

Appendix C: Evidence Table

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

Ref #	Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1	*Siegel RL, Kratzer TB, Wagle NS, Sung H, Jemal A. Cancer Statistics, 2026. CA: A Cancer Journal for Clinicians. https://doi.org/10.3322/caac.70043	Annual cancer statistics	This annual report provides the most current information about cancer.	To provide annual cancer statistics	A unique feature of these publications is their projections of the number of cancer cases and deaths expected in each state and in the nation in the current year. These widely cited projections serve as a basis for research and, but are also readily understood by the public. Each edition of Cancer Facts & Figures includes a Special Section of in-depth focus on a specific cancer, group of cancers, or population.	NA NOT USED AS PRIMARY EVIDENCE
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	Retrospective	In this manuscript, we review limitations of studies of borderline resectable PDAC reported to date, highlight important controversies related to this disease stage, emphasize the research infrastructure necessary for its future study, and present a recently-approved Intergroup pilot study (Alliance A021101) that will provide a foundation upon which subsequent well-designed clinical trials can be performed.	To outline methodological limitations of prior studies have prevented progress in the treatment of patients with borderline resectable pancreatic adenocarcinoma.	We identified twenty-three studies published since 2001 which report outcomes of patients with tumors labeled as borderline resectable and who were treated with neoadjuvant therapy prior to planned pancreatectomy. These studies were heterogeneous in terms of the populations studied, the metrics used to characterize therapeutic response, and the indications used to select patients for surgery. Mechanisms used to standardize these and other issues that are incorporated into Alliance A021101 are reviewed.	3 NOT USED AS PRIMARY EVIDENCE
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	Prospective randomized phase III	Open, multicenter, randomized controlled phase 3 trial with stratification for resection, tumor, and node status. Conducted from July 1998 to December 2004 in the outpatient setting at 88 academic and community-based oncology centers in Germany and Austria. A total of 368 patients with gross complete (R0 or R1) resection of pancreatic cancer and no prior radiation or chemotherapy were enrolled into 2 groups. Patients received adjuvant chemotherapy with 6 cycles of gemcitabine on days 1, 8, and 15 every 4 weeks	To test the hypothesis that adjuvant chemotherapy with gemcitabine administered after complete resection of pancreatic cancer improves disease-free survival by 6 months or more.	More than 80% of patients had R0 resection. The median number of chemotherapy cycles in the gemcitabine group was 6 (range, 0-6). Grade 3 or 4 toxicities rarely occurred with no difference in quality of life (by Spitzer index) between groups. During median follow-up of 53 months, 133 patients (74%) in the gemcitabine group and 161 patients (92%) in the control group developed recurrent disease. Median disease-free survival was 13.4 months in the gemcitabine group (95% confidence interval, 11.4-15.3) and 6.9 months in the control group (95% confidence interval, 6.1-7.8; P<.001, log-rank). Estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group, and 7.5% and 5.5% in the control group, respectively. Subgroup analyses showed that the effect of gemcitabine on disease-free survival was significant in patients	1

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			(n = 179), or observation ([control] n = 175).		with either R0 or R1 resection. There was no difference in overall survival between the gemcitabine group (median, 22.1 months; 95% confidence interval, 18.4-25.8; estimated survival, 34% at 3 years and 22.5% at 5 years) and the control group (median, 20.2 months; 95% confidence interval, 17-23.4; estimated survival, 20.5% at 3 years and 11.5% at 5 years; P = .06, log-rank).	
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	Systematic review and meta-analysis	The guideline development and revision include an extensive analysis of current medical literature from peer reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment.	To provide evidence-based guidelines for selection of adjuvant therapies for resectable pancreatic cancer.	Patients with no or few risk factors for local recurrence after surgical resection of their pancreatic cancer may benefit from adjuvant chemotherapy alone as suggested by the high-quality CONKO-001 study. Adjuvant chemotherapy alone may especially be useful when performance status is compromised and patients may not be able to tolerate concurrent chemoradiation. Patients undergoing surgical resection of pancreatic adenocarcinoma benefit from adjuvant therapy to include either chemotherapy or combinations of chemotherapy and concurrent chemoradiation. Appropriate selection of therapy includes patient ability to tolerate multimodality therapy and evaluation of risk factors for distant and local recurrence.	M NOT USED AS PRIMARY EVIDENCE
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	Systematic review and meta-analysis	The American Radium Society multidisciplinary gastrointestinal expert panel convened to develop Appropriate Use Criteria evaluating the evidence regarding neoadjuvant treatment for patients with PDAC, including surgery, systemic therapy, and radiotherapy, in terms of oncologic outcomes and quality of life. The evidence was assessed using the Population, Intervention, Comparator, Outcome, and Study (PICOS) design framework and "Preferred Reporting Items for Systematic	To provide evidence-based guidelines for selection of neoadjuvant therapies for resectable pancreatic cancer.	1The panel recommends strongly that neoadjuvant chemotherapy is may be appropriate procedure for the typical case with initially resectable PDAC. The panel recommends with strongly that neoadjuvant chemoRT/ neoadjuvant chemotherapy followed by RT is usually not appropriate for the typical case with initially resectable PDAC. The panel recommends strongly that neoadjuvant chemotherapy is usually appropriate procedure for the typical case with BR PDAC based on anatomy. The panel recommends strongly that neoadjuvant chemoRT/neoadjuvant chemotherapy followed by RT is usually appropriate procedure for the typical case with BR PDAC based on anatomy.	M NOT USED AS PRIMARY EVIDENCE

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			Reviews and Meta-analyses" 2020 methodology. Eligible studies included phases 2 to 3 trials, meta-analyses, and retrospective analyses published between January 1, 2012 and December 30, 2022 in the Ovid Medline database.		The panel recommends strongly that neoadjuvant chemotherapy is usually appropriate procedure for the typical case with BR PDAC based on biological features. The panel recommends strongly that neoadjuvant chemoRT/neoadjuvant chemotherapy followed by RT is usually appropriate procedure for the typical case with BR PDAC based on biological features. The panel recommends strongly that neoadjuvant chemotherapy is usually appropriate procedure for the typical case with BR PDAC based on clinical features. The panel recommends strongly that neoadjuvant chemoRT/neoadjuvant chemotherapy followed by RT is usually appropriate procedure for the typical case with BR PDAC based on clinical features. The panel recommends strongly that neoadjuvant chemotherapy may be appropriate procedure for the typical case with LA PDAC. The panel recommends strongly that neoadjuvant chemoRT/neoadjuvant chemotherapy followed by RT is usually appropriate procedure for the typical case with LA PDAC. The panel recommends strongly that neoadjuvant chemotherapy may be appropriate procedure for the typical case with LA PDAC unlikely to convert to resectable. The panel recommends strongly that neoadjuvant chemoRT/neoadjuvant chemotherapy followed by RT is usually appropriate procedure for the typical case with LA PDAC unlikely to convert to resectable.	
6	*Page MJ, Moher D, Bossuyt PM, et al: PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. The BMJ 2021: Vol.372, p.160	Methodology	The methods and results of systematic reviews should be reported in sufficient detail to allow users to assess the trustworthiness and applicability of the review findings. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was developed to facilitate transparent and complete reporting of systematic reviews and has been updated (to	To present the explanation and elaboration paper for PRISMA 2020, where we explain why reporting of each item is recommended, present bullet points that detail the reporting recommendations, and present	Changes to the content and structure of PRISMA 2020 will facilitate uptake of the guideline and lead to more transparent, complete, and accurate reporting of systematic reviews.	NA NOT USED AS PRIMARY EVIDENCE

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			PRISMA 2020) to reflect recent advances in systematic review methodology and terminology	examples from published reviews.		
7	*Page MJ, McKenzie JE, Bossuyt PM, et al: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021: Vol 372: n71	Methodology	The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, published in 2009, was designed to help systematic reviewers transparently report why the review was done, what the authors did, and what they found.	To present the PRISMA 2020 27-item checklist, an expanded checklist that details reporting recommendations for each item, the PRISMA 2020 abstract checklist, and the revised flow diagrams for original and updated reviews.	The PRISMA 2020 statement replaces the 2009 statement and includes new reporting guidance that reflects advances in methods to identify, select, appraise, and synthesize studies.	NA NOT USED AS PRIMARY EVIDENCE
8	*Fitch K, Bernsein SJ, Aguilar MD, Bunand B, LaCalle JR, Lazaro P, van het Loo M, McDonnell J, Vader J, Kahan DP. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica: Rand Corporation, 2001. https://www.rand.org/pubs/monograph_reports/MR1269.html . Also available in print form.	Methodology	The "RAND/UCLA Appropriateness Method" was developed in the 1980s. It has been further developed and refined in North America and, increasingly, in Europe. The rationale behind the method is that randomized clinical trials — the "gold standard" for evidence-based medicine — are generally either not available or cannot provide evidence at a level of detail sufficient to apply to the wide range of patients seen in everyday clinical practice.	This manual presents step-by-step guidelines for conceptualising, designing, and carrying out a study of the appropriateness of medical or surgical procedures (for either diagnosis or treatment) using the RAND/UCLA Appropriateness Method. The manual distills the experience of many researchers in North America and Europe and presents current (as of the year 2000) thinking on the subject.	Although robust scientific evidence about the benefits of many procedures is lacking, physicians must nonetheless make decisions every day about when to use them. Consequently, a method was developed that combined the best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of performing a procedure at the level of patient-specific symptoms, medical history, and test results.	NA NOT USED AS PRIMARY EVIDENCE
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.	Retrospective	Between 2001 and 2012, 968 patients who underwent upfront surgery with R0 or R1 resection for PDAC at seven high-volume centers in Japan were retrospectively reviewed. ER was	To determine the preoperative predictive factors for early recurrence after upfront surgical resection.	ER occurred in 239 patients (25%) with a median survival time (MST) of 8.8 months. Modified Glasgow prognostic score = 2 (odds ratio (OR) 2.06, 95% confidence interval (CI) 1.05-3.95; P = 0.044), preoperative CA19-9 ≥300 U/ml (OR 1.94, 1.29-2.90; P = 0.003), and tumor size ≥30 mm (OR	3 NOT USED AS PRIMARY EVIDENCE

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	Pancreatology. Nov-Dec 2015;15(6):674-80. doi: 10.1016/j.pan.2015.09.008		defined as relapse within 6 months after surgery. Study analysis stratified by resectable (R) and borderline resectable (BR) PDACs was conducted according to the National Comprehensive Cancer Network guidelines.		1.72, 1.16-2.56; P = 0.006), were identified as preoperative independent predictive risk factors for ER in patients with R-PDAC. In the R-PDAC patients, MST was 35.5, 26.3, and 15.9 months in patients with 0, 1 and ≥ 2 risk factors, respectively. There were significant differences in overall survival between the three groups (P < 0.001). No preoperative risk factors were identified in BR-PDAC patients with a high rate of ER (39%).	
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	Retrospective	We examine the prognostic significance of the SMAM distance in 411 consecutive pancreatic ductal adenocarcinoma patients who completed neoadjuvant therapy and pancreaticoduodenectomy	To examine the prognostic significance of the SMAM distance in pancreatic ductal adenocarcinoma patients who completed neoadjuvant therapy and pancreaticoduodenectomy	Per College of American Pathologists criteria, 32 (7.8%) had positive margins, and 379 (92.2%) had negative margins. Among margin-negative group, SMAM was ≤ 1 , 1.0 to 5.0, and >5.0 mm in 66, 145, and 168 patients, respectively. There was no difference in either disease-free survival (DFS) or overall survival (OS) between the positive-margin group and SMAM ≤ 1 mm (P > 0.05). However, patients with SMAM 1.0 to 5.0 mm had better OS than those with positive margins or SMAM ≤ 1 mm (P = 0.02). Patients with SMAM >5.0 mm had better DFS and OS than those with SMAM 1.0 to 5.0 mm and those with positive margins or SMAM ≤ 1 mm (P < 0.01). By multivariate analysis, the SMAM distance, tumor differentiation, lymph node metastasis, and histopathologic tumor response grade were independent prognostic factors for both DFS and OS. SMAM distance correlated with lower ypT and AJCC stages, smaller tumor size, better histopathologic tumor response grade, fewer lymph node metastases, and recurrences (P < 0.05).	3 NOT USED AS PRIMARY EVIDENCE
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	Retrospective	Retrospective multicenter analysis of 882 patients who have undergone curative-intent pancreatic resection with pathological evaluation of PALNs for pancreatic ductal adenocarcinoma between 2001 and 2012 was conducted. Clinicopathological data and outcomes were evaluated with	To reevaluate the postoperative prognostic value of para-aortic lymph node (PALN) metastasis in pancreatic cancer and to determine the validity of pancreatic surgery.	In total, 102 (12.4 %) patients had positive metastasis in PALN. Patients with metastatic PALN had significantly poorer survival than those without (17 vs. 23 months; p < 0.001). Multivariable analysis of 822 patients identified adjuvant chemotherapy, primary tumor status, regional lymph node metastasis, portal vein invasion, pre- and post-operative serum CA19-9 levels, and tumor grade as independent prognostic factors. In contrast, PALN metastasis did not have a significant prognostic value.	3 NOT USED AS PRIMARY EVIDENCE

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			univariate and multivariate analysis.		Furthermore, the multivariate prognostic analysis in patients with PALN metastasis revealed that adjuvant chemotherapy and the number of metastatic PALN were significantly associated with long-term survival. Lung metastasis as initial recurrence was observed more often in patients with PALN metastasis in comparison with those without.	
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	Retrospective	The Surveillance, Epidemiology, and End Results (SEER) database (1991–2005) was used to identify 8082 patients with resected PAC. The impact of grade on overall and stage-specific survival was assessed using Cox regression analysis. Variables in the model were age, sex, tumor size, lymph node status, and tumor grade.	To evaluate if tumor grade might be responsible for some of this variation and that the addition of grade to current AJCC staging would provide improved prognostication.	For each AJCC stage, survival was significantly worse for high-grade versus low-grade tumors. On multivariate analysis, high tumor grade was an independent predictor of survival for the entire cohort (hazard ratio [HR] 1.40, 95% confidence interval [95% CI] 1.31–1.48) as well as for stage I (HR 1.28, 95% CI 1.07–1.54), stage IIA (HR 1.43, 95% CI 1.26–1.61), stage IIB (HR 1.38, 95% CI 1.27–1.50), stage III (HR 1.28, 95% CI 1.02–1.59), and stage IV (HR 1.58, 95% CI 1.21–2.05) patients. The addition of grade to staging results in a statistically significant survival discrimination between all stages.	3 NOT USED AS PRIMARY EVIDENCE
13	Koelblinger C, Ba-Ssalamah A, Goetzinger 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	Prospective nonrandomized	Multidetector CT and MR imaging were performed in 89 patients (48 women aged 46-89 years [mean, 65.6 years] and 41 men aged 46-86 years [mean, 65.3 years]) suspected of having pancreatic cancer on the basis of findings from clinical examination or previous imaging studies. Two readers independently assessed the images to characterize lesions and determine the presence of focal masses, vascular invasion, distant metastases, and resectability. Findings from surgery, biopsy, endosonography, or follow-up imaging were used as the standard of reference. Logistic regression, the McNemar test, and κ values were used for statistical analysis.	To compare the diagnostic performance (detection, local staging) of multiphasic 64-detector row computed tomography (CT) with that of gadobenate dimeglumine-enhanced 3.0-T magnetic resonance (MR) imaging in patients suspected of having pancreatic cancer.	Focal pancreatic masses were present in 63 patients; 43 patients had adenocarcinoma. For reader 1, the sensitivities and specificities in the detection of pancreatic adenocarcinoma were 98% (42 of 43 patients) and 96% (44 of 46 patients), respectively, for CT and 98% (42 of 43 patients) and 96% (44 of 46 patients) for MR imaging. For reader 2, the sensitivities and specificities were 93% (40 of 43 patients) and 96% (44 of 46 patients), respectively, for CT and 95% (41 of 43 patients) and 96% (44 of 46 patients) for MR imaging. Vessel infiltration was determined in 22 patients who underwent surgery, and reader 1 obtained sensitivities and specificities of 90% (nine of 10 vessels) and 98% (119 of 122 vessels), respectively, for CT and 80% (eight of 10 vessels) and 96% (117 of 122 vessels) for MR imaging; for reader 2, those values were 70% (seven of 10 vessels) and 98% (120 of 122 vessels) for CT and 50% (five of 10 vessels) and 98% (120 of 122 vessels) for MR imaging. Both readers correctly assessed resectability in 87% (13 of 15 patients) of cases with CT and 93% (14	2 NOT USED AS PRIMARY EVIDENCE

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					of 15 patients) of cases with MR imaging. Nonresectability was assessed correctly with CT in 75% (six of eight patients) of cases by reader 1 and 63% (five of eight patients) of cases by reader 2; nonresectability was correctly assessed with MR imaging in 75% (six of eight patients) of cases by reader 1 and 50% (four of eight patients) of cases by reader 2. None of the differences between modalities and readers were statistically significant ($P > .05$).	
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. <i>Pancreas</i> . Jan 2013;42(1):11-9. doi:10.1097/MPA.0b013e3182550d77	Retrospective	Positron emission tomography/CE-CT was conducted in 108 patients with pancreatic cancer and in 41 patients with other pancreatic tumor diseases.	To evaluate PET/CE-CT images with regard to differential diagnosis, staging, treatment response, and postoperative recurrence in pancreatic cancer.	The maximum standardized uptake value (SUV (max)) overlapped in benign and malignant cases, suggesting that differential diagnosis of pancreatic tumors based on the SUV(max) is difficult. In the evaluation of staging in 31 resectable pancreatic cancer by PET/CE-CT, the diagnostic accuracy rate was more than 80% for most factors concerning local invasion and 94% for distant metastasis but only 42% for lymph node metastasis. Significant positive correlations were found between the SUV (max) and tumor size/markers, suggesting that SUV(max) may be a useful indicator for the treatment response. Regarding the diagnosis of the postoperative recurrence, PET/CE-CT correctly detected local recurrence in all the 11 cases of recurrence, whereas abdominal CE-CT detected only 7 of 11 cases, suggesting that PET/CE-CT is superior in this context.	3 NOT USED AS PRIMARY EVIDENCE
15	DePeralta DK, Ogami T, Zhou JM, et al. Completion of adjuvant therapy in patients with resected pancreatic cancer. <i>HPB (Oxford)</i> . Feb 2020;22(2):241-248. doi: 10.1016/j.hpb.2019.07.008	Retrospective	A retrospective analysis of outcomes of patients with resected PDAC over an 8-year period at H. Lee Moffitt Cancer Center (MCC) was performed.	To examine whether completion of AT is associated with improved survival in patients with resected PDAC.	From a total of 309 patients, 299 were included for further analysis. 242 (81%) initiated adjuvant therapy (AT) and 195 (65%) completed the intended course. The median time-to-initiation of AT was 53 days (7.6 weeks). The most common reasons for early discontinuation of AT ($n = 47$) were toxicity ($n = 29$), disease recurrence ($n = 9$), patient decision ($n = 4$), unrelated comorbidities ($n = 3$), and death ($n = 1$). Completion of AT was an independent predictor of overall survival (OS) and recurrence-free survival (RFS) on multivariable analysis (OS: HR 0.41, CI 0.27-0.61, $p < 0.001$; RFS: HR 0.52, CI 0.36-0.76, $p < 0.001$). Factors associated with early termination of AT were vascular resection (OR 0.29, CI 0.13-0.67, p	3 NOT USED AS PRIMARY EVIDENCE

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					= 0.004) and administration of AT with local oncologist as opposed to MCC (OR 0.41, CI 0.21-0.82, p = 0.010).	
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	Prospective randomized phase III	In a multicenter trial using a two-by-two factorial design, we randomly assigned 73 patients with resected pancreatic ductal adenocarcinoma to treatment with chemoradiotherapy alone (20 Gy over a two-week period plus fluorouracil), 75 patients to chemotherapy alone (fluorouracil), 72 patients to both chemoradiotherapy and chemotherapy, and 69 patients to observation.	To report the final results of the European Study Group for Pancreatic Cancer 1 Trial and update the interim results.	The analysis was based on 237 deaths among the 289 patients (82 percent) and a median follow-up of 47 months (interquartile range, 33 to 62). The estimated five-year survival rate was 10 percent among patients assigned to receive chemoradiotherapy and 20 percent among patients who did not receive chemoradiotherapy (P=0.05). The five-year survival rate was 21 percent among patients who received chemotherapy and 8 percent among patients who did not receive chemotherapy (P=0.009). The benefit of chemotherapy persisted after adjustment for major prognostic factors.	1
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	Meta-analysis	The ESPAC-1, ESPAC-1 plus, and early ESPAC-3(v1) results (458 randomized patients; 364 deaths) were used to estimate the effectiveness of adjuvant 5FU/FA vs resection alone for pancreatic cancer using meta-analysis.	To evaluate the effectiveness of adjuvant 5FU/FA vs resection alone for pancreatic cancer	The pooled hazard ratio of 0.70 (95% CI=0.55-0.88) P=0.003, and the median survival of 23.2 (95% CI=20.1-26.5) months with 5FU/FA vs 16.8 (95% CI=14.3-19.2) months with resection alone supports the use of adjuvant 5FU/FA in pancreatic cancer.	M
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. 2013;310(14):1473-1481.	Prospective randomized phase III	CONKO-001 (Charité Onkologie 001), a multicenter, open-label, phase 3 randomized trial to evaluate the efficacy and toxicity of gemcitabine in patients with pancreatic cancer after complete tumor resection. Patients with macroscopically completely removed pancreatic cancer entered the study between July 1998 and December 2004 in 88 hospitals in Germany and Austria. Follow-up ended in September 2012. After stratification for tumor stage, nodal status, and resection status, patients were randomly assigned to either adjuvant gemcitabine treatment (1g/m ² d 1, 8, 15, q 4 weeks) for 6 months or to observation alone. The primary end point was	To analyze whether previously reported improvement in DFS with adjuvant gemcitabine therapy translates into improved OS	A total of 368 patients were randomized, and 354 were eligible for intention-to-treat-analysis. By September 2012, 308 patients (87.0% [95% CI, 83.1%-90.1%]) had relapsed and 316 patients (89.3% [95% CI, 85.6%-92.1%]) had died. The median follow-up time was 136 months. The median disease-free survival was 13.4 (95% CI, 11.6-15.3) months in the treatment group compared with 6.7 (95% CI, 6.0-7.5) months in the observation group (hazard ratio, 0.55 [95% CI, 0.44-0.69]; P < .001). Patients randomized to adjuvant gemcitabine treatment had prolonged overall survival compared with those randomized to observation alone (hazard ratio, 0.76 [95% CI, 0.61-0.95]; P = .01), with 5-year overall survival of 20.7% (95% CI, 14.7%-26.6%) vs 10.4% (95% CI, 5.9%-15.0%), respectively, and 10-year overall survival of 12.2% (95% CI, 7.3%-17.2%) vs 7.7% (95% CI, 3.6%-11.8%).	1

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			disease-free survival. Secondary end points included treatment safety and overall survival, with overall survival defined as the time from date of randomization to death. Patients lost to follow-up were censored on the date of their last follow-up.			
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	Prospective randomized phase III	Eligibility criteria included macroscopically curative resection of invasive ductal carcinoma of the pancreas and no earlier radiation or chemotherapy. Patients were randomly assigned at a 1:1 ratio to either the gemcitabine group or the surgery-only group. Patients assigned to the gemcitabine group received gemcitabine at a dose of 1000 mg m (-2) over 30 min on days 1, 8 and 15, every 4 weeks for 3 cycles.	To determine whether adjuvant chemotherapy with gemcitabine improves the outcomes of patients with resected pancreatic cancer.	Between April 2002 and March 2005, 119 patients were enrolled in this study. Among them, 118 were eligible and analysable (58 in the gemcitabine group and 60 in the surgery-only group). Both groups were well balanced in terms of baseline characteristics. Although heamatological toxicity was frequently observed in the gemcitabine group, most toxicities were transient, and grade 3 or 4 non-heamatological toxicity was rare. Patients in the gemcitabine group showed significantly longer disease-free survival (DFS) than those in the surgery-only group (median DFS, 11.4 versus 5.0 months; hazard ratio=0.60 (95% confidence interval (CI): 0.40-0.89); P=0.01), although overall survival did not differ significantly between the gemcitabine and surgery-only groups (median overall survival, 22.3 versus 18.4 months; hazard ratio=0.77 (95% CI: 0.51-1.14); P=0.19).	1
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	Prospective randomized phase III	The European Study Group for Pancreatic Cancer (ESPAC)-3 trial, an open-label, phase 3, randomized controlled trial conducted in 159 pancreatic cancer centers in Europe, Australasia, Japan, and Canada. Included in ESPAC-3 version 2 were 1088 patients with pancreatic ductal adenocarcinoma who had undergone cancer resection; patients were randomized between July 2000 and January 2007 and underwent at least 2 years of follow-up. Patients received either fluorouracil plus	To determine whether fluorouracil or gemcitabine is superior in terms of overall survival as adjuvant treatment following resection of pancreatic cancer.	Final analysis was carried out on an intention-to-treat basis after a median of 34.2 (interquartile range, 27.1-43.4) months' follow-up after 753 deaths (69%). Median survival was 23.0 (95% confidence interval [CI], 21.1-25.0) months for patients treated with fluorouracil plus folinic acid and 23.6 (95% CI, 21.4-26.4) months for those treated with gemcitabine (chi(1)(2) = 0.7; P = .39; hazard ratio, 0.94 [95% CI, 0.81-1.08]). Seventy-seven patients (14%) receiving fluorouracil plus folinic acid had 97 treatment-related serious adverse events, compared with 40 patients (7.5%) receiving gemcitabine, who had 52 events (P < .001). There were no significant differences in either progression-free survival or global quality-of-life scores between the treatment groups.	1

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			folinic acid (folinic acid, 20 mg/m(2), intravenous bolus injection, followed by fluorouracil, 425 mg/m(2) intravenous bolus injection given 1-5 days every 28 days) (n = 551) or gemcitabine (1000 mg/m(2) intravenous infusion once a week for 3 of every 4 weeks) (n = 537) for 6 months.			
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	Prospective randomized phase III	We did a randomised, open-label, multicentre, non-inferiority phase 3 trial undertaken at 33 hospitals in Japan. Patients who had histologically proven invasive ductal carcinoma of the pancreas, pathologically documented stage I-III, and no local residual or microscopic residual tumour, and were aged 20 years or older were eligible. Patients with resected pancreatic cancer were randomly assigned (in a 1:1 ratio) to receive gemcitabine (1000 mg/m(2), intravenously administered on days 1, 8, and 15, every 4 weeks [one cycle], for up to six cycles) or S-1 (40 mg, 50 mg, or 60 mg according to body-surface area, orally administered twice a day for 28 days followed by a 14 day rest, every 6 weeks [one cycle], for up to four cycles) at the data centre by a modified minimisation method, balancing residual tumour status, nodal status, and institutions. The primary outcome was overall survival in the two treatment groups, assessed in the per-protocol population, excluding ineligible patients and those not receiving the allocated treatment. The protocol	To investigate the non-inferiority of S-1 to gemcitabine as adjuvant chemotherapy for pancreatic cancer in terms of overall survival.	385 patients were randomly assigned to treatment between April 11, 2007, and June 29, 2010 (193 to the gemcitabine group and 192 to the S-1 group). Of these, three were excluded because of ineligibility and five did not receive chemotherapy. The per-protocol population therefore consisted of 190 patients in the gemcitabine group and 187 patients in the S-1 group. On Sept 15, 2012, following the recommendation from the independent data and safety monitoring committee, this study was discontinued because the prespecified criteria for early discontinuation were met at the interim analysis for efficacy, when all the protocol treatments had been finished. Analysis with the follow-up data on Jan 15, 2016, showed HR of mortality was 0.57 (95% CI 0.44-0.72, non-inferiority<0.0001, p<0.0001 for superiority), associated with 5-year overall survival of 24.4% (18.6-30.8) in the gemcitabine group and 44.1% (36.9-51.1) in the S-1 group. Grade 3 or 4 leucopenia, neutropenia, aspartate aminotransferase, and alanine aminotransferase were observed more frequently in the gemcitabine group, whereas stomatitis and diarrhoea were more frequently experienced in the S-1 group.	1

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			prespecified that the superiority of S-1 with respect to overall survival was also to be assessed in the per-protocol population by a log-rank test, if the non-inferiority of S-1 was verified. We estimated overall and relapse-free survival using the Kaplan-Meier methods, and assessed non-inferiority of S-1 to gemcitabine using the Cox proportional hazard model. The expected hazard ratio (HR) for mortality was 0.87 with a non-inferiority margin of 1.25 (power 80%; one-sided type I error 2.5%).			
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. 2011;18(5):1319-1326.	Prospective randomized phase III	After resection of pancreatic adenocarcinoma, patients were randomized to pre- and post-CRT 5-FU versus pre- and post-CRT gemcitabine. 5-FU was provided continuously at 250 mg/m(2)/day, and gemcitabine was provided at 1000 mg/m(2) weekly. Both were provided over 3 weeks before and 12 weeks after CRT. CRT was provided at 50.4 Gy with continuously provided 5-FU. The primary end point was survival for all patients and for patients with tumor of the pancreatic head.	To report the impact of the addition of gemcitabine to 5-fluorouracil (5-FU) chemoradiation (CRT) on 5-year overall survival (OS) in resected pancreatic adenocarcinoma are presented with updated results of a phase III trial.	451 patients were eligible. Univariate analysis showed no difference in OS. Pancreatic head tumor patients (n = 388) had a median survival and 5-year OS of 20.5 months and 22% with gemcitabine vs 17.1 months and 18% with fluorouracil. On multivariate analysis, patients on the gemcitabine arm with pancreatic head tumors experienced a trend toward improved OS (P=0.08). First site of relapse local recurrence in 28% vs distant relapse in 73%.	1
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. 2008;299(9):1019-1026.	Prospective randomized phase III	Randomized controlled phase 3 trial of patients with complete gross total resection of pancreatic adenocarcinoma and no prior radiation or chemotherapy enrolled between July 1998 and July 2002 with follow-up through August 18, 2006, at 164 US and Canadian institutions. Chemotherapy with either fluorouracil (continuous	To determine if the addition of gemcitabine to adjuvant fluorouracil CRT (chemotherapy plus RT) improves survival for patients with resected PC.	A total of 451 patients were randomized, eligible, and analyzable. Patients with pancreatic head tumors (n = 388) had a median survival of 20.5 months and a 3-year survival of 31% in the gemcitabine group vs a median survival of 16.9 months and a 3-year survival of 22% in the fluorouracil group (hazard ratio, 0.82 [95% confidence interval, 0.65-1.03]; P = .09). The treatment effect was strengthened on multivariate analysis (hazard ratio, 0.80 [95% confidence interval, 0.63-1.00]; P = .05). Grade 4	1

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			infusion of 250 mg/m ² per day; n = 230) or gemcitabine (30-minute infusion of 1000 mg/m ² once per week; n = 221) for 3 weeks prior to chemoradiation therapy and for 12 weeks after chemoradiation therapy. Chemoradiation with a continuous infusion of fluorouracil (250 mg/m ² per day) was the same for all patients (50.4 Gy). Survival for all patients and survival for patients with pancreatic head tumors were the primary end points. Secondary end points included toxicity.		hematologic toxicity was 1% in the fluorouracil group and 14% in the gemcitabine group (P < .001) without a difference in febrile neutropenia or infection. There were no differences in the ability to complete chemotherapy or radiation therapy (>85%).	
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	Prospective randomized phase III	A phase 3, two-group, open-label, multicentre, randomised clinical trial at 92 hospitals in England, Scotland, Wales, Germany, France, and Sweden. Eligible patients were aged 18 years or older and had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection). We randomly assigned patients (1:1) within 12 weeks of surgery to receive six cycles of either 1000 mg/m ² gemcitabine alone administered once a week for three of every 4 weeks (one cycle) or with 1660 mg/m ² oral capecitabine administered for 21 days followed by 7 days' rest (one cycle). Randomisation was based on a minimisation routine, and country was used as a stratification factor. The primary endpoint was overall survival, measured as the time from randomisation until death from any cause, and assessed in the intention-to-treat population.	To determine the efficacy and safety of gemcitabine and capecitabine compared with gemcitabine monotherapy for resected pancreatic cancer.	Of 732 patients enrolled, 730 were included in the final analysis. Of these, 366 were randomly assigned to receive gemcitabine and 364 to gemcitabine plus capecitabine. The Independent Data and Safety Monitoring Committee requested reporting of the results after there were 458 (95%) of a target of 480 deaths. The median overall survival for patients in the gemcitabine plus capecitabine group was 28.0 months (95% CI 23.5-31.5) compared with 25.5 months (22.7-27.9) in the gemcitabine group (hazard ratio 0.82 [95% CI 0.68-0.98], p=0.032). 608 grade 3-4 adverse events were reported by 226 of 359 patients in the gemcitabine plus capecitabine group compared with 481 grade 3-4 adverse events in 196 of 366 patients in the gemcitabine group.	1

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			Toxicity was analysed in all patients who received trial treatment.			
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	Prospective randomized phase III	In an open-label, multicenter trial, patients were randomly assigned to one of two study arms: gemcitabine 1,000 mg/m ² days 1, 8, 15, every 4 weeks plus erlotinib 100 mg once per day (GemErlo) or gemcitabine (Gem) alone for six cycles. The primary end point of the study was to improve disease-free survival (DFS) from 14 to 18 months by adding erlotinib to gemcitabine.	To evaluate if erlotinib in combination with gemcitabine improves survival in patients with primarily resectable PDAC after R0 resection.	In all, 436 patients were randomly assigned at 57 study centers between April 2008 and July 2013. A total of 361 instances (83%) of disease recurrence were observed after a median follow-up of 54 months. Median treatment duration was 22 weeks in both arms. There was no difference in median DFS (GemErlo 11.4 months; Gem 11.4 months) or median overall survival (GemErlo 24.5 months; Gem 26.5 months). There was a trend toward long-term survival in favor of GemErlo (estimated survival after 1, 2, and 5 years for GemErlo was 77%, 53%, and 25% v 79%, 54%, and 20% for Gem, respectively). The occurrence or the grade of rash was not associated with a better survival in the GemErlo arm.	1
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	Prospective randomized phase III	We assigned 866 treatment-naïve patients with pancreatic ductal adenocarcinoma to nab-paclitaxel (125 mg/m ²) + gemcitabine (1,000 mg/m ²) or gemcitabine alone to one 30-40 infusion on days 1, 8, and 15 of six 28-day cycles. The primary end point was independently assessed disease-free survival (DFS). Additional end points included investigator-assessed DFS, overall survival (OS), and safety.	To compare the efficacy and safety of adjuvant nab-paclitaxel + gemcitabine with those of gemcitabine for resected pancreatic ductal adenocarcinoma	Two hundred eighty-seven of 432 patients and 310 of 434 patients completed nab-paclitaxel + gemcitabine and gemcitabine treatment, respectively. At primary data cutoff (December 31, 2018; median follow-up, 38.5 [interquartile range [IQR], 33.8-43 months), the median independently assessed DFS was 19.4 (nab-paclitaxel + gemcitabine) versus 18.8 months (gemcitabine; hazard ratio [HR], 0.88; 95% CI, 0.729 to 1.063; P = .18). The median investigator-assessed DFS was 16.6 (IQR, 8.4-47.0) and 13.7 (IQR, 8.3-44.1) months, respectively (HR, 0.82; 95% CI, 0.694 to 0.965; P = .02). The median OS (427 events; 68% mature) was 40.5 (IQR, 20.7 to not reached) and 36.2 (IQR, 17.7-53.3) months, respectively (HR, 0.82; 95% CI, 0.680 to 0.996; P = .045). At a 16-month follow-up (cutoff, April 3, 2020; median follow-up, 51.4 months [IQR, 47.0-57.0]), the median OS (511 events; 81% mature) was 41.8 (nab-paclitaxel + gemcitabine) versus 37.7 months (gemcitabine; HR, 0.82; 95% CI, 0.687 to 0.973; P = .0232). At the 5-year follow-up (cutoff, April 9, 2021; median follow-up, 63.2 months [IQR, 60.1-68.7]), the median OS (555 events; 88% mature) was 41.8 versus 37.7 months, respectively (HR, 0.80; 95% CI, 0.678 to	1

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					0.947; P = .0091). Eighty-six percent (nab-paclitaxel + gemcitabine) and 68% (gemcitabine) of patients experienced grade ≥ 3 treatment-emergent adverse events. Two patients per study arm died of treatment-emergent adverse events.	
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	Prospective randomized phase III	We randomly assigned 493 patients with resected pancreatic ductal adenocarcinoma to receive a modified FOLFIRINOX regimen (oxaliplatin [85 mg per square meter of body-surface area], irinotecan [180 mg per square meter, reduced to 150 mg per square meter after a protocol-specified safety analysis], leucovorin [400 mg per square meter], and fluorouracil [2400 mg per square meter] every 2 weeks) or gemcitabine (1000 mg per square meter on days 1, 8, and 15 every 4 weeks) for 24 weeks. The primary end point was disease-free survival. Secondary end points included overall survival and safety.	To compare the efficacy and safety of a modified FOLFIRINOX regimen with gemcitabine as adjuvant therapy in patients with resected pancreatic cancer.	At a median follow-up of 33.6 months, the median disease-free survival was 21.6 months in the modified-FOLFIRINOX group and 12.8 months in the gemcitabine group (stratified hazard ratio for cancer-related event, second cancer, or death, 0.58; 95% confidence interval [CI], 0.46 to 0.73; P<0.001). The disease-free survival rate at 3 years was 39.7% in the modified-FOLFIRINOX group and 21.4% in the gemcitabine group. The median overall survival was 54.4 months in the modified-FOLFIRINOX group and 35.0 months in the gemcitabine group (stratified hazard ratio for death, 0.64; 95% CI, 0.48 to 0.86; P=0.003). The overall survival rate at 3 years was 63.4% in the modified-FOLFIRINOX group and 48.6% in the gemcitabine group. Adverse events of grade 3 or 4 occurred in 75.9% of the patients in the modified-FOLFIRINOX group and in 52.9% of those in the gemcitabine group. One patient in the gemcitabine group died from toxic effects (interstitial pneumonitis).	1
28	Conroy, Thierry; Castan, Florence; Lopez, Anthony; Turpin, Anthony; Ben Abdelghani, Meher; Wei, Alice C.; Mitry, Emmanuel; Biagi, James J.; Evesque, Ludovic; Artru, Pascal; Lecomte, Thierry; Assenat, Eric; Bauguion, Lucile; Ychou, Marc; Bouche, Olivier; Monard, Laure; Lambert, Aurelien; Hammel, Pascal. Five-Year Outcomes of FOLFIRINOX vs Gemcitabine as Adjuvant Therapy for Pancreatic Cancer: A Randomized Clinical Trial. JAMA Oncology 11 01 2022;8(11):1571-1578. DOI: 10.1001/jamaoncol.2022.3829	Prospective randomized phase III	This open-label, phase 3 randomized clinical trial was conducted at 77 hospitals in France and Canada and included patients aged 18 to 79 years with histologically confirmed pancreatic ductal adenocarcinoma who had undergone complete macroscopic (R0/R1) resection within 3 to 12 weeks before randomization. Patients were included from April 16, 2012, through October 3, 2016. The cutoff date for this analysis was June 28, 2021. Interventions: A total of 493 patients were randomized (1:1) to receive	To report 5-year outcomes and explore prognostic factors for overall survival.	Of the 493 patients, 216 (43.8%) were women, and the mean (SD) age was 62.0 (8.9) years. At a median of 69.7 months' follow-up, 367 disease-free survival events were observed. In patients receiving chemotherapy with modified FOLFIRINOX vs gemcitabine, median disease-free survival was 21.4 months (95% CI, 17.5-26.7) vs 12.8 months (95% CI, 11.6-15.2) (hazard ratio [HR], 0.66; 95% CI, 0.54-0.82; P < .001) and 5-year disease-free survival was 26.1% vs 19.0%; median overall survival was 53.5 months (95% CI, 43.5-58.4) vs 35.5 months (95% CI, 30.1-40.3) (HR, 0.68; 95% CI, 0.54-0.85; P = .001), and 5-year overall survival was 43.2% vs 31.4%; median metastasis-free survival was 29.4 months (95% CI, 21.4-40.1) vs 17.7 months (95% CI, 14.0-21.2) (HR, 0.64; 95% CI, 0.52-0.80; P < .001); and median cancer-specific survival was 54.7 months	1

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			treatment with modified FOLFIRINOX (oxaliplatin, 85 mg/m ² of body surface area; irinotecan, 150-180 mg/m ² ; leucovorin, 400 mg/m ² ; and fluorouracil, 2400 mg/m ² , every 2 weeks) or gemcitabine (1000 mg/m ² , days 1, 8, and 15, every 4 weeks) as adjuvant therapy for 24 weeks. Primary end point was disease-free survival. Secondary end points included overall survival, metastasis-free survival, and cancer-specific survival. Prognostic factors for overall survival were determined.		(95% CI, 45.8-68.4) vs 36.3 months (95% CI, 30.5-43.9) (HR, 0.65; 95% CI, 0.51-0.82; P < .001). Multivariable analysis identified modified FOLFIRINOX, age, tumor grade, tumor staging, and larger-volume center as significant favorable prognostic factors for overall survival. Shorter relapse delay was an adverse prognostic factor. The final 5-year results from the PRODIGE 24/Canadian Cancer Trials Group PA6 randomized clinical trial indicate that adjuvant treatment with modified FOLFIRINOX yields significantly longer survival than gemcitabine in patients with resected pancreatic ductal adenocarcinoma.	
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	Retrospective	Patients with pancreatic ductal adenocarcinoma treated within the international, phase III, European Study Group for Pancreatic Cancer-3 (version 2) study were included if they had been randomly assigned to chemotherapy. Overall survival analysis was performed on an intention-to-treat basis, retaining patients in their randomized groups, and adjusting the overall treatment effect by known prognostic variables as well as the start time of chemotherapy.	To examine the optimal duration and time to initiate chemotherapy following resection of PDAC using data from a prospective randomized trial	There were 985 patients, of whom 486 (49%) received gemcitabine and 499 (51%) received fluorouracil; 675 patients (68%) completed all six cycles of chemotherapy (full course) and 293 patients (30%) completed one to five cycles. Lymph node involvement, resection margins status, tumor differentiation, and completion of therapy were all shown by multivariable Cox regression to be independent survival factors. Overall survival favored patients who completed the full six courses of treatment versus those who did not (hazard ratio [HR], 0.516; 95% CI, 0.443 to 0.601; P < .001). Time to starting chemotherapy did not influence overall survival rates for the full study population (HR, 0.985; 95% CI, 0.956 to 1.015). Chemotherapy start time was an important survival factor only for the subgroup of patients who did not complete therapy, in favor of later treatment (P < .001).	3
30	Palmer, D. H.; Jackson, R.; Springfield, C.; Ghaneh, P.; Rawcliffe, C.; Halloran, C. M.; Faluyi, O.; Cunningham, D.; Wadsley, J.; Darby, S.; Meyer, T.; Gillmore, R.; Lind, P.; Glimelius, B.; Falk, S.; Ma, Y. T.; Middleton, G. W.; Cummins, S.; Ross, P. J.; Wasan, H.; McDonald, A.; Crosby, T.; Hammel, P.; Borg, D.; Sothi, S.; Valle, J. W.; Mehrabi, A.; Bailey, P.; Tjaden, C.;	Prospective randomized phase III	The OS of 732 ESPAC4 patients comparing 367 randomly assigned to gemcitabine and 365 to GemCap was previously reported after a median follow-up time of 43.2 months (95% CI, 39.7 to 45.5) and 458 deaths. Analysis was now carried out after a median follow-up of 104	To analyze the ESPAC4 survival on long-term follow-up.	The median OS was 29.5 months (27.5-32.1) for all patients, 28.4 months (25.2-32.0) in the gemcitabine group and 31.6 months (26.5-38.0) in the GemCap group (hazard ratio [HR], 0.83 [0.71 to 0.98]; P = .031). R0 patients given gemcitabine had a median survival of 32.2 months (27.9-41.6) compared with 49.9 months (39.0-82.3) for those given GemCap (HR, 0.63 [0.47 to 0.84]; P = .002). Lymph node-negative	1

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	Michalski, C.; Hackert, T.; Buchler, M. W.; Neoptolemos, J. P. Pancreatic Adenocarcinoma: Long-Term Outcomes of Adjuvant Therapy in the ESPAC4 Phase III Trial. Journal of Clinical Oncology 01 Apr 2025;43(10):1240-1253.DOI: 10.1200/JCO.24.01118		months (101-108) and 566 deaths.		patients had significantly higher 5-year OS rates on GemCap (59% [49%-71%]) than gemcitabine (53% [42%-66%]; HR, 0.63 [0.41 to 0.98]; P = .04) but not those with positive lymph nodes (P = .225). The OS advantage for GemCap was retained in the PRODIGE24 subgroup of 193 (26.4%) ESPAC4 patients not eligible for PRODIGE24 with a median survival of 20.7 (16.2-27.3) months in patients allocated to gemcitabine compared with 25.9 (22.3-30.2) months for ineligible patients allocated to GemCap (HR, 0.71 [95% CI, 0.52 to 0.98]; χ^2 log-rank-1df = 4.31; P = .038).	
31	van Dam, J. L.; Verkolf, E. M. M.; Dekker, E. N.; Bonsing, B. A.; Bratlie, S. O.; Brosens, L. A. A.; Busch, O. R.; van Driel, L. M. J. W.; van Eijck, C. H. J.; Feshtali, S.; Ghorbani, P.; de Groot, D. J. A.; de Groot, J. W. B.; Haberkorn, B. C. M.; de Hingh, I. H.; van der Holt, B.; Karsten, T. M.; van der Kolk, M. B.; Labori, K. J.; Liem, M. S. L.; Loosveld, O. J. L.; Molenaar, I. Q.; Polee, M. B.; van Santvoort, H. C.; de Vos-Geelen, J.; Wumkes, M. L.; van Tienhoven, G.; Homs, M. Y. V.; Besselink, M. G.; Wilmink, J. W.; Groot Koerkamp, B. Perioperative or adjuvant mFOLFIRINOX for resectable pancreatic cancer (PREOPANC-3): study protocol for a multicenter randomized controlled trial. BMC Cancer Aug 07 2023;23(1):728. DOI: 10.1186/s12885-023-11141-5	Prospective randomized phase III	This multicenter, phase 3, RCT will include 378 patients with resectable pancreatic ductal adenocarcinoma with a WHO performance status of 0 or 1. Patients are recruited from 20 Dutch centers and three centers in Norway and Sweden. Resectable pancreatic cancer is defined as no arterial contact and ≤ 90 degrees venous contact. Patients in the intervention arm are scheduled for 8 cycles of neoadjuvant mFOLFIRINOX followed by surgery and 4 cycles of adjuvant mFOLFIRINOX (2-week cycle of oxaliplatin 85 mg/m ² , leucovorin 400 mg/m ² , irinotecan 150 mg/m ² at day 1, followed by 46 h continuous infusion of 5-fluorouracil 2400 g/m ²). Patients in the comparator arm start with surgery followed by 12 cycles of adjuvant mFOLFIRINOX. The primary outcome is overall survival by intention-to-treat. Secondary outcomes include progression-free survival, resection rate, quality of life, adverse events, and surgical	To compare perioperative (i.e., neoadjuvant and adjuvant) with (only) adjuvant administration of mFOLFIRINOX in a randomized controlled trial (RCT) to determine the optimal approach.	pending	1

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			complications. To detect a hazard ratio of 0.70 with 80% power, 252 events are needed. The number of events is expected to be reached after the inclusion of 378 patients in 36 months, with analysis planned 18 months after the last patient has been randomized.			
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	Prospective randomized phase III	To qualify for enrollment, patients must have biopsy-proven localized resectable pancreatic adenocarcinoma as defined by the National Comprehensive Cancer Network. Patients must have good performance status (ECOG 0 or 1) and be candidates to receive mFOLFIRINOX treatment. All patients enrolled undergo central radiologic eligibility review for quality control and are then randomized to either Arm 1 which consists of 8 cycles of neoadjuvant mFOLFIRINOX followed by 4 cycles of adjuvant mFOLFIRINOX or Arm 2 which includes upfront surgery followed by 12 cycles of adjuvant mFOLFIRINOX. The primary endpoint of the trial is overall survival with secondary endpoints evaluating disease-free survival, margin-negative resection rate, surgical complications, and chemotherapeutic adverse events. Additional correlative endpoints include quality of life and radiomic imaging assessments. A total enrollment of 352 patients is planned from the US and Canada; current enrollment for this trial is at 145	To evaluate the efficacy of perioperative chemotherapy with mFOLFIRINOX in patients with resectable pancreatic cancer		1

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			patients. An OS interim analysis will be performed when 50% of the events (124) are observed combining the two arms. If the trial continues after interim analysis, the final OS analysis will be performed with a total of 248 events (combined arms). If the Cox model (stratified by tumor location and ECOG PS) comparing OS between arms produces a one-sided p-value < 0.05, then we will conclude that the OS of the perioperative therapy arm is superior to adjuvant therapy. The Alliance A021806 phase III trial aims to define a new standard of care for patients with resectable pancreatic cancer.			
33	**Kaiser MH. Pancreatic Cancer. Archives of Surgery. 1985;120(8):899.	Prospective randomized phase III	22 patients randomized to no adjuvant treatment and 21 to combined therapy were analyzed.	To assess the value of this combination regimen in prolonging survival time and DFS time.	Neither life-threatening toxic reaction nor death due to toxic effect was encountered. The study was terminated prematurely because of an unacceptably low rate of accrual combined with the observation of increasingly large survival differences between the study arms. Median survival for the treatment group (20 months) was significantly longer than that observed for the control group (11 months). 4 patients, 3 in the treated and 1 in the control group, have survived 5 years or longer following surgery. The extent of the tumor and initial performance status were significantly and independently related to survival.	1
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-cnrcr2820591206>3.0.co;2-b	Prospective nonrandomized phase II	30 patients with resected PDAC who received adjuvant CRT	To demonstrate that the results of the randomized trial could be replicated.	The registered patients had median survival time of 18 months. 10 patients were alive at 18.9 to 42.4 months (median, 25.0). 2-year actuarial survival was 46% (95% CI, 0.28, 0.65) compared with 43% (95% CI, 0.25, 0.63) for 21 patients randomized to treatment and 18% (95% CI, 0.08, 0.36) for 22 patients randomized to control.	2
35	**Klinkenbijn JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5fluorouracil after curative resection of cancer of the pancreas and periampullary	Prospective randomized phase III	Between 1987 and 1995, 218 patients were randomized (108 patients in the observation group, 110 patients in the	To investigate the survival benefit of adjuvant RT and 5-fluorouracil vs	114 patients (55%) had PC (54 in the observation group and 60 in the treatment group). In the treatment arm, 21 patients (20%) received no treatment because of postoperative	1

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	region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776-782; discussion 782-774		treatment group). 11 patients were ineligible (5 in the observation group and 6 in the treatment group). Baseline characteristics were comparable between the 2 groups.	observation alone after surgery in patients with pancreatic head and periampullary cancers.	complications or patient refusal. In the treatment group, only minor toxicity was observed. The median duration of survival was 19.0 months for the observation group and 24.5 months in the treatment group (log-rank, P=0.208). The 2-year survival estimates were 41% and 51%, respectively. The results when stratifying for tumor location showed a 2-year survival rate of 26% in the observation group and 34% in the treatment group (log-rank, P=0.099) in pancreatic head cancer; in periampullary cancer, the 2-year survival rate was 63% in the observation group and 67% in the treatment group (log-rank, P=0.737). No reduction of locoregional recurrence rates was apparent in the groups.	
36	**Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358(9293):1576-1585.	Prospective randomized phase III	After resection, patients were randomly assigned to adjuvant chemoradiotherapy (20 Gy in ten daily fractions over 2 weeks with 500 mg/m ² fluorouracil intravenously on days 1-3, repeated after 2 weeks) or chemotherapy (intravenous fluorouracil 425 mg/m ² and folinic acid 20 mg/m ² daily for 5 days, monthly for 6 months). Clinicians could randomise patients into a two-by-two factorial design (observation, chemoradiotherapy alone, chemotherapy alone, or both) or into one of the main treatment comparisons (chemoradiotherapy versus no chemoradiotherapy or chemotherapy versus no chemotherapy). The primary endpoint was death, and all analyses were by intention to treat.	To assess the role of adjuvant chemotherapy and CRT for resected PDAC	541 eligible patients with pancreatic ductal adenocarcinoma were randomised: 285 in the two-by-two factorial design (70 chemoradiotherapy, 74 chemotherapy, 72 both, 69 observation); a further 68 patients were randomly assigned chemoradiotherapy or no chemoradiotherapy and 188 chemotherapy or no chemotherapy. Median follow-up of the 227 (42%) patients still alive was 10 months (range 0-62). Overall results showed no benefit for adjuvant chemoradiotherapy (median survival 15.5 months in 175 patients with chemoradiotherapy vs 16.1 months in 178 patients without; hazard ratio 1.18 [95% CI 0.90-1.55], p=0.24). There was evidence of a survival benefit for adjuvant chemotherapy (median survival 19.7 months in 238 patients with chemotherapy vs 14.0 months in 235 patients without; hazard ratio 0.66 [0.52-0.83], p=0.0005).	1
37	Chiu, Yen-Feng; Liu, Tsang-Wu; Shan, Yan-Shen; Chen, Jen-Shi; Li, Chung-Pin; Ho, Ching-Liang; Hsieh, Ruey-Kuen; Hwang, Tsann-Long; Chen, Li-Tzong; Ch'ang, Hui-Ju. Carbohydrate Antigen 19-9 Response	Prospective randomized phase III	CA19-9 levels in patients with resected PDAC in a prospective randomized trial of adjuvant chemotherapy with or without additional chemoradiation	To examine the predictive value of carbohydrate antigen 19-9 (CA19-9) for adjuvant	One hundred forty-seven patients were enrolled in this randomized trial. Twenty-two patients with CA19-9 levels always <=3 U/mL were excluded from the analysis. For the 125 participants, median overall survival (OS) and	1

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	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. International Journal of Radiation Oncology, Biology, Physics 09 01 2023;117(1):74-86. DOI: 10.1016/j.ijrobp.2023.02.061		therapy (CRT) were analyzed. Patients with postoperative CA19-9 ≤92.5 U/mL and serum bilirubin ≤2 mg/dL were randomized to 2 arms: patients in 1 arm received 6 cycles of gemcitabine, whereas those in the other received 3 cycles of gemcitabine followed by CRT and another 3 cycles of gemcitabine. Serum CA19-9 was measured every 12 weeks. Those who had CA19-9 levels always <3 U/mL were excluded from the exploratory analysis.	chemo(radiation) therapy of resected pancreatic adenocarcinoma (PDAC)	recurrence-free survival were 23.1 and 12.1 months, respectively, with no significant differences between the study arms. Postresection CA19-9 levels and, to a lesser extent, CA19-9 change predicted OS (P = .040 and .077, respectively). For the 89 patients who completed the initial 3 cycles of adjuvant gemcitabine, the CA19-9 response was significantly correlated with initial failure over the distant site (P = .023) and OS (P = .0022). Despite a trend of less initial failure over the locoregional area (P = .031), neither postoperative CA19-9 level nor CA19-9 response helped to select patients who might have a survival benefit from additional adjuvant CRT. CA19-9 response to initial adjuvant gemcitabine predicts survival and distant failure of PDAC after resection; however, it cannot select patients suited for additional adjuvant CRT. Monitoring CA19-9 levels during adjuvant therapy for postoperative patients with PDAC may guide therapeutic decisions to prevent distant failure.	
38	Kamarajah, Sivesh K.; Bundred, James R.; Alrawashdeh, Wasfi; Manas, Derek; White, Steven A. A systematic review and network meta-analysis of phase III randomised controlled trials for adjuvant therapy following resection of pancreatic ductal adenocarcinoma (PDAC). HPB 2020;22(5):649-659. DOI: 10.1016/j.hpb.2019.12.001	Systematic review and meta-analysis	A systematic review was conducted using MEDLINE, EMBASE, Cochrane Central and American Society of Clinical Oncology (ASCO) abstracts to identify published phase III RCTs articles up to 9th May 2019 that examined adjuvant systemic therapy in resected pancreatic cancer. Data including study characteristics and outcomes including overall survival (OS) and disease-free survival (DFS) were extracted. Indirect comparisons of all regimens were simultaneously compared using random-effects network meta-analyses (NMA) which maintains randomisation within trials.	To characterise the impact of adjuvant therapies on overall and disease-free survival in patients having resection of PDAC.	Twelve phase III RCTs involving 4947 patients and nine different regimens (5-Fluorouracil/Folinic acid (5-FU/FA), Gemcitabine, Gemcitabine/Erlotinib (GemErl), GemCap), mFFX, S1, chemoradiotherapy (CRT), CRT with either 5-FU or Gemcitabine) were identified. S1 was ranked best for overall and disease-free survival followed by mFFX. Whilst there were no significant difference between S1 and mFFX for overall survival (mean difference: 1.6 months, p = 0.8), S1 had significantly longer disease-free survival than mFFX (mean difference: 2.8 months, p < 0.001). Furthermore, S1 was ranked best for lowest overall and haematological grade 3/4 toxicities.	M
39	Ghaneh, Paula; Kleeff, Jorg; Halloran, Christopher M.; Raraty, Michael; Jackson, Richard; Melling, James; Jones, Owain;	Retrospective	Analyses were carried out to assess the association between clinical characteristics and margin	To provide improved understanding of resection margin	There were 1151 patients, of whom 505 (43.9%) had an R1 resection. The median and 95% confidence interval (CI) overall survival was 24.9	3

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	Palmer, Daniel H.; Cox, Trevor F.; Smith, Chloe J.; O'Reilly, Derek A.; Izbicki, Jakob R.; Scarfe, Andrew G.; Valle, Juan W.; McDonald, Alexander C.; Carter, Ross; Tebbutt, Niall C.; Goldstein, David; Padbury, Robert; Shannon, Jennifer; Dervenis, Christos; Glimelius, Bengt; Deakin, Mark; Anthoney, Alan; Lerch, Markus M.; Mayerle, Julia; Olah, Attila; Rawcliffe, Charlotte L.; Campbell, Fiona; Strobel, Oliver; Buchler, Markus W.; Neoptolemos, John P. The Impact of Positive Resection Margins on Survival and Recurrence Following Resection and Adjuvant Chemotherapy for Pancreatic Ductal Adenocarcinoma. Annals of Surgery 2019;269(3):520-529. DOI: 10.1097/SLA.0000000000002557		involvement as well as the effects of individual margin involvement on site of recurrence and overall and recurrence-free survival using individual patient data from the European Study Group for Pancreatic Cancer (ESPAC)-3 randomized controlled trial.	assessment to aid tailored therapies.	(22.9-27.2) months for 646 (56.1%) patients with resection margin negative (R0 >1 mm) tumors, 25.4 (21.6-30.4) months for 146 (12.7%) patients with R1<1 mm positive resection margins, and 18.7 (17.2-21.1) months for 359 (31.2%) patients with R1-direct positive margins (P < 0.001). In multivariable analysis, overall R1-direct tumor margins, poor tumor differentiation, positive lymph node status, WHO performance status >=1, maximum tumor size, and R1-direct posterior resection margin were all independently significantly associated with reduced overall and recurrence-free survival. Competing risks analysis showed that overall R1-direct positive resection margin status, positive lymph node status, WHO performance status 1, and R1-direct positive superior mesenteric/medial margin resection status were all significantly associated with local recurrence.	
40	Schiavo Lena, M.; Gasparini, G.; Crippa, S.; Belfiori, G.; Aleotti, F.; Di Salvo, F.; Redegalli, M.; Cangi, M. G.; Taveggia, C.; Falconi, M.; Doglioni, C. Quantification of perineural invasion in pancreatic ductal adenocarcinoma: proposal of a severity score system. Virchows Archiv August 2023;483(2):225-235. DOI: 10.1007/s00428-023-03574-x	Retrospective	In this monocentric retrospective study, 356 consecutive PDAC patients (61.8% upfront surgery patients, 38.2% received neoadjuvant therapy) were analyzed. PNI was scored as follows: 0: absent; 1: the presence of neoplasia along nerves < 3 mm in caliber; and 2: neoplastic infiltration of nerve fibers >= 3 mm and/or massive perineural infiltration and/or the presence of necrosis of the infiltrated nerve bundle. For every PNI grade, the correlation with other pathological features, disease-free survival (DFS), and disease-specific survival (DSS) were analyzed. Uni- and multivariate analysis for DFS and DSS were also performed.	To develop and validate a score system for PNI and to correlate it with other prognostic features.	PNI was found in 72.5% of the patients. Relevant trends between PNI score and tumor differentiation grade, lymph node metastases, vascular invasion, and surgical margins status were found. The latter was the only parameter statistically correlated with the proposed score. The agreement between pathologists was substantial (Cohen's K 0.61). PNI severity score significantly correlated also with decreased DFS and DSS at univariate analysis (p < 0.001). At multivariate analysis, only the presence of lymph node metastases was an independent predictor of DFS (HR 2.235 p < 0.001). Lymph node metastases (HR 2.902, p < 0.001) and tumor differentiation grade (HR 1.677, p = 0.002) were independent predictors of DSS. Our newly developed PNI score correlates with other features of PDAC aggressiveness and proved to have a prognostic role though less robust than lymph nodes metastases and tumor differentiation grade.	3
41	Di Martino, M. D.; Ielpo, B.; De Nova, J. L. M.; Munoz, E. A.; Santamaria, C.; Diago, V.; Martin-Perez, E. Lymph node ratio, perineural invasion and R1 resection as	Retrospective	From a prospectively maintained database, we reviewed 89 PDACs in patients who underwent pancreaticoduodenectomy from	To evaluate the prognostic significance of LN	Univariate analysis of DFS and OS showed that vascular resection, pT, pN, LNR15, microvascular, lymphatic, and perineural invasion, and R1 resection influenced survival. Only LNR15,	3

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	independent prognostic factors in pancreatic adenocarcinoma: A retrospective cohort study. Surgical Technology International May 2020;36():1-7		2010 to 2014. The impact of histopathologic or tumor-related data, including a lymph node ratio greater than 15% (LNR15), on survival was analyzed.	ration, PNI and R1 resection in PDAC	perineural invasion and R1 resection were independent predictors for both DFS (HR 6.39, p = 0.011; HR 8.53, p = 0.003; HR 9.68, p = 0.002, respectively) and OS (HR 4.21, p = 0.039; HR 5.41, p = 0.020; HR 4.41, p = 0.036, respectively). This study demonstrates that LNR15, perineural invasion and R1 resection are independently associated with DFS and OS.	
42	Elamir, A. M.; Hutchinson, S.; Albaba, H.; Keshavarzi, S.; Xu, W.; Moulton, C. A.; McGilvary, I.; Cleary, S.; Wei, A.; Dodd, A.; Knox, J.; O'Kane, G.; Prince, R. M.; Kalimuthu, S.; Kim, J.; Ringash, J.; Dawson, L. A.; Wong, R.; Barry, A.; Brierley, J.; Gallinger, S.; Hosni, A. A Risk Score Model for Locoregional Recurrence Following Upfront Surgery for Pancreatic Adenocarcinoma: Implications for Adjuvant Therapy. Clinical Oncology (Royal College of Radiologists) 08 2021;33(8):527-535. DOI: 10.1016/j.clon.2021.03.007	Retrospective	A retrospective review was conducted on patients with stages I-III pancreatic adenocarcinoma who underwent surgery at our institution (2005-2016). Univariable and then multivariable analyses were used to evaluate clinicopathological factors associated with LRF for patients who did not receive PORT. The risk score of LRF was calculated based on the sum of coefficients of the predictors of LRF. The model was applied to the entire cohort to evaluate the impact of PORT on the high- and low-risk groups for LRF.	To identify predictors of locoregional failure (LRF) following surgery for pancreatic adenocarcinoma, develop a prediction risk score model of LRF and evaluate the impact of postoperative radiation therapy (PORT) on LRF.	In total, 467 patients were identified (median follow-up 22 months). Among patients who did not receive PORT (n = 440), predictors of LRF were pN+, involved or close <=1 mm margin(s), moderately and poorly differentiated tumour grade and lymphovascular invasion. After adding patients who received PORT, the 2-year LRF in the high-risk group was 57% for patients who did not receive PORT (n = 242) and 32% among patients who received PORT (n = 22), with an absolute benefit to LRF of 25% (95% confidence interval 5-52%, P = 0.07). The 2-year overall survival for the high-versus the low-risk group was 36% versus 67% (P < 0.001).	3
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. 2008;26(21):3511-3516.	Retrospective	Retrospective review 472 consecutive patients who underwent complete resection with negative margins (R0) for invasive carcinoma (T1-3N0-1M0) of the pancreas between 1975 and 2005 at the Mayo Clinic in Rochester, MN. Exclusion criteria included metastatic or unresectable disease at surgery, positive surgical margins, and indolent tumor types (islet cell tumors and mucinous cystadenocarcinoma). Median RT dose was 50.4 Gy in 28 fractions; 98% of RT patients also received concurrent fluorouracil-based CT.	To determine prognostic factors and impact of adjuvant chemotherapy (CT) and radiotherapy (RT) on overall survival (OS) after resection of pancreatic adenocarcinoma.	Six patients died within 30 days of surgery. For the 466 surviving patients, median follow-up was 32.4 months; median OS was 21.6 months. Median OS after adjuvant CT-RT was 25.2 versus 19.2 months after no adjuvant therapy (P = .001). Two-year OS was 50% versus 39%, and 5-year OS was 28% versus 17%. Adverse prognostic factors identified by univariate and multivariate analysis included positive lymph nodes (risk ratio [RR] = 1.3; P < .001), high histologic grade (RR = 1.2; P < .001), and no adjuvant therapy (RR = 1.3; P < .001). Tumor extension beyond the pancreas was an adverse prognostic factor by univariate analysis alone (P = .03). Patients receiving adjuvant therapy had more adverse prognostic factors than those not receiving adjuvant therapy (P = .001).	3
44	**Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant	Retrospective	Between August 30, 1993, and February 28, 2005, a total of 908	To examine the efficacy of adjuvant	The median follow-up was 17.8 months (interquartile range, 9.7 to 33.5 months). Overall	3

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	chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. J Clin Oncol. 2008;26(21):3503-3510.		patients underwent PD for PC at JHH. A prospective database was reviewed to determine which patients received fluorouracil (FU) -based CRT. Excluded patients had metastatic disease, died 60 or fewer days after PD, received preoperative therapy, an experimental vaccine, adjuvant chemotherapy or radiation alone. The final cohort includes 616 patients.	chemoradiotherapy after PD for PC in patients undergoing resection at Johns Hopkins Hospital (JHH; Baltimore, MD).	median survival was 17.9 months (95% CI, 16.3 to 19.5 months). Groups were similar with respect to tumor size, nodal status, and margin status, but the CRT group was younger (P<.001), and less likely to present with a severe comorbid disease (P=.001). Patients with carcinomas >3 cm (P=.001), grade 3 and 4 (P<.001), marginpositive resection (P=.001), and complications after surgery (P=.017) had poor long-term survival. Patients receiving CRT experienced an improved median (21.2 vs 14.4 months; P<.001), 2-year (43.9% vs 31.9%), and 5-year (20.1% vs 15.4%) survival compared with no CRT. After controlling for high-risk features, CRT was still associated with improved survival (RR = 0.74; 95% CI, 0.62 to 0.89).	
35	Abrams, RA; Winter, KA; Goodman, KA; Regine, W; Safran, H; Berger, AC; Guha, C; Crane, CH. NRG Oncology/RTOG 0848: Results after adjuvant chemotherapy +/- chemoradiation for patients with resected periaampullary pancreatic adenocarcinoma (PA). Journal of Clinical Oncology. 2024. Volume 42, Number 16_suppl https://doi.org/10.1200/JCO.2024.42.16_suppl.4005	Prospective randomized Phase III	This was a 2 step NCTN randomized (rndmzd) trial. Step 1 rndmzd patients (pts) to 5 cycles of gemcitabine +/- Erlotinib. Step 2 rndmzd pts to a 6th cycle of the same chemo +/- 5FU/Capecitabine with 50.4 Gy in 28 fractions RT (chemo+CRT). Step 1 eligibility included: R0/R1 resection, M0, ECOG PS 0-1, CA19-9≤180. Step 2 eligibility included > 4 cycles chemo (gem, gem combo, (m)FOLFIRINOX). RT included real time 3D/IMRT treatment (RX) plan review, scoring, and approval. At Step 2, pts stratified by nodal status (+ vs -), CA19-9 (≤90 vs > 90-180), surgical margins (R0 vs R1), and adjuvant chemo. Primary endpoint was OS. Secondary endpoints are DFS and AEs (CTCAEv4). Assuming 17 months median OS (chemo) and hypothesized 22.5 months (chemo+CRT), sample size was 354 pts (HR = 0.76, 80% power, 1-sided α = 0.05, 316 OS events).	To evaluate if 5FU/Capecitabine sensitized radiotherapy is beneficial in the adjuvant management of PA after adjuvant chemotherapy	Accrual began 11/2009; closed 10/2018. 354 pts rndmzd (174 chemo, 180 chemo+CRT). Median follow-up for all & alive pts = 2 & 7 years, respectively, with 270 OS events. Median age 63, 45% female, 81% white, 13% AA. 83% R0, 26% node negative, 96% CA19-9 < 90. 13% of chemo+CRT pts did not receive RT. AEs were comparable (grade 4: 10% [chemo] vs 11% [chemo+CRT] and 1 grade 5 AE in each arm). Univariate OS/DFS results shown in Table. In initial MVA, RX, CA19-9, surgical margins were not statistically significantly associated with OS or DFS, but nodal status (OS, DFS) and race (OS) were. In further analyses, significant interactions were found between RX and nodal status for both OS and DFS. Node negative pts treated with chemo+CRT had better outcome than chemo pts; node positive pts did not. Chemo+CRT did not improve OS overall but did improve DFS. Both OS and DFS were improved with Chemo+CRT in node negative pts. Chemo+CRT did not increase Gr 4 or 5 AEs compared to chemo.	1

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			Due to lower than projected event rate, trial was amended to report at the earlier of (a) 316 observed OS events or (b) 5 years of follow-up time from Step 2 accrual closure (265 OS events, 72% power, same α). OS and DFS were estimated by Kaplan-Meier and arms compared using log-rank test. Multivariable analyses (MVA) used Cox proportional hazards models.			
46	Delpero, J. R.; Bachellier, P.; Regenet, N.; Le Treut, Y. P.; Paye, F.; Carrere, N.; Sauvanet, A.; Autret, A.; Turrini, O.; Monges-Ranchin, G.; Boher, J. M. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: A French multicentre prospective evaluation of resection margins in 150 evaluable specimens. HPB January 2014;16(1):20-33 DOI: 10.1111/hpb.12061	Retrospective	A total of 150 patients operated during 2008-2010 were included in a prospective multicentre study using a 'quality protocol'. Multicolour inking by the surgeon identified three resection margins: the portal vein-superior mesenteric vein margin (PV-SMVM) or mesenterico-portal vein groove; the superior mesenteric artery margin (SMAM), and the posterior margin. Resection margins were stratified by 0.5-mm increments (range: 0-2.0 mm). Pancreatic neck, bile duct and intestinal margins were also analysed. Correlations between histopathological factors and survival in the 0-mm resection margin group were analysed	To determine the impact of a standardized pathological protocol on resection margin status after pancreaticoduodenectomy (PD) for ductal adenocarcinoma.	Thirty-six patients (24%) had a PV-SMV resection (PV-SMVR). An analysis of resections categorized according to margin distances of 0 mm, <1.0 mm, <1.5 mm and <2.0 mm confirmed R1 resections in 35 (23%), 91 (61%), 94 (63%) and 107 (71%) patients, respectively. The most frequently invaded resection margin was the PV-SMVM (35% of all patients) and PV-SMVR was the only factor correlated with a higher risk for at least one 0-mm positive resection margin on multivariate analysis ($P < 0.001$). Two-year progression-free survival (PFS) and median PFS time in patients with R0 and R1 resections (at 0 mm), respectively, were 42.0% and 26.5%, and 19.5 months and 10.5 months, respectively ($P = 0.02$). A positive PV-SMVM and SMAM had significant impact on PFS, whereas a positive posterior margin had no impact.	3
47	Daamen, L. A.; van Goor, I. W. J. M.; Schouten, T. J.; Dorland, G.; van Roessel, S. R.; Besselink, M. G.; Bonsing, B. A.; Bosscha, K.; Brosens, L. A. A.; Busch, O. R.; van Dam, R. M.; Farina Sarasqueta, A.; Festen, S.; Groot Koerkamp, B.; van der Harst, E.; de Hingh, I. H. J. T.; Intven, M. P. W.; Kazemier, G.; de Meijer, V. E.; Nieuwenhuijs, V. B.; Raicu, G. M.; Roos, D.; Schreinemakers, J. M. J.; Stommel, M. W. J.; van Velthuysen, M. F.; Verheij, J.;	Retrospective observational cohort study	This nationwide observational cohort study included all patients who underwent upfront PDAC resection (2014-2016), as registered in the prospective Dutch Pancreatic Cancer Audit. Patients were subdivided into three groups: R0 (≥ 1 mm margin clearance), R1 (<1 mm margin clearance) or R1 (direct margin involvement). Survival was	To assess the prognostic value of different definitions for resection margin status on disease-free survival (DFS) and overall survival (OS) in pancreatic ductal adenocarcinoma (PDAC)	595 patients with a median OS of 18 months (IQR 10-32 months) months were analysed. R0 (≥ 1 mm) was achieved in 277 patients (47%), R1 (<1 mm) in 146 patients (24%) and R1 (direct) in 172 patients (29%). R1 (direct) was associated with a worse OS, as compared with both R0 (≥ 1 mm) (hazard ratio (HR) 1.35 [95% and confidence interval (CI) 1.08-1.70]; $P < 0.01$) and R1 (<1 mm) (HR 1.29 [95%CI 1.01-1.67]; $P < 0.05$). No OS difference was found between R0 (≥ 1 mm) and R1 (<1 mm) (HR 1.05 [95% CI 0.82-1.34]; $P =$	3

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	Verkooijen, H. M.; van Santvoort, H. C.; Molenaar, I. Q. Microscopic resection margin status in pancreatic ductal adenocarcinoma - A nationwide analysis. European Journal of Surgical Oncology March 2021; Part B. 47(3):708-716 DOI: 10.1016/j.ejso.2020.11.145		compared using multivariable Cox regression analysis. Logistic regression with baseline variables was performed to identify preoperative predictors of R1 (direct).		0.71). Preoperative predictors associated with an increased risk of R1 (direct) included age, male sex, performance score 2-4, and venous or arterial tumour involvement.	
48	Regine, William F.; Winter, Kathryn; Abrams, Ross A.; Safran, Howard; Kessel, Ivan L.; Chen, Yuhchyan; Fugazzi, James A.; Donnelly, Eric D.; DiPetrillo, Thomas A.; Narayan, Samir; Plastaras, John P.; Gaur, Rakesh; Delouya, Guila; Suh, John H.; Meyer, Joshua E.; Haddock, Michael G.; Didolkar, Mukund S.; Padula, Gilbert D. A.; Johnson, David; Hoffman, John P.; Crane, Christopher H. Postresection CA19-9 and margin status as predictors of recurrence after adjuvant treatment for pancreatic carcinoma: Analysis of NRG oncology RTOG trial 9704. Advances in radiation oncology Apr-Jun 2018;3(2): 154-162.DOI: 10.1016/j.adro.2018.01.003	Retrospective	This multicenter cooperative trial included participants who were enrolled as patients at oncology treatment sites in the United States and Canada. The study included 451 patients analyzable for SMS, of whom 385 were eligible for postresection CA19-9 analysis. Postresection CA19-9 was analyzed at cut points of 90, 180, and continuously. Patterns of disease recurrence included local/regional recurrence (LRR) and distant failure (DF). Multivariable analyses included treatment, tumor size, and nodal status. To adjust for multiple comparisons, a P value of $\leq .01$ was considered statistically significant and $> .01$ to $\leq .05$ to be a trend.	To assess the prognostic value of postresection CA19-9 and surgical margin status (SMS) in predicting patterns of disease recurrence.	For CA19-9, 132 (34%) patients were Lewis antigen-negative (no CA19-9 expression), 200 (52%) had levels <90 , and 220 (57%) had levels <180 . A total of 188 patients (42%) had negative margins, 152 (34%) positive, and 111 (25%) unknown. On univariate analysis, CA19-9 cut at 90 was associated with increases in LRR (trend) and DF. Results were similar at the 180 cut point. SMS was not associated with an increase in LRR on univariate or multivariate analyses. On multivariable analysis, CA19-9 ≥ 90 was associated with increased LRR and DF. Results were similar at the 180 cut point. In this prospective evaluation, postresection CA19-9 was a significant predictor of both LRR and DF, whereas SMS was not.	3
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 CONKO001 trial. Int J Radiat Oncol Biol Phys. 2012;84(3): e291-297.	Retrospective	CA 19-9 expression was analyzed as a dichotomized variable (≤ 90 vs >90 U/mL). Cox proportional hazard models were used to identify the impact of the CA 19-9 value on overall survival (OS). Actuarial estimates of OS were calculated using the Kaplan-Meier method.	To examine cutoff points of 90 U/mL and 180 U/mL, provide a 5-year update of trial 9704, and compare patients with CA 19-9 <90 U/mL to those in the CONKO-001 trial.	Both univariate (HR = 3.2; 95% CI, 2.3–4.3, $P<.0001$) and multivariate (HR = 3.1; 95% CI, 2.2–4.2, $P<.0001$) analyses demonstrated a statistically significant decrease in OS for CA 19-9 serum level of ≥ 90 U/mL. For patients in the gemcitabine treatment arm with CA 19-9 <90 U/mL, median survival was 21 months. For patients with CA 19-9 ≥ 90 U/mL, this number dropped to 10 months. In patients with pancreatic head tumors in the gemcitabine treatment arm with RT quality assurance per protocol and CA 19-9 of <90 U/mL, median survival and 5-year rate were 24 months and 34%. In comparison, the median survival and 5-year OS rate for patients in the gemcitabine arm of the CONKO trial were 22 months and 21%.	3

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50	**Hsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. <i>Ann Surg Oncol.</i> 2010;17(4):981-990.	Retrospective	Patients with pancreatic adenocarcinoma at Johns Hopkins Hospital (n = 794, 1993-2005) and Mayo Clinic (n = 478, 1985-2005) following resection who were observed (n = 509) or received adjuvant 5-FU based CRT (median dose 50.4 Gy; n = 583) were included. Cox survival and propensity score analyses assessed associations with overall survival. Matched-pair analysis by treatment group (1:1) based on institution, age, sex, tumor size/stage, differentiation, margin, and node positivity with N = 496 (n = 248 per treatment arm) was performed.	To examine efficacy of adjuvant CRT in resected pancreatic adenocarcinoma compared with surgery alone.	Median survival was 18.8 months. OS was longer among recipients of CRT vs surgery alone (median survival 21.1 vs 15.5 months, P<.001; 2- and 5-year OS 44.7% vs 34.6%; 22.3% vs 16.1%, P<.001). Compared with surgery alone, adjuvant CRT improved survival in propensity score analysis for all patients by 33% (P<.001), with improved survival when stratified by age, margin, node, and T-stage (RR = 0.57–0.75, P<.05). Matched-pair analysis demonstrated OS was longer with CRT (21.9 vs 14.3 months median survival; 2- and 5-year OS 45.5% vs 31.4%; 25.4% vs 12.2%, P<.001).	3
51	Cho, May; Wang-Gillam, Andrea; Myerson, Robert; Gao, Feng; Strasberg, Steven; Picus, Joel; Sorscher, Steven; Fournier, Chloe; Nagaraj, Gayathri; Parikh, Parag; Suresh, Rama; Linehan, David; Tan, Benjamin R. A phase II study of adjuvant gemcitabine plus docetaxel followed by concurrent chemoradiation in resected pancreaticobiliary carcinoma. <i>HPB Jul 2015;17(7): 587-93.DOI: 10.1111/hpb.12413</i>	Prospective nonrandomized phase II	After a curative-intent resection, eligible patients with pancreaticobiliary cancers were treated with two cycles of gemcitabine and docetaxel followed by 5FU-based chemoradiation. Four weeks after completing chemoradiation, two cycles of gemcitabine and docetaxel were administered. The primary endpoint was the incidence of severe toxicities. Secondary endpoints included disease-free survival (DFS) and overall survival (OS).	To investigate the feasibility and toxicity of gemcitabine with docetaxel before and after 5-fluorouracil (5FU)-based chemoradiation in the adjuvant pancreatic and biliary cancer setting	Fifty patients with pancreaticobiliary cancers were enrolled. Twenty-nine patients had pancreatic cancer whereas 21 patients had biliary tract or ampullary cancers. There was one death as a result of pneumonia, and 15% of patients experienced grade 3 or greater non-haematological toxicities. The median DFS and OS for patients with pancreatic cancer were 9.6 and 17 months, respectively, and for those with resected biliary tract cancer were 12 and 23 months, respectively	2
52	*Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, Peeters M, Polus M, Praet M, Mauer M, Collette L, Budach V, Lutz M, Van Cutsem E, Haustermans K. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. <i>J Clin Oncol.</i> 2010 Oct 10;28(29):4450-6. doi:	Prospective randomized phase II	Within 8 weeks after surgery, patients were randomly assigned to receive either four cycles of gemcitabine (control arm) or gemcitabine for two cycles followed by weekly gemcitabine with concurrent radiation (50.4 Gy; CRT arm). The primary objective was to exclude a < 60% treatment completion and a > 40% rate of grade 4 hematologic	To explore the feasibility and tolerability of a gemcitabine-based CRT regimen after R0 resection of pancreatic head cancer.	Between September 2004 and January 2007, 90 patients were randomly assigned (45:45). Patient characteristics were similar in both arms. Treatment was completed per protocol by 86.7% and 73.3% (80% CI, 63.1% to 81.9%; 95% CI, 58.1% to 85.4%) in the control and CRT arms, respectively, and grade 4 toxicity was 0% and 4.7% (two of 43; 80% CI, 1.2% to 11.9%), respectively. In the CRT arm, three patients experienced grade 3-related late toxicity. Median DFS was 12 months in the CRT arm and 11	1

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	10.1200/JCO.2010.30.3446. Epub 2010 Sep 13. PMID: 20837948; PMCID: PMC2988636.		or GI toxicity in the CRT arm with type I and II errors of 10%. Secondary end points were late toxicity, disease-free survival (DFS), and overall survival (OS).		months in the control arm. Median OS was 24 months in both arms. First local recurrence was less frequent in the CRT arm (11% v 24%).	
53	Lee, Kyung-Hun; Chie, Eui Kyu; Im, Seock-Ah; Kim, Jee Hyun; Kwon, Jihyun; Han, Sae-Won; Oh, Do-Youn; Jang, Jin-Young; Kim, Jae-Sung; Kim, Tae-You; Bang, Yung-Jue; Kim, Sun Whe; Ha, Sung W. Phase II Trial of Postoperative Adjuvant Gemcitabine and Cisplatin Chemotherapy Followed by Chemoradiotherapy with Gemcitabine in Patients with Resected Pancreatic Cancer. Cancer Research & Treatment Oct 2021;53(4):1096-1103. DOI: 10.4143/crt.2020.928	Prospective nonrandomized phase II	Patients with curatively resected stage IB-IIIB pancreatic adenocarcinoma were eligible. Treatment consisted of chemotherapy with gemcitabine 1,000 mg/m2 on days 1 and 8 and cisplatin 60 mg/m2 on day 1 every 3 weeks for two cycles, followed by chemoradiotherapy (50.4 Gy/28 fx) with weekly gemcitabine (300 mg/m2/wk), and then gemcitabine 1,000 mg/m2 on days 1 and 8 every 3 weeks for four cycles. The primary endpoint was 1-year disease-free survival rate. The secondary endpoints were disease-free survival, overall survival, and safety.	To determine if adjuvant gemcitabine and cisplatin chemotherapy followed by chemoradiotherapy with gemcitabine and maintenance gemcitabine showed efficacy and good tolerability in curatively resected pancreatic cancer.	Seventy-four patients were enrolled. One-year disease-free survival rate was 57.9%. Median disease-free and overall survival were 15.0 months (95% confidence interval [CI], 11.6 to 18.4) and 33.0 months (95% CI, 21.8 to 44.2), respectively. At the median follow-up of 32 months, 57 patients (77.0%) had recurrence including 11 patients whose recurrence was during the adjuvant treatment. Most of the recurrences were systemic (52 patients). Stage at the time of diagnosis (70.0% in IIA, 51.2% in IIB, p=0.006) were significantly related with 1-year disease-free survival rate. Toxicities were generally tolerable, with 53 events of grade 3 or 4 hematologic toxicity and four patients with febrile neutropenia	2
54	Schunke, Kathryn J.; Rosati, Lauren M.; Zahurak, Marianna; Herman, Joseph M.; Narang, Amol K.; Usach, Irina; Klein, Alison P.; Yeo, Charles J.; Korman, Larry T.; Hruban, Ralph H.; Cameron, John L.; Laheru, Daniel A.; Abrams, Ross A. Long-term analysis of 2 prospective studies that incorporate mitomycin C into an adjuvant chemoradiation regimen for pancreatic and periampullary cancers. Advances in radiation oncology Jan-Mar 2018;3(1):42-51. DOI: 10.1016/j.adro.2017.07.008	Prospective nonrandomized phase II	From 1996 to 2002, 119 patients received an adjuvant 4-drug chemotherapy regimen of 5-fluorouracil, leucovorin, MMC, and dipyrindamole with chemoradiation on 2 consecutive trials (trials A and B). Trial A patients received upfront chemoradiation (50 Gy split-course, 2.5 Gy/fraction) followed by 4 cycles of the 4-drug chemotherapy with bolus 5-fluorouracil. Trial B patients received 1 cycle of the 4-drug chemotherapy with continuous infusion 5-fluorouracil followed by continuous chemoradiation (45-54 Gy, 1.8 Gy/fraction) and 2 additional cycles of	To report toxicity and long-term survival outcomes of 2 prospective trials evaluating mitomycin C (MMC) with 5-fluorouracil-based adjuvant chemoradiation in resected periampullary adenocarcinoma.	Of the 62 trial A patients, 61% had pancreatic and 39% nonpancreatic periampullary carcinomas. Trial B (n = 57) consisted of 68% pancreatic and 32% nonpancreatic periampullary carcinomas. Resection margin and lymph node status were similar for both trials. Median follow-up was longer for trial A than trial B (197.5 vs 107.0 months), with median OS of 32.2 and 24.2 months, respectively. Rates of 3-, 5-, and 10-year OS were 48%, 31%, and 26% in trial A and 32%, 23%, and 9% in trial B. On multivariate analysis, lymph node-positive resection was the strongest prognostic factor for OS. A pancreatic primary and positive margin status were also associated with inferior survival (P < .05). Rates of grade ≥3 treatment-related toxicity in trials A and B were 2% and 7%, respectively. This is the first study to report long-term outcomes of MMC with 5-fluorouracil-based adjuvant chemoradiation in	2

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			chemotherapy. Cox proportional hazards models were performed to identify prognostic factors for overall survival (OS).		periampullary cancers. Because MMC may be considered in DNA repair-deficient carcinomas, randomized trials are needed to determine the true benefit of adjuvant MMC.	
55	Ohman, Kerri A.; Liu, Jingxia; Linehan, David C.; Tan, Marcus C.; Tan, Benjamin R.; Fields, Ryan C.; Strasberg, Steven M.; Hawkins, William G. Interferon-based chemoradiation followed by gemcitabine for resected pancreatic adenocarcinoma: long-term follow-up. HPB 2017;19(5):449-457. DOI: 10.1016/j.hpb.2017.01.012	Prospective nonrandomized phase II	From 2002 to 2005, 53 patients with PDAC underwent pancreaticoduodenectomy and received adjuvant interferon-based chemoradiation consisting of external-beam irradiation and simultaneous 3-drug chemotherapy of continuous daily 5-fluorouracil infusion, weekly intravenous bolus cisplatin, and subcutaneous interferon-alpha, followed by two months of weekly intravenous gemcitabine.	To report long-term follow up of a phase II, single-arm trial of resectable pancreatic ductal adenocarcinoma (PDAC) treated with adjuvant interferon-based chemoradiation followed by gemcitabine to determine survival, recurrence, and complications.	Actual overall survival for the 5- and 10-year periods were 26% and 10%, respectively, with a median overall survival of 25 months (95% CI: 16.4-38.5). Adverse prognostic factors on multivariate analysis were positive tumor margin ($p < 0.035$), lymphovascular invasion ($p < 0.015$), and perineural invasion ($p < 0.026$). Median time to recurrence was 11 months. Positive tumor margin was associated with lymph node involvement ($p < 0.005$), portal vein resection ($p < 0.038$), and metastases ($p < 0.018$). Late complications were frequent and predominated by gastrointestinal and infectious complications.	2
56	Berlin, Jordan D.; Feng, Yang; Catalano, Paul; Abbruzzese, James L.; Philip, Philip A.; McWilliams, Robert R.; Lowy, Andrew M.; Benson, Al B., III; Blackstock, A. William. 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	Prospective randomized phase II	Patients with R0/R1 resection were randomized 1:1 to cetuximab or bevacizumab administered in combination with gemcitabine for two treatment cycles. Next three cycles included concurrent cetuximab/bevacizumab plus chemoradiation, followed by one cycle of cetuximab/bevacizumab. Cycles 7-12 included cetuximab/bevacizumab with gemcitabine. Cycles were 2 weeks. Frequency of specific toxicities was summarized for each treatment arm at two times during the study, after chemotherapy but prior to chemoradiation and after all therapy.	To evaluate toxicity of two treatment arms, A (cetuximab) and B (bevacizumab), when combined with gemcitabine, and chemoradiation in patients with completely resected pancreatic carcinoma. Secondary objectives included overall survival (OS) and disease-free survival (DFS).	A total of 127 patients were randomized (A, n = 65; B, n = 62). Prior to chemoradiation, the overall rate for toxicities of interest was 10% for arm A and 2% for arm B. After all therapy, the overall rates for toxicities of interest were 30 and 25% for arms A and B, respectively. Overall median OS and DFS were 17 and 11 months, respectively, which is not a significant improvement over expected survival rates for historical controls.	1
57	*Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, Crosby T, Jephcott C, Roy R, Radhakrishna G, McDonald A, Ray R, Joseph G, Staffurth J,	Prospective randomized phase II	Patients aged 18 years or older with histologically proven, locally advanced pancreatic cancer (with a tumour diameter of 7 cm or	To assess the activity, safety, and feasibility of both gemcitabine-based and	114 patients were registered and 74 were randomly allocated (38 to the gemcitabine group and 36 to the capecitabine group). After 9 months, 22 of 35 assessable patients (62.9%, 80%	1

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	Abrams RA, Griffiths G, Maughan T. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol. 2013 Apr;14(4):317-26. doi: 10.1016/S1470-2045(13)70021-4. Epub 2013 Mar 6. PMID: 23474363; PMCID: PMC3620899.		less). After 12 weeks of induction gemcitabine and capecitabine chemotherapy (three cycles of gemcitabine [1000 mg/m ² on days 1, 8, 15 of a 28-day cycle] and capecitabine [830 mg/m ² twice daily on days 1–21 of a 28-day cycle]), patients with stable or responding disease, tumour diameter of 6 cm or less, and WHO performance status 0–1 were randomly assigned to receive a further cycle of gemcitabine and capecitabine chemotherapy followed by either gemcitabine (300 mg/m ² once per week) or capecitabine (830 mg/m ² twice daily, Monday to Friday only), both in combination with radiation (50.4 Gy in 28 fractions).	capecitabine-based chemoradiotherapy after induction chemotherapy for patients with locally advanced pancreatic cancer.	CI 50.6–73.9) in the capecitabine group and 18 of 35 assessable patients (51.4%, 39.4–63.4) in the gemcitabine group had not progressed. Median overall survival was 15.2 months (95% CI 13.9–19.2) in the capecitabine group and 13.4 months (95% CI 11.0–15.7) in the gemcitabine group (adjusted hazard ratio [HR] 0.39, 95% CI 0.18–0.81; p=0.012). 12-month overall survival was 79.2% (95% CI 61.1–89.5) in the capecitabine group and 64.2 (95% CI 46.4–77.5) in the gemcitabine group. Median progression-free survival was 12.0 months (95% CI 10.2–14.6) in the capecitabine group and 10.4 months (95% CI 8.9–12.5) in the gemcitabine group (adjusted HR 0.60, 95% CI 0.32–1.12; p=0.11).	
58	Patel, Ajay A.; Nagarajan, Sairaman; Scher, Eli D.; Schonewolf, Caitlin Ab; Balasubramanian, Sairam; Poplin, Elizabeth; Moss, Rebecca; August, David; Carpizo, Darren; Melstrom, Laleh; Jabbour, Salma K. Early vs. Late Chemoradiation Therapy and the Postoperative Interval to Adjuvant Therapy Do Not Correspond to Local Recurrence in Resected Pancreatic Cancer. Pancreatic Disorders & Therapy Jun 2015;5(2): DOI: 10.4172/2165-7092.1000151	Retrospective	After Institutional Review Board approval, resected pancreas cancer patient charts were evaluated for medical background, surgical, pathological, chemoradiation (CRT), and follow-up. Local recurrence (LR) was defined as failures occurring in the postoperative bed and regional lymph nodes. Early vs. late CRT was defined by whether CRT was given early (within 1-2 cycles of adjuvant chemotherapy) or late in the course of adjuvant chemotherapy (after the 3rd cycle of chemotherapy). The postoperative interval variance was compared to LR factors such as progression-free survival (PFS) and overall survival (OS).	To investigate whether the sequence of chemotherapy and chemoradiation and overall time to initiation of adjuvant therapy would impact local vs. distant recurrence	Of the 34 eligible patients, 47% (n=16) underwent early CRT and 41% (n=14) underwent late CRT. 12% (n=14) did not undergo any induction chemotherapy. At median follow-up of 22 months, 53% (n=18) had metastases, 24% (n=8) had LR, and 24% (n=8) were disease free. Kaplan-Meier curves revealed that early vs. late CRT did not appear to significantly impact OS (p=0.63), PFS (p=0.085) or LR (p=0.19). Postoperative interval did not affect PFS (p=0.42) or OS (p=0.93). Early vs. late CRT and the time to initiation of adjuvant therapy were not significantly associated with LR in patients with resected pancreatic cancer.	3
59	Ma, Sung J.; Iovoli, Austin J.; Hermann, Gregory M.; Prezzano, Kavitha M.; Singh,	Retrospective	The NCDDB was queried for resected primary stage I-II, cT1-	To determine if there is a survival benefit	Among 1577 patients, cohort I-II had 839 patients and cohort III had 738 patients. The longer	3

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	Anurag K. Duration of chemotherapy prior to chemoradiation affects survival outcomes for resected stage I-II or unresected stage III pancreatic cancer. Cancer Medicine 2019;8(9):4110-4123. DOI: 10.1002/cam4.2326		3N0-1M0, and unresected stage III, cT4N0-1M0 pancreatic adenocarcinoma treated with C + CRT (2004-2015). Cohorts I-II and III included stage I-II and stage III cases, respectively. Patients were stratified by short (short C) and long duration (long C) of chemotherapy based on their median durations. Baseline patient, tumor, and treatment characteristics were examined. The primary endpoint was overall survival (OS). Kaplan-Meier analysis, multivariable Cox proportional hazards method, and propensity score matching were used.	for using the longer duration of chemotherapy compared to the shorter duration for both resected stage I-II and unresected stage III pancreatic cancer.	duration of chemotherapy prior to CRT showed improved OS in the multivariate analysis in both cohort I-II (hazards ratio [HR] 0.72, P < 0.001) and cohort III (HR 0.83, P = 0.03). Using 1:1 propensity score matching, 610 patients for cohort I-II and 542 patients for cohort III were matched. After matching, long C remained statistically significant for improved OS compared with short C in both cohort I-II (median OS 26.1 vs 21.9 months; P = 0.003) and cohort III (median OS 16.7 vs 14.2; P = 0.02).	
60	Abrams, Ross A.; Winter, Kathryn A.; Safran, Howard; Goodman, Karyn A.; Regine, William F.; Berger, Adam C.; Gillin, Michael T.; Philip, Philip A.; Lowy, Andrew M.; Wu, Abraham; DiPetrillo, Thomas A.; Corn, Benjamin W.; Seaward, Samantha A.; Haddock, Michael G.; Song, Suisui; Jiang, Yixing; Fisher, Barbara J.; Katz, Alan W.; Mehta, Sharmila; Willett, Christopher G.; Crane, Christopher H. Results of the NRG Oncology/ROG 0848 Adjuvant Chemotherapy Question- Erlotinib+Gemcitabine for Resected Cancer of the Pancreatic Head: A Phase II Randomized Clinical Trial. American Journal of Clinical Oncology 03 2020;43(3):173-179. DOI: 10.1097/COC.000000000000063	Prospective randomized Phase III	In step 1 of this protocol, patients were randomized to adjuvant gemcitabine versus the combination of gemcitabine and erlotinib. This manuscript reports the final analysis of these step 1 data. Eligibility-within 10 weeks of curative intent pancreaticoduodenectomy with postoperative CA19-9<180. Gemcitabine arm-6 cycles of gemcitabine. Gemcitabine+erlotinib arm-gemcitabine and erlotinib 100 mg/d. Two hundred deaths provided 90% power (1-sided alpha=0.15) to detect the hypothesized OS signal (hazard ratio=0.72) in favor of the arm 2.	To determine whether adjuvant radiation with fluoropyrimidine sensitization improved survival following gemcitabine-based adjuvant chemotherapy for patients with resected pancreatic head adenocarcinoma.	From November 17, 2009 to February 28, 2014, 163 patients were randomized and evaluable for arm 1 and 159 for arm 2. Median age was 63 (39 to 86) years. CA19-9 <=90 in 93%. Arm 1: 32 patients (20%) grade 4 and 2 (1%) grade 5 adverse events; arm 2, 27 (17%) grade 4 and 3 (2%) grade 5. GI adverse events, arm 1: 22% grade >=3 and arm 2: 28%, (P=0.22). The median follow-up (surviving patients) was 42.5 months (min-max: <1 to 75). With 203 deaths, the median and 3-year OS (95% confidence interval) are 29.9 months (21.7, 33.4) and 39% (30, 45) for arm 1 and 28.1 months (20.7, 30.9) and 39% (31, 47) for arm 2 (log-rank P=0.62). Hazard ratio (95% confidence interval) comparing OS of arm 2 to arm 1 is 1.04 (0.79, 1.38). The addition of adjuvant erlotinib to gemcitabine did not provide a signal for increased OS in this trial.	1
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. 2013;119(12):2350-2357.	Retrospective	National Cancer Data Base (NCDB) data were obtained for all patients who received A-RT for resected PAC from 1998 through 2002. Univariate and multivariate survival analyses were performed along with Kaplan-Meier	To determine whether there is an association between overall survival (OS) and A-RT dose.	A total of 1385 patients met the inclusion criteria. The median age of the patients was 64 years (range, 29 years-87 years). All patients underwent surgical resection and A-RT with or without chemotherapy. A total of 231 patients were diagnosed with stage I disease, 273 were diagnosed with stage II disease, 734 were	3

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			estimates for A-RT levels < 40 grays (Gy), 40 Gy to < 50 Gy, 50 Gy to < 55 Gy, and ≥ 55 Gy.		diagnosed with stage III disease, and 126 were diagnosed with stage IVA disease (according to the fifth edition of the American Joint Committee on Cancer); 21 were found to have an unknown stage of disease. The median A-RT dose was 45 Gy (range, 1.63 Gy-69 Gy). The median OS was 21 months (95% confidence interval [95% CI], 19 months-23 months). On multivariate analysis, an A-RT dose < 40 Gy (hazards ratio [HR], 1.30 [95% CI, 1.03-1.66]; P = .031), an A-RT dose of 40 Gy to < 50 Gy (HR, 1.17 [95% CI, 1.00-1.37]; P = .05), and an A-RT dose ≥ 55 Gy (HR, 1.44 [95% CI, 1.08-1.93]; P = .013) predicted worse OS compared with the reference category of 50 Gy to < 55 Gy. A-RT doses of < 40 Gy, 40 Gy to < 50 Gy, and ≥ 55 Gy were found to be associated with an inferior OS. The dose of A-RT delivered appears to influence OS and a prospective study evaluating the addition of optimally delivered A-RT for patients with resected PAC is needed.	
62	Bernard, M. E.; Suter, P. A.; Iarrobino, N. A.; Quan, K.; Burton, S. A.; Bahary, N.; Hogg, M.; Zureikat, A.; Heron, D. E. Initial Results of a Prospective Study of Adjuvant Pancreatic Stereotactic Body Radiation Therapy for Close or Positive Margins. <i>Advances in radiation oncology</i> April - June 2019;4(2):294-301. DOI: 10.1016/j.adro.2018.11.007	Prospective nonrandomized phase II	Patients eligible for the study had pathologically proven T1-4N0-1M0 pancreatic adenocarcinoma with a positive margin (<=1 mm) or a close margin defined as <2.5 mm. Patients were treated with either neoadjuvant or adjuvant chemotherapy, if eligible for systemic therapy. All patients received 36 Gy in 3 fractions to the close or positive margin site.	To determine if adjuvant pancreatic SBRT is a safe and feasible treatment option for patients with high-risk pancreatic adenocarcinoma and close or positive margins.	From February 2013 to January 2018, 50 patients were enrolled with 49 patients treated on protocol and included in the analysis. The median age was 71 years. The median clinical target volume was 11.3 cc and median planning target volume 22.0 cc. The median overall survival was 23.7 months (95% confidence interval, 13.6-33.8). Local progression-free survival at 1 and 2 years was 85% and 77%, respectively. Regional progression-free survival at 1 and 2 years was 73% and 73%, respectively. Distant metastases-free survival was 57% and 49% at 1 and 2 years, respectively. Grade 3+ radiation toxicity was only 4.1% and occurred in 2 patients.	2
63	Ma, Tao; Bai, Xueli; Wei, Qichun; Shui, Yongjie; Lao, Mengyi; Chen, Wen; Huang, Bingfeng; Que, Risheng; Gao, Shunliang; Zhang, Yun; Chen, Wei; Wang, Ji; Liang, Tingbo. Adjuvant therapy with gemcitabine and stereotactic body radiation therapy versus gemcitabine alone for resected stage II pancreatic cancer: a prospective, randomized, open-	Prospective randomized phase III	In this single-center randomized controlled trial, patients with stage II PDAC that underwent margin-negative resection were randomly assigned to gemcitabine-alone adjuvant chemotherapy or adjuvant SBRT followed by gemcitabine chemotherapy. The primary endpoint was recurrence-free	To investigate the efficacy of gemcitabine combined with stereotactic body radiation therapy (SBRT) as adjuvant therapy for resected stage II PDAC.	Forty patients were randomly assigned to treatment between Sep 1, 2015 and Mar 31, 2018. Of these, 38 were included in the intention-to-treat analysis (20 in gemcitabine arm and 18 in gemcitabine plus SBRT arm). The median RFS and OS were 9.70, 28.0 months in the gemcitabine arm and 5.30, 15.0 months in the gemcitabine plus SBRT arm (RFS, P = 0.53; OS, P = 0.20), respectively. The median LRFS in both arms was unreached (P = 0.81). Grade 3 or 4 adverse events	1

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	label, single center trial. BMC Cancer Aug 08 2022;22(1):865. DOI: 10.1186/s12885-022-09974-7		survival (RFS). Secondary endpoints included locoregional recurrence-free survival (LRFS), overall survival (OS), and incidence of adverse events.		were all comparable between the two arms. Evaluation of data from the enrolled patients indicated that the addition of adjuvant SBRT was not associated with either better local disease control or recurrence-free survival.	
64	Weinberg, Benjamin A.; Wang, Hongkun; Noel, Marcus S.; He, Aiwu R.; Marshall, John L.; Weiner, Louis M.; Fishbein, Thomas M.; Hodgins, Nicole E.; Winslow, Emily R.; Jackson, Patrick G.; Guerra, Juan F.; Aguila, Francisco; Unger, Keith R. Phase 1 Study of Hypofractionated Proton Beam Radiation Therapy in Adjuvant Pancreatic Cancer (PROTON-PANC). International Journal of Radiation Oncology, Biology, Physics Feb 01 2024;118(2):362-367. DOI: 10.1016/j.ijrobp.2023.09.015	Prospective nonrandomized phase I	Nine patients were enrolled in a single-institution phase 1 trial (NCT03885284) between 2019 and 2022. Patients had PDAC of the pancreatic head and underwent R0 or R1 resection and adjuvant modified FOLFIRINOX (mFFX) chemotherapy. The primary endpoint was to determine the dosing schedule of adjuvant PBT (5 Gy x 5 fractions) using limited treatment volumes given between cycles 6 and 7 of mFFX. Patients received PBT on days 15 to 19 in a 28-day cycle before starting cycle 7 (dose level 1, DL1) or on days 8 to 12 in a 21-day cycle before starting cycle 7 (DL2).	To determine the safety of hypofractionated proton beam radiation therapy (PBT) during adjuvant chemotherapy	The median patient age was 66 years (range, 52-78), and the follow-up time from mFFX initiation was 12.5 months (range, 6.2-37.4 months). No patients received preoperative therapy. Four had R1 resections and 5 had node-positive disease. Three patients were enrolled on DL1 and 6 patients on DL2. One dose-limiting toxicity (DLT) occurred at DL2 (prolonged grade 3 neutropenia resulting in discontinuation of mFFX after cycle 7). No other DLTs were observed. Four patients completed 12 cycles of mFFX (range, 7-12; median, 11). No patients have had local recurrence. Five of 9 patients had recurrence: 3 in the liver, 1 in the peritoneum, and 1 in the bone. Six patients are still alive, 4 of whom are recurrence-free. The median time to recurrence was 12 months (95% CI, 4 to not reached [NR]), and median overall survival was NR (95% CI, 6 to NR; 2-year survival rate, 57%).	2
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. 2013;87(5):1007-1015	Retrospective	Consecutive patients with resectable PDA undergoing PD and 1 or more computed tomography (CT) scans more than 60 days after PD at our institution were reviewed. Patients were divided into 3 groups: no adjuvant treatment (NA), chemotherapy alone (CTA), or chemoradiation (CRT). Cross-sectional scans were centrally reviewed, and local recurrences were plotted to scale with respect to the celiac axis (CA), superior mesenteric artery (SMA), and renal veins on 1 CT scan of a template post-PD patient. An adjuvant clinical treatment volume comprising	To generate a map of local recurrences after pancreaticoduodenectomy (PD) for patients with resectable pancreatic ductal adenocarcinoma (PDA) and to model an adjuvant radiation therapy planning treatment volume (PTV) that encompasses a majority of local recurrences.	Of the 202 patients in the study, 40 (20%), 34 (17%), and 128 (63%) received NA, CTA, and CRT adjuvant therapy, respectively. The rate of margin-positive resections was greater in CRT patients than in CTA patients (28% vs 9%, P=.023). Local recurrence occurred in 90 of the 202 patients overall (45%) and in 19 (48%), 22 (65%), and 49 (38%) in the NA, CTA, and CRT groups, respectively. Ninety percent of recurrences were 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 expansion of the combined CA and SMA contours. Three simulated radiation treatment plans using these expansions with adjustments to avoid nearby structures were created to demonstrate the use of this treatment volume.	3

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			90% of local failures based on standard expansions of the CA and SMA was created and simulated on 3 post-PD CT scans to assess the feasibility of this planning approach.			
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. 2012;83(3):901-908.	Retrospective review and consensus guidelines	A consensus committee of six radiation oncologists with expertise in gastrointestinal radiotherapy developed stepwise contouring guidelines and an atlas for the delineation of the clinical target volume (CTV) in the postoperative treatment of pancreas cancer, based on identifiable regions of interest and margin expansions. Areas at risk for subclinical disease to be included in the CTV were defined, including nodal regions, anastomoses, and the preoperative primary tumor location. Regions of interest that could be reproducibly contoured on postoperative imaging after a pancreaticoduodenectomy were identified. Standardized expansion margins to encompass areas at risk were developed after multiple iterations to determine the optimal margin expansions.	To develop contouring guidelines to be used in the Radiation Therapy Oncology Group protocol 0848, a Phase III randomized trial evaluating the benefit of adjuvant chemoradiation in patients with resected head of pancreas cancer.	New contouring recommendations based on CT anatomy were established. Written guidelines for the delineation of the postoperative CTV and normal tissues, as well as a Web-based atlas, were developed.	3
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. 2011;79(1):158-162.	Retrospective	46 patients with pancreatic/ampullary cancer were treated with concurrent chemoradiation (CRT) using inverse-planned IMRT. All patients received CRT based on 5-fluorouracil in a schema similar to Radiation Therapy Oncology Group (RTOG) 97-04. Rates of acute gastrointestinal (GI) toxicity for this series of IMRT-treated patients were compared with	To investigate whether intensity-modulated radiation therapy (IMRT) can improve dose distributions to critical dose-limiting structures near the target.	The overall incidence of Grade 3-4 acute GI toxicity was low in patients receiving IMRT-based CRT. When compared with patients who had three-dimensional treatment planning (RTOG 97-04), IMRT significantly reduced the incidence of Grade 3-4 nausea and vomiting (0% vs. 11%, p = 0.024) and diarrhea (3% vs. 18%, p = 0.017). There was no significant difference in the incidence of Grade 3-4 weight loss between the two groups of patients. IMRT is associated with a statistically significant decrease in acute upper	3

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			those from RTOG 97-04, where all patients were treated with three-dimensional conformal techniques. Chi-square analysis was used to determine if there was a statistically different incidence in acute GI toxicity between these two groups of patients.		and lower GI toxicity among patients treated with CRT for pancreatic/ampullary cancers.	
68	Lee, K. J.; Yoon, H. I.; Chung, M. J.; Park, J. Y.; Bang, S.; Park, S. W.; Seong, J. S.; Song, S. Y. A comparison of gastrointestinal toxicities between intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for pancreatic cancer. <i>Gut & Liver</i> March 2016;10(2):303-309. DOI: 10.5009/gnl15186		Patients who received CCRT between July 2010 and June 2012 in Severance Hospital, Yonsei University College of Medicine, were enrolled prospectively. The patients underwent upper endoscopy before and 1 month after CCRT.	To evaluate the benefits of radiation modalities by comparing gastrointestinal toxicities between 3-D CRT and IMRT for locally-advanced PC.	A total of 84 patients were enrolled during the study period. The radiotherapy modalities delivered included 3D-CRT (n=40) and IMRT (n=44). The median follow-up period from the start of CCRT was 10.6 months (range, 3.8 to 29.9 months). The symptoms of dyspepsia, nausea/vomiting, and diarrhea did not differ between the groups. Upper endoscopy revealed significantly more gastroduodenal ulcers in the 3-D CRT group (p=0.003). The modality of radiotherapy (3D-CRT; odds ratio [OR], 11.67; p=0.011) and tumor location (body of pancreas; OR, 11.06; p=0.009) were risk factors for gastrointestinal toxicities.	3
69	*Nichols RC Jr, George TJ, Zaiden RA Jr, Awad ZT, Asbun HJ, Huh S, Ho MW, Mendenhall NP, Morris CG, Hoppe BS. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. <i>Acta Oncol.</i> 2013 Apr;52(3):498-505. doi: 10.3109/0284186X.2012.762997. PMID: 23477361.	Retrospective	From March 2009 through April 2012, 22 patients were treated with proton therapy and concomitant capecitabine (1000 mg PO twice daily) for resected (n = 5); marginally resectable (n = 5); and unresectable/inoperable (n = 12) biopsy-proven pancreatic and ampullary adenocarcinoma. Two patients with unresectable disease were excluded from the analysis for reasons unrelated to treatment. Proton doses ranged from 50.40 cobalt gray equivalent (CGE) to 59.40 CGE.	To review treatment toxicity for patients with pancreatic and ampullary cancer treated with proton therapy at our institution.	Median follow-up for all patients was 11 (range 5-36) months. No patient demonstrated any grade 3 toxicity during treatment or during the follow-up period. Grade 2 gastrointestinal toxicities occurred in three patients, consisting of vomiting (n = 3); and diarrhea (n = 2). Median weight loss during treatment was 1.3 kg (1.75% of body weight). Chemotherapy was well-tolerated with a median 99% of the prescribed doses delivered. Percentage weight loss was reduced (p = 0.0390) and grade 2 gastrointestinal toxicity was eliminated (p = 0.0009) in patients treated with plans that avoided anterior and left lateral fields which were associated with reduced small bowel and gastric exposure.	3
70	*Nichols RC Jr, Huh SN, Prado KL, Yi BY, Sharma NK, Ho MW, Hoppe BS, Mendenhall NP, Li Z, Regine WF. Protons offer reduced normal-tissue exposure for patients receiving postoperative radiotherapy for resected pancreatic head	Retrospective	8 consecutive patients with resected pancreatic head cancers underwent optimized intensity-modulated radiotherapy (IMRT) treatment planning. IMRT plans used between 10 and 18 fields	To determine the potential role for adjuvant proton-based radiotherapy (PT) for resected	All proton plans met all normal tissue constraints and were isoeffective with the corresponding IMRT plans in terms of PTV coverage. The proton plans offered significantly reduced normal-tissue exposure over the IMRT plans with respect to the following: median small bowel V20 Gy, 15.4%	3

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	cancer. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):158-63. doi: 10.1016/j.ijrobp.2011.05.045. Epub 2012 Jan 13. PMID: 22245197.		and delivered 45 Gy to the initial planning target volume (PTV) and a 5.4 Gy boost to a reduced PTV. PTVs were defined according to the Radiation Therapy Oncology Group 9704 radiotherapy guidelines. Optimized two- to three-field three-dimensional conformal proton plans were retrospectively generated on the same patients. The IMRT and proton plans were then compared.	pancreatic head cancer.	with protons versus 47.0% with IMRT (p = 0.0156); median gastric V20 Gy, 2.3% with protons versus 20.0% with IMRT (p = 0.0313); and median right kidney V18 Gy, 27.3% with protons versus 50.5% with IMRT (p = 0.0156).	
71	Ding X, Dionisi F, Tang S, Ingram M, Hung CY, Prionas E, Lichtenwalner P, Butterwick I, Zhai H, Yin L, Lin H, Kassaei A, Avery S. 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. 2014 Summer;39(2):139-45. doi: 10.1016/j.meddos.2013.11.005. Epub 2014 Mar 21. PMID: 24661778.	Retrospective	A total of 11 patients with postoperative pancreatic cancer who had been previously treated with PS PT in University of Pennsylvania Roberts Proton Therapy Center from 2010 to 2013 were identified. The clinical target volume (CTV) includes the pancreatic tumor bed as well as the adjacent high-risk nodal areas. Internal (iCTV) was generated from 4-dimensional (4D) computed tomography (CT), taking into account target motion from breathing cycle. Three-field and 4-field 3D conformal radiation therapy (3DCRT), 5-field intensity-modulated radiation therapy, 2-arc volumetric-modulated radiation therapy, and 2-field PS and MS PT were created on the patients' average CT. All the plans delivered 50.4Gy to the planning target volume (PTV).	To evaluate the potential advantage of using passive-scattering (PS) and modulated-scanning (MS) proton therapy (PT) to reduce normal tissue exposure in postoperative pancreatic cancer treatment.	Overall, 98% of PTV was covered by 95% of the prescription dose and 99% of iCTV received 98% prescription dose. The results show that all the proton plans offer significant lower doses to the left kidney (mean and V18Gy), stomach (mean and V20Gy), and cord (maximum dose) compared with all the photon plans, except 3-field 3DCRT in cord maximum dose. In addition, MS PT also provides lower doses to the right kidney (mean and V18Gy), liver (mean dose), total bowel (V20Gy and mean dose), and small bowel (V15Gy absolute volume ratio) compared with all the photon plans and PS PT.	3
72	Seufferlein, T; Uhl, W; Kornmann, M; Algul, H; Friess, H; Konig, A; Ghadimi, M. Perioperative or only adjuvant gemcitabine plus nab-paclitaxel for resectable pancreatic cancer (NEONAX)-a randomized phase II trial of the AIO	Prospective randomized phase II	NEONAX is a prospective, randomized phase II trial with two independent experimental arms. One hundred twenty-seven rPDAC patients in 22 German centers were randomized 1:1 to	To examine perioperative or adjuvant chemotherapy with gemcitabine plus	The primary endpoint was disease-free survival (DFS) at 18 months in the modified intention-to-treat (ITT) population [R0/R1-resected patients who started neoadjuvant chemotherapy (CTX) (A) or adjuvant CTX (B)]. The pre-defined DFS rate of 55% at 18 months was not reached in both arms	2

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	pancreatic cancer group. Ann Oncol. 2023 Jan;34(1):91-100. doi: 10.1016/j.annonc.2022.09.161.		perioperative (two pre-operative and four post-operative cycles, arm A) or adjuvant (six cycles, arm B) gemcitabine (1000 mg/m ²) and nab-paclitaxel (125 mg/m ²) on days 1, 8 and 15 of a 28-day cycle.	nab-paclitaxel in rPDAC	[A: 33.3% (95% confidence interval [CI] 18.5% to 48.1%), B: 41.4% (95% CI 20.7% to 62.0%)]. Ninety percent of patients in arm A completed neoadjuvant treatment, and 42% of patients in arm B started adjuvant chemotherapy. R0 resection rate was 88% (arm A) and 67% (arm B), respectively. Median overall survival (mOS) (ITT population) as a secondary endpoint was 25.5 months (95% CI 19.7-29.7 months) in arm A and 16.7 months (95% CI 11.6-22.2 months) in the upfront surgery arm. This difference corresponds to a median DFS (mDFS) (ITT) of 11.5 months (95% CI 8.8-14.5 months) in arm A and 5.9 months (95% CI 3.6-11.5 months) in arm B. Treatment was safe and well tolerable in both arms. The primary endpoint, DFS rate of 55% at 18 months (mITT population), was not reached in either arm of the trial and numerically favored the upfront surgery arm B. mOS (ITT population), a secondary endpoint, numerically favored the neoadjuvant arm A [25.5 months (95% CI 19.7-29.7 months); arm B 16.7 months (95% CI 11.6-22.2 months)]. There was a difference in chemotherapy exposure with 90% of patients in arm A completing pre-operative chemotherapy and 58% of patients starting adjuvant chemotherapy in arm B. Neoadjuvant/perioperative treatment is a novel option for patients with resectable PDAC.	
73	Cecchini, Michael; Salem, Ronald R.; Robert, Marie; Czerniak, Suzanne; Blaha, Ondrej; Zelterman, Daniel; Rajaei, Moein; Townsend, Jeffrey P.; Cai, Guoping; Chowdhury, Sumedha; Yugawa, Deanne; Tseng, Robert; Mejia Arbelaez, Carlos; Jiao, Jingjing; Shroyer, Kenneth; Thumar, Jaykumar; Kortmanský, Jeremy; Zaheer, Wajih; Fischbach, Neal; Persico, Justin; Stein, Stacey; Khan, Sajid A.; Cha, Charles; Billingsley, Kevin G.; Kunstman, John W.; Johung, Kimberly L.; Wiess, Christina; Muzumdar, Mandar D.; Spickard, Erik; Aushev, Vasily N.; Laliotis, George; Jurdi, Adham; Liu, Minetta C.; Escobar-Hoyos,	Prospective nonrandomized phase II	This open-label, single-arm, phase 2 nonrandomized controlled trial for resectable PDAC was conducted at the Yale Smilow Cancer Hospital from April 3, 2014, to August 16, 2021. Pancreatic protocol computed tomography was performed at diagnosis to assess surgical candidacy. Data were analyzed from January to July 2023. Interventions: Patients received 6 cycles of neoadjuvant mFOLFIRINOX before surgery and 6 cycles of adjuvant	To assess whether neoadjuvant modified 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (mFOLFIRINOX) leads to early control of micrometastasis and improves survival.	Of 46 patients who received mFOLFIRINOX, 31 (67%) were male, and the median (range) age was 65 (46-80) years. A total of 37 (80%) completed 6 preoperative cycles and 33 (72%) underwent surgery. A total of 27 patients (59%) underwent resection per protocol (25 with R0 disease and 2 with R1 disease); metastatic or unresectable disease was identified in 6 patients during exploration. Ten patients underwent surgery off protocol. The 12-month PFS was 67% (90% CI, 56.9-100); the median PFS and OS were 16.6 months (95% CI, 13.3-40.6) and 37.2 months (95% CI, 17.5-not reached), respectively. Baseline ctDNA levels were detected in 16 of 22 patients (73%) and in 3 of 17 (18%) after 6 cycles of	2

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	Luisa; Lacy, Jill. Perioperative Modified FOLFIRINOX for Resectable Pancreatic Cancer: A Nonrandomized Controlled Trial. JAMA Oncology Jun 20 2024;20():20. DOI: 10.1001/jamaoncol.2024.1575		mFOLFIRINOX. Whole blood was collected and processed to stored plasma for analysis of circulating tumor DNA (ctDNA) levels. Tumors were evaluated for treatment response and keratin 17 (K17) expression. The primary end point was 12-month progression-free survival (PFS) rate. Additional end points included overall survival (OS), ctDNA level, tumor molecular features, and K17 tumor levels. Survival curves were summarized using Kaplan-Meier estimator.		mFOLFIRINOX. Those with detectable ctDNA levels 4 weeks postresection had worse PFS (hazard ratio [HR], 34.0; 95% CI, 2.6-4758.6; P = .006) and OS (HR, 11.7; 95% CI, 1.5-129.9; P = .02) compared with those with undetectable levels. Patients with high K17 expression had nonsignificantly worse PFS (HR, 2.7; 95% CI, 0.7-10.9; P = .09) and OS (HR, 3.2; 95% CI, 0.8-13.6; P = .07). This nonrandomized controlled trial met its primary end point, and perioperative mFOLFIRINOX warrants further evaluation in randomized clinical trials. Postoperative ctDNA positivity was strongly associated with recurrence. K17 and ctDNA are promising biomarkers that require additional validation in future prospective studies.	
74	Ahmad, Syed A.; Duong, Mai; Sohal, Davendra P. S.; Gandhi, Namita S.; Beg, Muhammad Shaalan; Wang-Gillam, Andrea; Wade, James L., 3rd; Chiorean, Elena Gabriela; Guthrie, Katherine A.; Lowy, Andrew M.; Philip, Philip A.; Hochster, Howard S. Surgical Outcome Results From SWOG S1505: A Randomized Clinical Trial of mFOLFIRINOX Versus Gemcitabine/Nab-paclitaxel for Perioperative Treatment of Resectable Pancreatic Ductal Adenocarcinoma. Annals of Surgery 2020;272(3): 481-486.DOI: 10.1097/SLA.0000000000004155	Prospective randomized phase II	S1505 (NCT02562716) was a randomized phase II study of perioperative chemotherapy with mFOLFIRINOX (Arm 1) or gemcitabine/nab-paclitaxel (Arm 2). Measured parameters included resection rate, margin positivity, pathologic response, and toxicity.	To evaluate perioperative chemotherapy for resectable PDAC	Between 2015 and 2018, 147 patients were randomized. Of these, 44 (30%) were deemed ineligible (43 by central review). Of the 103 eligible patients, 77 (76%) completed preoperative therapy and underwent surgery; reasons patients did not undergo surgery included toxicity related to preoperative therapy (n = 9), progression (n = 9), or other (n = 7). Of the 77, 73 (95%) underwent successful resection; 21 (29%) required vascular reconstruction, 62 (85%) had negative (R0) margins, and 24 (33%) had a complete or major pathologic response to therapy. The grade 3-5 postoperative complication rate was 16%. Of the 73 patients completing surgery, 57 (78%) started and 46 (63%) completed postoperative therapy. This study represents the first prospective trial evaluating modern systemic therapy delivered in a neoadjuvant/perioperative format for resectable PDA.	1
75	Golcher, Henriette; Brunner, Thomas B.; Witzigmann, Helmut; Marti, Lukas; Bechstein, Wolf-Otto; Bruns, Christiane; Jungnickel, Henry; Schreiber, Stefan; Grabenbauer, Gerhard G.; Meyer, Thomas; Merkel, Susanne; Fietkau, Rainer; Hohenberger, Werner. Neoadjuvant chemoradiation therapy	Prospective randomized phase III	Patients with resectable adenocarcinoma of the pancreatic head were randomized to primary surgery (Arm A) or neoadjuvant chemoradiotherapy followed by surgery (Arm B), which was followed by adjuvant	To evaluate the neoadjuvant CRT followed by surgery and adjuvant chemotherapy in resectable PDAC	The trial was stopped after 73 patients; 66 patients were eligible for analysis. Twenty nine of 33 allocated patients received chemoradiotherapy. Radiotherapy was completed in all patients. Chemotherapy was changed in 3 patients due to toxicity. Tumor resection was performed in 23 vs. 19 patients (A vs. B). The R0 resection rate was 48 % (A) and	1

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	with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. Strahlentherapie und Onkologie Jan 2015;191(1):7-16. DOI: 10.1007/s00066-014-0737-7		chemotherapy in both arms. A total of 254 patients were required to detect a 4.33-month improvement in median overall survival (mOS).		52 % (B, P = 0.81) and (y)pN0 was 30 % (A) vs. 39 % (B, P = 0.44), respectively. Postoperative complications were comparable in both groups. mOS was 14.4 vs. 17.4 months (A vs. B; intention-to-treat analysis; P = 0.96). After tumor resection, mOS was 18.9 vs. 25.0 months (A vs. B; P = 0.79).	
76	Coveler, Andrew L.; Pillarisetty, Venu G.; Koh, Wui-Jin; Zhen, David B.; Park, James O.; King, Gentry G.; Sham, Jonathan G.; Hannan, Lindsay M.; Mann, Gary N.; Baker, Kelsey K.; Redman, Mary W.; Swanson, Paul E.; Chiorean, E. Gabriela; Whiting, Sam H. Perioperative Chemotherapy and Chemoradiotherapy for Patients With Resectable and Borderline Resectable Pancreatic Adenocarcinoma. Pancreas May 01 2023;52(5): e282-e287. DOI: 10.1097/MPA.0000000000002253	Prospective nonrandomized phase II	A single center, phase 2, trial of patients with resectable or borderline resectable PDA. Patients received neoadjuvant therapy with induction chemotherapy (gemcitabine, docetaxel, capecitabine) for 3 cycles, chemoradiation (intensity-modulated radiation therapy with capecitabine and oxaliplatin) followed by surgery, and 2 months of adjuvant gemcitabine and oxaliplatin and 2 months of gemcitabine. The primary endpoint was OS. The secondary endpoint was recurrence-free survival (RFS).	To evaluate multiagent perioperative therapy for potentially resectable PDA patients to improve OS.	Thirty-two eligible patients were enrolled. Twenty-two patients underwent surgical resection. After a median follow-up of 56.8 months, mOS was 31.6 months (95% confidence interval [CI], 14.2-58.1) for all patients, 58.1 months (95% CI, 31.6 to NR) for those who completed surgery. The mRFS was 31.3 months (95% CI, 12.5 to NR). Perioperative therapy with GTX, chemoradiotherapy, and adjuvant GemOx/Gem resulted in promising survival of 58 months for patients who underwent resection and may represent another treatment option for PDA.	2
77	Versteijne E, van Dam JL, Suker M, Janssen QP, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, Buijsen J, Busch OR, Creemers GM, van Dam RM, Eskens FALM, Festen S, de Groot JWB, Groot Koerkamp B, de Hingh IH, Homs MYV, van Hooft JE, Kerver ED, Luelmo SAC, Neelis KJ, Nuyttens J, Paardekooper GMRM, Patijn GA, van der Sangen MJC, de Vos-Geelen J, Wilmink JW, Zwinderman AH, Punt CJ, van Tienhoven G, van Eijck CHJ; Dutch Pancreatic Cancer Group. Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial. J Clin Oncol. 2022 Apr 10;40(11):1220-1230. doi:	Prospective randomized phase III	In this multicenter, phase III trial, patients with resectable and borderline resectable pancreatic cancer were randomly assigned (1:1) to neoadjuvant chemoradiotherapy or upfront surgery in 16 Dutch centers. Neoadjuvant chemoradiotherapy consisted of three cycles of gemcitabine combined with 36 Gy radiotherapy in 15 fractions during the second cycle. After restaging, patients underwent surgery followed by four cycles of adjuvant gemcitabine. Patients in the upfront surgery group underwent surgery followed by six cycles of adjuvant gemcitabine. The primary outcome was OS by intention-to-	The benefit of neoadjuvant chemoradiotherapy in resectable and borderline resectable pancreatic cancer remains controversial. Initial results of the PREOPANC trial failed to demonstrate a statistically significant overall survival (OS) benefit. The long-term results are reported.	Between April 24, 2013, and July 25, 2017, 246 eligible patients were randomly assigned to neoadjuvant chemoradiotherapy (n = 119) and upfront surgery (n = 127). At a median follow-up of 59 months, the OS was better in the neoadjuvant chemoradiotherapy group than in the upfront surgery group (hazard ratio, 0.73; 95% CI, 0.56 to 0.96; P = .025). Although the difference in median survival was only 1.4 months (15.7 months v 14.3 months), the 5-year OS rate was 20.5% (95% CI, 14.2 to 29.8) with neoadjuvant chemoradiotherapy and 6.5% (95% CI, 3.1 to 13.7) with upfront surgery. The effect of neoadjuvant chemoradiotherapy was consistent across the prespecified subgroups, including resectable and borderline resectable pancreatic cancer.	1

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	10.1200/JCO.21.02233. Epub 2022 Jan 27. PMID: 35084987.		treat. No safety data were collected beyond the initial report of the trial.			
78	Ma, Sung Jun; Serra, Lucas M.; Bartl, Austin J.; Han, Hye Ri; Fekrmandi, Fatemeh; Iovoli, Austin J.; Hermann, Gregory M.; Yu, Han; Singh, Anurag K. Adjuvant chemotherapy versus observation following neoadjuvant therapy and surgery for resectable stage I-II pancreatic cancer. Journal of Radiotherapy in Practice Sep 2022;21(3):383-392. DOI: 10.1017/s1460396921000194	Retrospective	The NCDB was queried for primary stage I-II cT1-3N0-1M0 resected pancreatic adenocarcinoma treated with NT (2004-2015). Baseline patient, tumor, and treatment characteristics were extracted. The primary endpoint was OS. With a 6-month conditional landmark, Kaplan-Meier analysis, multivariable Cox proportional hazards method, 1:1 propensity score matching were used to analyze the data.	To evaluate the outcomes of AC versus observation for resected pancreatic adenocarcinoma treated with NT.	A total of 1737 eligible patients were identified, of which 1247 underwent postoperative observation compared to 490 with AC. The overall median follow-up was 34.7 months. The addition of AC showed improved survival on the multivariate analysis (HR 0.78, p<0.001). Of 490 propensity-matched pairs, all variables were well balanced, including age (p=0.61), Charlson-Deyo comorbidity score (p=0.80), ypT stage (p=0.93), ypN stage (p=0.83), surgical margin (p=0.83), duration of postoperative inpatient admission (p=0.96), and 30-day unplanned readmission after resection (p=0.34). AC remained statistically significant for improved OS, with median OS of 26.3 months vs 22.3 months and 2-year OS of 63.9% vs 52.9% for the observation cohort (p<0.001). Treatment interaction analysis showed OS benefit of AC for patients with smaller tumors (HR 0.67, p<0.001 for <3.1 cm vs HR 0.93, p=0.48 for ≥3.1 cm).	3
79	de Geus, Susanna W. L.; Kasumova, Gylunara G.; Eskander, Mariam F.; Ng, Sing Chau; Kent, Tara S.; James Moser, A.; Vahrmeijer, Alexander L.; Callery, Mark P.; Tseng, Jennifer F. Is Neoadjuvant Therapy Sufficient in Resected Pancreatic Cancer Patients? A National Study. Journal of Gastrointestinal Surgery 2018;22(2):214-225. DOI: 10.1007/s11605-017-3541-8	Retrospective	We used the National Cancer Data Base between 2006 and 2013 to identify resected, non-metastatic pancreatic adenocarcinoma patients who received neoadjuvant chemo(radio)therapy followed by pancreatectomy. Kaplan-Meier and multivariate Cox proportional hazard regression analyses were performed to compare survival between groups.	To evaluate the impact of adjuvant therapy following neoadjuvant treatment and pancreatectomy in pancreatic cancer patients in a large national study.	In total, 1357 patients were identified. Of the patients, 38.6% (n = 524) were treated with postoperative therapy. There was no difference in unadjusted median overall survival between patients who did and did not receive postoperative therapy (median survival, 27.5 vs. 27.1 months, log-rank p = 0.5409). Postoperative therapy was not significantly associated with favorable prognosis in patients with positive resection margins (log-rank p = 0.6452) or positive lymph nodes (log-rank p = 0.6252). On multivariate analysis, receipt of postoperative therapy was not predictive of survival (hazard ratio 0.972; 95% CI 0.848-1.115; p = 0.6876).	3
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.	Prospective nonrandomized	Patients with early-stage pancreatic adenocarcinoma were enrolled following upfront resection at 26 Australian centres. Patients were ECOG 0-1 and fit for AC. A tumour-informed ctDNA assay was used to identify	To determine if a tumor informed ctDNA approach to AC selection is feasible for patients undergoing upfront resection of	A total of 102 patients were enrolled from March 2019 to Nov 2023. Median age was 68 years (range 41 – 86), with 50% male and 95% ECOG 0-1. Tumours were located in the head of pancreas in 72%. Histology revealed T1 (18%), T2 (50%), and T3 (32%) tumors, with nodal involvement in 71%, and an R0 resection in 77%. Post-operative	2

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	2024;42(16)(107) https://doi.org/10.1200/JCO.2024.42.16_suppl.10		somatic mutations for tracking in circulating cell-free DNA. ctDNA+ patients received 6 months of AC (FOLFIRINOX or gemcitabine/capecitabine selected at the clinician's discretion), while ctDNA- patients could de-escalate to 3 months at the clinician's discretion. ctDNA was assessed again at the end of AC. The primary study endpoint was the feasibility of ctDNA-guided therapy. Secondary endpoints included the association of ctDNA with clinicopathologic risk factors and survival outcomes.	pancreatic adenocarcinoma, with the first blood draw to be scheduled at week 5, allowing time for ctDNA analysis to determine AC selection.	Ca19-9 was elevated in 29%. Forty patients (40%) were ctDNA+ve post resection, 54 (53%) were ctDNA-ve, and no result was obtained in 4 (4%) due to the absence of tumor mutation, and as a result, they were considered ineligible. The presence or absence of ctDNA was not associated with known clinicopathologic risk factors. Median time to ctDNA collection was 5 weeks (range 3 – 9) and to commencing AC was 6 weeks (range 4-12). Of 54 ctDNA-ve patients, 24 (44%) were de-escalated to receive a planned 3 months of AC. With a median follow-up of 36 months (range 2-56) the median recurrence free survival (RFS) in ctDNA+ve patients was 13 months compared to 22 months for ctDNA-ve patients (HR 0.52, p = 0.003).	
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	Systematic review	ASCO convened an Expert Panel and conducted a systematic review to update guideline recommendations for second-line therapy for metastatic pancreatic cancer.	To provide an update to the ASCO guideline on metastatic pancreatic cancer pertaining to recommendations for therapy options after first-line treatment.	One randomized controlled trial of olaparib versus placebo, one report on phase I and II studies of larotrectinib, and one report on phase I and II studies of entrectinib met the inclusion criteria and inform the guideline update. New or updated recommendations for germline and somatic testing for microsatellite instability high/mismatch repair deficiency, BRCA mutations, and TRK alterations are provided for all treatment-eligible patients to select patients for recommended therapies, including pembrolizumab, olaparib, larotrectinib, or entrectinib, or potential clinical trials. The Expert Panel continues to endorse the remaining recommendations for second-line chemotherapy, as well as other recommendations related to treatment, follow-up, and palliative care from the 2018 version of this guideline.	3
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	Prospective randomized phase III	We conducted a randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy of olaparib as maintenance therapy in patients who had a germline BRCA1 or BRCA2 mutation and metastatic pancreatic cancer and disease that had not progressed during	To evaluate the efficacy of olaparib as maintenance therapy in patients who had a germline BRCA1 or BRCA2 mutation and metastatic pancreatic cancer and disease	Of the 3315 patients who underwent screening, 154 underwent randomization and were assigned to a trial intervention (92 to receive olaparib and 62 to receive placebo). The median progression-free survival was significantly longer in the olaparib group than in the placebo group (7.4 months vs. 3.8 months; hazard ratio for disease progression or death, 0.53; 95% confidence interval [CI], 0.35 to 0.82; P = 0.004). An interim	1

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			first-line platinum-based chemotherapy. Patients were randomly assigned, in a 3:2 ratio, to receive maintenance olaparib tablets (300 mg twice daily) or placebo. The primary end point was progression-free survival, which was assessed by blinded independent central review.	that had not progressed during first-line platinum-based chemotherapy.	analysis of overall survival, at a data maturity of 46%, showed no difference between the olaparib and placebo groups (median, 18.9 months vs. 18.1 months; hazard ratio for death, 0.91; 95% CI, 0.56 to 1.46; P = 0.68). There was no significant between-group difference in health-related quality of life, as indicated by the overall change from baseline in the global quality-of-life score (on a 100-point scale, with higher scores indicating better quality of life) based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (between-group difference, -2.47 points; 95% CI, -7.27 to 2.33). The incidence of grade 3 or higher adverse events was 40% in the olaparib group and 23% in the placebo group (between-group difference, 16 percentage points; 95% CI, -0.02 to 31); 5% and 2% of the patients, respectively, discontinued the trial intervention because of an adverse event.	
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	Prospective nonrandomized phase II	This open-label phase II study evaluated T-DXd (5.4 mg/kg once every 3 weeks) for HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing) locally advanced or metastatic disease after ≥1 systemic treatment or without alternative treatments. The primary end point was investigator-assessed confirmed objective response rate (ORR). Secondary end points included safety, duration of response, progression-free survival (PFS), and overall survival (OS).	To evaluate Trastuzumab deruxtecan (T-DXd) in locally advanced or metastatic Her-2 expressing tumors, including PDAC	At primary analysis, 267 patients received treatment across seven tumor cohorts: endometrial, cervical, ovarian, bladder, biliary tract, pancreatic, and other. The median follow-up was 12.75 months. In all patients, the ORR was 37.1% (n = 99; [95% CI, 31.3 to 43.2]), with responses in all cohorts; the median DOR was 11.3 months (95% CI, 9.6 to 17.8); the median PFS was 6.9 months (95% CI, 5.6 to 8.0); and the median OS was 13.4 months (95% CI, 11.9 to 15.5). In patients with central HER2 IHC 3+ expression (n = 75), the ORR was 61.3% (95% CI, 49.4 to 72.4), the median DOR was 22.1 months (95% CI, 9.6 to not reached), the median PFS was 11.9 months (95% CI, 8.2 to 13.0), and the median OS was 21.1 months (95% CI, 15.3 to 29.6). Grade ≥3 drug-related adverse events were observed in 40.8% of patients; 10.5% experienced adjudicated drug-related interstitial lung disease (ILD), with three deaths.	2
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.	Case Report	A BRAF point mutation in V600E is commonly reported in KRAS wild-type PDAC, and targeting BRAF_V600E is already being	To report outcome of a patient with BRAF N486_P490 deletion initiated on	The patient then presented with a partial response.	4

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	Front Oncol. 2022; 12:976450. doi:10.3389/fonc.2022.976450		applied to various carcinomas, including PDAC. Accumulated evidence also shows that not only BRAF_V600E but also short in-frame deletions of BRAF have an oncogenic function.	dabrafenib or trametinib after cytotoxic chemotherapy failure		
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	Prospective nonrandomized phase II	We enrolled patients with consecutively and prospectively identified TRK fusion–positive cancers, detected by molecular profiling as routinely performed at each site, into one of three protocols: a phase 1 study involving adults, a phase 1–2 study involving children, or a phase 2 study involving adolescents and adults. The primary end point for the combined analysis was the overall response rate according to independent review. Secondary end points included duration of response, progression-free survival, and safety.	To evaluate the efficacy and safety of larotrectinib, a highly selective TRK inhibitor, in adults and children who had tumors with fusions involving one of three tropomyosin receptor kinases (TRK)	A total of 55 patients, ranging in age from 4 months to 76 years, were enrolled and treated. Patients had 17 unique TRK fusion–positive tumor types. The overall response rate was 75% (95% confidence interval [CI], 61 to 85) according to independent review and 80% (95% CI, 67 to 90) according to investigator assessment. At 1 year, 71% of the responses were ongoing and 55% of the patients remained progression-free. The median duration of response and progression-free survival had not been reached. At a median follow-up of 9.4 months, 86% of the patients with a response (38 of 44 patients) were continuing treatment or had undergone surgery that was intended to be curative. Adverse events were predominantly of grade 1, and no adverse event of grade 3 or 4 that was considered by the investigators to be related to larotrectinib occurred in more than 5% of patients. No patient discontinued larotrectinib owing to drug-related adverse events.	2
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	Prospective nonrandomized phase II	The genomes of cancers deficient in mismatch repair contain exceptionally high numbers of somatic mutations. In a proof-of-concept study, we previously showed that colorectal cancers with mismatch repair deficiency were sensitive to immune checkpoint blockade with antibodies to programmed death receptor-1 (PD-1). We have now expanded this study to evaluate the efficacy of PD-1 blockade in patients with advanced mismatch repair-deficient cancers across 12 different tumor types.	To evaluate the efficacy of PD-1 blockade in patients with advanced mismatch repair-deficient cancers across 12 different tumor types.	Objective radiographic responses were observed in 53% of patients, and complete responses were achieved in 21% of patients. Responses were durable, with median progression-free survival and overall survival still not reached. Functional analysis in a responding patient demonstrated rapid in vivo expansion of neoantigen-specific T cell clones that were reactive to mutant neopeptides found in the tumor. These data support the hypothesis that the large proportion of mutant neoantigens in mismatch repair-deficient cancers make them sensitive to immune checkpoint blockade, regardless of the cancers' tissue of origin.	2

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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	Retrospective	Archival and prospectively acquired samples and matched normal DNA from N = 833 PDAC cases were analyzed using a hybridization capture-based, NGS assay designed to perform targeted deep sequencing of all exons and selected introns of 341 to 468 cancer-associated genes. A computational program using NGS data derived the MSI status from the tumor-normal paired genome sequencing data. Available germline testing, IHC, and microsatellite instability (MSI) PCR results confirmed MMR-D and MSI status.	To address questions on the appropriate screening, detection methods, patient selection, and initiation of therapy for MMR-D pancreatic ductal adenocarcinoma (PDAC) and assess the utility of next-generation sequencing (NGS) in providing additional prognostic and predictive info for MMR-D PDAC	MMR-D in PDAC is a rare event among PDAC patients (7/833), occurring at a frequency of 0.8%. Loss of MMR protein expression by IHC, high mutational load, and elevated MSI scores were correlated with MMR-D PDAC. All 7 MMR-D PDAC patients in the study were found to have Lynch syndrome. Four (57%) of the MMR-D patients treated with immune checkpoint blockade had treatment benefit (1 complete response, 2 partial responses, 1 stable disease).	3
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	Retrospective	In this retrospective analysis, treatment history and longitudinal survival outcomes were analysed in patients aged 18 years or older with biopsy-confirmed pancreatic cancer of any stage, enrolled in the KYT programme and who received molecular testing results. Since the timing of KYT enrolment varied for each patient, the primary outcome measurement of median overall survival was calculated from the initial diagnosis of advanced disease until death. We compared median overall survival in patients with actionable mutations who were treated with a matched therapy versus those who were not treated with a matched therapy.	To determine whether patients with pancreatic cancer whose tumours harboured such actionable molecular alterations and who received molecularly matched therapy had a longer median overall survival than similar patients who did not receive molecularly matched therapy.	Of 1856 patients with pancreatic cancer who were referred to the KYT programme between June 16, 2014, and March 31, 2019, 1082 (58%) patients received personalised reports based on their molecular testing results. Actionable molecular alterations were identified in 282 (26%) of 1082 samples. Among 677 patients for whom outcomes were available, 189 had actionable molecular alterations. With a median follow-up of 383 days (IQR 214-588), those patients with actionable molecular alterations who received a matched therapy (n=46) had significantly longer median overall survival than did those patients who only received unmatched therapies (n=143; 2.58 years [95% CI 2.39 to not reached] vs 1.51 years [1.33-1.87]; hazard ratio 0.42 [95% CI 0.26-0.68], p=0.0004). The 46 patients who received a matched therapy also had significantly longer overall survival than the 488 patients who did not have an actionable molecular alteration (2.58 years [95% CI 2.39 to not reached] vs 1.32 years [1.25-1.47]; HR 0.34 [95% CI 0.22-0.53], p<0.0001). However, median overall survival did not differ between the patients who received unmatched therapy and those without an actionable molecular alteration (HR 0.82 [95% CI 0.64-1.04], p=0.10).	3

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Article Key:

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.

ARS Appropriateness Criteria Evidence Table Key:

Study Quality Category Definitions

Category 1 The study is well-designed and accounts for common biases.

Category 2 The study is moderately well-designed and accounts for most common biases.

Category 3 There are important study design limitations.

Category 4 The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

- a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
- b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
- c) the study is an expert opinion or consensus document.

Category M The study is a meta-analysis and has not been rated for quality because the method is designed to evaluate individual studies only.

Abbreviations Key:

* Reference found by backward citation searching, identified by examining references cited in articles selected from the search strategy that were published prior to 1/1/2014 and significantly contributed to the literature.

** Reference retained from original 2017 AUC Resected Pancreatic Cancer bibliography if they were more than 10 years old and significantly contributed to the evidence.