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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Concurrent Selective Lymph Node Radiotherapy and S-1 Plus Cisplatin for Esophageal Squamous Cell Carcinoma: A Phase II Study

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ABSTRACT

Background. The efficacy, toxicity, and patterns of failure of esophageal squamous cell carcinoma (ESCC) treated with selective lymph node (SLN) conventional fraction radiotherapy (CFRT) and S-1 plus cisplatin (CDDP) were evaluated.

Patients and Methods. 67 Patients with clinical stage II–IVa ESCC were enrolled. The total dose of SLN CFRT was 60 Gy in 30 fractions over 6 weeks. The first course of radiation covered the primary and metastatic regional tumors and high-risk lymph nodal regions, given at 2 Gy/fraction for a dose of 40 Gy. In the second course, CFRT was delivered to the boost volume for an additional 20 Gy in 10 days, using 2 Gy/fraction. Two cycles of chemotherapy were given at the beginning of radiotherapy. CDDP at 25 mg/m^2/day was given on days 1–3 and days 22–24, and S-1 at 80 mg/m^2/day on days 1–14 and days 22–35. Patients achieving objective response after concurrent chemoradiotherapy underwent two additional cycles of chemotherapy.

Results. The objective response rate (ORR) was 82.5%. Grade 3 or 4 toxicities included leukopenia (23.8%), neutropenia (14.3%), thrombocytopenia (14.3%), hemoglobin (4.8%), gastrointestinal (12.7%), skin (1.6%), and esophagus fistula (1.6%). One patient died of severe pneumonia, and two died of late toxicity because of esophagus fistula. With median follow-up of 32 months, the overall survival (OS) and progression-free survival (PFS) at 1 year and 2 years were 81.0% and 73.0%, and 63.5% and 49.2%, respectively.

Conclusions. SLN RT concurrent with S-1 plus CDDP may represent a better strategy for treatment of ESCC patients.

Esophageal cancer (EC) is the eighth most common cancer and the sixth leading cause of cancer-related mortality worldwide.[1] In China and other East Asian countries, more than 90% of EC cases are esophageal squamous cell carcinoma (ESCC). Surgery is the standard treatment for patients with resectable esophageal cancer. However, more than 50% of newly diagnosed patients have no chance of surgery.

Concurrent chemoradiotherapy (CCRT) has been recognized as a standard approach to inoperable ESCC, based on the series of Radiation Therapy Oncology Group (RTOG) studies. In RTOG 85-01, it was proved that combined therapy provided a significant survival advantage over radiotherapy alone, and the 5-year survival rate of the chemoradiotherapy group reached 26%, compared with 0% following RT. To improve these results, RTOG 94-05 increased the radiation dose from 50.4 to 64.8 Gy, which did not improve local/regional control or survival.[2,3] It is noteworthy that SLN RT was used in RTOG 85-01 but was omitted in RTOG 95-04. Detailed analysis of patterns of failure showed that the local/regional failure rate was lower

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in RTOG 85-01 (44.3%) than the standard dose arm in RTOG 94-05 (55%), indicating that use of SLN RT might improve the local recurrence rate of EC patients. To date, several retrospective studies have compared SLN RT and conventional field irradiation (CFI), and the results suggest that SLN RT is no better than CFI in terms of local failure or acute toxicity. To date, use of SLN RT is still controversial because of the lack of prospective controlled study.

RTOG 85-01 demonstrated that CRT with 5-fluorouracil (5-FU) and cisplatin (CDDP) provided a significant survival advantage over radiation alone. Several subsequent studies have confirmed that ESCC patients may benefit from this regimen. S-1 is a fourth-generation, novel, orally active fluoropyrimidine with enhanced anticancer activity and reduced gastrointestinal toxicity.[4] S-1 is frequently used as a substitute for pyrimidine analog 5-FU in gastric cancer. CCRT combined with S-1 plus CDDP showed promising safety and efficacy for patients with locally advanced esophageal cancer (LAEC).[5,6]

Our previous studies showed that concurrent SLN RT and cisplatin-based chemotherapy for ESCC were safe and achieved encouraging outcomes. However, the toxicities are still somewhat higher than expected.[7–9] Our institution has engaged in clinical trials of SLN RT concurrently with S-1 and CDDP for ESCC since 2010. The results of our phase I study demonstrated that the outcomes of this treatment regimen were encouraging.[10] The results of a phase II study with longer follow-up are reported herein.

PATIENTS AND METHODS

Eligibility Criteria

The patients enrolled in the study had locally unresectable carcinoma such as a cervical carcinoma of the esophagus or had locally advanced carcinoma. The eligibility criteria included: (1) age 18–70 years, (2) previously untreated histologically confirmed stage IIa to IVa ESCC with bidimensionally measurable disease, (3) Karnofsky performance status (KPS) $\geq$ 70, (4) weight loss $\leq$ 5%, and (5) life expectancy $\geq$ 3 months. The minimum laboratory requirements were as follows: absolute white blood cell count (WBC) $\geq$ 4000/ml, platelet (PLT) count $\geq$ 100,000/ml, hemoglobin (Hb) $\geq$ 10 g/dl, total bilirubin level $\leq$ 1.5 mg/dl, serum creatinine level $\leq$ 1.5 times the upper limit of normal, and aspartate/alanine aminotransferase levels $\leq$ 2.5 times the upper limit of normal. T stage was assessed by computed tomography (CT) or endoscopic ultrasonogram. Tumor–node–metastasis (TNM) system staging was defined according to the American Joint Committee on Cancer staging system (2002, v.6.0). Informed consent was obtained before treatment.

Exclusion Criteria

Exclusion criteria were distant metastasis, radiographic or bronchoscopic evidence of esophageal perforation, or any other serious underlying medical condition such as significant cardiac disease, uncontrolled diabetes, central nervous system disorders, or psychological disability, previous surgery for squamous cell carcinoma of the head and neck, previous radiation therapy, previous systemic chemotherapy, previous immunotherapy, and second primary malignancy.

Pretreatment Evaluation

To exclude patients with distant events, evaluation was performed before initiation of treatment, including history taking and physical examinations (esophagoscopy, barium esophagogram, bone scan with single-photon-emission CT, and CT scan of the brain, neck, chest, and abdomen). Complete blood count with differential, serum chemistry test, liver function tests, coagulation panel, urinalysis, and electrocardiogram were also required. Bronchoscopy was performed if clinically necessary. The protocol was approved by our institutional review board, and written informed consent was obtained from all patients.

Radiotherapy

The radiation protocol was carried out by 6-MV X-ray using two-phase three-dimensional radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) with total dose of 60 Gy (first phase: 40 Gy in 20 fractions; second phase: 20 Gy in 10 fractions). The gross tumor volume (GTV), which included primary cancer (GTVp) and metastatic lymph nodes (GTVn), was defined on the basis of pretreatment staging examinations (thoracic CT, barium esophagogram, and esophageal endoscopy). SLN RT was adopted in the first 20 fractions; the initial treatment fields included GTV and high-risk lymph nodal regions (HRLNR).[11–13] The planning target volume (PTV) was defined as GTVp, adding a 3-cm margin superiorly and inferiorly and 1 cm laterally, GTVn, and HRLNR respectively adding a 0.8-cm margin. However, in the second phase of radiotherapy, the HRLNR were spared. Lymph node groups are named according to Japanese guidelines.[14] For patients with upper thoracic esophageal cancer, the selective lymph node areas of groups 104–107 and part of group 108 were covered. Groups 104, 106–108, and part of group 110 were included for patients with middle thoracic esophageal cancer. In case of patients with lower thoracic esophageal cancer, the lymph node areas of groups 104, part of 106 and 108, 1–3, 7, and 9 were covered. The dose volume histogram constraints of organs at risk (OARs)

were as follows: bilateral lung Dmean $\leq$ 16 Gy, V20 $\leq$ 30%, spinal cord Dmax $\leq$ 45 Gy, heart Dmean $<$ 26 Gy, V30 $\leq$ 40%; hepatic Dmean $\leq$ 30 Gy, gastric Dmax $\leq$ 50 Gy, intestinal Dmax $\leq$ 50 Gy.

Chemotherapy

In this regimen, CDDP was given at 25 mg/m^2/day on days 1–3 and days 22–24 by bolus intravenous infusion; S-1 was given at 80 mg/m^2/day on days 1–14 and days 22–35. Two cycles of concurrent chemotherapy were administrated during the process of RT. Patients achieving objective response after CCRT underwent two additional cycles of chemotherapy with S-1 and CDDP at the same dose level as during CCRT except in case of disease progression, serious adverse events, or patient refusal.

Adverse Effect Assessment and Response Evaluation

Adverse effect assessment was performed at least weekly during treatment and was graded chiefly according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 3.0).

The follow-up evaluations consisted of history, physical examination, and thoracic CT scans performed 4 weeks after completion of therapy, every 3 months during the first 2 years, and every 6 months thereafter. Other imaging examinations were obtained when recurrence was suspected. Patterns of first failure were classified as local, regional, or distant.

Treatment response was evaluated 6–8 weeks after completion of CCRT. The Response Evaluation Criteria in Solid Tumors (RECIST) were used to evaluate treatment response as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

End Points and Statistics

The primary endpoint of this study was OS, observed from date of treatment until death or last follow-up evaluation. Secondary endpoint was PFS, defined as time from start of treatment to identifiable time of first progression (local recurrence, regional failure, or distant metastasis, whichever occurred first), death from any cause, or last follow-up. The Kaplan–Meier method was used to estimate OS and PFS.

RESULTS

Patient Characteristics

Sixty-seven patients with ESCC (male/female 49/18; cervical/upper/mid/lower 8/29/24/6) were enrolled in the study from January 2010 to June 2016. Four of the patients gave up treatment halfway, and ultimately 63 patients completed treatment and were enrolled in the current study. Six patients were lost to follow-up. The remaining patients were followed until death or time of analysis. The patient characteristics are summarized in Table 1. All 63 patients completed radiotherapy concurrent with two cycles of chemotherapy with S-1 and CDDP. Twenty-nine patients completed two cycles of adjuvant chemotherapy. Due to serious adverse events (8), economic status (8), treatment compliance (7), or failure to achieve objective response (11), 34 patients did not receive or received only one cycle of adjuvant chemotherapy. Treatment was suspended for 7–14 days in 9 patients because of severe hematological toxicity, and 12 patients' doses of chemotherapy were modified (reduced $\leq$ 20%) in cases of severe hematological or nonhematological toxicities.

Toxicity

All patients were assessable for toxicity. The adverse effects are summarized in Table 2. Leukopenia and thrombocytopenia of grade 3–4 was recorded in 15 patients (23.8%) and 9 patients (14.3%), respectively. Treatment-related grade 3–4 gastrointestinal reaction was observed in eight patients (12.7%). One patient developed grade 4 dermatitis, and another had esophagus fistula of grade 3.

TABLE 1 Clinical characteristics of patients

Characteristic	Number	%
Age (years)		
Median	60	
Range	43–75	
Gender		
Male	46	73.0
Female	17	27.0
KPS		
Median	90	
Range	80–10	
TNM stage		
IIa	11	17.5
IIb	3	4.8
III	36	57.1
IVa	13	20.6
Tumor location		
Cervical	7	11.1
Upper thoracic	28	44.4
Mid-thoracic	23	36.5
Lower thoracic	5	7.9

TABLE 2 Adverse effects

Adverse effects	Grade 0–1	Grade 2	Grade 3	Grade 4	Grade 5
Acute toxicity					
Hematologic					
Leukopenia	21 (33.3%)	27 (42.9%)	14 (22.2%)	1 (1.6%)	0
Neutropenia	40 (63.5%)	14 (22.2%)	7 (11.1%)	2 (3.2%)	0
Hemoglobin	51 (81.0%)	9 (14.3%)	2 (3.2%)	1 (1.6%)	0
Thrombocytopenia	43 (68.3%)	11 (17.5%)	6 (9.5%)	3 (4.8%)	0
Gastrointestinal	49 (77.8%)	6 (9.5%)	7 (11.1%)	1 (1.6%)	0
Esophagitis	56 (88.9%)	7 (11.1%)	0	0	0
Lung	62 (98.4%)	0	0	0	1 (1.6%)
Esophagus fistula	62 (98.4%)	0	1 (1.6%)	0	0
Heart	61 (96.8%)	2 (3.2%)	0	0	0
Skin	58 (92.0%)	4 (6.3%)	0	1 (1.6%)	0
Late toxicity					
Esophagus fistula	59 (93.7%)	0	2 (3.2%)	0	2 (3.2%)
Lung	63 (100%)	0	0	0	0

One patient died of severe pneumonia. No patient developed high-grade ($\geq$ 3) esophagitis or heart toxicity. In the evaluation of late toxicity, two patients (3.2%) developed esophagus fistula of grade 3. Moreover, another two patients died of esophagus fistula. One patient (1.6%) developed grade 3 esophageal stenosis and received stent implantation. The leukopenia required recombinant human granulocyte colony stimulating factor treatment, and it took about 1 week for the patients to recovery completely from leutropenia. The neutropenia required granulocyte colony stimulating factor treatment and took 4–7 days for the patients to recover completely. The hemoglobin and thrombocytopenia was cured by blood transfusion, injecting recombinant human thrombocytopenia, and recombinant human interleukin-11. It took 5–14 days for the patients to recover completely from hemoglobin and thrombocytopenia. The dermatitis was cured by topical ointment, blowing oxygen, and keeping dry. It took about 1 month for the patients to recovery completely from dermatitis. The other one patient with grade 4 vomiting required 5-HT3 inhibitor, metoclopramide, and intravenous nutrition. It took 6 days for the patient to recover completely from vomiting.

Treatment Response

Six to eight weeks after CCRT, the response to treatment was evaluated by both thoracic CT scan and esophageal barium esophagogram. The response statuses are summarized in Table 3. The treatment response rates were encouraging, with an objective response rate (ORR) of 82.5%, while 12 (19.0%) patients achieved CR and 40 (63.5%) patients achieved PR.

Survival

Median follow-up was 32 months, with a range of 3–105 months until the last follow-up date of August 2018. Currently, a total of 31 (49.2%) patients are alive. Of the living patients, five (7.9%) patients developed locoregional recurrence, and one (1.6%) patient developed distant metastasis. The other 25 (39.7%) patients have no evidence of disease relapse. While 27 (42.9%) patients died of local disease recurrence or/and distant metastasis, 5 (7.9%) patients died of treatment-related complications. The Kaplan–Meier estimated OS rate at 1 year and 2 years was 81.0% and 63.5% (Fig. 1a), respectively. The PFS at l year and 2 years was 73.0% and 49.2% (Fig. 1B), respectively.

Patterns of Failure

The patterns of failure are summarized in Table 4. Twenty-five patients (39.7%) had local or/and regional disease presenting as the first failure. Distant metastasis as the first failure occurred in four (6.3%) patients: brain (one), lungs (two), and multiple metastasis (one). The rate of out-of-field nodal recurrence was 6.3% (4/63). Three (4.8%) patients developed recurrences in the high-dose volume. In addition, the recurrence rate for patients who completed or did not complete the entire protocol therapy was 41.3% (12/29) and 44.1% (15/34), respectively (p = 0.827).

TABLE 3 Treatment response

Response	Stage II (n = 14)	Stage III (n = 36)	Stage IVa (n = 13)	Total number (n = 63)
CR	2 (14.3%)	6 (16.7%)	4 (30.8%)	12 (19.0%)
PR	10 (71.4%)	24 (66.7%)	6 (46.2%)	40 (63.5%)
SD	2 (14.3%)	3 (8.3%)	1 (7.7%)	6 (9.5%)
PD	0	3 (8.3%)	2 (15.4%)	5 (7.9%)
ORR (CR, PR)	12 (85.7%)	30 (83.3%)	10 (76.9%)	52 (82.5%)
DCR (CR, PR, SD)	14 (100%)	33 (91.7%)	11 (84.6%)	58 (92.1%)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* objective response rate, *DCR* disease control rate

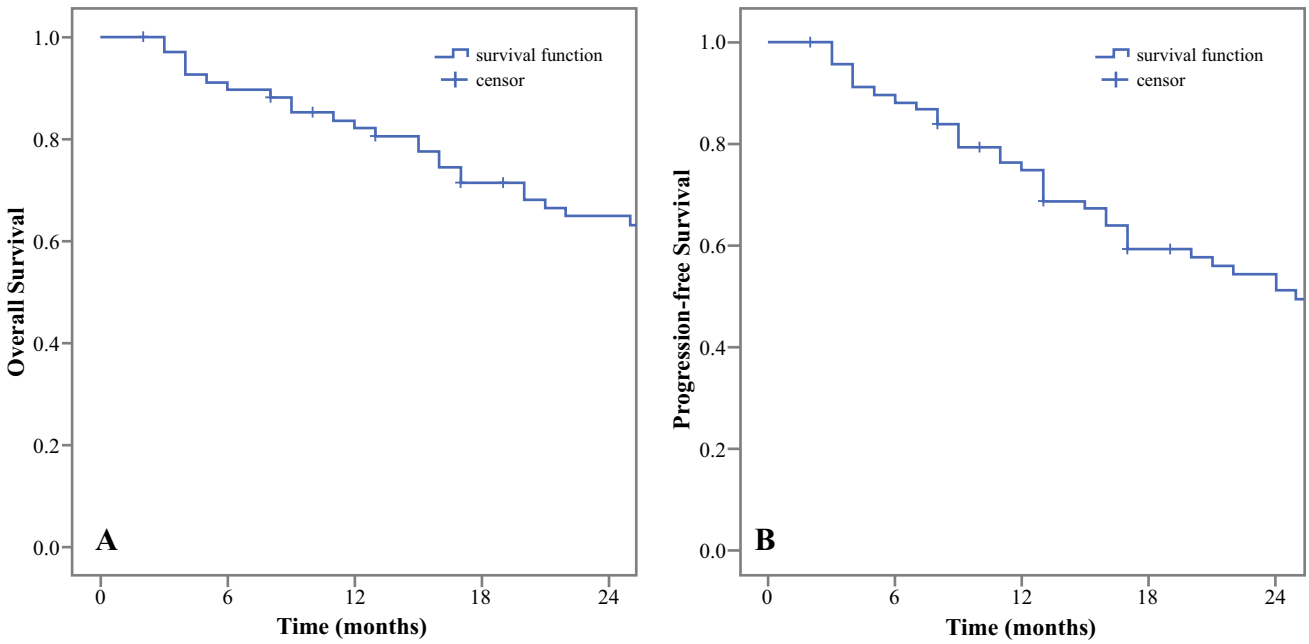

FIG. 1 Kaplan–Meier curves for OS (**a**) and PFS (**b**)

TABLE 4 Patterns of failure

Patterns of failure	Number	%
Locoregional recurrence only	25	39.7
Distant metastasis only	4	6.3
Locoregional failure plus distant metastasis	2	3.2
Out-of-field nodal recurrence	4	6.3
Dead of complication	7	11.1

DISCUSSION

We evaluated the efficacy, toxicities, and patterns of failure of SLN RT concurrent with S-1 plus CDDP delivered to 63 patients with ESCC. The results indicate that the treatment modality was effective and safe. The treatment response, OS, and PFS of the patients were satisfactory.

How to increase the local control rate of EC and minimize treatment-related toxicities has become a most important issue. Based on the results of RTOG 85-01, CCRT has been broadly applied as standard management for patients with locally advanced EC.[3] However, locoregional failure and life-threatening adverse effects were as high as 50% and 20%, respectively. RTOG 94-05 confirmed that an increase in the radiation dose did not reduce the locoregional failure rate (56% vs. 52%) or increase survival.[2] Therefore, new regimens with alternative radiosensitization and biochemical modulation of chemotherapeutic agents are under investigation to improve definitive CRT outcomes. CDDP has been proved to play a role in radiosensitization, and it has been hypothesized that EC patients could benefit from CCRT based on CDDP. Based on the result of RTOG trials and studies, the standard applicable regimen consisted of CDDP and 5-FU. Although this regimen is reasonably

effective, it is associated with high incidence of serious toxicity as well, such as approximately 50% acute grade 3–4 leukocytopenia, which leads to poor compliance.[15] The JCOG 9906 clinical trial enrolled 76 stage II or III ESCC patients treated with definitive CRT (CDDP and 5-FU); the results showed CR in 68% of patients with OS of 44.7% and 37% at 3 and 5 years, respectively. However, four (5.3%) patients died of treatment-related toxicity.[16] In our previous phase II study, the most frequent acute high-grade ($\geq$ 3) toxicities were esophagitis and leukopenia, occurring in 26.4% and 32.4% of patients.[8]

As a new biochemical modulator of 5-FU, S-1 is increasingly being used in clinical practice because of its advantages of oral formulation and continuous delivery without intravenous infusion compared with 5-FU. Moreover, S-1 might be a more powerful enhancer of radiosensitivity in cancer than 5-FU. JCOG 0604 [17] carried out phase I/II trials of CRT concurrent with S-1 and CDDP, and the recommend dosage of S-1 was determined to be 60 mg/m^2/day based on the result of the phase I study; the CR rate in phase II was 22/37 (59.5%), with 3-year PFS and OS of 48.4% and 61.9%, respectively. The most frequent acute high-grade ($\geq$ 3) toxicities were leukopenia (57.9%) and neutropenia (50%). No treatment-related deaths were observed. In our previous phase I study, the recommended dosage for S-1 was 80 mg/m^2/day.[10] The treatment response rates were encouraging (CR 19.0%, PR 63.5%) in the present phase II study. Grade 3 or 4 toxicities included leukopenia (23.8%), neutropenia (14.3%), hemoglobin (4.8%), and thrombocytopenia (14.3%). Finally, one patient (1.6%) died of severe pneumonia and two patients (3.2%) of late toxicity because of esophagus fistula. Standard chemotherapy concurrent with SLN RT has not been determined. Therefore, how to combine chemotherapy and radiotherapy regimens to maximize local control and survival is an important question.

There are still several weaknesses and limitations in our regime. Our single-center study with relatively small sample size may limit the generalization of our results. Further observation with longer follow-up and randomized phase III trial is currently underway.

CONCLUSIONS

This phase II study with a limited number of patients demonstrated that SLN RT concurrent with S-1 plus CDDP was generally tolerated, and the treatment outcome was satisfactory. Further trials and observation confirming the efficiency of RT concurrent with S-1 plus CDDP are still needed.

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DISCLOSURE The authors declare that they have no competing interests.

REFERENCES

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016; 66(2):115–32.
2. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol*. 2002;20(5):1167–74.
3. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). *Radiation Therapy Oncology Group. JAMA*. 1999; 281(17):1623–7.
4. Hirata K, Horikoshi N, Aiba K, et al. Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. *Clin Cancer Res*. 1999;5(8):2000–5.
5. Iwase H, Shimada M, Tsuzuki T, et al. Concurrent chemoradiotherapy with a novel fluoropyrimidine, S-1, and cisplatin for locally advanced esophageal cancer: long-term results of a phase II trial. *Oncology*. 2013;84(6):342–9.
6. Cho SH, Shim HJ, Lee SR, et al. Concurrent chemoradiotherapy with S-1 and cisplatin in advanced esophageal cancer. *Dis Esophagus*. 2008;21(8): 697–703.
7. Li BS, Zhou T, Wang ZT, et al. Phase I study of concurrent selective lymph node late course accelerated hyper-fractionated radiotherapy and capecitabine, cisplatin for locally advanced esophageal squamous cell carcinoma. *Radiother Oncol*. 2009; 93(3):458–61.
8. Wang D, Yang J, Zhu J, et al. Elective lymph node irradiation late course accelerated hyper-fractionated radiotherapy plus concurrent cisplatin-based chemotherapy for esophageal squamous cell carcinoma: a phase II study. *Radiat Oncol*. 2013; 8(1):108.
9. Li BS, Gong HY, Huang W, et al. Phase I study of concurrent selective lymph node late course accelerated hyper-fractionated radiotherapy and pemetrexed, cisplatin for locally advanced esophageal squamous cell carcinoma. *Dis Esophagus*. 2011; 24(4):251–7.
10. Li M, Fu C, Zhang W, et al. Phase I study of concurrent selective lymph node late-course accelerated hyperfractionated radiotherapy and S-1 plus cisplatin for locally advanced oesophageal squamous cell carcinoma. *Br J Radiol*. 2016;89(1060): 20150476.
11. Akiyama H, Tsurumaru M, Udagawa H, et al. Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg Oncol*. 1994; 220(3):364–73.
12. Natsugoe S, Matsumoto M, Okumura H, et al. Initial metastatic, including micrometastatic, sites of lymph nodes in esophageal squamous cell carcinoma. *J Surg Oncol*. 2005; 89(1):6–11.
13. Li H, Zhang Y, Cai H, et al. Pattern of lymph node metastases in patients with squamous cell carcinoma of the thoracic esophagus who underwent three-field lymphadenectomy. *Eur Surg Res*. 2007;39(1):1–6.
14. Isono K, Uchida Y, Watanabe H, et al. Guidelines for clinical and pathologic studies on carcinoma of the esophagus ninth edition. Preface general principles part I. *Esophagus*. 2004;1(2):61–88.
15. Sai H, Mitsumori M, Yamauchi C, et al. Concurrent chemoradiotherapy for esophageal cancer: comparison between

intermittent standard-dose cisplatin with 5-fluorouracil and daily low-dose cisplatin with continuous infusion of 5-fluorouracil. *Int J Clin Oncol*. 2004; 9(3):149–53.
16. Kato K, Muro K, Minashi K, et al. Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). *Int J Radiat Oncol Biol Phys*. 2011; 81(3):684–90.
17. Tahara M, Fuse N, Mizusawa J, et al. Phase I/II trial of chemoradiotherapy with concurrent S-1 and cisplatin for clinical stage II/III esophageal carcinoma (JCOG 0604). *Cancer Sci*. 2015;106(10):1414–20.