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# Decoding the Prognostic Significance of Lymphadenectomy Extent in Esophageal Cancer: A Navigational Study

## Özofagus Kanserinde Lenfadenektomi Genişliğinin Prognostik Etkisinin Çözümlenmesi: Bir Yönlendirici Çalışma

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### ABSTRACT

**Objective:** Esophageal cancer lacks a standard surgical approach, and opinions differ regarding the extent of lymphadenectomy. This study aimed to assess the correlation between the extent of lymphadenectomy, patient and tumor characteristics, and survival of esophageal cancer.

**Methods:** Data of 101 patients who underwent surgery for esophageal cancer between 1990 and 2022 were retrospectively analyzed. The mean survival and 1, 3, 5, and 10 year overall survival (OS) rates were examined. Overall survival rates for adenocarcinoma and squamous cell carcinoma were separately evaluated. The relationships among gender, age, tumor size, stage, total number of harvested lymph nodes, and survival were analyzed.

**Results:** Among 101 patients, 34 (33.7%) were female, and 67 (66.3%) were male, with a mean age of 61.01±12.01 years. Among the included patients, 82 (81.2%) had squamous cell carcinoma and 16 (15.8%) had adenocarcinoma. The mean follow-up was 61.2 months, and the OS averaged 61.01±12.01 months. Only the total harvested lymph node count had a statistically significant impact on survival (p=0.17).

**Conclusion:** There was a clear association between the total number of harvested lymph nodes and OS. In squamous cell cancers, the extent of lymph node dissection improves long-term survival. However, the routine use of extended lymphadenectomy for distal cancer remains a topic of debate.

**Keywords:** Esophageal cancer, lymphadenectomy, survival

### ÖZ

**Amaç:** Özofagus kanserinde halen standart bir cerrahi yaklaşım mevcut olmayıp özellikle lenfadenektomi genişliği konusunda farklı görüşler mevcuttur. Bu çalışmada lefadenektomi genişliği ile hasta ve tümör karakteristikleri arasındaki ilişkinin ve sağkalıma etkisinin incelenmesi amaçlanmıştır.

**Yöntemler:** 1990 ile 2022 yılları arasında özofagus kanseri nedeni ile cerrahi uygulanan 101 hastanın verileri retrospektif olarak analiz edildi. Serideki ortalama sağkalım, 1, 3, 5, ve 10 yıllık genel sağkalım (GS) oranları incelendi. Ayrıca GS adenokarsinom ve skuamöz hücreli karsinom grupları için ayrı ayrı değerlendirildi. Cinsiyet, yaş, tümör boyutu, evre, toplam çıkarılan lenf nodu sayısı ile sağkalım arasındaki ilişki analiz edildi.

**Bulgular:** Yüz bir hastanın 34'ü (%33,7) kadın, 67'si (%66,3) erkekti. Ortalama yaş 61,01±12,01 idi. Hastalardan 82'si (%81,2) skuamöz hücreli karsinom, 16'sı (%15,8) adenokarsinom tanısına sahipti. Ortalama takip süresi 61,2 ay, GS ortalaması 59,2±42,12 aydı. Sadece toplam çıkarılan lenf nodu sayısının sağkalım üzerinde istatistiksel olarak anlamlı bir etki gösterdiği görüldü (p=0,17).

**Sonuç:** Toplam çıkarılan lenf nodu sayısı ile GS arasında net bir ilişki bulunmaktadır. Skuamöz hücreli kanserlerde, genişletilmiş lenfadenektomi uzun vadeli sağkalımı arttırır. Ancak, distal yerleşimli kanserlerde genişletilmiş lenfadenektominin rutin uygulanması halen tartışmalıdır.

**Anahtar Sözcükler:** Özofagus kanseri, lenfadenektomi, sağkalım

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## INTRODUCTION

Esophageal cancer is characterized by its aggressive nature and high metastatic potential. Although the most prevalent histopathological type is squamous cell carcinoma, a remarkable increase in adenocarcinoma incidence, particularly in Western countries, has been observed over the past few decades (1-3). Despite surgery being the primary treatment, the overall 5-year survival rate varying between 15% and 25% has prompted a search for approaches to enhance treatment efficacy in esophageal cancer. However, there is still no standard algorithm for approaching esophageal cancer patients (4). Particularly, there are differences in opinion regarding surgical strategies and the extent of lymphadenectomy between Eastern and Western countries (5). Although neoadjuvant and/or adjuvant treatment regimens have been developed with the aim of improving prognosis, enhancing surgical procedures remains the ultimate goal. For patients with resectable non-metastatic cancer, radical en-bloc esophagectomy has been the standard treatment for many years (6). The combination of this approach with extended lymphadenectomy has generated conflicting views among Western and Eastern surgeons regarding its contribution to survival (3,5,7,8). Concerns regarding increased morbidity and mortality have led to a cautious approach toward the adoption of three-field lymphatic dissection in Western countries. However, Japanese researchers have reported significant survival advantages, and this strategy has been widely adopted as the standard for squamous cell carcinomas (9,10). According to the research conducted by Isono et al. (11) it was found that after radical en-bloc resection in thoracic esophageal cancers, the recurrence rate is significantly high in the upper mediastinal and cervical lymph nodes. The dissection of upper mediastinal, recurrent nerve, and neck lymph nodes reduces the recurrence rate and significantly increases survival (11). Kato et al. (12) reported that in transhiatal esophagectomy, metastatic lymph nodes can be left behind, leading to a recurrence rate of 50% in patients with pT1 cancer. These results have led to the adoption of radical esophagectomy, including three-field lymph node dissection, as the standard curative surgical approach for Japanese esophageal cancer treatment. Histopathology is a significant factor affecting survival in esophageal cancer. The extent of lymphadenectomy may vary according to the two common histopathological types (4). Lymph node status is a key determinant of survival. However, there are different opinions regarding the minimum number of lymph nodes that should be dissected for ideal treatment and staging (13). For node-negative squamous cell cancers, 5 year overall survival (OS) after surgery is reported to be 58%, whereas it decreases to 15.9% in cases with two or more lymph node metastases (14). The aim of this study was to evaluate the prognostic impact of lymphadenectomy extent in patients undergoing surgical treatment for esophageal cancer and to examine patient, tumor, and surgery-related factors influencing survival. The results are intended to provide guidance for determining the surgical approach and extent of lymphadenectomy in patients with resectable non-metastatic esophageal cancer.

## MATERIALS AND METHODS

Between December 1990 and December 2022, data on patients who underwent surgery for esophageal cancer were retrospectively collected through the hospital information management system and patient files. The inclusion criteria for the study were as follows: (1) histopathological diagnosis of esophageal cancer preoperatively, (2) preoperative assessment confirming resectable and non-metastatic cancer, (3) surgeries performed by the same surgical team. The exclusion criteria were: (1) benign histopathology and (2) inability to access patient data. The study encompasses a prolonged timeframe during which all patients in the series underwent surgery performed by a senior surgeon who served as team leader throughout the entire period. Throughout this entire period, there has been no major change in the surgical technique of esophagectomy and lymphadenectomy; only technological advancements have been integrated into these procedures. The study cohort consists of a group of patients who underwent standard extended lymphadenectomy. All procedures in this study were carried out following the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local Gazi University Clinical Research Ethics Committee (approval number: 643, date: 31.07.2023). The demographic characteristics (age and gender), tumor localization (upper, middle, and lower), organ used for reconstruction, pyloric drainage status (piloroplasty, pyloromyotomy, or no drainage procedure), jejunostomy for nutrition, chemotherapy, and radiotherapy (neoadjuvant and/or adjuvant), early and late complications, mortality, histopathology results, differentiation, tumor diameter, total number of removed lymph nodes, number of metastatic lymph nodes, postoperative stage, and follow-up duration were recorded. The average survival (months) in the series and the 1, 3, 5, and 10 year OS rates were calculated. The OS rates of the adenocarcinoma and squamous cell carcinoma groups were evaluated separately. The relationship between gender, age, tumor diameter, stage, and total number of removed lymph nodes and survival was analyzed. All data were transferred to a computer environment, and SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Categorical measurements were presented as numbers and percentages, while continuous measurements were presented as mean, standard deviation, and range. The Kaplan-Meier estimator was used for survival analysis according to stage and histopathology type. Cox regression analysis was used to evaluate factors associated with OS. In all statistical analyses, $p<0.05$ value was set as statistically significant.

## RESULTS

Among the 101 patients, 34 (33.7%) were female and 67 (66.3%) were male. The mean age of the patients was 61.01±12.01 years (range, 27-82). Tumors were localized in the upper esophagus in 6 patients (5.9%), middle esophagus in 57 patients (56.4%), and lower esophagus in 38 patients (37.6%). The histopathological results showed that 82 patients had squamous cell carcinoma (81.2%), 16 patients had adenocarcinoma (15.8%), 1 patient had both squamous cell carcinoma and leiomyosarcoma (1%), 1 patient had malignant melanoma (1%), and 1 patient had neuroendocrine tumor (1%). Upon examination of differentiation, 19 patients (19%) were poorly differentiated, 36 patients (36%) were moderately differentiated, 42 patients (42%) were well-differentiated, 2 patients (2%) were undifferentiated, and 1 patient (1%) was poorly differentiated. All adenocarcinomas were localized in the lower esophagus, as

expected. Among the squamous cell cancers, 5 (6.1%) were localized in the upper esophagus, 57 (69.5%) in the middle esophagus, and 20 (24.4%) in the lower esophagus. Regarding the organs used for reconstruction, 96 patients (95%) received a stomach, 3 patients (3%) received a jejunum, and 2 patients (2%) received the left colon. One patient (1%) underwent total gastrectomy. Pyloromyotomy and pyloroplasty were performed in 2 patients (2%), while pyloroplasty was performed in 96 patients (95%). Two patients (2%) did not undergo pyloric drainage. Jejunostomy for nutrition was performed in 71 patients (70.3%), but not in 30 patients (29.7%). Three patients (3%) received neoadjuvant chemotherapy, while 57 patients (56.4%) received adjuvant chemotherapy. Forty one patients (40.6%) did not receive any chemotherapy. Three patients (3%) received neoadjuvant radiotherapy, while 43 patients (42.6%) received adjuvant radiotherapy. Fifty five patients (54.5%) did not receive radiotherapy. Three patients who received neoadjuvant chemotherapy also received neoadjuvant radiotherapy. Consequently, the number of patients in the series who underwent neoadjuvant chemoradiation was limited to only 3 (3%). All of these patients have a diagnosis of squamous cell carcinoma, and the tumor was located in the upper esophagus.

Early postoperative complications were observed in 65 patients (64.4%), and late complications were observed in 14 patients (13.7%). The details of early and late complications are presented in Table 1. The perioperative mortality rate (within the first 30 days) was 2 patients (2%). One patient died on postoperative day 7 due to pneumonia and acute respiratory distress syndrome, while the other patient died on postoperative day 28 due to a cervical fistula and kidney failure. The mean tumor diameter was 4.62±1.57 cm (range, 0.6-9.5). The mean number of harvested lymph nodes was 62.2±27.81 (range, 9-138), and the mean number of metastatic lymph nodes was 2.14±6.25 (range, 0-58). For patients with adenocarcinoma, the mean number of harvested lymph nodes was 48.88±14.02 (range, 29-80), and the mean number of metastatic lymph nodes was 6.25±14.42 (range, 0-58). For patients with squamous cell carcinoma, the mean number of harvested lymph nodes was 65.41±29.33 (range, 9-138), and the mean number of metastatic lymph nodes was 1.22±1.78 (range, 0-7). The tumor characteristics of the two groups are presented in Table 2. Among patients with distal esophageal cancer who underwent three-field lymph node dissection, none had positive cervical lymph nodes. Staging was performed according to the current American Joint Committee on Cancer Staging System (8$^{th}$ edition staging esophagus and esophagogastric junction). According to postoperative staging, 21 patients (20.8%) were classified as stage 1, 36 patients (35.7%) as stage 2, 43 patients (42.6%) as stage 3, and 1 patient (1%) as stage 4. The distribution of patients according to disease stage is detailed in Table 3. The OS in the series was determined to be an mean of 59.2±42.12 months (range, 0-240). The median survival times for stages 1, 2, and 3 were 60, 60, and 59 months, respectively. The mean follow-up duration was 61.2 months (range, 0-244).

The 1, 3, 5, and 10 year OS rates in this series were 90.9%, 71.7%, 54.8%, and 16.7%, respectively. The 1, 3, and 5 year survival rates according to stages are presented in Table 4. The 1, 3, 5, and 10 year survival rates for the two main histopathological groups (adenocarcinoma and squamous cell carcinoma) are also presented in Table 4. The relationship between sex, age, tumor size, stage, total harvested lymph node count, and survival was examined, and only the total number of harvested lymph nodes showed a statistically significant effect on survival (p=0.17) [odds ratio=0.989, 95% confidence interval=0.980-0.998] (Table 5).

**Table 1.** Early and late complications after esophagectomy

| **Early complications** | **Number (n)** | **Percentage (%)** |
|---|---|---|
| Pneumonia | 34 | 52.3 |
| Pneumonia + pneumothorax | 1 | 1.5 |
| Pneumonia + leakage | 2 | 3.1 |
| Pneumonia + fistula | 3 | 4.7 |
| Pneumonia + left vocal cord paralysis | 4 | 6.2 |
| Left vocal cord paralysis | 1 | 1.5 |
| Cervical leakage | 2 | 3.1 |
| Cervical bleeding | 1 | 1.5 |
| Trachea injury | 2 | 3.1 |
| Pneumothorax | 1 | 1.5 |
| Fistula | 10 | 15.5 |
| Wound infection | 1 | 1.5 |
| Lymphatic leak | 1 | 1.5 |
| Lymphatic leak + left vocal cord paralysis | 1 | 1.5 |
| Transient stenosis | 1 | 1.5 |
| **Total** | 65 | 100 |
| **Late complications** | **Number (n)** | **Percentage (%)** |
| Stenosis | 10 | 71.4 |
| Fistula | 2 | 14.3 |
| Pneumonia | 2 | 14.3 |
| **Total** | **14** | **100** |

**Table 2.** Characteristics of patients with adenocarcinoma and squamous cell carcinoma

| **Characteristics** | **Squamous cell carcinoma (n=82) (mean ± SD) (range)** | **Adenocarcinoma (n=16) (mean ± SD) (range)** |
|---|---|---|
| **Age (year)** | 60.5±0.48 (27-81) | 62.68±13.66 (38-82) |
| **Tumor diameter (cm)** | 4.68±1.62 (0.6-9.5) | 4.51±1.35 (2-7) |
| **Total lymph nodes** | 65.41±29.33 (9-138) | 48.88±14.02 |
| **Metastatic lymph node** | 1.22±1.78 (0-7) | 6.25±14.42 (0-58) |

SD: Standart deviation.

**Table 3.** Distribution of patients according to the stages

| Stage | Number (n) | Percentage (%) |
|---|---|---|
| Stage IA | 8 | 7.9 |
| Stage IB | 13 | 12.9 |
| Stage IIA | 5 | 5 |
| Stage IIB | 31 | 30.7 |
| Stage IIIA | 20 | 19.8 |
| Stage IIIB | 14 | 13.9 |
| Stage IIIC | 9 | 8.9 |
| Stage IV | 1 | 1.0 |
| **Total** | **101** | **100** |

**Table 4.** Overall survival by stages and histopathology

| Stage | 1 year survival (%) | 3 year survival (%) | 5 year survival (%) | Median survival (months) |
|---|---|---|---|---|
| Stage 1 | 86 | 81 | 17 | 60 |
| Stage 2 | 86 | 76 | 13 | 60 |
| Stage 3 | 82 | 63 | 12 | 59 |
| **Histopathology** | **1 year survival (%)** | **3 year survival (%)** | **5 year survival (%)** | **10 year survival (%)** |
| Squamous cell carcinoma (n=82) | 92.5 | 68 | 64.9 | 18.5 |
| Adenocarcinoma (n=16) | 83.3 | 49.2 | 0 | 0 |

**Table 5.** Regression analysis of factors affecting survival

| Variable | p | OR (95% CI) |
|---|---|---|
| **Gender** | 0.161 | 1.443 (0.864-2.411) |
| **Age** | 0.165 | 1.014 (0.994-1.035) |
| **Tumor diameter** | 0.251 | 0.909 (0.772-1.070) |
| **Stage** | 0.095 | 1.145 (0.977-1.342) |
| **Total lymph nodes** | 0.017 | 0.989 (0.980-0.998) |

OR: Odds ratio, CI: Confidence intervale

## DISCUSSSION

Esophageal cancer is globally known to be predominantly squamous cell carcinoma. However, in recent times, there has been a recent shift toward adenocarcinoma predominance in Northern and Western Europe, the United Kingdom, Australia, and the United States (1,3,15). In Western countries, the prevalence of distal esophageal adenocarcinoma, which is associated with gastroesophageal reflux disease and Barrett's esophagus (5). Nevertheless, globally, squamous cell carcinoma remains the dominant histopathological type in the distal esophagus. In our series, the incidence of adenocarcinoma was 15.8%, whereas squamous cell carcinoma accounted for 81.2% of cases, confirming that squamous cell carcinoma remains the dominant histopathological type in Eastern countries known as the "Asian Esophageal Cancer Belt". The sharp increase in the incidence of adenocarcinoma in Western countries has further highlighted the significance of esophageal cancer in terms of cancer-related mortality (3). The two histopathological types exhibit important differences in tumor behavior, disease-free survival, and OS. In our study, the 1, 3, and 5 year OS rates were found to be 90.9%, 71.7%, and 54.8%, respectively. Compared with the literature's reported overall 5 year survival rate of 15-25%, the rate of 54.8% can be interpreted as quite favorable (3,16). However, it is noteworthy that the OS rates differ when separately calculated for the two histopathologies. When the squamous cell carcinoma group is analyzed alone, the overall 5 year survival increases to 64.9%, whereas no patient in the adenocarcinoma group survives for 5 years. Therefore, we believe that the relative superiority of survival rates is significantly influenced by the number of squamous cell carcinoma cases in our study group (more than 5 times). OS in esophageal cancer ranges from 4% to 40%, depending on the stage (16). For early-stage squamous cell carcinomas, endoscopic treatment has been reported to achieve nearly 100% long-term survival rates (17). In our study, the 1 and 3 year OS rates were promising for different stages (1 year OS for stages 1, 2, and 3 were 86%, 86%, and 82%, respectively; 3 year OS for stages 1, 2, and 3 were 81%, 76%, and 63%, respectively). However, the 5 year survival rates were found to be low for all stages (5 year OS for stages 1, 2, and 3 were 17%, 13%, and 12%, respectively). The relatively low long-term survival rates, even in early-stage cases, are surprising. Although we could not fully demonstrate the negative impact of aggressive behavior and the tendency for lymphatic spread in adenocarcinomas, there are indications that suggest their significant contribution to these outcomes. When examining the characteristics of the adenocarcinoma and squamous cell carcinoma groups in our study, it is evident that they are quite similar in terms of age (62.68 versus 60.5 years) and mean tumor diameter (4.51 cm versus 4.68 cm). Despite the significant advantage in the mean total harvested lymph node count in the squamous cell carcinoma group (61.41 versus 48.88), the remarkably high mean number of metastatic lymph nodes in the adenocarcinoma group (6.25 versus 1.22) is striking. In esophageal cancer, achieving the optimal survival goal while balancing surgical burden and postoperative quality of life is challenging. Surgical approaches include open three-field dissection, radical esophagectomy, and minimally invasive esophagectomy (10,18,19). Despite technical advancements, high complication rates, especially anastomotic leakage, remain a significant concern (19). In Ivor Lewis esophagectomy, the incidence rate of anastomotic leakage in the mediastinum ranges from 7.71% to 15.2% (20,21). McKeown esophagectomy avoids the fatal effects of mediastinal leakage and provides advantages in terms of pulmonary infection, blood loss, resection segment length, and number of harvested lymph nodes, it has disadvantages in terms of cervical anastomotic leakage, stricture, operation time, and length of hospital stay (21).

In a study involving 17.395 patients, Connors et al. (22) reported overall morbidity and mortality rates of 50.7% and 8.8%, respectively, after esophagectomy. In our study, the early postoperative complication rate was 64.4%, and pulmonary complications were dominant. We believe that the high rate of pulmonary complications in our country may be related to the high rate of smoking and the fact that female patients remain obese despite weight loss due to cancer. In addition, the late complication rate was 13.7%, and the mortality rate was 2%. In the initial cases in our series, we did not use a feeding jejunostomy,

but the correlation between postoperative nutrition, recovery, and complication management led us to an increasing trend in using a feeding jejunostomy in later cases. The current literature supports the opening of a simultaneous feeding jejunostomy with major gastrointestinal surgeries like esophagectomy (23). In our study, the impact of gender, age, tumor size, stage, and the number of harvested lymph nodes on OS was investigated, and only the total number of harvested lymph nodes was found to be an independent factor. This result supports the notion that extended lymphadenectomy confers a survival advantage for esophageal cancer, which is particularly supported by studies originating from Asian countries. However, the lack of knowledge regarding the relationship between the extent of lymphadenectomy and morbidity does not justify the hypothesis of performing three-field dissection for every patient. Additionally, the absence of metastatic cervical lymph nodes in our series of patients with distal esophageal cancer who underwent three-field lymph node dissection raises the question of whether routine cervical lymph node dissection is necessary in these patients. A more reasonable approach would be to adopt a selective approach regarding the extent of lymphadenectomy.

### *Study Limitations*

The most significant limitation of this study is its retrospective design. Due to the extensive time span covered by the study, the changes in the treatment strategies and their impact on the outcomes are significant. However, it should be noted that the entire series belongs to a senior surgeon in the position of team leader, and therefore, the surgical technique and dissection approach are standardized from this perspective. The positive or negative contributions of other treatments in combination with surgery are another subject of investigation. Indeed, neoadjuvant treatment may cause effects such as progression, loss of resectability, or morbidity and mortality secondary to adjuvant treatment. Some researchers have argued that the absence of involved lymph nodes after neoadjuvant chemoradiotherapy may be caused by the sterilizing effect of neoadjuvant treatment (5). Neoadjuvant chemoradiotherapy is widely recognized as a prognostic factor that influences both treatment response and survival. However, in our study, due to the limited number of patients receiving neoadjuvant chemoradiotherapy, specifically only 3 (3%), a robust statistical analysis concerning the impact of neoadjuvant treatment on survival was not feasible. Similarly, adjuvant therapies represent another perplexing limitation. The impact of adjuvant therapies on outcomes was not thoroughly examined in this study. Although these treatments have the potential to contribute positively to survival, they may also lead to treatment-related morbidity and mortality. Moreover, due to the broad time span of the study, inevitable changes in the indications and protocols for adjuvant chemotherapy are anticipated. These reasons have made it challenging to scrutinize the effects of adjuvant treatments in homogeneous subgroups.

## CONCLUSION

There is a clear relationship between the total number of harvested lymph nodes and OS in esophageal cancer. In particular, three-field lymph node dissection and radical surgical approaches increase long-term survival in patients with squamous cell cancers. However, there is a debate regarding the routine use of extended lymphadenectomy in distal cancers. In esophageal cancer, which has unique anatomical, histopathological, and behavioral characteristics, the width of lymphadenectomy should be determined with a selective approach for each patient without deviating from the maximum survival target.

### *Ethics*

**Ethics Committee Approval:** The study was approved by the local Gazi University Clinical Research Ethics Committee (approval number: 643, date: 31.07.2023).

**Informed Consent:** Retrospective study.

### *Footnotes*

### *Authorship Contributions*

Concept: S.Z.F., R.K., M.A., Design: S.Z.F., R.K., Supervision: S.Z.F., R.K., M.A., Data Collection or Processing: S.Z.F., R.K., Analysis or Interpretation: R.K., M.A., Literature Search: S.Z.F., R.K., M.A., Writing: S.Z.F., R.K., Critical Review: S.Z.F., R.K., M.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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