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ORIGINAL ARTICLE

Role of lymphadenectomy, adjuvant chemotherapy, and treatment at high-volume centers in patients with resected pancreatic cancer—a distinct view on lymph node yield

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Abstract

Purpose While the importance of lymphadenectomy is well-established for patients with resectable pancreatic cancer, its direct impact on survival in relation to other predictive factors is still ill-defined.

Methods The National Cancer Data Base 2006–2015 was queried for patients with resected pancreatic adenocarcinoma (stage IA–IIB). Patients were dichotomized into the following two groups, those with 1–14 resected lymph nodes and those with ≥ 15. Optimal number of resected lymph nodes and the effect of lymphadenectomy on survival were assessed using various statistical modeling techniques. Mediation analysis was performed to differentiate the direct and indirect effect of lymph node resection on survival.

Results A total of 21,912 patients were included; median age was 66 years (IQR 59–73), 48.9% were female. Median number of resected lymph nodes was 15 (IQR 10–22), 10,163 (46.4%) had 1–14 and 11,749 (53.6%) had ≥ 15 lymph nodes retrieved. Lymph node positivity increased by 4.1% per lymph node up to eight examined lymph nodes, and by 0.6% per lymph node above eight. Five-year overall survival was 17.9%. Overall survival was better in the ≥ 15 lymph node group (adjusted HR 0.91, CI 0.88–0.95, $p < 0.001$). On a continuous scale, survival improved with increasing LNs collected. Patients who underwent adjuvant chemotherapy and were treated at high-volume centers had improved overall survival compared with their counterparts (adjusted HR 0.59, CI 0.57–0.62, $p < 0.001$; adjusted HR 0.86, CI 0.83–0.89, $p < 0.001$, respectively). Mediation analysis revealed that lymphadenectomy had only 18% direct effect on improved overall survival, while 82% of its effect were mediated by other factors like treatment at high-volume hospitals and adjuvant chemotherapy.

Discussion While higher number of resected lymph nodes increases lymph node positivity and is associated with better overall survival, most of the observed survival benefit is mediated by chemotherapy and treatment at high-volume centers.

Keywords Pancreatic cancer · Lymph node · Mediation analysis · National Cancer Data Base · Surgery · Survival

Rene Warschkow and Catherine Tsai contributed equally to this work.

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Introduction

Pancreatic cancer is a lethal disease and is currently the fourth leading cause of cancer-related mortality in the Western world [1]. Due to its often late presentation, the majority of pancreatic cancer patients harbor metastatic disease at the time of diagnosis (~ 50%) while about 30% of the patients have locally advanced disease that preclude them from having surgical resection [2, 3]. Even for patients with surgically resectable disease, long-term survival remains poor with 5-year survival reported to be 5% and median survival times of 28–54 months [2, 4–6]. However, for such patients with locally confined disease, surgical resection in combination with systemic chemotherapy remains the only intervention proven to prolong survival with the potential for cure, and is the mainstay of treatment [2].

Adequate lymphadenectomy during pancreatectomy is associated with better local disease control, provides prognostic information, and is associated with improved long-term survival in patients with pancreatic adenocarcinoma [7]. However, there is still debate about the extent of adequate lymphadenectomy as well as its prognostic impact despite insights from five performed randomized controlled trials [8–13]. Most studies base their recommendations on a solitary threshold of harvested lymph nodes and suggest harvesting a minimum retrieval of 11–16 lymph nodes during lymphadenectomy [14–19] while one study showed improvement in overall survival with each additionally collected lymph node [20].

The extent of lymphadenectomy is one of many factors influencing survival outcomes after pancreatic cancer resection. However, when variables associated with survival are taken altogether, the degree to which lymphadenectomy has a direct therapeutic effect is still unclear. Causal mediation analysis is a concept first introduced in the field of psychology that allows exploration of causal mediation effects of exposure variables and outcomes of interest [21]. Only recently, mediation analysis methodology was expanded to examine the underlying mechanisms with direct and indirect natural effects on survival outcomes [22, 23].

Since then, mediation analyses have been proposed in evaluating the impact of various risk factors on developing cancer [24, 25]. Various statistical modeling techniques were used on a large cancer database to further explore the impact of lymphadenectomy on overall survival in resected pancreatic cancer patients. Specifically, we aimed to further explore the direct degree of this effect on overall survival in relation to other well-known predictors such as hospital volume, treatment with chemotherapy, age at diagnosis, Charlson-Deyo score, and tumor size. Such an analysis is found to help scale the direct impact of lymphadenectomy in relation to other predictive factors and assist in decision-making throughout the complex treatment pathway of patients with resectable pancreatic cancer.

Methods

Study population

The study was approved by the Duke Institutional Review Board. This is a retrospective cohort study of pancreatic cancer patients using the National Cancer Data Base (NCDB) from the USA. The NCDB is sponsored by the American College of Surgeons and the American Cancer Society and gathers hospital registry data from more than 1500 academic and community centers accredited by the Commission on Cancer. It is estimated to represent approximately 70% of all newly diagnosed cancer cases nationwide and contains nearly 34 million patient records [26].

The database was queried for all patients who were 18 years or older with histologically confirmed adenocarcinoma of the pancreas (histology codes: 8021, 8050, 8140, 8144, 8211, 8255, 8260, 8261, 8263, 8290, 8310, 8323, 8440, 8441, 8453, 8460, 8470, 8471, 8480, 8481, 8490, 8500, 8503, 8521–8523, 8550, 8551, 8560, 8570, 8574, and 8576), who had a tumor stage IA–IIB, and underwent a pancreaticoduodenectomy (PD), total pancreatectomy, or distal pancreatectomy between 2006 and 2015 (Fig. 1). Stage III pancreatic cancers were not included into the study because it is impossible to distinguish between cancer that is locally advanced versus borderline resectable, which would be treated differently. We included only patients that had a clear indication for surgery. Patients with pancreatic cancer following other malignancy, unknown grade, unknown resection margin, and unknown radiation or systemic therapy status were excluded.

Patient and tumor characteristics were included and grouped as follows: gender (male, female), race (white, black, other/unknown), age (< 60, 60–69, and 70 + years), Charlson-Deyo score (0, 1, 2 +), year of diagnosis (2006–2009, 2010–2012, 2013–2015), tumor stage (IA, IB, IIA, IIB), surgery type (PD, distal pancreatectomy, total pancreatectomy), tumor size, tumor location (head, body/tail), tumor grade (G1, G2, G3/4), resection margin (R0, R positive), chemotherapy (none, adjuvant, neoadjuvant), or radiation therapy (no, yes), and volume of the center at which surgery was performed. Given large discrepancies in the definition of "high-volume centers," this was defined as centers in which more than 30 pancreatectomy cases overall were performed per year [27, 28]. This dichotomizes hospital volumes into the lower two-thirds and the highest third of cases per year.

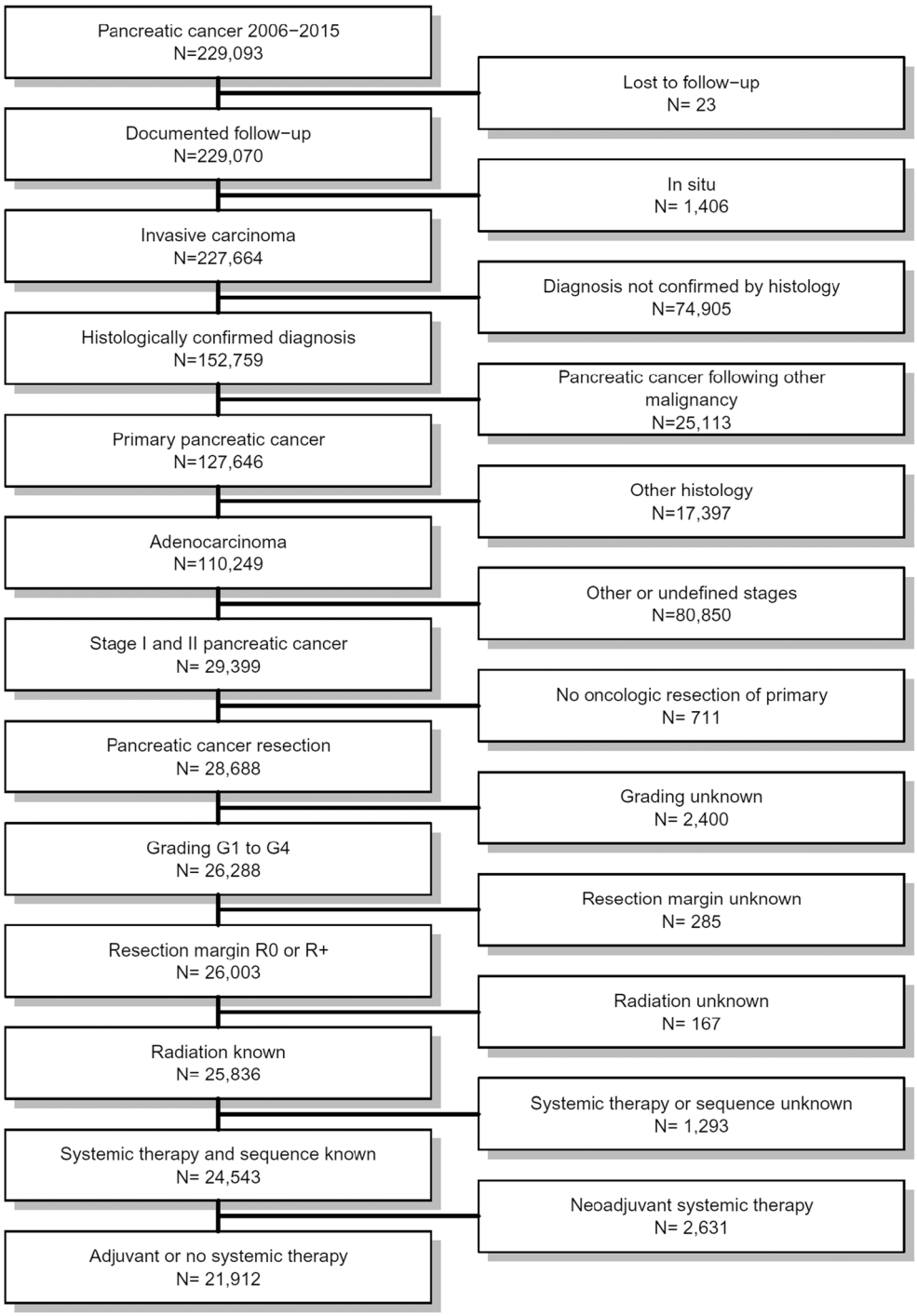

Fig. 1 Patient selection

Statistical analysis

The patient dataset was dichotomized into two subsets; lymph node yield of either 1–14 lymph nodes or ≥15 based on several prior outcomes studies suggesting that the minimum number of examined lymph node should be between 11 and 16 [16–19]. Logistic regression analyses yielding odds ratios were performed to assess the bias in the lymph node yield [29]. Multivariable adjusted cox regression analyses were performed to assess overall survival differences with number of resected lymph nodes as a binary outcome including all pertinent patient and tumor characteristics as potential confounders [30]. Overall survival was also assessed using propensity score weighted and matched analyses as well as near-far matching to account for unmeasured bias [31, 32]. Correlation analysis, joinpoint regression and LOESS regression were performed to assess necessary number of

lymph nodes to get at least one positive lymph node [33, 34]. To account for number of resected lymph nodes as a continuous measure, univariate, multivariable adjusted, and propensity score adjusted analyses were performed using number of resected lymph nodes on a continuous scale. Spline plots were created to represent relative death rate (%) per one incremental lymph node collected. All analyses were performed on the overall cohort and stratified by tumor stage. Finally, a mediation analysis was performed to measure the independent relative effect of number of retrieved lymph nodes on overall survival in relation to other assessed variables. The mediation analysis was modeled by multivariate additive regression trees with a Bernoulli distribution to deal with nonlinear relationships, hierarchical data structures, and a mixture of quantitative and qualitative variables fully considering interrelationships of the data [24].

Results

Patient characteristics and predictors of ≥ 15 LNs

A total of 21,912 patients were included in this study. Median age was 66 years (IQR 59 to 73 years), 10,705 (48.9%) were female. Median number of resected lymph nodes was 15 (IQR 10 to 22), 46.4% had 1–14 LN and 53.6% had ≥ 15 lymph node retrieved. After multivariable adjustment, patients with tumor stage IIB, tumors located in the head of the pancreas, patients undergoing PD and total pancreatectomy, patients with R0 resections, patients who got adjuvant chemotherapy, patients operated at high-volume centers, female patients, white patients, patients < 60 years old, and later year of diagnosis compared with their counterparts were more likely to have ≥ 15 lymph nodes examined (Table 1). There was an inverse relationship between lymphadenectomy and short-term outcomes. The 30-day and 90-day mortality were 2.2% and 4.6% for patients with lymphadenectomy of ≥ 15 lymph nodes compared with 3.5% and 6.8% in patients with only 1–14 lymph nodes removed ($p < 0.001$).

Positive lymph node yield compared with number of sampled lymph nodes

The rate of lymph node positivity was highly correlated with the number of retrieved lymph nodes ($r = 0.96$, $p < 0.001$). Based on joinpoint regression, the likelihood of a positive lymph node increased by 4.1% per lymph node up to eight examined lymph node and was 0.6% per lymph node examined above eight ($p < 0.001$) [33].

Overall survival analysis based on lymph node yield as a dichotomous predictor (1–14 and ≥ 15 LN)

Overall 5-year survival was 17.9% (95% CI 17.3 to 18.6%). In unadjusted and in multivariable adjusted analyses, overall survival for patients with ≥ 15 lymph nodes was better compared with their counterparts (Table 2). In multivariable analysis, patients with lower tumor stage, with tumor location in the pancreatic head, patients undergoing distal pancreatectomy, with lower tumor grades, with R0 resections, who received chemotherapy or radiation therapy as well as those treated at high-volume centers had better outcomes compared with their counterparts. Additionally, a survival benefit was observed for female patients, white patients, patients < 60 years old, with lower Charlson-Deyo score, and patients who were diagnosed in later years. When applying propensity score matched and weighted methods to the pre-defined cutoff of ≥ 15 lymph nodes collected, overall survival was improved in the overall cohort. Causal inference by near-far matching also confirmed improved overall survival for patients with ≥ 15 lymph nodes collected.

Results for lymph node as a continuous measure—spline plots

Additional analyses were performed using lymph node yield as a continuous variable. Spline plots were created after univariate, multivariable, and propensity score adjusted analyses (Fig. 2). This almost uniformly showed continued improvement (decrease in relative death rate) with an increasing number of collected lymph nodes.

Results from the mediation analysis

To further explore the improvement of overall survival with an increasing number of collected lymph nodes, a mediation analysis was performed. According to this analysis, the direct effect of lymphadenectomy (on a continuous scale) on overall survival was 18% while 82% of the effect of the extent of lymphadenectomy was mediated by other variables. Higher hospital volume and performance of adjuvant chemotherapy were mainly responsible for the positive effect of the extent of lymphadenectomy on overall survival and accounted for 40% and 37% of this effect. Later year of diagnosis accounted for 11% of the effect and age at diagnosis explained 12%. Factors such as tumor location, gender, race, or the Charlson-Deyo score did not relevantly contribute to the effect.

Subgroup analyses

The entire analysis was repeated for all subgroups by the baseline variables. Uniformly, overall survival was improved

Table 1 Patient demographics overall and grouped per number of lymph nodes (1–14, ≥15), univariate and multivariable adjusted predictors of at least 15 collected lymph nodes

Variable	Label	Descriptive			Logistic regression for collection of ≥ 15 LNs			
		Total ($N = 21,912$)	1–14 LN collected ($N = 10,163$)	≥ 15 LN collected ($N = 11,749$)	Univariate[A]		Multivariable[B]	
					OR (95% CI)	*P* value[C]	OR (95% CI)	*P* value[C]
Tumor stage	1A	841 (3.8%)	487 (4.8%)	354 (3.0%)	Reference	< 0.001	Reference	< 0.001
	1B	1303 (5.9%)	824 (8.1%)	479 (4.1%)	0.80 (0.67–0.95)		0.91 (0.76–1.10)	
	2A	4635 (21.2%)	2631 (25.9%)	2004 (17.1%)	1.05 (0.90–1.22)		0.99 (0.85–1.16)	
	2B	15,133 (69.1%)	6221 (61.2%)	8912 (75.9%)	1.97 (1.71–2.27)		1.79 (1.54–2.08)	
Surgery	PD	14,956 (68.3%)	6667 (65.6%)	8289 (70.6%)	Reference	< 0.001	Reference	0.035
	Distal pancreatectomy	2917 (13.3%)	1653 (16.3%)	1264 (10.8%)	0.62 (0.57–0.67)		0.88 (0.78–1.00)	
	Total pancreatectomy	4039 (18.4%)	1843 (18.1%)	2196 (18.7%)	0.96 (0.89–1.03)		1.05 (0.97–1.13)	
Tumor location	Head	17,753 (81.0%)	7808 (76.8%)	9945 (84.6%)	Reference	< 0.001	Reference	< 0.001
	Body/tail	4159 (19.0%)	2355 (23.2%)	1804 (15.4%)	0.60 (0.56–0.64)		0.69 (0.62–0.77)	
Tumor grade	G1	2119 (9.7%)	1078 (10.6%)	1041 (8.9%)	Reference	< 0.001	Reference	0.267
	G2	11,426 (52.1%)	5336 (52.5%)	6090 (51.8%)	1.18 (1.08–1.30)		1.02 (0.92–1.12)	
	G3/4	8367 (38.2%)	3749 (36.9%)	4618 (39.3%)	1.28 (1.16–1.40)		1.06 (0.96–1.18)	
Resection margin	R0	16,935 (77.3%)	7767 (76.4%)	9168 (78.0%)	Reference	0.005	Reference	< 0.001
	R positive	4977 (22.7%)	2396 (23.6%)	2581 (22.0%)	0.91 (0.86–0.97)		0.87 (0.81–0.93)	
Chemotherapy	None	6545 (29.9%)	3459 (34.0%)	3086 (26.3%)	Reference	< 0.001	Reference	< 0.001
	Adjuvant	15,367 (70.1%)	6704 (66.0%)	8663 (73.7%)	1.45 (1.37–1.54)		1.29 (1.20–1.38)	
Radiation	No	14,817 (67.6%)	6881 (67.7%)	7936 (67.5%)	Reference	0.800	Reference	0.253
	Yes	7095 (32.4%)	3282 (32.3%)	3813 (32.5%)	1.01 (0.95–1.07)		0.96 (0.90–1.03)	
Hospital volume per year	1–30	14,225 (64.9%)	7572 (74.5%)	6653 (56.6%)	Reference	< 0.001	Reference	< 0.001
	≥ 30	7687 (35.1%)	2591 (25.5%)	5096 (43.4%)	2.24 (2.11–2.37)		2.14 (2.01–2.27)	
Year of diagnosis	2006–2009	5265 (24.0%)	3065 (30.2%)	2200 (18.7%)	Reference	< 0.001	Reference	< 0.001
	2010–2012	7871 (35.9%)	3637 (35.8%)	4234 (36.0%)	1.62 (1.51–1.74)		1.52 (1.41–1.63)	
	2013–2015	8776 (40.1%)	3461 (34.1%)	5315 (45.2%)	2.14 (2.00–2.29)		1.99 (1.85–2.14)	
Age	< 60	5775 (26.4%)	2454 (24.1%)	3321 (28.3%)	Reference	< 0.001	Reference	< 0.001
	60–69	7613 (34.7%)	3411 (33.6%)	4202 (35.8%)	0.91 (0.85–0.98)		0.89 (0.83–0.95)	
	≥ 70	8524 (38.9%)	4298 (42.3%)	4226 (36.0%)	0.73 (0.68–0.78)		0.74 (0.69–0.80)	
Gender	Male	11,207 (51.1%)	5291 (52.1%)	5916 (50.4%)	Reference	0.012	Reference	< 0.001
	Female	10,705 (48.9%)	4872 (47.9%)	5833 (49.6%)	1.07 (1.02–1.13)		1.13 (1.07–1.19)	
Race	White	18,624 (85.0%)	8608 (84.7%)	10,016 (85.2%)	Reference	0.136	Reference	0.054
	Black	2260 (10.3%)	1047 (10.3%)	1213 (10.3%)	1.00 (0.91–1.09)		1.00 (0.91–1.10)	
	Other/unknown	1028 (4.7%)	508 (5.0%)	520 (4.4%)	0.88 (0.78–1.00)		0.85 (0.74–0.97)	
Charlson-Deyo score	0	14,123 (64.5%)	6486 (63.8%)	7637 (65.0%)	Reference	0.188	Reference	0.789
	1	5923 (27.0%)	2793 (27.5%)	3130 (26.6%)	0.95 (0.90–1.01)		0.98 (0.92–1.05)	
	≥ 2	1866 (8.5%)	884 (8.7%)	982 (8.4%)	0.94 (0.86–1.04)		1.02 (0.92–1.13)	

N (%) and odds ratio (OR) with 95% confidence intervals (CI) of Wald type [29]

[A] Univariate logistic regression analysis

[B] Multivariable logistic regression

[C] Likelihood ratio tests

LN, lymph node; *PD*, pancreaticoduodenectomy

Table 2 Overall survival analysis

Variable	Label	Univariate Cox regression[A] ($N = 21,912$)		Multivariate Cox regression[B] ($N = 21,912$)	
		HR (95% CI)	P value[C]	HR (95% CI)	P value[C]
Number of LNs collected	1–14	Reference	< 0.001	Reference	< 0.001
	≥ 15	0.92 (0.89–0.95)		0.91 (0.88–0.95)	
Tumor stage	1A	Reference	< 0.001	Reference	< 0.001
	1B	1.53 (1.36–1.73)		1.49 (1.32–1.69)	
	2A	1.93 (1.74–2.14)		2.01 (1.81–2.24)	
	2B	2.88 (2.61–3.18)		3.12 (2.81–3.47)	
Surgery	PD	Reference	< 0.001	Reference	0.016
	Distal pancreatectomy	0.87 (0.83–0.91)		0.91 (0.84–0.98)	
	Total pancreatectomy	1.03 (0.99–1.07)		1.00 (0.96–1.05)	
Tumor location	Head	Reference	< 0.001	Reference	0.024
	Body/tail	0.90 (0.87–0.94)		1.07 (1.01–1.14)	
Tumor grade	G1	Reference	< 0.001	Reference	< 0.001
	G2	1.46 (1.38–1.54)		1.38 (1.30–1.47)	
	G3/4	1.90 (1.79–2.02)		1.75 (1.65–1.87)	
Resection margin	R0	Reference	< 0.001	Reference	<0.001
	R positive	1.62 (1.56–1.67)		1.54 (1.48–1.60)	
Chemotherapy	None	Reference	< 0.001	Reference	< 0.001
	Adjuvant	0.62 (0.60–0.64)		0.59 (0.57–0.62)	
Radiation	No	Reference	< 0.001	Reference	< 0.001
	Yes	0.77 (0.75–0.80)		0.82 (0.79–0.85)	
Hospital volume per year	1–30	Reference	< 0.001	Reference	< 0.001
	≥ 30	0.89 (0.86–0.92)		0.86 (0.83–0.89)	
Year of diagnosis	2006–2009	Reference	< 0.001	Reference	< 0.001
	2010–2012	0.93 (0.89–0.96)		0.93 (0.89–0.97)	
	2013–2015	0.88 (0.85–0.92)		0.90 (0.86–0.94)	
Age	< 60	Reference	< 0.001	Reference	< 0.001
	60–69	1.05 (1.01–1.09)		1.04 (1.00–1.09)	
	≥ 70	1.26 (1.22–1.31)		1.16 (1.11–1.21)	
Gender	Male	Reference	0.001	Reference	< 0.001
	Female	0.95 (0.92–0.98)		0.95 (0.92–0.98)	
Race	White	Reference	< 0.001	Reference	< 0.001
	Black	1.03 (0.98–1.09)		1.07 (1.01–1.13)	
	Other/unknown	0.84 (0.78–0.91)		0.83 (0.76–0.90)	
Charlson-Deyo score	0	Reference	< 0.001	Reference	< 0.001
	1	1.10 (1.06–1.14)		1.09 (1.05–1.13)	
	≥ 2	1.32 (1.25–1.39)		1.28 (1.21–1.36)	
Variable	Label	PS matched and weighted Cox regression[D] ($N = 21,820$)		Near-far matching Cox regression[E] ($N = 12,746$)	
		HR (95% CI)	P value[C]	HR (95% CI)	P value[C]
Number of LNs collected	1–14	Reference	< 0.001	Reference	< 0.001
	≥ 15	0.87 (0.83–0.90)		0.90 (0.87–0.94)	

Hazard ratio (HR) with 95% confidence intervals (CI) of Wald type [30]

[A] Univariate Cox regression analysis

[B] Multivariable Cox regression analysis

[C] Likelihood ratio tests

[D] Full bipartite matching and weighting for potential confounders with stratification for year of diagnosis, analysis with sandwich variance estimator and with stratification for tumor stage after exclusion of 92 unmatched patients

[E] Near-far matching with matching of discouraged and encouraged hospitals after exclusion of 10,168 unmatched patients [31, 32]

LN, lymph node; *PD*, pancreaticoduodenectomy; *PS*, propensity score

when ≥ 15 lymph nodes were collected in univariable, multivariable, propensity score, and near-far matching adjusted analyses in all subgroups (Fig. 3). Additional mediation analyses were performed in the subgroups built by the type of operation. The survival benefit obtained by harvesting more lymph nodes was mediated by higher hospital volume and performance of chemotherapy in 39% and 42% in PD, in 33% and 42% in total pancreatectomy and in 29% and 15% in distal pancreatectomy, respectively.

Discussion

To the best of our knowledge, this is the first study analyzing the differential effect of the extent of lymphadenectomy compared with other components of treatment using mediation analyses among patients with resected pancreatic adenocarcinoma. Our findings are consistent with prior studies concluding that higher number of collected lymph nodes translates to an overall survival benefit

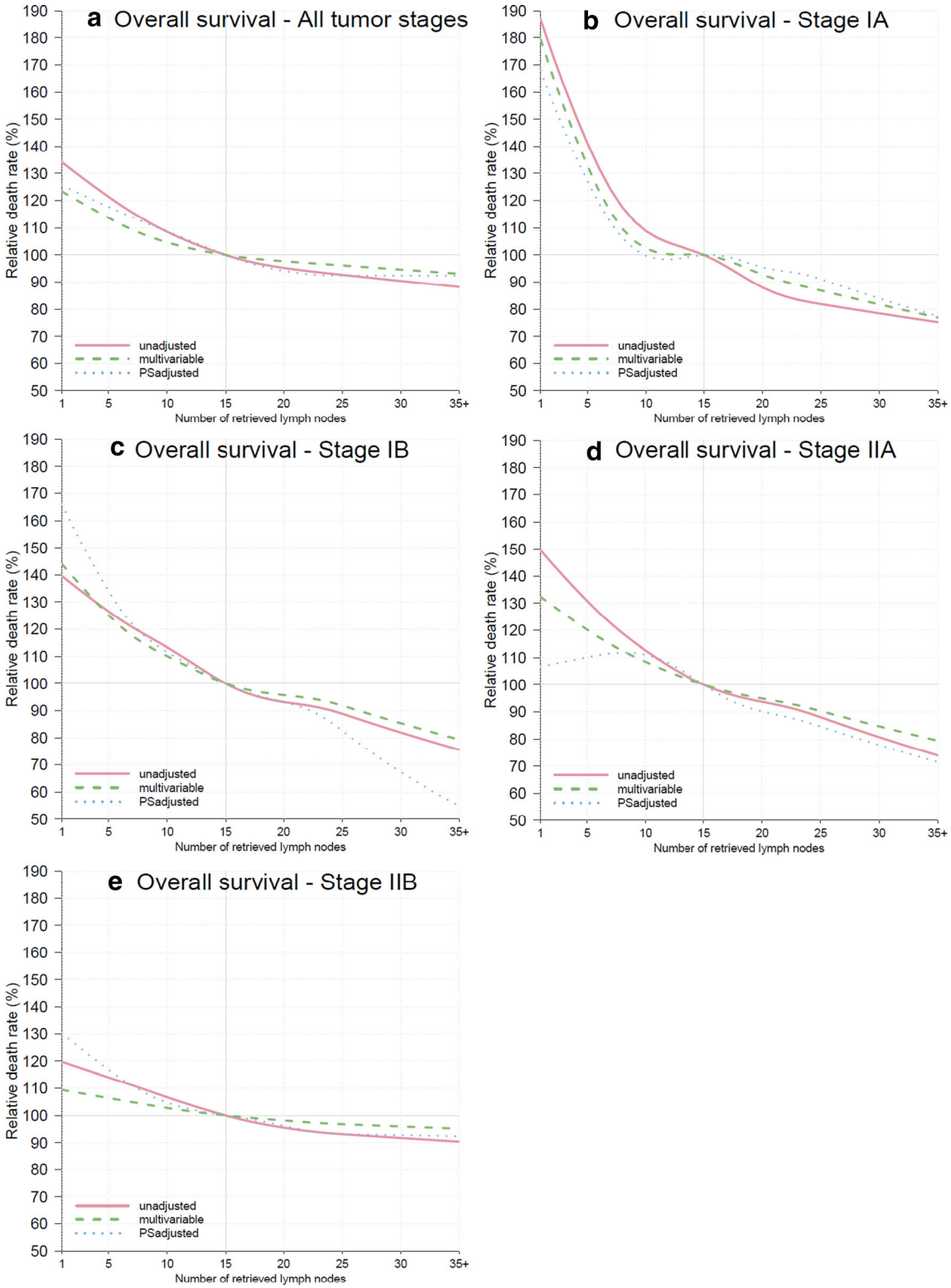

Fig. 2 Spline plots assessing relative death rate per number of retrieved lymph node stratified by tumor stage (A, all stages; B, 1A; C, 1B; D, 2A; E, 2B)

across most resectable tumor stages. This association was confirmed using statistical methods for adjustment, near-far matching and propensity score matching, and additionally in multiple subgroup analyses. Mediation analysis revealed the underlying mechanism: the beneficial effect of lymphadenectomy on survival is mostly explained by treatment at high-volume centers and performance of adjuvant chemotherapy.

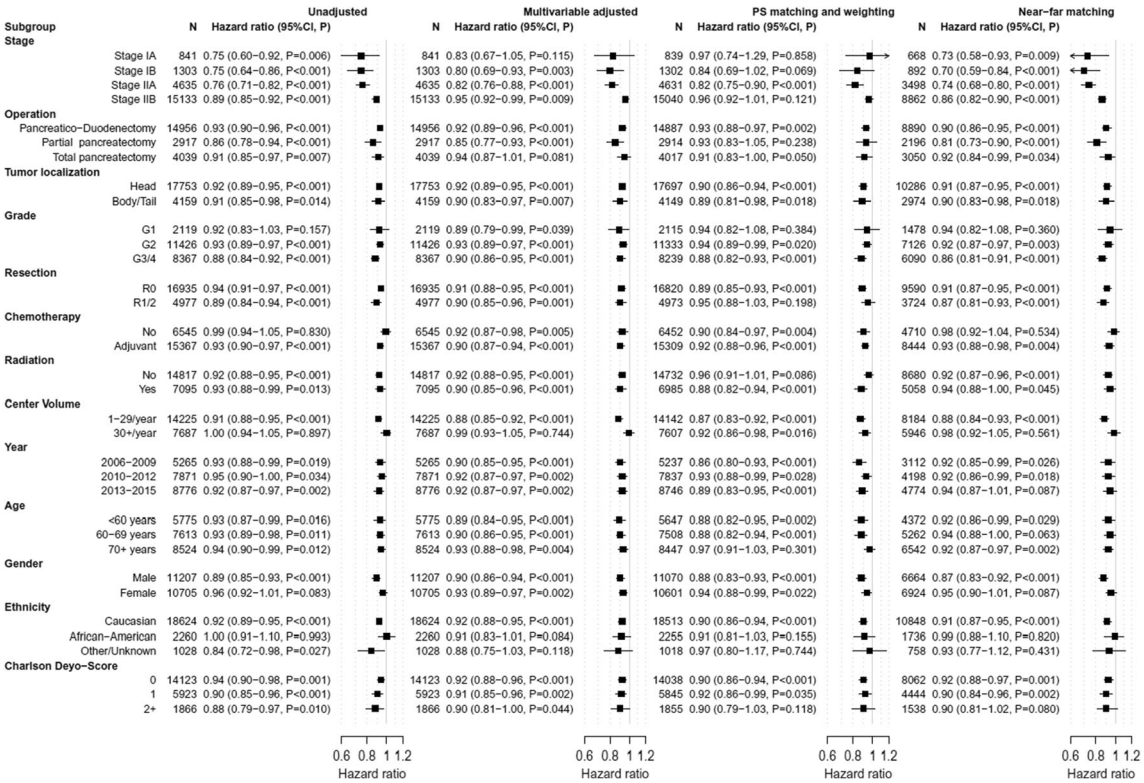

Fig. 3 Forest plot for subgroup analyses [30]

While it is unambiguous that pancreatic resection should be an integral part of any treatment among patients with resectable pancreatic cancer, the role of the extent of lymphadenectomy is still under debate. Several prior analyses of patients undergoing surgical resection of pancreatic adenocarcinoma have been performed to confirm the significance of lymphadenectomy. The importance of this concept has been adopted over the last decades. While based on an analysis using the Surveillance, Epidemiology, and End Results Program (SEER) database from 1973 to 2000, the median numbers of lymph nodes examined was only seven while in the present study, this number increased to 15 [16]. Current recommendations on minimal number of lymph node collection vary between 11 and 16 [8–13]. Clear cutoff recommendations are based on binomial analysis, which are difficult to apply to general clinical practice as it is inherently impossible to count resected lymph nodes during surgery and it implies that if less lymph nodes were sampled, the patient would experience worse results. Based on the results of this study, even after stratification into multiple patient and tumor characteristics, overall survival steadily improves with an increasing number of collected lymph nodes while any specific cutoff would suffer imprecision. As such, absolute number of collected lymph nodes was proposed as one of the quality measures for a high quality pancreatic cancer program [20]. However, the surgical collection of as many lymph nodes as possible must be counterbalanced by increased postoperative complications and decreasing quality of life with limited benefit for improved oncological long-term outcomes [9–13, 35, 36]. Therefore, extensive sampling of lymph nodes is recommended only in experienced hands with a well-established treatment team to minimize postoperative morbidity and to facilitate adjuvant treatment.

One prior study using NCDB helped to understand what constitutes an adequate lymphadenectomy. Contreras et al. found that patients who had more retrieved lymph nodes were more likely to have a classical PD rather than a pylorus-preserving PD, were more likely to have a negative margin resection, and more likely to be performed at academic institutions (mean 13.5 lymph nodes retrieved) compared with non-academic institutions (mean 11.9 lymph nodes retrieved), which was associated with better overall survival [20]. In addition to the overall number of collected lymph nodes, it has also been shown that the number of positive lymph nodes has prognostic value [37–40]. For instance, in a large and recent study done by Strobel et al., 811 patients underwent surgical resection for pancreatic cancer with an average lymph node retrieval of 24 lymph nodes [39]. They found that median survival was 33.2 months among patients without positive lymph nodes, 31.1 months for 1 positive lymph node, 26.1 months for 2–3 lymph nodes, 21.9 months for 4–7 positive lymph node, and 18.3 months in patients with 8 or more positive lymph nodes. However, while the number of positive lymph nodes was inversely associated with overall survival,

interestingly, the total number of collected lymph nodes had no prognostic impact on overall survival in this study from a single, very high-volume center.

While many studies highlight the importance of lymphadenectomy in the surgical treatment of pancreatic cancer, our study has the relevant added value of identifying reasons for this effect. Using mediation analyses, the direct and indirect effect size of the extent of lymphadenectomy on overall survival could be calculated. Our findings show that the degree to which lymph node retrieval on a continuous scale contributes directly to overall survival is only 18%. The indirect effect of the positive effect of extend of lymphadenectomy was mainly mediated by treatment at a high-volume center (40%) and application of adjuvant chemotherapy (37%). This highlights the difficulty of the discussion on lymph node retrieval among patients undergoing pancreatic resections as those factors are very closely interrelated. In other words, increasing the extent of lymphadenectomy without taking into consideration the importance of performing surgical resection at a high-volume center and without achieving high adjuvant chemotherapy rates will not most suitably increase survival. In the study performed by Strobel et al. [39], the number of resected lymph nodes did per se not impact survival which could be explained by our findings that this is significantly mediated by high-volume center and adjuvant chemotherapy, both of which is present at this institution. With only 29% of patients receiving adjuvant chemotherapy in our study compared with 84% in the study of Strobel et al., there is still significant room for improvement. It has been widely shown that adjuvant chemotherapy provides significant benefit [5, 41–45]. The focus on adjuvant chemotherapy might be even more impactful given that recent data show that adjuvant mFOLFIRINOX can achieve a median overall survival of 54 months compared with 35 months with Gemcitabine only [39]. Our results highlight the importance of adding systemic treatment to well-performed resections with adequate lymph node retrieval.

In addition, our results stress the importance of performing pancreatectomies at high-volume centers given its improved short-term and long-term outcomes and also its association with evaluating more lymph nodes [46–51].

However, surgery at high-volume centers is not only an independent factor for improving overall survival but also positively mediates the impact of the extent of lymphadenectomy. As such, further emphasis and effort should be placed on centralizing pancreatic cancer treatment given that this is one of the most influential factors to improve long-term outcomes among resectable pancreatic cancer patients [52, 53].

Despite NCDB being a large and valuable dataset, it has several constraints. In addition to the inherent limitation of the retrospective nature of this study, not all fields in the NCDB registry are uniformly populated, thus the analysis does not include all possible data points. The NCDB also includes data only from centers accredited by the CoC, thus data from all centers performing surgical resection of pancreatic cancer in the USA is not complete. Furthermore, the pathological evaluation of lymph nodes is also not standardized across centers and dependent on many factors including the perseverance of pathologists.

Conclusion

We conclude that among patients with resectable pancreatic cancer, increased lymph node retrieval leads to increased lymph node positivity and is associated with overall survival. However, the positive effect of the increasing number of collected lymph nodes is largely mediated by performance of adjuvant chemotherapy and resections at high-volume centers. These findings further stress that pancreatic resections should be performed at high-volume centers where surgical resections with adequate lymphadenectomy can be performed safely with interdisciplinary collaborations that allow high rates of adjuvant chemotherapy.

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Authors' contributions R.W, C.T, and M.W. participated in the conceptualization of the study; R.W. and M.W. worked on the methodology; R.W. participated in formal analysis and investigation; R.W, C.T, and M.W. participated in the writing of the original draft; S.E, N. K, B.S, D.N, B.G, and S.A.M reviewed and edited the manuscript; D.N, D.B, and M.W. provided the resources; and B.S, B.G, S.A.M, and D.B. were the ones who supervised.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This retrospective cohort study was approved by the Duke Institutional Review Board. This article does not contain any studies with human participants performed by any of the authors.

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