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# Chemotherapy and radiation components of neoadjuvant treatment of pancreatic head adenocarcinoma: Impact on perioperative mortality and long-term survival

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## Abstract

*Background*: We compared outcomes of neoadjuvant therapy delivered as chemotherapy-only (Chemo) versus concurrent chemoradiation (ChemoRT) versus chemotherapy followed by radiation (Chemo–ChemoRT) among pancreatic head adenocarcinoma patients receiving pancreaticoduodenectomy.
*Methods*: National Cancer Data Base cases diagnosed 2006–2011 treated by neoadjuvant therapy and pancreaticoduodenectomy.
*Results*: 1163 pts received neoadjuvant treatment with Chemo (n = 309; 26.6%), ChemoRT (n = 626; 53.8%), or Chemo–ChemoRT (n = 228; 19.6%). Odds of 30-day and 90-day mortality were not influenced by delivery of any neoadjuvant therapy type. Median overall survival for Chemo, ChemoRT, and Chemo–ChemoRT groups were 25.6 (95% confidence interval 23.1–28.7), 22.9 (21.4–24.8), and 26.9 (23.7–29.4) months, respectively. There was no statistically significant difference between Chemo and Chemo–ChemoRT groups (log rank test p = 0.854), while there was significant difference of ChemoRT (p = 0.017 versus Chemo; p = 0.021 versus Chemo–ChemoRT). Multivariate model suggests delivery of concurrent ChemoRT as opposed to neoadjuvant therapy with full dose systemic chemotherapy is associated with shortened survival (aHR = 1.311, p = 0.001).
*Conclusions*: There is no detectable difference in early outcomes (30-day and 90-day postsurgical mortality) among pancreaticoduodenectomy patients treated with various types of neoadjuvant therapy. Overall survival appears better among patients exposed preoperatively to full dose systemic chemotherapy rather than concurrent chemoradiation only. Further studies with more detailed data sources are needed.


*Keywords:* Preoperative systemic therapy; Whipple procedure; Resection; Pancreatic cancer; Chemoradiation; Chemotherapy

## Introduction

Neoadjuvant therapy in pancreatic cancer has gained considerable acceptance in the United States despite the absence of randomized trials comparing it directly to treatment administered after resection of the primary tumor.[1–4] Hypothetically, neoadjuvant therapy addresses earlier treatment of micrometastatic disease thought to be present in the majority of cases despite apparent resectability.[5] It may also downsize large tumors to allow for margin-negative resection, facilitate improved patient selection for resection by revealing biological aggressiveness, allow for further observation of indeterminate extrapancreatic lesions prior to resection, and enable medical optimization prior to surgery.[1–3,6–9]

Options for neoadjuvant treatment include radiation therapy (RT, typically as chemoradiation), systemic chemotherapy alone, or sequencing of chemotherapy followed by RT. There is little data support for the use of chemotherapy alone versus chemoradiation in the neoadjuvant setting.[10] Meanwhile, uncertainty about the overall value of radiation therapy in pancreatic cancer remains, especially as some randomized trials have shown lack of benefit in locally advanced disease[11] and even detriment in adjuvant settings,

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thought to be secondary to the suboptimal chemotherapy that accompanies the use of RT.[12,13]

Therefore, we compared patterns of practice and outcomes of neoadjuvant chemotherapy and radiotherapy among pancreatic cancer patients receiving pancreaticoduodenectomy.

## Methods

Data for this retrospective study was drawn from the National Cancer Data Base (NCDB) – a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The NCDB is a nationwide oncology data program that captures about 70% of all newly diagnosed malignancies in the US through facility-based reporting. The study is exempt from human subjects research as defined by US Code of Federal Regulations Title 45 [§46.102(f)].

Cases of invasive pancreatic head adenocarcinoma treated with neoadjuvant chemoradiation or chemotherapy and diagnosed between 2006 and 2011 were included. We analyzed multiple patient-, disease-, and treatment-related variables available in the NCDB Participant User File – December 2014 extract with follow-up data through December 2013. Patients with *International Classification of Diseases for Oncology*, 3rd edition (ICD-O-3) histology codes for invasive adenocarcinoma (8140/3) and infiltrating duct carcinoma (8500/3) for the primary disease site "C25.0 – pancreatic head" with clinical stage I–III were included if they received any pre-resection chemotherapy, radiation or both. Patients with any neoadjuvant therapy combined with adjuvant chemotherapy were included. However, patients with neoadjuvant therapy who received adjuvant radiation were excluded from main analysis to avoid bias, but were included in a sensitivity analysis.

Patients were divided into three groups according to type of neoadjuvant therapy: (1) Chemotherapy-only patients received neoadjuvant systemic chemotherapy without radiation (Chemo); (2) Chemoradiation group (ChemoRT) patients receiving concurrent chemotherapy and radiation, where chemotherapy started less than 30 days before RT; and (3) Chemo–ChemoRT group, where patients received systemic chemotherapy alone for $\geq$30 days, and subsequently radiation therapy.

*Comorbidity burden* was provided by a modified Charlson-Deyo comorbidity index (expressed in this report as no comorbidity versus at least one condition). *Household income* in this analysis refers to quartiles of 2012 adjusted household annual income geo-assigned by corresponding individual patient's zip code (1st <$38,000; 2nd $38,000–$47,999; 3rd $48,000–$62,999; 4th >$63,000). *Treatment facility types* were coded as community cancer center, comprehensive community cancer center, or academic/research center (including NCI-designated cancer centers). For the purpose of this analysis the two community center groups were grouped together, to enable analysis as 'community' versus 'academic' centers. *Pathological nodal status* was analyzed as either 'node-negative' (ypN0) or 'node-positive' (ypN+). *Resection margin status* was graded as 'negative' (R0; generally, no ink on tumor in the USA) or 'involved' (R1 or R2).

We examined multiple factors in relationship to outcomes, all selected based on prior literature and feasibility given the database limitations. Univariate, full multivariate, and stepwise multivariate regression models are presented. Stepwise models were built based on all variables used in full multivariate models.

Primary outcome measures were 30-day and 90-day postsurgical mortality, and overall survival (OS). Data are expressed as mean ± standard deviation (SD) or as proportions as appropriate. Continuous variables were tested using Student *t*-test or one-way analysis of variance. Proportions were compared using Pearson $\chi^2$-test. Logistic regression models were used to analyze binary outcomes, and goodness of fit was assessed by Hosmer–Lemeshow test and Pearson's test. We required both tests to be negative to accept the model as consistent with data ($p > 0.05$ for each test), but reported the former only as we found no inconsistencies. Survival was assessed by Kaplan–Meier estimates. Proportional hazard assumption was tested by Schoenfeld's residuals and graphical assessment. An alpha value of $<0.05$ was used to determine statistical significance. All analyses were done using STATA 10 (StataCorp LP, College Station, TX, USA).

## Results

Of a total 1163 patients that satisfied the inclusion and exclusion criteria, 309 patients (26.6%) received neoadjuvant chemotherapy only, 626 patients (53.8%) received concurrent neoadjuvant chemoradiation, and the remaining 228 patients (19.6%) received neoadjuvant chemotherapy followed by RT (Chemo–ChemoRT group).

### *Patient characteristics*

Demographic, disease- and treatment-related variables were compared between all cohorts (Table 1). Most but not all pretreatment characteristics were similar, including age, gender distribution, comorbidity rate, and pretreatment clinical lymph node status. There were, however, pretreatment differences in some other demographic, referral, and clinical characteristics. Most notably a higher rate of cT4 tumors was associated with the more intensive therapy combination (Chemo-only versus ChemoRT, $p = 0.011$; ChemoRT versus Chemo–ChemoRT, $p = 0.043$; Chemo-only versus Chemo–ChemoRT, $p < 0.001$; Table 1).

Length of neoadjuvant period was defined as days elapsed between diagnosis and pancreaticoduodenectomy (this period included both neoadjuvant treatment and recovery before operation). There was no statistical difference between the length of neoadjuvant period of

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