Clinical Outcomes and Prognostic Factors of Chemoradiotherapy for Postoperative Lymph Node Recurrence of Esophageal Cancer

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Running Title

CRT for postoperative LN recurrence of ESCC

Keywords

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Abbreviations

ESCC, esophageal squamous cell carcinoma; RT, radiotherapy; CRT, chemoradiotherapy; LN, lymph node; 2D-RT, two-dimensional conventional radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; OS, overall survival; MST, median survival time; FP, 5-fluorouracil and cisplatin; DOC, docetaxel

Abstract

【Background】 The therapeutic strategies and prognostic risk factors in patients with lymph node (LN) recurrence of esophageal cancer remain controversial. We assessed clinical outcomes and prognostic factors related to the use of chemoradiotherapy (CRT) for LN recurrence of esophageal squamous cell carcinoma (ESCC) after curative resection.

【Methods】 We retrospectively evaluated 57 patients with LN recurrence of ESCC after curative resection. Patients received CRT using 5-fluorouracil plus cisplatin (FP) or docetaxel. Radiotherapy was delivered at 2 Gy (total dose, 60–66 Gy; median, 60 Gy). We evaluated the survivals and prognostic factors.

【Results】 The median follow-up duration was 24 months (range, 3–116). The overall survival (OS) rates at 2, 3 and 5 years were 43.7%, 36.9%, and 27.6%, respectively. In the univariate analysis of OS, treatment with FP, a single LN recurrence, and a single regional recurrence were associated with a significantly better prognosis ($p = 0.04$, $p = 0.027$, and $p = 0.0001$, respectively). In the multivariate analysis, the combination chemotherapy regimen (hazard ratio [HR], 2.50; 95% confidence interval [CI], 1.23–5.07) and the number of the regional LNs with recurrence (HR, 5.76: 95% CI, 1.22–27.12) were independent prognostic factors.

【Conclusion】 Approximately 28% of ESCC patients with LN recurrence after curative resection could achieve long-term survival with CRT. Treatment with FP or patients with a single regional recurrence might improve the treatment outcome.

Mini abstract

Approximately 28% of ESCC patients with LN recurrence after curative resection could achieve long-term survival with CRT. Treatment with FP or patients with a single regional recurrence might improve survivals.

Introduction

Esophagectomy remains a standard treatment for resectable esophageal cancer; however, 27.1% to 52.6% of patients who undergo this procedure experience postoperative recurrence, and 47.3% to 78.0% of these recurrences are locoregional(1-8). Treatments for such recurrences include surgical resection, chemoradiotherapy (CRT), radiotherapy (RT), or chemotherapy.

A phase II trial of CRT demonstrated this modality to be a safe and effective salvage option for postoperative locoregional recurrences of esophageal cancer(9, 10). Surgery to remove recurrent lesions is also considered a good salvage option after curative resection(11-13). Long-term survivors with postoperative locoregional recurrence have been reported, and studies suggested that patients with LN recurrence have better survival than those with local (anastomotic) recurrence(14, 15). Controversy remains regarding the most effective therapeutic strategies and most accurate prognostic risk factors for LN recurrence of esophageal cancer.

In our hospital, we perform CRT for LN recurrence of esophageal squamous cell carcinoma

(ESCC) after curative resection. The main aim of this retrospective study was to evaluate the clinical outcomes and prognostic factors related to the use of CRT for LN recurrence after the curative resection of ESCC.

Materials and Methods

Study population. We retrospectively reviewed the medical records, RT treatment plans, and diagnostic images of patients with ESCC who satisfied the following criteria: (i) pathologically proven ESCC, (ii) Eastern Cooperative Oncology Group performance status of 0 to 2, (iii) treatment with definitive concurrent CRT, (iv) no other active cancer, and (v) regional LN recurrence after complete resection (radical esophagectomy with 2- or 3-field LN dissection). Patients with para-aortic LN recurrence at the upper abdominal level were included. We excluded patients with distant metastases or anastomotic recurrences in addition to LN recurrence. LN recurrence was diagnosed comprehensively with ultrasonography, computed tomography, positron emission tomography and physical findings. Between April 2006 and January 2015, 57 patients with LN recurrence of ESCC after curative resection were treated with definitive concurrent CRT at Komagome Hospital and satisfied the selection criteria.

Treatment. External radiation therapy was administered with the 6- or 10-MV X-ray of a linear accelerator. The daily fractional dose of RT was 2.0 Gy, administered 5 days per week, and the total dose was 60 to 66 Gy. Four patients underwent irradiation with 66 Gy in the supraclavicular region, and the remaining 53 patients underwent irradiation with 60 Gy. A T-shaped field including the bilateral supraclavicular and mediastinal regions was used for 15 patients, and a local field covering recurrent tumors with a margin of 2 to 3 cm was used for 42 patients. Two-dimensional conventional RT (2D-RT) was used for 17 patients, and three-dimensional conformal RT (3D-CRT) was used for 40 patients. We used 2 to 4 fields to avoid the spinal cord. In the patients who received 2-field irradiation, the beam direction was changed after irradiation with 40 Gy. Before the introduction of the 3D-CRT in September 2008, patients were treated with the 2D-RT. T-shaped field tended to be used in patients with the 2D-RT.

Chemotherapy was combined with RT in all patients. Twenty-four patients received a chemotherapy regimen consisting of either 5-fluorouracil (5-FU; 700 mg/m^2 on day 1–4 per 4-week) plus cisplatin (CDDP; 70 mg/m^2 on day 1 per 4-week). The remaining 33 patients

received a chemotherapy regimen consisting of docetaxel (DOC; 20 mg/m^2 on day 1 per 1-week). DOC regimen tended to be used in patients with refractory to neoadjuvant chemotherapy with FP regimen by December 2013. FP regimen was used in all patients since January 2014.

After the completion of therapy, the patients were followed at 1- or 3-month intervals. Follow-up evaluations included a history and physical examination, endoscopy, ultrasonography, computed tomography and positron emission tomography. The Response Evaluation Criteria in Solid Tumors criteria were used to determine the tumor response(16), and we defined disease progression as treatment failure (relapse) according to those criteria.

Statistical analyses. Survival was calculated from the start of treatment. Progression-free survival and overall survival (OS) were estimated with the Kaplan–Meier method, and the differences in survival in the univariate analysis were assessed with the log-rank test. Following previous studies, we entered the following parameters into the log-rank test: age ($\geq$65 years versus <65 years), initial pathological stage (I and II versus III [UICC 2010](17)), performance status (0 and 1 versus 2 [Eastern Cooperative Oncology Group](18)), interval

between surgery and recurrence (≥8 months versus <8 months), long diameter of the metastatic LN (≥35 mm versus <35 mm), number of recurrent nodes (single versus multiple), region of recurrent nodes (single region versus multiple regions), radiation field (T-shaped versus local), radiation technique (two-dimensional conventional RT versus three-dimensional conformal RT), and combination chemotherapy regimen (FP versus DOC)(10, 12, 14, 15, 19-25).

Baseline variables with p values of <0.05 in the univariate analysis were included in the multivariable models. Cox's regression analysis was used in the multivariate analysis. All statistical analyses were performed with EZR version 1.32(26), and p values of <0.05 (two-sided) were considered statistically significant. Toxicity was assessed and documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0(27). Grade 3 or worse toxicities were recorded and were defined as acute or late if they occurred within 3 months or longer than 3 months after treatment, respectively. The retrospective study protocol was reviewed and approved by the Komagome Hospital review board.

Results

Patients and tumor characteristics. Table 1 shows a summary of patient and tumor characteristics. The median follow-up time for the patients was 24 months (range, 3–116 months). All patients completed the RT treatment, and 83.3% (20/24) and 100% (33/33) of patients received the FP or DOC regimen, respectively. The remaining patients received 1 cycle of FP.

Treatment outcome. The overall response rate, including complete responses in 25 patients and partial responses in 22 patients, was 82.5% (Table 2). The 2-, 3- and 5-year progression-free survival rates were 26.3% (95% confidence interval [CI], 15.7–38.1), 21.7% (95% CI, 11.8–33.5), and 19.0% (95% CI, 9.6–30.9), respectively. The 2-, 3- and 5-year OS rates were 43.7% (95% CI, 30.3–56.3), 36.9% (95% CI, 23.9–49.8), and 27.6% (95% CI, 15.3–41.4), respectively, with a median survival time (MST) of 22.0 months (Figure).

Toxicity. Grade 3 esophagitis was observed in 1 patient (1.8%) with T-shaped field. Grade 3 leukocytopenia was observed in 6 patients (25.0%) in the FP regimen. No grade 3 or worse late toxicities were observed. No grade 4 or 5 toxicities were observed in any patient.

Analysis of survival. In the univariate analysis of OS, treatment with the FP regimen, a single LN recurrence, and a single regional recurrence were associated with a significantly better prognosis ($p = 0.04$, $p = 0.027$, $p = 0.0001$, respectively; Table 3). In the multivariate analysis, the combination chemotherapy regimen (hazard ratio [HR], 2.50; 95% CI, 1.23–5.07) and the number of the regional LNs with recurrence (HR, 5.76; 95% CI, 1.22–27.12) were the independent prognostic factors (Table 4).

Discussion

We retrospectively evaluated treatment outcomes and prognostic factors in a group of patients treated with CRT for LN recurrence of ESCC after curative resection. Our results showed that approximately 28% of patients could achieve long-term survival with CRT. The results also suggested that treatment with the FP regimen or patients with a single regional recurrence might improve the treatment outcome.

Other studies have examined the efficacy of CRT for the treatment of the locoregional recurrence of esophageal cancer after curative resection (Table 5)(9, 10, 21, 24, 25, 28-30) and reported generally high response rates of >70%. However, survival varied greatly, with

the MST ranging from 13 to 43 months, the 2-year OS ranging from 31% to 57%, and the 3-year OS ranging from 10.5% to 51.8%. Several factors might account for this discrepancy. First, those studies were primarily retrospective studies with small sample sizes, and therefore, selection bias may exist. Second, some studies included patients with anastomotic recurrence. Third, even among patients receiving CRT, the chemotherapy regimens were diverse. Finally, the treatment target volume definition and irradiation dose also varied. These factors could have had a remarkable influence on the clinical outcomes. Our study also had the discrepancy. However, the clinical outcome in our study was generally favourable compared with the outcomes of these previous studies.

Several prognostic factors for ESCC have been suggested (Table 6). For example, high RT dose, single node recurrence, single regional recurrence, and the use of a combination taxane-based plus CDDP regimen are reportedly associated with better outcomes(10, 12, 14, 15, 19-25). Among studies reporting prognostic factors, we focused on those of Bao et al. and Zhang et al. In the former, a total of 83 patients with postoperative locoregional recurrence of ESCC were treated with concurrent CRT. Patients treated with the DOC + CDDP regimen had a 3-year OS rate (59.2%) superior to that of patients receiving the FP regimen

(43.3%)(25). In the latter study, 50 patients with postoperative locoregional recurrence of ESCC were treated with concurrent CRT. Patients who received the paclitaxel + CDDP regimen had an MST (median, 16.3 months) superior to that of patients who received the FP regimen (median, 9.8 months)(24). These previous studies reported excellent results for patients receiving RT combined with a taxane-based regimen in a comparison with a regimen of RT combined with FP (FP-RT). However, the outcomes of treatment with RT combined with DOC alone (DOC-RT; MST, 14 months; 3-year OS rate, 30.5%) were worse than those of treatment with FP-RT (MST, 25 months; 3-year OS rate, 43.9%) in our study. These results suggest that CDDP may be a key drug in the RT treatment of postoperative LN recurrence of ESCC.

No previous studies have examined the effectiveness of RT combined with DOC alone (DOC-RT) for the treatment of postoperative LN recurrences of ESCC. The results of a phase I trial demonstrated promising efficacy and an acceptable toxicity profile for DOC-RT in patients with inoperable esophageal cancer(31). Haematological toxicity (<10% grade 3/4 toxicities) with this treatment was lower than that with FP-RT; 26% grade 3/4 toxicities). However, the MST (6 months) and 1-year OS (35%) were lower than those with FP-RT (MST,

13.1 months; 1-year OS, 56%)(32). The results of our study demonstrated that DOC-RT is a safe treatment for postoperative LN recurrences of ESCC, and the MST and OS for patients with DOC-RT were also lower than FP-RT.

Previous studies have reported excellent results with CRT for esophageal cancer patients with recurrence in a single region or single node after curative resection(8, 10, 12, 14, 22). Outcomes in patients with recurrence in a single region or single node were also significantly better than those for patients with recurrence in multiple regions or multiple nodes in our univariate analysis. This result supports our hypothesis that the concept of oligo-recurrence might be applicable to postoperative esophageal cancer(33).

In regard to RT field size, previous study has reported in CRT for postoperative loco-regional recurrent. Jingu et al. showed overall survival rate and irradiated-field control rate in patients treated with involved field irradiation were significantly better than those in patients treated with elective nodal irradiation(34). However, our study showed RT field size was not associated with prognosis. In regard to toxicities, we considered T-shaped field including elective irradiation was not

necessary.

The present study has several limitations associated with its retrospective design. First, we could not demonstrate a survival benefit of treatment with CRT compared with chemotherapy alone. A previous study suggested that CRT (MST, 20.3 months) is superior to chemotherapy alone or palliative care (MST, <12 months) for LN recurrence after esophagectomy(12). In our study, the MST was 24 months for patients with recurrence in a single region or single node. Given this result, CRT may be a recommended minimum treatment for patients with oligo-recurrence in the LNs in esophageal cancer. Second, this study has selection biases. We enrolled patients with LN recurrence, and there was non-uniformity in the combined chemotherapy regimens and RT techniques. Therefore, a prospective study with a uniform strategy such as FP-RT for cervical LN recurrence is essential.

In conclusion, we found that CRT was a safe and effective salvage treatment for LN recurrence after curative resection in ESCC. Approximately 28% of patients could achieve long-term survival with CRT. Our results also suggest that treatment with FP regimen or patients with a single regional recurrence may provide superior outcomes.

Author contributions

TK prepared the manuscript and the literature search; TK reviewed and edited the manuscript; and TK, KN, KS and KK reviewed the manuscript. All authors read and approved the final manuscript.

Additional Information

Ethical Statement

This study used no human or animal subjects.

Competing interests

The authors declare that they have no competing interests.

References

1. Bhansali MS, Fujita H, Kakegawa T et al. Pattern of recurrence after extended radical esophagectomy with three-field lymph node dissection for squamous cell carcinoma in the thoracic esophagus. World J Surg. 1997;21(3):275-81.

2. Hulscher JB, van Sandick JW, Tijssen JG, Obertop H, van Lanschot JJ. The recurrence pattern of esophageal carcinoma after transhiatal resection. J Am Coll Surg. 2000;191(2):143-8.

3. Kato H, Miyazaki T, Nakajima M et al. Prediction of hematogenous

recurrence in patients with esophageal carcinoma. Jpn J Thorac Cardiovasc Surg. 2003;51(11):599-608.

4. Kyriazanos ID, Tachibana M, Shibakita M et al. Pattern of recurrence after extended esophagectomy for squamous cell carcinoma of the esophagus. Hepatogastroenterology. 2003;50(49):115-20.

5. Mariette C, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. Cancer. 2003;97(7):1616-23.

6. Nakagawa S, Kanda T, Kosugi S, Ohashi M, Suzuki T, Hatakeyama K. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. J Am Coll Surg. 2004;198(2):205-11.

7. Natsugoe S, Matsumoto M, Okumura H et al. Clinical course and outcome after esophagectomy with three-field lymphadenectomy in esophageal cancer. Langenbecks Arch Surg. 2010;395(4):341-6.

8. Jingu K, Ariga H, Nemoto K et al. Long-term results of radiochemotherapy for solitary lymph node metastasis after curative resection of esophageal cancer. Int J Radiat Oncol Biol Phys. 2012;83(1):172-7.

9. Jingu K, Nemoto K, Matsushita H et al. Results of radiation therapy combined with nedaplatin (cis-diammine-glycoplatinum) and 5-fluorouracil for postoperative locoregional recurrent esophageal cancer. BMC Cancer. 2006;6:50.

10. Ma DY, Tan BX, Liu M, Li XF, Zhou YQ, Lu Y. Concurrent three-dimensional conformal radiotherapy and chemotherapy for postoperative recurrence of mediastinal lymph node metastases in patients with esophageal squamous cell carcinoma: a phase 2 single-institution study. Radiat Oncol. 2014;9:28.

11. Matsubara T, Ueda M, Takahashi T, Nakajima T, Nishi M. Localization of recurrent disease after extended lymph node dissection for carcinoma of the thoracic esophagus. J Am Coll Surg. 1996;182(4):340-6.

12. Nakamura T, Ota M, Narumiya K et al. Multimodal treatment for lymph node recurrence of esophageal carcinoma after curative resection. Ann Surg Oncol. 2008;15(9):2451-7.

13. Ma X, Zhao K, Guo W et al. Salvage lymphadenectomy versus salvage radiotherapy/chemoradiotherapy for recurrence in cervical lymph node after curative resection of esophageal squamous cell carcinoma. Ann Surg Oncol.

2015;22(2):624-9.

14. Jingu K, Matsushita H, Takeda K et al. Long-term results of radiotherapy combined with nedaplatin and 5-fluorouracil for postoperative loco-regional recurrent esophageal cancer: update on a phase II study. BMC Cancer. 2012;12:542.

15. Baxi SH, Burmeister B, Harvey JA, Smithers M, Thomas J. Salvage definitive chemo-radiotherapy for locally recurrent oesophageal carcinoma after primary surgery: retrospective review. J Med Imaging Radiat Oncol. 2008;52(6):583-7.

16. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

17. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer. TNM classification of malignant tumours. 7th ed. Chichester, West Sussex, UK ; Hoboken, NJ: Wiley-Blackwell; 2010.

18. Common Toxicity Criteria, Version2.0 Publish Date April 30. 1999.

19. Nemoto K, Ariga H, Kakuto Y et al. Radiation therapy for loco-regionally recurrent esophageal cancer after surgery. Radiother Oncol. 2001;61(2):165-8.

20. Shioyama Y, Nakamura K, Ohga S et al. Radiation therapy for recurrent esophageal cancer after surgery: clinical results and prognostic factors. Jpn J Clin Oncol. 2007;37(12):918-23.

21. Lu J, Kong C, Tao H. Radiotherapy with or without concurrent chemotherapy for lymph node recurrence after radical surgery of thoracic esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2010;78(3):710-4.

22. Kosuga T, Shiozaki A, Fujiwara H et al. Treatment outcome and prognosis of patients with lymph node recurrence of thoracic esophageal squamous cell carcinoma after curative resection. World J Surg. 2011;35(4):798-804.

23. Fakhrian K, Gamisch N, Schuster T, Thamm R, Molls M, Geinitz H. Salvage radiotherapy in patients with recurrent esophageal carcinoma. Strahlenther Onkol. 2012;188(2):136-42.

24. Zhang J, Peng F, Li N et al. Salvage concurrent radio-chemotherapy for post-operative local recurrence of squamous-cell esophageal cancer. Radiat Oncol. 2012;7:93.

25. Bao Y, Liu S, Zhou Q et al. Three-dimensional conformal radiotherapy with concurrent chemotherapy for postoperative recurrence of esophageal squamous cell carcinoma: clinical efficacy and failure pattern. Radiat Oncol. 2013;8:241.

26. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452-8.

27. National Cancer Institute (U.S.). Common terminology criteria for adverse events (CTCAE). Rev. ed. Bethesda, Md.: U.S. Dept. of Health and Human Services, National Institutes of Health, National Cancer Institute; 2009.

28. Tsuchida E, Sakai K, Yasuo M et al. Concurrent chemoradiotherapy using low-dose continuous infusion of 5-fluorouracil for postoperative regional lymph node recurrence of esophageal squamous cell carcinoma. Esophagus. 2005;2:25-31.

29. Maruyama K, Motoyama S, Anbai A et al. Therapeutic strategy for the treatment of postoperative recurrence of esophageal squamous cell carcinoma: clinical efficacy of radiotherapy. Dis Esophagus. 2011;24(3):166-71.

30. Kobayashi R, Yamashita H, Okuma K, Shiraishi K, Ohtomo K, Nakagawa K. Salvage radiation therapy and chemoradiation therapy for postoperative locoregional recurrence of esophageal cancer. Dis Esophagus. 2014;27(1):72-8.

31. Font A, Arellano A, Fernandez-Llamazares J et al. Weekly docetaxel with concomitant radiotherapy in patients with inoperable oesophageal cancer. Clin Transl Oncol. 2007;9(3):177-82.

32. Shinoda M, Ando N, Kato K et al. Randomized study of low-dose versus standard-dose chemoradiotherapy for unresectable esophageal squamous cell carcinoma (JCOG0303). Cancer science. 2015;106(4):407-12.

33. Niibe Y, Hayakawa K. Oligometastases and oligo-recurrence: the new era of cancer therapy. Jpn J Clin Oncol. 2010;40(2):107-11.

34. Jingu K, Umezawa R, Yamamoto T et al. Elective nodal irradiation is not necessary in chemoradiotherapy for postoperative loco-regional recurrent esophageal cancer. Jpn J Clin Oncol. 2017;47(3):200-5.