Resectable Pancreatic 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. Cress RD, Yin D, Clarke L, Bold R, Holly EA. Survival among patients with adenocarcinoma of the pancreas: a population-based study (United States). *Cancer Causes Control.* 2006;17(4):403-409.	Review/Other-Tx	10,612 patients	To evaluate survival of patients diagnosed in California with adenocarcinoma of the pancreas by demographic and tumor-related factors.	A total of 10,612 eligible patients were identified of whom 1674 (15.8%) underwent surgical resection. Patients of lower socioeconomic status were less likely to undergo resection and somewhat less likely to survive. Median survival was 3.5 months for patients who were not resected and 13.3 months for those who underwent resection. Adjuvant therapy was associated with a decreased risk of death among patients who underwent resection.	4

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3. Narimatsu H, Iwasaki H, Nakayama F, et al. Lewis and secretor gene dosages affect CA19-9 and DU-PAN-2 serum levels in normal individuals and colorectal cancer patients. *Cancer Res.* 1998;58(3):512-518.	Review/Other-Dx	400 normal individuals; 168 patients with colorectal cancer	To examine larger numbers of normal individuals and colorectal cancer patients to determine both of the Le and Se genotypes to determine to what extent the Le and Se gene dosages affect the CA19-9 and DU-PAN-2 values.	The 400 normal individuals were separated into 9 groups by their Le and Se genotypes, as follows: group 1, Le/Le and se/se; group 2, Le/le and se/se; group 3, Le/Le and Se/se; group 4, Le/le and Se/se; group 5, Le/Le and Se/Se; group 6, Le/le and Se/Se; group 7, le/le and se/se; group 8, le/le and Se/se; and group 9, le/le and Se/Se. The group 1 individuals, having homozygous inactive Se alleles (se/se) and homozygous active Le alleles (Le/Le), exhibited the highest mean CA19-9 value. The CA19-9 value clearly ranged from a high in group 1 to a low in group 9. All of the Le-negative individuals who had the le/le genotype (groups 7, 8, and 9) had completely negative CA19-9 values, ie, under 1.0 unit/mL, irrespective of the Se genotype. Group 7 individuals (le/le and se/se) showed a higher mean DU-PAN-2 value than did individuals in other groups. The Le-negative individuals in groups 8 and 9 also showed a higher mean DU-PAN-2 value than did the Le-positive individuals in groups 1-6. We recommend that the revised Le and Se genotype-dependent positive/negative cutoff values for CA19-9 and DU-PAN-2, determined in this study, be applied for more accurate cancer diagnoses. The Le and Se genotypes of 168 patients with colorectal cancer were also examined, and the CA19-9 and DU-PAN-2 values were measured before surgical resection. All 15 Le-negative patients (le/le) with colorectal cancer again showed undetectable CA19-9 values, ie, under 1.0 unit/mL, but many of them exhibited highly positive DU-PAN-2 values. In contrast, many of the Le-positive patients (Le/Le or Le/le) had positive CA19-9 values, whereas very few of them exhibited positive DU-PAN-2 values.	4

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4. Hartwig W, Strobel O, Hinz U, et al. CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy. *Ann Surg Oncol.* 2013;20(7):2188-2196.	Observational-Tx	1,543 patients with preoperative serum levels; control cohort of 706 patients with chronic pancreatitis	To determine the prognostic role of perioperative serum tumor marker CA19-9 in PC, with a focus on implications for pre- and postoperative therapeutic consequences.	The more that preoperative CA19-9 increased, the lower were tumor resectability and survival rates. Resectability and 5-year survival varied from 80% to 38% and from 27% to 0% for CA19-9 <37 vs ≥4,000 U/mL, respectively. The R0 resection rate was as low as 15% in all patients with CA19-9 levels ≥1,000 U/mL. CA19-9 increased with the stage of the disease and was highest in American Joint Commission on Cancer (AJCC) stage IV. Patients with an early postoperative CA19-9 increase had a dismal prognosis. Hyperbilirubinemia did not markedly affect CA19-9 levels (correlation coefficient ≤0.135).	2
5. Kinsella TJ, Seo Y, Willis J, et al. The impact of resection margin status and postoperative CA19-9 levels on survival and patterns of recurrence after postoperative high-dose radiotherapy with 5-FU-based concurrent chemotherapy for resectable pancreatic cancer. *Am J Clin Oncol.* 2008;31(5):446-453.	Observational-Tx	75 patients	To analyze the impact of surgical margins and other clinicopathological data on treatment outcomes on 75 patients treated from 1999 to 2006 by initial potentially curative surgery (+/- intraoperative RT), followed by high-dose 3D-CRT and concomitant fluoropyrimidine-based chemoradiotherapy.	With a median follow-up of 28 months, the median, 2-year and 5-year OS rates were 18.1 month, 41% and 23.6%, respectively. DFS rates were of 11.4 months, 35% and 20%, respectively. Only 2 clinicopathological features, positive ≤1 mm) surgical margins (P<0.05) and a 2-fold (>70 U/mL) elevation of the postoperative serum CA19-9 (P<0.001) impacted OS and DFS. In patients with negative (>1 mm) surgical margins and a low ≤70 U/mL) postoperative CA19-9, the projected 2- and 5-year OS rates were 80% and 65%, respectively, compared with 40% and 10% with positive surgical margins and a low CA19-9 and to 10% and 0% with positive or negative surgical margins and a high (>70 U/mL) CA19-9. Positive surgical margins (P<0.001) and an elevated postoperative CA19-9 (P<0.001) also predicted early development of distant metastases, whereas isolated loco-regional failure was less common and not affected by these or other clinicopathological features.	2

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6. Kim J-E, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. *Journal of Gastroenterology and Hepatology.* 2004;19(2):182-186.	Observational-Dx	70,940 asymptomatic persons	To determine the clinical usefulness of CA 19-9 as a screening tool for PC in asymptomatic subjects.	The number of subjects with a level of CA 19-9 above the cutoff of 37 U/mL was 1063 (1.5%), including 4 cases diagnosed with PC. The prevalence of PC over the age of 30 years is 13.66 per 100,000 population in Korea. Therefore, the sensitivity is 100% and the specificity 98.5%. However, the positive predictive value of CA 19-9 for detecting PC is only 0.9% in the asymptomatic population.	3
7. Steinberg W. The clinical utility of the CA 19-9 tumor-associated antigen. *Am J Gastroenterol.* 1990;85(4):350-355.	Review/Other-Dx	N/A	To review the clinical utility of the CA 19-9 tumor-associated antigen.	Since Koprowski and coworkers discovered the CA 19-9 antigen 10 years ago, it has become the most useful blood test in the diagnosis and management of patients with cancer of the pancreas. With an upper limit of normal of 37 U/mL, the assay's overall sensitivity is approximately 80% and its specificity is 90%. If higher cutoffs are used, the specificity rises so that, at levels greater than 1000 U/mL, the marker's specificity approaches 100%. Acute cholangitis and cirrhosis are 2 benign conditions that might raise this assay significantly. This tumor-associated marker is also helpful in predicting unresectability of PC, as 96% of tumors that result in blood levels >1000 U/mL have been found to be unresectable. After potentially curative surgery, the CA 19-9 can help prognosticate survival. Patients who normalize their CA 19-9 postoperatively live longer than those who do not. Furthermore, the assay, when used serially, predicts recurrence of disease prior to radiographic or clinical findings. The CA 19-9 is currently the "gold" standard marker for PC, against which other assays in this field will be judged.	4

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8. Alexakis N, Gomatos IP, Sbarounis S, et al. High serum CA 19-9 but not tumor size should select patients for staging laparoscopy in radiological resectable pancreas head and peri-ampullary cancer. *Eur J Surg Oncol.* 2015;41(2):265-269.	Observational-Dx	126 patients	To validate current recommendations for the selective use of staging laparoscopy in patients with radiological resectable pancreas head and peri-ampullary tumors.	Over a 6 year time period, 136 patients were evaluated, 126 patients were deemed radiological resectable and underwent laparotomy and 10 patients were characterized radiological unresectable. There were 111 patients with pancreas head resection and 15 without resection (8 due to extensive vascular involvement and 3 due to peritoneal/liver metastases). The sensitivity, specificity, positive predictive value and negative predictive value of preoperative radiological imaging in determining unresectability due to liver/peritoneal metastases were 42%, 100%, 100% and 94.7%, respectively. There was a significant difference in CA 19-9 values between metastatic and nonmetastatic disease (P=0.020). Receiver operating characteristic curve analysis calculated the optimal CA 19-9 cutoff point for predicting metastasis at 215.37 U/mL with a sensitivity of 72.7%, a specificity of 58.3%, positive predictive value of 15.1% and negative predictive value of 95.5%. Tumor diameter was not a significant factor in predicting resectability. Laparoscopy would have been useful in only 5.3% of patients in the present series.	3
9. Brown EG, Canter RJ, Bold RJ. Preoperative CA 19-9 kinetics as a prognostic variable in radiographically resectable pancreatic adenocarcinoma. *J Surg Oncol.* 2015;111(3):293-298.	Observational-Tx	72 patients	To investigate the kinetics of CA 19-9 in the absence of therapy.	47/72 patients (65%) had resectable disease. Unresectable patients had higher absolute change in CA 19-9 than patients with resectable disease (97 U/mL vs -34 U/mL) as well as higher rate of change (4 U/mL/day vs -1 U/mL/day). Receiver operating characteristic curves identified predictive thresholds for absolute (≥50 U/mL) and rate of CA 19-9 change (≥1 U/mL/day) that accurately identified unresectable patients. Survival analysis revealed that a change in CA 19-9 <50 U/mL and a rate of change <1 U/mL/day predicted improved survival (P=0.04, P=0.02); however, for patients with resectable disease, CA 19-9 changes did not predict survival.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
10. Konigsrainer I, Zieker D, Symons S, Horlacher K, Konigsrainer A, Beckert S. Do patient- and tumor-related factors predict the peritoneal spread of pancreatic adenocarcinoma? *Surg Today*. 2014;44(2):260-263.	Observational-Tx	29 patients with PC; 29 patients without	To compare the tumor- and patient-related variables in patients with and without intraoperatively confirmed PC who were operated on with the intention of curative resection.	Clinical jaundice and diarrhea were more frequently present in patients without PC. The CA 19-9 levels were significantly higher in patients with PC compared to those in patients without PC. No other differences were observed in the patient- or tumor-related factors between the 2 groups.	2
11. Winter JM, Yeo CJ, Brody JR. Diagnostic, prognostic, and predictive biomarkers in pancreatic cancer. *J Surg Oncol*. 2013;107(1):15-22.	Review/Other-Dx	N/A	To review diagnostic, prognostic, and predictive biomarkers in PC.	No results stated in abstract.	4
12. Bardeesy N, Cheng KH, Berger JH, et al. Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer. *Genes Dev*. 2006;20(22):3130-3146.	Observational-Dx	unknown quantity of mice	To understand the role of Smad4 in normal pancreas development and physiology as well as in the genesis and progression of PDAC, alone or together with other common PDAC genetic lesions.	Selective SMAD4 deletion in the pancreatic epithelium had no discernable impact on pancreatic development or physiology. However, when combined with the activated KRAS(G12D) allele, SMAD4 deficiency enabled rapid progression of KRAS(G12D)-initiated neoplasms. While KRAS(G12D) alone elicited premalignant pancreatic intraepithelial neoplasia (PanIN) that progressed slowly to carcinoma, the combination of KRAS(G12D) and SMAD4 deficiency resulted in the rapid development of tumors resembling intraductal papillary mucinous neoplasia (IPMN), a precursor to PDAC in humans. SMAD4 deficiency also accelerated PDAC development of KRAS(G12D) INK4A/ARF heterozygous mice and altered the tumor phenotype; while tumors with intact SMAD4 frequently exhibited epithelial-to-mesenchymal transition (EMT), PDAC null for SMAD4 retained a differentiated histopathology with increased expression of epithelial markers. SMAD4 status in PDAC cell lines was associated with differential responses to transforming growth factor-beta (TGF-beta) in vitro with a subset of SMAD4 wild-type lines showing prominent TGF-beta-induced proliferation and migration.	4

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13. Blackford A, Serrano OK, Wolfgang CL, et al. SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer. *Clin Cancer Res.* 2009;15(14):4674-4679.	Observational-Dx	89 patients	To determine if any genes with somatic changes correlate with patient outcome following surgical resection.	When adjusted for age, lymph node status, margin status, and tumor size, SMAD4 gene inactivation was significantly associated with shorter OS (HR, 1.92; 95% CI, 1.20–3.05; *P*=0.006). Patients with SMAD4 gene inactivation survived a median of 11.5 months, compared with 14.2 months for patients without SMAD4 inactivation. By contrast, mutations in CDKN2A or TP53 or the presence of multiple (≥4) mutations or homozygous deletions among the 39 most frequently mutated genes were not associated with survival.	3
14. Oshima M, Okano K, Muraki S, et al. Immunohistochemically detected expression of 3 major genes (CDKN2A/p16, TP53, and SMAD4/DPC4) strongly predicts survival in patients with resectable pancreatic cancer. *Ann Surg.* 2013;258(2):336-346.	Observational-Dx	106 patients	To clarify the clinical implications of the status of the 3 major genes (CDKN2A/p16, TP53, and SMAD4/DPC4).	Abnormal immunolabeling of p53 was detected in 81.1% of PDACs and was significantly associated with tumor dedifferentiation (*P*=0.022) and the presence of locoregional recurrence (*P*=0.020). Loss of p16 and Smad4/Dpc4 immunolabeling was identified in 67.0% and 60.4%, respectively. Loss of p16 immunolabeling was associated with lymphatic invasion (*P*=0.012) and postoperative widespread metastases (*P*<0.001). A significant correlation was found between Smad4/Dpc4 immunolabeling and tumor size (*P*=0.006), lymphatic invasion (*P*=0.033), and lymph node metastasis (*P*=0.006). Interestingly, all of the 6 patients demonstrating 5-year survival had intact SMAD4/DPC4. Kaplan-Meier survival analysis showed that lymph node metastasis (*P*=0.001), lymphatic invasion (*P*=0.008), the tumor (T) factor (T3 vs T1/T2, *P*=0.004), loss of p16 immunolabeling (*P*=0.029), and loss of Smad4/Dpc4 immunolabeling (*P*<0.001) were significantly associated with shorter OS. Multivariate analysis revealed that loss of Smad4/Dpc4 immunolabeling was an independent and significant poor prognostic factor for OS and DFS. On analysis of combinations of the status of these 3 genes, increasing number of alterations reflected poorer survival.	3

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15. 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
16. Campbell F, Smith RA, Whelan P, et al. Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. *Histopathology.* 2009;55(3):277-283.	Observational-Tx	163 patients	To identify the proportion of pancreatoduodenectomy specimens in which 'equivocal' resection margins are present (tumor involvement within 1 mm of, but not directly reaching, 1 or more resection margins) and whether the survival of these patients was similar to that of patients with 'unequivocal' resection margin involvement.	Patients with histologically confirmed PDAC undergoing pancreatoduodenectomy between 1997 and 2007 (n = 163) were identified from a prospective database. 128 cases (79%) were classified as R1. Of these, 57 (45% of all R1 cases) were based on 'equivocal' margin involvement. There was no significant difference in OS between equivocal and unequivocal R1 resections (log rank, *P*=0.102). All R1 resections had a poorer survival on univariate (log rank, *P*=0.013), but not multivariate, analysis (Cox, *P*=0.132).	2
17. Chang DK, Johns AL, Merrett ND, et al. Margin clearance and outcome in resected pancreatic cancer. *J Clin Oncol.* 2009;27(17):2855-2862.	Observational-Tx	365 patients	To identify a clinically relevant definition of margin-positive status (R1) that would better reflect outcome after pancreatectomy and to address the issue of estimating the risk of local recurrence and stratification of patients for entry into clinical trials.	Microscopic involvement of a resection margin by tumor was associated with a poor prognosis. Stratifying the minimum clearance of resection margins by 0.5-mm increments demonstrated that although median survival was no different to clear margins based on these definitions, it was not until the resection margin was clear by more than 1.5 mm that optimal long-term survival was achieved.	2

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18. Neoptolemos JP, Stocken DD, Dunn JA, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. *Ann Surg.* 2001;234(6):758-768.	Experimental-Tx	541 patients	To assess the influence of resection margins on survival for patients with resected PC treated within the context of the adjuvant European Study Group for Pancreatic Cancer-1 (ESPAC-1) study.	Of 541 patients with a median follow-up of 10 months, 101 (19%) had R1 resections. Resection margin status was confirmed as an influential prognostic factor, with a median survival of 10.9 months for R1 vs 16.9 months for patients with R0 margins. Resection margin status remained an independent factor in a Cox proportional hazards model only in the absence of tumor grade and nodal status. There was a survival benefit for chemotherapy but not CRT, irrespective of R0/R1 status. The median survival was 19.7 months with chemotherapy vs 14.0 months without. For patients with R0 margins, chemotherapy produced longer survival compared with to no chemotherapy. This difference was less apparent for the smaller subgroup of R1 patients, but there was no significant heterogeneity between the R0 and R1 groups.	1
19. Bhatti I, Peacock O, Awan AK, Semeraro D, Larvin M, Hall RI. Lymph node ratio versus number of affected lymph nodes as predictors of survival for resected pancreatic adenocarcinoma. *World J Surg.* 2010;34(4):768-775.	Observational-Tx	84 patients	To compare the prognostic significance of the LNR with the absolute number of affected lymph nodes for resected PDAC.	An LNR of ≥0.2 (median survival 8.1 vs 35.7 months with LNR <0.2; $P<0.001$) and ≥0.3 (median survival 5.9 vs 29.6 months with LNR <0.3; $P<0.001$), tumor size ($P<0.017$), positive resection margin ($P<0.001$), and nodal involvement ($P<0.001$) were found to be significant prognostic markers following univariate analysis. Following multivariate analysis, only LNR at both levels ≥0.2 ($P=0.05$; HR 1.8) and LNR of ≥0.3 ($P=0.01$; HR 2.7)] were independent predictors of a poor outcome. The number of lymph nodes examined had no effect on OS in either node-positive patients ($P=0.339$) or node-negative patients ($P=0.473$).	2

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20. Pawlik TM, Gleisner AL, Cameron JL, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. *Surgery*. 2007;141(5):610-618.	Observational-Tx	905 PD patients	To investigate the ratio of the number of lymph nodes harboring metastatic cancer to the total number of lymph nodes examined (LNR) with regard to outcome after PD for ductal cancer of the pancreas.	There were 187 (20.7%) of the 905 patients who had negative peripancreatic lymph nodes (N0), whereas 718 (79.3%) of the 905 patients had lymph node metastases (N1). The median number of lymph nodes evaluated in the N0 group was 15 vs 18 in the N1 group (P=.12). At median follow-up of 24 months, the median survival for all patients was 17.4 months, and the 5-year actuarial survival rate was 16.1%. Patients with lymph node metastases had a shorter median OS (16.5 months) compared with patients with negative lymph nodes (25.3 months; P=.001). Compared with the total number of lymph nodes examined or total number of lymph node metastases, LNR was the most compelling predictor of survival. As the LNR increased, median OS decreased (LNR = 0, 25.3 months; LNR >0 to 0.2, 21.7 months; LNR >0.2 to 0.4, 15.3 months; LNR >0.4, 12.2 months; P=.001). After adjusting for other factors associated with survival, LNR remained an independent predictor of OS (P<.001).	2

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21. Riediger H, Keck T, Wellner U, et al. The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. *J Gastrointest Surg.* 2009;13(7):1337-1344.	Observational-Tx	182 patients	To evaluate potential prognostic factors in 182 patients after resection of PC including assessment of LNR.	In all 204 resected patients, operative mortality was 3.9% (n = 8). In the 182 patients with follow-up, 70% had free resection margins, 62% had G1- or G2-classified tumors, and 70% positive LN. Median tumor size was 30 (7–80) mm. The median number of examined LN was 16 and median number of involved LN 1 (range 0–22). Median LNR was 0.1 (0–0.79). Cumulative 5-year survival in all patients was 15%. In univariate analysis, a LNR ≥0.2 (5-year survival 6% vs 19% with LNR <0.2; *P*=0.003), LNR ≥0.3 (5-year survival 0% vs 18% with LNR <0.3; *P*<0.001), a positive resection margin (*P*<0.01) and poor differentiation (G3/G4; *P*<0.03) were associated with poorer survival. In multivariate analysis, a LNR ≥0.2 (*P*<0.02; RR 1.6), LNR ≥0.3 (*P*<0.001; RR 2.2), positive margins (*P*<0.02; RR 1.7), and poor differentiation (*P*<0.03; RR 1.5) were independent factors predicting a poorer outcome. The conventional nodal status or the number of examined nodes (in all patients and in the subgroups of node positive or negative patients) had no significant influence on survival. Patients with 1 metastatic LN had the same outcome as patients with negative nodes, but prognosis decreased significantly in patients with 2 or more LN involved.	2

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22. Gleisner AL, Spolverato G, Ejaz A, Pawlik TM. Time-related changes in the prognostic significance of the total number of examined lymph nodes in node-negative pancreatic head cancer. *J Surg Oncol*. 2014;110(7):858-863.	Observational-Tx	3,406 patients	To assess time trends in the association between the total number of lymph nodes examined and survival in patients operated for adenocarcinoma of the head of pancreas.	A total of 3,406 patients were included. Although total number of lymph nodes examined was associated with survival, the effect was not uniform. Compared to patients with >12 total number of lymph nodes examined, survival decreased with lower total number of lymph nodes examined (4–12 total number of lymph nodes examined: HR 1.27, 95% CI, 1.10–1.46; <4 total number of lymph nodes examined: HR 1.39, 95% CI, 1.20–1.60) among patients diagnosed between 1988 and 2002. In contrast, for those diagnosed between 2003 and 2007, while there was decreased survival for those with <4 nodes (HR 1.44, 95% CI, 1.22–1.71), no effect was seen for patients with total number of lymph nodes examined 4–12 (HR 0.98, 95% CI, 0.85–1.14).	2
23. Artinyan A, Soriano PA, Prendergast C, Low T, Ellenhorn JD, Kim J. The anatomic location of pancreatic cancer is a prognostic factor for survival. *HPB (Oxford)*. 2008;10(5):371-376.	Observational-Tx	33,752 patients	To examine the relationship between tumor location and survival.	Median survival for the entire cohort was 5 months and was significantly lower for body and tail compared to head lesions (4 vs 6 months, $P<0.001$). Distant metastases (67% vs 36%, $P<0.001$) were greater and cancer-directed surgery (16% vs 30%, $P<0.001$) was lower for body and tail tumors. Of 6443 resected patients, head lesion patients (n=5118) were younger, had a greater number of harvested lymph nodes, were more likely to be lymph node-positive, and had a higher proportion of T3/T4 lesions. Significant univariate predictors of survival included age, T-stage, number of positive and harvested lymph nodes. On multivariate analysis, body and tail location was a significant prognostic factor for decreased survival (odds ratio 1.11, 95% CI, 1.00–1.23, $P=0.05$).	2

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24. Kaiser MH. Pancreatic Cancer. *Archives of Surgery*. 1985;120(8):899.	Experimental-Tx	43 patients	To assess the value of this combination regiment in prolonging survival time and DFS time.	22 patients randomized to no adjuvant treatment and 21 to combined therapy were analyzed. 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
25. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer*. 1987;59(12):2006-2010.	Experimental-Tx	30 patients	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

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26. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg.* 1999;230(6):776-782; discussion 782-774.	Experimental-Tx	207 patients	To investigate the survival benefit of adjuvant RT and 5-fluorouracil vs observation alone after surgery in patients with pancreatic head and periampullary cancers.	Between 1987 and 1995, 218 patients were randomized (108 patients in the observation group, 110 patients in the 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. 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 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.	1
27. Garofalo MC, Regine WF, Tan MT. On statistical reanalysis, the EORTC trial is a positive trial for adjuvant chemoradiation in pancreatic cancer. *Ann Surg.* 2006;244(2):332-333; author reply 333.	Review/Other-Tx	N/A	No abstract available.	N/A	4

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28. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med.* 2004;350(12):1200-1210.	Experimental-Tx	289 patients	To report the final results of the ESPAC-1 Trial and update the interim results.	The analysis was based on 237 deaths among the 289 patients (82%) and a median follow-up of 47 months (interquartile range, 33 to 62). The estimated 5-year survival rate was 10% among patients assigned to receive chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy (P=0.05). The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (P=0.009). The benefit of chemotherapy persisted after adjustment for major prognostic factors.	1
29. 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.	Experimental-Tx	353 patients	To assess the roles of chemoradiotherapy and chemotherapy in a randomized study.	541 eligible patients with PDAC were randomized: 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; HR 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; HR 0.66 [0.52–0.83], P=0.0005).	1
30. Choti MA. Adjuvant therapy for pancreatic cancer--the debate continues. *N Engl J Med.* 2004;350(12):1249-1251.	Review/Other-Tx	N/A	No abstract available.	N/A	4
31. Koshy MC, Landry JC, Cavanaugh SX, et al. A challenge to the therapeutic nihilism of ESPAC-1. *Int J Radiat Oncol Biol Phys.* 2005;61(4):965-966.	Review/Other-Tx	N/A	No abstract available.	N/A	4

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007;297(3):267-277.	Experimental-Tx	368 patients	To test the hypothesis that adjuvant chemotherapy with gemcitabine administered after complete resection of PC improves DFS 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 DFS was 13.4 months in the gemcitabine group (95% CI, 11.4–15.3) and 6.9 months in the control group (95% CI, 6.1–7.8; *P*<.001, log-rank). Estimated DFS 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 DFS was significant in patients with either R0 or R1 resection. There was no difference in OS between the gemcitabine group (median, 22.1 months; 95% CI, 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% CI, 17–23.4; estimated survival, 20.5% at 3 years and 11.5% at 5 years; *P*=.06, log-rank).	1

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. 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.	Experimental-Tx	354 patients	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 DFS 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 (HR, 0.55 [95% CI, 0.44–0.69]; *P*<.001). Patients randomized to adjuvant gemcitabine treatment had prolonged OS compared with those randomized to observation alone (HR, 0.76 [95% CI, 0.61–0.95]; *P*=.01), with 5-year OS of 20.7% (95% CI, 14.7%–26.6%) vs 10.4% (95% CI, 5.9%–15.0%), respectively, and 10-year OS of 12.2% (95% CI, 7.3%–17.2%) vs 7.7% (95% CI, 3.6%–11.8%).	1
34. 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.	Experimental-Tx	451 patients	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 (HR, 0.82 [95% CI, 0.65–1.03]; *P*=.09). The treatment effect was strengthened on multivariate analysis (HR, 0.80 [95% CI, 0.63–1.00]; *P*=.05). Grade 4 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 RT (>85%).	1

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Berger AC, Winter K, Hoffman JP, et al. Five year results of US intergroup/RTOG 9704 with postoperative CA 19-9 </=90 U/mL and comparison to the CONKO-001 trial. *Int J Radiat Oncol Biol Phys.* 2012;84(3):e291-297.	Observational-Tx	385 patients	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%.	2
36. Abrams RA, Winter KA, Regine WF, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704--a phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys.* 2012;82(2):809-816.	Observational-Tx	416 patients	To explore whether failure to adhere to specified RT guidelines influenced survival and/or toxicity.	RT was scored for 416 patients: 216 per protocol and 200 less than per protocol. For all pancreatic sites (head, body/tail) median survival for per protocol vs less than per protocol was 1.74 vs 1.46 years (log-rank *P*=0.0077). In multivariate analysis, per protocol vs less than per protocol score correlated more strongly with median survival than assigned treatment arm (*P*=0.014, *P*=NS, respectively); for patients with pancreatic head tumors, both per protocol score and gemcitabine treatment correlated with improved median survival (*P*=0.016, *P*=0.043, respectively). For all tumor locations, per protocol score was associated with decreased risk of failure (*P*=0.016) and, for gemcitabine patients, a trend toward reduced Grade 4/5 nonhematologic toxicity (*P*=0.065).	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Berger AC, Garcia M, Jr., Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. *J Clin Oncol.* 2008;26(36):5918-5922.	Experimental-Tx	385 patients	To evaluate the ability of postresectional CA 19-9 to predict survival.	385 patients had assessable CA 19-9 levels. The majority had a CA 19-9 level lower than 180 or ≤90 (n = 220 and 200, respectively), while 34% were Le negative and 33 (9%) and 53 (14%) patients had levels higher than 180 and higher than 90. When CA 19-9 was analyzed as a dichotomized variable, there was a significant survival difference favoring patients with CA 19-9 lower than 180 (HR, 3.53; *P*<.0001). This corresponds to a 72% reduction in the risk of death for patients with a CA 19-9 lower than 180. This was also true for patients with CA 19-9 ≤90 (HR, 3.4; *P*<.0001). Multivariate analyses confirmed that CA 19-9, when analyzed as both a continuous and a dichotomized variable, is a highly significant predictor of OS in patients with resected PC.	1
38. 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.	Experimental-Tx	451 patients	To report the long term results of this 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% of patients vs distant relapse in 73%.	1

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA*. 2010;304(10):1073-1081.	Experimental-Tx	1,088 patients	To determine whether fluorouracil or gemcitabine is superior in terms of OS as adjuvant treatment following resection of PC.	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% 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; HR, 0.94 [95% CI, 0.81–1.08]). 77 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
40. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol*. 2014;32(6):504-512.	Observational-Tx	985 patients	To investigate the effect that the time between surgery and the start of chemotherapy, as well as the completion of planned chemotherapy, had on the long-term survival of patients in this trial.	There were 985 patients, of whom 486 (49%) received gemcitabine and 499 (51%) received fluorouracil; 675 patients (68%) completed all 6 cycles of chemotherapy (full course) and 293 patients (30%) completed 1 to 5 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. OS favored patients who completed the full 6 courses of treatment vs those who did not (HR, 0.516; 95% CI, 0.443 to 0.601; *P*<.001). Time to starting chemotherapy did not influence OS 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).	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Sinn M, Liersch T, Gellert K, et al. CONKO-005: Adjuvant therapy in R0 resected pancreatic cancer patients with gemcitabine plus erlotinib versus gemcitabine for 24 weeks—A prospective randomized phase III study. *J Clin Oncol.* 2015;33(suppl; abstr 4007).	Experimental-Tx	436 patients	To evaluate an additional effect of the EGFR-tyrosinkinase-inhibitor erlotinib (Erlo 100 mg p.o. daily) in combination with Gem (1000 mg/m² i.v. day 1,8,15, q29) for 24 weeks in pts after R0 resection.	Between April 2008 and July 2013, 219 pts were randomized to GemErlo and 217 to Gem. Patient characteristics are well balanced (GemErlo/Gem): age (median 63/65 years), tumor status (T3/T4 88/86%), nodal status (N pos 64/66%), grading (G3 33/34%). After a median follow up of 41 months (March 2015), 350 events (80%) occurred. Median treatment duration was 22 weeks in both groups. Grade 3/4 toxicities were (GemErlo%/Gem%): rash 7/0.4, diarrhea 5/1, nausea 2/2, fatigue 5/2, hypertension 3/1,GGT 9/9, neutropenia 27/28, thrombopenia 5/2. There was no difference in DFS (median: GemErlo 11.6 months, Gem 11.6 months; HR 0.89, 95%CI 0.72-1.10) or OS (median: GemErlo 24.6 months, Gem 26.5 months; HR 0.90, 95%CI 0.71-1.15). There was no correlation between the grade of rash and an improved DFS in the GemErlo group (median: rash grade 0–1 vs ≥grade 2 12.2 vs 11.0 months; HR 0.91, 95% CI, 0.66–1.25). OS curves show a late divergence in favor of GemErlo (estimated survival after 2/3/4/5-years: 54/36/31/28% vs 53/33/22/19%).	1

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. *J Gastrointest Surg.* 2006;10(4):511-518.	Review/Other-Tx	27 autopsied patients	To determine the sites of recurrence after curative resection of PC by histopathological examination of autopsied specimens.	The pattern of recurrence was classified as follows: (1) local recurrence, (2) hepatic metastasis, (3) peritoneal dissemination, (4) para-aortic lymph node metastasis, and (5) distant metastasis not including hepatic metastasis, peritoneal dissemination, and para-aortic lymph node metastasis. Of the 27 autopsied patients, recurrence was confirmed for 22 of 24 patients, except for 3 who died of early postoperative complications. 18 (75%) of the 24 patients had local recurrence, 12 (50%) had hepatic metastasis, and 11 (46%) had both. For 4 patients, local recurrence confirmed by autopsy was undetectable by CT, because the recurrent lesions had infiltrated without forming a tumor mass. Peritoneal dissemination, para-aortic lymph node metastasis, and distant metastasis were found for 8 (33%), 5 (21%), and 18 (75%) of the cases, respectively. 20 patients died of cancer, but local recurrence was judged to be the direct cause of death of only 4. Local recurrence frequently occurs, but is rarely a direct cause of death, and most patients died of metastatic disease.	4

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol.* 2008;26(21):3503-3510.	Observational-Tx	616 patients	To examine the efficacy of adjuvant chemoradiotherapy after PD for PC in patients undergoing resection at Johns Hopkins Hospital (JHH; Baltimore, MD).	The median follow-up was 17.8 months (interquartile range, 9.7 to 33.5 months). Overall 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), margin-positive 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).	2
44. 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.	Observational-Tx	472 patients	To determine prognostic factors and impact of adjuvant chemotherapy and RT on OS after resection of PC.	6 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 chemotherapy-RT was 25.2 vs 19.2 months after no adjuvant therapy (P=.001). 2-year OS was 50% vs 39% and 5-year OS was 28% vs 17%. Adverse prognostic factors identified by univariate and multivariate analysis included positive lymph nodes (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).	2

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Hsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Ann Surg Oncol.* 2010;17(4):981-990.	Observational-Tx	1,092	To examine efficacy of adjuvant CRT in resected PC 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).	2
46. Colbert LE, Hall WA, Nickleach D, et al. Chemoradiation therapy sequencing for resected pancreatic adenocarcinoma in the National Cancer Data Base. *Cancer.* 2014;120(4):499-506.	Observational-Tx	5,414 patients	To use the large National Cancer Data Base, which contains detailed patient-linked data on approximately 70% of newly diagnosed cancer cases in the United States, to provide a rationale for a randomized study to evaluate the role of neoadjuvant therapy in PC in the future?	A total of 5414 patients were identified. Of these, 277 received preoperative RT and 5137 received postoperative RT. Overall, 92.9% received chemotherapy and 7.1% received RT alone; 56% (2990/5307) of patients had stage III disease, according to AJCC staging manual, 5th edition. Median tumor size was 3 cm (range: 0–9.9 cm); 82% (199/244) of patients with preoperative RT had negative surgical margins; 72% (3383/4699) of patients with postoperative RT had negative margins. 41% (71/173) of patients with preoperative RT were lymph node-positive; 65% (3159/4833) of patients with postoperative RT were lymph node-positive. Median OS for patients with preoperative RT was 18 months (95% CI = 18–19 months) and for patients with postoperative RT, 19 months (95% CI = 17–22 months).	2

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. 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
48. 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 gemcitabine-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

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol.* 2015;191(1):7-16.	Experimental-Tx	66 patients	To examine the value of neoadjuvant chemoradiotherapy in PC in a randomized phase II trial.	The trial was stopped after 73 patients; 66 patients were eligible for analysis. 29 of 33 allocated patients received chemoradiotherapy. RT 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 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. Median OS was 14.4 vs 17.4 months (A vs B; intention-to-treat analysis; *P*=0.96). After tumor resection, median OS was 18.9 vs 25.0 months (A vs B; *P*=0.79).	1
50. 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 PDAC 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 progression-free survival 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

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. Kharofa J, Tsai S, Kelly T, et al. Neoadjuvant chemoradiation with IMRT in resectable and borderline resectable pancreatic cancer. *Radiother Oncol.* 2014;113(1):41-46.	Observational-Tx	69 patients	To evaluate the acute toxicity, clinical outcomes, and patterns of failure in resectable and borderline resectable PC patients treated with neoadjuvant CRT utilizing an IMRT approach.	Neoadjuvant CRT was completed in 69 patients (39 borderline resectable and 30 resectable). Induction chemotherapy was used in 32 (82%) of the 39 patients with borderline resectable disease prior to CRT. All resectable patients were treated with CRT alone. Following neoadjuvant treatment, 48 (70%) of the 69 patients underwent successful pancreatic resection with 47 (98%) being margin negative (R0). In 30 of the borderline resectable patients who had arterial abutment or SMV occlusion, 19 (63%) were surgically resected and all had R0 resections. The cumulative incidence of local failure at 1 and 2 years was 2% (95% CI, 0%–6%) and 9% (95% CI, 0.6%–17%) respectively. The median OS for all patients, patients undergoing resection, and patients without resection were 20, 26 and 11 months respectively. 16 (23%) of the 69 patients are alive without disease with a median follow-up of 47 months (36–60).	2
52. 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 electron-beam intraoperative RT 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 electron-beam intraoperative RT. 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

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. 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 gemcitabine and cisplatin followed by gemcitabine-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
54. 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 pancreaticoduodenectomies 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

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
55. 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 gemcitabine administered before and during concurrent 3D-CRT in patients with nonmetastatic pancreatic cancer.	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
56. Brunner TB, Baum U, Grabenbauer GG, Sauer R, Lambrecht U. Large topographic variability of upper abdominal lymphatics and the consequences for radiation treatment planning. *Radiother Oncol.* 2006;81(2):190-195.	Review/Other-Tx	104 patients scans	To quantify the substantial variability of the morphology and location of the upper abdominal vessels by the analysis of the vascular anatomy in CT scans.	Vascular origin varied most for the inferior mesenteric artery with substantial PTV size differences. Volumetric variability was analyzed for PDAC (inferior mesenteric artery vs renal hilum as caudal margin). Additional PTV for inferior mesenteric artery was <100 cc (median) but ranged up to 350 cc in CT (100–199 mL in 14/34 and >200 mL in 3/34 patients). Data from treatment planning confirmed this observation.	4
57. van der Geld YG, van Triest B, Verbakel WF, et al. Evaluation of four-dimensional computed tomography-based intensity-modulated and respiratory-gated radiotherapy techniques for pancreatic carcinoma. *Int J Radiat Oncol Biol Phys.* 2008;72(4):1215-1220.	Observational-Tx	10 patients	To compare conformal RT, IMRT, and respiration-gated RT planning techniques for PC.	Compared with the conformal RT plans, IMRT significantly reduced the mean volume of right kidney exposed to 20 Gy from 27.7% +/- 17.7% to 16.0% +/- 18.2% (standard deviation) (P<0.01), but this was not achieved for the left kidney (11.1% +/- 14.2% to 5.7% +/- 6.5%; P=0.1). The IMRT plans also reduced the mean gastric, hepatic, and small bowel doses (P<0.01). No additional reductions in the dose to the kidneys or other organs at risk were seen when respiration-gated RT plans were combined with either conformal RT or IMRT, and the findings for respiration-gated RT in end-expiration and end-inspiration were similar.	2

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Landry JC, Yang GY, Ting JY, et al. Treatment of pancreatic cancer tumors with intensity-modulated radiation therapy (IMRT) using the volume at risk approach (VARA): Employing dose-volume histogram (DVH) and normal tissue complication probability (NTCP) to evaluate small bowel toxicity. *Medical Dosimetry*. 2002;27(2):121-129.	Experimental-Tx	10 patients	To evaluate the influence of IMRT with inverse treatment planning on the dose-volume histograms of normal tissue compared to standard 3D-CRT in patients with PC.	The average dose delivered to one third of the small bowel was lower with the IMRT plan compared to 3D-CRT. The IMRT plan resulted in one third of the small bowel receiving 30.2 ± 12.9 Gy vs 38.5 ± 14.2 Gy with 3D-CRT (P=0.006). The median volume of small bowel that received greater than either 50 or 60 Gy was reduced with IMRT. The median volume of small bowel exceeding 50 Gy was 19.2 ± 11.2% (range 3% to 45%) compared to 31.4 ± 21.3 (range 7% to 70%) for 3D-CRT (P=0.048). The median volume of small bowel that received greater than 60 Gy was 12.5 ± 4.8% for IMRT compared to 19.8 ± 18.6% for 3D-CRT (P=0.034). The volume at risk approach employing IMRT techniques resulted in a lower dose per volume of small bowel that exceeded 60 Gy. We used the Lyman-Kutcher models to compare the probability of small bowel injury employing IMRT compared to 3D-CRT. The BIOPLAN model predicted a small bowel complication probability of 9.3 ± 6% with IMRT compared to 24.4 ± 18.9% with 3D-CRT delivery of dose (P=0.021).	2
59. 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.	Observational-Tx	46 patients	To evaluate acute toxicity outcomes at 2 university hospitals (the University of Maryland Medical Center and the University of Medicine and Dentistry of New Jersey) and compares these data with toxicity results from the recently reported US Intergroup adjuvant CRT trial (Radiation Therapy Oncology Group [RTOG] 97-04), where all patients were treated with conventional 3-D planning techniques.	The overall incidence of Grade 3-4 acute gastrointestinal toxicity was low in patients receiving IMRT-based CRT. When compared with patients who had 3-D 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 2 groups of patients.	2

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Bhasin DK, Rana SS, Jahagirdar S, Nagi B. Does the pancreas move with respiration? *J Gastroenterol Hepatol.* 2006;21(9):1424-1427.	Observational-Tx	22 patients	To assess the movement of pancreas with respiration using fluoroscopy, a simple and inexpensive method.	22 patients (mean age 35.45 + or - 11.29 years, 17 men) with chronic pancreatitis were included in the study. 10 patients had pancreatic calcification and 12 had an indwelling pancreatic duct stent (2 in the dorsal duct, 10 in the ventral duct). In all patients, the pancreas moved downward in the craniocaudal direction on deep inspiration. Pancreatic excursion from maximum inspiration to maximum expiration ranged from 0.1 to 3.4 cm. In addition, a medial movement of the head of pancreas was also noted in most of the patients. On univariate analysis, no association was found between the range of movement and the age or sex of the patient, duration or etiology of disease, presence or absence of calcification, severity of ductal changes of chronic pancreatitis and the length or diameter of the pancreatic stent placed.	2
61. Horst E, Micke O, Moustakis C, Schuck A, Schafer U, Willich NA. Conformal therapy for pancreatic cancer: variation of organ position due to gastrointestinal distention--implications for treatment planning. *Radiology.* 2002;222(3):681-686.	Experimental-Tx	20 patients	To quantify nonrespiratory organ motion in the pancreatic region and its effect on clinical target volume.	Significant translations of the volume of interest were observed. The most mobile parts of the target organs were the pancreatic tail (P=.001) and the superior mesenteric artery (P=.01). Larger variations from the mean in the planning CT protocol in which negative contrast material was used usually resulted in a slightly larger clinical target volume expansion.	2

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
62. Whitfield G, Jain P, Green M, et al. Quantifying motion for pancreatic radiotherapy margin calculation. *Radiother Oncol.* 2012;103(3):360-366.	Observational-Tx	13 patients, 109 cone beam CT scans	To quantify 3D target motion in patients undergoing pancreatic RT, allowing subsequent calculation of treatment margins to incorporate the observed group motion.	Using an off-line cone beam CT correction protocol, systematic (random) setup errors were 2.4 (3.2), 2.0 (1.7) and 3.2 (3.6)mm laterally (left-right), vertically (anterior-posterior) and longitudinally (craniocaudal), respectively. Fiducial motion varied substantially. Random inter-fractional changes in mean fiducial position were 2.0, 1.6 and 2.6 mm; 95% of intra-fractional peak-to-peak fiducial motion was up to 6.7, 10.1 and 20.6mm, respectively. Calculated clinical target volume to PTV margins were 1.4 cm laterally, 1.4 cm vertically and 3.0 cm longitudinally for 3D-CRT, reduced to 0.9, 1.0 and 1.8 cm, respectively, if using 4D planning and online setup correction.	2
63. Huguet F, Goodman KA, Azria D, Racadot S, Abrams RA. Radiotherapy technical considerations in the management of locally advanced pancreatic cancer: American-French consensus recommendations. *Int J Radiat Oncol Biol Phys.* 2012;83(5):1355-1364.	Review/Other-Tx	N/A	To propose consensus recommendations for use in the development of future trials testing new chemotherapy combinations with RT.	Based on this analysis of the literature, we recommend either 3D-CRT or IMRT to a total dose of 50 to 54 Gy at 1.8 to 2 Gy per fraction. We propose gross tumor volume identification to be followed by an expansion of 1.5 to 2 cm anteriorly, posteriorly, and laterally, and 2 to 3 cm craniocaudally to generate the PTV. The craniocaudal margins can be reduced with the use of respiratory gating. Organs at risk are liver, kidneys, spinal cord, stomach, and small bowel. Stereotactic body RT should not be used for PC outside of clinical trials. RT quality assurance is mandatory in clinical trials.	4

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
64. 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.	Observational-Tx	202 patients	To generate a map of local recurrences after PD for patients with resectable PDAC and to model an adjuvant RT PTV that encompasses a majority of local recurrences.	Of the 202 patients in the study, 40 (20%), 34 (17%), and 128 (63%) received no adjuvant treatment, chemotherapy alone, and CRT adjuvant therapy, respectively. The rate of margin-positive resections was greater in CRT patients than in chemotherapy alone patients (28% vs 9%, *P*=.023). Local recurrence occurred in 90/202 patients overall (45%) and in 19 (48%), 22 (65%), and 49 (38%) in the no adjuvant treatment, chemotherapy alone, and CRT groups, respectively. 90% 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 celiac axis and superior mesenteric artery 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.	2
65. 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.	Review/Other-Tx	N/A	To develop contouring guidelines to be used in the RTOG protocol 0848, a phase III randomized trial evaluating the benefit of adjuvant CRT 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 clinical target volume and normal tissues, as well as a Web-based atlas, were developed.	4

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Yovino S, Maidment BW, 3rd, Herman JM, et al. Analysis of local control in patients receiving IMRT for resected pancreatic cancers. *Int J Radiat Oncol Biol Phys*. 2012;83(3):916-920.	Observational-Tx	71 patients	To analyze patterns of first failure among patients treated with IMRT for resected PC.	At median follow-up of 24 months, 49/71 patients (69%) had failed. The predominant failure pattern was distant metastases in 35/71 patients (49%). The most common site of metastases was the liver. 14 patients (19%) developed locoregional failure in the tumor bed alone in 5 patients, regional nodes in 4 patients, and concurrently with metastases in 5 patients. Median OS was 25 months. On univariate analysis, nodal status, margin status, postoperative CA 19-9 level, and weight loss during treatment were predictive for OS. On multivariate analysis, higher postoperative CA19-9 levels predicted for worse OS on a continuous basis ($P<0.01$). A trend to worse OS was seen among patients with more weight loss during therapy ($P=0.06$). Patients with positive nodes and positive margins also had significantly worse OS (HR for death 2.8, 95% CI, 1.1–7.5; HR for death 2.6, 95% CI, 1.1–6.2, respectively). Grade 3-4 nausea and vomiting was seen in 8% of patients. Late complication of small bowel obstruction occurred in 4 (6%) patients.	2

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
67. 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.	Observational-Tx	1,385 patients	To determine whether there is an association between OS and adjuvant RT dose.	A total of 1,385 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 adjuvant 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 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 adjuvant RT dose was 45 Gy (range, 1.63 Gy–69 Gy). The median OS was 21 months (95% CI, 19 months–23 months). On multivariate analysis, an adjuvant RT dose <40 Gy ([HR, 1.30; [95% CI, 1.03–1.66]; *P*=.031), an adjuvant RT dose of 40 Gy to <50 Gy (HR, 1.17 [95% CI, 1.00–1.37]; *P*=.05), and an adjuvant 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.	2
68. Melo SA, Luecke LB, Kahlert C, et al. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. *Nature.* 2015;523(7559):177-182.	Observational-Dx	breast cancer patients (n = 32), PDAC patients (n = 190) and healthy donors (n = 100)	To identify and isolate cancer specific exosomes in body fluids to enable the identification of DNA, RNA and proteins without contamination from noncancer exosomes, and aid in the treatment and management of cancer.	GPC1(+) crExos were detected in the serum of patients with PC with absolute specificity and sensitivity, distinguishing healthy subjects and patients with a benign pancreatic disease from patients with early- and late-stage PC. Levels of GPC1(+) crExos correlate with tumor burden and the survival of pre- and post-surgical patients. GPC1(+) crExos from patients and from mice with spontaneous pancreatic tumors carry specific KRAS mutations, and reliably detect pancreatic intraepithelial lesions in mice despite negative signals by magnetic resonance imaging.	1

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
69. RTOG 0848 Protocol Information. A Phase IIR and A Phase III Trial Evaluating Both Erlotinib (Ph IIR) And Chemoradiation (Ph III) As Adjuvant Treatment For Patients With Resected Head Of Pancreas Adenocarcinoma. 2014; Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0848.	Review/Other-Tx	Ongoing	Phase II-R: To determine whether the addition of erlotinib to gemcitabine adjuvant chemotherapy shows a signal for improved survival as compared to gemcitabine alone following R0 or R1 resection of head of pancreas adenocarcinoma (including adenocarcinoma of the head, neck, and uncinate process). Phase III-To determine whether the use of concurrent fluoropyrimidine and RT following adjuvant gemcitabine based chemotherapy further enhances survival for such patients who are without evidence of progressive disease after 5 cycles of gemcitabine based chemotherapy.	This trial is still recruiting study subjects and results are not available yet.	4
70. Franke AJ, Rosati LM, Pawlik TM, Kumar R, Herman JM. The role of radiation therapy in pancreatic ductal adenocarcinoma in the neoadjuvant and adjuvant settings. *Semin Oncol.* 2015;42(1):144-162.	Review/Other-Tx	N/A	To review the data supporting or refuting the role of RT in the neoadjuvant and adjuvant settings of pancreatic ductal adenocarcinoma management, with a particular focus on determining which patients may be more likely to benefit from RT.	Results not stated in abstract.	4

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. 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 gemcitabine, oxaliplatin, and RT in patients with localized pancreatic cancer.	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

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
72. Le DT, Wang-Gillam A, Picozzi V, et al. Safety and survival with GVAX pancreas prime and Listeria Monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. *J Clin Oncol.* 2015;33(12):1325-1333.	Experimental-Tx	90 patients	To compare Cy/GVAX followed by CRS-207 with Cy/GVAX alone in patients with metastatic PDAC.	A total of 90 patients were treated (arm A, n = 61; arm B, n = 29); 97% had received prior chemotherapy; 51% had received ≥2 regimens for metastatic disease. Mean number of doses (+/- standard deviation) administered in arms A and B were 5.5 +/- 4.5 and 3.7 +/- 2.2, respectively. The most frequent grade 3 to 4 related toxicities were transient fevers, lymphopenia, elevated liver enzymes, and fatigue. OS was 6.1 months in arm A vs 3.9 months in arm B (HR, 0.59; *P*=.02). In a prespecified per-protocol analysis of patients who received at least 3 doses (2 doses of Cy/GVAX plus 1 of CRS-207 or 3 of Cy/GVAX), OS was 9.7 vs 4.6 months (arm A v B; HR, 0.53; *P*=.02). Enhanced mesothelin-specific CD8 T-cell responses were associated with longer OS, regardless of treatment arm.	1
73. Lutz E, Yeo CJ, Lillemoe KD, et al. A lethally irradiated allogeneic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine for pancreatic adenocarcinoma. A Phase II trial of safety, efficacy, and immune activation. *Ann Surg.* 2011;253(2):328-335.	Experimental-Tx	60 participants	To test the safety and efficacy of a granulocyte-macrophage colony-stimulating factor-based immunotherapy administered in patients with resected PC.	The median DFS is 17.3 months (95% CI, 14.6–22.8) with median survival of 24.8 months (95% CI, 21.2–31.6). The administration of immunotherapy was well tolerated. In addition, the post-immunotherapy induction of mesothelin-specific CD8+ T cells in HLA-A1+ and HLA-A2+patients correlates with DFS.	1
74. Laheru D, Jaffee EM. Immunotherapy for pancreatic cancer - science driving clinical progress. *Nat Rev Cancer.* 2005;5(6):459-467.	Review/Other-Tx	N/A	To review new developments in immunotherapy for PC.	No results stated in abstract.	4

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
75. Ng SSW, Tsao MS, Chow S, Hedley DW. Inhibition of phosphatidylinositide 3-kinase enhances gemcitabine-induced apoptosis in human pancreatic cancer cells. *Cancer Res.* 2000;60(19):5451-5455.	Review/Other-Tx	N/A	To investigate the significance of PI3K-PKB/Akt cell survival pathway in mediating drug resistance and the effects of PI3K inhibitors on gemcitabine treatment in human PC cells.	After exposure to 20 microM gemcitabine for 48 h and in the continuous presence of the drug, treatment with the P13K inhibitors wortmannin (50-200 nM) and LY294002 (15-120 microM) for 4 h substantially enhanced apoptosis in a concentration-dependent manner as compared with treatment with gemcitabine alone, as determined by the loss of mitochondrial membrane potential and the increase in propidium iodide uptake using flow cytometry. Furthermore, Western blotting showed that the reduction of phosphorylated PKB/Akt levels correlated with the enhancement of gemcitabine-induced apoptosis, suggesting that the PI3K-PKB/Akt pathway plays a significant role in mediating drug resistance in human PC cells.	4
76. 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 gemcitabine 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 gemcitabine group (HR for death, 0.57; 95% CI, 0.45 to 0.73; $P<0.001$). Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine 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 gemcitabine 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 gemcitabine group (HR, 0.47; 95% CI, 0.30 to 0.70; $P<0.001$).	1

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
77. 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 stereotactic body RT in the treatment of locally advanced PC and borderline resectable PC.	A total of 88 patients were included in the analysis, 74 with locally advanced PC and 14 with and borderline resectable PC. The median age at diagnosis was 67.2 years, and median follow-up from date of diagnosis for locally advanced PC and borderline resectable PC patients was 14.5 and 10.3 months, respectively. Median OS from date of diagnosis was 18.4 months (locally advanced PC, 18.4 mo; and borderline resectable PC, 14.4 mo) and median progression-free survival 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 locally advanced PC patients and 84% had margin-negative resections.	2

Resectable Pancreatic Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
78. 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 gemcitabine monotherapy in patients with metastatic PC.	A total of 861 patients were randomly assigned to nab-paclitaxel plus gemcitabine (431 patients) or gemcitabine (430). The median OS was 8.5 months in the nab-paclitaxel-gemcitabine group as compared with 6.7 months in the gemcitabine 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-gemcitabine group vs 22% in the gemcitabine group at 1 year, and 9% vs 4% at 2 years. The median progression-free survival was 5.5 months in the nab-paclitaxel-gemcitabine group, as compared with 3.7 months in the gemcitabine 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-gemcitabine group vs 27% in the gemcitabine 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-gemcitabine group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days.	1

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

3D-CRT = 3-dimensional conformal radiation therapy

CA19-9 = Carbohydrate antigen 19-9

CI = Confidence interval

CRT = Chemoradiation

CT = Computed tomography

DFS = Disease-free survival

HR = Hazard ratio

IMRT = Intensity-modulated radiotherapy

Le = Lewis gene

LNR = Lymph node ratio

OS = Overall survival

PC = Pancreatic adenocarcinoma

PD = Pancreaticoduodenectomy

PDAC = Pancreatic ductal adenocarcinoma

PTV = Planning treatment volume

RR = Risk ratio

RT = Radiation therapy

Se = Secretor gene