



## Examining the relationship between lymph node harvest and survival in patients undergoing colectomy for colon adenocarcinoma



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### ABSTRACT

**Background:** Current standards for lymph node harvest in colorectal cancer surgery may be inadequate. Higher lymph node yield may improve survival, but the number of lymph nodes needed to optimize survival is unknown. The objective of this study was to examine the relationship between lymph node yield and overall survival in patients undergoing colectomy for nonmetastatic colon adenocarcinoma.

**Methods:** The 2010 to 2014 National Cancer Database was queried for patients undergoing colectomy for nonmetastatic colon adenocarcinoma. Adjusted restricted cubic splines were used to model the nonlinear relationship between lymph node harvest and overall survival. Cox proportional hazard determined independent predictors of overall survival.

**Results:** A total of 261,423 patients were included. Restricted cubic splines demonstrated that the adjusted improvements in overall survival stabilized after 24 nodes. Patients were divided into: <12, 12 to 23, and  $\geq 24$  nodes. On survival analysis, patients with  $\geq 24$  nodes had better survival across all N stages compared to other groups ( $P < .001$ ). Lymph node harvest  $\geq 24$  nodes was independently associated with improved overall survival compared to 12 to 23 nodes (hazard ratio 0.82; 95% confidence interval, 0.80–0.85).

**Conclusion:** Lymph node harvest  $\geq 24$  nodes is associated with improved survival in colorectal cancer patients. These data may provide indirect evidence for a more extensive lymphadenectomy for colon cancer.

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### Introduction

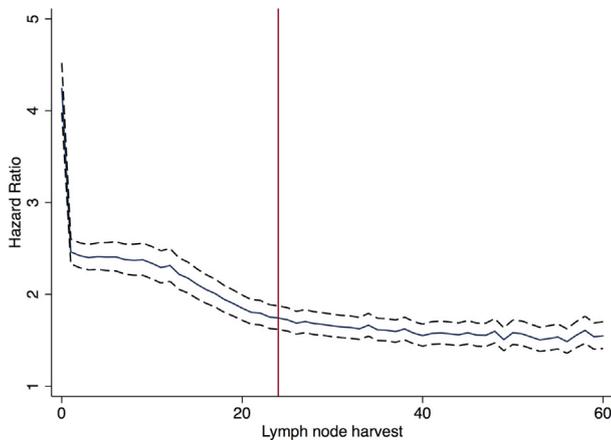
Appropriate lymphadenectomy is essential for final pathology staging and allows for the appropriate selection of colorectal cancer patients who may benefit from adjuvant systemic therapy following resection. The minimum number of lymph nodes examined per specimen required to provide accurate staging while limiting underdiagnosis of nodal involvement was determined by an expert committee in 1990.<sup>1</sup> Multiple studies reported a minimum of 12 to 18 lymph nodes required to accurately predict regional node negativity, but a cut-off value of 12 nodes was chosen since to correctly diagnose N0 disease 90% of the time.<sup>2,3</sup> This threshold was then integrated into the TNM classification and the National Comprehensive Cancer Network, American Joint

Committee on Cancer (AJCC) and College of American Pathologists guidelines have since continued to recommend the retrieval of at least 12 lymph nodes.<sup>2,4,5</sup>

However, more recently, several studies have reported that colorectal cancer patients with larger numbers of lymph nodes identified in the pathological specimen have improved overall survival (OS).<sup>6–8</sup> In fact, in those studies, higher lymph node harvest independently predicted better oncological outcomes, especially in stage III disease.<sup>6–8</sup> These data suggest that the current standards for lymph node harvest in oncologic resections for colon cancer may be inadequate, but this remains controversial from a therapeutic perspective.<sup>9</sup> Although several studies have suggested different sampling thresholds, the number of lymph nodes needed to optimize survival for nonmetastatic colon adenocarcinoma has not yet been clearly characterized.<sup>7</sup> Therefore, the objective of this study is to examine the relationship between the number of resected lymph nodes and OS in colorectal cancer patients undergoing colectomy for nonmetastatic disease.

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**Fig 1.** Restricted cubic spline plot demonstrating the non-linear relationship in the hazard ratio of overall survival against the total lymph node harvest for the whole cohort. The red line demonstrates where the slope plateaus and corresponds to 24 lymph nodes on the x-axis.

## Material and Methods

### Data source and study population

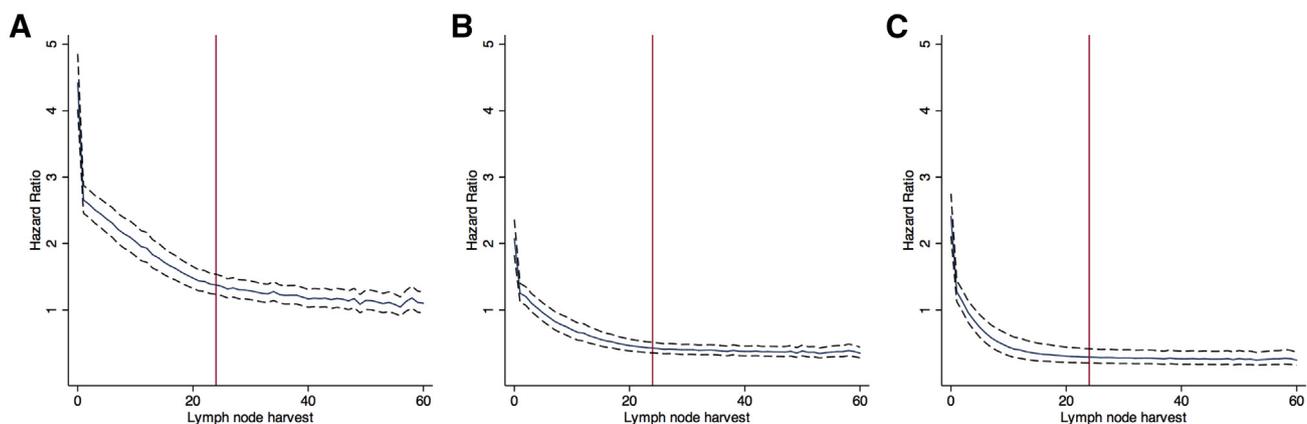
An analysis of the National Cancer Database (NCDB) 2010 to 2014 colon and rectosigmoid junction cancer participant user file was performed. The NCDB is the world's largest cancer dataset and is sponsored by the American College of Surgeons, the Commission on Cancer, and the American Cancer Society. Approximately 70% of all new cancer diagnoses in the United States are recorded and consist of >1 million new cases per year from >1,500 different hospitals.<sup>10</sup> Several tumor characteristics, such as lymphovascular invasion, perineural invasion, and tumor deposits, as well as surgical approach have only been included in the NCDB since 2010. We thus included patients diagnosed with colorectal cancer starting 2010 to adjust for those covariates in our analysis. Rectal cancer patient user files were not included in this report. Patients were further excluded if they had metastatic disease at diagnosis, received neoadjuvant therapy, no surgery was performed, or for histology other than colonic adenocarcinoma. Variable definitions can be found at <http://ncdbpuf.facs.org/node/259>.

Patient characteristics included age, sex, race or ethnicity, comorbidities, insurance status, population density of the patient's

ZIP code, and distance traveled to the reporting institution. Patient comorbidities were defined according to the Deyo classification of the Charlson Comorbidity Index.<sup>11</sup> The NCDB does not provide more detailed information on specific comorbidities or body mass index. Hospital characteristics included hospital type and facility location. Facility type is determined by type of cancer programs and designated a specific category as per Commission on Cancer accreditation criteria based on number of new cancer diagnoses, program structure, services provided, research, and resident training. Variable definition can be found at <https://www.facs.org/quality-programs/cancer/accredited/about/categories>. Hospital location is based on US census information. Annual hospital volume was divided based on the median number of colon cancer cases per year (90 resections) and divided into low- (<90 cases) and high-volume ( $\geq 90$  cases) status. Tumor-related variables included tumor size, grade, location, lymphovascular, perineural invasion and American Joint Committee on Cancer (AJCC) stage. We calculated lymph node ratio from available data. Given the large variability in suggested thresholds, we dichotomized the variable as  $<0.04$  and  $\geq 0.04$  as well as  $<0.10$  and  $\geq 0.10$ , based on the lowest and most cited suggested values.<sup>5,12</sup> Treatment-related variables included surgical procedure and approach, lymph node yield (total number of harvested and positive nodes), margin status, length of primary inpatient stay, 30-day readmissions, 30- and 90-day mortality, and follow-up duration with vital status at last contact. The NCDB does not provide any information on local recurrence or metastatic disease and their treatment(s).

### Outcomes and statistical analysis

The primary outcome of this study was 5-year OS. Oncologic outcomes were defined using OS as the NCDB does not record local recurrence or metastatic disease, and therefore, disease-free survival could not be reported.<sup>13</sup> Restricted cubic splines were used to model the nonlinear relationship between the number of resected lymph nodes and OS. This function can flexibly examine the association between a predictor and an outcome without having to assume a specific prior relationship. A Cox proportional hazard regression of OS against a restricted cubic spline function of the total number of retrieved lymph nodes with 4 knots chosen according to Harrell's recommended percentiles (0.05, 0.35, 0.65, and 0.95) was modeled for all N stages (all, 0, 1, and 2) further adjusting for: age, sex, ethnicity (redefined as white, black, other and unknown), insurance status, comorbidities (defined on a scale of 0–3 according to total Charlson-Deyo comorbidity score), yearly facility



**Fig 2.** Restricted cubic spline plot demonstrating the non-linear relationship in the hazard ratio of overall survival against the total lymph node harvest in (A) N0 stage, (B) N1 stage, and (C) N2 stage. The red line demonstrates where the slope plateaus and corresponds to 24 lymph nodes on the x-axis.

case volume, tumor grade (redefined as low, high, and indeterminate), margin status, presence of tumor deposits and receipt of adjuvant systemic chemotherapy.<sup>14</sup> A threshold number of lymph nodes was then identified from these models. This value corresponds to the number of lymph nodes at which the derivative (ie, the slope) of the curve plateaus and becomes zero (Figs 1 and 2). We then categorized lymph node harvest based on this threshold value (24 lymph nodes) and patients were divided into 2 groups: <24 and ≥24 lymph nodes retrieved. We further divided the <24 group into <12 and 12 to 23 lymph nodes based on current lymph node standards.

Data are represented as n (%) for categorical variables and mean (standard deviation [SD]) for continuous variables. The 3 groups mentioned above were compared. Univariate analyses were performed using one-way analysis of variance for continuous variables and  $\chi^2$  test for categorical variables. Kaplan-Meier curves were used to describe 5-year OS and log-rank tests to compare the cumulative survival distributions. Multiple regression analyses were performed using Cox proportional hazard models to identify independent predictors of 5-year OS, adjusting for potential confounders (Table III). The interactive effect of nodal status and varying numbers of resected

lymph nodes on OS was also explored in our models. Trends of positive lymph node status as well as number of patients with >24 lymph nodes retrieved over time were examined using variance-weighted least squares testing. Subgroup analyses were performed for patients with nodal involvement, those who received adjuvant chemotherapy, those with a lymph node ratio ≥0.04 and ≥0.10 as well as patients with tumor deposits. All analyses were performed using STATA 12.1 (StataCorp, College Station, TX).

## Results

A total of 261,423 patients were included in our study. The cohort baseline demographics, tumor and treatment characteristics are summarized in Tables I and II. In our cohort, the mean follow-up duration was 31.3 months (SD 17.6). The proportion of patients with node-positive disease remained stable over time (35.3% in 2010 to 35.7% in 2014,  $P = .176$ ), as did the mean number of involved nodes (1.3 nodes SD 3.1) in 2010 to 1.3 nodes (SD 3.0) in 2014,  $P = .298$ ). However, the average nodal harvest increased from 19.1 nodes (SD 10.5) in 2010 to 20.3 nodes (SD 11.1) in 2014. This increase over time was significant ( $P < .001$ ).

**Table I**  
Overall cohort demographics

Variables	Overall cohort n = 261,423	<12 LN n = 36,877 (14.11)	12–23 LN n = 377,121 (53.37)	≥24 LN n = 167,606 (32.52)
Mean age, y (SD)	68.04 (13.70)	69.13 (12.68)	68.85 (13.04)	65.84 (14.31)
Male	128,508 (49.16)	19,385 (52.57)	76,573 (49.04)	32,550 (47.58)
Charlson-Deyo score				
0	178,642 (68.33)	24,501 (66.44)	104,956 (67.22)	49,185 (71.89)
1	59,508 (22.76)	8,712 (23.62)	36,654 (23.48)	14,142 (20.67)
2	23,273 (8.90)	3,664 (9.94)	14,521 (9.30)	5,088 (7.44)
Ethnicity				
White	218,026 (83.44)	30,561 (82.90)	129,970 (83.28)	57,495 (84.07)
Black	30,758 (11.77)	4,712 (12.78)	18,523 (11.87)	7,523 (11.00)
Other	8,020 (3.07)	995 (2.70)	4,890 (3.13)	2,135 (3.12)
Unknown	4,507 (1.72)	597 (1.62)	2,675 (1.71)	1,235 (1.81)
Insurance status				
No insurance	8,159 (3.12)	1,001 (2.71)	4,690 (3.00)	2,468 (3.61)
Private	86,353 (33.03)	11,367 (30.82)	49,405 (31.64)	25,581 (37.39)
Medicare/Medicaid	163,082 (62.38)	23,958 (64.97)	99,864 (63.96)	39,260 (57.39)
Unknown/missing	3,829 (1.46)	551 (1.49)	2,172 (1.39)	1,106 (1.62)
Median household income				
<\$38,000	45,595 (17.51)	7,292 (19.86)	27,297 (17.55)	11,006 (16.15)
\$38,000–\$47,999	60,877 (23.38)	9,163 (24.96)	36,298 (23.33)	15,416 (22.63)
\$48,000–\$62,999	70,461 (27.06)	9,908 (26.99)	41,733 (26.83)	18,820 (27.62)
≥\$63,000	83,471 (32.05)	10,353 (28.20)	50,224 (32.29)	22,894 (33.60)
Without high-school degree				
<7%	61,400 (23.57)	7,542 (20.53)	27,305 (17.54)	11,051 (16.21)
7%–12.9%	85,770 (32.92)	11,886 (32.36)	40,622 (26.10)	17,083 (25.06)
13%–20.9%	68,072 (26.13)	10,367 (28.22)	51,140 (32.86)	22,744 (33.36)
≥21%	45,292 (17.38)	6,936 (18.88)	36,568 (23.50)	17,290 (25.36)
Distance traveled				
<30 miles	224,174 (85.75)	31,930 (86.59)	134,575 (86.19)	57,669 (84.29)
30–60 miles	21,984 (8.41)	2,989 (8.11)	12,872 (8.24)	6,123 (8.95)
60–100 miles	7,681 (2.94)	1,001 (2.71)	4,441 (2.84)	2,239 (3.27)
>100 miles	7,584 (2.90)	957 (2.60)	4,243 (2.72)	2,384 (3.48)
Facility type				
Community	35,061 (13.73)	6,563 (18.02)	21,385 (13.93)	7,113 (10.86)
Comprehensive	123,977 (48.54)	18,544 (50.92)	74,963 (48.85)	30,470 (46.50)
Academic/research	68,492 (26.82)	7,830 (21.50)	40,429 (26.34)	20,233 (30.88)
Integrated	27,879 (10.92)	3,482 (9.56)	16,692 (10.88)	7,705 (11.76)
Population density				
Metro	216,012 (82.63)	29,662 (80.43)	129,560 (82.98)	56,790 (83.01)
Urban	34,208 (13.09)	5,437 (14.74)	19,996 (12.81)	8,775 (12.83)
Rural	4,805 (1.84)	784 (2.13)	2,839 (1.82)	1,182 (1.73)
Unknown	6,398 (2.45)	994 (2.70)	3,736 (2.39)	1,668 (2.44)
High volume hospital (≥90 cases per year)	131,233 (50.20)	15,904 (43.13)	78,536 (50.30)	36,793 (53.78)

LN, lymph nodes.

Data presented as n (%) unless otherwise specified.

**Table II**  
Overall cohort tumor and treatment characteristics

Variables	Overall cohort n = 261,423	<12 LN n = 36,877 (14.11)	12–23 LN n = 139,523 (53.37)	≥24 LN n = 85,023 (32.52)
<b>Tumor location</b>				
Right	126,993 (48.58)	12,930 (35.07)	77,061 (49.36)	37,002 (54.09)
Transverse	24,656 (9.43)	4,206 (11.41)	13,785 (8.83)	6,665 (9.74)
Left	79,396 (30.37)	14,512 (39.36)	47,572 (30.47)	17,312 (25.31)
Rectosigmoid	23,639 (9.04)	4,306 (11.68)	13,965 (8.94)	5,368 (7.85)
Other	6,729 (2.57)	919 (2.49)	3,745 (2.40)	2,065 (3.02)
<b>Procedure</b>				
Partial colectomy	248,995 (95.25)	35,281 (95.67)	150,571 (96.44)	63,143 (92.29)
Total colectomy	7,133 (2.73)	803 (2.18)	3,228 (2.07)	3,102 (4.53)
Total proctocolectomy	1,629 (0.62)	146 (0.40)	550 (0.35)	933 (1.36)
Not otherwise specified	3,666 (1.40)	647 (1.75)	1,782 (1.14)	1,237 (1.81)
<b>Surgical approach</b>				
MIS	118,848 (45.46)	15,625 (42.37)	71,928 (46.07)	31,295 (45.74)
Open	126,995 (48.58)	18,693 (50.69)	75,795 (48.55)	32,507 (47.51)
Missing	15,580 (5.96)	2,559 (6.94)	8,408 (5.39)	4,613 (6.74)
<b>pT stage</b>				
1	48,400 (18.84)	13,134 (36.95)	26,773 (17.39)	8,493 (12.59)
2	41,672 (16.22)	5,782 (16.27)	26,195 (17.01)	9,695 (14.38)
3	132,443 (51.54)	12,742 (35.85)	80,974 (52.59)	38,727 (57.42)
4	34,434 (13.40)	3,885 (10.93)	20,022 (13.00)	10,527 (15.61)
<b>pN stage</b>				
0	162,797 (63.51)	23,477 (72.02)	99,001 (63.46)	40,319 (59.54)
1	56,455 (22.03)	6,194 (19.00)	34,989 (22.43)	15,272 (22.55)
1c	6,396 (2.50)	1,020 (3.13)	3,830 (2.46)	1,546 (2.28)
2	30,672 (11.97)	1,908 (5.85)	18,179 (11.65)	10,585 (15.63)
<b>AJCC TNM stage</b>				
I	61,779 (27.02)	10,828 (39.96)	38,096 (27.17)	12,855 (20.96)
II	73,125 (31.98)	7,015 (25.89)	45,104 (32.17)	21,006 (34.25)
III	93,748 (41.00)	9,255 (34.15)	57,026 (40.67)	27,467 (44.79)
Mean total number of lymph nodes (SD)	19.62 (10.78)	6.81 (3.64)	16.74 (3.29)	33.36 (10.94)
Mean number of positive lymph nodes (SD)	1.30 (3.03)	0.64 (1.51)	1.21 (2.57)	1.81 (4.24)
<b>Lymph node ratio (in N+)</b>				
<0.04	7,288 (7.90)	0	0	7,288 (27.45)
≥0.04	84,942 (92.10)	12,380 (100)	53,300 (100)	19,262 (72.55)
<b>Lymph node ratio (in N+)</b>				
<0.10	34,413 (37.31)	678 (5.48)	19,527 (36.64)	14,208 (53.51)
≥0.10	57,817 (62.69)	11,702 (94.52)	33,773 (63.36)	12,342 (46.49)
<b>Tumor deposits</b>	23,092 (8.83)	2,934 (7.96)	13,723 (8.79)	6,435 (9.41)
<b>Mean tumor size, mm (SD)</b>	12.28 (26.19)	21.29 (37.40)	10.75 (23.81)	10.92 (22.84)
<b>Grade</b>				
Well/moderately differentiated	197,170 (75.42)	26,502 (71.87)	120,060 (76.90)	50,608 (73.97)
Poorly differentiated	46,049 (17.61)	4,897 (13.28)	27,088 (17.35)	14,064 (20.56)
Unknown	18,204 (6.96)	5,478 (14.85)	8,983 (5.75)	3,743 (5.47)
<b>Lymphovascular invasion</b>				
Yes	58,706 (22.46)	5,974 (16.20)	35,572 (22.78)	17,160 (25.08)
No	176,690 (67.59)	25,168 (68.25)	106,873 (68.45)	44,649 (65.26)
Missing	26,027 (9.96)	5,735 (15.55)	13,686 (8.77)	6,606 (9.66)
<b>Perineural invasion</b>				
Yes	22,160 (8.48)	2,230 (6.05)	13,398 (8.58)	6,532 (9.55)
No	209,870 (80.28)	27,704 (75.13)	127,176 (81.45)	54,990 (80.38)
Missing	29,393 (11.24)	6,943 (18.83)	15,557 (9.96)	6,893 (10.08)
<b>Margin status</b>				
R0	246,678 (94.36)	34,146 (92.59)	148,179 (94.91)	64,353 (94.06)
R1	6,349 (2.43)	987 (2.68)	3,717 (2.38)	1,645 (2.40)
R2	598 (0.23)	118 (0.32)	343 (0.22)	137 (0.20)
Unknown/missing	7,798 (2.98)	1,626 (4.41)	3,892 (2.49)	2,280 (3.33)
<b>Adjuvant systemic therapy</b>	86,329 (33.64)	8,647 (24.33)	51,046 (33.24)	26,636 (39.44)
Mean length of stay, days (SD)	6.70 (6.64)	6.93 (7.21)	6.72 (6.67)	6.56 (6.22)
30-day mortality	6,066 (2.89)	1,331 (4.29)	3,581 (2.87)	1,154 (2.14)
90-day mortality	10,000 (4.77)	2,155 (6.95)	5,851 (4.69)	1,994 (3.70)
Mean follow-up, months (SD)	31.33 (17.56)	30.82 (18.31)	31.26 (17.46)	31.79 (17.33)

LN, lymph nodes; MIS, minimally invasive surgery.  
Data presented as n (%) unless otherwise specified.

When we modeled our Cox proportional hazard regression of OS against the restricted cubic spline function of total number of retrieved lymph nodes, we noted that the adjusted improvements in OS stabilized after 24 nodes as shown in Fig 1. Beyond this threshold, higher lymph node harvest did not provide additional benefit in OS. This observation was seen across all N stages,

including node-negative stages (N0 and N1c disease; Fig 2). Based on this cut-off point, 3 groups were created for comparison. A total of 36,877 patients were included in the <12 lymph nodes group, 377,121 in the 12 to 23 group and 167,606 patients in the ≥24 group. Differences in patient, tumor, facility, and operative characteristics between groups are shown in Tables I and II. Due to the

large sample size, all variables were statistically different ( $P < .001$ ), but clinically important differences (defined as  $\geq 5\%$ ) were seen in: sex, Charlson-Deyo score, facility type, hospital volume, AJCC stage, tumor location, presence of lymphovascular invasion, poorly differentiated tumors and receipt of adjuvant systemic therapy. Patients with  $\geq 24$  lymph nodes retrieved were less likely to be male and comorbid but were more commonly treated at academic and high-volume centers when compared to patients in the 2 other groups. In addition, they had more right-sided cancers, advanced TNM stage, poorly differentiated tumors and lymphovascular invasion than patients with  $< 24$  lymph nodes. A greater proportion of patients with  $\geq 24$  nodes received adjuvant systemic therapy.

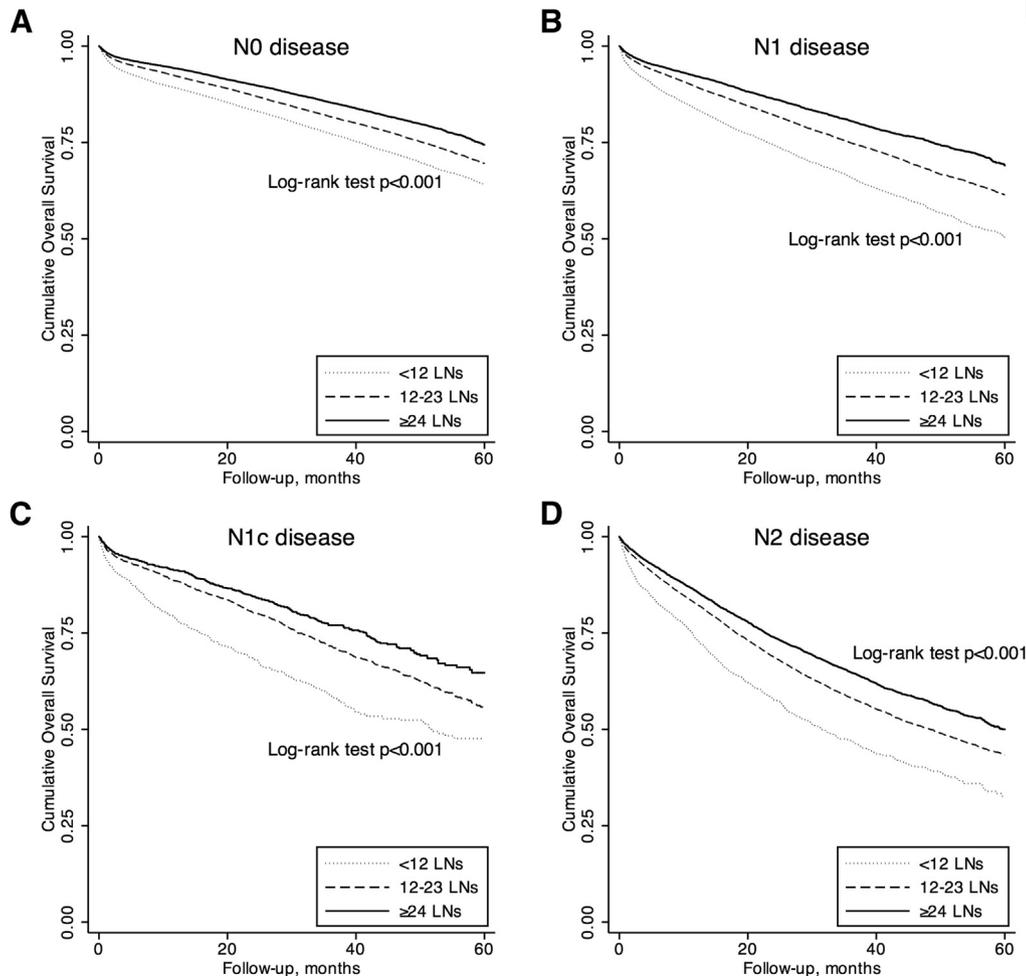
On Kaplan-Meier survival analysis, lymph node harvest of  $\geq 24$  lymph nodes was associated with higher 5-year cumulative OS compared to  $< 12$  and 12 to 23 lymph node groups (71.7% vs 62.8% vs 66.9%, log-rank  $P < .001$ ). When stratified by N stage, high lymph node yield ( $\geq 24$ ) was associated with a statistically significant improvement in OS compared to the 2 other groups in N0 (77.0% vs 66.7% vs 71.9%, log-rank  $P < .001$ ), N1 (73.0% vs 56.4% vs 65.4% log-rank  $P < .001$ ), N1c (63.0% vs 36.4% vs 52.8%, log-rank  $P < .001$ ) as well as N2 disease (52.9% vs 45.5% vs 36.0%, log-rank  $P < .001$ ; Fig 3, A–D). In the subgroup analyses of patients with high lymph node ratio ( $\geq 0.04$ ; Fig 4, A), a total number of lymph nodes retrieved of  $\geq 24$  was also associated with a higher proportion of patients alive at 5 years (59.9% vs 55.0% vs 57.4%, log-rank  $P < .001$ ). This was however not observed with a lymph node ratio of  $\geq 0.10$  (Fig 4, B). In

patients with nodal involvement who received adjuvant chemotherapy, improved OS was also observed in lymph node harvest of  $\geq 24$  (72.1% vs 62.9% vs 68.1%, log-rank  $P < .001$ ; Fig 4, C). Patients with  $< 12$  lymph nodes identified had worse OS than 12 to 23 and  $\geq 24$  groups in all survival analyses, except for the group with lymph node ratio  $\geq 0.10$ .

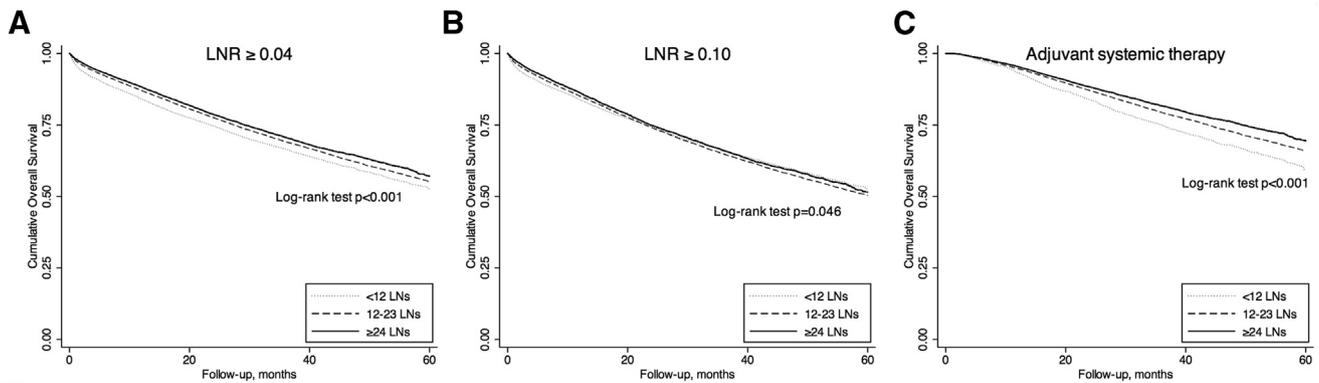
Results of adjusted multiple Cox proportional hazard regression model are shown in Table III. After adjusting for confounders, lymph node harvest  $\geq 24$  nodes was independently associated with improved OS compared to patients with 12 to 23 nodes. The retrieval of fewer than 12 lymph nodes as well as node-positive disease independently predicted worse OS. The interaction between nodal status and varying numbers of resected lymph nodes on OS was not significant. Similar results were observed when subgroup analyses were performed for node-positive patients and are presented in Table III. In the presence of nodal involvement, lymph node yield  $\geq 24$  nodes independently predicted better survival compared to patients with current lymph node harvest standards, even when adjusted for lymph node.

**Discussion**

The data supporting current standards of lymph node harvest are limited and there is increasing evidence supporting improved oncological outcomes with higher lymph node harvest. The optimal number of lymph nodes to retrieve has however not been clearly



**Fig 3.** Kaplan-Meier 5-year overall survival curves for (A) N0 disease, (B) N1 disease, (C) N1c disease, and (D) N2 disease.



**Fig 4.** Kaplan-Meier 5-year overall survival curves for node-positive disease with (A) lymph node ratio  $\geq 0.04$ , (B) lymph node ratio  $\geq 0.10$ , and with (C) receipt of adjuvant systemic chemotherapy.

described.<sup>2–4</sup> Therefore, there exists an important need to identify the relationship between the total number of lymph nodes identified and OS.

In the present study of the NCDB, we demonstrated a nonlinear relationship between nodal harvest and OS. A lymph node yield of  $\geq 24$  nodes was associated with improved OS in colorectal cancer patients with nonmetastatic disease when compared to patients with  $<12$  and 12 to 23 lymph nodes. There was no additional benefit in OS seen with lymph node harvest  $\geq 24$ . Our results are consistent with previous studies that have reported superior oncological outcomes with greater lymph node harvest.<sup>6–8</sup> This study adds to the growing body of evidence suggesting that the current standard may be inadequate.

The results of this study highlight that, despite adverse prognostic factors (right-sided, poorly differentiated tumors, lymphovascular invasion, advanced stage), patients with higher total number of lymph node retrieved had better survival. Multiple subgroup analyses were performed and revealed that the retrieval of  $\geq 24$  lymph nodes was associated with improved survival irrespective of N stage, lymph node ratio  $\geq 0.04$  and receipt of adjuvant systemic chemotherapy. As confirmed by our adjusted multivariate analysis, this further suggests that higher lymph node yield is independently associated with improved OS. Better OS with higher harvest was, however, not observed with lymph node ratio  $\geq 0.10$ . Although log-rank test comparing all 3 groups was significant, only the 12 to 23 group had worse OS. There was no difference in OS between  $<12$  and  $\geq 24$  groups (62.8% vs 71.7%, log-rank test  $P = .414$ ). These results may be explained by imbalances in possible confounding variables between groups since lymph node harvest  $\geq 24$  independently predicted better OS in the adjusted multivariate analysis adjusting for lymph node ratio  $\geq 0.10$ .

The mechanism by which higher lymph node harvest is associated with better survival is still not fully understood. There are several hypotheses to explain our results. First, there is a higher likelihood of missing positive nodal disease with low lymph node harvests, which may result in understaging and subsequently adversely affect patient selection for adjuvant systemic therapy. The exact probability of missing node-positive disease based on the total number of lymph nodes retrieved is unknown.<sup>15</sup> However, a higher lymph node harvest can potentially prevent understaging by causing a shift of cases towards higher TNM stages. Better survival from higher lymph node yields may be secondary to stage migration and improved patient selection for adjuvant systemic therapy.<sup>16,17</sup> Alternatively, a more extensive lymphadenectomy might have a therapeutic effect by achieving better locoregional control and reduce metastatic spread through tumor debulking.<sup>18</sup> However, in our study, higher lymph node harvest was associated with

improved survival even in N0 and N1c patients, suggesting that the effect of a higher lymphadenectomy may extend beyond N-positive disease. Lastly, lymph node harvest may also be a proxy for the quality of the surgical resection, a factor that accounts for improved outcomes.<sup>6</sup> In the present study, a larger proportion of patients with  $\geq 24$  lymph nodes identified in pathology specimen underwent surgical resection at an academic center or high-volume hospital compared to patients with lower lymph node yield. In addition, treatment at an academic center and high-volume hospital independently predicted better OS in our model. These results may reflect the presence of subspecialized treating teams and better overall multidisciplinary colorectal cancer care in such centers.

Furthermore, the number of identified lymph nodes in the specimen may also be a proxy for the quality of the pathology assessment. Previous studies have suggested significant variability between pathologists regarding the total number of lymph nodes reported.<sup>19,20</sup> It is therefore unclear if the survival benefit seen with higher harvest results from better retrieval or better identification. Moreover, there is evidence to suggest that antitumor immune response causes lymph node enlargement and improve node detectability by pathologists.<sup>7,21</sup> This anticancer immune response also leads to better cancer-specific survival and may confound the effect of higher lymph node yield on OS.<sup>7,21</sup> Additionally, the total number of nodes reported by pathologists does not take into account their location along the vascular pedicle. There are increasing data to suggest improved oncological outcomes with higher vascular ligation and retrieval of nodes at the origin of major feeding vascular pedicles (ie, D2-3 nodes according to the Japanese Classification of Colorectal Cancer).<sup>22,23</sup> However, the specific nodal locations are not routinely reported in North America, and NCDB does not provide this information.

Efforts to increase nodal harvest must also be balanced with potential morbidity and negative impact on patient-reported outcomes. Although lymph node yield can be improved by increasing the length of resection and by performing a higher vascular ligation (such as in a complete mesocolic excision), this may result in worse functional outcomes and lower patient satisfaction.<sup>24</sup> Furthermore, central vascular ligation is associated with a significantly higher risk of short-term complications, including intraoperative injury to other organs, such as splenic and superior mesenteric veins, in addition to postoperative sepsis and respiratory failure. It is unclear whether potentially improved oncologic outcomes are balanced by the worse functional outcomes and increased risk of perioperative complications.

The results of this study should be interpreted in view of several other limitations. First, the NCDB does not include data on

**Table III**  
Multivariate analysis of independent predictors of OS

Variables	Whole cohort HR (95% CI)	N+ disease HR (95% CI)	N+ disease HR (95% CI)
Age	1.04 (1.03–1.04)	1.02 (1.02–1.02)	1.02 (1.02–1.02)
Male	0.84 (0.82–0.85)	0.86 (0.83–0.88)	0.85 (0.83–0.88)
Charlson-Deyo score			
0	ref	ref	ref
1	1.22 (1.19–1.25)	1.14 (1.11–1.18)	1.14 (1.11–1.18)
2	1.82 (1.77–1.87)	1.58 (1.51–1.65)	1.57 (1.51–1.64)
Ethnicity			
White	ref	ref	ref
Black	1.14 (1.11–1.18)	1.10 (1.05–1.15)	1.10 (1.05–1.15)
Other	0.90 (0.83–0.98)	0.83 (0.76–0.91)	0.83 (0.76–0.91)
Insurance status			
No insurance	ref	ref	ref
Private	0.72 (0.67–0.77)	0.79 (0.72–0.87)	0.79 (0.72–0.87)
Medicare/Medicaid	0.90 (0.84–0.97)	1.00 (0.91–1.09)	1.00 (0.91–1.09)
Facility type			
Community	ref	ref	ref
Comprehensive	0.99 (0.96–1.02)	1.02 (0.97–1.06)	1.02 (0.97–1.06)
Academic/research	0.92 (0.89–0.95)	0.93 (0.88–0.98)	0.93 (0.88–0.98)
Integrated	0.99 (0.95–1.03)	1.03 (0.97–1.10)	1.03 (0.97–1.10)
High volume hospital ( $\geq 90$ cases per year)	0.95 (0.93–0.97)	0.96 (0.93–1.00)	0.96 (0.93–1.00)
Tumor location			
Right	ref	ref	ref
Transverse	1.05 (1.02–1.08)	1.02 (0.97–1.07)	1.02 (0.97–1.07)
Left	0.98 (0.95–1.00)	0.84 (0.82–0.87)	0.84 (0.82–0.87)
Rectosigmoid	0.92 (0.89–0.96)	0.77 (0.72–0.81)	0.77 (0.72–0.81)
Surgery			
Partial colectomy	ref	ref	ref
Total colectomy	1.51 (1.43–1.59)	1.46 (1.35–1.57)	1.46 (1.35–1.58)
Total proctocolectomy	1.44 (1.25–1.65)	1.54 (1.28–1.85)	1.54 (1.28–1.85)
Not otherwise specified	1.06 (0.97–1.15)	1.00 (2.36–2.94)	1.00 (0.89–1.14)
pT stage			
1	ref	ref	ref
2	1.30 (1.25–1.36)	1.16 (1.03–1.31)	1.16 (1.03–1.31)
3	1.82 (1.75–1.89)	1.65 (1.49–1.84)	1.64 (1.47–1.82)
4	3.09 (2.96–3.23)	2.63 (2.36–2.94)	2.61 (2.34–2.91)
pN stage			
0	ref	-	-
1	1.56 (1.51–1.61)	ref	ref
2	1.95 (1.87–2.04)	1.26 (1.22–1.31)	1.21 (1.16–1.26)
Total number of positive nodes	1.05 (1.04–1.05)	1.05 (1.05–1.05)	1.05 (1.05–1.05)
Total lymph node harvest			
<12	1.42 (1.37–1.47)	1.41 (1.35–1.47)	1.37 (1.31–1.43)
12–23	ref	ref	ref
$\geq 24$	0.82 (0.80–0.85)	0.80 (0.77–0.83)	0.80 (0.77–0.83)
Interaction term			
<12 LN x N1	0.94 (0.87–1.01)	-	-
<12 LN x N2	1.00 (0.92–1.08)	-	-
$\geq 24$ LN x N1	0.98 (0.93–1.05)	-	-
$\geq 24$ LN x N2	0.99 (0.93–1.05)	-	-
Lymph node ratio $\geq 0.04$	-	1.12 (1.04–1.21)	-
Lymph node ratio $\geq 0.10$	-	-	1.11 (1.07–1.16)
High tumor grade	1.11 (1.09–1.13)	1.18 (1.15–1.21)	1.18 (1.15–1.21)
Perineural invasion	1.03 (1.02–1.05)	1.06 (1.03–1.08)	1.06 (1.03–1.08)
Lymphovascular invasion	1.06 (1.05–1.08)	1.07 (1.04–1.09)	1.07 (1.04–1.09)
Tumor deposits	1.39 (1.35–1.43)	1.33 (1.29–1.38)	1.33 (1.29–1.38)
Margins status			
R0	ref	ref	ref
R1	1.53 (1.46–1.60)	1.47 (1.40–1.56)	1.48 (1.40–1.56)
R2	2.09 (1.85–2.36)	1.80 (1.53–2.12)	1.81 (1.54–2.13)
Adjuvant systemic therapy	0.48 (0.47–0.49)	0.34 (0.33–0.36)	0.34 (0.33–0.36)

CI, confidence interval; ref, reference category.

recurrence and their treatment(s).<sup>13</sup> We could therefore not study and report recurrence rate and disease-free survival. In addition, the database does not include detailed data on adjuvant systemic therapy that may impact risk of recurrence such as appropriateness, dosing, tolerance, and completion. Tumor genetics are also not reported in the NCDB and may affect survival. Given our large sample size and the 66% NCDB case coverage for colon cancer, we do think that our results are externally valid. However, previous

studies some subgroups of the US population are underrepresented in the NCDB and our results may not be generalizable to those.<sup>25</sup>

In conclusion, our data show that a lymph node harvest of at least 24 nodes is associated with improved survival for patients with nonmetastatic colon adenocarcinoma undergoing surgery with curative intent. This association remains significant in all stages and even in patients with node-positive disease that received adjuvant systemic therapy. Lymph node harvest beyond

24 nodes did not seem to provide additional benefit. These data call into question the current 12 lymph node minimum standard and may provide indirect evidence for a more extensive lymphadenectomy for colon cancer.

### Conflict of interest/Disclosure

Dr Nassif is a consultant for Mallinckrodt and for Applied Medical. Dr Albert is consultant and stock options from Applied Medical, and a consultant for Stryker, KCI, and Conmed. Dr Monson is a consultant for Medtronic and Twistle. Dr Lee is the recipient of an investigator-initiated research grant from Johnson & Johnson. Drs Trepanier and Erkan and Araz Kouyoumdjian have no conflict of interest or financial ties to disclose.

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## Discussion

**Dr Shawn Safford** (Roanoke, VA): I thank the Association for the opportunity to do the discussion. The paper was excellent and fantastic in quality and well written.

The paper by Trepanier challenges the current recommendations by AJC and NCC for adequate lymph node harvest. The authors have used relevant and impactful statistical analysis to evaluate the outcomes for patients with colon cancer and the number of lymph nodes biopsied during dissection.

I have the following questions:

In general, the outcome of patients with colon cancer is impacted by presence of tumor in the lymph nodes. The number of lymph nodes present is shown to be associated with improved outcomes and at this point the AJCC standards harvest at least 12 lymph nodes, and multiple studies demonstrating improving survival, these associations are weak.

Do you feel that the lymph nodes are marker for tumor aggressiveness, or do you believe that debulking is associated with these improved outcomes?

During your analysis, you subcategorized patients into 12, 12 to 24, and >24 lymph nodes. Different than these other centers to date, you have performed a restricted cubic spline to determine the adjusted overall survival stabilized for 24 nodes. I'm assuming you made the second category based on the current AJCC recommendations. However, in Figure 1, you demonstrated there is a perceived slope that looks like it's above that point that we might potentially look at. It looks like, based on the Figure, around 18. Did you perform an additional analysis at that level? Did you perform an independent analysis for higher lymph nodes harvest numbers? Other than that, other studies have recommended up to 30 nodes improved outcomes. Did you consider looking at higher numbers than 24?



On review of the overall cohort tumor and treatment characteristics, you have a 2-fold greater number of total colectomy patients in the >24 lymph nodes. Did you break down these for further analysis for various subgroup in those variables?

Finally, interestingly, as more of the aggressive tumor traits are still improved and surviving in those with >24 lymph nodes harvested, how can you account for these?

In this study overall, it involves the problems of determining outcomes based on lymph node status. The question comes down to whether it's based on health care system, lymph nodes, the surgeon, the tumor, the patient. So, from this, have you been able to determine from your study which of these do you think provides a bigger role—the tumor, the patient, surgeon, or health care system?

Finally, a question that I've not addressed before which was if you have a patient with 6 lymph nodes harvested or 18, what are your recommendations?

**Dr Maude Trepanier:** Thank you for your questions. First of all, with regards to the tumor characteristics and the colectomy question, for both of these things we actually adjusted in our multivariate analysis. The NCDB does not provide length of specimen. We only code procedures as partial colectomies or total colectomies. So we did not adjust specifically for the length of the specimen. We also could not adjust for the height of the ligation, so we don't know if they have central vascular ligation, if that impacts the number of lymph nodes we see in the specimen. Although we adjusted for that in our multivariate analysis, we didn't perform a subgroup analysis for the total colectomy patients.

With regards to the tumor that also we adjusted for in our analysis. It is interesting that we see a better survival despite the fact that they have aggressive tumors, but we did adjust for that in our analysis.

For the cutoff point that we identified, so when we looked at the confidence interval that I did not show in the graph, although it looks like the slope is still going down in restricted spline plot, that was not significant. So beyond 24, there were no added benefits of collecting more nodes.

In terms of the impact of our study, it's hard to tell what exactly is the cause behind that explains our results. I think it's multifactorial. We do find in our study and the data that most patients with higher lymph node harvest received care at high-volume hospitals. Does that reflect better cancer care overall? We don't know.

A few studies have shown that the number of lymph nodes actually a proxy measure of quality of surgical resection, but it also depends on your pathology assessment. It's very hard to determine what is the main cause. I think that our study brings awareness that a high lymph node harvest improves survival. I think we will need prospective studies to determine exactly the length of the

specimen. Did they have higher ligation? Who looked at the specimen? And where? Was it at a high-volume hospital or was it more a community hospital? I think our findings just bring awareness that higher lymph node harvest may actually improve survival and we should be aware of that.

**Dr Margo Shoup** (Danbury, Ct): I enjoyed your paper very much, and maybe you said this and I missed it. As we know, the reason for the higher lymph node dissection, the purpose of obtaining more lymph nodes is to more appropriately stage so then we can more appropriately treat and come up with a prognosis. My question to you is, as you noticed in a later time period, those patients had greater than 22 lymph nodes harvested, if you compared them to those that had between 12 and 22 lymph nodes, say, was there a higher percentage of patients with positive nodes? In other words, did it really improve the staging and that's what associated us with improved survival?

**Dr Maude Trepanier:** In our study, we did not observe that. We had more stage 3 patients in the higher lymph node harvest category but we didn't specifically try to look at the probability of predicting lymph node positivity with higher lymph node harvest. When they decided on the current standards of 12, the studies have shown that there is basically a specificity of 12 lymph nodes is .9, but in our study, we didn't really try to predict that probability.

**Dr Margo Shoup** (Danbury, CT): From my perspective, I think that would be interesting information to have because that would further lead credibility to the argument that we should be harvesting more nodes, which makes more sense. Truly, the purpose of a lymph node dissection is to stage the patient. It's not necessarily been thought to improve survival, which is improving staging accuracy.

**Dr Maude Trepanier:** In our study, we found that association in N-0 patients, even in the absence of lymph node positivity, we found that higher lymph node harvest was associated with better survival. We're not really clear as to what mechanism can explain that right now, but that's one of the associations that we found.

**Dr Carmen Mueller** (Montreal, QC): One more quick question. How do you feel that this data relates to literature in gastric cancer, for example, where D2 extended lymphadenectomy has been shown to improve survival, not just improve staging?

**Dr Maude Trepanier:** Like I said, the fact that we saw an improvement in overall survival in N1 disease and N0 disease suggests that maybe there is a tumor debulking effect. We do not believe that stage migration is the only explanation for our results. The evidence for tumor debulking effect with extensive lymphadenectomy and colorectal cancer is still growing, and I think there will be more studies on this in the near future.