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ORIGINAL ARTICLE

Lymph Node Harvest During Esophagectomy Is Not Influenced by Use of Neoadjuvant Therapy or Clinical Disease Stage

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Abstract
Introduction The purpose of this study was to evaluate the effects of neoadjuvant therapy on lymph node harvest (LNH), lymph node ratio (LNR), and overall survival rates after esophagectomy.
Methods A retrospective analysis of 111 patients who underwent esophagectomy for esophageal adenocarcinoma from 2001 to 2010 was performed. Patients were divided into two groups: neoadjuvant chemoradiotherapy prior to surgery (NEOSURG) versus surgery alone (SURG).
Results There were 83 patients (75 %) in the NEOSURG group and 28 (25 %) in the SURG group with a mean age of 66 and 67 years, respectively. The median LNH in the NEOSURG group and SURG group was 16.0 and 15.5, respectively (p=0.57). Within the NEOSURG group, the median LNH was 16 for complete responders, 14 for partial responders, 16 for nonresponders, and 18 in those who were pathologically upstaged (p=0.434). The median LNR was 0, 0, 0.1, and 0.2, respectively (p<0.001). Complete response after neoadjuvant therapy demonstrated a trend toward improved survival (p=0.056).
Conclusion The LNH was not significantly influenced by neoadjuvant treatment or pathologic response. The LNR was inversely related to pathologic response after neoadjuvant therapy. Complete pathologic response to neoadjuvant therapy trends to improve survival rates.

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Keywords Neoadjuvant therapy · Esophageal cancer · Oesophageal cancer · Esophagectomy · Lymph node harvest · Adenocarcinoma · Lymph node ratio

Introduction

Surgery remains a primary treatment modality for esophageal cancer, despite relatively poor overall survival rates. Over the past two decades, the use of neoadjuvant (induction) chemoradiotherapy prior to surgery has gained popularity. The objective of this combined strategy is to decrease tumor volume in order to increase the likelihood of achieving a R0 surgical resection, minimize local and distant recurrence rates, and ultimately increase overall survival rates. There has been an ongoing debate concerning the influence of neoadjuvant therapy on lymph node harvest and the prognostic value of this information following esophagectomy for esophageal adenocarcinoma.

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A number of published reports have correlated the number of lymph nodes harvested with better prognosis in patients who undergo esophagectomy for esophageal cancer.[1–4] The majority of this data, however, is derived from cohorts of patients who have not been treated with neoadjuvant therapy prior to surgery.[1,2,4] Further, some authors have reported that induction therapy decreases the number of lymph node harvested after esophagectomy for cancer.[5] In aggregate, these reports tend to present a confusing picture of how neoadjuvant therapy influences nodal harvest and, by extension, the overall treatment strategy for esophageal cancer patients undergoing surgical resection. The specific aim of this study was to evaluate the effects of neoadjuvant therapy on the number of lymph nodes harvested and on lymph node ratio (number of positive nodes over total of nodes resected) after esophagectomy for cancer. In addition, we also wished to evaluate the effect of this data on overall survival rate of patients with esophageal cancer undergoing curative resection.

Material and Methods

Study Population and Preoperative Management

This study was approved by the Institutional Review Board (IRB) at Oregon Health and Science University (OHSU, IRB1759). One hundred and eleven consecutive patients with adenocarcinoma of the esophagus treated with two- or three-field esophagectomy between January 1, 2001, and December 31, 2010, were identified from a prospectively maintained cancer registry. All patients were grouped depending on whether or not they received neoadjuvant therapy followed by surgery (NEOSURG) or surgery alone (SURG). All patients underwent clinical staging prior to treatment. This included upper endoscopy, endoscopic ultrasonography (EUS), computed tomography (CT) of the chest, abdomen, and pelvis, and radiolabeled (flouride-18) fluorodeoxyglucose whole-body positron emission tomography (PET). Based on the results of these studies, those with clinical stage II or III esophageal cancer were offered neoadjuvant chemoradiotherapy followed by esophagectomy 6–8 weeks after completing induction therapy, or early stage patients were offered surgery alone.

Neoadjuvant Approach

In the NEOSURG group, induction treatment consisted of multimodality chemoradiotherapy prior to surgery. The most common chemotherapy regimen was 5-fluoracil combined with cisplatin or carboplatin combined with paclitaxel. External beam radiation therapy (EBRT) was administered in daily fractions of 1.8 Gy each (Monday to Friday) to a total dose of 40.5 to 50.4 Gy.

Operative Approach

Two (Ivor Lewis) or three-field (McKeown) esophagectomy was performed, depending on the patient's body habitus, pulmonary status, previous operative history, and the year of esophagectomy. In the two-field approach, the anastomosis was performed in the right chest, while the three-field approach had the anastomosis located in the neck. No cervical lymphadenectomy was performed for any technique.

Open esophagectomy was performed, as originally described by Lewis, with minor modifications.[6] After abdominal exploration, the stomach was mobilized on the right gastric and right gastroepiploic arteries. The left gastric artery was divided at its origin, and all lymph nodes were harvested with the vessel. Lymph nodes extending from the right gastric vessel, through the base of the celiac axis, and nodes superior to the proximal portion of the splenic artery, as well as those along the lesser curvature and upper greater curve of the stomach were included in the resection (stations 1–3, 4a, 5, 7–9, and 11p).[7] A pyloroplasty/pyloromyotomy was performed on all patients. Once the abdominal portion was complete, the patient was repositioned, and a right posterolateral thoracotomy was performed. The esophagus was mobilized, all paraesophageal lymph nodes (including, station 7 and levels 8R, 8L, and 9) were removed, and the specimen was resected. An esophagogastric anastomosis was constructed in the chest. Most often, a hand-sewn two-layer anastomosis was used for the open approach, and the remainder was performed, using a linear or circular stapler. Chest tubes were placed and the thoracotomy was closed. For the MIE approach, the abdominal and chest incisions were laparoscopic ports, instead of the larger incisions used for the open approach.

A three-field MIE was performed, as previously described.[8] The patient was initially positioned in a left lateral decubitus position to perform the chest portion of the procedure. Thoracoscopic esophageal mobilization with en bloc lymphadenectomy of subcarinal (station 7), paraesophageal (level 8), and pulmonary ligament nodes (levels 9) was performed through the right side of the chest. In addition, superior mediastinal nodes (stations 3P, 2R, and 4R) were removed in the dissection. The abdominal portion of the operation consisted of laparoscopic conduit preparation, with an en bloc upper abdominal central lymphadenectomy (stations 1–3, 4a, 5, 7–9, and 11p).[7] A left neck approach was performed through a cervical incision, and the conduit was brought up into the neck, where an end-to-side stapled cervical esophagogastric anastomosis was created, using a modification of the technique originally described by Orringer.[9]

Postoperative Pathology Review

Patients treated with NEOSURG were further subdivided, according to their response to the treatment. Complete

pathologic responders (pCR) were defined by having no cancer observed on final pathologic examination by a board-certified pathologist. Partial responders were identified, based on the final pathological stage (pStage) being lower than the pre-neoadjuvant clinical stage (cStage). Nonresponders were identified if pStage and cStage were identical on postoperative review. Patients were considered to have progressive disease or to be upstaged if pStage was higher than cStage. The data was further analyzed, according to lymph node harvest, lymph node ratio (defined as the ratio between the number of positive over the total number of lymph nodes), and overall survival. Staging was established according to the seventh edition of the AJCC Cancer Staging Manual.[10]

Statistical Methods

The Pearson test was used to compare categorical variables and the Wilcoxon test to compare continuous variables. The nonparametric Kruskal-Wallis test was used to compare more than two independent samples. R software (version 2.13.1, R Development Core Team, Vienna, Austria) was used for statistical analysis. p Values ≤ 0.05 were considered significant. Values between 0.10 and 0.05 were regarded as a trend toward significance.

Results

Three hundred and sixty patients were surveyed, and 111 patients with esophageal cancer were included in the study group. There were 95 males and 16 females. Overall, the median age was 67 years (range 39–89), and the majority (97 %) were Caucasians. Eighty three (75 %) patients received neoadjuvant therapy prior to esophagectomy (NEOSURG), and 28 patients (25 %) were treated with surgery alone (SURG). Patients treated with neoadjuvant therapy had more advanced disease at the time of clinical staging. Twenty-three (92 %) patients in the SURG group had no evidence of nodal disease (N0), based on pre-operative testing, while 20 patients (24 %) in the NEOSURG group were clinically node-negative (N0) ($p<0.001$, Table 1). More lymph nodes were removed by the MIE, as compared to the open approach, and this was consistent within each group. Overall volume in the two groups, however, was similar ($p=0.57$, Table 2).

After resection, pathology revealed that 18 NEOSURG patients (22 %) were complete responders and 37 (45 %) were partial responders. In 19 (23 %), the pathological stage was the same as clinical stage, and seven (8 %) were upstaged (Table 3). Pathology reports were not available for two patients, and they were excluded from the lymph nodal analyses.

Table 1 Demographics for the 111 patients in the current study

	SURG (N=28)	NEOSURG (N=83)	p value
Age[a]	67 (61–73)	66 (60–74)	0.77[b]
Gender (%)			0.55[c]
M	23 (82 %)	72 (87 %)	
F	5 (18 %)	11 (13 %)	
Approach (%)			0.007[c]
Minimally invasive	8 (29 %)	48 (58 %)	
Open	20 (71 %)	35 (42 %)	
Clinical stage (N (%))			<0.001[c]
0: Tis,N0,M0	2 (7 %)	0 (0 %)	
IA	13 (48 %)	1 (1 %)	
IIA	8 (30 %)	18 (22 %)	
IIB	0 (0 %)	10 (12 %)	
III	2 (7 %)	47 (57 %)	
IVA	0 (0 %)	7 (8 %)	
N/A	2 (7 %)	0 (0 %)	
Clinical nodes (N (%))			<0.001[c]
N0	23 (92 %)	20 (24 %)	
N1	2 (8 %)	59 (71 %)	
N2	0 (0 %)	4 (5 %)	
Mortality (N)	1 (3.6 %)	5 (6 %)	0.62[c]

[a] Values are median and inter quartile range (IQR)

[b] Wilcoxon test

[c] Pearson test

Upstaged patients had a significantly higher rate of lymph node positivity and lymph node ratio than complete or partial responders ($p<0.001$, Table 3.).

Overall, the entire cohort had a 5-year survival rate of 40 %. Overall survival was 49 % in the SURG group, and 39 % in the NEOSURG group ($p=0.08$, Fig. 1). The presence of nodal involvement in the resected specimen trended toward decreased survival, when compared with patients without nodal disease ($p=0.07$, Fig. 2). In the NEOSURG group, complete responders had a trend to a better overall survival rate, when compared to noncomplete responders ($p=0.056$).

Table 2 Comparison of node harvest with consideration for surgical approach

	SURG (N=28)	NEOSURG (N=83)	p value
Nodes removed[a]	15.5 (10.5–19.8)	16 (11.5–22.0)	0.57[b]
Open	13.4 (8.5–17.2)	12.1 (6.5–15.0)	
MIE	24.25 (15.7–32.5)	22.1 (15.0–26.5)	
Lymph node ratio[a]	0 (0.0–0.09)	0 (0–0.08)	0.79[b]

[a] Values are median and inter quartile range (IQR)

[b] Wilcoxon test

Table 3 Comparisons of node characteristics based on response to neoadjuvant therapy within the NEOSURG group

	Complete response (*N*=18)	Partial response (*N*=37)	No response (*N*=19)	Upstaged (*N*=7)	*p* value[b]
Nodes removed[a]	16 (9.5–21.5)	14 (9.0–25.0)	16 (12.0–18.0)	18 (15.5–38.5)	0.434
Positive nodes[a]	0 (0)	0 (0–1.0)	1 (1.0–2.0)	2.0 (1.0–6.5)	<0.001
Lymph node ratio[a]	0 (0)	0 (0–0.06)	0.1 (0–0.15)	0.20 (0.04–0.2)	<0.001

[a] Median and inter quartile range (IRQ)

[b] Kruskal-Wallis test

Discussion

Our study found no difference between the SURG and the NEOSURG group in terms of lymph node harvest (15.5 vs 16 lymph nodes, respectively, Table 2). This contrasts with the findings of the Surveillance, Epidemiology, and End Results (SEER) database[11] and is also contrary to a retrospective analysis by others who reported a decrease in total lymph node count in those patients who underwent neoadjuvant therapy, in comparison to those who did not.[5] The authors of the latter study found that the neoadjuvant group had an average of 17 lymph nodes, when compared to 23 found in those undergoing surgery alone.[5] It should be noted that their operative technique was that of an open en bloc esophagectomy, while our study utilized either a conventional open Ivor Lewis or laparoscopic three-field technique. These distinct approaches may well underlie the difference in reported lymph node harvest and may also influence the SEER report. In addition, we have also found that the number of lymph nodes harvested was not affected by the pathologic response to neoadjuvant therapy. Here, patients with a complete response had a mean nodal harvest of 16, and this was similar to that found throughout the pathologic spectrum of partial and nonresponders in our NEOSURG group.

An additional finding from our study is the difference between lymph node harvests from the open versus MIE approach (Table 2). Interestingly, this proportion is also consistent within the SURG and NEOSURG groups. We believe that these differences are the result of a number of factors. First, our study extended over a 10-year span, and this allowed for the collection of data related to long-term changes in technique and treatment of this disease. The number of MIE cases

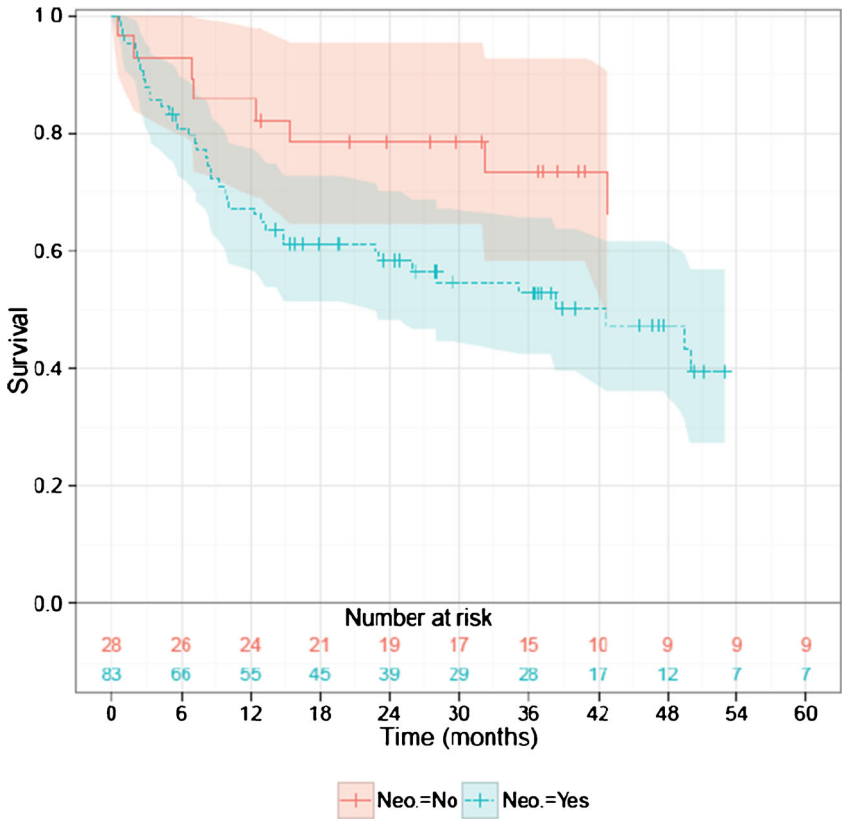

Fig. 1 Kaplan-Meier analysis of overall survival for patients in the NEOSURG group (Neo=yes) in comparison to those in the SURG group (Neo=no). *p*=0.08

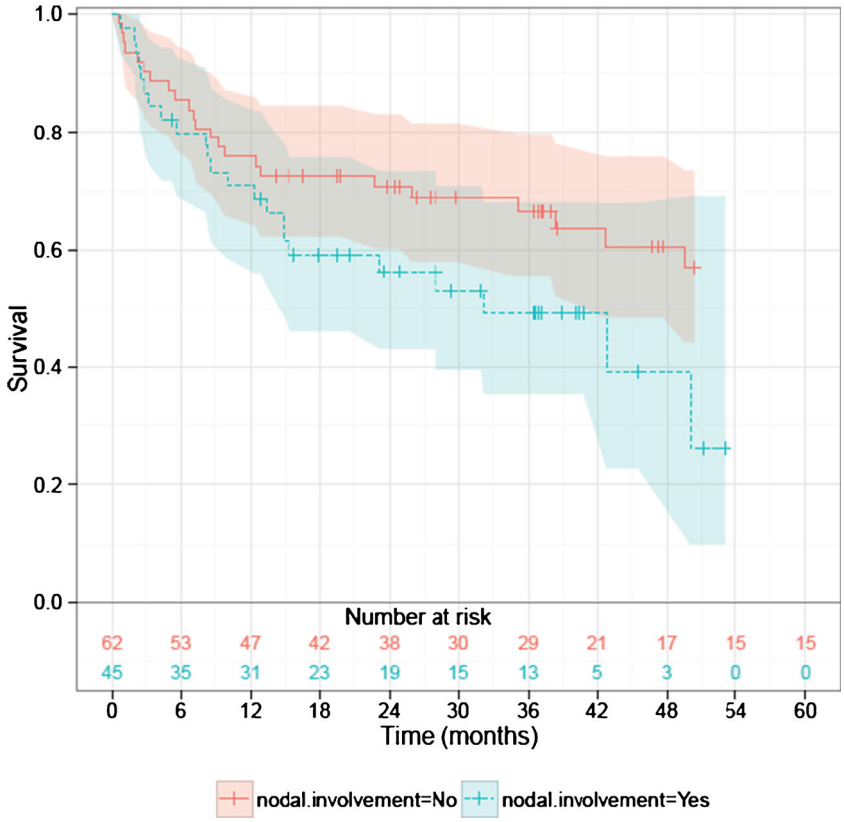

Fig 2 Kaplan-Meier analysis of long-term survival in patients with node-negative disease after pathology review in comparison to those with node-positive disease. $p=0.07$

increased over time, with open cases being concentrated at the beginning of the study. Second, the relevance of lymphadenectomy and its relationship with survival lead to a thorough effort by surgeons and pathologists to harvest and identify as many nodes as possible. The initiation of a bi-weekly Multidisciplinary Care Conference has also served to emphasize node number as an important aspect of treatment. Finally, for the MIE technique, superior mediastinal nodes (stations 3P, 2R, and 4R) were removed for dissection. This dissection was not performed for the Ivor Lewis approach and may also account for the difference in node harvest between the two techniques. Our group did not find any increased technical difficulties related to dissection or resection after neoadjuvant therapy. There was also no significant increase in morbidity or mortality in this group of patients.

Node harvest did not appear to have significant influence on overall survival between either of our study groups. Approximately 50 % of patients in our NEOSURG group and 70 % of our SURG group were alive at 42 weeks. This trend, however, did not reach significance ($p=0.08$, Fig. 1). Our analysis did not extend to 60 months, and we would anticipate that a significant difference between these groups might exist if extended out this long. Our overall survival rates compare favorably with those of the current literature.[12–14] Our patients with node-negative disease had increased survival rates, when compared to those with node-positive disease ($p=0.07$, Fig. 2). Again, this trend did not reach significance, probably due to short-term follow-up and sample size. Other authors have found that a reduction in lymph node metastasis after neoadjuvant therapy does predict better prognosis.[15]

Finally, we also found a trend towards better overall survival rates in patients with a complete response to neoadjuvant treatment. In all, 66 % of our patients had a complete response or were downstaged by neoadjuvant treatment. Overall survival rates were influenced by whether or not the patient experienced a complete pathologic response. This correlates with established findings,[16] but our small study group prevents firm conclusions regarding overall survivability. Taken together, our findings that complete response likely favors overall survival, and neoadjuvant therapy does not appear to influence the extent of lymphadenectomy, adds to other reports in the literature that suggest survival rates are influenced by presence of nodal disease and the degree of response to neoadjuvant therapy.[5,17,18] Our hospital mortality was acceptable and not influenced by neoadjuvant therapy. This is in agreement with the current literature.[19,20]

There are a number of limitations to our study. These include the retrospective design and the differences between the two treatment groups in regards of stage of disease. It is unclear whether or not disease stage may influence the number of lymph nodes harvested. Lymph nodes occupy defined locations but may differ in absolute number between individual patients. This lends itself to sampling error, depending on technique. To counter this, we believe that experienced

surgeons and consistent mature technique do influence lymph node retrieval. In this study, we have had a consistent cadre of three experienced general surgeons and two experienced thoracic surgeons who utilized a standard technique across the study period, which should minimize variation. It should also be understood that preoperative staging can be inaccurate, despite the use of current technologies,[21] which is another important limitation in this study. We have used clinical staging as a baseline reference against which to judge the response to neoadjuvant treatment. As new technology such as endoscopic ultrasound (EUS) and PET/CT scan were added to the staging protocol, staging precision has improved but it should still be considered imprecise based on our experience. The low accuracy of clinical staging is frequently reported in the literature, and it continues to be a limitation of the available staging tools.[22–24]

Conclusion

Total number of lymph nodes harvested after esophagectomy was not significantly influenced by neoadjuvant treatment or by the pathologic response to treatment. The lymph node ratio is inversely related to response to the neoadjuvant therapy. Complete pathologic responders after neoadjuvant therapy have a trend towards better survival rate than noncomplete responders, but larger numbers may be needed to determine significance.

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