



Adequate Lymphadenectomy as a Quality Measure in Esophageal Cancer: Is there an Association with Treatment Approach?

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ABSTRACT

Background. The national comprehensive cancer network defines adequate lymphadenectomy as evaluation of ≥ 15 lymph nodes in esophageal cancer. However, varying thresholds have been suggested following neoadjuvant therapy.

Objectives. Our objectives were to (1) explore trends in adequate lymphadenectomy rates over time; (2) evaluate unadjusted lymphadenectomy yield by treatment characteristics; and (3) identify independent factors associated with adequate lymphadenectomy.

Methods. The National Cancer Data Base was used to identify patients who underwent esophagectomy for cancer from 2004 to 2015. Adequate lymphadenectomy trends over time were evaluated using the Cochrane–Armitage test, and lymph node yield by treatment approach was compared using the Mann–Whitney *U* and Kruskal–Wallis tests. Associations with treatment factors were assessed by multivariable logistic regression.

Results. Among 24,413 patients, 9919 (40.6%) had adequate lymphadenectomy. Meeting the nodal threshold increased over time (52.6% in 2015 vs. 26.0% in 2004; $p < 0.01$). Lymph node yield did not differ based on

neoadjuvant therapy (median 12 [interquartile range 7–19] with and without neoadjuvant therapy; $p = 0.44$). Adequate lymphadenectomy was not associated with neoadjuvant therapy (40.5% vs. 40.8%, odds ratio [OR] 0.94, 95% confidence interval [CI] 0.82–1.07), but was associated with surgical approach (52.7% of laparoscopic cases, OR 1.28, 95% CI 1.06–1.56; 61.2% of robotic cases, OR 1.71, 95% CI 1.34–2.19, vs. 43.5% of open cases), and increasing annual esophagectomy volume (55.6% in the fourth quartile vs. 32.6% in the first quartile; OR 3.57, 95% CI 2.35–5.43).

Conclusions. Despite increases over time, only 50% of patients undergo adequate lymphadenectomy during esophageal cancer resection. Adequate lymphadenectomy was not associated with neoadjuvant therapy. Focusing on surgical approach and esophagectomy volume may further improve adequate lymphadenectomy rates.

Esophageal cancer is a common and lethal condition, with 5-year population-based survival rates of $< 20\%$.¹ Multimodal treatment is recommended based on tumor stage, and may include chemotherapy, radiation, and/or surgical resection.² Among patients who undergo surgical resection, adequate lymphadenectomy is essential for accurate staging, which is an important predictor of survival.^{3,4} Additionally, several studies have shown that adequate lymphadenectomy is associated with improved survival in esophageal cancer, likely due to improved operative staging.^{5–8}

Despite the importance of adequate lymphadenectomy, there is not widespread agreement on how adequate lymphadenectomy is defined in esophageal cancer. The National Comprehensive Cancer Network (NCCN)

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guidelines recommend analysis of at least 15 lymph nodes to sufficiently evaluate for nodal metastases.² However, many studies have suggested varying thresholds, ranging from 10 to 40 nodes.^{9–14} Unfortunately, evaluation of adequate lymphadenectomy thresholds has traditionally been performed for primary surgical resection.⁹ Studies stratifying lymphadenectomy rates by the use of neoadjuvant therapy have found lymph node harvest to be lower in patients following neoadjuvant therapy, while others have concluded more lymph nodes must be harvested to achieve the same staging accuracy.^{4,15,16} Hypotheses that neoadjuvant therapy decreases lymphadenectomy yield are rooted in lymphocyte depletion and diminished lymph node size following neoadjuvant therapy, making it more difficult to pathologically identify lymph nodes.^{17,18} Alternatively, fewer lymph nodes may be found in surgical specimens altogether based on pathologic changes such as fibrosis and increased vascularity that lead to alterations in surgical technique.^{19,20}

Quality improvement initiatives in the past decade have emphasized adherence to quality measures, such as those put forward by the NCCN. As such, analyses of the impact of quality measure adherence on overall survival in esophageal cancer have relied on the NCCN definition of at least 15 lymph nodes for adequate lymphadenectomy, regardless of the use of neoadjuvant therapy.²¹ However, we question whether treatment approaches, such as neoadjuvant therapy, are associated with the likelihood of achieving adequate lymphadenectomy by this definition given the variation in lymphadenectomy thresholds proposed in prior studies and the potential histopathologic changes noted after neoadjuvant therapy. Thus, the objectives of this study were to (1) explore trends in adequate lymphadenectomy rates over time; (2) evaluate unadjusted lymphadenectomy yield in esophageal cancer based on treatment characteristics; and (3) identify independent factors associated with adequate lymphadenectomy.

METHODS

Data Source and Study Population

The National Cancer Data Base (NCDB) is a joint effort of the American College of Surgeons and the American Cancer Society, through which all Commission on Cancer (CoC)-accredited facilities submit data.^{22,23} Trained nurse abstractors submit clinical data for 100% of the cancer patients treated at CoC facilities, thereby capturing 72% of patients treated for malignancy in the US across more than 1500 facilities.²⁴ In return, participating institutions receive benchmarked data for quality improvement. Regular audits ensure data appropriateness, completeness, and excellent inter-rater reliability.²⁵

From 2004 to 2015, 42,925 patients who underwent esophagectomy were identified in the esophageal cancer participant use file (PUF). Patients were categorized by International Classification of Diseases for Oncology, Third Edition (ICD-0-3) histologic codes based on the location in which the reporting physician believed the tumor to arise; those patients with primary gastric or gastroesophageal junction cancer extending into the esophagus were not included in this analysis. Patients were excluded for clinical stage IV disease ($n = 1541$), histology other than adenocarcinoma or squamous cell carcinoma ($n = 1958$), or second primary malignancy ($n = 7692$). Additionally, patients were excluded if there was no documented lymph node surgery ($n = 5595$) or an undocumented number of lymph nodes were sampled ($n = 1726$). Some patients were noted to have undergone surgical lymphadenectomy, but no lymph nodes were identified on pathologic evaluation. These patients remained in the study cohort and were coded as having zero lymph nodes evaluated. Thus, a total of 24,413 patients were included for analysis.

Primary Outcome and Predictors

The primary outcome was adequate lymphadenectomy, defined by the NCCN guidelines as evaluation of at least 15 lymph nodes following esophagectomy.² The number of evaluated lymph nodes is abstracted from final pathology reports in the NCDB. Possible predictors of adequate lymphadenectomy were identified a priori based on a review of the literature and clinical face validity.

Patient-specific predictors included age, sex, race/ethnicity, insurance status, Charlson–Deyo Index (CDI), and income; hospital-specific predictors included distance to the treating hospital, facility type, and hospital location; tumor-specific predictors included histologic morphology, pathologic *T* stage, pathologic *N* stage, grade, and tumor size; and treatment-specific variables included use of neoadjuvant therapy (chemotherapy and/or radiation), surgical approach, and annual esophagectomy volume. The above NCDB variables are defined as follows: income is reported for each patient as the median income estimate based on ZIP code census data, which is divided into quartiles by the NCDB. Pathologic staging is based on the American Joint Committee on Cancer (AJCC) definitions that were used at the time of treatment. Facility type is determined by standard CoC definitions. Hospital location is based on Department of Agriculture Economic Research Service rural–urban continuum codes, which were subsequently categorized into metropolitan, urban, and rural. Distance to the hospital is calculated as the aerial distance between the center of the patient’s ZIP code and the street address of the reporting CoC facility. Annual

esophagectomy volume was calculated as the number of esophagectomies reported to the NCDB per facility in this study divided by the number of years that had elapsed since the first esophagectomy was reported to the NCDB from that facility. Age, tumor size, distance to treating hospital, and hospital annual esophagectomy volume were subsequently divided into quartiles for ease of analysis.

Statistical Analysis

Time trends in achievement of adequate lymphadenectomy were evaluated using the Cochran–Armitage test for trend. The number of lymph nodes evaluated by tumor and treatment characteristics were compared using the Mann–Whitney *U* test for two groups or Kruskal–Wallis test for multiple groups. The proportion of patients achieving adequate lymphadenectomy by patient-, tumor-, hospital-, and treatment-specific predictors were individually assessed on bivariate analysis using separate Chi-square tests. Predictors that were statistically significant with a predetermined *p* value < 0.05, as well as all treatment-specific factors regardless of *p* value, were entered into a multivariable logistic regression model with facility-level clustering to account for variation within facilities. This model was used to estimate associations of predictors with adequate lymphadenectomy achievement. Model diagnostics included calculation of the C-statistic, a test of model discrimination, with a value approaching 1.0 indicating better discrimination, and the Hosmer and Lemeshow Chi-square, a test of model calibration, with any *p* value < 0.05 indicating poor calibration.^{26,27} A sensitivity analysis was performed with a restricted cohort of advanced-stage patients who would be recommended to receive neoadjuvant therapy.

The predetermined two-sided level of significance was 0.05 for all analyses, which were performed using Stata version 14.2 (StataCorp LLC, College Station, TX, USA). This study was determined to be exempt from review by the Institutional Review Board of Northwestern University based on the use of de-identified data.

RESULTS

Of the 24,413 analyzed patients, the mean age was 62.3 years. The majority of patients were male (83.6%) and of White ethnicity (89.8%), while 48.3% of patients had private insurance, followed by 40.7% of patients who had Medicare insurance (Table 1). Over half of the patients were treated at academic or research facilities (53.0%) and in metropolitan locations (80.2%). Treated tumors were more commonly adenocarcinomas (82.8%) and node negative (60.9%). Overall, 60.8% of patients received

neoadjuvant therapy (including 61.9% of patients with T3 or T4 disease and 60.2% of patients with N+ disease on final pathology). Open esophagectomy was performed on 67.1% of patients, 24.9% of patients underwent esophagectomy via a laparoscopic approach, and 8.0% of patients via a robotic approach. Hospitals in the lowest volume quartile performed fewer than 1.7 mean cases per year, while those in the highest quartile performed more than 10.0. Additional demographic information can be found in Table 1.

Trends in Adequate Lymphadenectomy Over Time

Overall, 40.6% of patients in this study underwent an adequate lymphadenectomy during esophagectomy. Adequate lymphadenectomy rates increased over time, with 26.0% (standard error [SE] 1.0%) of patients receiving adequate lymphadenectomy in 2004, and 52.6% (SE 1.1%) in 2015 (*p* < 0.01) (Fig. 1). The proportion of patients with adequate lymphadenectomy increased each year of the study, with the greatest gain of 3.8% occurring between 2007 and 2008, and the smallest increase of 0.1% occurring between 2009 and 2010.

Lymphadenectomy Yield by Treatment Characteristics

The median number of pathologically examined lymph nodes was 12 (interquartile range [IQR] 7–19) for patients who received neoadjuvant therapy as well as those who did not (*p* = 0.44) (Fig. 2). However, a larger proportion of patients had zero lymph nodes identified on pathologic evaluation following neoadjuvant therapy than those patients without (5.7% of patients following neoadjuvant therapy vs. 1.2% without; *p* < 0.01). Median lymphadenectomy yield progressively increased for the laparoscopic and robotic surgical approaches compared with the open approach (median 13 [IQR 8–19] for the open approach; 15 [IQR 9–22] for the laparoscopic approach; and 17 [IQR 11–23] for the robotic approach; *p* < 0.01) (Fig. 3), as well as with increasing annual hospital esophagectomy volume (median 10 [IQR 5–17] for quartile 1; 11 [IQR 6–17] for quartile 2; 13 [IQR 7–18] for quartile 3; 16 [IQR 10–23] for quartile 4; *p* < 0.01) (Fig. 4).

Independent Factors Associated with Adequate Lymphadenectomy

Many patient factors had no association with achievement of adequate lymphadenectomy. For example, there was no difference in adequate lymphadenectomy rates based on age (e.g. 40.0% of patients ≥ 75 years of age vs. 40.0% of patients < 55 years of age; *p* = 0.22) or sex

TABLE 1 Characteristics of patients undergoing esophagectomy for malignancy

Patient characteristics [<i>n</i> = 24,413]	<i>n</i> (%)
Age, years [mean (SD)]	62.3 (9.9)
Sex	
Male	20,398 (83.6)
Female	4015 (16.5)
Race/ethnicity	
White	21,930 (89.8)
Black	1061 (4.4)
Hispanic	695 (2.9)
Other	727 (3.0)
Insurance status	
Private	11,800 (48.3)
Medicare	9944 (40.7)
Medicaid	1360 (5.6)
Other Government	778 (3.2)
Uninsured	531 (2.2)
Charlson–Deyo index	
0	17,787 (72.9)
1	5257 (21.5)
2	1064 (4.4)
≥ 3	305 (1.3)
Median zip code income, US\$	
< 38,000	3644 (15.2)
38,000–47,999	5969 (24.9)
48,000–62,999	6857 (28.6)
≥ 63,000	7549 (31.4)
Quartile of distance to hospital (miles)	
1 (≤ 7.0)	6015 (25.0)
2 (7.1–17.8)	6032 (25.1)
3 (17.9–47.7)	5987 (24.9)
4 (≥ 47.8)	5996 (25.0)
Facility type	
Academic/research	12,758 (53.0)
Integrated Network Cancer Program	2577 (10.7)
Comprehensive Community Cancer Program	7517 (31.3)
Community Cancer Program	1205 (5.0)
Hospital location	
Metropolitan	18,875 (80.2)
Urban	4123 (17.5)
Rural	527 (2.2)
Histologic morphology	
Adenocarcinoma	20,222 (82.8)
Squamous cell carcinoma	4191 (17.2)
Pathologic <i>T</i> stage	
<i>T0/Tis</i>	2990 (14.7)
<i>T1</i>	5754 (28.3)
<i>T2</i>	3564 (17.5)
<i>T3</i>	7626 (37.5)
<i>T4</i>	386 (1.9)

TABLE 1 (continued)

Patient characteristics [<i>n</i> = 24,413]	<i>n</i> (%)
Pathological <i>N</i> stage	
<i>N0</i>	12,609 (60.9)
<i>N1</i>	6428 (31.0)
<i>N2</i>	1164 (5.6)
<i>N3</i>	507 (2.5)
Tumor grade	
Well-differentiated	1659 (7.8)
Moderately differentiated	9121 (43.0)
Poorly differentiated	10,094 (47.6)
Undifferentiated	322 (1.5)
Tumor size, cm	
≤ 2.0	4999 (27.2)
2.1–4.0	6419 (35.0)
4.1–6.0	4199 (22.9)
> 6.0	2732 (14.9)
Neoadjuvant therapy	
No	9565 (39.2)
Yes	14,848 (60.8)
Surgical approach ^a	
Open	6906 (67.1)
Laparoscopic	2557 (24.9)
Robotic	824 (8.0)
Mean annual hospital esophagectomy volume quartile (<i>n</i> /year)	
1 (< 1.7)	6113 (25.1)
2 (1.7–4.2)	6079 (24.9)
3 (4.3–10.0)	6174 (25.3)
4 (> 10.0)	6014 (24.7)

SD Standard deviation

^a Surgical approach available beginning in 2010

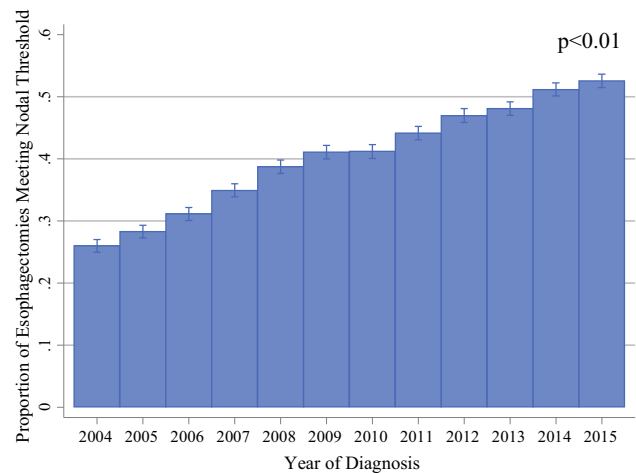


FIG. 1 Proportion of patients with ≥ 15 lymph nodes examined, by year

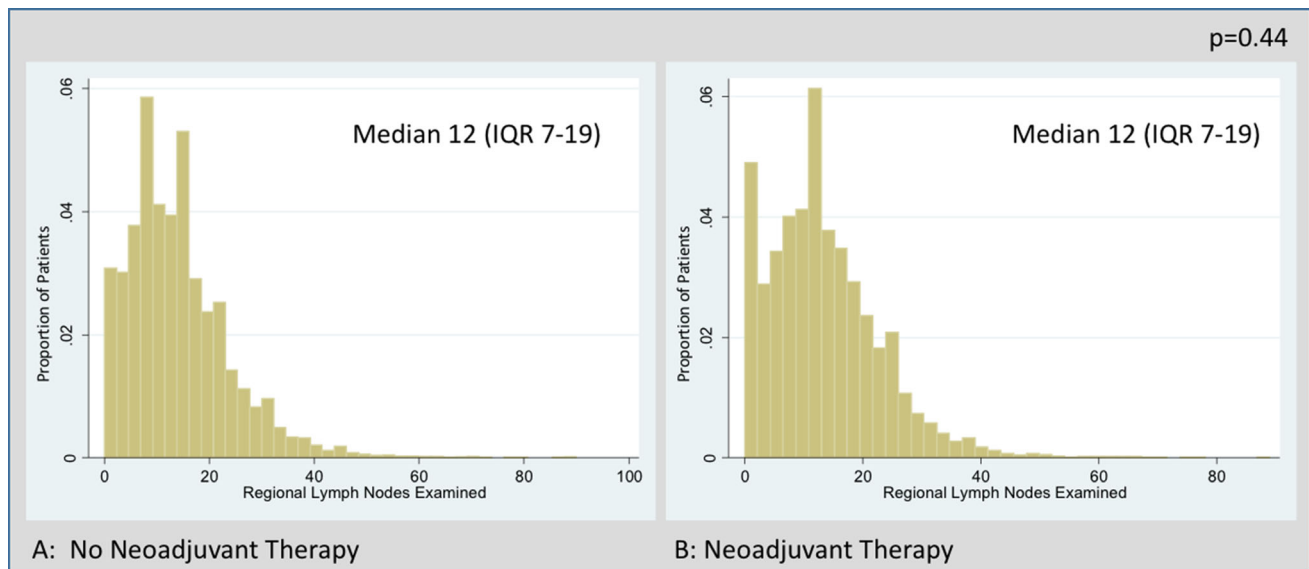


FIG. 2 Pathologically examined lymph nodes following esophagectomy either (a) without neoadjuvant therapy or (b) following neoadjuvant therapy. *IQR* interquartile range

(40.8% of males vs. 39.7% of females; $p = 0.17$) (Table 2). Hispanic patients and patients with a race/ethnicity other than White, Black, or Hispanic were more likely to achieve adequate lymphadenectomy than White patients (41.2% of Hispanic patients, odds ratio [OR] 1.50, 95% confidence interval [CI] 1.09–2.06; 48.0% of other race, OR 1.42, 95% CI 1.05–1.91; vs. 40.7% of White patients) [Table 3]. Patients with private insurance more frequently achieved adequate lymphadenectomy than patients with other insurance types on bivariate analysis (41.8% vs. 39.8% of Medicare patients, 38.3% of Medicaid patients, and 36.0% of uninsured patients; $p < 0.01$), but these differences were not significant after adjusting for other factors on multivariable logistic regression (see Table 3). Similarly, patients with a lower CDI more frequently achieved adequate lymphadenectomy on bivariate analysis, but not after adjusting for other factors (41.2% if CDI 0 vs. 35.1% if $\text{CDI} \geq 3$, $p = 0.01$; OR 0.88, 95% CI 0.57–1.37). Patients with higher median zip code incomes were more likely to have adequate lymphadenectomy than those from lower-income zip codes (43.9% of patients with a median zip code income $> \text{US}\$63,000$ vs. 36.6% of those $< \text{US}\$38,000$; OR 1.28, 95% CI 1.03–1.59).

Being in the fourth quartile of distance traveled to the treating facility was associated with adequate lymphadenectomy (47.1% vs. 36.4% in the first quartile; OR 1.31, 95% CI 1.07–1.60). Patients treated at academic or research hospitals more frequently achieved adequate lymphadenectomy on bivariate analysis, but not after adjusting for other factors on multivariable logistic regression (Tables 2, 3). However, treatment at an urban hospital was associated with a decreased likelihood of

achieving adequate lymphadenectomy (39.3% at urban hospitals vs. 41.2% at metropolitan hospitals, OR 0.81, 95% CI 0.67–0.98).

With regard to tumor-specific factors, patients with squamous cell carcinomas less frequently had adequate lymphadenectomy than patients with adenocarcinomas on bivariate analysis, but not after adjusting for other predictors (39.2% vs. 40.9% for adenocarcinomas, $p = 0.04$; OR 1.10, 95% CI 0.95–1.27). Adequate lymphadenectomy was more frequently achieved with increasing pathologic *T* stage, but no association was found on multivariable modeling (see Tables 2 and 3). However, increased pathologic *N* stage was associated with adequate lymphadenectomy (e.g. 76.5% of patients with N3 disease vs. 39.2% of patients with N0 disease; OR 5.06, 95% CI 3.77–6.79). The likelihood of achieving adequate lymphadenectomy increased as pathologic grade increased on bivariate analysis, but there was no association between pathologic grade and adequate lymphadenectomy on adjusted analyses (e.g. 47.5% of undifferentiated tumors vs. 37.9% of well-differentiated, $p < 0.01$; OR 0.92, 95% CI 0.54–1.58). Likewise, there was no association between adequate lymphadenectomy rates and tumor size based on the multivariable model, despite increased lymphadenectomy rates with increasing tumor size on bivariate analysis (e.g. 46.9% of tumors > 6.0 cm in size vs. 40.2% of tumors ≤ 2.0 cm in size, $p < 0.01$; OR 1.02, 95% CI 0.84–1.24).

Finally, with regard to specific treatment approaches, neoadjuvant therapy was not associated with achieving adequate lymphadenectomy (40.5% vs. 40.8%, $p = 0.64$; OR 0.94, 95% CI 0.82–1.07). However, both laparoscopic

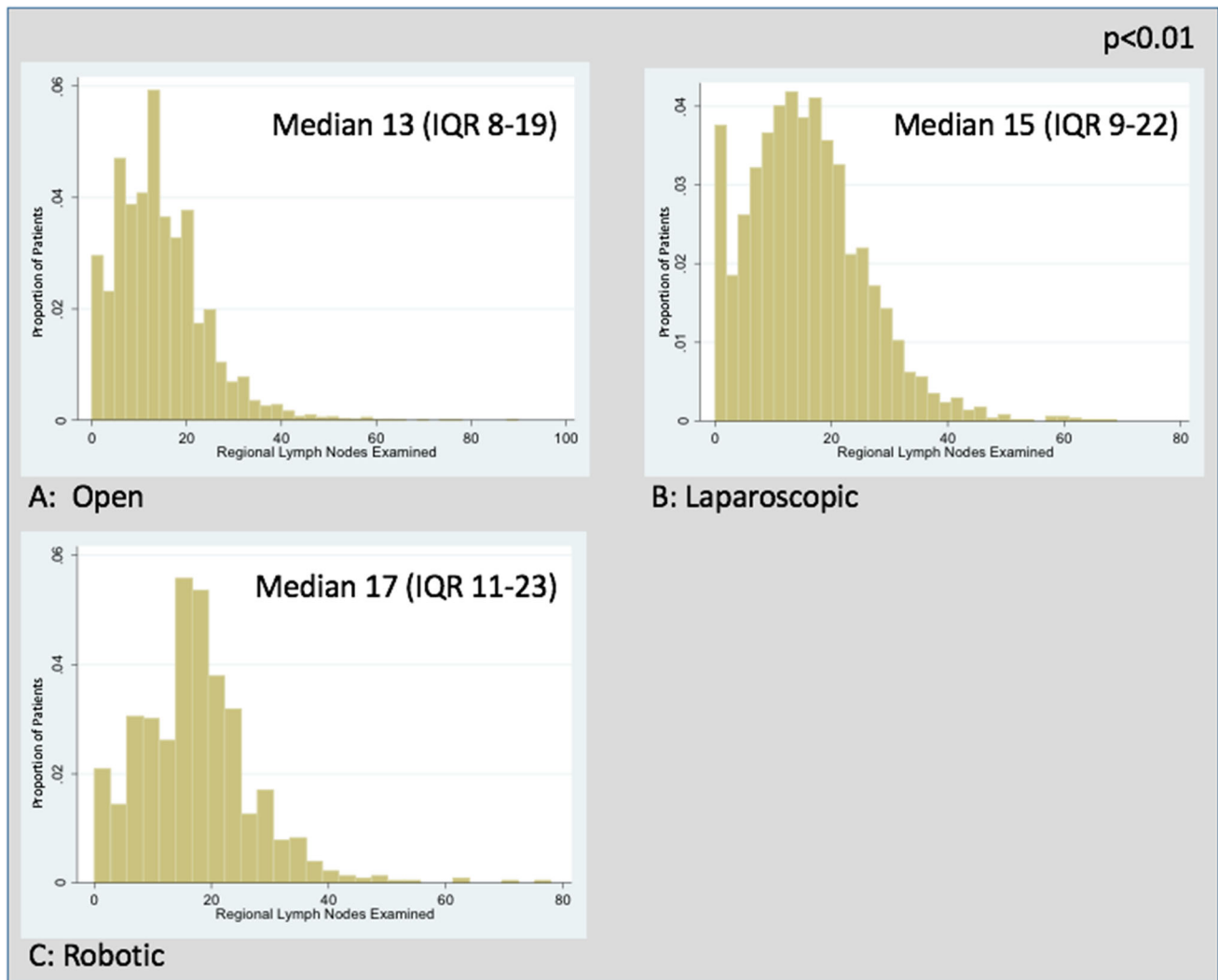


FIG. 3 Pathologically examined lymph nodes following esophagectomy via the (a) open approach, (b) laparoscopic approach, or (c) robotic approach. *IQR* interquartile range

and robotic surgical approaches were associated with an increased likelihood of achieving adequate lymphadenectomy (52.7% of laparoscopic cases, OR 1.28, 95% CI 1.06–1.56; 61.2% of robotic cases, OR 1.71, 95% CI 1.34–2.19; vs. 43.5% of open cases). Furthermore, increasing mean annual hospital esophagectomy volume was associated with achieving adequate lymphadenectomy (e.g. 55.6% in the fourth quartile vs. 32.6% in the first quartile; OR 3.57, 95% CI 2.35–5.43).

This model was found to have good discrimination (C-statistic 0.68) and calibration (Hosmer and Lemeshow Chi-square $p = 0.34$). Sensitivity analyses evaluating the association between treatment factors and adequate lymphadenectomy in the subset of patients with advanced tumors who would meet recommendations for neoadjuvant therapy yielded qualitatively similar results.

DISCUSSION

Adequate lymphadenectomy is important for accurate staging in esophageal cancer. The NCCN guidelines have defined adequate lymphadenectomy as evaluation of at least 15 lymph nodes following esophagectomy for esophageal cancer. However, various studies have advocated for differing lymphadenectomy thresholds, which may vary by treatment approach. In this study, 40.6% of patients achieved adequate lymphadenectomy overall, with the proportion of patients meeting this threshold increasing over the course of the study. Several patient, tumor, and hospital characteristics were associated with adequate lymphadenectomy, including Hispanic ethnicity and race/ethnicity other than White, Black, or Hispanic, higher median ZIP code income, greater distance traveled to the treating hospital, hospital location in a metropolitan area,

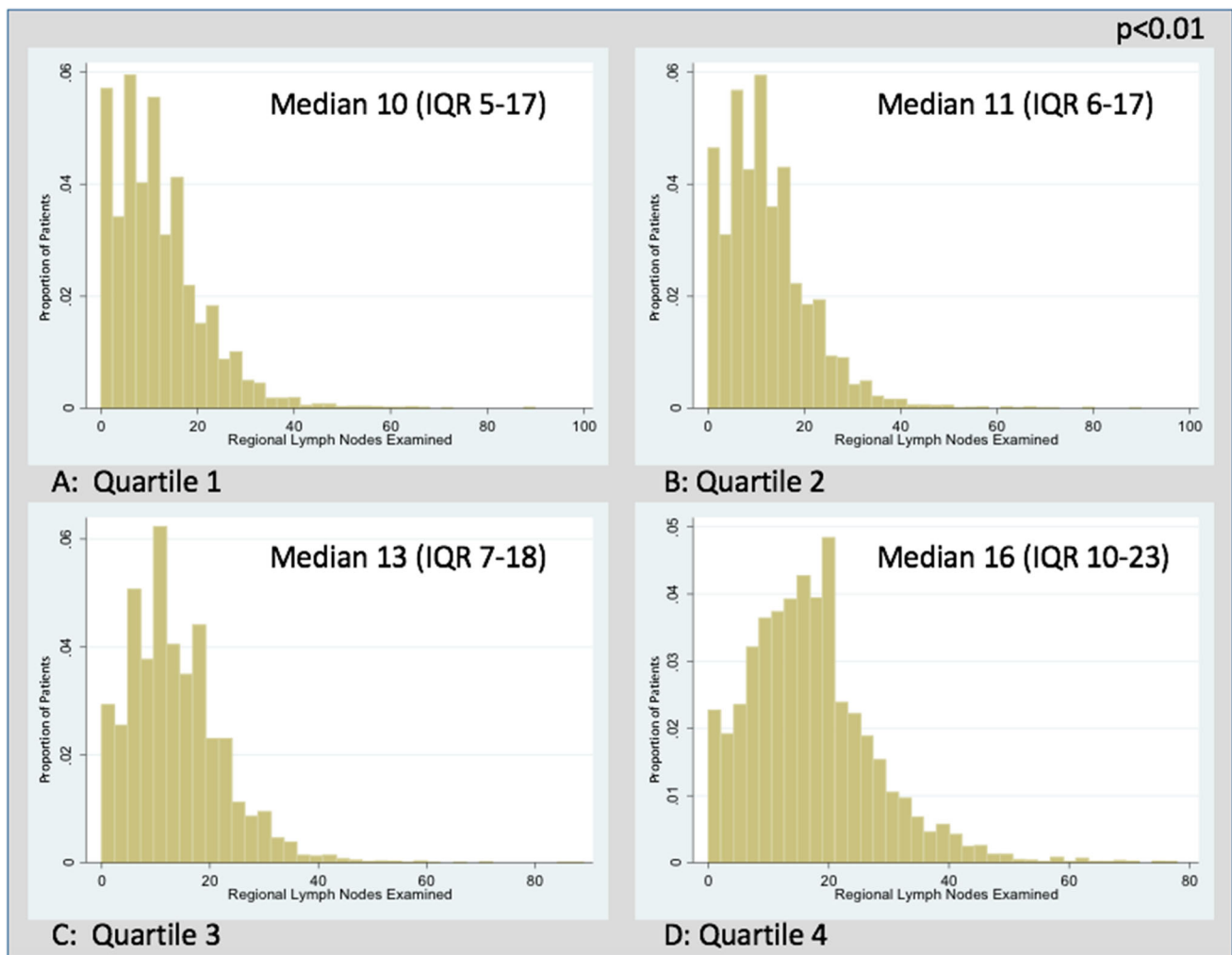


FIG. 4 Pathologically examined lymph nodes, by quartile of hospital annual esophagectomy volume. (a) Quartile 1; (b) Quartile 2; (c) Quartile 3; (d) Quartile 4. *IQR* interquartile range

and increasing pathologic *N* stage. With regard to treatment approaches specifically, no association was found between the use of neoadjuvant therapy and achieving adequate lymphadenectomy. However, both the laparoscopic and robotic surgical approaches, as well as increasing annual esophagectomy volume, were associated with adequate lymphadenectomy.

Trends in Adequate Lymphadenectomy Over Time

Although the overall rate of adequate lymphadenectomy was 40.6% in this study, the proportion of patients achieving adequate lymphadenectomy increased each year. These findings are concordant with our prior study examining only patients who underwent primary esophagectomy without neoadjuvant therapy, which found that rates of adequate lymphadenectomy improved from 23.5% from 1998 to 2001 to 34.4% from 2005 to 2007.²⁸ There has been an increasing focus on quality initiatives and quality

improvement in cancer care over the past several decades, which could be the predominant driver of the improvements seen in adequate lymphadenectomy rates.²⁹ Furthermore, adequate lymphadenectomy may serve as a surrogate for unmeasured quality factors such as surgical technique, thoroughness of pathologic evaluation, or improved processes of care.^{30,31}

Lymphadenectomy Yield and Adequate

Lymphadenectomy Rates by Treatment Characteristics

By comparing the distribution of the number of lymph nodes examined following esophagectomy, we identified variation based on some treatment characteristics. The median number of examined lymph nodes and the *IQR* were identical in patients with or without neoadjuvant therapy. Prior studies have shown that the mean number of examined lymph nodes was lower in patients receiving neoadjuvant therapy.^{4,32,33} In fact, we too identified that

TABLE 2 Likelihood of adequate lymphadenectomy (≥ 15 nodes examined) by sample characteristics

	<15 nodes examined [<i>n</i> (%)]	≥ 15 nodes examined [<i>n</i> (%)]	<i>p</i> value ^a
Total cases	14,494 (59.4)	9919 (40.6)	
Age, years			0.22
< 55	3145 (60.0)	2098 (40.0)	
55–64	5118 (58.5)	3631 (41.5)	
65–74	4654 (59.7)	3139 (40.3)	
≥ 75	1577 (60.0)	1051 (40.0)	
Sex			0.17
Male	12,071 (59.2)	8327 (40.8)	
Female	2423 (60.4)	1592 (39.7)	
Race/ethnicity			< 0.01
White	13,007 (59.3)	8923 (40.7)	
Black	700 (66.0)	361 (34.0)	
Hispanic	409 (58.9)	286 (41.2)	
Other	378 (52.0)	349 (48.0)	
Insurance status			< 0.01
Private	6874 (58.3)	4926 (41.8)	
Medicare	5983 (60.2)	3961 (39.8)	
Medicaid	839 (61.7)	521 (38.3)	
Other government	458 (58.9)	320 (41.1)	
Uninsured	340 (64.0)	191 (36.0)	
Charlson–Deyo index			0.01
0	10,464 (58.8)	7323 (41.2)	
1	3176 (60.4)	2081 (39.6)	
2	656 (61.7)	408 (38.4)	
≥ 3	198 (64.9)	107 (35.1)	
Median zip code income, US\$			< 0.01
< 38,000	2311 (63.4)	1333 (36.6)	
38,000–47,999	3629 (60.8)	2340 (39.2)	
48,000–62,999	4045 (59.0)	2812 (41.0)	
$\geq 63,000$	4239 (56.2)	3310 (43.9)	
Quartile of distance to hospital (miles)			< 0.01
1 (≤ 7.0)	3826 (63.6)	2189 (36.4)	
2 (7.1–17.8)	3685 (61.1)	2347 (38.9)	
3 (17.9–47.7)	3544 (59.2)	2443 (40.8)	
4 (≥ 47.8)	3172 (52.9)	2824 (47.1)	
Facility type			< 0.01
Academic/research	6809 (53.4)	5949 (46.6)	
Integrated Network Cancer Program	1705 (66.2)	872 (33.8)	
Comprehensive Community Cancer Program	4992 (66.4)	2525 (33.6)	
Community Cancer Program	780 (64.7)	425 (35.3)	
Hospital location			< 0.01
Metropolitan	11,093 (58.8)	7782 (41.2)	
Urban	2502 (60.7)	1621 (39.3)	
Rural	339 (64.3)	188 (35.7)	

TABLE 2 (continued)

	<15 nodes examined [n (%)]	≥15 nodes examined [n (%)]	<i>p</i> value ^a
Histologic morphology			
Adenocarcinoma	11,946 (59.1)	8276 (40.9)	0.04
Squamous cell carcinoma	2548 (60.8)	1643 (39.2)	
Pathologic <i>T</i> stage			
<i>T0/Tis</i>	1798 (60.1)	1192 (39.9)	0.01
<i>T1</i>	3319 (57.7)	2435 (42.3)	
<i>T2</i>	2048 (57.5)	1516 (42.5)	
<i>T3</i>	4275 (56.1)	3351 (43.9)	
<i>T4</i>	219 (56.7)	167 (43.3)	
Pathologic <i>N</i> stage			
<i>N0</i>	7672 (60.9)	4937 (39.2)	< 0.01
<i>N1</i>	3588 (55.8)	2840 (44.2)	
<i>N2</i>	511 (43.9)	653 (56.1)	
<i>N3</i>	119 (23.5)	388 (76.5)	
Tumor grade			
Well-differentiated	1031 (62.2)	628 (37.9)	< 0.01
Moderately differentiated	5402 (59.2)	3719 (40.8)	
Poorly differentiated	5790 (57.4)	4304 (42.6)	
Undifferentiated	169 (52.5)	153 (47.5)	
Tumor size, cm			
≤ 2.0	2989 (59.8)	2010 (40.2)	< 0.01
2.1–4.0	3819 (59.5)	2600 (40.5)	
4.1–6.0	2321 (55.3)	1878 (44.7)	
> 6.0	1451 (53.1)	1281 (46.9)	
Neoadjuvant therapy			
No	5661 (59.2)	3904 (40.8)	0.64
Yes	8833 (59.5)	6015 (40.5)	
Surgical approach ^b			
Open	3904 (56.5)	3002 (43.5)	< 0.01
Laparoscopic	1209 (47.3)	1348 (52.7)	
Robotic	320 (38.8)	504 (61.2)	
Mean annual hospital esophagectomy volume quartile (n/year)			
1 (< 1.7)	4122 (67.4)	1991 (32.6)	< 0.01
2 (1.7–4.2)	4023 (66.2)	2056 (33.8)	
3 (4.3–10.0)	3653 (59.2)	2521 (40.8)	
4 (> 10.0)	2671 (44.4)	3343 (55.6)	

^aChi-square tests^bSurgical approach available beginning in 2010

mean lymph node harvest was lower following neoadjuvant therapy versus without (13.5 vs. 14.1; $p < 0.01$); however, based on the nonparametric data distribution, comparison of medians is more statistically appropriate.

Based on the previously reported variation in lymphadenectomy yield following neoadjuvant therapy, prior studies have advocated for adjustments to the nodal threshold defining adequate lymphadenectomy following

neoadjuvant therapy.^{5,16,32,34} However, this study demonstrates that there is no difference in the likelihood of evaluating 15 or more lymph nodes following neoadjuvant therapy. Considering this finding in light of the fact that many patients do not achieve adequate lymphadenectomy, we argue that the oncologic community should accept a generalized lymphadenectomy threshold regardless of the therapeutic approach, and instead focus on modifiable

TABLE 3 Association between patient and hospital factors and adequate lymphadenectomy (≥ 15 nodes examined)

	Adjusted OR (95% CI)	<i>p</i> value
Race/ethnicity		
White	1.00	Ref
Black	0.95 (0.72–1.24)	0.70
Hispanic	1.50 (1.09–2.06)	0.01
Other	1.42 (1.05–1.91)	0.02
Insurance status		
Private	1.00	Ref
Medicare	0.92 (0.82–1.03)	0.14
Medicaid	0.87 (0.68–1.10)	0.24
Other government	0.98 (0.67–1.45)	0.93
Uninsured	0.80 (0.53–1.20)	0.28
Charlson–Deyo index		
0	1.00	Ref
1	0.99 (0.87–1.13)	0.93
2	1.10 (0.88–1.38)	0.40
≥ 3	0.88 (0.57–1.37)	0.58
Median zip code income, US\$		
< 38,000	1.00	Ref
38,000–47,999	1.04 (0.87–1.24)	0.69
48,000–62,999	1.18 (0.97–1.44)	0.10
$\geq 63,000$	1.28 (1.03–1.59)	0.02
Quartile of distance to hospital (miles)		
1 (≤ 7.0)	1.00	Ref
2 (7.1–17.8)	1.02 (0.86–1.21)	0.78
3 (17.9–47.7)	1.06 (0.88–1.28)	0.53
4 (≥ 47.8)	1.31 (1.07–1.60)	0.01
Facility type		
Academic/research	1.00	Ref
Integrated Network Cancer Program	0.88 (0.69–1.13)	0.32
Comprehensive Community Cancer Program	0.90 (0.69–1.18)	0.45
Community Cancer Program	1.18 (0.70–1.99)	0.54
Hospital location		
Metropolitan	1.00	Ref
Urban	0.81 (0.67–0.98)	0.03
Rural	0.91 (0.67–1.23)	0.53
Histologic morphology		
Adenocarcinoma	1.00	Ref
Squamous cell carcinoma	1.10 (0.95–1.27)	0.22
Pathologic <i>T</i> stage		
<i>T0/Tis</i>	1.00	Ref
<i>T1</i>	1.18 (1.00–1.39)	0.06
<i>T2</i>	1.17 (0.96–1.44)	0.12
<i>T3</i>	0.93 (0.78–1.10)	0.38
<i>T4</i>	0.83 (0.51–1.33)	0.44
Pathologic <i>N</i> stage		
<i>N0</i>	1.00	Ref
<i>N1</i>	1.45 (1.27–1.65)	< 0.01
<i>N2</i>	1.77 (1.48–2.12)	< 0.01
<i>N3</i>	5.06 (3.77–6.79)	< 0.01

TABLE 3 (continued)

	Adjusted OR (95% CI)	<i>p</i> value
Tumor grade		
Well-differentiated	1.00	Ref
Moderately differentiated	0.89 (0.73–1.09)	0.27
Poorly differentiated	0.87 (0.71–1.06)	0.17
Undifferentiated	0.92 (0.54–1.58)	0.77
Tumor size, cm		
≤ 2.0	1.00	Ref
2.1–4.0	0.96 (0.83–1.11)	0.58
4.1–6.0	1.10 (0.93–1.29)	0.26
> 6.0	1.02 (0.84–1.24)	0.82
Neoadjuvant therapy		
No	1.00	Ref
Yes	0.94 (0.82–1.07)	0.35
Surgical approach		
Open	1.00	Ref
Laparoscopic	1.28 (1.06–1.56)	0.01
Robotic	1.71 (1.34–2.19)	< 0.01
Mean annual hospital esophagectomy volume quartile (<i>n</i> /year)		
1 (< 1.7)	1.00	Ref
2 (1.7–4.2)	1.37 (1.09–1.73)	0.01
3 (4.3–10.0)	2.04 (1.52–2.74)	< 0.01
4 (> 10.0)	3.57 (2.35–5.43)	< 0.01

OR Odds ratio, CI confidence interval

targets for lymphadenectomy improvement, such as surgical approach and hospital volume.

With regard to surgical approach, we found an increased number of examined lymph nodes with laparoscopic and robotic surgery in comparison with the open approach. Several single-institution studies have evaluated lymphadenectomy yield in esophageal cancer across surgical approaches and have found that lymphadenectomy yield is greater with robotic esophagectomy than laparoscopic esophagectomy, which may be driven by improved dissection around the recurrent laryngeal nerve with the robotic approach.^{35–37} However, a meta-analysis of 1862 patients from eight studies found no difference in lymphadenectomy yield between robotic and laparoscopic esophagectomy.³⁸ Several studies have attributed adequate lymphadenectomy rates in laparoscopic esophagectomy to improved visualization in the thorax compared with open surgery, but have largely shown no difference in lymphadenectomy yield in laparoscopic versus open esophagectomy.^{39–41} Other studies have suggested that the challenging learning curve faced in laparoscopic

esophagectomy may lead to fewer harvested lymph nodes early in a surgeon's experience, but that lymph node yield increases over time.⁴² Still, others have reported increased lymph node yield in laparoscopic esophagectomy compared with open esophagectomy.^{43,44} Our finding that laparoscopic and robotic surgical approaches are associated with an increased likelihood of achieving adequate lymphadenectomy after adjusting for potential confounders is a potential target for continued improvement in adequate lymphadenectomy rates.

Finally, we identified a trend toward greater lymphadenectomy yield with each increasing volume quartile. After adjusting for potential confounders in the multivariable logistic regression model, patients treated at hospitals in the fourth volume quartile had 3.5-fold increased odds of achieving adequate lymphadenectomy than those in the first quartile. These findings are consistent with our previous study of patients undergoing primary esophagectomy, as well as others.^{21,28,45,46} Increased distance traveled to the treatment center is associated with adequate lymphadenectomy, and may further support this

finding, as greater distance traveled is likely a surrogate for treatment at a referral center. Considering that adequate lymphadenectomy is associated with accurate staging, which may lead to improved survival, these findings support the notion that surgical esophageal cancer care is best achieved at centralized, high-volume centers.^{47–49}

Although regionalized, high-volume esophagectomy care may be ideal, it is not always possible.^{50,51} In instances where regionalized and high-volume care is not possible, providers could consider offering minimally invasive surgical techniques to patients, as this is another modifiable factor associated with achieving adequate lymphadenectomy. Furthermore, we demonstrate that neoadjuvant therapy is not associated with achieving adequate lymphadenectomy, and providers should maintain the same lymphadenectomy standards following neoadjuvant therapy as those standards used in primary surgical resection.

Limitations

This study should be interpreted in light of several limitations. First, this was a retrospective study, from which we can identify associations but not causation. Thus, we are not able to draw conclusions as to why the identified factors are or are not associated with adequate lymphadenectomy; however, we attempted to control for confounding by adjusting for all known predictors of adequate lymphadenectomy. Second, the NCDB collects data on patients with malignancy treated at all CoC hospitals, but these data may not be representative of the entire population. However, most large hospitals are CoC-accredited, and those missing from the NCDB are likely small hospitals, which would bias our results toward the null hypothesis. Third, although this study focuses on the association between the use of neoadjuvant therapy and adequate lymphadenectomy, we are unable to evaluate treatment response in this study. However, on the whole, neoadjuvant therapy has been shown to be beneficial in advanced-stage esophageal cancer, which has been demonstrated in other studies of esophageal cancer using the NCDB. Fourth, we were unable to determine the specific surgical approach based on the data available to us (e.g. transhiatal, Ivor Lewis, or McKeown esophagectomy). Finally, nodal evaluation is dependent not only on the surgical resection but also on the pathologic identification of lymph nodes, both of which can be variable. We were unable to standardize either of these aspects of care in this retrospective study, which may limit the interpretation of our findings. Nonetheless, both adequate surgical resection and pathologic evaluation are necessary for cancer staging, which is the intended quality focus of this study.

CONCLUSION

Adequate lymphadenectomy was achieved in 40.6% of patients overall, but increased over each year of this study. We found no difference in the likelihood of achieving adequate lymphadenectomy based on neoadjuvant therapy, but laparoscopic and robotic surgical approaches and treatment at higher-volume centers were associated with adequate lymphadenectomy. Although others have advocated for separate nodal thresholds when evaluating the quality of surgical resection after neoadjuvant therapy, our findings support the use of a generalized lymphadenectomy quality measure regardless of the treatment approach. However, a focus on surgical approach and esophagectomy volume, which are modifiable factors associated with adequate lymphadenectomy, may promote continuous quality improvement in esophageal cancer care.

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