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How many nodes need to be removed to make esophagectomy an adequate cancer operation, and does the number change when a patient has chemoradiotherapy before surgery?

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Abstract

Purpose and Design—Node dissection during esophagectomy is an important aspect of esophageal cancer staging. Controversy remains as to how many nodes need to be resected in order to properly stage a patient and whether the removal of more nodes carries a stage-independent survival benefit. A review of literature may help define a minimum accepted number of lymph nodes to be resected in both primary surgery and post-induction therapy scenarios.

Results and Conclusions—The existing evidence generally supports the goal of obtaining a minimum of 15 lymph nodes for pathological examination in both primary surgery and post-induction therapy scenarios.

PURPOSE

Likely as a result of the rich lymphatic networks of the esophagus, esophageal cancer tends to spread early to lymph nodes. Moreover, the longitudinal nature of this lymphatic drainage results in many potential lymph node stations for spread, with some stations more likely to be involved, depending on the location of the primary tumor.[1] Indeed, the American Joint Committee on Cancer staging classification considers nodes from the cervical axis to the celiac axis to be “paraesophageal.” Clearly, esophageal resection must include a proper node dissection, but controversy exists as to how many nodes need to be resected in order to

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properly stage a patient and whether the removal of more nodes portends a stage-independent survival benefit. While the current N classification is based on the number of involved lymph nodes, the denominator is not specified. Moreover, as multimodality treatment is increasingly being used for the treatment of node-positive disease, it is additionally unclear how preoperative chemoradiotherapy affects the nodal yield. In this review, we examine the current literature in an attempt to define a minimum accepted number of lymph nodes to be resected.

DESIGN

A search of the MEDLINE database using PubMed was performed using the following National Library of Medicine Medical Subject Headings (MeSH) terms. Terms of more than one word were enclosed in quotation marks. An identification of the type of term and the PubMed search directions are entered in brackets. Parentheses delineate search series: (*esophageal cancer* [All Fields] OR *esophageal neoplasms* [MeSH Term] OR (*esophageal* [All Fields] AND *neoplasms* [All Fields]) OR *esophageal neoplasms* [All Fields] OR (*esophageal* [All Fields] AND *cancer* [All Fields]) OR *esophageal cancer* [All Fields]) AND *extent* [All Fields] AND (*lymph node excision* [MeSH Term] OR (*lymph* [All Fields] AND *node* [All Fields] AND *excision* [All Fields]) OR *lymph node excision* [All Fields] OR *lymphadenectomy* [All Fields]). Embedded references from the primary articles were reviewed by a group of surgeons considered expert in esophagectomy. The group selected articles for review if they included information on the number of lymph nodes resected in patients.[19]

RESULTS AND CONCLUSIONS

Four main issues were discussed: 1) how much do the surgeon's efforts to do a thorough lymphadenectomy matter? 2) how important is the histology of the primary tumor? 3) how much do the pathologist's efforts to be thorough in specimen processing matter? 4) how are these factors affected by neoadjuvant therapy?

Ensuring Adequacy of Lymphadenectomy

In the recent era of esophagectomy, operative mortality has been reduced to less than 5% in high-volume centers.[2] As a result, there has been increasing focus on technical aspects of the operation that impact longer term outcomes, especially cancer-specific outcomes. There is no doubt that lymph node involvement portends a poor prognosis in esophageal cancer and that lymphadenectomy plays an important role in staging. However, whether extensive lymphadenectomy during esophageal cancer can improve survival because of better control of locoregional disease or simply reflects better staging (i.e., a stage migration phenomenon) remains less clear. Moreover, given that the number of nodes resected is largely independent of patient disease burden and comorbidities, it has potential to act as a surrogate marker for esophagectomy quality. Thus, it is important to define the role of lymphadenectomy at the time of esophagectomy using all the data and evidence available. Therefore, we strive to answer the following question: How many nodes need to be removed to make esophagectomy an adequate cancer operation?

In considering this question, the number of lymph nodes necessary to achieve accurate staging and the number needed to potentially influence survival were both considered. Population-based studies using the National Cancer Institute's SEER database aimed to address this question. Groth et al.[3] demonstrated that a minimum of 12 lymph nodes was required to show any improvement in mortality across all stages, a conclusion based on comparisons with a group that had no lymph nodes resected. Survival was maximized, however, when more than 30 lymph nodes were removed. While their multivariable model did not include the number of positive lymph nodes, in order to reduce multicollinearity, interestingly, when they stratified their results by the number of positive lymph nodes, their results were unchanged.

Greenstein et al.[4] limited their study to T1–3N0 patients without induction radiotherapy. They found that these patients had superior survival rates if more than 10 lymph nodes were removed in T2–3 disease and if more than 18 lymph nodes were removed in T1 disease. Thus, they recommended that greater than 18 nodes be removed. Schwarz et al.[5] used the SEER database to examine the relationship between the number of lymph nodes examined and overall survival. They found total lymph node count to be an independent prognostic variable independent of T and N categories, among others, with greater total (>30) and negative (>15) lymph node counts to be associated with longer survival. A decade later, Samson et al.[6] published a report that examined the National Cancer Database in the United States. Using the National Comprehensive Cancer Network guideline target of 15 or more nodes, they assessed compliance to the guideline and results of studies in which patients underwent esophagectomy with or without induction therapy. Over the study period of 2006–2012, the rate of obtaining 15 or more lymph nodes increased in both community (22.4% to 36.8%) and academic centers (33.4% to 49.5%) over time. In their Cox proportional hazards model, sampling more than 15 lymph nodes was associated with lower long-term mortality. They further explored the number of lymph nodes needed to obtain the greatest influence on long-term mortality and found that a threshold of 25 lymph nodes examined was best. Like all population-based studies, these are limited by the administrative nature of data: there are no details on performance status, comorbidities, use of preoperative chemotherapy, or institution or surgical volume (i.e., more experienced centers typically perform guideline-conforming lymphadenectomy more often and record higher survival rates than do centers performing fewer esophagectomies). Moreover, these databases are not designed to answer questions of surgical technique.

Others have examined this question using institutional databases. In an international multicenter study, Peyre et al.[7] examined the records of 2,303 patients with esophageal cancer from nine international centers who had an R0 esophagectomy and were followed at regular intervals for 5 years or until death. The median number of nodes removed was 17, and Cox regression analysis showed that the number of lymph nodes removed was an independent predictor of survival. Indeed, it was the third most important factor after number of lymph nodes involved and depth of invasion. They reported that resection of 23 lymph nodes was the optimal threshold for lymph node removal based on their Cox model. They also found that an en bloc removal was most likely to get 23 nodes and that survival rates were lower if an en bloc resection was not performed, even if more than 23 nodes were

obtained. Because the number of nodes was modeled as a continuous variable, they believed this represented actual improved locoregional control rather than stage migration.

Single-institution studies include one by Bollschweiler et al.,[8] who showed that in patients with disease staged as N0, survival was improved if more than 15 lymph nodes were examined. Rizk et al.[9] examined reports on 336 patients who underwent esophagectomy without neoadjuvant treatment. Among patients with 0–4 involved lymph nodes, survival was better if more than 18 nodes were removed. Interestingly, they showed that if more than 18 nodes were removed, prognosis could be determined simply on how many involved nodes were present (0, 1–4, or >4, where >4 was equated with M1 disease). Altorki et al.[10] retrospectively reviewed 264 patients who underwent esophagectomy without neoadjuvant therapy and found that higher lymph node counts were associated with improved survival; however, it was dependent on N status.[10] In N1 patients, examining more than 17 nodes maximized survival, whereas in patients with N0, examining more than 40 appeared to improve survival. This result is similar to that found by Rizk et al.[11] when they examined the Worldwide Esophageal Cancer Collaboration data in 2010. In their study, they recommend different targets for lymphadenectomy, depending on T stage. In earlier cancers, fewer nodes are needed, and in more advanced cancers, more nodes are needed. Specifically, they recommend 10 nodes for pT1, 20 for pT2, and 30 or more for pT3/T4. Most recently, the Worldwide Esophageal Cancer Collaboration again studied this question using their multi-institutional database relying on modern machine learning analysis strategies.[12] They found that short cancers (<2.5 cm) require 60 nodes to accurately detect node-positive disease. In contrast, cancers greater than 2.5 cm in length require only 20 nodes. However, as the above studies have shown, the more advanced the cancer, the more resected nodes needed to provide a potential survival benefit. The two goals are therefore in opposition: the earlier the cancer, the more nodes needed for staging, but the fewer nodes needed for survival benefit and vice versa. Overall, given that the survival of patients with more than eight involved nodes is not influenced by the type of operation and extent of node dissection, the maximal clinical benefit of good lymphadenectomy is likely in those with earlier tumors and limited nodal disease.

Two studies have demonstrated that the extent of lymphadenectomy may not influence survival. Lagergren et al.[13] followed 606 patients at a single high-volume center and found that patients who were in the fourth quartile for number of resected nodes (21–52) did not have a statistically significantly lower 5-year mortality than those in the lowest quartile (0–10 nodes). Members of this group and others performed another study using a nationwide, Swedish population–based cohort and similarly found that increased lymph node clearance did not decrease mortality.[14] In fact, in the early T stages (Tis-T1), poorer survival with more lymphadenectomy was found, likely owing to surgical complication. However, again, in that cohort, the fourth quartile for number of resected nodes was relatively low at 16–114. These studies challenge the notion that the more extensive the lymph node dissection, the better the survival and support the alternative hypothesis that an involved lymph node simply represents disseminated disease. Moreover, the lower survival with early T stages implies that aggressive lymph node dissection may result in higher complications and death. It is however somewhat difficult to believe that in a resection specimen, regardless of how conservative a lymph node dissection may be, that 0 – 10 lymph nodes only were resected. It

may be instead that lymph nodes are not being examined by the pathologist, but they were actually resected. Nonetheless, more study is needed as perhaps only a few lymph nodes are needed for staging.

Along those lines, lymph node ratio (LNR), that is, the ratio of the number of metastatic lymph nodes to the total number of lymph nodes, has been purported to be a superior prognostic factor. As a feature that combines the value of positive nodes with the value of nodes resected, whether it adds any additional prognostic knowledge over simply the number of positive lymph nodes remains debated across many cancer types. In gastric cancer, there has been some evidence that LNR is an independent prognostic factor,[15] but LNR is less helpful with head and neck cancers.[16] Like identifying the number of lymph nodes that should be resected, selecting a cutoff ratio also remains controversial. Among others, Rizk et al. identified a lymph node ratio of greater than 0.3 to be associated with the poorest survival rate.[9] Greenstein et al.[17] identified an LNR of greater than 0.2 and Hagen et al.[18] identified an LNR of greater than 0.1 to be significant. It is clear however, that while LNR may have a role in prognosis, it does not obviate the need to perform an adequate lymphadenectomy. An adequate number of lymph nodes must be sampled to provide an adequate nodal “repertoire.”

Effect of the Histology of the Cancer on the Need for Lymphadenectomy

The majority of studies from North America have combined adenocarcinoma and squamous cell carcinoma into a general esophageal cancer group. Asian studies, however, due to epidemiology have more studies with homogeneous populations of squamous cell carcinoma. Squamous cell carcinoma remains the primary form of esophageal cancer in Asia due to smoking, alcohol use, consumption of hot beverages, and poor nutrition. In contrast, adenocarcinoma is increasing in the Western world because of smoking, obesity, and gastroesophageal reflux.[19,20] Molecular epidemiology may also differ between the two populations; thus, some considerations need to be made when extrapolating Asian data to Western populations. Nonetheless, Hu et al.[21] recently performed a large retrospective review in Chinese patients with squamous cell carcinoma. In 1,098 patients who underwent esophagectomy without neoadjuvant treatment, patients with six or more lymph nodes resected had a higher rate of positive lymph nodes than those who had fewer than six nodes resected, and in pathologically node-negative disease, patients who had more than six nodes resected had superior survival. Interestingly, in their study, only a median of four lymph nodes were removed. This is significantly lower than the number reported in other studies. Their cutoff was also low at six compared with that of other studies, but they were still able to show a survival difference using this cutoff point. Peng et al.[22] reviewed reports of 2,033 patients with squamous cell carcinoma and also found that resecting at least six to seven lymph nodes resulted in superior survival. Though this may suggest that fewer nodes need to removed to have an impact on survival rates in squamous cell carcinoma, in the Hu study, only a median of four (interquartile range, 2–6) nodes were removed and thus the investigators may not have been able to reveal improved survival with a more extensive lymphadenectomy.[21]

Effect of the Pathologist

It should be noted that the number of lymph nodes resected is dependent not only on the surgeon but also on the pathologist. The degree of meticulousness of the pathology team in examining the specimen for lymph nodes can influence the count and disposition or categorization of lymph nodes. In the Veeramachaneni et al.[23] study, submission of separate nodal stations to pathologists resulted in 16+/−9 nodes examined, whereas submission of an entire en bloc specimen resulted in only 10+/−8 nodes, a statistically significant difference. Another issue that can arise with picking nodes out individually is the risk of damaging them and/or submitting incomplete rather than entire nodes. Manual node dissection has its limitations; other techniques have been applied with good success to increase the pathologist's retrieval of nodes. In other gastrointestinal cancers (gastric and colon) a meta-analysis indicates that fat-clearing and methylene blue staining increase mean node counts by 13–15 nodes compared to manual lymph node dissection from the surgical specimen. Many of these nodes are 2–5 mm in size but remain important, and despite their small size often harbor malignant cells.[24] The increase in node harvest with these techniques is significant even after neoadjuvant therapy.

Induction Chemoradiotherapy and Lymph Node Yield

The large majority of studies reported above were performed on patients without induction therapy. However, with the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, among others, induction chemoradiotherapy is increasingly being utilized for locally advanced disease, and its use poses the question of whether the induction therapy affects the lymph node yield.[25] There are two explanations: either surgeons put less importance on lymphadenectomy in the setting of induction therapy, or chemoradiation induces regression of lymph nodes.[26] In the CROSS trial, the median lymph node harvest was 15 in the induction group and 18 in the surgery-only group. This difference was not statistically significant ($P = .77$). Luna et al.[27] studied retrospectively 83 patients who received induction chemoradiotherapy and compared them to 28 patients who did not. They found no difference in lymph node harvest between groups. Similarly, Taylor et al.[28] examined propensity score–matched cohorts of patients who received induction chemoradiotherapy and compared them with those who did not. While differences were not statistically significant ($P = .06$), investigators examined only 13 nodes in the induction chemoradiotherapy cohort versus 15 in the surgery-only group. In contrast, Mariette et al.[29] studied 536 patients, of whom 276 (51.5%) received induction chemoradiotherapy, and found that patients who received induction therapy had a statistically significantly lower lymph node harvest (16.9 vs 22.7). In a "real world" nationwide population-based representing 98% of all esophagectomies performed in Sweden over a 13 year period (n=1821), lymph node retrieval was lower after neoadjuvant therapy (median 6, IQR 3–12), than surgery alone (median 8, IQR 5–16). When adjusted for multiple factors including histology, T stage, surgeon volume, and other patient factors, the yield of nodes was 24% lower after neoadjuvant therapy (RR 0.76, 95% CI 0.69–0.84).[31] Another population-based study from the Netherlands over a 5 year period (n=3970) showed a steady increase in median number of nodes harvested overall, starting at 15 in 2011 and increasing to 20 by 2016; the percentage of patients achieving ≥15 LN harvested rose from 51% to 81%.[32] They did identify a statistically significantly removal of less than 15 LN in patients who had

neoadjuvant chemoradiotherapy. No therapy (OR 1.73, p<0.001), or chemotherapy alone (OR 2.15, p<0.001), as induction were more likely to yield ≥15LN. Taken together, the evidence would seem to indicate that induction chemoradiotherapy does have an effect on lymph node harvest yields, but current studies have yet to fully define how this impacts survival. Brescia et al, in a single center study, showed that yields were similar between induction patients and non-induction patients (15[5–46 vs 17[2–47], respectively.[33] Number of positive lymph nodes correlated with survival, much like the non-induction population of Rizk et al. However, number of lymph nodes resected in the induction population did not affect survival. Hanna et al, also in a single center study, specifically examined the number of lymph nodes needed to affect survival post-induction chemoradiotherapy and found that patients with pT3–4 N0 disease, survival was poorer when less than 7 lymph nodes were resected and no pN0 patient died if >27 lymph nodes were resected.[34] This study had a median lymph node yield of only 8, but a range of 0–63 suggesting they had the range of patients to study this issue, but it is unclear if 8 is the usual number resected or if it is a result of the induction therapy. Using the NCDB, Samson et al found that induction therapy led to a decreased likelihood of retrieving more than 15 lymph nodes, but that a sampling of 10–15 lymph nodes was associated with an optimal survival benefit.[30] In the majority of studies with neoadjuvant therapy, the number of nodes removed is ≥ 15. Therefore, lowering the minimum standard for node harvest after chemoradiotherapy is hard to justify. To be clear, the median total nodes removed after induction therapy tends to be lower than with surgery alone, but still should be at least 15 lymph nodes.

Conclusion

Review of the primary data from a group of surgeons considered expert in esophagectomy was inconclusive for an exact cutoff number for how many nodes should be removed to achieve an adequate cancer operation with esophagectomy. The group agreed that the majority of the studies recommend at least 10 nodes should be resected and suggest that more is better, especially in early stage tumors. In centers with the most experience, extent of lymphadenectomy does not correlate with significant risk. Moreover, clinically, it is the early cancers that are most likely to be curative with surgery, and in these cases the danger of compromising outcomes through ineffective lymphadenectomy is greatest. The earlier the cancer, the more nodes that are needed for staging, but the fewer nodes that are needed for survival benefit and vice versa.

Multiple groups have utilized different strategies in studying the number of lymph nodes needed for an adequate lymphadenectomy in esophageal cancer. Administrative databases, collaborative institutional databases, as well as single institution databases have been studied in pursuit of an answer. No prospective or randomized studies have been performed, nor likely will there ever be, given the subject at hand; no surgeon would willingly leave nodal tissue behind. Consequently, each study is along the spectrum of the trade-off between high quality data and high number of patients. Among these studies, Peyre et al[7] and Samson et al[30] have indicated that greater than 23 and 25 nodes, respectively, are the cutoff point beyond which improved survival is appreciated. Most other studies have shown that at least 12 lymph nodes is required and the variable cutoffs may indeed be due to the data source utilized to study the question. If the data source has a low median lymph node recovery, then

the resulting cutoff will be lower as there is a lack of repertoire in the data to identify a higher number of lymph nodes as a cutoff. The Lagergren et al studies indicate that extent of lymphadenectomy makes no difference to survival and may be an extreme example of this issue, given that the median lymph nodes harvests were low. Consequently, due to limitations of the data sources as described above, it is premature to set minimum standards at either of these levels. We therefore recommend the removal of at least 15 lymph nodes as suggested by the previous literature, but urge surgeons to strive for higher numbers whenever possible and especially in patients with early stage cancer. Working with the pathology team to use additional tissue processing techniques beyond manual lymph node harvest is strongly recommended and consistently increases the number of nodes available for examination in other gastrointestinal cancers. Lymphadenectomy should be performed in patients who receive induction chemoradiotherapy in the same manner as patients having de novo surgery; overall node retrieval rate may be lower due to involution of nodes, but more than 15 nodes can be removed in the majority of these cases.

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Synopsis:

The optimal number of lymph nodes that should be harvested with esophagectomy for cancer is debated. The existing evidence generally supports the goal of obtaining a minimum of 15 lymph nodes for pathological examination in both primary surgery and post-induction therapy scenarios.