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Postoperative Lymph Node Recurrence in Esophageal Cancer After Surgery and Prognosis of Chemoradiotherapy

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Abstract. *Background/Aim: This study aimed to evaluate the long-term prognosis of definitive chemoradiotherapy and clinical features of postoperative lymph node (LN) recurrence after curative resection of thoracic esophageal squamous cell cancer (ESCC). Patients and Methods: A total of 586 patients who underwent radical resection of ESCC at the Hiroshima University Hospital from January 2000 to December 2019 were reviewed retrospectively. This study analyzed the clinical characteristics of 54 patients who developed recurrence in a solitary LN by comparing them to 182 patients who experienced total recurrence. Additionally, we analyzed the prognostic factors of 50 patients who received chemo-radiotherapy (CRT). Results: The results revealed a tendency for a higher incidence of solitary LN recurrence in cases of early esophageal cancer and upper thoracic esophageal cancer among all recurrence cases. The 3-, 5-, and 7-year overall survival (OS) rates were 40.5%, 37.8% and 34.6%, respectively, with a median survival time of 27.9 months. Univariate analysis of OS factors, such as age, depth of the primary tumor at the initial surgery, time to LN recurrence after surgery, site of LN recurrence, and the number of the regional LNs with recurrence showed no significant impact on OS. Conclusion: Approximately 35% of patients with ESCC who experienced LN recurrence after curative resection achieved long-term survival through CRT. Despite the absence of identifiable prognostic factors, CRT proves to be a valuable initial treatment option for LN recurrence.*

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The most frequent type of recurrence following curative resection for esophageal cancer is the recurrence in lymph nodes (LN). Solitary lymph node recurrence after radical resection in esophageal squamous cell carcinoma (ESCC) represents 45-55% of all recurrence cases (1, 2). LN resection and chemoradiotherapy are used for patients with solitary lymph node recurrence; however, the prognosis is poor in most cases. Nevertheless, certain cases have been reported to exhibit a relatively more favorable outcome. While researchers are actively exploring prognostic factors, no definitive prognostic factor has been established (3, 4).

In our department, chemoradiotherapy is generally administered patients with LN recurrence without distant metastasis. In instances where a solitary recurrence of a cervical LN was amenable to surgical removal from the neck, the patient underwent chemoradiotherapy following the resection.

The objective of this study was to examine the clinical characteristics of patients in our department who experienced solitary lymph node recurrence following curative resection of esophageal cancer. Additionally, the study aimed to assess the outcomes and prognostic factors related to chemoradiotherapy.

Patients and Methods

Patients. We conducted a retrospective analysis of medical records for 586 surgeries involving patients with thoracic ESSC who underwent procedures at Hiroshima University Hospital between January 2000 and December 2019, excluding cases of salvage surgery and noncurative resection.

Radical esophagectomy with two- or three-field lymph node dissection was performed using either an open or thoracoscopic approach. There were 182 cases of recurrence including 54 cases of lymph node alone recurrence, and 4 cases were treated with systemic chemotherapy. Out of the 50 patients who received chemoradiotherapy, 11 had resectable cervical LN recurrence and underwent prophylactic chemoradiotherapy following the surgical removal of lymph nodes in the neck. In the present study, we

Table I. *Comparison of patient characteristics at the time of initial esophagectomy among those who presented with solitary lymph node (LN) recurrence and all recurrence cases.*

		Solitary LN recurrence cases N=54	All recurrence cases N=182	*p*-Value
Age [Median (range)]		65(43-77)	65(45-81)	*p*=0.672
Sex	Male	48	165	*p*=0.594
	Female	6	17	
Location	Ut	17	36	*p*=0.013
	Mt	30	104	
	Lt	7	42	
cT	1	24	35	*p*<0.00
	2	4	17	
	3	25	121	
	4	1	9	1
cN	0	30	63	*p*<0.05
	1	15	59	
	2	7	43	
	3	2	17	
Neoadjuvant therapy	None	20	59	*p*<0.001
	Chemotherapy	16	42	
	Chemoradiotherapy	18	81	

Ut: Upper thorax; Mt: middle thorax; Lt: lower thorax.

Table II. *Clinical characteristics of patients with solitary lymph node recurrence treated with radical chemoradiotherapy.*

	N=50
Interval to recurrence (month) [median (range)]	14 (3-115)
Lymph node recurrence site no. (%)	
Cervix	27 (46.7%)
Upper thoracic	18 (31.0%)
Middle thoracic	5 (8.6%)
Lower thoracic	4 (6.9%)
Abdominal	4 (6.9%)
Number of clinically detected node	
Solitary	24
Multiple	16
Region of recurrent node	
Sigle	38
Multiple	12
Combined chemotherapy regimen	
CF	41
DF	3
5-FU, S-1	6
Treatment for recurrence	
Surgery and adjuvant CRT	11
CRT	39

CF: Cisplatin+5-fluorouracil; DF: docetaxel+5-fluorouracil; 5-FU: 5-fluorouracil; CRT: chemoradiotherapy.

analyzed the characteristics of 54 patients who experienced solitary lymph node recurrence and investigated the prognosis and prognostic factors of the 50 patients who received chemoradiotherapy, excluding the four patients who were treated with systemic chemotherapy. LN recurrence was diagnosed using computed tomography (CT) or positron emission tomography.

Treatments. External beam radiotherapy was administered using a 6 or 10 MV photon beam. Three-dimensional radiotherapy was planned for all patients. The daily fractional dose of radiotherapy was 2.0 Gy, which was administered five days per week. Most patients received 40 Gy of prophylactic irradiation to the lymph node region around the lymph node metastasis, followed by 20 Gy of boost irradiation to the gross lesions. The spinal cord received no more than 40 Gy of radiation.

The combination chemotherapy regimen included CF [cisplatin at a dose of 70 mg/m^2 on days 1 and 29, and 5-fluorouracil (5-FU)] at a dose of 700 mg/m^2 on days 1-4 and 29-32) for 41 patients, docetaxel, and 5-FU for three patients, and 5-FU monotherapy or orally administered S-1 for six patients. Every patient who underwent chemoradiotherapy successfully completed the procedure.

Following the CRT, all patients underwent regular medical examinations, blood tests, and CT imaging every 6 months for a minimum of 5 years post-surgery. A more in-depth assessment was also conducted to identify any reported symptoms.

Statistical analysis. All analyses were performed with the SPSS® software program, ver. 26 (IBM, Armonk, NY, USA), and *p*-values <0.05 were considered significant. The study protocol was approved by the Ethics Committee of the Hiroshima University Hospital (IRB number 3280).

Results

The median age of the 182 patients who faced recurrence following radical surgery for esophageal squamous cancer, was 65 years and 90.7% of them were male.

Within this group of 182 patients with recurrence, 54 experienced solitary lymph node recurrence. Table I presents the clinical characteristics at the time of their initial surgery. In comparison to the entire pool of recurrence cases, those with solitary lymph node recurrence exhibited a significant inclination toward having early-stage cancer (T1 depth) and no lymph node metastasis. Consequently, there were more instances of preoperative chemotherapy as opposed to preoperative chemoradiotherapy. Additionally, the primary tumor site was more likely to involve a single lymph node in the upper thoracic region.

Table II summarizes the clinical features of the recurrent nodes among the 50 patients. The majority of LN recurrences were concentrated in the cervical and superior mediastinal regions. The median time for recurrence was 14 months, with 16 cases showed multiple lymph node recurrences, including 12 cases with recurrences in multiple regions.

Among these cases, 39 patients received definitive CRT, while 11 patients underwent prophylactic CRT following lymph node resection.

The 3, 5, and 7-year progression-free survival rates were 37.1, 27.0, and 27.0%, respectively. The 3, 5, and 7-year OS

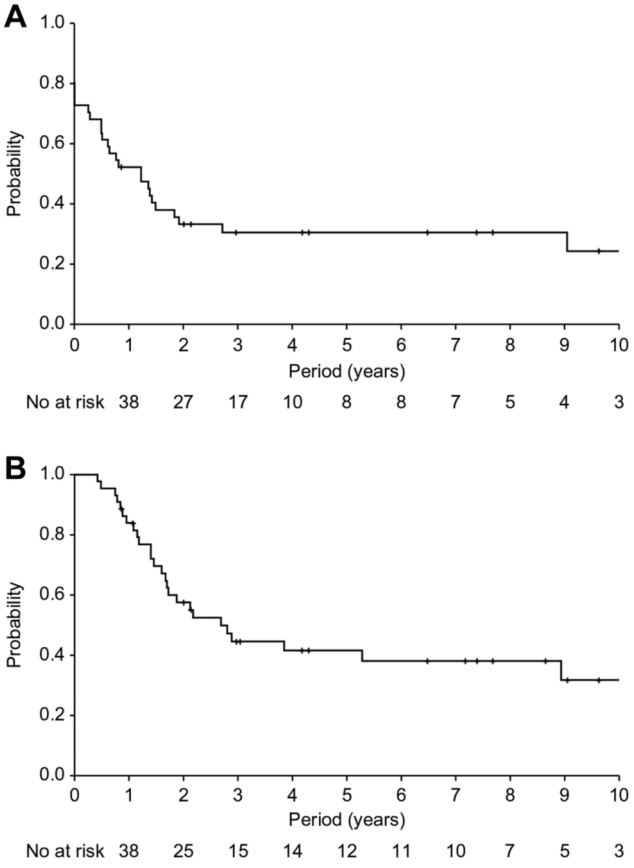

Figure 1. *Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) in patients with postoperative solitary lymph node metastasis from esophageal cancer.*

rates were 40.5, 37.8, and 34.6%, respectively, with a median survival time (MST) of 27.9 months (Figure 1A and B).

We conducted a univariate analysis to investigate whether age, the depth of primary tumor at the initial surgery', time elapsed since lymph node recurrence after surgery, the location of lymph node recurrence, or number of recurrence LN regions had any impact on overall survival. However, the results did not reveal any significant differences in these factors, and no specific prognostic factors could be discerned (Table III).

Table IV provides a breakdown of the 14 cases of supraclavicular LN recurrence. In 11 cases, cervical lymph node dissection was not performed during the initial surgery, and it was considered possibility that the omission of cervical lymph node dissection was the cause of recurrence. Therefore, in addition to resection of the recurrent lymph nodes, postoperative chemoradiotherapy with prophylactic irradiation fields in the bilateral neck and supraclavicular regions was administered to these 11 patients. Three patients experienced recurrence even though they had undergone

Table III. *Prognostic factors for overall survival.*

Factor	Group	n	Median survival (months)	*p*-Value
Age	≥65	23	26	0.172
	<65	27	51	
cT factor	cT1	24	34	0.173
	cT2-T4	26	26	
cN factor	cN0	22	33	0.593
	cN1-N2	22	26	
Interval between surgery and recurrence	≥12	28	33	0.373
	<12	22	26	
Metastatic region	Cervical	21	38	0.351
	Mediastinal and abdominal	29	26	
Region of recurrent nodes	Single	38	33	0.413
	Multiple	12	26	

cervical dissection during the initial surgery. One of these patients underwent resection and received prophylactic chemoradiotherapy with irradiation focused on the recurrent side in the supraclavicular region. Meanwhile, two patients had radical chemoradiotherapy due to the metastatic lymph nodes invading surrounding organs and being inoperable. Regrettably, all three of these patients eventually faced recurrences, leading to cancer-related fatalities.

Discussion

This study retrospectively evaluated the long-term outcomes of CRT in patients with solitary lymph node recurrence after radical resection of ESSC. Patients experiencing LN recurrence tended to have earlier preoperative clinical stages compared to those with different types of recurrences. Preoperative CRT was less frequently employed in these cases, and the upper thoracic region was the primary site affected. The 5 and 7 year survival rates for these patients were 41.6 and 38.1%, respectively, with a MST of 32.3 months.

Outcomes of CRT for lymph node recurrence after radical esophageal cancer resection have been reported in other studies, and they range between 13.3 to 35 months MST (4-7).

In comparison to findings from other authors, the treatment outcomes in this study were relatively favorable. These results were attributed to a combination of two potent chemotherapeutic drugs used in 44 out of the 50 patients and a high-dose irradiation of 60 Gy, except for prophylactic irradiation. This study failed to pinpoint any significant prognostic factors for chemoradiotherapy in patients experiencing solitary LN recurrence. In cases of solitary lymph node recurrence, the potential for radical curative treatment with chemoradiotherapy seems more

Table IV. *Clinical features and outcomes of patients with recurrent supraclavicular lymph nodes.*

No	Age	Location	cTNM	NeoTx	Recurrence LN	Dissection field	Time to recurrence	Post-relapse survival	Status
1	51M	Mt	cT1bN0M0	-	104R	2FD	1Y7M	18Y3M	Alive
2	67M	Mt	cT3N1M0	CRT	104R	2FD	3Y3M	8Y10M	DO
3	52M	Mt	cT3N0M0	CRT	104L	2FD	9M	5Y3M	DC
4	72M	Mt	cT1aN0M0	-	102L104L	2FD	1Y11M	2Y2M	DC
5	60M	Ut	cT1bN0M0	CT	104L	3FD	2Y7M	1Y	DC
6	71M	Mt	cT1bN0M0	-	104L	2FD	5M	6Y5M	Alive
7	61M	Ut	cT1bN2M0	CT	101R104R	3FD	10M	1Y5M	DC
8	63M	Lt	cT1aN0M0	-	104L	2FD	1Y2M	4Y7M	Alive
9	65M	Lt	cT1aN0M0	-	1004L	2FD	1Y2M	3Y5M	Alive
10	67M	Lt	cT1bN0M0	-	104R	2FD	1Y8M	2Y	Alive
11	77M	Mt	cT3N1M0	CT	104R16pre	3FD	6M	1Y4M	DC
12	65M	Ut	cT3N1M0	CRT	104R	2FD	2Y	5Y5M	Alive
13	81F	Mt	cT3N2M0	CT	104R104L	2FD	1Y	3Y11M	DC
14	65M	Mt	cT3N1M0	CT	104R104L101L	2FD	3Y	2Y	Alive

Ut: Upper thorax; Mt: middle thorax; Lt: lower thorax; LN: lymph node; Neo Tx: Neoadjuvant therapy; CT: chemotherapy; CRT: chemoradiotherapy; DC: death from cancer; DO: death from other disease.

promising when the cancer is localized, suggesting that factors influencing cancer localization could serve as prognostic indicators.

In previous studies, it was reported that the group with early recurrence within one year after surgery had a higher grade of malignancy and poorer prognosis than the group with late recurrence (8, 9). However, in this study, the early recurrence group did not exhibit a worse prognosis. This discrepancy may arise from the inclusion of patients with early recurrence due to incomplete lymph node dissection, in the group of those with early recurrence due to high malignancy. We postulate that patients with early regional lymph node recurrence due to incomplete dissection may have a better chance of a cure through radical chemoradiotherapy, and their presence in the early recurrence group might have mitigated potential adverse prognosis.

In patients with multiple recurrences who underwent CRT in this study, the recurrences were confined to the same region, such as the cervical region or upper mediastinum, often neighboring cervical areas. In cases with a poor prognosis, like those with upper mediastinal and abdominal lymph node recurrences or more than three recurrences, systemic chemotherapy was chosen at the physician's discretion. Hence, the authors suggest that the lack of a significant difference in prognosis may be due to CRT being administered to a subset of patients with multiple recurrences who had a relatively positive prognosis. Preoperative clinical stage did not emerge as a prognostic factor, indicating that all patients with advanced cancer had undergone preoperative therapy.

According to the TNM classification (10), supraclavicular lymph node metastases are considered distant lymph node metastases, and prophylactic neck dissection is generally not recommended in the United States or Europe. At our institution, cervical dissection is carried out in cases where the primary lesion is located in the upper or middle thoracic region, except for cases involving preoperative chemoradiotherapy when the lesion is deeper than the intrinsic muscular layer. Few studies have explored the outcomes of patients with postoperative esophageal cancer and recurrent supraclavicular lymph nodes. In this study, we evaluated the prognosis of 14 patients who received definitive chemoradiotherapy for recurrent supraclavicular lymph nodes without the development of distant metastases. Among them, 11 patients underwent prophylactic CRT after the removal of metastatic lymph nodes from the neck. Although there isn't clear evidence for its effectiveness, adjuvant chemoradiotherapy was considered given the risk of recurrence in an area not dissected during the initial surgery and the established utility of this therapy in head and neck cancers (11).

Of the 14 patients, six succumbed to cancer, five experienced distant metastases as a recurrence pattern, and only case No. 7 in Table IV faced cancer-related death due to lymph node recurrence progression. There were five cases of supraclavicular lymph node recurrence despite cervical dissection in the initial surgery or lymph node recurrence not only in the supraclavicular lymph nodes but also in other regions, with four cases leading to cancer-related death.

The study's limitations are its retrospective nature at a single institution and a relatively small sample size. Previously, only limited chemotherapy regimens were available for recurrent esophageal cancer; however, with the advent of immune checkpoint inhibitors (ICIs), the option of

using ICIs in combination with chemotherapy, rather than chemoradiotherapy for lymph node recurrence, has emerged (12, 13). Consequently, future research may require a comparison of these treatment approaches.

Conclusion

In summary, the use of chemoradiotherapy for LN recurrence following radical ESCC resection resulted in a 5-year survival rate of 37.8% and favorable long-term survival outcomes. Although specific prognostic factors remain elusive, chemoradiotherapy proves to be a valuable initial treatment for lymph node recurrence.

Conflicts of Interest

The Authors declare no conflicts of interest that may have influenced the results of this study.

Authors' Contributions

Conception and design: Manabu Emi and Morihito Okada. Contribution to patient care: Yuji Murakami, Ikuno Nishibuchi, Toru Yoshikawa, Ryosuke Hirohata, Manato Osawa. Collection and assembly of data: Manabu Emi and Yoichi Hamai. Data analysis and interpretation: Manabu Emi, Yoichi Hamai, and Yuji Murakami. Manuscript writing: Manabu Emi. Final approval of the manuscript: All Authors.

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