The impact of lymphadenectomy on lymph node recurrence after performing various treatments for esophageal squamous cell carcinoma

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Abstract

Background

Treatment for regional lymph node recurrence after initial treatment for esophageal squamous cell carcinoma (ESCC) differs among institutions. Though some retrospective cohort studies have shown that lymphadenectomy for cervical lymph node recurrence is safe and leads to long-term survival, the efficacy remains unclear. In this study, we investigated the long-term outcomes of patients who underwent lymphadenectomy for regional recurrence after treatment for ESCC.

Patients and methods

We retrieved 20 cases in which lymphadenectomy was performed for lymph node recurrence after initial treatment for ESCC in our hospital from January 2003 to December 2016. Initial treatments included esophagectomy, endoscopic resection (ER) and chemoradiotherapy/chemotherapy (CRT/CT). Overall survival (OS) and recurrence-free survival (RFS) after lymphadenectomy were calculated by the Kaplan-Meier method. We also used a univariate analysis with a Cox proportional hazards model to determine factors influencing the long-term outcomes.

Results

The 5-year OS and RFS of patients who underwent secondary lymphadenectomy for recurrence after initial treatment were 55.0% and 35.3%, respectively. The 5-year overall survival rates of patients who received esophagectomy, ER and CRT/CT as initial treatments, were 45.5%, 80.0% and 50.0%, respectively. The 5-year OS rates of patients with pStage I and pStage II-IVB lymph node recurrence were 75.0% and 41.7%, respectively.

Conclusions

Lymphadenectomy for regional recurrence after initial treatment for ESCC is effective to some degree. Patients with regional recurrence after initial treatment for Stage I ESCC have a good prognosis; thus, lymphadenectomy should be considered for these cases.

Introduction

Esophageal squamous cell carcinoma (ESCC) is likely to spread to the cervical, mediastinal and abdominal lymph nodes through the lymphatic system [1]. In Japan, the recurrence rates after radical esophagectomy for ESCC are 29.0-43.0% [2–4]. Despite improvement of lymphadenectomy, lymph node recurrence accounts for 22.0-68.0% of all recurrence [2–7]. While some retrospective studies showed that the resection of regional lymph node recurrence had a good prognostic effect, the evidence was not strong [8–11].

As the adoption of endoscopic resection (ER) for superficial esophageal cancer became broader, more cases of lymph node recurrence after ER were reported [12–14]. Minasaki et al. suggested that the lymph node recurrence rate after ER of ESCC was approximately 4.0% [15]. The Japan Clinical Oncology Group (JCOG) reported a high complete response (CR) rate after radical chemoradiotherapy (CRT) for advanced ESCC (62.2%) [16]. However, their 5-year progression-free survival rate was no more than 25.6%, and lymph node recurrence after CRT for ESCC is common. In spite of the high recurrence rate, there have been few studies about the treatment of lymph node recurrence after ER and CRT.

In this study, we investigated the short- and long-term outcomes of patients who had lymphadenectomy for regional lymph node recurrence after treatment for ESCC.

Patients And Methods

Data collection

We retrieved 20 cases of patients who underwent lymphadenectomy for regional lymph node recurrence after initial treatment for ESCC in our hospital from January 2003 to December 2016. We retrospectively collected the clinical data from patient records. This study was approved by Institutional Review Board of Tokyo Medical and Dental University (IRB number: M2021-267).

Patients

Characteristics of 20 patients (male, n=17; female, n=3; median age, 67 years) who underwent lymphadenectomy for regional lymph node recurrence after initial treatment for ESCC are shown in Table 1. The initial treatments for ESCC included had esophagectomy (n=11), ER (n=5) and CRT or chemotherapy (CT) (n=4 [CRT, n=3; CT, n=1]).

Table 1
Characteristics of patients who received lymphadenectomy for lymph node recurrence

	Esophagectomy (n=11)	**ER (n=5)**	**CRT/CT (n=4)**	**Total (n=20)**
Age, median (range)	64 (56-84)	73(65-81)	65(56-73)	67(56-84)
Sex (%)				
Male	10 (90.9)	4 (80.0)	3 (75.0)	17 (85.0)
Female	1(9.1)	1 (20.0)	1 (25.0)	3 (15.0)
Location, Ce/Ut/Mt/Lt				
Ce	0 (0)	0 (0)	1 (25.0)	1 (5.0)
Ut	0 (0)	1 (20.0)	0 (0)	1 (5.0)
Mt	9 (81.8)	3 (60.0)	2(50.0)	14 (70.0)
Lt	2 (18.2)	1 (20.0)	1 (25.0)	4 (20.0)
Stage (%)				
I	3 (27.3)	5 (100)	0 (0)	8 (40.0)
II	1 (9.1)	0 (0)	1 (25.0)	2 (10.0)
III	4 (36.4)	0 (0)	0 (0)	4 (20.0)
IVA	2 (18.2)	0 (0)	1 (25.0)	3 (15.0)
IVB	1 (9.1)	0 (0)	2 (50.0)	3 (15.0)
Initial lymphadenectomy range				
3-field	9 (81.8)	NA	NA	NA
the others	2 (18.2)	NA	NA	NA
pR0	10 (90.9)	5 (100)	NA	NA
Adjuvant therapy	4 (36.4)	0(0)	NA	NA
RFS	13.4	50.5	19.9	15.9
(months)	(3.3-68.4)	(12.1-61.8)	(6.5-28.7)	(3.3-68.4)
Site of recurrence				

ER, endoscopic resection; CT, chemotherapy; CRT, chemoradiotherapy pR, pathological residual tumor; NA, not applicable; RFS, recurrence-free survival.

The stages of esophagectomy and ER are pathological. The stage of CRT/CT is clinical.

	Esophagectomy (n=11)	ER (n=5)	CRT/CT (n=4)	Total (n=20)
Cervical	9 (81.8)	3 (60.0)	1 (25.0)	13 (65.0)
Mediastinal	1 (9.1)	2 (40.0)	2 (50.0)	5 (25.0)
Abdominal	1 (9.1)	0 (0)	1 (25.0)	2 (10.0)
ER, endoscopic resection; CT, chemotherapy; CRT, chemoradiotherapy pR, pathological residual tumor; NA, not applicable; RFS, recurrence-free survival.				
The stages of esophagectomy and ER are pathological. The stage of CRT/CT is clinical.				

The disease stages (according to the 8th edition of the UICC TNM Classification) of the 11 patients who received esophagectomy as an initial treatment were as follows: pStage I (n=3), pStage II (n=1), pStage III (n=4), pStage IVA (n=2), and pStage IVB (n=1; left deep cervical lymph nodes). All 5 patients who had ER had pStage I disease. Among 4 patients who had CRT or CT as initial treatment, 1 was cStage II,1 was cStage IVA and 2 were cStage IVB (PUL and LNs around the abdominal aorta). Among the 11 patients who had esophagectomy as an initial treatment, 9 patients (81.8%) had 3-field lymph node dissection. Among patients who received esophagectomy, 90.9% of patients achieved pathological residual tumor (pR) 0; among patients who received ER, this rate was 100%. All patients who had CRT or CT could achieve a clinical complete response (cCR) after initial treatment, based on the RECIST guidelines with endoscopic examination and enhanced computed tomography.

The median time from initial treatment to lymph node recurrence was 15.9 months. In cases involving esophagectomy and ER, the initial date was defined as the date of the operation or ER. In cases involving CRT or CT, we set the last date of CRT or CT treatment as the initial date. The median time from the initial treatment to lymph node recurrence was 13.4 months for esophagectomy, 50.5 months for ER and 19.9 months for CRT/CT. Thirteen patients (65.0%) had cervical lymph node recurrence, 5 (25.0%) had mediastinal lymph node recurrence, and 2 (10.0%) had abdominal lymph node recurrence. The median follow-up time after the resection of lymph node recurrence was 49.0 months.

Exclusion criteria

We excluded cases of double cancer, with the exception of early-stage cancer, distant recurrence other than supraclavicular lymph node recurrence, and lymph node recurrence in multiple fields.

Diagnosis of recurrence

The diagnosis of recurrence was based on imaging studies, including computed tomography and ^{18}F-fluorodeoxy glucose emission tomography (FDG-PET).

Statistical analysis

Statistical analyses were performed using the Stata/SE 16 software program. Overall survival (OS) and recurrence-free survival (RFS) were calculated by the Kaplan-Meier method. A univariate analysis was performed using a Cox proportional hazards model. *P* values of <0.05 were considered to indicate statistical significance.

Results

The short-term outcomes of lymphadenectomy for recurrence are shown in Table 2. Seventeen patients (85.0%) achieved pR0. Histopathologically, 7 patients had only 1 metastatic lymph node. Two patients had no metastatic lymph nodes. One patient had some cancer cells, but not in the lymph nodes. The rate of Clavien-Dindo grade ≥II complications was 30.0%, and that of Clavien-Dindo grade ≥III complications was 15.0%; these included 3 cases of postoperative bleeding, lymphatic leakage and cervical abscess. The median hospital stay after lymphadenectomy was 4.5 days. The numbers of lymphadenectomy cases with perioperative therapy, according to initial treatment are shown in Table 3. Thirteen patients (85.0%) had perioperative treatment (e.g., CRT or radiation therapy [RT]) before and after lymphadenectomy for recurrence. Four patients (25.0%) had CRT as a neoadjuvant therapy. Three patients (15.0%) had RT as an adjuvant therapy, and 6 patients (30.0%) had CRT as an adjuvant therapy.

Table 2
The short- and long-term outcomes of lymphadenectomy for lymph node recurrence

	Esophagectomy (n = 11)	**ER (n = 5)**	**CRT/CT (n = 4)**	**Total (n = 20)**
Short-term outcomes				
Curability R0/R1/R2	9/1/1	4/0/1	4/0/0	17/1/2
No. of metastatic nodes, median (range)	2 (0-29)	2 (0-6)	5 (0-8)*	2 (0-29)
Postoperative hospital stay (days) median (range)	5 (2-26)	3 (3-15)	5 (3-13)	4.5 (2-26)
Complication (%) (Clavien-Dindo Classification ≥ II)	27.3	20	25.0	25
Long-term outcomes				
5-year survival rate (%) (95% CI)	45.5 (16.7-70.7)	80.0 (20.4-97.0)	50.0 (5.8-84.5)	55.0 (31.3-73.5)
5-year recurrence-free survival rate (%) (95% CI)	33.3** (7.8-62.3)	50.0 *** (5.8-84.5)	25.0 (0.9-66.5)	35.3 (14.5-57.0)

* We removed one patient with no lymph node recurrence.

** We removed two patients for whom R0 resection could not be achieved.

*** We removed one patient for whom R0 resection could not be achieved.

ER, endoscopic resection; CT, chemotherapy; CRT: chemoradiotherapy.

Table 3
The number of lymphadenectomy cases with perioperative therapy

	Esophagectomy (n = 11)	**ER (n = 5)**	**CRT/CT (n = 4)**	**Total (n = 20)**
Neoadjuvant therapy CT/RT/CRT	0/0/4	0/0/0	0/0/0	0/0/4
Adjuvant therapy CT/RT/CRT	0/1/3	0/2/1	0/0/2	0/3/6

CT, chemotherapy; RT, radiation therapy; CRT, chemoradiotherapy.

The long-term outcomes of lymphadenectomy for recurrence are shown in Table 2. The 5-year OS and RFS rates were 55.0% and 35.3%, respectively. According to the initial treatments, the 5-year OS and RFS rates were 45.5% and 33.3%, respectively for esophagectomy; 80.0% and 50.0% for ER; and 50.0% and 25.0% for CRT and CT. These OS and RFS rates are also shown using the Kaplan-Meier method in Figures 1 and 2. The results of the univariate analysis of overall survival with a Cox proportional hazards model are shown in Table 4. There were no significant differences in OS according to the initial treatment; the hazard ratios (HRs) for esophagectomy, ER and CRT/CT were 1.00, 0.20 (p=0.14) and 0.70 (p=0.66), respectively. When the locations of recurrence were compared, there were no significant differences in OS; the HRs for cases involving the cervical, mediastinal and abdominal areas were 1.00, 0.95 and 4.44, respectively (p=0.09). When cases in which pR0 was achieved were compared with those in which pR0 was not achieved, pR0 did not significantly improve the OS; the HR of pR1-2 was 1.76 (p=0.48). When initial Stage I and Stage II-IVB were compared (Figure 3), the HRs for OS and RFS in patients with Stage ≥II disease were 2.27 (p=0.19) and 2.27 (p=0.19). We also examined the re-recurrence patterns after the resection of lymph node recurrence and showed the results in Table 5. Among the 8 patients with initial Stage I, 3 patients had re-recurrence; 1 patient had distant recurrence and 2 patients had regional lymph node recurrence. Among the 12 patients with initial Stage ≥II disease, 7 patients had re-recurrence; 4 patients had distant recurrence and 3 patients had regional lymph node recurrence.

Table 4. Results of the univariate analysis of factors associated with overall survival using a Cox proportional hazards model

varieties	Hazard Ratio	95% Confidence Interval	p-value
Sex			
Male	1.00	Reference	Reference
Female	1.59	0.33-7.67	0.56
Age (per year)	0.99	0.91-1.09	0.82
No. of metastatic nodes	1.05	0.96-1.14	0.27
Stage			
Stage I	1.00	Reference	Reference
Stage ≥II	2.44	0.62-9.63	0.20
Initial treatment	1.00	Reference	Reference
Esophagectomy			
ER	0.20	0.02-1.65	0.14
CRT/CT	0.70	0.15-3.39	0.66
Recurrent part			
Cervical	1.00	Reference	Reference
Mediastinal	0.95	0.23-3.98	0.94
Abdominal	4.44	0.79-25.1	0.09
pR			
0	1.00	Reference	Reference
1≤	1.76	0.36-8.50	0.48

ER, endoscopic resection; CT, chemotherapy; CRT, chemoradiotherapy; pR, pathological residual tumor.

Table 5. Patterns of re-recurrence after lymphadenectomy for lymph node recurrence

	Stage I (n=8)	Stage ≥II(n=12)	Total (n=20)
Distant recurrence (n=5)	1 (12.5%)	4 (33.3%)	5 (25.0%)
Regional lymph node recurrence (n=5)	2 (25.0%)	3 (25.0%)	5 (25.0%)

Discussion

Some previous studies showed that the complication rate of lymphadenectomy for recurrence was 8.0–21.1% [8–11]. When these results are compared with our results, the complication rate in our study was slightly higher in comparison to previous studies. Four of 6 patients who had complications had esophagectomy, and 3 of them had CRT before lymphadenectomy for recurrence (lymphatic leakage, aspiration pneumonia and mediastinal abscess [n=1 each]). We suspect that tissues were scarred and weakened from previous operations and CRT, which led to postoperative complications. We should carefully perform lymphadenectomy in cases after esophagectomy and CRT. The pR0 rate after lymphadenectomy for recurrence was nearly the same as the rate reported by Watanabe et al. (78.9%) and Nakamura et al. (88.2%) [8–10]. In addition, they reported median postoperative hospital stays of 7 days and 10.5 days, respectively. In our study, the length of postoperative hospital stay was shorter in comparison to those previous studies.

Nakamura et al. reported that the median OS of 22 patients who received CRT for lymph node recurrence after esophagectomy for ESCC was 20.3 months [10]. This study also showed that the rate of lymph node recurrence did not differ to a statistically significant extent between lymphadenectomy and CRT. In our study, the median OS of patients who received lymphadenectomy after esophagectomy for ESCC was 30.5 months, which could indicate a prognostic improvement. However, 8 of the 11 patients who received esophagectomy as an initial treatment also received CRT or RT; thus, the combination of lymphadenectomy and adjuvant therapy may have led to a good prognosis.

There are few case reports about treatment for regional lymph node recurrence after ER for ESCC [12–14]. We performed lymphadenectomy for 5 patients with lymph node recurrence after ER for ESCC. Our study could not demonstrate that the prognosis of patients who received ER as an initial treatment for ESCC was significantly better in comparison to patients who had esophagectomy and CRT/CT; however, the results might imply the possibility that patients who received ER had a better prognosis. In addition, the interval from ER to lymph node recurrence was longer than from other initial treatments to lymph node recurrence. As Kanda et al. and Ono et al. reported lymph node recurrence 2 years after ER, regular and long-term follow-up are required to enable early intervention [17, 18].

In our study, we could not show a prognostic difference between initial Stage I and Stage II-IVB. However, patients with Stage I disease tended to show a better prognosis in comparison to those with higher disease stages. Ozawa et al. reported that the 5-year OS rates of patients with pStage I disease who had recurrence after esophagectomy for ESCC was 9.3-13.6%, which represents a poor prognosis [19]. Approximately 25% of the cohort of that study was composed of patients with distant metastatic recurrence; thus, we cannot simply compare the results with ours. However, the 5-year OS rate of patients with pStage I disease who had regional lymph node recurrence was no less than 60%, which is a valuable result, even considering the unmatched cohort. Our results suggest that lymphadenectomy can lead to a good prognosis in patients diagnosed with pStage I ESCC who have regional lymph node recurrence.

The present study was associated with some limitations. This was a retrospective single-arm analysis of a limited number of cases. The indication of lymphadenectomy was based on the surgeons' experience; thus, it is likely that there was a selection bias. We lacked information about some confounding factors, such as the performance status, the medical and social history, and the histopathological type. In addition, we could not perform a multivariate analysis because of the small study population. There is the possibility that we could not correctly assess the efficacy of lymphadenectomy itself because most of the patients who received lymphadenectomy also received some adjuvant therapy.

Conclusions

Lymphadenectomy can be expected to be effective in the treatment of regional recurrence after the initial treatment of ESCC. In particular, patients with regional lymph node recurrence after initial treatment for Stage I ESCC had a good prognosis; thus, we should consider lymphadenectomy for these cases.

Abbreviations

- ESCC: esophageal squamous cell carcinoma
- ER: endoscopic resection
- chemoradiotherapy/chemotherapy: CRT/CT
- RT: radiation therapy
- OS: overall survival
- RFS: recurrence free survival
- JCOG: Japan Clinical Oncology Group
- pR: pathological residual tumor
- cCR: clinical complete response

FDG-PET: ^{18}F-fluorodeoxy glucose emission tomography

HRs: hazard ratios

Declarations

Ethics approval and consent to participate

This research involving human data, was performed in accordance with the Declaration of Helsinki. This study did not include the intervention for patients. In addition, the authors did not use samples obtained from human bodies and used only anonymized patients' data. The authors used the opt out approach to get patients' consent to participate. The authors notified and disclosed information about this study on the official website of Tokyo Medical and Dental University, and guarantee the opportunity for refusal by document, call or e-mail whenever possible. This study was approved by Institutional Review Board of Tokyo Medical and Dental University (IRB number: M2021-267).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TS and AH analyzed and interpreted the patient data. All authors discussed the interpretation about the results. They read and approved the final manuscript.

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Figures

Figure 1

Kaplan-Meier estimates for patients who received lymphadenectomy. a) Overall survival rate. b) Recurrence-free survival rate. RFS: recurrence-free survival.

Figure 2

Kaplan-Meier estimates for patients who received lymphadenectomy, separated by initial treatment. a) Overall survival rate. b) Recurrence-free survival rate. ER, endoscopic resection; CT, chemotherapy; CRT, chemoradiotherapy; RFS: recurrence-free survival.

Figure 3

Kaplan-Meier estimates for patients who received lymphadenectomy, separated by stage. a) Overall survival rate. b) Recurrence-free survival rate. RFS, recurrence-free survival.