-225. doi:10.1007/s11605-017-3541-8
80. Lee B, Tie J, Wang Y, et al. The potential role of serial circulating tumor DNA (ctDNA) testing after upfront surgery to guide adjuvant chemotherapy for early stage pancreatic cancer: The AGITG DYNAMIC-Pancreas trial.. *J Clin Oncol.* 2024;42(16)(107)doi:https://doi.org/10.1200/JCO.2024.42.16_suppl.10
81. Sohal DPS, Kennedy EB, Cinar P, et al. Metastatic Pancreatic Cancer: ASCO Guideline Update. *J Clin Oncol.* Sep 20 2020;38(27):3217-3230. doi:10.1200/JCO.20.01364
82. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *N Engl J Med.* Jul 25 2019;381(4):317-327. doi:10.1056/NEJMoa1903387
83. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. *J Clin Oncol.* Jan 1 2024;42(1):47-58. doi:10.1200/JCO.23.02005
84. Shin JE, An HJ, Park HS, Kim H, Shim BY. Efficacy of dabrafenib/trametinib in pancreatic ductal adenocarcinoma with BRAF NVTAP deletion: A case report. *Front Oncol.* 2022;12:976450. doi:10.3389/fonc.2022.976450
85. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med.* Feb 22 2018;378(8):731-739. doi:10.1056/NEJMoa1714448
86. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science.* Jul 28 2017;357(6349):409-413. doi:10.1126/science.aan6733
87. Hu ZI, Shia J, Stadler ZK, et al. Evaluating Mismatch Repair Deficiency in Pancreatic Adenocarcinoma: Challenges and Recommendations. *Clin Cancer Res.* Mar 15 2018;24(6):1326-1336. doi:10.1158/1078-0432.CCR-17-3099
88. Pishvaian MJ, Blais EM, Brody JR, et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial. *Lancet Oncol.* Apr 2020;21(4):508-518. doi:10.1016/S1470-2045(20)30074-7

Variant 1: Resected Node-Negative Pancreatic Cancer

64 year-old male (BMI = 26) undergoes pancreaticoduodenectomy for an anatomically resectable, stage pT1N0M0 moderately differentiated adenocarcinoma of the pancreatic head. Final pathology shows a 1.8 cm tumor with negative margins, 0 of 18 involved lymph nodes, and absence of lymphovascular or perineural invasion. Pre-operative CA 19-9 was 119 and post-operative CA 19-9 is 22. Restaging contrast-enhanced CT of the chest, abdomen, and pelvis shows no evidence of distant metastases. The patient is recovering well and gaining weight - ECOG 1.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
• Observation	U	2	8	4	0	0	0	0	0	0	2		S	↑
• Adjuvant chemotherapy alone	A	0	0	0	1	0	0	1	11	1	8		S	↑
• Adjuvant radiation alone	U	0	12	2	0	0	0	0	0	0	2		EC	↑
• Adjuvant chemoradiation	U	0	3	8	1	1	1	0	0	0	3		S	↑
• Adjuvant chemotherapy followed by chemoradiation	M	0	0	0	3	6	4	0	0	1	5		S	↑

Variant Discussion:

Adjuvant therapy should be considered for the majority of patients with resected PDAC who have adequately recovered from surgery and should ideally begin within 12 weeks.

Prospective trials have demonstrated improvement in overall survival with the addition of 6 months of postoperative chemotherapy for patients with resected PDAC. Modified FOLFIRINOX is considered the preferred adjuvant chemotherapy for fit patients following surgery, whereas in patients for whom mFOLFIRINOX would be deemed poorly tolerated, gemcitabine plus capecitabine or gemcitabine alone are appropriate options.

The role of postoperative chemoradiation following surgery for resectable PDAC is less clear. In general, postoperative treatment should be sequenced with initial systemic therapy and the addition of postoperative chemoradiation may be selectively considered in those that do not have distant metastatic disease progression on interval imaging. Multiple factors such as margin status, lymph node status, tumor grade, perineural invasion, or lymphovascular invasion have demonstrated prognostic associations and should be incorporated into treatment decisions regarding the role of radiotherapy.

Gemcitabine, 5-FU, or capecitabine are each considered appropriate options for concurrent delivery with postoperative radiotherapy.

Postoperative chemoradiation should generally be delivered to a dose of 50-54 Gy in 1.8-2.0 Gy fractions encompassing the postoperative resection bed, pancreaticojejunostomy, and adjacent areas of risk including the celiac, superior mesenteric, porta hepatis, and periaortic/retroperitoneal lymph node regions. Both 3D-CRT or IMRT are appropriate. IMRT offers improved high dose conformity and an associated reduction in gastrointestinal toxicity. At present, there is insufficient data to provide strong support of post-operative SBRT or alternative fractionation schemes.

In this case of pT1N0M0 PDAC resected with negative margins and no other high-risk features for recurrence, postoperative chemotherapy should be considered. The addition of chemoradiation following initial systemic therapy may also be reasonable to consider if there is no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9.

Necessary components of care:

- Restaging imaging and CA 19-9 should be repeated after each treatment modality
- Adjuvant therapy for a patient with localized PDAC who has not received neoadjuvant therapy

Variant 2: Resected Node-Positive Pancreatic Cancer

59 year-old male (BMI = 23) undergoes pancreaticoduodenectomy for an anatomically resectable, stage pT2N1M0 moderately differentiated adenocarcinoma of the pancreatic head. Final pathology shows a 3.1 cm tumor with negative margins, 2 of 22 involved lymph nodes (peripancreatic), with lymphovascular and perineural invasion. Pre-operative CA 19-9 was 280 and post-operative CA 19-9 is 130. Restaging contrast-enhanced CT of the chest, abdomen, and pelvis shows no evidence of distant metastases. The patient is recovering well and gaining weight - ECOG 1.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
• Observation	U	5	7	2	0	0	0	0	0	0	2		S	↑
• Adjuvant chemotherapy alone	A	0	0	0	0	0	0	5	7	2	8		S	↑
• Adjuvant radiation alone	U	3	7	4	0	0	0	0	0	0	2		EC	↑
• Adjuvant chemoradiation	U	1	4	9	0	0	0	0	0	0	3		S	↑
• Adjuvant chemotherapy followed by chemoradiation	M	0	0	0	2	7	2	2	1	0	5		S	↑

Variant Discussion:

Adjuvant therapy should be considered for the majority of patients with resected PDAC who have adequately recovered from surgery and should ideally begin within 12 weeks.

Prospective trials have demonstrated improvement in overall survival with the addition of 6 months of postoperative chemotherapy for patients with resected PDAC. Modified FOLFIRINOX is considered the preferred adjuvant chemotherapy for fit patients following surgery, whereas in patients for whom mFOLFIRINOX would be deemed poorly tolerated, gemcitabine plus capecitabine or gemcitabine alone are appropriate options.

The role of postoperative chemoradiation following surgery for resectable PDAC is less clear. In general, postoperative treatment should be sequenced with initial systemic therapy and the addition of postoperative chemoradiation may be selectively considered in those that do not have distant metastatic disease progression on interval imaging. Multiple factors such as margin status, lymph node status, tumor grade, perineural invasion, or lymphovascular invasion have demonstrated prognostic associations and should be incorporated into treatment decisions regarding the role of radiotherapy.

Gemcitabine, 5-FU, or capecitabine are each considered appropriate options for concurrent delivery with postoperative radiotherapy.

Postoperative chemoradiation should generally be delivered to a dose of 50-54 Gy in 1.8-2.0 Gy fractions encompassing the postoperative resection bed, pancreaticojejunostomy, and adjacent areas of risk including the celiac, superior mesenteric, porta hepatis, and periaortic/retroperitoneal lymph node regions. Both 3D-CRT or IMRT are appropriate. IMRT offers improved high dose conformity and an associated reduction in gastrointestinal toxicity. At present, there is insufficient data to provide strong support of post-operative SBRT or alternative fractionation schemes.

In this case of pT2N1M0 PDAC resected with negative margins but high-risk features for recurrence including positive lymph nodes, lymphovascular invasion, perineural invasion, and elevated post-operative CA 19-9, postoperative chemotherapy should be considered. The addition of chemoradiation following initial systemic therapy may also be reasonable to consider if there no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9.

Necessary components of care:

- Restaging imaging and CA 19-9 should be repeated after each treatment modality
- Adjuvant therapy for a patient with localized PDAC who has not received neoadjuvant therapy with high-risk pathologic features (including positive surgical margin, node-positive disease, lymphovascular and perineural invasion)

Variant 3: Resected Node-Negative Pancreatic Cancer with Positive Surgical Margin (R1)

67 year-old female (BMI = 25) undergoes pancreaticoduodenectomy for an initially anatomically resectable, stage pT4N0M0 poorly differentiated adenocarcinoma of the pancreatic neck. Final pathology shows a 4.1 cm tumor with microscopic positive surgical margin at the SMA, 0 of 21 involved lymph nodes, and presence of lymphovascular and perineural invasion. Pre-operative CA 19-9 was 198 and post-operative CA 19-9 is 120. Restaging contrast-enhanced CT of the chest, abdomen, and pelvis shows no evidence of local recurrence or distant metastases. The patient is recovering well and gaining weight - ECOG 1.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
• Observation	U	8	4	1	0	1	0	0	0	0	1		S	↑
• Adjuvant chemotherapy alone	A	0	0	0	0	0	0	6	8	0	8		S	↑
• Adjuvant radiation alone	U	4	9	1	0	0	0	0	0	0	2		EC	↑
• Adjuvant chemoradiation	U	4	3	5	0	0	0	2	0	0	3		S	↑
• Adjuvant chemotherapy followed by chemoradiation	A	0	0	0	0	1	2	10	1	0	7		S	↑

Variant Discussion:

Adjuvant therapy should be considered for the majority of patients with resected PDAC who have adequately recovered from surgery and should ideally begin within 12 weeks.

Prospective trials have demonstrated improvement in overall survival with the addition of 6 months of postoperative chemotherapy for patients with resected PDAC. Modified FOLFIRINOX is considered the preferred adjuvant chemotherapy for fit patients following surgery, whereas in patients for whom mFOLFIRINOX would be deemed poorly tolerated, gemcitabine plus capecitabine or gemcitabine alone are appropriate options.

The role of postoperative chemoradiation following surgery for resectable PDAC is less clear. In general, postoperative treatment should be sequenced with initial systemic therapy and the addition of postoperative chemoradiation may be selectively considered in those that do not have distant metastatic disease progression on interval imaging. Multiple factors such as margin status, lymph node status, tumor grade, perineural invasion, or lymphovascular invasion have demonstrated prognostic associations and should be incorporated into treatment decisions regarding the role of radiotherapy. Gemcitabine, 5-FU, or capecitabine are each considered appropriate options for concurrent delivery with postoperative radiotherapy. Postoperative chemoradiation should generally be delivered to a dose of 50-54 Gy in 1.8-2.0 Gy fractions encompassing the postoperative resection bed, pancreaticojejunostomy, and adjacent areas of risk including the celiac, superior mesenteric, porta hepatis, and periaortic/retroperitoneal lymph node regions. Extrapolating from retrospective data from locally advanced PDAC, focal radiation dose intensification targeting identifiable gross residual disease and/or compromised margin may be considered, however, highest priority should be placed on limiting dose to gastrointestinal luminal organs. Both 3D-CRT or IMRT are appropriate. IMRT offers improved high dose conformity and an associated reduction in gastrointestinal toxicity and is preferred when considering dose escalation. At present, there is insufficient data to provide strong support of post-operative SBRT or alternative fractionation schemes.

In this case of pT4N0M0 PDAC resected with positive margins and other high-risk features for recurrence including lymphovascular invasion, perineural invasion, and elevated post-operative CA 19-9, postoperative chemotherapy should be considered. The addition of chemoradiation following initial systemic therapy would also be reasonable to consider if there is no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9.

Necessary components of care:

- Restaging imaging and CA 19-9 should be repeated after each treatment modality
- Adjuvant therapy for a patient with localized PDAC who has not received neoadjuvant therapy with high-risk pathologic features (including positive surgical margin, node-positive disease, lymphovascular and perineural invasion)

Variant 4: Resected Node-Negative Pancreatic Cancer Who Received Neoadjuvant Chemotherapy

65 year-old male (BMI = 26) presented with a CA 19-9 of 210 and a cT3N0M0 moderately differentiated adenocarcinoma of the head of the pancreas with tumor abutting < 180 degrees of the portal vein and no evidence of distant metastases on contrast-enhanced CT of the chest, abdomen, and pelvis. After multidisciplinary discussion, the patient received 6 cycles of neoadjuvant modified FOLFIRINOX followed by restaging imaging demonstrating good local response and no progression of disease. CA 19-9 was 66. The patient underwent pancreaticoduodenectomy with venous resection and reconstruction. Final pathology shows a 2.1 cm tumor with negative margin, 0 of 19 involved lymph nodes, and absence of lymphovascular and perineural invasion. Post-operative CA 19-9 is 32. The patient is recovering well and gaining weight - ECOG 1.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
• Observation		0	3	4	7	0	0	0	0	0	4	X	S	↑
• Adjuvant chemotherapy alone	A	0	0	0	0	0	0	2	12	0	8		S	↑
• Adjuvant radiation alone	U	2	9	3	0	0	0	0	0	0	2		EC	↑
• Adjuvant chemoradiation	U	2	8	4	0	0	0	0	0	0	2		S	↑
• Adjuvant chemotherapy followed by chemoradiation	M	0	0	0	10	3	1	0	0	0	4		S	↑

Variant Discussion:

For patients who receive neoadjuvant systemic therapy prior to curative-intent resection for PDAC, the current standard approach is to complete a total of 6 months of chemotherapy if less than 6 months were administered in the neoadjuvant setting.

The role of postoperative chemoradiation in patients who received neoadjuvant chemotherapy has not been defined. Considering the paucity of literature, the indications and use of post-operative chemoradiation are extrapolations from data for post-operative chemoradiation following up-front surgical resection. In such circumstances, multiple factors such as pathologic response, margin status, lymph node status, tumor grade, perineural invasion, or lymphovascular invasion have demonstrated prognostic associations and should be incorporated into treatment decisions regarding the role of radiotherapy.

Gemcitabine, 5-FU, or capecitabine are each considered appropriate options for concurrent delivery with postoperative radiotherapy.

Postoperative chemoradiation should generally be delivered to a dose of 50-54 Gy in 1.8-2.0 Gy fractions encompassing the postoperative resection bed, pancreaticojejunostomy, and adjacent areas of risk including the celiac, superior mesenteric, porta hepatis, and periaortic/retroperitoneal lymph node regions. Both 3D-CRT or IMRT are appropriate. IMRT offers improved high dose conformality and an associated reduction in GI toxicity. At present, there is insufficient data to provide strong support of post-operative SBRT or alternative fractionation schemes.

In this case ypT2N0M0 PDAC resected with negative margins and no additional high-risk features, an additional 3 months of post-operative chemotherapy should be considered to complete a total of 6 months. The addition of chemoradiation following initial systemic therapy may also be reasonable to consider if there is no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9.

Necessary components of care:

- Restaging imaging and CA 19-9 should be repeated after each treatment modality

Variant 5: Resected Node-Positive Pancreatic Cancer Who Received Neoadjuvant Chemotherapy

68 year-old female (BMI = 27) presented with a CA 19-9 of 250 and a cT3N0M0 moderately differentiated adenocarcinoma of the uncinate process of the pancreas with tumor abutting < 180 degrees of the SMV. There is no evidence of distant metastases on contrast-enhanced CT of the chest, abdomen, and pelvis. After multidisciplinary discussion, the patient received 6 cycles of neoadjuvant modified FOLFIRINOX followed by restaging imaging demonstrating good local response and no progression of disease. CA 19-9 was 195. The patient underwent pancreaticoduodenectomy with venous resection and reconstruction. Final pathology shows a 3.1 cm tumor with negative surgical margin, 1 of 21 involved lymph nodes (peripancreatic), with lymphovascular and perineural invasion. Post-operative CA 19-9 is 120. The patient is recovering well and gaining weight - ECOG 1.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
• Observation	U	4	6	4	0	0	0	0	0	0	2		S	↑
• Adjuvant chemotherapy alone	A	0	0	0	1	0	0	2	9	2	8		S	↑
• Adjuvant radiation alone	U	2	9	3	0	0	0	0	0	0	2		EC	↑
• Adjuvant chemoradiation	U	2	7	4	0	0	1	0	0	0	2		S	↑
• Adjuvant chemotherapy followed by chemoradiation	M	0	0	0	3	7	3	0	1	0	5		S	↑

Variant Discussion:

For patients who receive neoadjuvant systemic therapy prior to curative-intent resection for PDAC, the current standard approach is to complete a total of 6 months of chemotherapy if less than 6 months were administered in the neoadjuvant setting.

The role of postoperative chemoradiation in patients who received neoadjuvant chemotherapy has not been defined. Considering the paucity of literature, the indications and use of post-operative chemoradiation are extrapolations from data for post-operative chemoradiation following up-front surgical resection. In such circumstances, multiple factors such as pathologic response, margin status, lymph node status, tumor grade, perineural invasion, or lymphovascular invasion have demonstrated prognostic associations and should be incorporated into treatment decisions regarding the role of radiotherapy.

Gemcitabine, 5-FU, or capecitabine are each considered appropriate options for concurrent delivery with postoperative radiotherapy.

Postoperative chemoradiation should generally be delivered to a dose of 50-54 Gy in 1.8-2.0 Gy fractions encompassing the postoperative resection bed, pancreaticojejunostomy, and adjacent areas of risk including the celiac, superior mesenteric, porta hepatis, and periaortic/retroperitoneal lymph node regions. Both 3D-CRT or IMRT are appropriate. IMRT offers improved high dose conformity and an associated reduction in GI toxicity. At present, there is insufficient data to provide strong support of post-operative SBRT or alternative fractionation schemes.

In this case of ypT2N1M0 PDAC resected with negative margins but high-risk features for recurrence including positive lymph nodes, lymphovascular invasion, perineural invasion, and elevated post-operative CA 19-9, an additional 3 months of post-operative chemotherapy should be considered to complete a total of 6 months. The addition of chemoradiation following initial systemic therapy may also be reasonable to consider if there is no evidence of distant metastasis upon interval imaging assessment and stable CA 19-9.

Necessary components of care:

- Restaging imaging and CA 19-9 should be repeated after each treatment modality
- Completion of 6 months of systemic therapy if not administered preoperatively

Variant 6: Resected Node-Positive Pancreatic Cancer with Poor Postoperative Performance Status

70 year-old male (BMI = 22) with performance status ECOG 1 undergoes pancreaticoduodenectomy for a stage pT2N1M0 moderately differentiated adenocarcinoma of the pancreatic head. Final pathology shows a 3.6 cm tumor with negative margins, 3 of 19 involved lymph nodes (peripancreatic) with perineural invasion but no lymphovascular invasion. Pre-operative CA 19-9 was 212 and post-operative CA 19-9 is 120. Restaging contrast-enhanced CT of the chest, abdomen, and pelvis shows no evidence of distant metastases. The patient developed an anastomotic leak requiring surgical intervention. The recovery is prolonged and at 12 weeks following initial resection the patient is not yet gaining weight and has performance status ECOG 2.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
• Observation with supportive care	A	1	0	1	0	1	0	6	4	1	7		S	↑
• Adjuvant chemotherapy alone	M	0	0	0	12	2	0	0	0	0	4		S	↑
• Adjuvant radiation alone	U	3	9	2	0	0	0	0	0	0	2		EC	↑
• Adjuvant chemoradiation	U	3	9	2	0	0	0	0	0	0	2		S	↑
• Adjuvant chemotherapy followed by chemoradiation	U	1	8	4	0	1	0	0	0	0	2		S	↑

Variant Discussion:

Adjuvant therapy should be considered for the majority of patients with resected PDAC who have adequately recovered from surgery and should ideally begin within 12 weeks.

In this case of pT2N1M0 PDAC resected with negative margins but other high-risk features for recurrence including positive lymph nodes, perineural invasion, and elevated post-operative CA 19-9, postoperative chemotherapy is generally indicated. However, due to post-operative complications and poor performance status, medical management and supportive care with the goal of optimization of patient performance status should be pursued prior to consideration of adjuvant therapies. Adequate recovery from surgery is required for consideration of multi-agent chemotherapy. For patients with borderline performance status (ECOG 2), single agent chemotherapy could be considered with caution.

Necessary components of care:

- Medical management and supportive care with the goal of optimization of patient performance status prior to consideration of adjuvant therapies
- Interval restaging imaging and CA 19-9

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the references associated with the recommendation.

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Necessary Procedure:

- 1) The procedure must be without disagreement.
- 2) It would be considered improper care not to provide this service.
- 3) There is a reasonable chance that this procedure will benefit the patient.
- 4) The benefit to the patient is not small.

Key:

BMI: Body mass index

CA 19-9: Carbohydrate antigen 19-9

CT: Computed Tomography

ECOG: Eastern Cooperative Oncology Group

PDAC: Pancreatic ductal adenocarcinoma

FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin

5-FU: 5-fluorouracil

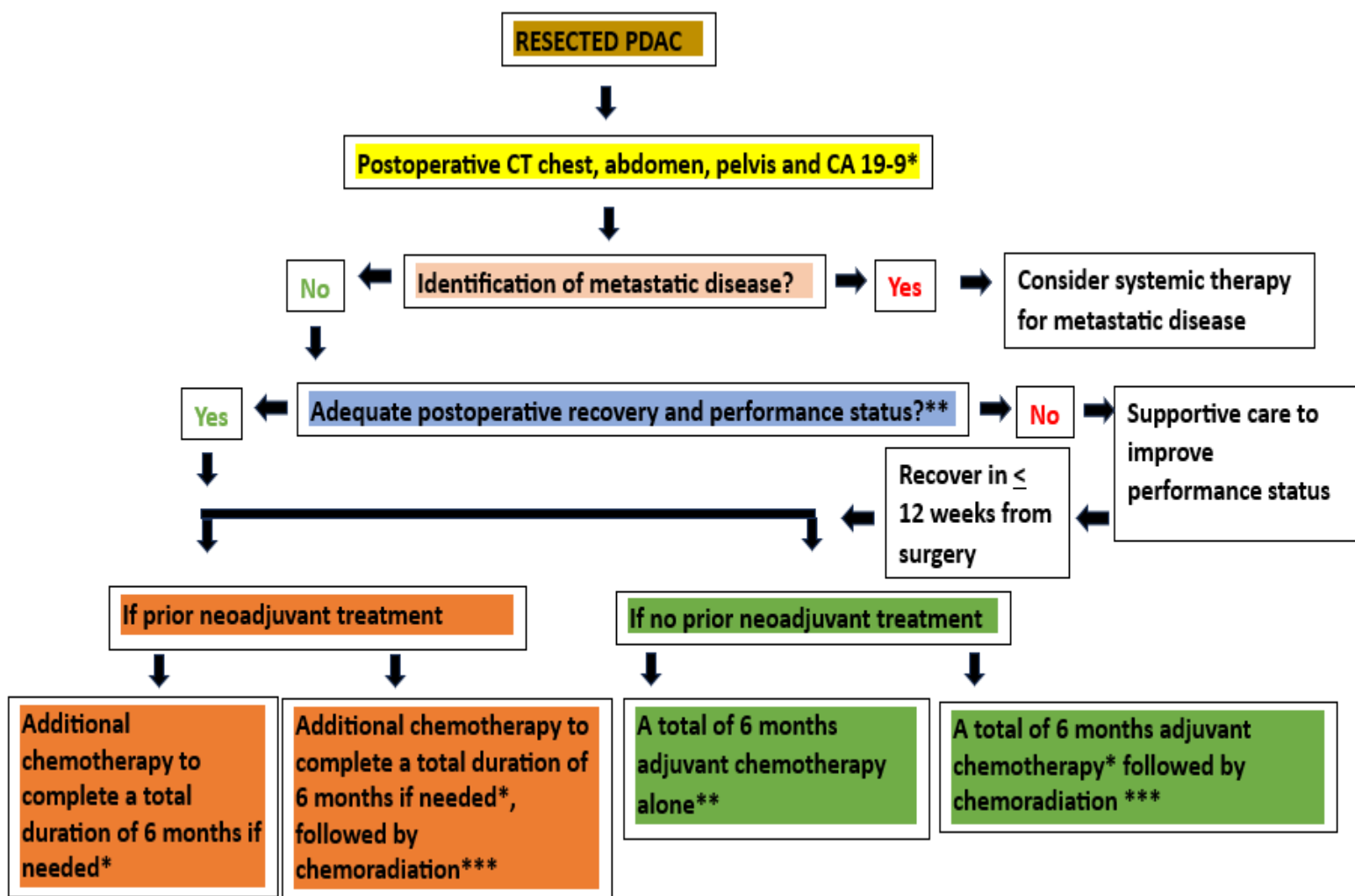
Gy: Gray

3D-CRT: 3-dimensional conformal radiotherapy

IMRT: Intensity-modulated radiation therapy

SBRT: Stereotactic Body Radiotherapy

TREATMENT ALGORITHM FOR ADJUVANT THERAPY FOR RESECTED ADENOCARCINOMA OF THE PANCREAS



*Restaging imaging and CA 19-9 should be repeated after each treatment modality (Elevated CA 19-9 without other evidence of disease recurrence is not a clear indication of recurrence)

**Adjuvant therapy should be considered for patients who have adequately recovered from surgery and should ideally begin within 12 weeks

***Chemoradiation may be considered in those who do not have metastatic disease progression after initial post-operative chemotherapy, and should be considered for those with positive surgical margins

Performed on July 11, 2024; Updated February 13, 2026

A comprehensive search of several databases was performed on July 11, 2024 and updated February 13, 2026. Results were limited by study design, English Language, and date from 2014 forward. Databases searched were Ovid MEDLINE(R) (1946+ including epub ahead of print, in-process, and other nonindexed citations), Ovid Embase (1974+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), and Scopus via Elsevier (1970+).

The search strategies were designed and conducted by a medical librarian with input from the study investigators. Controlled vocabulary supplemented with keywords was used. The actual strategies listing all search terms used and how they are combined is available in the supplemental material.

#	Searches
1	exp *Pancreatic Neoplasms/
2	*Carcinoma, Pancreatic Ductal/
3	*pancreatic intraductal neoplasms/
4	(pancrea* adj3 (cancer* or carcino* or neoplas* or malignan* or tumor* or tumour* or adenocarcinoma*)).ti.
5	or/1-4
6	Surgical Procedures, Operative/ or su.fs.
7	(surger* or surgical* or resection* or resected or pancreatectom* or pancreaticoduodenectom* or whipple* or operat* or operab* or "post-operativ*" or postoperativ*).ti,ab,kf.
8	6 or 7
9	5 and 8
10	exp *Antineoplastic Agents/
11	Antineoplastic Combined Chemotherapy Protocols/ (Abecma or Abemaciclib or "Abiraterone-Acetate" or Abraxane or ABVD or ABVE or "ABVE-PC" or Acalabrutinib or "AC-T" or Actemra or Adagrasib or Adcetris or "Ado-Trastuzumab-Emtansine" or Adriamycin or Adstiladrin or "Afatinib-Dimaleate" or Afinitor or Aflibercept or Akeega or "Akynzeo-Netupitant-and-Palonosetron-Hydrochloride" or "Aldara-Imiquimod" or Aldesleukin or "Alecensa-Alectinib" or Alectinib or Alemtuzumab or "Alimta-Pemetrexed-Disodium" or Alkeran or "alkylating-agent*" or "alkylating-drug*" or Aloxi or Alpelisib or Alunbrig or Alymsys or Ameluz or Amifostine or "Aminolevulinic-Acid-Hydrochloride" or Amivantamab or Amtagvi or Anastrozole or "Angiogenesis-Inhibitor*" or Anktiva or anticancer* or "anti-cancer*" or Anticarcinogenic* or "Anti-carcinogenic*" or antimetabolite* or "anti-metabolite*" or Antimitotic* or "Anti-mitotic*" or antineoplastic* or "anti-neoplastic*" or antitumor or "anti-tumor" or antitumour or "anti-tumour" or Apalutamide or Aprepitant or Aranesp or Aredia or Arimidex or Aromasin or Arranon or "Arsenic-Trioxide" or Arzerra or "Asciminib-Hydrochloride" or "Asparaginase-Erwinia-Chrysanthemi" or Asparlas or Atezolizumab or Augtyro or Avapritinib or Avastin or Avelumab or "Axicabtagene-Ciloleucel" or Axitinib or Ayvakit or Azacitidine or Azedra or Balversa or Bavencio or BEACOPP or Beleodaq or Belinostat or Belzutifan or "Bendamustine-Hydrochloride" or Bendeka or berzoserib or Besponsa or Besremi or Bevacizumab or
12	Bevcizumab or Bexarotene or Bicalutamide or BiCNU or Binimetinib or "Bleomycin-Sulfate" or Blinatumomab or Blinecyto or Bortezomib or Bosulif or Bosutinib or Braftovi or "Brentuximab-Vedotin" or "Brexucabtagene-Autoleucel" or Breyanzi or Brigatinib or Brukinsa or BuMel or Busulfan or Busulfex or Cabazitaxel or Cablivi or Cabometyx or "Cabozantinib-S-Malate" or Calaspargase or "Calaspargase-Pegol-mknl" or Calquence or Campath or Camptosar or Capecitabine or Capivasertib or Caplacizumab or "Capmatinib-Hydrochloride" or CAPOX or Carac or Carboplatin or "CARBOPLATIN-TAXOL" or Carfilzomib or Carmustine or Carvykti or Casodex or CEM or Cemiplimab or Ceritinib or Cervarix or Cetuximab or chemotherap* or chemoradio* or Chlorambucil or CHOP or "Ciltacabtagene-Autoleucel" or Cisplatin or Cladribine or Clofarabine or Clolar or "Cobimetinib-Fumarate" or Columvi or Cometriq or COPDAC or Copiktra or Cosmegen or Cotellic or Crizotinib or Cyclophosphamide or Cyramza or Cytarabine or "Dabrafenib-Mesylate" or Dacarbazine or Dacogen or Dacomitinib or Dactinomycin or Danyelza or Daratumumab or Darbepoetin or Darolutamide or Darzalex or Dasatinib or "Daunorubicin-Hydrochloride" or Daurismo or Decitabine or "Defibrotide-Sodium" or Defitelio or Degarelix or "Denileukin-Diftitox" or Denosumab or Dexamethasone or "Dexrazoxane-Hydrochloride" or Dinutuximab or Docetaxel or Dostarlimab or Doxil or Doxorubicin or Durvalumab or Duvelisib or "Eflornithine-Hydrochloride" or Efudex or "Elacestrant-Dihydrochloride" or Elahere or Eligard or Elitek or Ellence or

Elotuzumab or Eloxatin or Elranatamab or Elrexio or "Eltrombopag-Olamine" or Elzonris or Emapalumab or Emend or Emlipicit or "Enasidenib-Mesylate" or Encorafenib or "Enfortumab-Vedotin" or Enhertu or Entrectinib or Enzalutamide or Eporitamab or "Epirubicin-Hydrochloride" or EpiKinly or "Epoeti-Alfa" or Epogen or Erbitux or Erdafitinib or "Eribulin-Mesylate" or Erivedge or Erleada or "Erlotinib-Hydrochloride" or Erwinaze or Ethyol or Etopophos or Etoposide or Everolimus or Evista or Evomela or Exemestane or Fareston or Faslodex or "Fedratinib-Hydrochloride" or Femara or Filgrastim or Firmagon or "Fludarabine-Phosphate" or Fluoroplex or Fluorouracil or Flutamide or FOLFIRI or FOLFIRINOX or FOLFOX or Folutyn or "Fostamatinib Disodium" or Fotivda or Fruquintinib or Fruzaqla or Fulphila or "FU-LV" or Fulvestrant or Futibatinib or Fyarro or Gamifant or Gardasil or Gavreto or Gazyva or Gefitinib or Gemcitabine or Gemtuzumab or Gemzar or Gilotrif or "Gilteritinib Fumarate" or "Glasdegib-Maleate" or Gleevec or "Gliadel-Wafer" or Glofitamab or Glucarpidase or "Goserelin-Acetate" or Granisetron or Granix or Halaven or Hemangeol or Hepzato or Herceptin or "Herceptin-Hylecta" or "HPV-Bivalent-Vaccine*" or "HPV-Nonavalent-Vaccine*" or "HPV-Quadrivalent-Vaccine*" or Hycamtin or Hydrea or Hydroxyurea or "Hyper-CVAD" or Ibrance or Ibritumomab or Ibrutinib or Iclusig or "Idamycin-PFS" or "Idarubicin-Hydrochloride" or "Idacabtagene-Vicleucel" or Idelalisib or Idhifa or Ifex or Ifosfamide or "IL-2" or "Imatinib-Mesylate" or Imbruvica or Imfinzi or Imiquimod or Imjudo or Imlygic or Inbakicept or Infugem or Inlyta or "Inotuzumab-Ozogamicin" or Inqovi or Inrebic or "Interferon-Alfa-2b" or "Interleukin-2" or "Intron-A" or Iobenguane or Ipilimumab or Iressa or "Irinotecan Hydrochloride" or "Irinotecan-Sucrosolate" or Isatuximab or Istodax or Ivosidenib or Iwifin or Ixabepilone or "Ixazomib-Citrate" or Ixempra or Jakafi or Jaypirca or Jelmyto or Jemperli or Jevtana or Kadcyla or Kepivance or Keytruda or Kimmtrak or Kisqali or Koselugo or Krazati or Kymriah or Kypolis or "Lanreotide-Acetate" or "Lapatinib Ditosylate" or "Larotrectinib-Sulfate" or Lenalidomide or "Lenvatinib-Mesylate" or Lenvima or Letrozole or "Leucovorin-Calcium" or Leukeran or "Leuprolide-Acetate" or "Levulan-Kerastick" or Libtayo or Lifileucel or "Lisocabtagene-Maraleucel" or Lomustine or "Loncastuximab-Tesirine" or Lonsurf or Loqtorzi or Lorbrina or Lorlatinib or Lumakras or Lumoxiti or Lunsumio or "Lupron-Depot" or Lurbinectedin or Luspatercept or Lutathera or Lutetium or Lynparza or Lytobi or Margenza or Margetuximab or Matulane or "Mechlorethamine-Hydrochloride" or "Megestrol-Acetate" or Mekinist or Mektovi or Melphalan or "Melphalan-Hydrochloride" or Mercaptopurine or Mesna or Mesnex or "Methotrexate-Sodium" or "Methylnaltrexone-Bromide" or Midostaurin or "Mirvetuximab-Soravtansine" or Mitomycin or "Mitoxantrone-Hydrochloride" or Mogamulizumab or "Momelotinib-Dihydrochloride-Monohydrate" or Monjuvi or MOPP or Mosunetuzumab or "Moxetumomab-Pasudotox" or Mozobil or "MTOR-Inhibitor*" or MVAC or Mvasi or "Myeloablative-Agonist*" or Myleran or Mylotarg or Nadofaragene or "Nadofaragene-Firadenovec" or Naxitamab or "Naxitamab-gqgk" or Necitumumab or Nelarabine or "Neratinib-Maleate" or Nerlynx or "Netupitant-and-Palonosetron-Hydrochloride" or Neulasta or Neupogen or Nexavar or Nilandron or Nilotinib or Nilutamide or Ninlaro or "Niraparib-Tosylate-Monohydrate" or "Nirogacestat-Hydrobromide" or Nivestym or Nivolumab or Nogapendekin or "Nogapendekin-Alfa" or Nplate or Nubeqa or Nyvepria or Obinutuzumab or Odomzo or Ofatumumab or Ogsiveo or Ojemda or Ojjaara or Olaparib or Olutasidenib or "Omacetaxine-Mepesuccinate" or Oncaspar or "Ondansetron-Hydrochloride" or Onivyde or Ontak or Onureg or Opdivo or Opdualag or OPPA or Orgovyx or Orserdu or "Osimertinib-Mesylate" or Oxaliplatin or Ozogamicin or Paclitaxel or "Pacritinib Citrate" or Padcev or Palbociclib or Palifermin or "Palonosetron-Hydrochloride" or "Pamidronate-Disodium" or Panitumumab or Paraplatin or "Pazopanib-Hydrochloride" or Pegaspargase or Pegfilgrastim or Pemazyre or Pembrolizumab or "Pemetrexed-Disodium" or Pemigatinib or Perjeta or Pertuzumab or "Pexidartinib-Hydrochloride" or Phesgo or Piqray or Pirtobrutinib or "platinum-based" or Plerixafor or Pluvicto or "Polatuzumab Vedotin" or Polivy or "Polymerase-Inhibitor*" or Pomalidomide or Pomalyst or "Ponatinib-Hydrochloride" or Portrazza or Poteligeo or Pralatrexate or Pralsetinib or Prednisone or "Procarbazine-Hydrochloride" or Procrit or Proleukin or Prolia or Promacta or "Propranolol-Hydrochloride" or Provenge or "purine-analog*" or "purine-antagonist*" or Purinethol or Purixan or Qinlock or "Quizartinib-Dihydrochloride" or "Radium-223-Dichloride" or "Raloxifene-Hydrochloride" or Ramucirumab or Rasburicase or Ravulizumab or "R-CHOP" or "R-CVP" or Reblozyl or "Recombinant-HPV-Bivalent-Vaccine*" or "Recombinant-HPV-Nonavalent-Vaccine*" or "Recombinant-HPV-Quadrivalent-Vaccine*" or "Recombinant-Human-Papillomavirus-Bivalent-Vaccine*" or "Recombinant-Human-Papillomavirus-Nonavalent-Vaccine*" or "Recombinant-Human-Papillomavirus-Quadrivalent-Vaccine*" or "Recombinant-Interferon-Alfa-2b" or Regorafenib or Relistor or Relugolix or "R-EPOCH" or Repotrectinib or Retacrit or Retevmo or Retifanlimab or Revlimid or Rezlidhia or Riabni or Ribociclib or "R-ICE" or Ripretinib or Rituxan or Rituximab or "Rolapitant-Hydrochloride" or Romidepsin or Romiplostim or "Ropeginterferon-Alfa" or Rozlytrek or Rubraca or "Rucaparib-Camsylate" or Ruxience or "Ruxolitinib-Phosphate" or Rybrevant or Rydapt or Rylaze or "Sacituzumab-Govitecan" or Sancuso or Sarelisa or Scemblix or "Sclerosol-Intrapleural" or Selinexor or Selpercatinib or "Selumetinib-Sulfate" or Siltuximab or "Sipuleucel-T" or "Sirolimus-Protein-Bound-Particle*" or Soltamox or "Somatuline-Depot" or Sonidegib or "Sorafenib-Tosylate" or Sotorasib or Sprycel or Steritalc or Stivarga or "Sunitinib-Malate" or Sustol or Sutent or Sylvant or Synribo or "systemic-therap*" or Tabrecta or Tafasitamab or Tafinlar or Tagraxofusp or Tagrisso or "Talazoparib-Tosylate" or "Talimogene-Laherparepvec" or

Talquetamab or Talvey or Talzena or "Tamoxifen-Citrate" or Tarceva or Targretin or Tassigna or Tavalisse or taxane* or Taxotere or "Tazemetostat-Hydrobromide" or Tazverik or Tebentafusp or Tecartus or Tecentriq or Teclistamab or Tecvayli or Temodar or Temozolomide or Tamsirolimus or Tepadina or Tepmetko or "Tepotinib-Hydrochloride" or Tevimbra or Thalidomide or Thalomid or Thioguanine or Thiotepa or Tibsovo or Tisagenlecleucel or Tislelizumab or "Tisotumab-Vedotin" or Tiuxetan or Tivdak or "Tivozanib-Hydrochloride" or Tocilizumab or Tolak or "Topoisomerase-Inhibitor*" or "Topotecan-Hydrochloride" or Toremifene or Toripalimab or Torisel or Totect or Tovorafenib or TPF or Trabectedin or Trametinib or Trastuzumab or "Trastuzumab-Deruxtecan" or Treanda or Tremelimumab or Trexall or "Trifluridine-and-Tipiracil" or Trisenox or Trodelvy or Truqap or Truxima or Tucatinib or Tukysa or Turalio or Tykerb or Ultomiris or Undenocycyca or Unituxin or "Uridine-Triacetate" or Valrubicin or Valstar or Vandetanib or Vanflyta or Varubi or Vectibix or Velcade or Vemurafenib or Venclexta or Venetoclax or Verzenio or Vidaza or "Vinblastine Sulfate" or "vinca-alkaloid*" or "Vincristine-Sulfate" or "Vinorelbine-Tartrate" or Vismodegib or Vistogard or Vitakvi or Vizimpro or Vonjo or Voraxaze or Vorinostat or Votrient or Vyxeos or Welireg or Xalkori or Xatmep or XELIRI or Xeloda or XELOX or Xgeva or Xofigo or Xospata or Xpovio or Xtandi or Yervoy or Yescarta or Yondelis or Yonsa or Zaltrap or Zanubrutinib or Zaxio or Zejula or Zelboraf or Zepzelca or Zevalin or Ziextenzo or Zinecard or Zirabev or "Ziv-Aflibercept" or Zofran or Zoladex or "Zoledronic-Acid" or Zolanza or Zometa or Zyclara or Zydelig or Zykadia or Zynlonta or Zynyz or Zytiga).ti.

13 10 or 11 or 12

14 exp Radiotherapy/

15 Radiosurgery/

16 (radiotherap* or radiat* or irradiat* or chemoradi* or brachytherap* or SBRT or SABR or stereotactic or IMRT or VMAT or "volumetric-modulated-arc-therapy").ti,ab,kf.

17 or/14-16

18 13 or 17

19 9 and 18

20 clinical trial, phase II/ or clinical trial, phase III/ or clinical trial, phase IV/ or Meta-Analysis/ or exp prospective study/ or prospective studies/

21 (prospective or "phase-2" or "phase-II" or "phase-ii" or "phase-3" or "phase-III" or "phase-iii" or "phase-4" or "phase-IV" or "phase-iv" or "meta-analysis" or metaanalysis*).ti,ab,kf.

22 20 or 21

23 19 and 22

24 (conference abstract or conference review or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts).mp. or conference abstract.st.

25 23 not 24

26 (exp animals/ or exp nonhuman/) not exp humans/

27 ((alpaca or alpacas or algae* or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or bats or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or canis or carp or cats or catfish or cattle or chameleo* or chameleon* or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or groundhog or groundhogs or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or iguana or iguanas or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or "laboratory animal*" or lagomorph or lagomorphs or lamb or lambs or lemur or lemurs or lemuridae or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or muskrat or muskrats or nematode or nematodes or newt or newts or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or poultry or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or tilapia or

tilapias or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or weasel or weasels or wolf or wolves or worm or worms or wrass* or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kf.

- 28 (rat or rats or mice or mouse or murine or pig or pigs or porcine or swine or dog or dogs).ti.
- 29 or/26-28
- 30 25 not 29
- 31 limit 30 to english language [Limit not valid in CDSR; records were retained]
- 32 limit 31 to yr="2014 -Current"
- 33 remove duplicates from 32

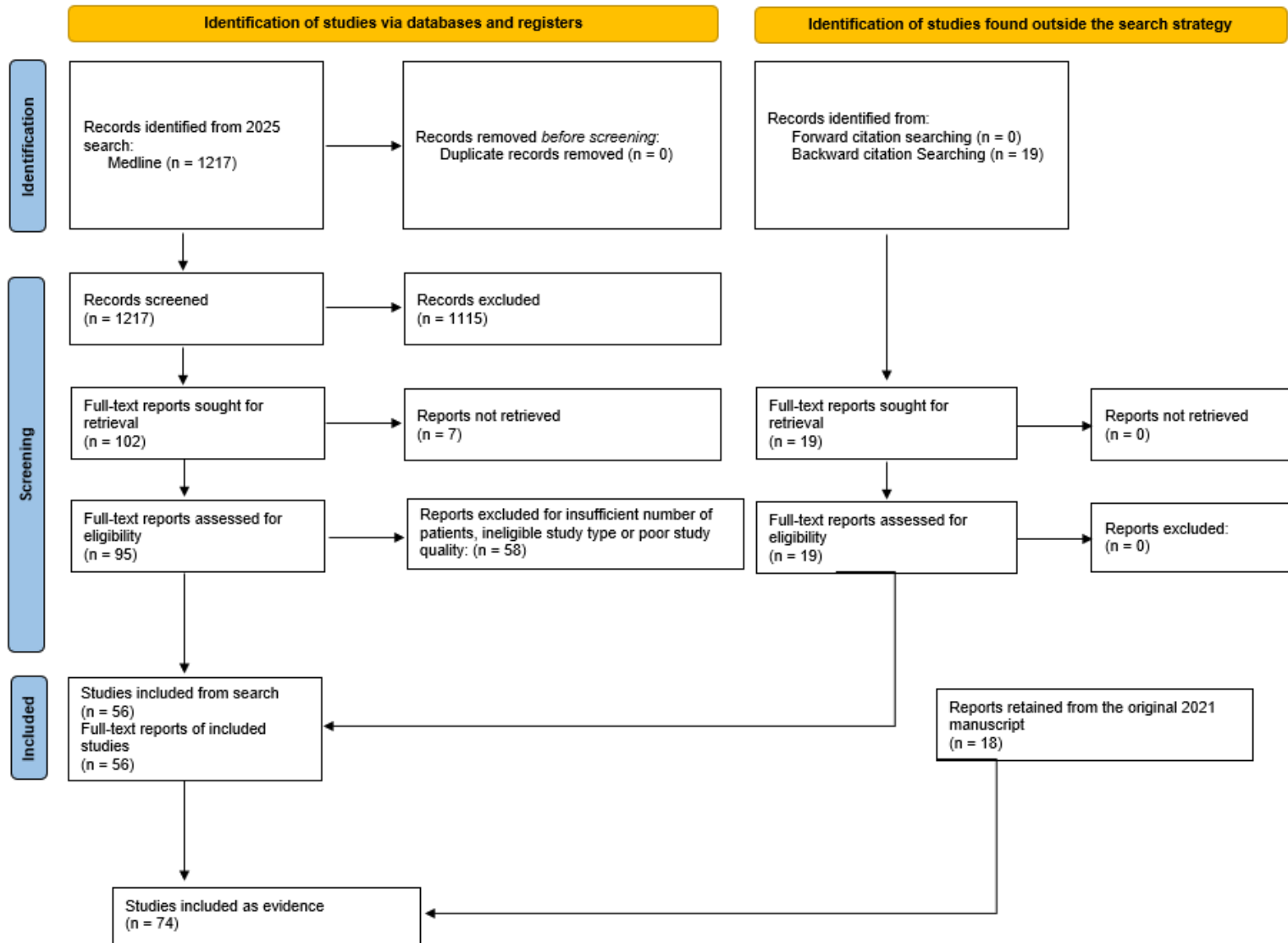
SCOPUS

- 1 TITLE (pancrea* W/3 (cancer* OR carcino* OR neoplas* OR malignan* OR tumor* OR tumour* OR adenocarcinoma*))
- 2 TITLE (surger* OR surgical* OR resection* OR resected OR pancreatectom* OR pancreaticoduodenectom* OR whipple* OR operat* OR operab* OR "post-operativ*" OR postoperativ*)
- 3 1 and 2
- 4 TITLE (abecma OR abemaciclib OR "Abiraterone-Acetate" OR abraxane OR abvd OR abve OR "ABVE-PC" OR acalabrutinib OR "AC-T" OR actemra OR adagrasib OR adcetris OR "Ado-Trastuzumab-Emtansine" OR adriamycin OR adstiladrin OR "Afatinib-Dimaleate" OR afinitor OR aflibercept OR akeega OR "Akynzeo-Netupitant-and-Palonosetron-Hydrochloride" OR "Aldara-Imiquimod" OR aldesleukin OR "Alecensa-Alectinib" OR alectinib OR alemtuzumab OR "Alimta-Pemetrexed-Disodium" OR alkeran OR "alkylating-agent*" OR "alkylating-drug*" OR aloxi OR alpelisib OR alunbrig OR alymsys OR ameluz OR amifostine OR "Aminolevulinic-Acid-Hydrochloride" OR amivantamab OR amtagvi OR anastrozole OR "Angiogenesis-Inhibitor*" OR anktiva OR anticancer* OR "anti-cancer*" OR anticarcinogenic* OR "Anti-carcinogenic*" OR antimetabolite* OR "anti-metabolite*" OR antimitotic* OR "Anti-mitotic*" OR antineoplastic* OR "anti-neoplastic*" OR antitumor OR "anti-tumor" OR antitumour OR "anti-tumour" OR apalutamide OR aprepitant OR aranesp OR aredia OR arimidex OR aromasin OR arranon OR "Arsenic-Trioxide" OR arzerra OR "Asciminib-Hydrochloride" OR "Asparaginase-Erwinia-Chrysanthemi" OR asparlas OR atezolizumab OR augtyro OR avapritinib OR avastin OR avelumab OR "Axicabtagene-Ciloleucel" OR axitinib OR ayvakit OR azacitidine OR azedra OR balversa OR bavencio OR beacopp OR beleodaq OR belinostat OR belzutifan OR "Bendamustine-Hydrochloride" OR bendeka OR berzoserib OR besponsa OR besremi OR bevacizumab OR bevcizumab OR bexarotene OR bicalutamide OR bicnu OR binimetinib OR "Bleomycin-Sulfate" OR blinatumomab OR blincyto OR bortezomib OR bosulif OR bosutinib OR braftovi OR "Brentuximab-Vedotin" OR "Brexucabtagene-Autoleucel" OR breyanzi OR brigatinib OR brukinsa OR bumel OR busulfan OR busulfex OR cabazitaxel OR cablivi OR cabometyx OR "Cabozantinib-S-Malate" OR calaspargase OR "Calaspargase-Pegol-mknl" OR calquence OR campath OR camptosar OR capecitabine OR capivasertib OR caplacizumab OR "Capmatinib-Hydrochloride" OR capox OR carac OR carboplatin OR "CARBOPLATIN-TAXOL" OR carfilzomib OR carmustine OR carvykti OR casodex OR cem OR cemiplimab OR ceritinib OR cervarix OR cetuximab OR chemotherap* OR chemoradio* OR chlorambucil OR chop OR "Ciltacabtagene-Autoleucel" OR cisplatin OR cladribine OR clofarabine OR clolar OR "Cobimetinib-Fumarate" OR columvi OR cometriq OR copdac OR copiktra OR cosmegen OR cotellc OR crizotinib OR cyclophosphamide OR cyramza OR cytarabine OR "Dabrafenib-Mesylate" OR dacarbazine OR dacogen OR dacomitinib OR dactinomycin OR danyelza OR daratumumab OR darbepoetin OR darolutamide OR darzalex OR dasatinib OR "Daunorubicin-Hydrochloride" OR daurismo OR decitabine OR "Defibrotide-Sodium" OR defitelio OR degarelix OR "Denileukin-Diftitox" OR denosumab OR dexamethasone OR "Dexrazoxane-Hydrochloride" OR dinutuximab OR docetaxel OR dostarlimab OR doxil OR doxorubicin OR durvalumab OR duvelisib OR "Eflornithine-Hydrochloride" OR efudex OR "Elacestrant-Dihydrochloride" OR elahere OR eligard OR elitek OR ellence OR elotuzumab OR eloxatin OR elranatamab OR elrexfio OR "Eltrombopag-Olamine" OR elzonris OR emapalumab OR emend OR empliciti OR "Enasidenib-Mesylate" OR encorafenib OR "Enfortumab-Vedotin" OR enhertu OR entrectinib OR enzalutamide OR epcoritamab OR "Epirubicin-Hydrochloride" OR epkinly OR "Epoeti-Alfa" OR epogen OR erbitux OR erdafitinib OR "Eribulin-Mesylate" OR erivedge OR erleada OR "Erlotinib-Hydrochloride" OR erwinaze OR ethyol OR etopophos OR etoposide OR everolimus OR evista OR evomela OR exemestane OR fareston OR faslodex OR "Fedratinib-Hydrochloride" OR femara OR filgrastim OR firmagon OR "Fludarabine-Phosphate" OR fluoroplex OR fluorouracil OR flutamide OR folfiri OR folfirinox OR folfox OR folotyng OR "Fostamatinib Disodium" OR fotivda OR fruquintinib OR fruzaqla OR fulphila OR "FU-LV" OR fulvestrant OR futibatinib OR fyarro OR gamifant OR gardasil OR gavreto OR gazyva OR gefitinib OR gemcitabine OR gemtuzumab OR gemzar OR gilotrif OR "Gilteritinib Fumarate" OR "Glasdegib-Maleate" OR gleevec OR "Gliadel-Wafer" OR glogitamb OR glucarpidase OR "Goserelin-Acetate"

OR granisetron OR granix OR halaven OR hangeol OR hepzato OR herceptin OR "Herceptin-Hylecta" OR "HPV-Bivalent-Vaccine*" OR "HPV-Nonavalent-Vaccine*" OR "HPV-Quadrivalent-Vaccine*" OR hycamtin OR hydrea OR hydroxyurea OR "Hyper-CVAD" OR ibrance OR ibritumomab OR ibrutinib OR iclusig OR "Idamycin-PFS" OR "Idarubicin-Hydrochloride" OR "Idacabtagene-Vicleucel" OR idelalisib OR idhifa OR ifex OR ifosfamide OR "IL-2" OR "Imatinib-Mesylate" OR imbruvica OR imfinzi OR imiquimod OR injudo OR imlygic OR inbakicept OR infugem OR inlyta OR "Inotuzumab-Ozogamicin" OR inqovi OR inrebic OR "Interferon-Alfa-2b" OR "Interleukin-2" OR "Intron-A" OR iobenguane OR ipilimumab OR iressa OR "Irinotecan Hydrochloride" OR "Irinotecan-Sucrosfate" OR isatuximab OR istodax OR ivosidenib OR iwilfin OR ixabepilone OR "Ixazomib-Citrate" OR ixempra OR jakafi OR jaypirca OR jelmtyo OR jemperi OR jevtana OR kadcyla OR kepivance OR keytruda OR kimmtrak OR kisqali OR koselugo OR krazati OR kymriah OR kyprolis OR "Lanreotide-Acetate" OR "Lapatinib Ditosylate" OR "Larotrectinib-Sulfate" OR lenalidomide OR "Lenvatinib-Mesylate" OR lenvima OR letrozole OR "Leucovorin-Calcium" OR leukeran OR "Leuprolide-Acetate" OR "Levulan-Kerastick" OR libtayo OR lifileucel OR "Lisocabtagene-Maraleucel" OR lomustine OR "Loncastuximab-Tesirine" OR lonsurf OR loqtorzi OR lorbreina OR lorlatinib OR lumakras OR lumoxiti OR lunsumio OR "Lupron-Depot" OR lurbinectedin OR luspatercept OR lutathera OR lutetium OR lynparza OR lytgobi OR margenza OR margetuximab OR matulane OR "Mechlorethamine-Hydrochloride" OR "Megestrol-Acetate" OR mekinist OR mektovi OR melphalan OR "Melphalan-Hydrochloride" OR mercaptopurine OR mesna OR mesnex OR "Methotrexate-Sodium" OR "Methylnaltrexone-Bromide" OR midostaurin OR "Mirvetuximab-Soravtansine" OR mitomycin OR "Mitoxantrone-Hydrochloride" OR mogamulizumab OR "Momelotinib-Dihydrochloride-Monohydrate" OR monjuvi OR mopp OR mosunetuzumab OR "Moxetumomab-Pasudotox" OR mozobil OR "MTOR-Inhibitor*" OR mvac OR mvasi OR "Myeloablative-Agonist*" OR myleran OR mylotarg OR nadofaragene OR "Nadofaragene-Firadenovec" OR naxitamab OR "Naxitamab-gqgk" OR necitumumab OR nelarabine OR "Neratinib-Maleate" OR nerlynx OR "Netupitant-and-Palonosetron-Hydrochloride" OR neulasta OR neupogen OR nexavar OR nilandron OR nilotinib OR nilutamide OR ninlaro OR "Niraparib-Tosylate-Monohydrate" OR "Nirogacestat-Hydrobromide" OR nivestym OR nivolumab OR nogapendekin OR "Nogapendekin-Alfa" OR nplate OR nubeqa OR nyvepria OR obinutuzumab OR odomzo OR ofatumumab OR ogsiveo OR ojemda OR ojjaara OR olaparib OR olutasidenib OR "Omacetaxine-Mepesuccinate" OR oncaspar OR "Ondansetron-Hydrochloride" OR onivyde OR ontak OR onureg OR opdivo OR opdualag OR oppa OR orgovyx OR orserdu OR "Osimertinib-Mesylate" OR oxaliplatin OR ozogamicin OR paclitaxel OR "Pacritinib Citrate" OR padcev OR palbociclib OR palifermin OR "Palonosetron-Hydrochloride" OR "Pamidronate-Disodium" OR panitumumab OR paraplatin OR "Pazopanib-Hydrochloride" OR pegaspargase OR pegfilgrastim OR pemazyre OR pembrolizumab OR "Pemetrexed-Disodium" OR pemigatinib OR perjeta OR pertuzumab OR "Pexidartinib-Hydrochloride" OR phesgo OR piqray OR pirtobrutinib OR "platinum-based" OR plerixafor OR pluvicto OR "Polatuzumab Vedotin" OR polivy OR "Polymerase-Inhibitor*" OR pomalidomide OR pomalyst OR "Ponatinib-Hydrochloride" OR portrazza OR poteligeo OR pralatrexate OR pralsetinib OR prednisone OR "Procarbazine-Hydrochloride" OR procrit OR proleukin OR prolia OR promacta OR "Propranolol-Hydrochloride" OR provenge OR "purine-analog*" OR "purine-antagonist*" OR purinethol OR purixan OR qinlock OR "Quizartinib-Dihydrochloride" OR "Radium-223-Dichloride" OR "Raloxifene-Hydrochloride" OR ramucirumab OR rasburicase OR ravulizumab OR "R-CHOP" OR "R-CVP" OR reblozyl OR "Recombinant-HPV-Bivalent-Vaccine*" OR "Recombinant-HPV-Nonavalent-Vaccine*" OR "Recombinant-HPV-Quadrivalent-Vaccine*" OR "Recombinant-Human-Papillomavirus-Bivalent-Vaccine*" OR "Recombinant-Human-Papillomavirus-Nonavalent-Vaccine*" OR "Recombinant-Human-Papillomavirus-Quadrivalent-Vaccine*" OR "Recombinant-Interferon-Alfa-2b" OR regorafenib OR relistor OR relugolix OR "R-EPOCH" OR repotrectinib OR retacrit OR retevmo OR retifanlimab OR revlimid OR rezlidhia OR riabni OR ribociclib OR "R-ICE" OR ripretinib OR rituxan OR rituximab OR "Rolapitant-Hydrochloride" OR romidepsin OR romiplostim OR "Ropeginterferon-Alfa" OR rozlytrek OR rubraca OR "Rucaparib-Camsylate" OR ruxience OR "Ruxolitinib-Phosphate" OR rybrevant OR rydapt OR rylaze OR "Sacituzumab-Govitecan" OR sancuso OR sarclisa OR scemblix OR "Sclerosol-Intrapleural" OR selinexor OR selpercatinib OR "Selumetinib-Sulfate" OR siltuximab OR "Sipuleucel-T" OR "Sirolimus-Protein-Bound-Particle*" OR soltamox OR "Somatuline-Depot" OR sonidegib OR "Sorafenib-Tosylate" OR sotorasib OR sprycel OR steritalc OR stivarga OR "Sunitinib-Malate" OR sustol OR sutent OR sylvant OR synribo OR "systemic-therap*" OR tabrecta OR tafasitamab OR tafinlar OR tagraxofusp OR tagrisso OR "Talazoparib-Tosylate" OR "Talimogene-Laherparepvec" OR talquetamab OR talvey OR talzena OR "Tamoxifen-Citrate" OR tarceva OR targretin OR tassigna OR tavalisse OR taxane* OR taxotere OR "Tazemetostat-Hydrobromide" OR tazverik OR tebentafusp OR tecartus OR tecentriq OR teclistamab OR tecvayli OR temodar OR temozolomide OR temsirolimus OR tepadina OR tepmetko OR "Tepotinib-Hydrochloride" OR tevimbra OR thalidomide OR thalomid OR thioguanine OR thiotepa OR tibsovo OR tisagenlecleucel OR tislelizumab OR "Tisotumab-Vedotin" OR tiuxetan OR tivdak OR "Tivozanib-Hydrochloride" OR tocilizumab OR tolak OR "Topoisomerase-Inhibitor*" OR "Topotecan-Hydrochloride" OR toremifene OR toripalimab OR torisel OR torect OR tovorafenib OR tpf OR trabectedin OR trametinib OR

- trastuzumab OR "Trastuzumab-Deruxtecán" OR treanda OR tremelimumab OR trexall OR "Trifluridine-and-Tipiracil" OR trisenox OR trodelvy OR truqap OR truxima OR tucatinib OR tukysa OR turalio OR tykerb OR ultomiris OR undenocicly OR unituxin OR "Uridine-Triacetate" OR valrubicin OR valstar OR vandetanib OR vanflyta OR varubi OR vectibix OR velcade OR vemurafenib OR venclexta OR venetoclax OR verzenio OR vidaza OR "Vinblastine Sulfate" OR "vinca-alkaloid*" OR "Vincristine-Sulfate" OR "Vinorelbine-Tartrate" OR vismodegib OR vistogard OR vitrakvi OR vizimpro OR vonjo OR voraxaze OR vorinostat OR votrient OR vyxeos OR welireg OR xalkori OR xatmep OR xeliri OR xeloda OR xelox OR xgeva OR xofigo OR xospata OR xpovio OR xtandi OR yervoy OR yescarta OR yondelis OR yonsa OR zaltrap OR zanubrutinib OR zarxio OR zejula OR zelboraf OR zepzelca OR zevalin OR ziextenzo OR zinecard OR zirabev OR "Ziv-Aflibercept" OR zofran OR zoladex OR "Zoledronic-Acid" OR zolinza OR zometa OR zyclara OR zydelig OR zykadia OR zynlonta OR zynyz OR zytiga)
- 5 TITLE (radiotherap* OR radiat* OR irradiat* OR chemoradi* OR brachytherap* OR sbrt OR sabr OR stereotactic OR imrt OR vmat OR "volumetric-modulated-arc-therapy")
- 6 4 or 5
- 7 3 and 6
- 8 TITLE-ABS-KEY (prospective or "phase-2" or "phase-II" or "phase-ii" or "phase-3" or "phase-III" or "phase-iii" or "phase-4" or "phase-IV" or "phase-iv" or "meta-analysis" or metaanalys*)
- 9 7 and 8
- 10 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
- 11 9 not 10
- 12 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
- 13 11 not 12
- 14 (TITLE-ABS-KEY ((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans OR patient OR patients)))
- 15 13 not 14
- 16 LIMIT-TO (LANGUAGE , "English") AND (LIMIT-TO (SRCTYPE , "j") AND PUBYEAR > 2013

Appendix B: PRISMA 2020 Study Selection Flow Diagram for Adjuvant Therapy for Resected Adenocarcinoma of the Pancreas



Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	¶2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	¶2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	¶1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	¶1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix A: Search Strategy
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	¶1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	¶1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	¶1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	¶1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Appendix C: Evidence Table
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A



Appendix D: PRISMA 2020 Checklist for Adjuvant Therapy for Resected Adenocarcinoma of the Pancreas

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	¶2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	¶2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	¶1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	¶1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix A: Search Strategy
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	¶1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	¶1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	¶1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	¶1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Appendix C: Evidence Table
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	SUMMARY OF LITERATURE REVIEW Topics 1 - 4
	23b	Discuss any limitations of the evidence included in the review.	N/A
	23c	Discuss any limitations of the review processes used.	N/A
	23d	Discuss implications of the results for practice, policy, and future research.	N/A
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title Page
Competing interests	26	Declare any competing interests of review authors.	Title Page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	https://www.americanradiumsociety.org/page/aucmethodology

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: <http://www.prisma-statement.org/>