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Lymph Node Status after Neoadjuvant Chemoradiation Therapy for Esophageal Cancer according to Radiation Field Coverage

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Background: To explore the effect of radiation on metastatic lymph nodes (LNs) after neoadjuvant chemoradiation therapy (nCRT), we examined the metastatic features of LNs according to their inclusion in the radiation field. **Methods:** The patient group included 88 men and 2 women, with a mean age of 61.1±8.1 years, who underwent esophagectomy and lymphadenectomy after nCRT. Dissected LNs were compared in terms of clinical suspicion of metastasis, nodal station, and inclusion in the radiation field. **Results:** LN positivity did not differ between LNs that were inside (in-field [IF]) and outside (out-field [OF]) of the radiation field (IF: 40 of 465 [9%], OF: 40 of 420 [10%]; p=0.313). In clinical N+ nodal stations, IF stations had a lower incidence of metastasis than OF stations (IF/cN+: 16 of 142 [11%], OF/cN+: 9/30 [30%]; p=0.010). However, in clinical N- nodal stations, pathological positivity was not affected by whether the nodal stations were included in the radiation field (IF/cN-: 24 of 323 [7%], OF/cN-: 31 of 390 [8%]; p=0.447). **Conclusion:** Radiation therapy for nCRT could downstage clinically suspected nodal metastasis. However, such therapy was ineffective when used to treat nodes that were not suspicious for metastasis. Because significant numbers of residual metastases were identified irrespective of coverage by the radiation field, lymphadenectomy should be performed to ensure complete removal of residual nodal metastases after nCRT.

Key words: 1. Esophageal neoplasms
2. Esophageal surgery
3. Lymph nodes
4. Neoadjuvant therapy
5. Radiotherapy

Introduction

Radical lymphadenectomy has been advocated as an important surgical procedure for curative resection of esophageal cancer, and it is associated with improved survival after esophagectomy. However, the importance of radical lymphadenectomy has been questioned in the present era of tri-modal strategies, including neoadjuvant chemoradiation therapy (nCRT) followed by surgical resection. Although the results have been interpreted differently, retrospective analyses of data from 2 multicenter randomized controlled studies showed that radical lymphadenectomy did not increase the num-

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ber of metastatic lymph nodes (mLNs) [1,2]. Based on these results, Talsma et al. [1,3] proposed that any therapeutic or diagnostic role for radical lymphadenectomy was limited in patients who underwent nCRT. However, no randomized controlled study has confirmed this suggestion. It also remains unclear how many lymph nodes should be removed and how many nodal stations should be explored during esophagectomy after nCRT. Furthermore, it is not clear how radiation affects the metastatic status of lymph nodes. We thus explored the metastatic status of lymph nodes in terms of inclusion within the radiation field. Our aim was to elucidate the role of radiation in lymph node metastasis and to explore the utility of radical lymphadenectomy combined with esophagectomy after nCRT.

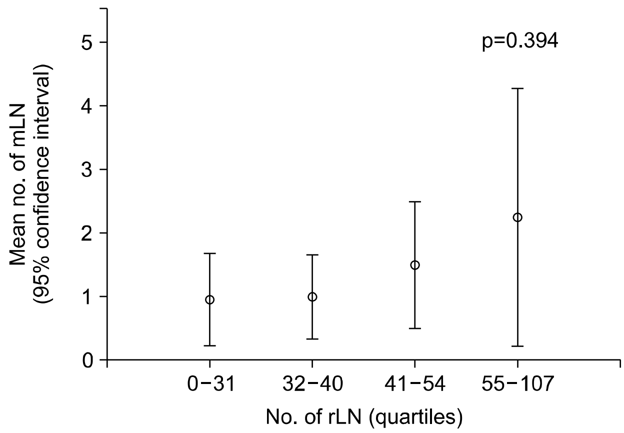

Fig. 1. Change in the number of mLNs according to the number of rLNs in patients who underwent surgery after neoadjuvant chemoradiation therapy. LN, lymph node; mLN, metastatic LN; rLN, resected LN.

Methods

1) Study population and specimen collection

The Institutional Review Board of Seoul National University Hospital approved this research (1701-088-824) and waived the requirement for informed consent. A total of 97 patients underwent esophageal resection and lymphadenectomy after nCRT at our institution from February 1998 to May 2016. The inclusion criteria were: (1) lymphadenectomy after nCRT; (2) availability of detailed information on the radiation field; and (3) availability of information on the metastatic status of specific nodal stations. Seven patients were excluded because they dropped out of nCRT or because preoperative radiation therapy was performed at other hospitals that did not keep adequate records of the details of the radiation fields. In the 90 included patients, 3,904 lymph nodes were resected after lymphadenectomy and grouped by nodal station. Thoracic, abdominal, and cervical regional nodal stations were defined using the staging classification of the American Joint Cancer Committee [4]. A total of 3,904 lymph nodes were assigned to 885 nodal stations.

2) Neoadjuvant treatment and the surgical approach

Pre-treatment clinical staging was performed with the aid of endoscopic ultrasonography, chest and abdominal computed tomography, and 18F-fluorodeoxyglucose positron emission tomography. All patients underwent nCRT 4–6 weeks prior to surgical resection. The radiation fields were designed by radiation oncologists. The nodal stations included in the planning target volumes (PTVs) were considered to be affected by the radiation field. Almost all patients underwent transthoracic esophagectomy and thoracic and abdominal lymphadenectomy. Cervical lymphadenectomy was added selectively based on clinical judgment. Minimally invasive approaches, such as thoracoscopic or robot-assisted approaches, were chosen for selected patients. In such cases, lymphadenectomy was performed in a manner consistent with open surgery.

3) Statistical analysis

Nodal stations and individual lymph nodes were divided into in-field (IF) and out-field (OF) groups according to coverage by the PTV radiation. Categorical variables, including pretreatment lymph node clinical and pathological status, are shown as frequencies with percentages and were compared using the chi-square test and the Fisher exact test. The numbers of resected lymph nodes (rLNs) and mLNs per patient are given as means±standard deviations. The mean number of mLNs by the number of rLNs was investigated using analysis of variance and was displayed graphically (Fig. 1). Multiple logistic regression analysis was used to identify factors influencing pathological lymph node involvement. A 2-sided p-value <0.05 was considered to reflect statistical significance. All statistical analyses were performed

Table 1. Patient characteristics (N=90)

Characteristic	Value
Male sex	88 (97)
Age (yr)	61.1±8.1
Body weight (kg)	60.3±9.0
Body mass index (kg/m^2)	21.8±2.9
Body weight loss (kg/3 mo)	2.6±3.7
Smoking status	
Never-smoker	8 (9)
Ex-smoker[a)]	28 (31)
Current smoker	54 (60)
Pack-years	30.1±17.5
Alcohol use (g/day)	44.0±41.2
Eastern Cooperative Oncology Group performance score	
0	21 (23)
1	63 (70)
2	6 (7)
Charlson comorbidity index	
2	62 (69)
3	20 (22)
4	4 (4)
6	3 (3)
7	1 (1)
Tumor location	
Cervix	4 (4)
Upper thorax	21 (23)
Mid-thorax	50 (56)
Lower thorax-gastroesophageal junction	15 (17)
cT stage	
1a	2 (2)
1b	1 (1)
2	23 (26)
3	64 (71)
cN stage	
0	8 (9)
1	53 (59)
2	27 (30)
3	2 (2)
Chemotherapy regimen	
5-Fluorouracil/cisplatin	42 (47)
Docetaxel/cisplatin	33 (37)
Cisplatin	8 (9)
Paclitaxel/carboplatin	6 (7)
Paclitaxel/carboplatin/cetuximab	1 (1)
Radiation therapy technique	
Three-dimensional conformal radiation therapy	86 (96)
Intensity-modulated radiation therapy	4 (4)

(Continued to the next page)

Table 1. Continued

Characteristic	Value
Radiation dose (cGy)	
4,500	40 (44)
4,860–4,940	3 (3)
5,040	37 (41)
5,120–6,120	10 (11)
Lymphadenectomy	
2-Field	54 (60)
3-Field	36 (40)
Minimally invasive surgery	29 (32.22)
Histological type	
Adenocarcinoma	1 (1.11)
Squamous cell carcinoma	89 (98.89)
ypT stage	
yT0	35 (38.89)
yTis	1 (1.11)
yT1a	2 (2.22)
yT1b	9 (10)
yT2	9 (10)
yT3	33 (37)
yT4a	1 (1)
ypN stage	
yN0	48 (53)
yN1	26 (29)
yN2	10 (11)
yN3	6 (7)
Complete resection	
R0	84 (93)
R1	5 (6)
R2	1 (1)
No. of resected LNs	45.4±21.0
No. of metastatic LNs	1.4±2.9

Values are presented as frequency (%) or mean±standard deviation.
LN, lymph node; cT, clinical tumor; cN, clinical node; yp, post-therapy pathologic.
[a)]An ex-smoker was defined as a smoker who had quit at least 6 months prior.

using PASW SPSS software ver. 18.0.0 (SPSS Inc., Chicago, IL, USA).

Results

1) Patient and primary tumor characteristics

Table 1 shows the clinical characteristics of all patients and their primary tumor evaluations. All patients except 2 were men, and more than 90% had an Eastern Cooperative Oncology Group performance status ≤1. Squamous cell carcinoma was the pre-

Table 2. Pathological involvement of LN stations: coverage by radiation field (out-field vs. in-field) stratified by pre-treatment and clinical metastatic status (cN-/cN+)

	Out-field (n=420)	In-field (n=465)	p-value
cN-	31/390 (8)	24/323 (7)	0.796
cN+	9/30 (30)	16/142 (11)	0.013

Values are presented as number (%).
LN, lymph node; cN-, clinically non-metastatic LN stations; cN+, clinically metastatic LN stations.

Table 3. Pathological involvement of individual LNs by exposure to radiation field (out-field vs. in-field) stratified by pre-treatment and clinical metastatic status (cN-/cN+)[a]

	Out-field (n=1,842)	In-field (n=2,062)	p-value
cN-	54/1,658 (3)	31/1,401 (2)	0.080
cN+	20/184 (11)	23/661 (3)	$<$0.001
Total	74/1,842 (4)	54/2,062 (3)	0.014

Values are presented as number (%).
LN, lymph node; cN-, clinically non-metastatic LN stations; cN+, clinically metastatic LN stations.
[a]The frequencies of LN involvement are shown as ratios (%).

dominant histologic type. Docetaxel/cisplatin and 5-fluorouracil/cisplatin were the most frequently chosen chemotherapy regimens. Paclitaxel/carboplatin with or without cetuximab was chosen for 7 patients. Most radiation doses were 4,500–5,040 cGy, with variation in whether a reduced field boost was applied. Almost all patients underwent both thoracic and abdominal lymphadenectomy. Lymphadenectomy along the bilateral recurrent laryngeal nerve was performed in >75% of patients, and cervical lymphadenectomy in 40%. The number of rLNs per patient was 45.4±21.0. R0 resection was achieved in 93% of patients and pathological complete response (pCR) of the primary tumor was recorded in 39%.

We found no significant intergroup differences when the number of mLNs was compared among groups with different numbers of rLNs. However, mLN numbers tended to increase commensurate with an increase in the number of rLNs (Fig. 1).

2) Comparison of dissected lymph nodes by in-field and out-field status

Of the 885 nodal stations dissected, 420 (47%) were OF and 465 (53%) were IF. The number of rLNs per nodal station was comparable (OF: 4.4±4.0, IF: 4.4±3.7; p=0.850). Neither the presence nor number of mLNs differed significantly between OF and IF nodal stations (OF: 0.2±0.7, IF: 0.1±0.4; p=0.134). However, the anatomical distribution of nodal stations and the pretreatment clinical metastatic status of the various stations differed significantly. Nodal IF stations were more frequently clinically suspicious for metastasis, and were located principally in the upper-mid thorax.

Table 4. Pathological involvement of individual LNs by exposure to radiation field (out-field vs. in-field) stratified by LN location[a]

LN location	Out-field (n=1,842)	In-field (n=2,062)	p-value
Cervix	31/305 (10)	5/135 (4)	0.023
Upper thorax	9/274 (3)	28/888 (3)	0.914
Mid-thorax	5/270 (2)	12/594 (2)	0.869
Lower thorax–abdomen	29/993 (3)	9/445 (2)	0.326

Values are presented as number (%).
LN, lymph node.
[a]The frequencies of LN involvement are shown as ratios (%).

Because of this heterogeneity, the pathological status of nodal stations was compared after stratification by the pretreatment clinical metastatic status (cN+/cN-) (Table 2). Pathological involvement was more common in cN+ nodal stations than in cN- stations (cN-: 55 of 713 [8%], cN+: 24 of 172 [15%]; p=0.005). When the effect of radiation field coverage was examined according to the clinical metastatic status of nodal stations, radiation clearly decreased the metastatic frequency of cN+ nodal stations (p=0.013), but not that of cN- nodal stations.

The effects of neoadjuvant radiation were assessed for 3,904 individual lymph nodes. When the pathological involvement of individual lymph nodes was compared between IF and OF, IF lymph nodes exhibited less frequent pathological involvement (Table 3). However, such a difference was not evident in the cN- subgroup. When lymph nodes were grouped by anatomical location, the effect of radiation was statistically significant only in the cervical area (Table 4).

We performed a multiple logistic regression analysis to identify factors associated with pathological involvement of rLNs (Table 5). Pretreatment clinical nodal metastasis, a cervical location, and incomplete resection independently increased the risk of pathological lymph node involvement, whereas coverage by the radiation field (IF versus OF status), pCR of the

Table 5. Multiple logistic regression analysis of the extent of pathological involvement of individual resected LNs

Variable	Exp(B) (95% confidence interval)	p-value
ypT stage (vs. ypT0)		<0.001
T1a	4.54 (1.48–13.94)	0.008
T1b	2.27 (0.89–5.81)	0.088
T2	5.70 (3.00–10.83)	<0.001
T3	5.02 (2.89–8.71)	<0.001
T4a	6.66 (1.28–34.52)	0.024
LN location (vs. lower thorax–abdomen)		<0.001
Cervix	2.62 (1.60–4.30)	<0.001
Upper thorax	1.56 (0.94–2.58)	0.086
Mid-thorax	0.92 (0.50–1.70)	0.791
Clinically metastatic (cN+=1)	2.51 (1.66–3.80)	<0.001
Complete resection (R1 or R2=1)	2.25 (1.27–3.99)	0.006
Infield vs. outfield (infield=1)	0.51 (0.33–0.78)	0.002
Body weight loss >10% over 3 months (kg)	0.27 (0.14–0.50)	<0.001

LN, lymph node; yp, post-therapy pathologic; cN+, clinically metastatic LN stations.

primary tumor, and preoperative body weight loss >10% over 3 months reduced the risk of pathological involvement.

Discussion

Radical lymphadenectomy has been shown to be both prognostically and therapeutically beneficial when used to treat esophageal cancer [5-7]. Although the survival benefit afforded by radical lymphadenectomy can be attributed to a stage purification effect, which means minimization of missed mLNs (false pN0 status), the surgical sterilization of lymphatic system drainage is a critical treatment principle for patients with locally advanced esophageal cancer. As evidence on the survival benefits of nCRT has been accumulated in several retrospective studies, recent multicenter randomized controlled trials have shown that nCRT followed by surgery affords greater survival benefits than surgery alone [8,9]. In this tri-modal approach to esophageal cancer treatment, radical lymphadenectomy and neoadjuvant radiation therapy are combined to optimize locoregional control.

However, the importance of radical lymphadenectomy has been questioned after a retrospective post-hoc analysis of data from the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) and FFCD (Fédération Francophone de Cancérologie Digestive) 9,901 trials. Robb et al. [2,10] found no association between the number of rLNs and overall survival. Additionally, lymphadenectomy yielded inconsistent results; an increase in the number of rLNs was not associated with a rise in the number of hidden mLNs in nCRT patients. It was suggested that rLN numbers were lower because the smaller size of the individual lymph nodes after nCRT rendered pathological evaluation difficult, and the prognostic role played by rLN numbers thus disappeared after nCRT. However, the cited authors emphasized that this finding should not be misunderstood as indicating that less radical lymphadenectomy was not inferior oncologically. Erroneous staging (ypN0) remained a possibility when mLNs were missed upon inadequate lymphadenectomy. However, Talsma et al. [1,3] reached more progressive conclusions after analyzing the same data. Without negating the prognostic role played by rLN number, those authors asserted that radical lymphadenectomy was therapeutically unnecessary.

We plotted graphs depicting the associations between the number of rLNs and mLNs. Unlike previous studies, as almost all patients (87 of 90) underwent radical lymphadenectomy (≥18 LNs) [11], our medians and quartiles differed from those of the CROSS trial. Although the rLN distributions were right-shifted in our patients, the association between rLN and mLN number was not statistically significant. Similar results were found in earlier evaluations of patients who underwent lymphadenectomy after nCRT. However, the average number of mLNs trended upward as the rLN number increased, implying a possible useful role for radical lymphadenectomy. Further research with larger case series is required.

We found significant numbers of residual mLNs irrespective of radiation field coverage status, indicating that nCRT did not sterilize regional lymph nodes to an extent that would allow lymphadenectomy to be omitted. However, radiation played a useful role when metastatic nodal stations were clinically suspected. Radiation significantly decreased the metastatic rate, from 30% to 11%. The sterilizing effect of radiation was also evident in an analysis of individual lymph nodes. A previous comparison between involved-field and elective nodal irradiation in patients undergoing definitive chemoradiation therapy (dCRT) revealed no survival difference between the 2 groups [12-14]. This suggested that irradiation of non-suspicious lymph nodes was not especially beneficial, which is consistent with our subgroup analysis.

Although radiation therapy did affect clinically suspicious lymph nodes, such therapy cannot safely substitute for lymphadenectomy because the risk of pathological nodal involvement of each nodal station remained >7% even when the station was covered by the radiation field and was not under clinical suspicion. IF failure is not unique to nCRT, as it has also been documented in approximately 40% of esophageal cancer patients treated via dCRT [15]; this indicates that lymph node sterilization via chemoradiation does not eliminate the role of surgery.

In the subgroup analysis by lymph node location, coverage by the radiation field significantly affected only cervical lymph nodes, not intrathoracic or abdominal lymph nodes. No lucid explanation for this finding is apparent. It is possible that, as the cervical lymph nodes were irradiated mainly in patients clinically suspected of cervical nodal involvement, radiation therapy may have exhibited better effects than in intrathoracic or abdominal lymph nodes, which were frequently covered in elective nodal irradiation. However, the apparent differences in radiation effects by location should be further investigated using various radiation doses and radiation techniques; it is not yet possible to draw firm conclusions.

Including the 2 randomized clinical trials mentioned above, many studies have shown that nCRT did not increase perioperative mortality or morbidity [16]. After nCRT, however, fibrosis and adhesion constitute technical obstacles that surgeons must overcome when completing radical lymphadenectomy. Devascularization caused by radiation adds to concerns about the risks of postoperative anastomotic leakage and development of tracheogastric fistulae associated with ischemia [17-19]. Thus, it would be useful to perform only selective lymphadenectomy, thereby sparing patients who underwent nCRT from extensive dissection, if doing so does not compromise the oncological outcomes. This is why a reliable pre-treatment method of predicting the chemoradiation sensitivity of esophageal cancer in individual patients is urgently required.

We sought to identify risk factors for pathological involvement in rLNs. In logistic regression analysis, ypT0 stage and R0 resection were positive predictors of pathological negativity. It is known that pCR reduces the number of involved lymph nodes. Thus, Chao et al. [20] explored the benefits of radical lymphadenectomy by stratifying their data in terms of the tumor response to nCRT. Radical lymphadenectomy was of no benefit in the pCR group, whereas inadequate lymphadenectomy negatively impacted survival in the non-pCR group. Currently, however, no reliable preoperative diagnostic method is available to confirm pCR. Decisions on R0 resection must be made intraoperatively. This means that the predictive utility of these variables does not extend to identifying sterilized lymph nodes before lymphadenectomy. Individualized lymphadenectomy and radiation therapy are future goals of tri-modal therapy. However, in the absence of an effective tool for evaluating of nCRT efficacy, radical lymphadenectomy remains an essential component of esophageal cancer treatment.

We evaluated the features of lymph node metastasis in terms of radiation field exposure and found that radiation reduced metastasis in clinically suspicious nodal stations, but not in unsuspicious stations. However, significant residual nodal metastasis was identified irrespective of the extent of radiation field exposure. Although we were able to identify the effect of radiation on nodal metastasis in this study, it did not reach a degree that would allow the omission of radical lymphadenectomy. Radical lymphadenectomy is still valuable for predicting the prognosis and improving locoregional control in surgical resection after nCRT in patients with esophageal cancer.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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