

Clinical Outcomes and Prognostic Factors of Salvage Treatment for Local Lymph Node Recurrence After Radical Resection of Oesophageal Carcinoma

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Background: There are no standard therapeutic strategies for local lymph node (LN) recurrence after radical resection of oesophageal squamous cell carcinoma (ESCC), and prognostic risk factors remain controversial. We assessed clinical outcomes and prognostic factors of chemoradiotherapy (CRT) or radiotherapy (RT) for LN recurrence of ESCC after curative resection.

Methods: A total of 117 ESCC patients with LN recurrence after radical resection receiving salvage treatment at our hospital were retrospectively reviewed from 2014 to 2017. Overall survival (OS) was estimated using the Kaplan–Meier method; clinical characteristics were assessed using the Log rank test in the univariate analysis. Multivariate prognostic analysis was performed using the Cox proportional hazard model.

Results: With a median follow-up of 19 months, the 1-, 2- and 3-year OS rates were 75.2%, 40.2% and 27.4%, respectively. The median survival time (MST) was 19.0 months. On univariate analysis for OS, pathological TNM stage, number of LN metastasis, LN maximum (Max) diameter, salvage treatment mode and tumor response were significantly associated with OS ($P = 0.0074$, $P = 0.015$, $P = 0.0011$, $P = 0.028$, $P < 0.000$, respectively). On multivariate analysis, tumor response [Response vs No-response hazard ratio (HR), 2.43; 95% confidence interval (CI), 1.53–3.90, $P < 0.000$] and LN Max diameter (≤ 28 mm vs > 28 mm HR, 2.07; 95% CI, 1.33–3.32, $P = 0.012$) were independent prognostic factors.

Conclusion: Salvage CRT or RT was safe and effective for treating LN recurrence after radical resection in ESCC. Patients with the small LN Max diameter (≤ 28 mm) and obtained response after salvage therapy appeared to achieve long-term OS.

Keywords: oesophageal cancer, lymph node recurrence, chemoradiotherapy

Introduction

Oesophageal cancer (EC) is the seventh most common cancer and the sixth most common cause of cancer-related deaths worldwide.¹ Oesophagectomy remains a standard treatment for resectable oesophageal cancer. However, lymph node (LN) recurrence is one of the main types of treatment failure and is noted in up to 23.8–58.0% of cases. The most common LN recurrence sites are supraclavicular lymph nodes and mediastinal lymph nodes; the median time to recurrence ranges from 10 to 12 months.^{2–7} Although chemotherapy alone or best supportive care can prolong survival, the outcomes in patients treated with chemotherapy alone were

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significantly worse than in patients treated with other therapies.^{8,9} Therefore, chemotherapy alone or best supportive care is usually not first reserved for patients with LN recurrence. For cervical lymph node recurrence or solitary lymph node recurrence, lymphadenectomy is considered a good salvage option and may offer a survival benefit for appropriately selected patients.^{9–12} When surgery is not an option or contraindicated, radiotherapy (RT) or radiochemotherapy (CRT) show promising results in controlling lymph node recurrence after curative resection. RT is effective for the relief of symptoms,¹³ and several studies have verified the effectiveness of CRT to achieve long-term survival.^{14–17} However, the most effective therapeutic strategies are inconclusive, and the most accurate prognostic risk factors are controversial for LN recurrence of EC.

We mainly perform CRT or RT for LN recurrence of oesophageal squamous cell carcinoma (ESCC) after curative oesophagectomy at our hospital. This retrospective study aimed to evaluate clinical outcomes and prognostic factors related to the use of CRT or RT for LN recurrence after curative resection of ESCC.

Materials and Methods

Study Population

We retrospectively reviewed the medical records, RT treatment plans and diagnostic images of patients who underwent CRT or RT for postoperative regional lymph node recurrence after curative oesophagectomy in Taixing People's Hospital, Jiangsu, China, from October 2014 to October 2017. The inclusion criteria were as follows: (a) curative oesophagectomy with 2- or 3-field LN dissection and pathologically confirmed SCC; (b) initial treatment received without prior or postoperative radiotherapy; (c) diagnosis of recurrence within the bilateral supraclavicular region and mediastinum using ultrasonography, computed tomography (CT), positron emission tomography (PET) or histological confirmation by biopsy; (d) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and no clear contraindications to radiotherapy and chemotherapy. Exclusion criteria were anastomotic recurrence, LN recurrence at the abdominal level and distant metastasis. Finally, 117 patients were enrolled in the study. The study was approved by the ethics committee of Taixing people's Hospital and all patients provided informed consent.

Treatment

All patients received three-dimensional conformal RT (3DCRT). With the patient in the supine position, a cradle for immobilisation was made with vacuum. Each patient was scanned from the Atlas (C1) to the second lumbar vertebra (L2) level to cover the entire neck, lung and oesophagus. CT enhancement scans were performed with 5 mm thickness slices, and the images were transferred to the Treatment Planning System (TPS) to determine the target area and the radiation therapy plan. The gross tumour volume (GTV) was defined as recurrent lymph nodes identified by CT scans or PET/CT. Two clinical target volumes (CTV) were defined. The extended-field (T-shaped field) CTV (CTV1) included the bilateral supraclavicular and mediastinal regions (station 1–5 and 7 lymph nodes)⁶ and GTV plus a margin of 10 mm around GTV. The involved-field CTV (CTV2) only included GTV plus a margin of 10 mm around GTV. The planning tumour volume (PTV) was defined as the CTV plus the placement of 5 mm around the CTV. PTV1 and PTV2 were defined by CTV1 and CTV2. The extended-field prescription dose was 50 Gy to PTV1 and then adding 8–14 Gy dose to PTV2. The median dose was 60 Gy to PTV2 (range from 50 to 64 Gy) in the involved-field. All patients were treated with a 6-MV linear accelerator. The daily fractional dose of RT was 1.8–2.0 Gy, 5 days per week. Dose constraint for critical organs was administered as follows: maximum dose of spinal cord < 46 Gy, mean lung dose < 17 Gy and V20 <30%, mean heart dose <35Gy. The extended-field RT was used for 28 patients and the involved-field RT for 89 patients.

Thirty-one patients received RT alone, and the remaining 86 patients received combination of RT with chemotherapy. Among them, 22 patients received chemotherapy sequentially following RT, 16 patients received CRT without sequential chemotherapy, and 48 patients received consolidation chemotherapy after CRT. The concurrent chemotherapy regimen included paclitaxel (T; 135–175 mg/m² on Day 1 for 4 weeks) plus cisplatin (CDDP; 25 mg/m² on Day 1–3 for 4 weeks) in 41 patients, T (45–50 mg/m² on Day 1 for 1 week) alone in 21 patients and Tegafur Gimeracil Oteracil Potassium Capsule (S1) alone in 2 patients. The sequential chemotherapy regimen consisted of TP (T plus CDDP) in 67 patients and 5-fluorouracil + CDDP in 3 patients, administered in 2–4 cycles.

Follow-Up and Response Assessment

The beginning of the follow-up period was defined as the last date of RT. All the patients were followed-up at 1- or 3-month intervals. Follow-up evaluations included contrasted CT of the neck, thorax and upper abdomen, ultrasonography of the neck and upper abdomen and nuclear bone scanning. Additionally, endoscopy, magnetic resonance, PET or cytologic puncture was needed. The Response Evaluation Criteria in Solid Tumours (version 1.1)¹⁸ were used to determine tumour response. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE 4.0).

Statistical Analysis

The study endpoint was overall survival (OS), defined as the interval between LN recurrence and death from any cause, loss to follow-up or last follow-up. OS was estimated using the Kaplan–Meier method, and the differences in survival in the univariate analysis were assessed with the Log rank test. P-values of < 0.05 in the univariate analysis were included in the multivariable models. Multivariate analysis for OS was performed with a Cox proportional hazards model, and the variables were selected by the stepwise method. P-values < 0.05 were considered indicative of statistical significance. All the statistical analyses were performed using R software (version 3.5.3, <http://www.r-project.org/>).

Results

Patients and Tumour Characteristics

A summary of patient and tumour characteristics is detailed in [Table 1](#). Primary histopathological diagnosis of squamous cell carcinoma was established for all patients. The median age was 64 years (range, 46–80 years). The male-to-female ratio was 97:20. The primary tumour location was the upper thoracic region in 6 patients, middle thoracic in 80 patients and lower thoracic in 31 patients. The post-resection pathological stage I was present in 23 patients, stage II in 39 patients and stage III in 55 patients. The median interval time between surgery for the primary lesion to identifying LN recurrence was 11 months (range, 1–120 months). The median LN maximum (Max) diameter, defined as the longest diameter of the recurrence LN in the axial plane in CT, was 28 mm (range, 6–67 mm). Ten patients developed supraclavicular LN recurrence, and 98 patients showed mediastinal LN recurrence; 9 patients had both regions involved. Eighty

patients had single LN metastasis, and 37 had multiple LN metastases. Only 48 patients received postoperative prophylactic chemotherapy.

Treatment Outcome

With a median follow-up of 19 months (range, 4–70 months), the 1-, 2- and 3-year OS rates were 75.2% [95% confidence interval (CI), 67.8–83.5], 40.2% (95% CI, 32.2–50.1) and 27.4% (95% CI, 20.3–30.6), respectively. The median survival time (MST) was 19.0 months. The overall response rate (including complete responses and partial responses) was 70.0% (82/117) in all patients, 62.2% (33/53) in RT ± C patients and 76.5% (49/64) in CRT ± C patients. The response group had a better OS than the non-response group ($p = 0.00024$, [Figure 1](#)).

Toxicity

G3 neutropenia was observed in 22 patients (34.3%) in the CRT ± C group and 11 patients (20.7%) in the RT ± C group. Grade 3 oesophagitis or gastritis was noted in 6 patients (9.3%) in the CRT ± C group; G3 vomiting was observed in 9 out of 64 patients (14.1%) in the CRT ± C group. No Grade 4 or 5 toxicities were present in any patient, and there were no treatment-related deaths.

Analysis of Survival

On univariate analysis for OS, pathological TNM stage, number of LN metastasis, LN Max diameter, salvage treatment mode and tumor response were significantly associated with OS ($P = 0.0074$, $P = 0.015$, $P = 0.0011$, $P = 0.028$, $P < 0.000$, respectively) ([Table 1](#)). The 3-year OS was 52.2% (95% CI: 35.3–77.2%), 23.1% (95% CI: 13.0–40.9%) and 18.2% (95% CI: 10.4–31.9%) in pathological Ia + Ib, IIa + IIb and IIIa + IIIb groups, respectively. The patients in the Ia + Ib group had a better prognosis than those in the IIa + IIb and IIIa + IIIb groups ($P = 0.0074$, 0.049, respectively), but there was no difference in survival time between IIa + IIb and IIIa + IIIb groups ($P = 0.12$, [Figure 2](#)). The CRT ± C group achieved a 3-year OS of 29.7% (95% CI: 20.0–43.3%) compared to 22.6% (95% CI: 13.8–37.2%) for RT ± C ($P = 0.028$). In the subgroup analysis, the 3-year OS and MST were 22.6% and 13.0 months, 22.7% and 17.5 months, 25.0% and 24.0 months and 31.2% and 22.5 months in RT, RT + C, CRT and CRT + C groups, respectively. The survival of the CRT + C group was longer than that of the RT group ($P = 0.031$). There was no statistical difference in the other groups ([Figure 3](#)). There was no statistical difference in

Table 1 Patient Clinical Characteristics and Univariate Analysis

Factor	No. /117 (%)	MST (Month)	P-value
Sex			
Male	97 (82.9)	18	0.32
Female	20 (17.1)	19.5	
Age, years			
≤64	65 (55.5)	24	0.098
>64	52 (44.5)	16	
Performance status (ECOG)			
0	21 (17.9)	20	0.16
1	73 (62.4)	20	
2	23 (19.7)	15	
Primary tumour location			
Upper	6 (5.1)	28	0.62
Middle	80 (68.4)	17.5	
Lower	31 (26.5)	20	
Radical surgery			
Two-fields resection	102 (87.2)	18.5	0.82
Three-fields resection	15 (12.8)	19	
Differentiation degree			
Well	11 (9.4)	26	0.23
Median	87 (74.4)	19	
Poor	19 (16.2)	14	
Pathological TNM stage*			
Ia + Ib	23 (19.7)	NA	0.0074
IIa + IIb	39 (33.3)	22	
IIIa + IIIb	55 (47.0)	16	
LN recurrence site			
Supraclavicular	10	21	0.74
Mediastinal	98	18	
Both	9	17	
Interval to recurrence			
≤11 months	55 (47.0)	18	0.78
>11 months	62 (53.0)	19.5	
No. of LN metastasis			
Mono	80 (68.4)	22	0.015
Multiple	37 (31.6)	16	
LN Max diameter			
≤28 mm	62 (53.0)	25.5	0.0011
>28 mm	55 (47.0)	16	
POST-C			
Yes	48 (41.0)	19.5	0.97
No	69 (59.0)	17	
Salvage Treatments			
RT ± C	53 (45.3)	16	0.028

(Continued)

Table 1 (Continued).

Factor	No. /117 (%)	MST (Month)	P-value
CRT ± C	64 (54.7)	22.5	
Irradiation field			
Involved-field	89 (76.1)	20	0.22
Extended-field	28 (23.9)	16	
Radiation dose			
≥60 Gy	92 (78.6)	20	0.095
<60 Gy	25 (21.3)	16	
Tumor response			
Response (CR+PR)	82 (70.0)	24.5	0.000
No-response (SD+PD)	35 (30.0)	16	

Note: *AJCC 8th edition.**Abbreviations:** No., number; MST, median survival time; CI, confidence interval; LN, lymph node; POST-C, postoperative adjuvant chemotherapy; C, chemotherapy; RT, radiotherapy; CRT, chemoradiation; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

OS between the concurrent chemotherapy regimens T and TP in 48 patients who received CRT and consolidation chemotherapy ($P = 0.25$, see [Supplementary Materials Fig.s1](#)). The 3-year OS and MST were 39.7% and 25.5 months for LN Max diameter ≤ 28 mm, compared to 14.5% and 16 months for LN Max diameter >28 mm ($p = 0.0011$, [Figure 4](#)).

On multivariate analysis, tumor response [Response vs No-response hazard ratio (HR), 2.43; 95% confidence interval (CI), 1.53–3.90, $P < 0.000$] and LN Max diameter (≤ 28 mm vs >28 mm HR, 2.07; 95% CI, 1.33–3.32, $P = 0.012$) were independent prognostic factors ([Table 2](#)).

Discussion

Previous studies suggested that successful management of initial LN recurrence provided survival benefits for post-operative LN recurrence of oesophageal cancer.^{9,19} Ni et al⁷ evaluated the therapeutic efficacy of salvage therapy along with the prognostic factors in LN recurrent after radical esophagectomy. The 3-year OS rates was only 2.9% with chemotherapy alone or best supportive care, significantly worse than those treated with salvage RT or CRT. The patients after curative resection of ESCC treated with the salvage lymphadenectomy for supraclavicular recurrence LN had better OS than those treated with the salvage RT or CRT in Ni⁷ and Nakamura⁸ studies. But the report of the salvage lymphadenectomy for mediastinal LN was seldom. Although optimal salvage strategies in

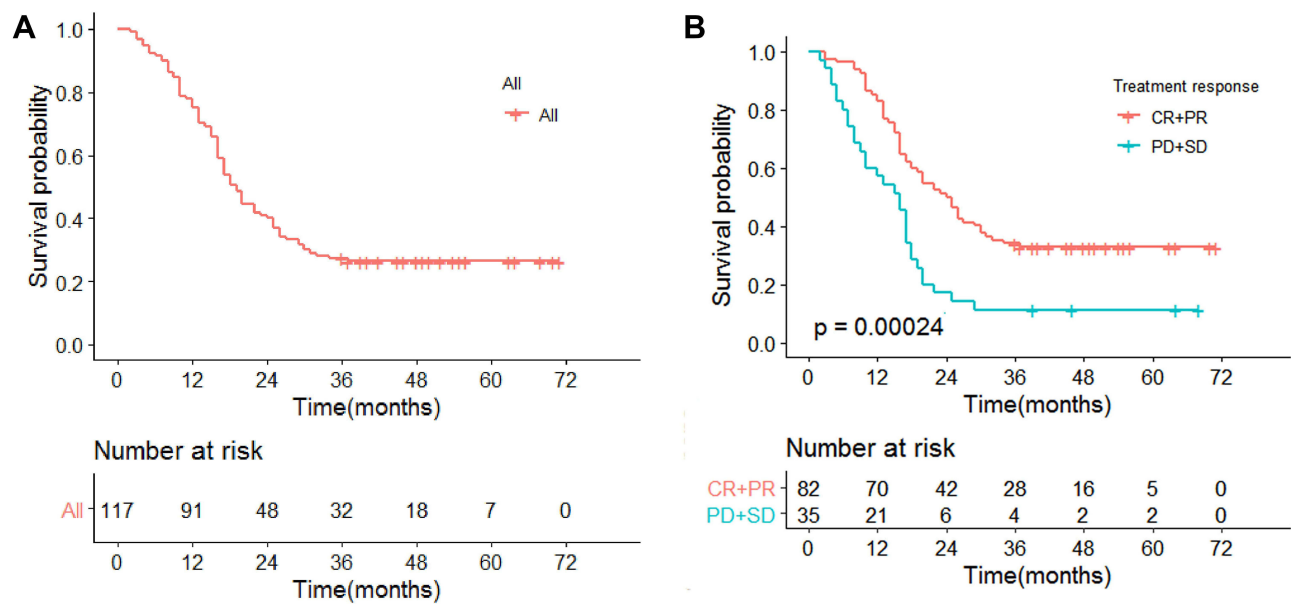


Figure 1 (A) Overall survival curves for all patients; (B) Overall survival of patients with different treatment responses.

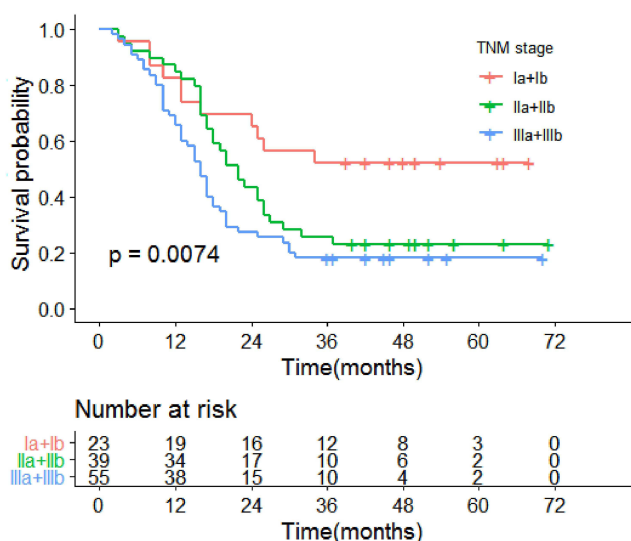


Figure 2 Kaplan–Meier estimates of overall survival for pathological TNM stage.

patients with LN recurrence remain controversial, many retrospective studies suggest that RT or CRT is an effective and feasible salvage treatment for LN recurrence after radical resection of ESCC, particularly CRT.^{7,14–17,20–23}

CRT appears to be superior to RT in OS for treating the locoregional recurrence of esophageal cancer after curative resection in most studies, but some studies found that CRT may not improve treatment outcomes compared to RT alone. A multi-institutional study of 237 patients for lymph node oligo-recurrence of oesophageal cancer by

Yamashita et al¹⁴ found that the 3-year OS was 39.7% with an MST of 26 months in patients receiving CRT; the 3-year OS was 20.8% with an MST of 10.8 months with RT alone ($p = 0.00055$). However, Chen et al¹⁷ retrospectively analysed 83 patients with LN recurrence after radical resection of ESCC and observed that the 3-year OS was 47.5% in patients treated with RT alone and 41.9% in patients receiving CRT ($p = 0.570$). In this study, the MST was 19.0 months, and the 3-year OS was 27.4% (95% CI, 20.3–30.6). The CRT ± C group achieved a 3-year OS of 29.7% (95% CI: 20.0–43.3%) compared to 22.6% (95% CI: 13.8–37.2%) for RT ± C ($P = 0.028$), consistent with the reports of Ni⁷ and Zhou.¹⁶

Several prognostic factors, such as age, postoperative TNM stage, LN Max diameter, GTV volume of radiation, number of LN recurrence, irradiation dose and combined chemotherapy regimen, have been reported (Supplementary Materials Table.s1).^{7,14–17,20,22–24} In the Yamashita et al¹⁴ study, a total of 237 patients with LN oligo-recurrence (from 1 to 5 LN recurrences) of ESCC were treated with RT or CRT. They found that the 3-year OS was 42.1% for LN Max diameter ≤ 22 mm and 30.2% for LN Max diameter >22 mm ($p = 0.0052$), and LN Max diameter (HR = 0.65, $p = 0.012$) was significant on multivariate analysis for OS. In the present study, LN Max diameter was also an independent prognostic factor in the multivariate analysis for OS. The 3-year OS was 39.7% with an MST of 25.5 months for LN Max diameter

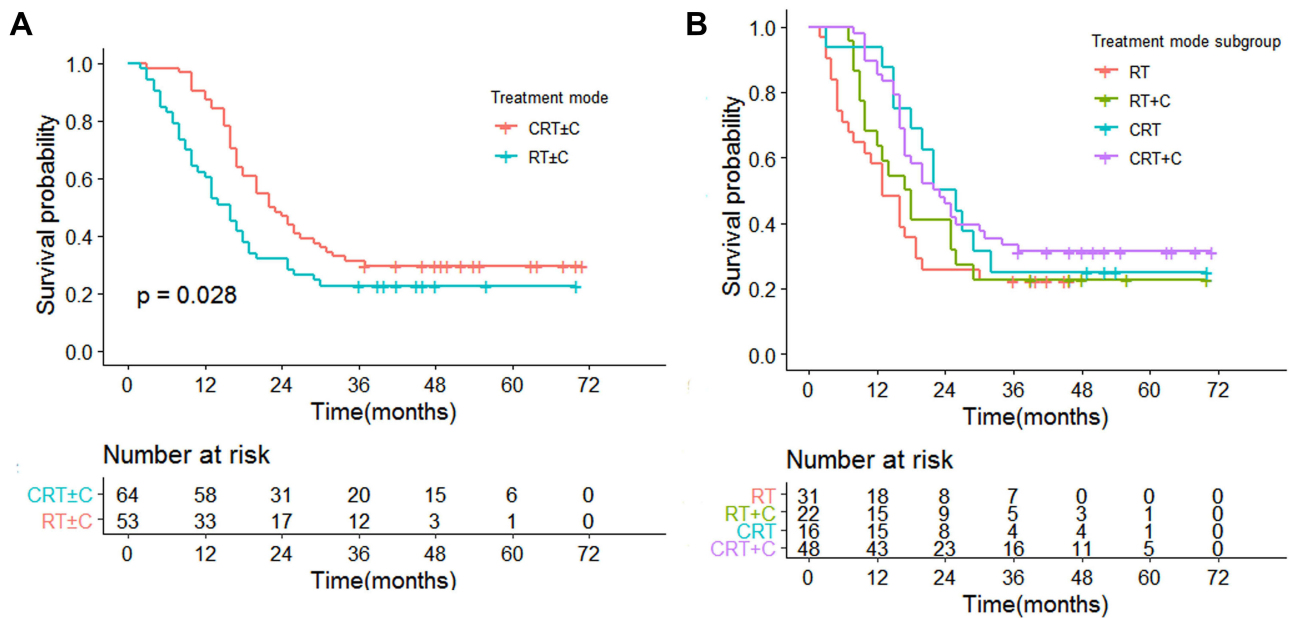


Figure 3 (A) Kaplan–Meier estimates of overall survival curves for different salvage treatment modes; **(B)** Kaplan–Meier estimates of overall survival curves for different subgroup salvage treatment modes.

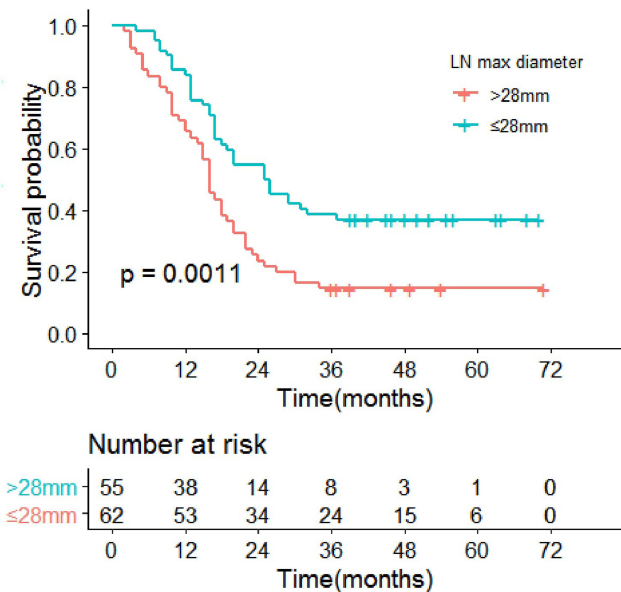


Figure 4 Kaplan–Meier estimates of overall survival for LN Max diameter.

≤ 28 mm, and the 3-year OS was 14.5% with an MST of 16 months for LN Max diameter >28 mm (p = 0.0011). Although local recurrence might have a relationship with the occurrence of distant metastasis, controlling local lesions also potentially affected survival as a whole. In this study, the response group had a better OS than the non-response group (p = 0.00024, Figure 1) and found tumor response was one of the independent predictors of

OS in multivariate analysis (p < 0.000, Table 2), consistent with the report of Bao.²⁰

Although the RT or CRT is an effective salvage treatment for LN recurrence after curative resection of ESCC, the survival varied greatly, with the MST ranged between 13.3 and 43 months in the CRT group and between 10.8 and 22 months in the RT group. Several factors may

Table 2 Multivariate Analysis

Factor	HR	95% CI	P-value
Pathological TNM stage			
Ia + Ib	I		
IIa + IIb	1.61	0.78–3.30	0.193
IIIa + IIIb	1.96	0.98–3.92	0.057
LN Max diameter			
≤28 mm	I		
>28 mm	2.07	1.33–3.32	0.012
No. of LN metastasis			
Mono	I		
Multiple	1.51	0.95–2.40	0.080
Salvage Treatments			
RT± C	I		
CRT± C	0.75	0.48–1.64	0.198
Tumor response			
Response (CR+PR)	I		
No-response (SD+PD)	2.43	1.53–3.90	<0.000

account for this discrepancy. First, selection bias may occur in retrospective studies, small sample sizes and mono-institutional studies in most research. Second, chemotherapy regimens of CRT were diverse. Zhang et al²⁴ reported that ESCC patients with postoperative LN recurrence who received the paclitaxel + CDDP (TP) regimen had significantly improved median OS than those receiving the FP regimen (16.3 months vs 9.8 months, $p = 0.012$). The sub-group analysis of the Kawamoto et al¹⁵ study showed that treatment outcomes with DOC alone combined with RT (MST, 14 months; 3-year OS rate, 30.5%) were worse than those with FP combined RT (MST, 25 months; 3-year OS rate, 43.9%), suggesting that CDDP may be a key drug in CRT treatment for postoperative LN recurrence of ESCC. But the sub-group analysis in the present study showed that MST and 3-year OS of the 17 patients who received the T regimen were not worse than those of the 31 patients receiving the TP regimen ($p = 0.25$). Third, the inclusion criteria are somewhat different. Some studies included patients with anastomotic recurrence and upper abdominal LN recurrence showing worse survival than those with the bilateral supraclavicular and mediastinum LN recurrence.^{8,25} Some studies did not exclude patients with postoperative adjuvant chemotherapy or RT. Zhou et al¹⁶ reported that 1- and 3-year OS after salvage CRT in patients without postoperative adjuvant chemotherapy or RT were better than those receiving postoperative adjuvant chemotherapy or RT ($P = 0.0005$). In this study, a total of 41% of patients received adjuvant chemotherapy, but we found that postoperative adjuvant chemotherapy was not associated with prognosis.

No previous studies have examined the effectiveness of consolidation chemotherapy (CCT) after CRT for treating postoperative LN recurrences of ESCC. However, there are no large-scale clinical trials, and there is no unanimous conclusion on the efficacy of CCT after CRT in nonsurgical EC patients.^{26–29} A systematic review,³⁰ including 11 retrospective studies and 2008 patients, showed that CCT after CRT provided remarkable survival benefits in EC patients. In the present study, we analysed the efficacy of CCT after CRT or RT for treating postoperative LN recurrences of ESCC. Although CCT improved MST and 3-year OS of patients, there was no statistically significant difference compared to CRT or RT (Figure 3). The current retrospective study has limitations, and further clinical trials are required to evaluate

the efficacy of CCT in ESCC patients with LN recurrences.

The present study has several limitations associated with its retrospective design. This study did not evaluate whether the irradiation field affected clinical outcomes. Involved-field CRT may reduce the incidence of treatment toxicity compared to elective nodal irradiation, and it was a treatment option worth considering for LN recurrence of ESCC.³¹ Moreover, there were some selection biases, and large-scale prospective studies are necessary to confirm these findings.

Conclusion

Salvage CRT or RT was a safe and effective treatment for LN recurrence after oesophagectomy in ESCC. Patients with the small LN Max diameter (≤ 28 mm) and obtained response after salvage therapy appeared to achieve long-term OS.

Abbreviations

EC, oesophageal cancer; ESCC, esophageal squamous cell cancer; LN, lymph node; CRT, chemoradiotherapy; RT, radiotherapy; CT, computed tomography; 3DRT, three-dimensional conformal radiation therapy; GTV, Gross tumor volume; CTV, Clinical target volume; PTV, Planning target volume; POST-C, postoperative adjuvant chemotherapy; T, paclitaxel; CDDP, cisplatin; OS, overall survival; MST, median survival time; CI, confidence interval; HR, hazard ratio.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of Taixing people's Hospital (XJS20200022) and was performed in accordance with the standards of the Declaration of Helsinki. Written informed consent was obtained from all participants in the study.

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Disclosure

All authors reported no conflicts of interest for this work.

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