Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29.	Review/Other-Tx	N/A	To provide the expected numbers of new cancer cases and deaths in 2015 nationally and for each state, as well as a comprehensive overview of cancer incidence, mortality, and survival rates and trends using the most current population-based data. The article also estimates the total number of deaths averted nationally during the past 2 decades and by state in 2011 as a result of the continual decline in cancer death rates and present actual number of deaths reported in 2011 by age for the 10 leading causes of death and for the 5 leading causes of cancer death.	Cancer death rates have been continuously declining for the past 2 decades. Overall, the risk of dying from cancer decreased by 22% between 1991 and 2011. Regionally, progress has been most rapid for residents of the Northeast, among whom death rates have declined by 25% to 30%, and slowest in the South, where rates declined by about 15%. Further reductions in cancer death rates can be accelerated by applying existing cancer control knowledge across all segments of the population, with an emphasis on those in the lowest socioeconomic bracket and other disadvantaged populations.	4
2. Wolfgang CL, Herman JM, Laheru DA, et al. Recent progress in pancreatic cancer. *CA Cancer J Clin.* 2013;63(5):318-348.	Review/Other-Tx	N/A	To review recent progress in PC, with emphasis on genetic advances and the multidisciplinary team approach to patient care.	No results stated in abstract.	4
3. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;364(19):1817-1825.	Experimental-Tx	342 patients	To further explore FOLFIRINOX as compared with single agent GEM as first-line treatment in patients with metastatic PC.	The median OS was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the GEM group (HR for death, 0.57; 95% CI, 0.45 to 0.73; $P<0.001$). Median PFS was 6.4 months in the FOLFIRINOX group and 3.3 months in the GEM group (HR for disease progression, 0.47; 95% CI, 0.37 to 0.59; $P<0.001$). The objective response rate was 31.6% in the FOLFIRINOX group vs 9.4% in the GEM group ($P<0.001$). More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropenia. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life vs 66% in the GEM group (HR, 0.47; 95% CI, 0.30 to 0.70; $P<0.001$).	1

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4. Pawlik TM, Laheru D, Hruban RH, et al. Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. *Ann Surg Oncol.* 2008;15(8):2081-2088.	Observational-Tx	203 patients	To evaluate the impact of a multidisciplinary clinic on the clinical care recommendations of patients with PC compared with the recommendations the patients received prior to review by the multidisciplinary tumor board.	On presentation, the outside CT report described locally advanced/unresectable disease (34.9%), metastatic disease (17.7%), and locally advanced disease with metastasis (1.1%). On review of submitted imaging and imaging performed at Hopkins, 38/203 (18.7%) patients had a change in the status of their clinical stage. Review of the histological slides by dedicated pancreatic pathologists resulted in changes in the interpretation for 7/203 patients (3.4%). Overall, 48/203 (23.6%) patients had a change in their recommended management based on clinical review of their case by the multidisciplinary tumor board. Enrollment into the National Familial Pancreas Tumor Registry increased from 52/106 (49.2%) patients in 2005 to 158/203 (77.8%) with initiation of the multidisciplinary clinic.	2
5. Fong Y, Gonen M, Rubin D, Radzyner M, Brennan MF. Long-term survival is superior after resection for cancer in high-volume centers. *Ann Surg.* 2005;242(4):540-544; discussion 544-547.	Observational-Tx	2,592 pancreatectomies and 3,734 hepatectomies	To examine the relationship between hospital volume with long-term survival in patients with cancer subjected to pancreatectomy or hepatectomy using a national database.	In the study period, there were 2592 pancreatectomies and 3734 hepatectomies performed at 1101 and 1284 institutions, respectively. High-volume center was defined as >25 cases/year. By this definition, there were 10 high-volume centers for pancreatectomy and 12 centers for hepatectomy performing 11% (n = 291) of the pancreatectomies and 12% (n = 474) of the hepatectomies in this study period. Comparison by log-rank demonstrated superior survival for patients resected at high-volume centers (pancreatectomy: P=0.001; hepatectomy: P=0.02). This was confirmed by multivariate analysis. All analyses included an adjustment for within-center correlation.	2

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6. Katz MH, Marsh R, Herman JM, et al. Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol.* 2013;20(8):2787-2795.	Review/Other-Tx	N/A	To review limitations of studies of BRPC 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.	We identified 23 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.	4
7. Tummala P, Junaidi O, Agarwal B. Imaging of pancreatic cancer: An overview. *J Gastrointest Oncol.* 2011;2(3):168-174.	Review/Other-Dx	N/A	To review the relative advantages and shortcomings of imaging modalities available for evaluation of patients with suspected PC and for preoperative determination of resectability.	No results stated in abstract.	4
8. Schima W, Ba-Ssalamah A, Goetzinger P, Scharitzer M, Koelblinger C. State-of-the-art magnetic resonance imaging of pancreatic cancer. *Top Magn Reson Imaging.* 2007;18(6):421-429.	Review/Other-Dx	N/A	To review the relative advantages and shortcomings of imaging modalities available for evaluation of patients with suspected PC and for preoperative determination of resectability.	No results stated in abstract.	4
9. Vachiranubhap B, Kim YH, Balci NC, Semelka RC. Magnetic resonance imaging of adenocarcinoma of the pancreas. *Top Magn Reson Imaging.* 2009;20(1):3-9.	Review/Other-Dx	N/A	To describe the attribute of magnetic resonance imaging for evaluating PC.	No results stated in abstract.	4
10. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. Version 2.2015. 2015; Available at: http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf.	Review/Other-Tx	N/A	To provide NCCN practice guidelines on PC.	No abstract available.	4

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11. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol.* 2009;27(11):1806-1813.	Observational-Tx	76 patients	To present the clinical and pathologic features at autopsy of the first 76 patients with PC who participated in this program with particular reference to the histopathologic findings and genetic status in relation to patterns of failure.	At autopsy, 30% of patients died with locally destructive PC, and 70% died with widespread metastatic disease. These divergent patterns of failure found at autopsy (locally destructive vs metastatic) were unrelated to clinical stage at initial presentation, treatment history, or histopathologic features. However, DPC4 immunolabeling status of carcinoma tissues harvested at autopsy, a sensitive marker of DPC4 genetic status, was highly correlated with the presence of widespread metastasis but not with locally destructive tumors (*P*=.007).	2
12. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer.* 1981;48(8):1705-1710.	Experimental-Tx	194 patients	To evaluate the effectiveness of split course RT to 6000 rads by controlled study attempts to confirm the value of combined radiation + 5-FU therapy demonstrated in the earlier Mayo Clinic study.	Median survival with radiation alone was only 51/2 months from date of diagnosis. Both 5-FU-containing treatment regimens produced a highly significant survival improvement when compared with radiation alone. 40% of patients treated with the combined regimens were still living at 1-year compared with 10% of patients treated with radiation only. Survival differences between 4000 rads + 5-FU and 6000 rads + 5-FU were not significant with an overall median survival of 10 months. Significant prognostic variables, in addition to treatment, were pretreatment performance status and pretreatment CEA level.	1
13. Cohen SJ, Dobelbower R, Jr., Lipsitz S, et al. A randomized phase III study of radiotherapy alone or with 5-fluorouracil and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas: Eastern Cooperative Oncology Group study E8282. *Int J Radiat Oncol Biol Phys.* 2005;62(5):1345-1350.	Experimental-Tx	104 patients	To determine whether the addition of 5-FU and mitomycin-C to RT improves outcome in this patient population.	104 patients were evaluable for efficacy. Hematologic and nonhematologic toxicities were more common in the combination arm. The response rates were 6% in the RT arm and 9% in the combination arm. There were no differences in median DFS time or OS time between the combination and RT alone arms: 5.1 vs 5.0 months, respectively, for DFS (*P*=0.19) and 8.4 vs 7.1 months, respectively, for OS (*P*=0.16).	1

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14. Moertel CG, Childs DS, Jr., Reitemeier RJ, Colby MY, Jr., Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet.* 1969;2(7626):865-867.	Experimental-Tx	187 patients	To determine the dosage of 5-FU that would produce definite but clinically tolerable toxicity when used in combination with RT applied to the abdomen or pelvis.	A prospective, controlled double-blind study involving a substantial number of patients suggests that 5-FU significantly augments the effectiveness of RT for locally unresectable carcinoma of the stomach, pancreas, and large bowel. It is also possible that rarely this therapy may be curative. This approach should not be advocated as routine treatment since the vast majority of these patients still die of their cancer; and, if the present results are not spurious, the method offers only a few extra months of life. These results should, however, serve as stimulus and foundation for continued study of augmented RT.	1
15. Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Gastrointestinal Tumor Study Group. *Cancer.* 1985;56(11):2563-2568.	Experimental-Tx	143 patients	To compare, in patients with localized but unresectable PC, programs of treatment of (1) 6000 rad of RT administered as a double-split course and complemented by 5-FU (as administered in its previous study), with (2) 4000 rad delivered as a continuous course and complemented by Adriamycin administration.	A total of 138 of 143 analyzable patients have died, and no differences in the relative survival impact of the treatments have been observed ($P>0.8$). Toxicity on the Adriamycin arm was more substantial ($P<0.05$) and primarily attributable to Adriamycin chemotherapy after the completion of RT.	1
16. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst.* 1988;80(10):751-755.	Experimental-Tx	43 patients	To compare the survival of patients treated with multidrug chemotherapy [streptozocin, mitomycin, and 5-FU] vs radiation combined with 5-FU followed by the same three-drug [streptozocin, mitomycin, and 5-FU] combination.	In 43 patients randomly allocated between these 2 arms, an improved median survival for the combined-modality therapy (42 weeks) compared with chemotherapy alone (32 weeks) was demonstrated. OS following this combined-modality treatment program (41% at 1 year) was significantly superior to that following streptozocin, mitomycin, and 5-FU chemotherapy alone (19% at 1 year), by a two-tailed log rank test ($P<.02$).	1

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17. Klaassen DJ, MacIntyre JM, Catton GE, Engstrom PF, Moertel CG. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil--an Eastern Cooperative Oncology Group study. *J Clin Oncol.* 1985;3(3):373-378.	Experimental-Tx	148 patients	To compare 5-FU alone with radiation plus concurrent and maintenance 5-FU.	The median survival time was similar for both treatment programs and for both types of primary carcinoma, and was as follows: gastric primary carcinoma, 5-FU, 9.3 months; 5-FU plus RT, 8.2 months; pancreatic primary carcinoma, 5-FU, 8.2 months; 5-FU plus RT, 8.3 months. Substantially more toxicity was experienced by patients treated with the combined modality arm than by those patients receiving 5-FU alone. Severe or worse toxicity experienced by patients with gastric primary carcinoma treated by 5-FU was 19%, and the combined modality arm was 31%. The toxicity experienced by patients with pancreatic primary carcinoma treated with 5-FU was 27%, and the combined modality arm was 51%. Significant prognostic variables included: weight loss in stomach-cancer patients; and performance status, degree of anaplasia, and reduced appetite in pancreas-cancer patients.	1
18. Boz G, De Paoli A, Innocente R, et al. Radiotherapy and continuous infusion 5-fluorouracil in patients with nonresectable pancreatic carcinoma. *Int J Radiat Oncol Biol Phys.* 2001;51(3):736-740.	Experimental-Tx	42 patients	To report on our experience with the combination of RT and continuous infusion 5-FU in a group of patients with locally nonresectable PC.	All patients completed the RT as planned, and 33 (78%) completed the full regimen of chemotherapy. 10 patients (23%) had a partial response, and 32 (77%) had stable disease. Subjective response, defined as the disappearance of symptoms observed at diagnosis, was also evaluated. Two patients (6%) had a complete, and 24 (75%) a partial, remission of symptoms. The median time to progression was 6.2 months, and the median survival time was 9.1 months.	2
19. Whittington R, Neuberg D, Tester WJ, Benson AB, 3rd, Haller DG. Protracted intravenous fluorouracil infusion with radiation therapy in the management of localized pancreaticobiliary carcinoma: a phase I Eastern Cooperative Oncology Group Trial. *J Clin Oncol.* 1995;13(1):227-232.	Experimental-Tx	25 patients	To determine the maximum-tolerated dose of 5-FU administered as a protracted intravenous infusion with concurrent radiation in patients with PC.	The maximum-tolerated dose of 5-FU was 250 mg/m2/d. The dose-limiting toxicity was oral mucositis. The median survival duration of all patients treated was 11.9 months and the 2-year survival rate was 19%. 11/25 patients remain free of local progression and 4 patients are without evidence of progression at 18+, 18+, 34+, and 44+ months following treatment.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
20. Loehrer PJ, Sr., Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol.* 2011;29(31):4105-4112.	Experimental-Tx	71 patients	To evaluate the role of RT with concurrent GEM compared with GEM alone in patients with localized unresectable PC.	Of 74 patients entered on trial and randomly assigned to receive GEM alone (arm A; n = 37) or GEM plus radiation (arm B; n = 34), patients in arm B had greater incidence of grades 4 and 5 toxicities (41% vs 9%), but grades 3 and 4 toxicities combined were similar (77% in A vs 79% in B). No statistical differences were seen in quality of life measurements at 6, 15 to 16, and 36 weeks. The primary end point was survival, which was 9.2 months (95% CI, 7.9 to 11.4 months) and 11.1 months (95% CI, 7.6 to 15.5 months) for arms A and B, respectively (one-sided *P*=.017 by stratified log-rank test).	1
21. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol.* 2008;19(9):1592-1599.	Experimental-Tx	119 patients	To compare an intensified induction phase with CHRT combining infusion 5-FU and cisplatin, followed by maintenance GEM with GEM alone in histologically or cytologically proven LAPC.	OS was shorter in the CHRT than in GEM arm [median survival 8.6 (99% CI, 7.1–11.4) and 13 months (8.7–18.1), *P*=0.03]. 1-year survival was, respectively, 32% and 53%. These results were confirmed in a per-protocol analysis for patients who received 75% or more of the planned dose of RT. More overall grades 3-4 toxic effects were recorded in the CHRT arm, both during induction (36% vs 22%) and maintenance (32% vs 18%).	1
22. Sultana A, Tudur Smith C, Cunningham D, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer.* 2007;96(8):1183-1190.	Meta-analysis	11 trials; 794 patients	To review systematically the published and unpublished literature, comparing the following therapies: 1) Chemoradiotherapy, followed by chemotherapy vs best supportive care; 2) RT vs chemoradiotherapy; 3) RT vs chemoradiotherapy, followed by chemotherapy; 4) Chemotherapy vs chemoradiotherapy, followed by chemotherapy (combined modality therapy); 5) 5-FU-based chemoradiotherapy followed by chemotherapy vs another agent-based chemoradiotherapy, followed by chemotherapy.	Length of survival with CRT was increased compared with RT alone (2 trials, 168 patients, HR 0.69; 95% CI, 0.51–0.94), but CRT followed by chemotherapy did not lead to a survival advantage over chemotherapy alone (2 trials, 134 patients, HR 0.79; CI 0.32–1.95). Meta-analyses could not be performed for the other comparisons. A survival benefit was demonstrated for CRT over RT alone. CRT followed by chemotherapy did not demonstrate any survival advantage over chemotherapy alone, but important clinical differences cannot be ruled out due to the wide CI.	M

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23. Hammel P, Huguet F, Van Laethem J-L, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. *ASCO Meeting Abstracts.* 2013;31(15_suppl):LBA4003.	Experimental-Tx	269 patients	To define the role of 1) CRT after disease control with GEM, 2) erlotinib in LAPC.	From 442 patients included for R1, 269 patients reached R2 (arm1:136; arm 2:133). Main baseline characteristics in arms 1/2: female 44%/56%, mean age 63/62, head tumor 65%/62%, PS 0 56%/48%. After a median follow-up of 36 months, 221 deaths had occurred allowing the planned interim analysis (information fraction 56.4%). OS in R2 patients was 16.5 months [15.5–18.5] and 15.3 months [13.9–17.3] in arms 1 and 2, respectively (HR=1.03 [0.79–1.34], *P*=0.83). IDMC has confirmed that the futility boundary for the hypothesis of CRT superiority was crossed and considered this as the final analysis of the study.	1
24. Huguet F, Hammel P, Vernerey D, et al. Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study. *J Clin Oncol.* 2014;32(5s):(suppl; abstr 4001^).	Experimental-Tx	442 patients	To study giving GEM together with or without capecitabine and/or RT to see how well it works compared with giving GEM together with or without erlotinib in treating patients with LAPC that cannot be removed by surgery.	Among the 442 included patients, 269 patients had tumor control after 4 months of induction chemotherapy and were randomized to either the CRT arm (n=133) or the chemotherapy arm (n=136). The OS was not significantly different between the 2 arms (15.2 vs 16.5 months, *P*=0.8). At the time of analysis, 238 patients had a tumor progression, which was locoregional in 96 patients (50.5%) and metastatic in 97 patients (49.5%). In the CRT arm, patients had significantly less local tumor progression compared to the chemotherapy arm (34% vs 65%, *P*<0.0001). Median time without treatment (ie, reintroduction of chemotherapy) was longer in the CRT arm compared to the chemotherapy arm (159 vs 96 days, respectively, *P*=0.05).	1

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25. Mohiuddin M, Regine WF, Stevens J, et al. Combined intraoperative radiation and perioperative chemotherapy for unresectable cancers of the pancreas. *J Clin Oncol.* 1995;13(11):2764-2768.	Experimental-Tx	49 patients	To evaluate the effectiveness of combined IORT and perioperative chemotherapy in the management of unresectable PC.	The incidence of perioperative mortality was 0%. Early postsurgical morbidity (grade 3/4) was observed in 7/49 patients (14%) and late treatment-related morbidity (grade 3/4) in 8/43 patients (19%) alive beyond 6 months. Morbidity was primarily gastrointestinal, with no hematologic toxicities observed. The median survival time in the total group of patients is 16 months, with a 2-year survival rate of 22% and a 4-year survival rate of 7%. Freedom from local progression of disease was achieved in 71% of patients.	2
26. Willett CG, Del Castillo CF, Shih HA, et al. Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer. *Ann Surg.* 2005;241(2):295-299.	Observational-Tx	150 patients	To analyze the effects of a treatment program of EB-IORT and external beam RT and chemotherapy on the outcome of patients with unresectable or LAPC.	The 1-, 2-, and 3-year actuarial survival rates of all 150 patients were 54%, 15%, and 7%, respectively. Median and mean survival rates were 13 and 17 months, respectively. Long-term survival has been observed in 8 patients. Five patients have survived beyond 5 years and 3 more between 3 and 4 years. There was a statistically significant correlation of survival to the diameter of treatment applicator (a surrogate for tumor size) used during EB-IORT. For 26 patients treated with a small-diameter applicator (5 cm or 6 cm), the 2- and 3-year actuarial survival rates were 27% and 17%, respectively. In contrast, none of the 11 patients treated with a 9 cm diameter applicator survived beyond 18 months. Intermediate survival rates were seen for patients treated with a 7- or 8-cm-diameter applicator. Operative mortality was 0.6%, and postoperative and late complications were 20% and 15%, respectively.	2

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27. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer.* 2013;119(15):2692-2700.	Experimental-Tx	68 patients	To evaluate preoperative treatment with full-dose GEM, oxaliplatin, and RT in patients with localized PC.	68 evaluable patients received treatment at 4 centers. By central radiology review, 23 patients had resectable disease, 39 patients had borderline resectable disease, and 6 patients had unresectable disease. 66 patients (97%) completed cycle 1 with RT, and 61 patients (90%) completed cycle 2. Grade ≥3 adverse events during preoperative therapy included neutropenia (32%), thrombocytopenia (25%), and biliary obstruction/cholangitis (14%). 43 patients underwent resection (63%), and complete (R0) resection was achieved in 36 of those 43 patients (84%). The median OS was 18.2 months (95% CI, 13–26.9 months) for all patients, 27.1 months (95% CI, 21.2–47.1 months) for those who underwent resection, and 10.9 months (95% CI, 6.1–12.6 months) for those who did not undergo resection. A decrease in CA 19-9 level after neoadjuvant therapy was associated with R0 resection (*P*=.02), which resulted in a median survival of 34.6 months (95% CI, 20.3–47.1 months). 14 patients (21%) are alive and disease free at a median follow-up of 31.4 months (range, 24–47.6 months).	1

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28. Small W, Jr., Berlin J, Freedman GM, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial. *J Clin Oncol.* 2008;26(6):942-947.	Experimental-Tx	39 patients	To assess safety and efficacy of full-dose GEM administered before and during concurrent 3D-CRT in patients with nonmetastatic PC.	41 patients enrolled at 6 institutions between April 2002 and October 2003. Among the 39 treated patients, the most common toxicities were grade 3 neutropenia (12.8%), grade 3 nausea (10.3%), and grade 3 vomiting (10.3%). The response rate was 5.1% and disease control rate was 84.6%. Mean post-treatment CA 19-9 levels (228 +/- 347 U/mL) were significantly (*P*=.006) reduced compared with pretreatment levels (1,241 +/- 2,124 U/mL). 13 (81%) of 16 patients initially judged resectable, 3 (33%) of 9 borderline-resectable patients, and 1 (7%) of 14 unresectable patients underwent resection after therapy. 1-year survival rates were 73% for all patients, 94% for resectable patients, 76% for borderline-resectable patients, and 47% for unresectable patients.	1
29. Small W, Jr., Mulcahy MF, Rademaker A, et al. Phase II trial of full-dose gemcitabine and bevacizumab in combination with attenuated three-dimensional conformal radiotherapy in patients with localized pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2011;80(2):476-482.	Experimental-Tx	28 patients	To evaluate response rate, survival, and toxicity in patients with nonmetastatic PC treated with GEM, bevacizumab, and RT.	28/32 enrolled patients completed all 3 cycles. The median follow-up was 11.07 months. Most grade 3 or 4 toxicities occurred in the initial treatment phase; the most frequent toxicities were leukopenia (21%), neutropenia (17%), and nausea (17%). At week 10, 1 patient (4%) had a complete response, 2 patients (7%) had partial responses, 21 patients (75%) had stable disease, and 4 patients (14%) had progressive disease. The median pretreatment and post-treatment CA 19-9 levels (25 patients) were 184.3 and 57.9 U/mL, respectively (*P*=0.0006). 1 of 10 patients proceeding to surgery experienced a major complication. 2 of 6 patients undergoing resection had complete pathologic responses. The median PFS and OS durations were 9.9 months and 11.8 months, respectively.	1

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30. Ben-Josef E, Schipper M, Francis IR, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2012;84(5):1166-1171.	Experimental-Tx	50 patients	To determine the maximum tolerated radiation dose delivered by IMRT with fixed-dose rate GEM, freedom from local progression, and OS.	50 patients were accrued. Dose-limiting toxicities were observed in 11 patients: G3/4 anorexia, nausea, vomiting, and/or dehydration (7); duodenal bleed (3); duodenal perforation (1). The recommended dose is 55 Gy, producing a probability of dose-limiting toxicity of 0.24. The 2-year freedom from local progression is 59% (95% CI: 32–79). Median and 2-year OS are 14.8 months (95% CI: 12.6–22.2) and 30% (95% CI: 17–45). 12 patients underwent resection (10 R0, 2 R1) and survived a median of 32 months.	2
31. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I/II study of Proton-based Short Course Chemoradiation and Early Surgery for Adenocarcinoma of the Pancreas. *International Journal of Radiation Oncology*Biology*Physics.* 2010;78(3, Supplement):S99-S100.	Experimental-Tx	27 patients	To explore the safety and efficacy of a 1-week course of pre-op CRT with proton beam therapy and cape followed by early PD.	31 patients were enrolled on study. 27 patients are eligible for this analysis. 3 patients were treated at each of dose levels 1-3. 6 patients were at dose level 4, which was selected as maximum-tolerated dose. No dose limiting toxicities were observed. Grade 3 toxicity was noted in 4 patients (pain-1, gastrointestinal-1, and stent obstruction- 2). An additional 16 patients were treated at the maximum-tolerated dose for the phase II portion. 21 patients underwent resection. Reasons for no resections were: metastatic disease-4, unresectable tumor-1, and unrelated to disease/therapy-1. Mean time from last therapy to surgery was 22 days (10–47). Mean post-PD length of stay was 8 days (range, 5–47). There was one unexpected SAE, grade 3 postoperative gastroparesis; no other unexpected 30-day post-operative complications noted in comparison to historical controls. 4 of 21 resected patients had positive margins. 17 of 21 had positive nodes. Median follow-up is 10 months. There have been 2 local failures/progression in ALL patients, both with synchronous metastatic disease (at 10 months and 17 months). Metastatic failure has occurred in 15 out of 27 patients (56%).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Hong TS, Ryan DP, Borger DR, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. *Int J Radiat Oncol Biol Phys.* 2014;89(4):830-838.	Experimental-Tx	50 patients	To evaluate the safety, efficacy and biomarkers of short-course proton beam radiation and capecitabine, followed by PD in a phase 1/2 study in pancreatic ductal adenocarcinoma patients.	The phase 2 dose was established at 5 daily doses of 5 GyE. 50 patients were enrolled, of whom 35 patients were treated in the phase 2 portion. There were no grade 4 or 5 toxicities, and only 2 of 35 patients (4.1%) experienced a grade 3 toxicity event (chest wall pain grade 1, colitis grade 1). Of 48 patients eligible for analysis, 37 underwent PD. 30 of 37 (81%) had positive nodes. Locoregional failure occurred in 6 of 37 resected patients (16.2%), and distant recurrence occurred in 35 of 48 patients (72.9%). With median follow-up of 38 months, the median PFS for the entire group was 10 months, and OS was 17 months. Biomarker studies showed significant associations between worse survival outcomes and the KRAS point mutation change from glycine to aspartic acid at position 12, stromal CXCR7 expression, and circulating biomarkers CEA, CA19-9, and HGF (all, $P<.05$).	2
33. Kozak KR, Kachnic LA, Adams J, et al. Dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment. *Int J Radiat Oncol Biol Phys.* 2007;68(5):1557-1566.	Observational-Tx	9 patients	To evaluate tumor and normal tissue dosimetry of a 5 cobalt gray equivalent x 5 fraction proton RT schedule, before initiating a clinical trial of neoadjuvant, short-course proton RT for PC.	Hypofractionated proton and conventionally fractionated IMRT plans both provided acceptable target volume coverage and dose homogeneity. Improved dose conformality provided by the hypofractionated proton regimen resulted in significant sparing of kidneys, liver, and small bowel, evidenced by significant reductions in the mean doses, expressed as percentage prescribed dose, to these structures. Kidney and liver sparing was most evident in low-dose regions (≤20% prescribed dose for both kidneys and ≤60% prescribed dose for liver). Improvements in small-bowel dosimetry were observed in high- and low-dose regions. Mean stomach and duodenum doses, expressed as percentage prescribed dose, were similar for the 2 techniques.	2

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Schellenberg D, Kim J, Christman-Skieller C, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2011;81(1):181-188.	Experimental-Tx	20 patients	To evaluate the toxicity, local control, and OS in patients treated with sequential GEM and linear accelerator-based single-fraction SBRT.	All patients completed SBRT and a median of 5 cycles of chemotherapy. Follow-up for the 2 remaining alive patients was 25.1 and 36.4 months. No acute Grade 3 or greater nonhematologic toxicity was observed. Late Grade 3 or greater toxicities occurred in 1 patient (5%) and consisted of a duodenal perforation (G4). 3 patients (15%) developed ulcers (G2) that were medically managed. Overall, median survival was 11.8 months, with 1-year survival of 50% and 2-year survival of 20%. Using serial CT, the freedom from local progression was 94% at 1 year.	2
35. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer.* 2015;121(7):1128-1137.	Experimental-Tx	49 patients	To determine whether GEM with fractionated SBRT results in acceptable late grade 2 to 4 gastrointestinal toxicity when compared with a prior trial of GEM with single-fraction SBRT in patients with LAPC.	The median follow-up was 13.9 months (range, 3.9–45.2 months). The median age of the patients was 67 years and 84% had tumors of the pancreatic head. Rates of acute and late (primary endpoint) grade ≥2 gastritis, fistula, enteritis, or ulcer toxicities were 2% and 11%, respectively. QLQ-C30 global quality of life scores remained stable from baseline to after SBRT (67 at baseline, median change of 0 at both follow-ups; $P>.05$ for both). Patients reported a significant improvement in pancreatic pain ($P=.001$) 4 weeks after SBRT on the QLQ-PAN26 questionnaire. The median plasma CA 19-9 level was reduced after SBRT (median time after SBRT, 4.2 weeks; 220 U/mL vs 62 U/mL [$P<.001$]). The median OS was 13.9 months (95% CI, 10.2 months–16.7 months). Freedom from local disease progression at 1 year was 78%. 4 patients (8%) underwent margin-negative and lymph node-negative surgical resections.	1

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol.* 2015;54(7):979-985.	Observational-Tx	159 patients	To update the outcomes and toxicity using induction chemotherapy and SBRT for BRPC and LAPC in our institutional experience of 159 patients.	We identified 159 patients, 110 BRPC and 49 LAPC, with 14.0 months median overall follow-up. The resection and margin negative (R0) rate for BRPC patients who completed neoadjuvant therapy was 51% and 96%, respectively. Estimated median OS was 19.2 months for BRPC patients and 15.0 months for LAPC patients (P=0.402). Median OS was 34.2 months for surgically resected patients vs 14.0 months for unresected patients (P<0.001). 5 of 21 (24%) LAPC patients receiving FOLFIRINOX chemotherapy underwent R0 resection. In LAPC, FOLFIRINOX recipients underwent R0 resection more often than other chemotherapy recipients (5 of 21 vs 0 of 28, P=0.011). There was a trend for improved survival in those resected LAPC patients (P=0.09). For those not undergoing resection, 1 year local regional control was 78%. Any grade ≥3 potentially radiation-related toxicity rate was 7%.	2
37. Moningi S, Dholakia AS, Raman SP, et al. The Role of Stereotactic Body Radiation Therapy for Pancreatic Cancer: A Single-Institution Experience. *Ann Surg Oncol.* 2015;22(7):2352-2358.	Observational-Tx	88 patients	To review our institutional experience of SBRT in the treatment of LAPC and BRPC.	A total of 88 patients were included in the analysis, 74 with LAPC and 14 with BRPC. The median age at diagnosis was 67.2 years, and median follow-up from date of diagnosis for LAPC and BRPC patients was 14.5 and 10.3 months, respectively. Median OS from date of diagnosis was 18.4 months (LAPC, 18.4 mo; BRPC, 14.4 mo) and median PFS was 9.8 months (95% CI, 8.0–12.3). Acute toxicity was minimal with only 3 patients (3.4%) experiencing acute grade ≥3 toxicity. Late grade ≥2 gastrointestinal toxicity was seen in 5 patients (5.7%). Of the 19 patients (21.6%) who underwent surgery, 79% were LAPC patients and 84% had margin-negative resections.	2

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS. National failure to operate on early stage pancreatic cancer. *Ann Surg.* 2007;246(2):173-180.	Observational-Tx	9,559 patients	To evaluate utilization of surgery in early stage disease and identify factors predicting failure to undergo surgery.	Of clinical stage I patients 71.4% (6823/9559) did not undergo surgery; 6.4% (616/9559) were excluded due to comorbidities; 4.2% (403/9559) refused surgery; 9.1% (869/9559) were excluded due to age; and 38.2% (3,644/9559) with potentially resectable cancers were classified as "not offered surgery." Of the 28.6% (2736/9559) of patients who underwent surgery, 96.0% (2630/2736) underwent pancreatectomy, and 4.0% (458/2736) had unresectable tumors. Patients were less likely to undergo surgery if they were older than 65 years, were black, were on Medicare or Medicaid, had pancreatic head lesions, earned lower annual incomes, or had less education (P<0.0001). Patients were less likely to receive surgery at low-volume and community centers. Patients underwent surgery more frequently at National Cancer Institute/National Comprehensive Cancer Network-designated cancer centers (P<0.0001). Patients who were not offered surgery had significantly better survival than those with stage III or IV disease but worse survival than patients who underwent pancreatectomy for stage I disease (P<0.0001).	2
39. Ishikawa O, Ohigashi H, Imaoka S, et al. Is the long-term survival rate improved by preoperative irradiation prior to Whipple's procedure for adenocarcinoma of the pancreatic head? *Arch Surg.* 1994;129(10):1075-1080.	Observational-Tx	54 patients	To determine whether or not both regional control and long-term survival rate were improved by preoperative irradiation prior to curative pancreatectomy for adenocarcinoma of the pancreatic head.	At laparotomy, curative pancreatectomy was possible in 17 patients (74%) in group A and 19 (61%) in group B (not significant). In patients undergoing resection, the 1-year survival rate was 75% in group A and 43% in group B (P<.05). However, 3- and 5-year survival rates were almost the same in both groups (28% vs 32% and 22% vs 26%, respectively). With regard to the cause of death after pancreatectomy, group A had a significantly lower incidence of deaths due to regional recurrence within 1.5 postoperative years compared with group B, whereas deaths due to hepatic metastasis were markedly higher after 1 postoperative year in group A compared with group B.	2

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg.* 1992;127(11):1335-1339.	Review/Other-Tx	28 patients	To determine the morbidity and mortality of preoperative CRT followed by PD in patients with adenocarcinoma of the pancreas and to document the radiologic and pathologic response to preoperative CRT.	Hospital admission because of gastrointestinal toxic effects was required in 9 patients, yet no patient experienced a delay in operation. Restaging was performed 4 to 5 weeks after completion of CRT, and 5 patients were found to have metastatic disease; the 23 patients without evidence of progressive disease underwent laparotomy. At laparotomy, 3 patients were found to have unsuspected metastatic disease, 3 patients had unresectable locally advanced disease, and 17 patients were able to undergo PD. One perioperative death resulted from myocardial infarction, and perioperative complications occurred in 3 patients. Histologic evidence of tumor cell injury was present in all resected specimens.	4
41. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008;26(21):3496-3502.	Experimental-Tx	86 patients	To assess the outcomes of patients who received preoperative GEM-based CRT and PD for stage I/II PC.	The study enrolled 86 patients. At the time of restaging, disease progression or a decline in performance status precluded 13 patients from surgery. 73 (85%) of 86 patients were taken to surgery, extrapancreatic disease was found in 9, and 64 (74%) of 86 underwent a successful PD. Median OS (86 patients) was 22.7 months with a 27% 5-year survival. Median survival was 34 months for the 64 patients who underwent PD and 7 months for the 22 unresected patients ($P<.001$). The 5-year survival for those who did and did not undergo PD was 36% and 0%, respectively.	2
42. Pisters PW, Abbruzzese JL, Janjan NA, et al. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. *J Clin Oncol.* 1998;16(12):3843-3850.	Experimental-Tx	35 patients	To evaluate the toxicities, radiographic and pathologic responses, and event-free outcomes with combined modality treatment that involves preoperative rapid-fractionation CRT, PD, and EB-IORT for patients with resectable PC.	35 patients were entered onto the study and completed CRT, 34 (97%) as outpatients. 3 patients (9%) experienced grade 3 nausea and vomiting; no other grade 3 or 4 toxicities were observed. Of the 27 patients taken to surgery, 20 patients (74%) underwent PD with EB-IORT. All patients had a less than grade III pathologic response to preoperative CRT. At a median follow-up of 37 months, the 3-year survival rate in patients who underwent combined modality therapy was 23%.	2

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Pisters PW, Wolff RA, Janjan NA, et al. Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol.* 2002;20(10):2537-2544.	Experimental-Tx	35 patients	To evaluate the toxicity of a preoperative regimen of paclitaxel and concurrent external-beam RT, PD, and EB-IORT for patients with resectable PC.	35 patients completed CRT; 16 (46%) experienced grade 3 toxicity. 4 patients (11%) required hospitalization for dehydration due to grade 3 nausea and vomiting. 20 (80%) of 25 patients who underwent surgery underwent pancreatectomy; EB-IORT was used in 13 patients. There were no histologic complete responses to preoperative therapy; 21% of specimens demonstrated more than 50% nonviable cells (grade 2b treatment effect). With a median follow-up period of 46 months, the 3-year OS rate with CRT and pancreatectomy was 28%.	2
44. Talamonti MS, Small W, Jr., Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. *Ann Surg Oncol.* 2006;13(2):150-158.	Experimental-Tx	20 patients	To evaluate the toxicity associated with this neoadjuvant regimen in a multi-institutional setting; to determine radiographic, tumor marker, and pathologic responses to treatment; to evaluate morbidity and mortality among patients who undergo resection after completion of therapy; and to estimate OS in patients treated with this approach.	There were 10 men and 10 women, with a median age of 58 years (range, 50–80 years). 19 patients (95%) completed therapy without interruption, and 1 experienced grade 3 gastrointestinal toxicity. The mean weight loss after therapy was 4.0%. Of 20 patients taken to surgery, 17 (85%) underwent resections (16 PDs and 1 distal pancreatectomy). The complication rate was 24%, with an average length of stay of 13.5 days. There were no operative deaths. Pathologic analysis revealed clear margins in 16 (94%) of 17 and uninvolved lymph nodes in 11 (65%) of 17 specimens. One specimen contained no residual tumor, and 3 specimens revealed only microscopic foci of residual disease. With a median follow-up of 18 months, 7 (41%) of the 17 patients with resected disease are alive with no recurrence, 3 (18%) are alive with distant metastases, and 7 (41%) have died.	1

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008;26(21):3487-3495.	Experimental-Tx	90 patients	To report the results of a phase II trial of preoperative GEM and cisplatin followed by GEM-based CRT in stage I/II adenocarcinoma of the pancreatic head.	The study enrolled 90 patients; 79 patients (88%) completed chemo-CRT. 62 (78%) of 79 patients were taken to surgery and 52 (66%) of 79 underwent PD. The median OS of all 90 patients was 17.4 months. Median survival for the 79 patients who completed chemo-CRT was 18.7 months, with a median survival of 31 months for the 52 patients who underwent PD and 10.5 months for the 27 patients who did not undergo surgical resection of their primary tumor (P<.001).	1
46. White RR, Tyler DS. Neoadjuvant therapy for pancreatic cancer: the Duke experience. *Surg Oncol Clin N Am.* 2004;13(4):675-684, ix-x.	Review/Other-Tx	N/A	To summarize the authors' experience with neoadjuvant CRT over the past 10 years and how it has affected the management of patients with PC at Duke University Medical Center.	No results stated in abstract.	4

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med.* 2010;7(4):e1000267.	Meta-analysis	111 studies; 4,394 patients	To systematically review studies concerning the effects of neoadjuvant therapy on tumor response, toxicity, resection, and survival percentages in PC.	A total of 111 studies (n = 4,394) including 56 phase I-II trials were analyzed. A median of 31 (interquartile range 19–46) patients per study were included. Studies were subdivided into surveys considering initially resectable tumors (group 1) and initially nonresectable (borderline resectable/unresectable) tumors (group 2). Neoadjuvant chemotherapy was given in 96.4% of the studies with the main agents GEM, 5-FU (and oral analogues), mitomycin C, and platinum compounds. Neoadjuvant RT was applied in 93.7% of the studies with doses ranging from 24 to 63 Gy. Averaged complete/partial response probabilities were 3.6% (95% CI, 2%–5.5%)/30.6% (95% CI, 20.7%–41.4%) and 4.8% (95% CI, 3.5%–6.4%)/30.2% (95% CI, 24.5%–36.3%) for groups 1 and 2, respectively; whereas progressive disease fraction was estimated to 20.9% (95% CI, 16.9%–25.3%) and 20.8% (95% CI, 14.5%–27.8%). In group 1, resectability was estimated to 73.6% (95% CI, 65.9%–80.6%) compared to 33.2% (95% CI, 25.8%–41.1%) in group 2. Higher resection-associated morbidity and mortality rates were observed in group 2 vs group 1 (26.7%, 95% CI, 20.7%–33.3% vs 39.1%, 95% CI, 29.5%–49.1%; and 3.9%, 95% CI, 2.2%–6% vs 7.1%, 95% CI, 5.1%–9.5%). Combination chemotherapies resulted in higher estimated response and resection probabilities for patients with initially non-resectable tumors (“non-resectable tumor patients”) compared to monotherapy. Estimated median survival following resection was 23.3 (range 12–54) months for group 1 and 20.5 (range 9–62) months for group 2 patients.	M

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. *Int J Radiat Oncol Biol Phys.* 2011;79(1):151-157.	Experimental-Tx	15 patients	To evaluate the safety of 1 week of CRT with proton beam therapy and capecitabine followed by early surgery.	3 patients were treated at Dose Levels 1 to 3 and 6 patients at Dose Level 4, which was selected as the maximum-tolerated dose. No dose limiting toxicities were observed. Grade 3 toxicity was noted in 4 patients (pain in 1; stent obstruction or infection in 3). 11 patients underwent resection. Reasons for no resection were metastatic disease (3 patients) and unresectable tumor (1 patient). Mean postsurgical length of stay was 6 days (range, 5–10 days). No unexpected 30-day postoperative complications, including leak or obstruction, were found.	2
49. Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol.* 2007;25(3):326-331.	Observational-Tx	181 patients	To assess whether initial chemotherapy effectively identified patients with rapidly progressing disease who were unlikely to benefit from RT and to evaluate the potential benefit of administering CRT after initial chemotherapy in patients whose disease had not progressed and who had an Eastern Cooperative Oncology Group performance status of <2.	Median PFS and OS times for the 181 patients were 6.3 and 11.4 months, respectively. 53 patients (29.3%) had metastatic disease after 3 months of chemotherapy and were not eligible for CRT. Among the 128 remaining patients (70.3%) who had no disease progression and who were, therefore, eligible for CRT, 72 (56%) received CRT (group A), whereas 56 (44%) continued with CT (group B). The 2 groups were balanced for initial characteristics (performance status, sex, age, and type of chemotherapy), as well as for induction chemotherapy results. In groups A and B, the median PFS times were 10.8 and 7.4 months, respectively (P=.005), and the median OS times were 15.0 and 11.7 months, respectively (P=.0009).	2

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
50. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer.* 2007;110(1):47-55.	Observational-Tx	323 patients	To determine whether there were differences in outcome for patients with unresectable LAPC who received treatment with CRT vs induction chemotherapy followed by CRT.	The median follow-up was 5.5 months (range, 1–63 months). For all patients, the median OS and PFS were 9 months and 5 months, respectively, and the 2-year estimated OS and PFS rates were 9% and 5%, respectively. The median OS and PFS were 8.5 months and 4.2 months, respectively, in the CRT group and 11.9 months and 6.4 months, respectively, in the induction chemotherapy followed by CRT group (both $P<.001$). The median times to local and distant progression were 6.0 months and 5.6 months, respectively, in the CRT group and 8.9 and 9.5 months, respectively, in the induction chemotherapy followed by CRT group ($P=.003$ and $P=.007$, respectively). There was no significant difference in the patterns of failure with the use of induction chemotherapy.	2
51. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol.* 2005;23(15):3509-3516.	Experimental-Tx	313 patients	To further explore the GemOx combination regimen and compare it to the standard GEM treatment in a phase III trial.	326 patients were enrolled; 313 were eligible, and 157 and 156 were allocated to the GemOx and GEM arms, respectively. GemOx was superior to GEM in terms of response rate (26.8% vs 17.3%, respectively; $P=.04$), PFS (5.8 vs 3.7 months, respectively; $P=.04$), and clinical benefit (38.2% vs 26.9%, respectively; $P=.03$). Median OS for GemOx and GEM was 9.0 and 7.1 months, respectively ($P=.13$). GemOx was well tolerated overall, although a higher incidence of National Cancer Institute Common Toxicity Criteria grade 3 and 4 toxicity per patient was observed for platelets (14.0% for GemOx vs 3.2% for GEM), vomiting (8.9% for GemOx vs 3.2% for GEM), and neurosensory symptoms (19.1% for GemOx vs 0% for GEM).	1

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
52. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013;369(18):1691-1703.	Experimental-Tx	861 patients	To investigate the efficacy and safety of the combination vs GEM monotherapy in patients with metastatic PC.	A total of 861 patients were randomly assigned to nab-paclitaxel plus GEM (431 patients) or GEM (430). The median OS was 8.5 months in the nab-paclitaxel-GEM group as compared with 6.7 months in the GEM group (HR for death, 0.72; 95% CI, 0.62 to 0.83; *P*<0.001). The survival rate was 35% in the nab-paclitaxel-GEM group vs 22% in the GEM group at 1 year, and 9% vs 4% at 2 years. The median PFS was 5.5 months in the nab-paclitaxel-GEM group, as compared with 3.7 months in the GEM group (HR for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; *P*<0.001); the response rate according to independent review was 23% vs 7% in the 2 groups (*P*<0.001). The most common adverse events of grade 3 or higher were neutropenia (38% in the nab-paclitaxel-GEM group vs 27% in the GEM group), fatigue (17% vs 7%), and neuropathy (17% vs 1%). Febrile neutropenia occurred in 3% vs 1% of the patients in the 2 groups. In the nab-paclitaxel-GEM group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days.	1

Borderline and Unresectable Pancreas Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg.* 2015;261(1):12-17.	Observational-Tx	188 patients	To evaluate the accuracy of imaging in determining the resectability of PDAC and to determine the surgical and clinicopathologic outcomes of pancreatic resections after neoadjuvant FOLFIRINOX therapy.	Of 188 patients undergoing resection for PDAC, 40 locally advanced/borderline received FOLFIRINOX and 87 received no neoadjuvant therapy. FOLFIRINOX resulted in a significant decrease in tumor size, yet 19 patients were still classified as locally advanced and 9 as borderline. Despite post-FOLFIRINOX imaging suggesting continued unresectability, 92% had an R0 resection. When compared with no neoadjuvant therapy, FOLFIRINOX resulted in significantly longer operative times (393 vs 300 minutes) and blood loss (600 vs 400 mL), but significantly lower operative morbidity (36% vs 63%) and no postoperative pancreatic fistulas. Length of stay (6 vs 7 days), readmissions (20% vs 30%), and mortality were equivalent (1% vs 0%). On final pathology, the FOLFIRINOX group had a significant decrease in lymph node positivity (35% vs 79%) and perineural invasion (72% vs 95%). Median follow-up was 11 months with a significant increase in overall survival with FOLFIRINOX.	2

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.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

5-FU = 5-fluorouracil

3D-CRT = 3-dimensional conformal radiation therapy

BRPC = Borderline resectable pancreatic cancer

CA19-9 = Carbohydrate antigen 19-9

CI = Confidence interval

CRT = Chemoradiation

CT = Computed tomography

DFS = Disease-free survival

EB-IORT = Electron-beam intraoperative radiation therapy

GEM = Gemcitabine

HR = Hazard ratio

IMRT = Intensity-modulated radiotherapy

LAPC = Locally advanced pancreatic cancer

OS = Overall survival

PC = Pancreatic adenocarcinoma

PD = Pancreaticoduodenectomy

PFS = Progression-free survival

RT = Radiation therapy

SBRT = Stereotactic body radiation therapy