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ORIGINAL ARTICLE

Lymph Node Ratio in Pancreatic Adenocarcinoma After Preoperative Chemotherapy vs. Preoperative Chemoradiation and Its Utility in Decisions About Postoperative Chemotherapy

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Abstract

Background Single-center studies in pancreatic adenocarcinoma have suggested that preoperative chemotherapy (PCT) is associated with higher lymph node ratio (LNR) than preoperative chemoradiation (PCRT). The association of postoperative chemotherapy with overall survival (OS) in patients treated with PCT and PCRT remains unclear. Our objectives were to investigate whether (1) PCT is associated with higher LNR than PCRT and (2) postoperative chemotherapy is associated with longer OS after PCT and PCRT in LNR-stratified cohorts.

Methods A retrospective cohort study was performed of patients with pancreatic adenocarcinoma treated with PCT or PCRT followed by resection between 2006 and 2014 in the National Cancer Database. Temporal trends were evaluated with Cuzick's test. OS was evaluated with multivariable Cox regression and inverse probability weighted (IPW) Cox regression.

Results Of 4187 patients, 1993 (47.6%) received PCT. PCT rates were stable at approximately 30% in 2006–2010 ($p = 0.33$) but increased to 64.9% by 2014 ($p < 0.001$). Node positivity rates were higher after PCT than PCRT (62.7 vs. 41.8%, $P < 0.001$) and mean LNR was higher (0.10 [95% CI 0.096, 0.11] vs. 0.058 [95% CI 0.052, 0.063], $P < 0.001$). Postoperative chemotherapy was associated with longer OS in patients with LNR 0.01–0.149 after PCT by univariate analysis (median OS 34.5 vs. 26.5 months, $P = 0.002$), multivariable Cox regression (HR 0.64, 95% CI 0.48, 0.84), and IPW Cox regression (HR 0.72, 95% CI 0.55, 0.94). Postoperative chemotherapy was not associated with longer OS for patients who were node-negative or who had LNR ≥ 0.15 after PCT or for any patient subgroups after PCRT.

Conclusions PCT is associated with a higher LNR and higher rates of node positivity than PCRT. Postoperative chemotherapy is associated with longer OS than observation in patients with a LNR of 0.01–0.149 after PCT.

Keywords LNR · Lymph node ratio · Nodal status · Pancreatic adenocarcinoma · PDAC · Neoadjuvant · Preoperative · Adjuvant · Postoperative · Chemotherapy · Chemoradiation

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Introduction

Randomized controlled trials (RCTs) demonstrate that adjuvant treatment after R0–R1 resection of pancreatic ductal adenocarcinoma (PDAC) increases 5-year survival to 20–30% from approximately 10% with surgery alone.[1–5] Accordingly, the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend 6 months of adjuvant chemotherapy.[5,6] Preoperative therapy is recommended for borderline resectable (BR) PDAC and is increasingly being used for resectable tumors.[5–7] Pathologic nodal status is among the most important prognostic factors for resected PDAC after preoperative therapy, and patients treated with preoperative therapy have lower rates of node positivity and lower lymph node ratios (LNRs) than patients who undergo upfront surgery.[8–14]

Current guidelines recommend that patients who received preoperative therapy be considered for additional postoperative chemotherapy; ASCO guidelines recommend a total of 6 months of "adjuvant" therapy, including the preoperative regimen.[5,6] These guidelines are based on informal expert consensus and extrapolation from adjuvant therapy trials; no RCTs address this topic.[5,6] Three recent observational studies attempted to define nodal-based subgroups who may benefit from postoperative chemotherapy, but they had partially conflicting results.[15–17] Roland et al. reported on 263 patients from the MD Anderson Cancer Center and found that postoperative chemotherapy was associated with longer overall survival (OS) in patients with LNR < 0.15 (including node-negative) but not those with LNR ≥ 0.15.[15] A study of 234 patients by Barnes et al. found that postoperative chemotherapy was associated with longer OS in node-positive but not node-negative patients.[16] Finally, a National Cancer Database (NCDB) study that stratified patients as node-negative/positive *and* LNR < 0.15/≥ 0.15 found no survival benefit for postoperative chemotherapy in any subgroup.[17] Importantly, these studies did not separately analyze OS of patients with a minimal burden of positive nodes (i.e., LNR 0.01–0.149). Furthermore, they grouped together patients that received preoperative chemotherapy (PCT) and preoperative chemoradiation (PCRT). This is relevant because single-center studies have reported that rates of node positivity are higher after PCT than PCRT.[18–20] Broader confirmation of this finding would suggest that LNR values should be stratified by preoperative therapy type in clinical decision-making.

Given the uncertainty of the existing literature, our primary aims were to use the NCDB to investigate: (1) whether PCRT is associated with decreased nodal burden compared to PCT in a multi-institutional, national dataset and (2) whether patients with a minimal burden of positive nodes (i.e., LNR 0.01–0.149) benefit from postoperative chemotherapy after preoperative therapy. We also investigated factors associated with utilization of PCT vs. PCRT and with utilization of postoperative chemotherapy.

Methods

Data and Exclusions

This study uses the 2015 participant user file of the NCDB, a facility-level database managed by the American College of Surgeons' Commission on Cancer (CoC) and the American Cancer Society that captures 70% of cancer diagnoses in the USA.[21,22] Exclusion criteria are shown in Fig. 1. The first year was 2006 because that is when the NCDB started reporting sequencing of chemotherapy and radiation in relation to surgery. Patients diagnosed in 2015 were excluded because their survival data are unavailable. Patients with unusually short or long diagnosis-to-surgery intervals were excluded due to concerns that this was reflective of non-completion of planned preoperative therapy or inordinate delays. Patients receiving intraoperative radiation, palliative doses, or unrealistically high doses were also excluded.[23]

Analytic Cohorts and Outcomes

The flowchart of analytic cohorts is shown in Fig. 1. Factors predicting utilization of PCT vs. PCRT were examined in the overall cohort. Predictors of LNR categories were examined after excluding patients with ≤ 6 nodes examined or missing information on number of nodes examined/positive. The LNR threshold of 0.15 was chosen based on previous studies.[9,15] Although examination of ≥ 11 lymph nodes is recommended,[24] we included patients with 7–10 nodes examined ($N = 552$) to avoid decreasing sample size too drastically. Notably, patients with 7–10 nodes examined and 1–2 positive would fall into the same LNR categories as those with 11–13 examined, whereas those with ≤ 6 examined would not.

Patients with 90-day postoperative mortality were excluded from analyses of utilization of postoperative chemotherapy and survival to address survivor-treatment bias.[25] Patients who received postoperative radiation without chemotherapy were also excluded. Analyses of utilization of postoperative chemotherapy were conducted separately based on preoperative therapy type. Importantly, NCDB variables do not allow *definitive* identification of patients who received PCRT only (i.e., preoperative radiation with a radiosensitizer) from those who received PCRT after induction chemotherapy (iCT). Survival analyses were further stratified by LNR category resulting in six survival cohorts (Fig. 1). The predictor variable in survival analyses was postoperative chemotherapy. Comparisons were not made between postoperative chemotherapy vs. postoperative chemoradiation because the number of patients in each cohort that received postoperative radiation was relatively small.

Covariate Selection

Multivariable models only included variables available at the decision about the predictor variable of interest to avoid overadjustment bias.[26] Patients who underwent surgery at a facility other than the reporting facility were included to maximize sample size, which precluded calculation of surgical volume. Patients who underwent surgery at a facility other than the reporting facility are represented as "Unknown" in the variable "Facility type." Community facilities were combined with Comprehensive Community facilities.

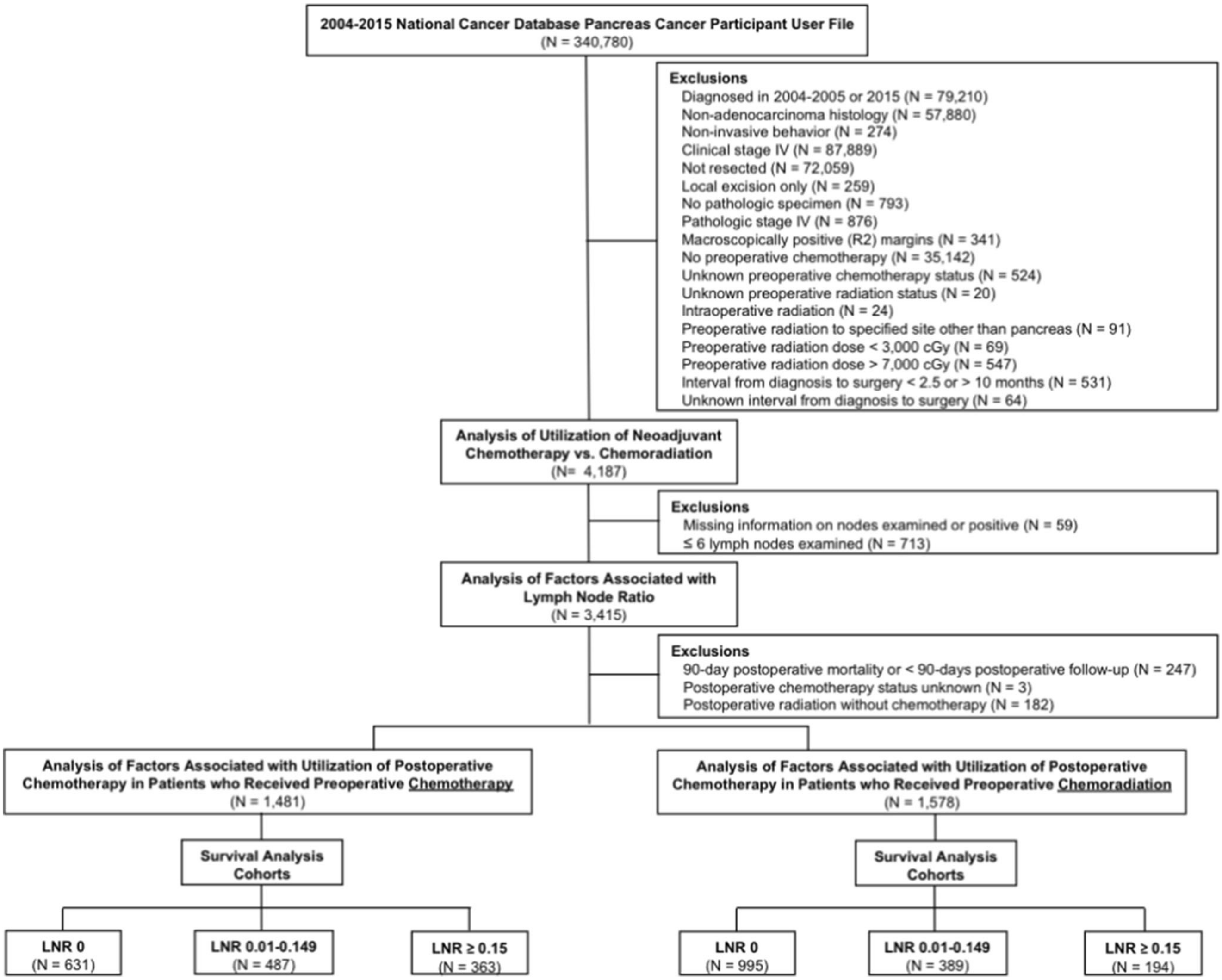

Fig. 1 Flowchart of exclusion criteria and analytic cohorts

Statistical Analysis

Univariate analyses of associations between covariates and binary outcomes (preoperative therapy type, utilization of postoperative chemotherapy) and the multi-categorical outcome of LNR category were performed using chi-squared tests. Temporal trends were evaluated with Cuzick's trend test.[27] Covariates with a univariate $P < 0.1$ were included in multivariable models. Multivariable analysis of binary outcomes was performed using logistic regression. A multinomial logistic regression model was used to identify covariates independently associated with having a LNR of 0.01–0.14 and ≥ 0.15 (vs. 0). A linear regression model adjusted for the same covariates was used to obtain adjusted mean LNRs among patients treated with PCT vs. PCRT. Odds ratios are exaggerated estimates of effect size and are often misinterpreted as risk ratios (RRs).[28,29] Therefore, we used average marginal estimation (marginal standardization) to compute adjusted RRs.[30,31] Confidence intervals (CIs) for these RRs were based on complex survey design adjusted linearized standard errors.[31]

OS was right-censored at 5 years post-diagnosis. The association between postoperative chemotherapy and OS was examined with multivariable Cox proportional hazards models. Covariates with a univariate $P < 0.1$ were included in multivariable Cox models. The proportional hazards assumption was verified graphically.

To confirm similar results after attempting to control for confounding by indication, inverse probability of treatment weighted (IPTW) analyses were performed. Propensity scores (PS) were estimated using multivariable logit models with postoperative chemotherapy as the outcome. After excluding patients in whom the common support assumption was not met, PS overlap was assessed with kernel density plots. Weights were calculated as (1 / PS) for the postoperative chemotherapy group and [1 − (1 / PS)] for the observation group. Weights were normalized by dividing by the sum of the weights.[32,33] Standardized differences (SDs) for each covariate in PS models were assessed to evaluate whether weighting achieved balance; a SD < 0.1 was considered well-balanced. IPTW Cox regression was performed, and weighted KM curves were generated. Finally, an IPTW regression-adjusted estimator (Stata's stteffects ipwra) was used to quantify the average treatment effect (ATE) or the difference in predicted mean survival if all patients received postoperative chemotherapy vs. observation.[34]

Sensitivity Analyses

Five sensitivity analyses were performed in which multivariable Cox models were repeated to verify robust results. Analyses were repeated with survival defined as starting at surgery (vs. diagnosis) because diagnosis-to-surgery interval was shorter in postoperative chemotherapy patients (mean 4.6 vs. 5.3 months, $P <$ 0.001). Second, node-positive patients were stratified as 1–2 nodes positive vs. ≥ 3 instead of LNR categories because this schema is also prognostic after preoperative therapy.[10] Third, we limited analyses to patients with ≥ 11 nodes examined, the minimum number recommended for accurate staging.[6,24] Fourth, analyses were repeated with a more stringent 6-month post-surgery landmark, as in the previous NCDB study.[17] Finally, we used definitions proposed in a recent study to limit analyses to patients who received concurrent PRCT (chemotherapy and radiation started within 30 days of each other) without iCT (chemotherapy > 30 days before radiation) since it seems logical that postoperative chemotherapy might be more important in such patients.[23] For this analysis, patients with missing diagnosis-to-chemotherapy and/or diagnosis-to-radiation intervals ($N = 141$) were excluded. Given that these five sensitivity analyses were exploratory in nature, statistical adjustment for multiple comparisons was not performed.

Statistical analyses were performed in STATA 14.2 (StataCorp; College Station, TX). A $P < 0.05$ was considered statistically significant. Tests were two-sided. This study was exempt from institutional review board review.

Results

Utilization of PCT vs. PCRT

Of 4187 patients included in the analysis of utilization of PCT vs. PCRT, 2045 (48.8%) were female, median age was 64 years (standard deviation 9.8), and 3545 (84.7%) were non-Hispanic White. Univariate and multivariable analyses of factors associated with preoperative therapy type are shown in Table 1. PCT rates ranged from 34.7% in the East North Central region to 70.7% in the Pacific region. Rates of PCT/PCRT were stable from 2004 to 2010 ($P = 0.33$), but PCT utilization increased dramatically in 2011–2014 ($P < 0.001$) (Fig. 2). Utilization of PCRT was independently associated with comorbidities, residence in lower income areas, and cT4 tumors (vs. cT3). Predictors of PCT included unknown graduation rates, certain census divisions, unknown cT and cN stages, and treatment after 2008.

Factors Associated with LNR Categories

There were 3415 patients with complete information on nodes examined/positive and ≥ 7 nodes examined. Of the 713 patients who were excluded for having < 7 nodes examined, 470 (65.9%) received PCRT while 243 (43.1%) received PCT. The mean number of nodes examined was 20.8 (95% CI 20.3, 21.3) after PCT vs. 17.3 (95% CI 16.9, 17.7) after PCRT ($P < 0.001$, two-sided t test). Univariate analyses of predictors of LNR categories are shown in Supplemental Table 1. Among patients treated with PCT, LNR was 0 in 41.8%, 0.01–0.149 in 32.8%, and ≥ 0.15 in 25.4%. Among patients treated with PCRT, LNR was 0 in 62.7%, 0.01–0.149 in 24.7%, and ≥ 0.15 in 12.6%. The mean LNR was 0.10 (95% CI 0.096, 0.11) in patients treated with PCT vs. 0.058 (95% CI 0.052, 0.063) in patients treated with PCRT ($P < 0.001$, two-sided t test).

The multivariable analysis of factors associated with LNR categories is shown in Table 2. LNR of 0.01–0.149 was independently predicted by PCT, rural/unknown urban/rural status, overlapping/unspecified tumor locations, cN1 or cNX status, and examination of ≥ 12 nodes. LNR of ≥ 0.15 was twice as likely if treated with PCT and was also predicted by male sex and cN1 status. LNR of ≥ 0.15 was less likely in patients with non-pancreatic head tumors and those with ≥ 12 nodes examined. The adjusted mean LNR of patients treated with PCT was 0.10 (95% CI 0.097, 0.11) vs. 0.058 (95% CI 0.051, 0.064) for those who received PCRT ($P < 0.001$).

Postoperative Chemotherapy Utilization

Of 1481 patients treated with PCT included in survival analyses, 673 (45.4%) received postoperative chemotherapy. The rate did not change over time ($P = 0.57$). Postoperative chemotherapy rates by LNR were 39.0% in node-negative, 52.4% in LNR 0.01–0.149, and 47.4% in LNR ≥ 0.15. The multivariable analysis of factors associated with postoperative chemotherapy in patients who received PCT is shown in Supplemental Table 2. Utilization of postoperative chemotherapy was predicted by male sex, area non-graduation rates of 7–12.9%/unknown, surgery at a facility other than the reporting facility, and LNR of 0.01–0.149 or ≥ 0.15. Observation was predicted by treatment in the West South

Table 1 Factors associated with utilization of preoperative chemotherapy vs. preoperative chemoradiation

	Univariate analysis			Multivariable analysis
	Preoperative chemotherapy N = 1993	Preoperative chemoradiation N = 2194	P	RR for preoperative chemotherapy (95% CI)
Sex				
Female	949 (47.6%)	1096 (50.0)	0.13	–
Male	1044 (52.4%)	1098 (50.1%)		–
Age, years				
18–49	160 (8.0%)	186 (8.5%)	0.75	–
50–59	510 (25.6%)	557 (25.4%)		–
60–69	765 (38.4%)	872 (39.7%)		–
70–79	476 (23.9%)	489 (22.3%)		–
≥ 80	82 (4.1%)	90 (4.1%)		–
Race/ethnicity				
NH White	1684 (84.5%)	1861 (84.8%)	< 0.001	1.00 (Ref)
NH Black	149 (7.5%)	227 (10.4%)		0.93 (0.82, 1.04)
Hispanic	82 (4.1%)	51 (2.3%)		1.14 (0.97, 1.33)
Asian	52 (2.6%)	28 (1.3%)		1.11 (0.90, 1.36)
Other	26 (1.3%)	27 (1.2%)		1.00 (0.77, 1.30)
Insurance status				
Uninsured	33 (1.7%)	47 (2.1%)	0.30	–
Private	970 (48.7%)	1054 (48.0%)		–
Medicaid	81 (4.1%)	100 (4.6%)		–
Medicare	865 (43.4%)	927 (42.3%)		–
Other/unknown	44 (2.2%)	66 (3.0%)		–
Charlson-Deyo score				
0	1406 (70.6%)	1411 (64.3%)	< 0.001	1.00 (Ref)
1	484 (24.3%)	615 (28.0%)		**0.91 (0.85, 0.98)**
≥ 2	103 (5.2%)	168 (7.7%)		**0.82 (0.72, 0.95)**
Cancer history				
No	1632 (81.9%)	1792 (81.7%)	0.86	–
Yes	361 (18.1%)	402 (18.3%)		–
Median area income				
< $38,000	271 (13.6%)	331 (15.1%)	0.001	**0.88 (0.78, 0.99)**
$38,000–$47,999	436 (21.9%)	523 (23.8%)		**0.93 (0.83, 1.03)**
$48,000–$62,999	558 (28.0%)	626 (28.5%)		**0.88 (0.79, 0.99)**
≥ $63,000	716 (35.9%)	680 (31.0%)		1.00 (Ref)
Unknown	12 (0.6%)	34 (1.6%)		0.56 (0.01, 3.90)
Area % without high school degree				
≥ 21%	259 (13.0%)	243 (11.1%)	0.006	1.12 (0.99, 1.28)
13–20.9%	259 (22.1%)	514 (23.4%)		1.04 (0.94, 1.15)
7–12.9%	682 (34.2%)	792 (36.1%)		0.99 (0.91, 1.08)
< 7%	599 (30.1%)	612 (27.9%)		1.00 (Ref)
Unknown	12 (0.6%)	33 (1.5%)		**2.14 (1.97, 2.32)**
Urban/rural status				
Metropolitan	1598 (80.2%)	1720 (78.4%)	0.45	–
Urban	292 (14.7%)	361 (16.5%)		–
Rural	38 (1.9%)	40 (1.8%)		–
Unknown	65 (3.3%)	73 (3.3%)		–
Census division				

Table 1 (continued)

	Univariate analysis			Multivariable analysis
	Preoperative chemotherapy $N = 1993$	Preoperative chemoradiation $N = 2194$	P	RR for preoperative chemotherapy (95% CI)
New England	84 (4.2%)	139 (6.3%)	< 0.001	1.03 (0.85, 1.23)
Mid-Atlantic	436 (21.9%)	358 (16.3%)		**1.54 (1.39, 1.71)**
South Atlantic	342 (17.2%)	598 (27.3%)		1.00 (Ref)
East NC	307 (15.4%)	577 (26.3%)		0.96 (0.85, 1.08)
East SC	90 (4.5%)	80 (3.7%)		**1.46 (1.25, 1.71)**
West NC	223 (11.2%)	196 (8.9%)		**1.43 (1.26, 1.62)**
West SC	157 (7.9%)	68 (3.1%)		**1.81 (1.60, 2.05)**
Mountain	82 (4.1%)	65 (3.0%)		**1.44 (1.22, 1.71)**
Pacific	272 (13.7%)	113 (5.2%)		**1.86 (1.67, 2.08)**
Tumor location				
Head	1536 (77.1%)	1702 (77.6%)	0.22	–
Body	145 (7.3%)	182(8.3%)		–
Tail	103 (5.2%)	89 (4.1%)		–
Overlapping/NOS	209 (10.5%)	221 (10.1%)		–
Clinical T stage				
cT1	109 (5.5%)	116 (5.3%)	< 0.001	1.07 (0.94, 1.22)
cT2	511 (25.6%)	514 (23.4%)		1.05 (0.98, 1.13)
cT3	974 (48.9%)	1111 (50.6%)		1.00 (Ref)
cT4	243 (12.2%)	366 (16.7%)		**0.84 (0.76, 0.93)**
cTX (unknown)	156 (7.8%)	87 (4.0%)		**1.30 (1.13, 1.49)**
Clinical N stage				
cN0	1269 (63.7%)	1442 (65.7%)	< 0.001	1.00 (Ref)
cN1	579 (29.1%)	655 (29.9%)		1.04 (0.97, 1.11)
cNX (unknown)	145 (7.3%)	97 (4.4%)		**1.25 (1.07, 1.45)**
Year of diagnosis				
2006–2008	144 (7.2%)	363 (16.6%)	< 0.001	1.00 (Ref)
2009–2011	481 (24.1%)	822 (37.5%)		**1.39 (1.19, 1.63)**
2012–2014	1368(68.6%)	1009 (46.0%)		**2.16 (1.87, 2.51)**
CoC facility type				
Community	278 (14.0%)	263 (12.0%)	0.03	1.00 (0.91, 1.09)
Academic	1204 (60.4%)	1375 (62.7%)		1.00 (Ref)
Integrated Network	142 (7.1%)	191 (8.7%)		1.08 (0.96, 1.20)
Unknown	369 (18.5%)	365 (16.6%)		1.08 (0.99, 1.17)

Univariate data are presented as *N* (%). Percentages may not add up to 100 because of rounding. Significance for bold values in multivariable model is $P < 0.05$

RR risk ratio, *CI* confidence interval, *NH* non-Hispanic, *Ref* referent, *NC* North Central, *SC* South Central, *NOS* not otherwise specified, *CoC* Commission on Cancer

Central region, pTX status, length of stay (LOS) ≥ 14 days or unknown, and 30-day readmissions.

Of 1578 patients treated with PCRT who were included in survival analyses, 475 (30.1%) received postoperative chemotherapy. The rate did not change over time ($P = 0.58$). Postoperative chemotherapy rates by LNR were 27.1% in node-negative, 37.3% in LNR 0.01–0.149, and 30.9% in LNR ≥ 0.15. The multivariable analysis of factors associated with utilization of postoperative chemotherapy in patients who received PCRT is shown in Supplemental Table 2. Utilization of postoperative chemotherapy was predicted by LNR of 0.01–0.149, size > 4 cm, and unknown grade. Omission of postoperative chemotherapy was predicted by other/unknown insurance status, Integrated Network facilities, and LOS ≥ 14 days.

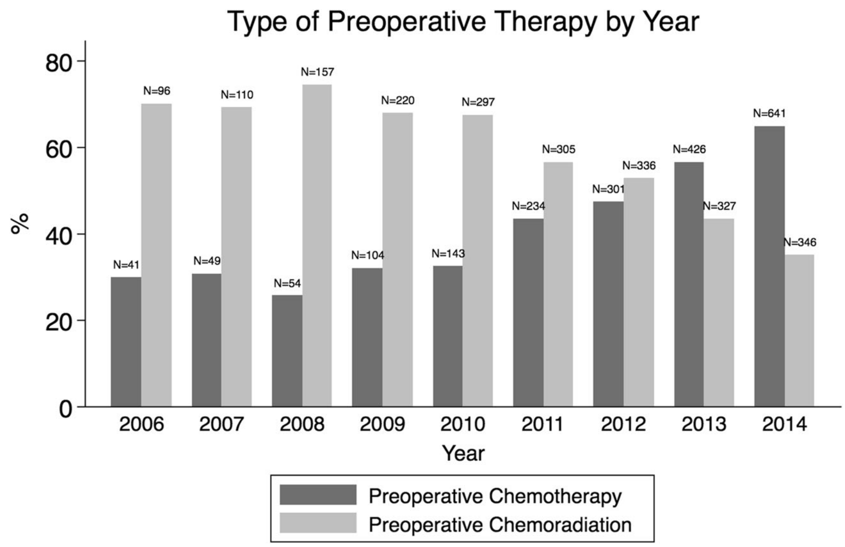

Fig. 2 Yearly rates of preoperative chemotherapy and preoperative chemoradiation among 4187 patients who received preoperative therapy

Survival Analyses

In multivariable Cox models, patients with an LNR of 0.01–0.149 after PCT who received postoperative chemotherapy had longer adjusted OS than those who were observed, but postoperative chemotherapy was not associated with longer adjusted OS in node-negative patients who received PCT, patients with an LNR ≥ 0.15 after PCT, or any patients who received (Table 3). In the six IPW analyses, there was adequate overlap of the PS for postoperative chemotherapy vs. observation patients after excluding those in whom the common support assumption was not met (Supplemental Fig. 1). Weighting successfully balanced covariates (Supplemental Fig. 2). Results of the IPW Cox models were similar to univariate and traditional multivariable analyses (Table 3 and Fig. 3). For patients with LNR of 0.01–0.149 after PCT, an ATE of 9.4 months (95% CI 2.3, 16.5) was predicted by the IPWRA-based estimator.

Sensitivity Analyses

Postoperative chemotherapy remained associated with longer OS than observation only in patients with a LNR of 0.01–0.149 (or 1–2 nodes positive) who received PCT in the 5 sensitivity analyses (Supplemental Table 3). Postoperative chemotherapy was associated with higher overall mortality in patients with ≥ 3 nodes positive and when limited to patients with LNR ≥ 0.15 who had ≥ 11 nodes examined.

Discussion

In this observational study using the 2006–2014 NCDB, PCT was used in 47.6% of patients, and utilization of PCT doubled over these 9 years. PCT was associated with a higher rate of node positivity and a higher LNR despite being used less often than PCRT in cT4 tumors, confirming previous single-center studies.[18–20] Postoperative chemotherapy was associated with longer OS in patients with a LNR of 0.01–0.14 (or 1–2 nodes positive) after PCT, but there were no significant differences in OS in node-negative patients and those with LNR ≥ 0.15 after PCT. Postoperative chemotherapy was not associated with longer OS in patients who received PCRT, regardless of LNR.

The increase in PCT utilization starting in 2011 coincides with early reports of FOLFIRINOX in the BR setting and the 2011 RCT demonstrating efficacy in the metastatic setting.[35–37] PCT was used less in patients with comorbidities, which could reflect hesitance to use FOLFIRINOX in frail patients given its toxicities.[37] The regional variation in PCRT utilization may reflect institutional variation, as some institutions use radiation in over 90% of preoperatively treated patients,[12,18,38] while others use it infrequently.[13,19] Finally, cT4 tumors were more likely to receive PCRT, making the lower rate of node positivity in PCRT patients even more notable.

Our results support the idea that PCRT is more effective at sterilizing lymph nodes than PCT. In a study of 472 patients, Cloyd et al. found that absence of radiation was associated with a higher rate of node positivity (no radiation 81.5%, hypofractionated radiation 58.9%, and standard fractionation 46.2%; $P < 0.01$) and higher LNR.[18] However, only 27 patients (5.7%) received PCT due to institutional preference for PCRT.[18,39] Kim reported node positivity rates in a study of 26 BR patients treated with preoperative FOLFIRINOX ± radiation.[19] Node positivity occurred in 9/22 patients (40.9%) who received FOLFIRINOX alone vs. 0/4 who received FOLFIRINOX with radiation.[19] Hackert reported that 38/76 patients (50.0%) resected after PCT (FOLFIRINOX) were node-positive compared to 63/150 (42.3%) after PCRT.[20] Similarly, single-arm, phase II trials of PCT without radiation reported node positivity in 57–79%.[40–42] Our study confirms

Table 2 Multinomial logistic regression analysis of factors associated with elevated lymph node ratio

	LNR 0.01–0.149 RR (95% CI)	LNR ≥ 0.15 RR (95% CI)
Sex (Ref female)		
Male	0.92 (0.83, 1.02)	**1.25 (1.09, 1.44)**
Cancer history (Ref no)	0.98 (0.86, 1.13)	0.87 (0.72, 1.05)
Urban/rural status (Ref Metropolitan		
Urban	1.12 (0.98, 1.29)	1.02 (0.84, 1.24)
Rural	**1.40 (1.03, 1.92)**	1.32 (0.86, 2.02)
Unknown	**1.32 (1.03, 1.68)**	0.89 (0.59, 1.34)
Census division (Ref South Atlantic)		
New England	0.82 (0.60, 1.11)	0.94 (0.66, 1.34)
Mid-Atlantic	0.99 (0.85, 1.16)	1.04 (0.85, 1.28)
East NC	0.97 (0.83, 1.13)	0.90 (0.73, 1.12)
East SC	1.11 (0.85, 1.46)	1.12 (0.79, 1.58)
West NC	0.97 (0.80, 1.19)	0.94 (0.72, 1.22)
West SC	1.11 (0.87, 1.41)	1.00 (0.73, 1.37)
Mountain	0.90 (0.66, 1.24)	0.84 (0.56, 1.28)
Pacific	1.07 (0.88, 1.30)	0.99 (0.77, 1.28)
Tumor location (Ref head)		
Body	1.07 (0.87, 1.30)	**0.52 (0.36, 0.76)**
Tail	1.09 (0.85, 1.40)	**0.61 (0.41, 0.93)**
Overlapping/NOS	**1.25 (1.07, 1.46)**	**0.68 (0.51, 0.89)**
Clinical T stage (Ref cT3)		
cT1	1.01 (0.79, 1.28)	0.90 (0.64, 1.26)
cT2	1.11 (0.98, 1.25)	1.09 (0.93, 1.29)
cT4	0.94 (0.80, 1.11)	0.89 (0.71, 1.22)
cTX (unknown)	0.92 (0.67, 1.27)	1.36 (0.96, 1.91)
Clinical N stage (Ref cN0)		
cN1	**1.47 (1.32, 1.64)**	**1.61 (1.40, 1.86)**
cNX (unknown)	**1.36 (1.02, 1.82)**	1.21 (0.82, 1.80)
Preoperative therapy (Ref preoperative chemoradiation)		
Preoperative chemotherapy	**1.16 (1.04, 1.30)**	**2.04 (1.74, 2.39)**
Lymph nodes examined (Ref 7–11)		
12–17	**1.37 (1.12, 1.66)**	**0.84 (0.70, 0.998)**
18–23	**1.91 (1.57, 2.32)**	**0.73 (0.59, 0.89)**
≥ 24	**2.35 (1.95, 2.82)**	**0.68 (0.56, 0.83)**
Year of diagnosis (Ref 2006–2008)		
2009–2011	1.03 (0.84, 1.26)	0.91 (0.71, 1.16)
2012–2014	1.05 (0.87, 1.28)	0.92 (0.73, 1.17)

This table shows the results of a multinomial (polytomous) logistic regression model. The outcome variable, lymph node ratio (LNR), has three categories (0, 0.1–0.14, and ≥ 0.15). The base (referent) outcome was a LNR of 0, which is not shown. Significance for bold values is $P < 0.05$

LNR lymph node ratio, *RR* risk ratio, *CI* confidence interval, *Ref* referent, *NC* North Central, *SC* South Central, *NOS* not otherwise specified

these observations in a national cohort. The disparate rates of node positivity after PCT and PCRT (approximately 60 and 40%, respectively) suggest that nodal status has different meanings after PCT vs. PCRT. Specifically, a given number of positive nodes may signify more recalcitrant disease after PCRT (vs. PCT). Studies have also reported higher rates of primary tumor response[18,19,39] and lower rates of locoregional recurrence after PCRT.[18] The ongoing ALLIANCE A021501 trial, which is comparing 8 cycles modified FOLFIRINOX vs. 7 cycles followed by hypofractionated radiation for BR PDAC, may further clarify the additive effect of radiation in addition to modern chemotherapy on nodal status.[43,44]

Table 3 Summary of results of multivariable Cox models and inverse propensity weighted models examining the association between postoperative chemotherapy and overall survival

	Multivariable Cox models	IPW Cox models	IPWRA-based estimator of potential outcome means and ATE		
	HR (95% CI)	HR (95% CI)	Mean OS in months if all untreated (95% CI)	Mean OS in months if all treated (95% CI)	ATE in months (95% CI)
Patients who received preoperative chemotherapy					
LNR 0 (*N* = 631/621)	0.97 (0.75, 1.25)	1.00 (0.77, 1.29)	50.1 (43.6, 56.5)	48.1 (40.8, 55.5)	− 1.9 (− 11.7, 7.8)
LNR 0.01–0.149 (*N* = 487/452)	**0.64 (0.48, 0.84)**	**0.72 (0.55, 0.94)**	33.4 (29.2, 37.6)	42.8 (36.8, 48.8)	**9.4 (2.3, 16.5)**
LNR ≥ 0.15 (*N* = 363/359)	0.98 (0.74, 1.30)	0.86 (0.66, 1.13)	28.2 (25.0, 31.3)	30.8 (26.6, 35.1)	2.7 (− 2.5, 7.9)
Patients who received preoperative chemoradiation					
LNR 0 (*N* = 995/971)	0.91 (0.75, 1.10)	0.99 (0.81, 1.20)	43.8 (40.5, 47.2)	42.7 (38.1, 47.2)	− 1.2 (− 6.8, 4.5)
LNR 0.01–0.149 (*N* = 383/368)	0.96 (0.72, 1.27)	0.91 (0.70, 1.19)	35.1 (30.3, 39.9)	38.9 (30.9, 46.8)	3.8 (− 5.5, 13.1)
LNR ≥ 0.15 (*N* = 194/174)[a]	1.19 (0.82, 1.71)	1.25 (0.87, 1.78)	27.6 (22.8, 32.4)	23.6 (19.9, 27.4)	− 3.9 (− 10.0, 2.2)

Bold values for HR (95% CI) in the multivariable, IPW Cox models, and the ATE (95% CI) in the IPW-based estimator of ATE represents significance at $P < 0.05$. The first *N* for each survival cohort indicates the number of patients included in the multivariable Cox model. The second smaller *N* indicates the number included in the IPW Cox models and the IPW-based estimator of ATE. The second *N* is smaller because some patients in each cohort were excluded because the assumption of common support was not satisfied

IPW inverse propensity weighted, *IPWRA* inverse probability weighted regression adjustment, *ATE* average treatment effect, *HR* hazard ratio, *CI* confidence interval, *LNR* lymph node ratio

[a] The variable cN status was omitted in this cohort for the IPW model because propensity score balance could not be achieved with it included

Patients who received PCT had higher rates of postoperative chemotherapy than PCRT patients (45.4% vs. 30.1%), and postoperative chemotherapy was utilized most often in patients with a LNR of 0.01–0.149 after PCT and PCRT. The lower utilization of postoperative chemotherapy in patients with a prolonged LOS and among readmitted patients in the PCT cohort recapitulates what was observed after upfront resection: complications decrease the likelihood of postoperative treatment.[45,46]

This is the first study to specifically evaluate whether postoperative chemotherapy is associated with longer OS in patients who received PCT without radiation. We observed a consistent association between postoperative chemotherapy and longer OS among patients with a LNR of 0.01–0.149 (or 1–2 nodes positive) after PCT, but no differences in OS among node-negative patients and those with a LNR ≥ 0.15 (or ≥ 3 nodes positive). In the Roland study, all patients received PCRT.[15] In Barnes' study, only 37 patients (16%) received PCT without radiation.[16] Although the previous NCDB analysis probably included a similar distribution of patients treated with PCT, analyses were not stratified by preoperative therapy type.[17] Due to the Roland and Barnes studies, we hypothesized that patients with LNR of 0.01–0.149 were an intermediate-risk group that would benefit from postoperative chemotherapy.[15,16] As articulated by Roland, patients with a persistently high LNR after preoperative therapy likely have adverse tumor biology, and they may be less likely to benefit from further cytotoxic therapy.[15] Importantly, our finding that postoperative chemotherapy was not associated with longer OS in patients with a high nodal disease burden is supported by the two previous single-center studies on this topic even though those studies did not separately analyze patients who received PCT. In the study by Roland et al., postoperative chemotherapy was not associated with longer OS in patients with a LNR ≥ 0.15.[15] In the study by Barnes et al., postoperative chemotherapy was not associated with longer OS in patients with ≥ 4 positive nodes while it was in those with 1–3 positive nodes.[16] As recognized by the modification of the N stage classification in the eighth edition AJCC staging system, patients with numerous positive nodes have a worse prognosis than those with a minimal burden of nodal disease,[47] and these data suggest that postoperative chemotherapy is not associated with longer OS in patients with a high burden of nodal disease after PCT. Conversely, given that patients are rendered node-negative less often by PCT, node-negative patients after PCT may represent a group who have already had such a good response that they are less likely to benefit from more chemotherapy.

We advise cautious interpretation of our finding that postoperative chemotherapy was not associated with longer OS after PCRT, regardless of LNR. It is logical to hypothesize that postoperative chemotherapy would be more important for patients who received PCRT without iCT, but our data do not support this hypothesis. NCDB variables do not permit *definitive* differentiation of patients who received PCRT alone (i.e., preoperative radiation with a fluoropyrimidine or gemcitabine as a radiosensitizer) from those who received PCRT after iCT. We attempted to exclude patients who

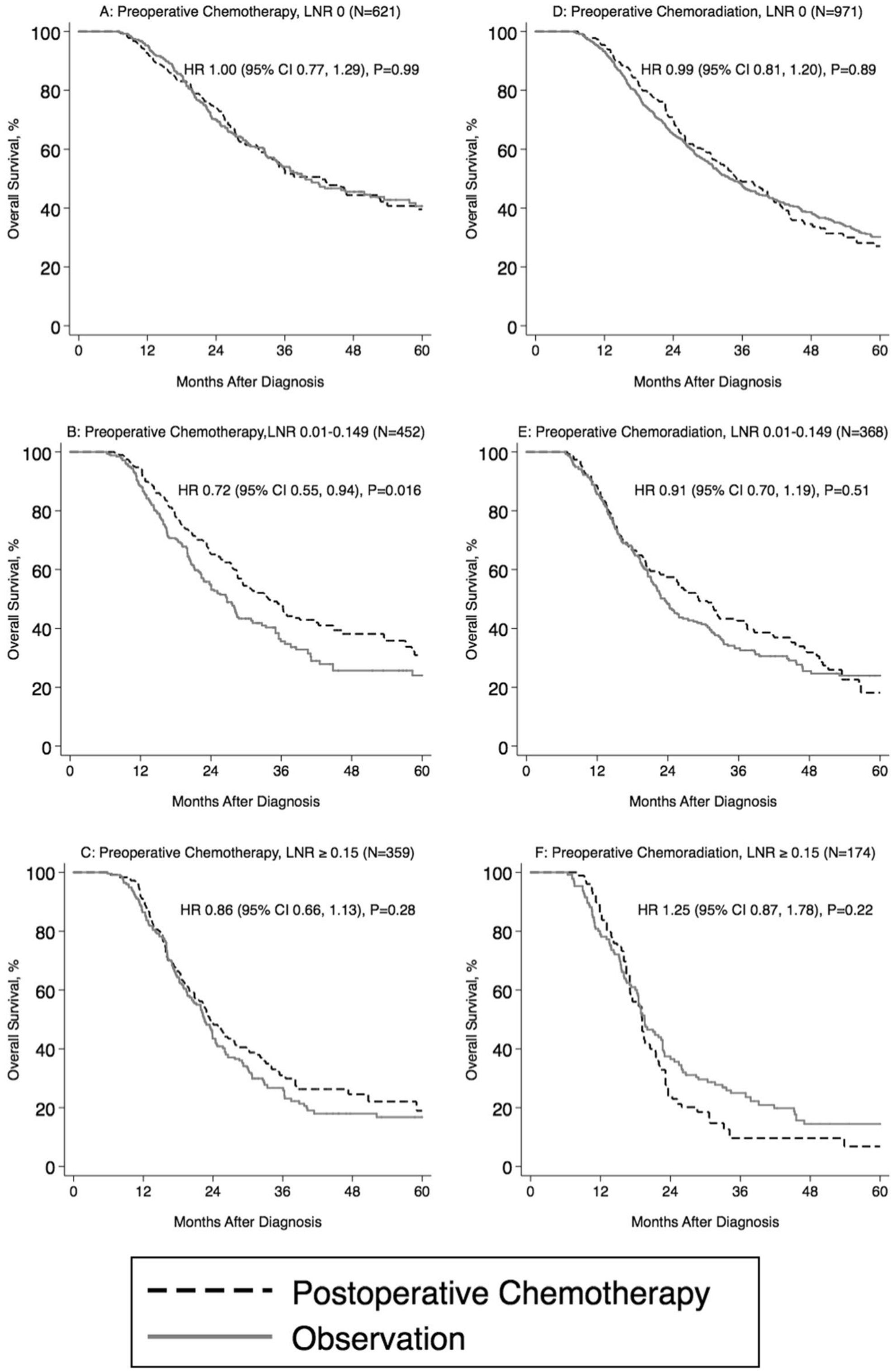

Fig. 3 Inverse propensity weighted survival curves stratified by use of postoperative chemotherapy

received iCT in Sensitivity Analysis 5, but this also required excluding 141 patients, and the LNR-stratified cohorts were small. Contrarily, Roland's and Barnes' studies seem to signal that some node-negative and/or LNR 0.01–0.149 patients after PCRT *do* benefit from postoperative chemotherapy.[15,16] In Roland's study, 30/214 patients (14.0%) with an LNR < 0.15 (63% node-negative) received postoperative therapy, which was associated with longer OS.[15] In their study, 49% of patients received iCT before PCRT.[15] In Barnes' study, 64/92 node-positive patients (69.6%) received postoperative chemotherapy, which was associated with longer OS.[16] In their study, 50% of patients received PCRT after iCT, 34% received

PCRT alone, and 16% received PCT.[16] Notably, a secondary analysis showed that this survival benefit was limited to patients with one to three positive nodes.[16] Future studies should stratify patients who received PCRT by whether iCT was given. Whether postoperative chemotherapy is associated with longer OS after PCRT for some subgroups remains a question without a definitive answer.

A secondary analysis of ESPAC-3 found that completion of 6 cycles of chemotherapy was associated with longer OS than 1–5.[48] A single-center analysis of 522 patients found that completion of ≥ 6 cycles, whether preoperative, postoperative, or both, was associated with longer OS than < 6 cycles in any sequence.[49] Furthermore, patients who completed 6 cycles of chemotherapy, with some before surgery and some after, had similar OS to patients who completed 6 cycles postoperatively.[49] Ideally, future studies on postoperative chemotherapy after preoperative therapy will stratify results by number of preoperative cycles.

Several limitations must be considered when interpreting our results. Most importantly, we could not separately analyze by or control for chemotherapy regimen, number of cycles, or changes between regimens. Second, the rate of PCRT (vs. PCT) was higher in patients that were excluded for having < 7 nodes examined. This could have biased results, but these patients did not have adequate nodal sampling to address our study objectives. Third, although more patients treated with PCRT had cT4 tumors, it is possible that patients with more advanced disease, which is not fully reflected by the clinical T and N stage, were selected for PCT. If patients who received PCT had more advanced disease that was unmeasured, this could have accounted for their higher LNR. Fourth, our sensitivity analysis of patients who received PCRT without iCT is limited by the number of patients with missing data and the fact that NCDB variables do not *definitively* specify whether iCT was given. Fifth, we did not stratify patients by whether they received postoperative radiation in addition to chemotherapy. Some of the treatment effect attributed to postoperative chemotherapy could be due to radiation. Sixth, in observational research, there is always a trade-off between using strict exclusions to define a homogenous population and generalizability. We tried to strike a reasonable balance, but it is possible that different exclusions could change results. Finally, we attempted to control for confounding by indication using IPW. PS methods require the assumption that treatment decisions are random after conditioning on available covariates (i.e., conditional exchangeability).[50] Since empiric verification of this assumption is impossible, we cannot guarantee the absence of indication bias.

In conclusion, utilization of PCT for preoperative treatment of PDAC has increased since 2010, and PCT is associated with higher node positivity rates and higher LNRs. Postoperative chemotherapy was consistently associated with a meaningful survival benefit in patients with a LNR of 0.01–0.149 after PCT. While these results should not be viewed as practice-changing given limitations of all analyses that use the NCDB to estimate treatment effects, they do corroborate the observation that pathologic lymph node status may be useful in selecting patients for postoperative chemotherapy after preoperative treatment.[15,16] Future studies using more granular data sources should separately analyze patients treated with PCRT without iCT and should stratify results by number of cycles of preoperative chemotherapy. While a RCT addressing these questions would be ideal, a retrospective, multi-institutional study with strict inclusions and definitions might be a more readily achievable way to gain further insights.

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Compliance with Ethical Standards

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