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Salvage radiochemotherapy for lymph node recurrence after radical surgery of esophageal cancer

Yi-Qin Zhou, MD, Nai-Xin Ding, MD, Li-Jun Wang, MD, Wei Liu, MD, Ming Jiang, MD, Jin-Cheng Lu, MD*

Abstract

To evaluate the efficacy of salvage radiochemotherapy (SRC) in patients with recurrent lymph node after radical surgery in esophageal cancer.

This study enrolled 58 patients with esophageal squamous cell carcinoma who underwent SRC for lymph node recurrence after radical surgery from August 2011 to November 2015 at our hospital. Survival rates were calculated by the Kaplan–Meier method with the log-rank test. Multivariate analysis was conducted using the Cox model.

The overall 1-, 3-, and 5-year survival rates after radical surgery were 94.8%, 53.0%, and 29.6%, respectively. The 1- and 3-year survival rates after SRC were 68.7% and 26.9%, respectively. The major acute toxicities were esophagitis and neutropenia, while most toxicities were grade 1 or 2. There was no unexpected increase in serious adverse events or treatment-related deaths. The results of multivariate analysis showed that time to recurrence (odds ratio [OR]: 0.25, 95% confidence interval [CI]: 0.11–0.53, $P = .0004$), T stage (OR: 2.75, 95%CI: 1.16–6.49, $P = .021$), and prophylactic radiotherapy/chemotherapy (PRC, OR: 0.39, 95%CI: 0.16–0.98, $P = .045$) were determinants of postoperative overall survival, and PRC was the only factor affecting the outcome of SRC (OR: 0.28, 95%CI: 0.12–0.70, $P = .006$).

SRC is an effective treatment for recurrent lymph node after radical surgery of esophageal cancer.

Abbreviations: CI = confidence interval, GTV = gross tumor volume, OR = odds ratio, PRC = prophylactic radiotherapy/chemotherapy, PTV = planning target volume, SRC = salvage radiochemotherapy.

Keywords: esophageal cancer, radiochemotherapy, recurrence, surgery

1. Introduction

The common view at present is that prophylactic radiotherapy/chemotherapy (PRC) can significantly reduce recurrence in patients with pathology lymph node positive after esophageal cancer radical surgery.[1–5] The lymph node recurrence is the main cause of failure after radical surgery in esophageal cancer.[6] However, if patients who receive salvage radiochemotherapy (SRC) after lymph node recurrence fare worse than those who do not receive PRC, the efficacy of PRC would be called into question. Even if the time from surgery to lymph node recurrence plus the survival time after SRC is the same between those who receive PRC and those who do not, it makes more sense to give no prophylactic intervention. This is because giving no prophylactic intervention may benefit patients who will not develop lymph node recurrence and does no harm to patients who do have recurrence. Those who really benefit from PRC are patients in whom prophylactic intervention has suppressed any potential recurrences. PRC cannot demonstrate its full value unless salvage therapy results in more favorable outcomes in patients with lymph node recurrence after PRC than those who do not receive PRC. Therefore, the present study sought to examine this issue by reviewing clinical data of patients who received SRC for lymph node recurrence after radical surgery of esophageal cancer.

2. Materials and methods

2.1. Inclusion criteria

This study enrolled patients who underwent SRC for lymph node recurrence after radical surgery of esophageal squamous cell carcinoma from August 2011 when electronic records were adopted at our hospital on November, 2015. Those who had received neoadjuvant therapy before surgery were excluded from this study.

2.2. Diagnosis of lymph node recurrence

Some cases with lymph node recurrences were pathologically confirmed; 2 consecutive CT scans at an interval of 1 month or more showed lymph nodes continued to increase, with a short diameter greater than 1 cm, or lymph nodes did not increase but clinical symptoms became significantly worsened. Patients without pathological diagnosis were discussed at department meetings before treatment.

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Department of Radiation Oncology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing Medical University Affiliated Cancer Hospital, Xuanwu District, Nanjing, Jiangsu Province, P.R. China.

** Correspondence: Jin-Cheng Lu, Department of Radiotherapy, Jiangsu Cancer Hospital, Nanjing 210009, P.R. China (e-mail: 13901585956@139.com).*

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2.3. SRC regimen

As described elsewhere,[7] for patients who received radiotherapy, the gross tumor volume (GTV) of recurrent lymph nodes was delineated, and the planning target volume (PTV) of GTV, namely P-GTV was defined as GTV with 0.5-1 cm margin expansion. For the areas that have been irradiated, it must be at least 1 year intervals for salvage radiotherapy. For patients who did not receive radiotherapy, in addition to the delineation of GTV and P-GTV as above, the area where recurrent lymph nodes resided was also delineated as the clinical target volume, and clinical target volume with 0.5 to 1 cm margin expansion was defined as the PTV. All radiation treatment was delivered as intensity-modulated radiotherapy, and P-GTV: 60 Gy/30 times, PTV: 54 Gy/30 times, maximum dose for normal tissues: spinal cord <40 Gy, lung V20 $<30\%$. Main chemotherapy regimen: docetaxel 80 mg/m^2, nedaplatin 80 mg/m^2. All patients received more than 2 courses of chemotherapy.

2.4. Statistical analysis

The date of surgery was used as the starting date for the calculation of time to recurrence. The date of recurrence was used as the starting date for the evaluation of the efficacy of salvage treatment. By May 2017, the follow-up rate was 100%. Survival rates were calculated using the Kaplan–Meier curves and tested using the log-rank test. The Cox regression model was adopted for multivariate analysis. Statistical analysis was performed using SPSS version 21.0 (SPSS Inc, Chicago, IL). Statistical significance was defined as a 2-sided P value of .05 or less.

3. Results

3.1. General information

A total of 58 patients who met the inclusion criteria were enrolled in this study, including 47 males and 11 females. The patients had a median age of 60 years (range: 46–76 years). There were 24 patients (5 cases of radiotherapy, 4 cases of radiotherapy and chemotherapy, and 15 cases of chemotherapy) who received PRC and 34 patients who did not receive PRC. The patients were staged according to the 7th edition of AJCC staging systems,[8] including 7 in upper segment, 41 in middle segment, and 10 in lower segment. There were 24 lymph node positive patients (N1: 16 cases, N2: 6 cases, nd N3: 2 cases) and 34 lymph node negative patients. In terms of T stages, there were 8 cases of T1, 14 cases of T2, 30 cases of T3, and 6 cases of T4. Information about TN stages was collected from pathological reports after surgery. In terms of site of recurrence, there were 13 cases in supraclavicular area, 31 in mediastinum, 5 in abdominal cavity, and 9 in 2 or more sites. Of 9 cases of recurrence after prophylactic radiotherapy, 8 were in-field and 1 in out-of-field. Median time to recurrence was 12.5 months (range: 1–87 months).

3.2. Univariate analysis

The overall 1-, 3-, and 5-year survival rates were 94.8%, 53.0%, and 29.6%, respectively. As shown in Fig. 1, the 1-, 3-, and 5-year overall survival rates in patients with or without PRC were 91.7%, 41.7%, 23.2% and 97.1%, 60.8%, 35.3% ($P=.013$). The 1- and 3-year survival rates after SRC were 68.7% and 26.9%, respectively. As shown in Fig. 2, the 1- and 3-year survival rates after SRC in patients with or without PRC were 54.2%, 6.5% and 88.1%, 46.2% ($P=.0005$). The results of univariate analysis are shown in Table 1.

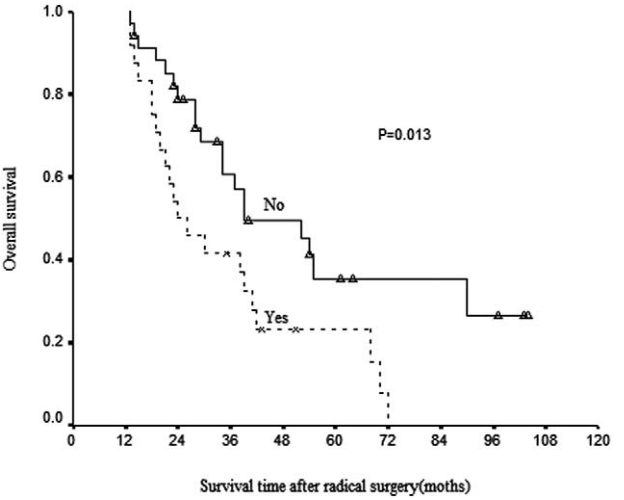

Figure 1. Comparisons of overall survival rates after radical surgery between patients with or without prophylactic radiotherapy/chemotherapy.

3.3. Multivariate analysis

The results of multivariate analysis are shown in Table 2. The outcomes showed that time to recurrence (odds ratio [OR]: 0.25, 95% confidence interval [CI]: 0.11–0.53, $P=.0004$), T stage (OR: 2.75, 95% CI: 1.16–6.49, $P=.021$), and PRC (OR: 0.39, 95% CI: 0.16–0.98, $P=.045$) were determinants of postoperative overall survival. Moreover, PRC was the only factor affecting the outcome of SRC (OR: 0.28, 95% CI: 0.12–0.70, $P=.006$).

3.4. Adverse events

It was not possible to report incidence and grade of toxicity from the retrospective experience. The major acute toxicities were esophagitis and neutropenia, while the vast majority of toxicities

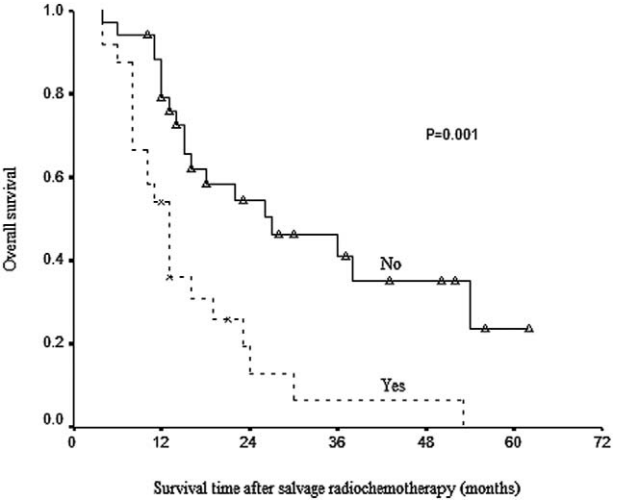

Figure 2. Comparisons of overall survival rates after salvage radiochemotherapy between patients with or without prophylactic radiotherapy/chemotherapy.

Table 1

Univariate analysis for survival rate.

		After radical surgery				After salvage radiochemotherapy		
	n	1-y	3-y	5-y	*P*	1-y	3-y	*P*
Ages, y					.45			.19
>60	34	97.1	60.1	38.3		73.5	39.2	
≤60	24	91.7	43.8	24.6		74.6	14.4	
Sex					.81			.98
Males	47	95.7	52.6	32.7		76.5	27.1	
Females	11	90.9	54.6	32.7		63.6	36.4	
T stage					.70			.35
T1 + T2	22	94.4	55.4	32.3		75.0	34.3	
T3 + T4	36	95.5	50.0	25.0		72.4	24.2	
Pathology of lymph nodes					.03			.04
Negative	34	97.1	62.1	38.6		79.2	37.6	
Positive	24	91.7	40.6	16.9		66.7	20.1	
Tumor location					.33			.88
Upper	7	85.7	51.4	34.3		85.7	0.00	
Middle	41	95.1	54.2	25.6		75.6	29.0	
Lower	10	80.0	50.0	-		60.0	0.00	
Time to recurrence, mo					<0.01			.83
>12	29	93.1	69.0	37.6		75.6	33.1	
≤12	29	90.0	36.6	22.9		69.0	26.0	
Recurrence site					0.54			.48
Supraclavicular	13	92.3	44.9	18.0		61.5	30.8	
Mediastinum	31	96.8	54.4	30.2		77.2	29.8	
Abdominal cavity	5	80.0	40.0	-		80.0	0.00	
Two or more sites	9	88.9	55.6	37.0		77.8	38.9	
PRC					0.01			<.01
Yes	24	91.7	41.7	23.2		54.2	6.5	
No	34	97.1	60.8	35.3		88.1	46.2	

PRC = prophylactic radiotherapy/chemotherapy.

Table 2

Multivariate analysis for survival time.

	After radical surgery		After salvage radiochemotherapy	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Ages, y				
>60	Reference		Reference	
≤60	0.76 (0.30–1.94)	.68	0.87 (0.35–2.16)	.76
Sex				
Males	Reference		Reference	
Females	1.24 (0.50–3.08)	.65	1.22 (0.49–3.04)	.68
T stage				
T1 + T2	Reference		Reference	
T3 + T4	2.75 (1.16–6.49)	.02	2.31 (1.00–5.37)	.05
Pathology of lymph nodes				
Negative	Reference		Reference	
Positive	1.98 (0.81–4.85)	.13	1.41 (0.59–3.37)	.45
Tumor location				
Upper	Reference		Reference	
Middle	0.54 (0.13–2.28)	.40	0.80 (0.19–3.46)	.77
Lower	1.64 (0.55–4.90)	.38	1.82 (0.60–5.52)	.29
Time to recurrence, mo				
>12	Reference		Reference	
≤12	0.25 (0.11–0.53)	<.01	0.69 (0.35–1.39)	.30
Recurrence site				
Supraclavicular	Reference		Reference	
Mediastinum	2.86 (0.83–9.83)	.10	2.01 (0.59–6.78)	.26
Abdominal cavity	1.31 (0.45–3.85)	.63	1.03 (0.36–2.91)	.96
Two or more sites	0.83 (0.19–3.71)	.81	0.94 (0.21–4.11)	.93
PRC				
Yes	Reference		Reference	
No	0.39 (0.16–0.98)	.04	0.28 (0.12–0.70)	<.01

CI = confidence interval, OR = odds ratio, PRC = prophylactic radiotherapy/chemotherapy.

were grade 1 or 2. However, grade 4 neutropenia was not observed in any of the patients. There was no unexpected increase in serious adverse events or treatment-related deaths.

4. Discussion

The 3-year overall survival rate of this group after SRC was 26.9%, among which without PRC was as high as 46.2%. Compared with previous studies,[7] the present result was favorable and encouraging. For patients with lymph node recurrence after radical surgery of esophageal cancer, intensity-modulated radiotherapy concurrent chemotherapy significantly improved the survival. The reason may be that, in addition to intensity-modulated radiotherapy, the innovation of chemotherapy protocols may be another factor.[6,9–11] Furthermore, we analyzed the prognostic factors of SRC in patients with lymph node recurrence after radical surgery of esophageal cancer and found that PRC significantly reduced the efficacy of SRC in patients with lymph node recurrence. Similar results were also found in the reports of Jingu et al.[12] The reason may be that the target of the SRC is more pertinency than the PRC, and patients who do not have PRC have a good tolerance to SRC after the recurrence.

In our study, many patients with postoperative pathology positive lymph nodes underwent PRC, which partly explain why univariate analysis revealed a decline in overall survival in patients who received PRC (Fig. 1). However, survival after SRC was significantly shorter in patients with prevention than in those without prevention (Fig. 2), which was further confirmed by multivariate analysis (Table 2). This indicates that PRC may only delay time to recurrence, and once cancer recurs, SRC after PRC provided significantly less benefit than no PRC (Table 1). The net result is that the real determinants of survival time following radical surgery of esophageal cancer are time to recurrence ($P=.0004$), T stage ($P=.021$), and PRC ($P=.045$) rather than pathology of lymph nodes (Table 2). Therefore, we speculate that time to recurrence is a major determinant of outcomes after radical surgery of esophageal cancer. Looking for factors able to predict the time to recurrence (factors other than TN staging, especially cytokine levels after surgery) may represent a future research direction. This effort may lead to the identification of specific indications for PRC, thereby avoiding changes in beneficiaries.

It is worth mentioning that not all patients who underwent radical resection of esophageal cancer would develop lymph node recurrence and that the current study population includes only patients who received SRC after recurrence. Moreover, this was a retrospective study conducted in a single institution with a limited number of patients. Therefore, our study cannot deny the role of PRC after radical surgery. After all, there are too limited number of patients with radiotherapy and radiochemotherapy in PRC. It simply demonstrates that in patients who developed lymph node recurrence after radical surgery of esophageal cancer, SRC after PRC offered less benefit than no PRC. However, our study suggests that further research is necessary to determine whether patients receiving PRC have higher survival rates than those who do not undergo PRC but receive SRC for recurrence. On the other hand, only a small number of patients received prophylactic radiotherapy or radiochemotherapy in this study. Further research is required to determine whether such regimen reduces lymph node recurrence or some patients with short-term recurrence seek treatment at chemotherapy departments.

5. Conclusions

SRC is an effective treatment for recurrent lymph node after radical surgery of esophageal cancer. PRC may reduce the efficacy of SRC in patients with lymph node recurrence after radical surgery of esophageal cancer. Further research is necessary to determine whether patients receiving PRC have higher survival rates than those who do not undergo PRC but receive SRC after recurrence.

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