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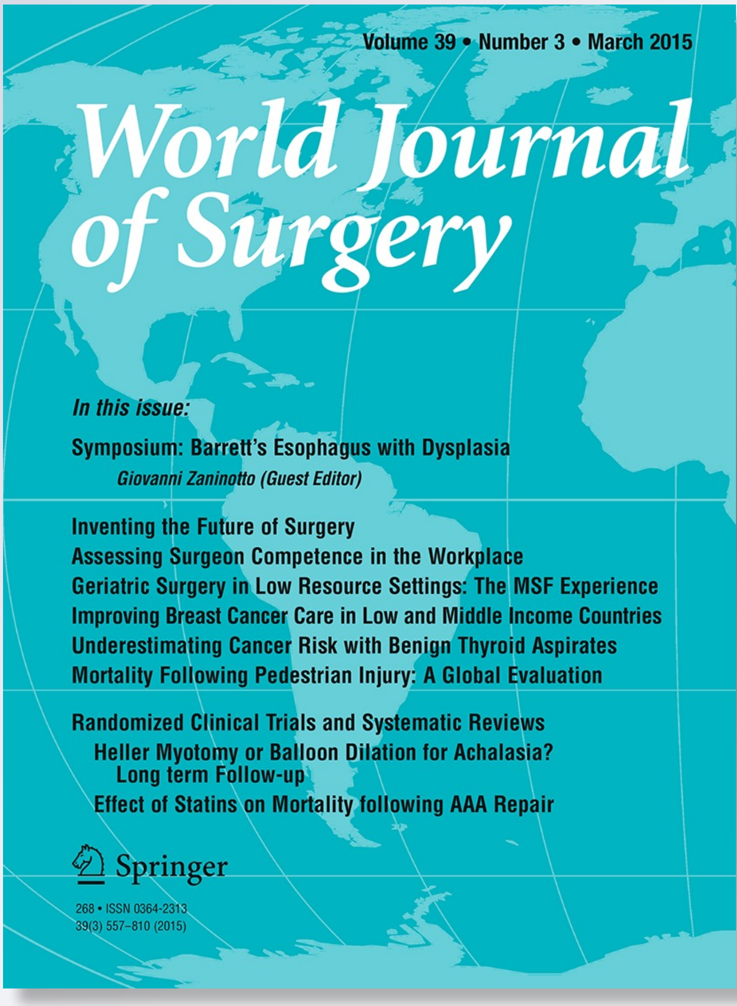

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ORIGINAL SCIENTIFIC REPORT

Preoperative Chemoradiation Therapy Decreases the Number of Lymph Nodes Resected During Esophagectomy

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Abstract

Background This study aimed to analyze the effect of preoperative chemoradiation on the adequacy of lymph node dissection.

Methods Patients with esophageal cancer treated with esophagectomy by the same surgeon between 2004 and 2011 were reviewed. Specimens were examined by the same pathologist. Patients were grouped into two depending on the type of treatment received.

Results Forty-seven patients with curative esophagectomy were included in the study. Twenty patients had preoperative chemoradiation followed by surgery and 27 had surgery alone. Open and hybrid esophagectomy approaches were used. The average number of lymph nodes dissected was 16 ± 10 (1–39). There was a significant decrease in the number of lymph nodes examined in patients with preoperative chemoradiotherapy in comparison to surgery alone ($p = 0.001$). Median length of stay was 12 days. R0 resection rate was 96 %. The median survival was 36.3 months, with a 42 % 5-year survival. Seven patients (25 %) had complete pathologic response following chemoradiation. No significant difference was recorded in terms of disease recurrence ($p = 0.3$). While morbidity was higher in the preoperative therapy group with 30 day mortality of 10 %, type of surgical approach does not seem to influence the number of lymph nodes dissected ($p = 0.7$).

Conclusions Preoperative chemoradiation decreases the number of harvested lymph nodes following esophagectomy regardless of the surgical technique used. The optimum number of lymph nodes currently recommended to be dissected for accurate nodal staging and survival needs revision in this group of patients.

A. Issaka · N. O. Ermerak · Z. Bilgi · V. H. Kara · H. F. Batirel (✉)
Department of Thoracic Surgery, Marmara University Medical Faculty Hospital, 7th Floor. Fevzi Cakmak Mahallesi, Mimar Sinan Caddesi No: 41, Ust Kaynarca, Pendik, 34899 Istanbul, Turkey
e-mail: hbatirel@marmara.edu.tr

C. A. Celikel
Department of Pathology, Marmara University Medical Faculty Hospital, Istanbul, Turkey

Introduction

Esophageal cancer is the sixth most common cause of cancer death worldwide. Its treatment is quite challenging due to late presentation with a 10–15 % overall survival, 40–70 % morbidity, and 2–4 % mortality [1]. Surgical resection and lymph node (LN) dissection is recommended for the treatment of early stage disease. Recent studies suggest improved long-term survival in esophageal cancer patients with wider extent of lymph node dissection [2, 3]. Using the Worldwide

Table 1 Patient demographics between the surgery alone and preoperative chemoradiotherapy group

	Surgery alone ($n = 27$)	Preop CRT ($n = 20$)	p value	Total ($n = 47$)
Age (years)	57.4	54.5	0.6	56
Gender M/F	10/17	9/11	0.9	19/28
FEV1 (L)	2.16 (87.5 %)	2.73 (87.8 %)	0.07	2.41 (87.6 %)
Median length of stay (days)	12 (7–36)	14 (8–127)	0.38	12 (7–127)
30 day mortality (n)	2	2	0.9	4
R0 resection (%)	92	100	0.9	96

Esophageal Cancer Collaboration (WECC) data, Rizk et al. recommended a minimum lymph node dissection of 10 for T1 cancer, 20 for T2 cancer, and 30 or more for T3/T4 cancers to maximize 5-year survival [4]. Many esophageal cancer patients present with locally advanced disease, although other treatment modalities are available, it is a common practice to give preoperative chemoradiotherapy (CRT) followed by surgery to patients with locally advanced disease with no involvement of the tracheobronchial tree or aorta and no distant metastases. Literature review on the extent of lymph node dissection on survival following preoperative CRT is limited and needs to be challenged. Most reported literature on the number of lymph nodes represents mixtures of cases with and without preoperative therapy. The optimal number of LNs to be dissected in patients with preoperative CRT is yet to be elucidated. Reports in current literature on the number of LN harvested have surgeon and pathologist dependant variability, hence in this study we tried to eliminate these bias by providing a more accurate information pertaining to the effect of preoperative chemoradiotherapy on the adequacy of LN dissection in patients with curative esophagectomy.

Materials and methods

The study was a retrospective review of a prospective database of patients with esophagectomy performed for esophageal cancers by the same surgeon (HFB) in the Marmara University Medical Faculty Hospital, Thoracic Surgery Department, Istanbul, Turkey between January 2004 and December 2011. Forty-seven patients who had esophagectomy for esophageal cancer during this period were included in the study. Data analyzed included patient demographics, histologic type, number of LNs examined, preoperative chemoradiotherapy regime, surgical approach, length of stay, 30 day mortality, R0 resection, recurrence, and complications. The histology of 43 patients (91 %) was squamous cell carcinoma located in the middle or lower thoracic esophagus. None of the patients had cervical esophageal cancer. Patient history, physical examination, laboratory tests, upper gastrointestinal endoscopy, computerized tomography of the chest and upper abdomen, positron emission tomography and/or endoscopic ultrasound were used in the clinical diagnosis and staging. Patients were classified into two groups according to the mode of treatment as "preop CRT" for patients with preoperative CRT followed by surgery and "surgery alone" for patients with surgery alone. Patient demographics between the two groups is given in Table 1.

Chemoradiation regimen

Our routine neoadjuvant CRT protocol entails the use of radiotherapy (RT) administered by linear accelerators with 6–15 MV photons. Patients received a total dose of 46–50 Gy radiation delivered in daily fractions of 2 Gy, five times in a week. Concurrent chemotherapy (CT) of cisplatin (40 mg/m^2 per week) was administered weekly, and 300 mg/m^2 Tegafur/uracil (UFT) was administered orally, divided into two daily doses, for 5 days from Monday to Friday, starting on the first day and ending on the last day of radiation.

Esophagectomy and lymph node dissection technique

Between 2004 and 2008, only open three incisional esophagectomy was performed. After 2008, we incorporated the video assisted thoracic surgery (VATS) procedure and started using a hybrid three-hole esophagectomy approach. The open three-hole esophagectomy encompassed a right thoracotomy to mobilize the esophagus, laparotomy to make the gastric conduit and placement of a feeding jejunostomy, and left cervical incision for cervical esophagogastric anastomosis. In the hybrid three incisional esophagectomy, thoracotomy was replaced with VATS mobilization of the esophagus. In open Ivor-Lewis esophagectomy, laparotomy was used to make the gastric conduit and placement of a feeding jejunostomy, followed by a right thoracotomy to mobilize the esophagus and a high intrathoracic esophagogastric anastomosis.

Irrespective of the surgical technique used, all patients routinely had a two-field lymphadenectomy of the mediastinal and abdominal LNs. The nodes were usually resected en bloc with the specimen. All specimen and LNs were examined by the same pathologist (CAC) according to standardized protocol during the study period. Specimens were fixed in 5 % formaldehyde and embedded in paraffin. The LNs

Table 2 Distribution of clinical (cTN) and pathologic (pTN) stages in the surgery alone and preoperative chemoradiotherapy group

	Clinical Stage	Pathologic Stage
TisN0	1 (0)	1 (0)
T0N0[a]	0 (0)	0 (7)
T1N0	5 (0)	3 (1)
T1N1	0 (0)	2 (0)
T2N0	5 (1)	6 (3)
T2N1	1 (0)	2 (2)
T3N0	13 (1)	13 (3)
T3N1	8 (5)	10 (3)
T3N2	1 (0)	0 (0)
T4N0	6 (6)	0 (1)
T4N1	5 (5)	0 (0)
T4Nx	2 (2)	0 (0)

Preoperative chemoradiotherapy patients in brackets

[a] Post chemoradiotherapy pathologic complete response

were counted and a series of sections from each node was selected and stained with haematoxylin and eosin, as well as periodic acid-Schiff. All dissected LNs from the subcarinal, bronchial, paraesophageal, pulmonary ligament, gastric, and celiac region were examined and microscopically analyzed for metastatic disease.

Statistical analysis

Data were collected prospectively, and analyses of data were performed retrospectively. Median follow-up was measured from the date of surgery to the end of follow-up for censored patients or deceased time.

Pearson's χ^2 test was used for comparison between non-parametric groups. Kaplan–Meier plots were used to plot survival distribution. Due to the limited size of patient population, survival analyses between stages were not carried out. The level of significance was set at $p < 0.05$. All statistical analyses were performed using SPSS 16 (SPSS Inc., Chicago, IL, USA).

Results

The median age of patient was 56 years with female predominance ($n = 28$, 59.6 %). Majority of patients had squamous cell carcinoma ($n = 43$), three adenocarcinoma, and one basaloid squamous cell carcinoma. Twenty patients had preoperative chemoradiation (eight salvage), and 27 patients had surgery alone. Most patients (44 %) in the surgery alone group were evaluated to have T3N0 disease, while the preop CRT had heterogeneous distribution with stage T3N1, T4N0, and T4N1 disease. Detailed pretreatment clinical stage of patients is shown in Table 2. Open three-hole esophagectomy was used on 27, open Ivor-Lewis esophagectomy in 3, and hybrid three-hole esophagectomy in 17 patients. Seven patients (25 %) in the preoperative CRT group had complete pathologic response with a median of 10 (1–12) LNs dissected. In total, an average of 16 ± 10 (1–39) LNs was dissected. The number of dissected LNs was significantly less in patients with preoperative chemoradiation compared to surgery alone group (11.3 ± 4.6 vs. 19.7 ± 10.6; $p = 0.001$). There was no statistical difference in the number of dissected LNs between open or hybrid three incisional esophagectomies (19 ± 10 vs. 21 ± 12, $p = 0.7$) (Table 3). During the study period, two patients with preop CRT were operated on with the hybrid procedure. The median survival and 5-year survival for the study group was 36.3 months and 42 %, respectively. Median length of stay was similar between groups (14 vs 12 days). The R0 resection was achieved in all patients in the preop CRT patients, and two patients in the surgery alone group had R1 resection (Table 1).Three patients in the preoperative CRT and four in the surgery alone group had disease recurrence (six locoregional and one distant) with no statistical difference between groups ($p = 0.3$). The rate of intraoperative and postoperative complications was higher in the preop CRT group. Chylothorax and recurrent laryngeal nerve injury (RLNI) occurred more often in the surgery alone group, while anastomotic leakage, arrhythmia, pneumonia was frequent in the preop CRT group (Table 4).

Discussion

Previously published studies have attempted to define the extent of LN dissection in patients undergoing esophagectomy for esophageal cancer [2, 5]. The seventh American Joint Committee on Cancer (AJCC) staging system of

Table 3 The number of LNs dissected among the different treatment groups

	Patients (n)	Number of dissected LN (n)	p
Surgery alone vs. preoperative CRT	27 vs. 20	19.7 ± 10.6 vs. 11.3 ± 4.6	0.001
Open vs. hybrid three incisional esophagectomy	30 vs. 17	15 ± 9.5 vs. 18.2 ± 9.5	0.30
Open vs. hybrid three-hole esophagectomy (surgery alone)	12 vs. 15	20.6 ± 12 vs. 19.1 ± 9.7	0.70

The number of LNs dissected was significantly less in the preoperative CRT group

CRT chemoradiotherapy

Table 4 Intraoperative and postoperative complication rates recorded between preop CRT and surgery alone group

	Surgery alone *n* (%)	Preop CRT *n* (%)
Intraoperative complications[a]	1 (4)	4 (20)
Chylothorax	4 (15)	2 (10)
RLNI	4 (14)	2 (10)
Arrhythmia	1 (4)	5 (25)
Anastomotic leakage	3 (11)	6 (30)
Pneumonia	5 (19)	7 (35)

Complications rates were higher in patients who had preop CRT

[a] Intraoperative complication including hemorrhage, esophageal injury, thoracic duct injury, and aortic injury which was managed during surgery

esophageal and gastroesophageal junction cancer in comparison to the sixth edition, categorizes LN involvement according to the number of metastatic LNs involved rather than their anatomical locations. Other studies also confirmed the survival benefit of LN involvement when optimum LN dissection is achieved [4, 6, 7]. The optimum number of LNs to be dissected during esophagectomy is inconclusive [4–6, 8–10]. Bollschweiler et al. in their retrospective review of 213 esophageal cancer patients who had surgical resection with curative intent determined examination of 16 or more LNs [9]. In a recursive partitioning analysis of 336 patients with esophagectomy without chemoradiotherapy, a minimum number of 18 LNs was identified as the required number for accurate cancer staging [6]. Altorki et al. reviewed 264 patients with esophagectomy without induction therapy. They grouped patients into quartiles based on the number of LNs examined and noticed improved survival when 26 or more LNs were examined for N0 disease, patients with N1 disease, however, required examination of more than 40 LNs to achieve a significant improvement in survival [11]. Using the WECC database, Rizk et al. analyzed LN status in esophageal cancer patients treated with only surgery and reported an improved 5-year survival with increasing extent of lymphadenectomy [4]. In LN negative cancers, no optimum lymphadenectomy was defined for pTis; optimum lymphadenectomy was 10–12 nodes for pT1, 15–22 for pT2, and 31–42 for pT3/T4, depending on histopathological cell type, whereas in LN positive cancers, optimum lymphadenectomy was 10 for pT1, 15 for pT2, and 29–50 for pT3/T4 [4]. Groth et al. using the Surveillance Epidemiology and End Results (SEER) database included patients with neoadjuvant radiotherapy with patients who completed neoadjuvant radiation therapy having significantly lower LNs examined when compared to patients who did not ($p < 0.0001$) [10]. Their results also showed that in comparison to patients who had no LN evaluation, only patients with more than 12 LNs examined had significant improvement in mortality; patients who had 30 or more LNs examined had significantly much lower mortality rates than the other groups. They concluded that, in order to maximize all-cause and cancer-specific survival, esophageal cancer patients should have at least 30 LNs examined pathologically [10]. The mechanisms underlying LN counts with survival are poorly understood. Improved local tumor control due to clearing of more LNs, hence ensuring the removal of occult or overt metastasis may reduce local recurrence rates, as recurrent disease is almost uniformly fatal. A more accurate cancer staging by removing more LNs is another mechanism, where the risk of failing to detect LN metastasis and hence preventing patients from receiving optimal cancer therapy due to downstaging is lessened [11]. Studies especially in the field of colorectal cancer have shown that reduction in number of LNs after preoperative treatment possibly results from radiation-induced lymphocyte destruction and stromal fibrosis, which may render LNs difficult to detect with the use of radiation-induced therapy [12]. Various published literature related to the gastrointestinal system other than the esophagus has shown reduction in the number of dissected LNs due to the effect of preoperative chemoradiotherapy without affecting survival [13–15]. To date, limited data on the effect of chemoradiotherapy on the histopathological structures of LNs in esophageal cancer exist. The very few studies that compared the number of dissected LNs between surgery alone and preoperative therapy followed by surgery, and the effect on survival have diverse results. Bollschweiler et al. and Castoro et al. achieved the optimum number of LNs in their studies with no significant decrease in the number of dissected LNs in the preoperative treatment groups [9, 16, 17]. Our results and most of the published literature show that it is difficult to achieve the optimum number of dissected LNs in these group of patients especially when radiotherapy-based regimen is used [10, 15, 18, 19]. Other factors like difficulty by the surgeon in acquisition of LNs and the pathologist having a harder time finding or counting LNs may affect the number of LNs harvested after neoadjuvant therapy. According to current colorectal cancer surgery guidelines, the recommended minimum number of LNs to be examined is set to at least 12 [20], whereas, Marks et al. and Govindarajan et al. demonstrated that this optimum number of 12 LN is not achievable after neoadjuvant treatment with no significant effect on survival [15, 19].

Although, results and outcomes of surgical resection for esophageal carcinoma have improved remarkably in recent years, the risk of recurrence after curative treatment still exists [21–23]. Lou et al. in their recent analyses of recurrence after complete resection of esophageal cancer reported a 38 % recurrence rate (distant 55 %, locoregional 28 %, or both 17 %) [21]. Recurrence rate recorded was highest in the first years and significantly decreased after six years. Compared with surgery alone, patients with neoadjuvant therapy interestingly had higher recurrence rate in the first 2 years (14 per 100 person-years versus 35 per 100 person-years, respectively, $p < 0.001$) [21]. Sugiyama et al. also reported a 29 % recurrence rate (locoregional 54 %, distant 36 %, or mixed type 10 %) with 84 % of the patients having recurrence in the first 2 years [22]. Also, patients with treatable recurrence had significantly longer survival than those with untreatable recurrence disease ($p = 0.016$) [22]. Nakagawa et al. in their study to clarify the pattern and timing of recurrence after extended radical esophagectomy reported a 43.3 % recurrence rate (locoregional 18 %, haematogenous 14 %, or both 3 %) and an overall 5-year survival rate of 56 % [23]. They concluded that locoregional recurrence is mainly associated with the extent of local tumor and LN metastasis; whereas, hematogenous recurrence is associated with tumor stage and oncologic behavior of the tumor [22]. Our recurrence rate of 15 % was lower compared to the general recurrence reported. In our study, seven patients had recurrence (six locoregional and one distant); three in the preoperative chemoradiotherapy and four in the surgery alone ($p = 0.3$). We recorded an overall 5-year survival of 42 % and a median survival of 36.3 months.

In comparison to previously published literature which included predominant adenocarcinoma, our study had predominant squamous cell carcinoma, which might have contributed to the difference in results. It is worth mentioning that SCC is still the predominant esophageal cancer histology type in developing countries and the Eastern part of the word.

The peculiarity of our study, despite limitations peculiar to all retrospective studies with limited subject population, lies in the fact that all patients had been treated by the same surgeon and LNs were examined by the same pathologist, hence the bias of less LN dissection due to different surgeons or different counting by different pathologists is eliminated. Learning curve is important in the number of harvested lymph nodes during esophagectomy. This was very well demonstrated in the extensive experience by Luketich et al. in 2012 showing an increase of 5 lymph nodes on average between the former and latter 500 esophagectomy cases [24]. Our experience is also subject to an increase in experience. However, the distribution of cases who received chemoradiation and no upfront treatment during this period was well balanced, eliminating the bias by forming an internal control. Our results showed that increase in preoperative therapy dosage results in lesser LN numbers with significant statistical decrease in the number of dissected LNs in the preoperative chemoradiotherapy group compared with the surgery alone group. The increase in intraoperative complications, though managed intraoperatively suggest a more technically challenging operation after induction treatment which might have to some extent influenced the decrease in dissected LNs. Nonetheless, two patients with preop CRT were treated with the hybrid esophagectomy procedure.

Preoperative chemoradiation therapy reduces the number of harvested LNs due to the primary effect of induction chemoradiotherapy on LNs, and hence the optimum number of LNs currently recommended to be dissected for accurate nodal staging and survival needs revision in this group of patients. A larger study group with analyses on survival data would elucidate the effect of less LN count on survival after preoperative chemoradiotherapy.

Conflict of interest None.

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