JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2014;44(6)534–540
doi:10.1093/jjco/hyu047
Advance Access Publication 24 April 2014

High-dose Versus Standard-dose Radiotherapy with Concurrent Chemotherapy in Stages II–III Esophageal Cancer

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Received September 5, 2013; accepted March 20, 2014

Objective: In this study, we investigated the effects of radiotherapy ≥60 Gy in the setting of concurrent chemo-radiotherapy for treating patients with Stages II–III esophageal cancer.
Methods: A total of 126 patients treated with 5-fluorouracilbased concurrent chemo-radiotherapy between January 1998 and February 2008 were retrospectively reviewed. Among these patients, 49 received a total radiation dose of <60 Gy (standard-dose group), while 77 received a total radiation dose of ≥60 Gy (high-dose group). The median doses in the standard- and high-dose groups were 54 Gy (range, 45–59.4 Gy) and 63 Gy (range, 60–81 Gy), respectively.
Results: The high-dose group showed significantly improved locoregional control (2-year locoregional control rate, 69 versus 32%, $P < 0.01$) and progression-free survival (2-year progression-free survival, 47 versus 20%, $P = 0.01$) than the standard-dose group. Median overall survival in the high- and the standard-dose groups was 28 and 18 months, respectively ($P = 0.26$). In multivariate analysis, 60 Gy or higher radiotherapy was a significant prognostic factor for improved locoregional control, progression-free survival and overall survival. No significant differences were found in frequencies of late radiation pneumonitis, post-treatment esophageal stricture or treatment-related mortality between the two groups.
Conclusions: High-dose radiotherapy of 60 Gy or higher with concurrent chemotherapy improved locoregional control and progression-free survival without a significant increase of in treatment-related toxicity in patients with Stages II–III esophageal cancer. Our study could provide the basis for future randomized clinical trials.

Key words: esophageal cancer – radiotherapy – chemotherapy – concurrent chemo-radiotherapy

INTRODUCTION

Esophageal cancer has a poor prognosis due to high rates of local recurrence and distant metastasis (1,2). About one half of patients presented with locally advanced stage at the time of diagnosis (3) and have a 5-year survival rate of <30% after surgical resection or multimodality therapy. In the past decade, numerous single institutions and cooperative groups have investigated the use of concurrent chemo-radiotherapy (CCRT) as a definitive treatment or as a preoperative treatment for patients with localized esophageal cancer. Definitive CCRT or preoperative CCRT with surgery results in better survival than single-modality treatments such as surgery or radiotherapy (4–10). Consequently, the National Comprehensive Cancer Network (NCCN) esophageal cancer guidelines recommend preoperative CCRT or definitive CCRT for the patients with Stages II or III esophageal cancer. However, in the setting of definitive CCRT, the dose of radiotherapy requires further investigation. Generally, 45–50 Gy radiation dose is adequate to control microscopic tumors, and 60 Gy or higher radiotherapy is required to control gross tumors at conventional fractionation (11–13). In the Radiation Therapy Oncology Group (RTOG)

trial 94-05 study, which compared 50.4 Gy radiotherapy with 64.8 Gy radiotherapy in a CCRT setting, there was no significant difference in overall survival (OS) and locoregional control (LRC) between the high- and standard-dose treatment arms (14). However, Zhang et al. (15) reported that radiation doses >51 Gy improved LRC, disease-free survival and survival in patients treated with 5-fluorouracil (5-FU) based chemotherapy. These authors also reported a positive correlation between radiation dose and LRC. However, in this study, the role of 60 Gy or higher dose radiotherapy was unclear as only 26 patients received radiotherapy >51 Gy.

In this study, we investigated the effects of 60 Gy or higher radiotherapy with concurrent chemotherapy on LRC, progression-free survival (PFS) and OS in patients with Stages II–III esophageal cancer.

PATIENTS AND METHODS

Patients

Between January 1998 and February 2008, a total of 264 patients with Stages II–III esophageal cancer were treated by CCRT at our institution. One hundred and twenty-six of the 264 patients treated with CCRT were included for this study. The remaining patients were excluded from this analysis for the following reasons: (i) they received low-dose radiotherapy with palliative intent ($n = 36$); (ii) they underwent esophagectomy after CCRT ($n = 47$); (iii) they had a recurrent tumor and received CCRT for salvage purposes ($n = 35$) and (iv) they had other primary tumors ($n = 20$). Ultimately, the medical records of total 126 patients treated with CCRT were retrospectively reviewed for this study.

Pretreatment evaluation included a medical history, physical examination focusing on performance status and a history of dysphagia. Laboratory studies included a complete blood cell count and blood chemistries. For stage workup, barium swallow, chest computerized tomography (CT) and transesophageal endoscopic ultrasonography were performed. To evaluate if there was distant metastasis, patients were evaluated by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), bone scans and abdomen CT.

Radiotherapy

Radiotherapy was delivered using 10 MV photons starting on Day 1 of chemotherapy. A conventional fractionation schedule (5 days per week, 1.8–2.0 Gy/fraction daily) and cone-down technique were used in all patients. Prior to the 2000s, a two-dimensional plan was used, and thereafter, a three-dimensional plan. The primary tumor was confirmed by correlation with barium swallow and CT images in two-dimensional plans. In three-dimensional plans, gross tumor volume was delineated using CT–PET fusion on a Pinnacle radiotherapy treatment planning system (Phillips Medical Systems, Andover, MA,

Table 1. Chemotherapy regimens

Characteristic	No. of patients (%)		*P* value
	Standard dose ($n = 49$)	High dose ($n = 77$)	
Regimen			
5-FU + cisplatin	44 (90)	68 (88)	0.22
5-FU monotherapy	5 (10)	5 (7)	
Others	0 (0)	4 (5)	
Median dose of chemotherapy			
5-FU (mg/m^2/week)[a]	800 (750–1250)	800 (750–1250)	0.16
Cisplatin (mg/m^2/week)[a]	20 (10–25)	20 (10–25)	0.67
Maintenance chemotherapy			
Yes	25 (53)	57 (74)	0.01
No	23 (47)	20 (26)	
No. of chemotherapy cycles			
2 Cycles	23 (47)	20 (26)	0.09
3 Cycles	2 (4)	4 (5)	
4 Cycles	3 (6)	18 (23)	
≥5 Cycles	21 (43)	35 (46)	

5-FU, 5-fluorouracil; CCRT, concurrent chemo-radiotherapy.
[a]The values were expressed as the median with range.

USA). The initial target volume encompassed the primary tumor with a margin of at least 5 cm above and below the tumor and 2 cm radially. The initial target volume was treated with 30.6–45 Gy (median dose, 36 Gy) before cone down. To reduce lung irradiation, anterior–posterior parallel opposite fields were used in these phases. In the boost phase of radiation, the final target volume encompassed the primary tumor with a margin of at least 2 cm above and below the tumor and 2 cm radially. To restrict the spinal cord dose, left–right parallel opposite fields or two posterior oblique fields were used in two-dimensional plans. In three-dimensional plans, three to five multi-ports fields were used. The total radiation dose ranged between 43.2 and 75.6 Gy (median dose, 63 Gy). The spinal cord dose was limited to within 45 Gy, and the lung volume exposed to 25 Gy was limited to 20%.

Chemotherapy

All patients received 5-FU-based chemotherapy, and 89% of the patients ($n = 112$) were treated with both 5-FU and cisplatin. 5-FU was administered at 750–1250 mg/m^2 daily as a continuous infusion using a portable electronic pump on Days 1–4 and cisplatin was administered at 40–100 mg/m^2 on Day 1, and during radiotherapy. Ten patients (8%) received 5-FU monotherapy. Among the rest of four patients, three patients received 5-FU, docetaxel and cisplatin, and one patient received 5-FU and carboplatin. The mean dose of 5-FU per week was higher in the high-dose group; however, this result was not statistically significant (846 mg/m^2/week versus 815 mg/m^2/week, $P = 0.16$). Mean doses of cisplatin per week in both groups were 19 mg/m^2/week. Each cycle of chemotherapy was repeated every 28 days, and two cycles of chemotherapy were administered with radiotherapy. After CCRT, 66% of patients ($n = 83$) received maintenance chemotherapy for 1–6 cycles (median, four cycles). The frequency of patients who received maintenance chemotherapy was significantly higher in the high-dose group than the standard-dose group. The details of chemotherapy are summarized in Table 1.

Follow-Up

During radiotherapy, patients were examined weekly to monitor treatment-related toxicities and general condition. Barium swallow, chest CT and FDG-PET were performed within 2 months after completion of radiotherapy. Treatment response was evaluated according to response evaluation criteria in solid tumors (RECIST; version 1.1) (16) with some modifications. A clinically complete response was defined as no histologic evidence of cancer from endoscopic biopsy or no pathologic FDG uptake on FDG-PET on follow-up visits. Partial response was defined as a reduction in tumor size of >30% on chest CT and endoscopy. No response was defined as a reduction in tumor size of <30%, no reduction in size or increased tumor size. Sites of local failure were allocated to one of three categories based on the pattern of failure; (i) 'central failure', occurring within the final radiotherapy field; (ii) 'marginal failure', within the initial radiotherapy fields, but outside of the final radiotherapy field and (iii) 'out-field failure' occurring outside of the initial radiotherapy field. Survival duration was calculated from the date of initiation of CCRT to that of the first occurrence of the considered event (locoregional recurrence, distant metastasis or death).

Statistical Analysis

Late radiation pneumonitis, which is developed 90 days after the completion of radiotherapy, was scored according to the RTOG late radiation morbidity scoring system. Other treatment-related toxicities were graded according to the common toxicity criteria for adverse events (version 4.0). Patients were grouped by total radiation dose (≥60 and <60 Gy). Statistical analyses were conducted using SPSS 18 (SPSS Inc., Chicago, IL, USA). Pearson's χ^2 test was used to assess measures of association in frequency tables. Difference

Table 2. Patient characteristics

Characteristic	No. of patients (%)		*P* value
	Standard dose ($n = 49$)	High dose ($n = 77$)	
Age (years)			0.44
Median	65	66	
Range	50–80	30–79	
Sex			0.74
Male	45 (92)	72 (93)	
Female	4 (8)	5 (7)	
Performance status			0.15
KPS 90–100	31 (63)	38 (49)	
KPS 60–80	18 (37)	39 (51)	
Pathology			0.84
SCC	45 (92)	72 (93)	
AdenoCa	3 (6)	3 (4)	
Unknown	1 (2)	2 (3)	
Tumor location			0.13
Cervical	1 (2)	9 (12)	
Upper thoracic	10 (20)	14 (18)	
Middle thoracic	24 (49)	41 (53)	
Lower thoracic	14 (29)	13 (17)	
Primary tumor size			0.86
≤5 cm	25 (51)	41 (53)	
>5 cm	24 (49)	36 (37)	
Stage			<0.01
II	17 (35)	9 (12)	
III	32 (65)	68 (88)	

KPS, Karnofsky performance status; SCC, squamous cell carcinoma; AdenoCa, adenocarcinoma.

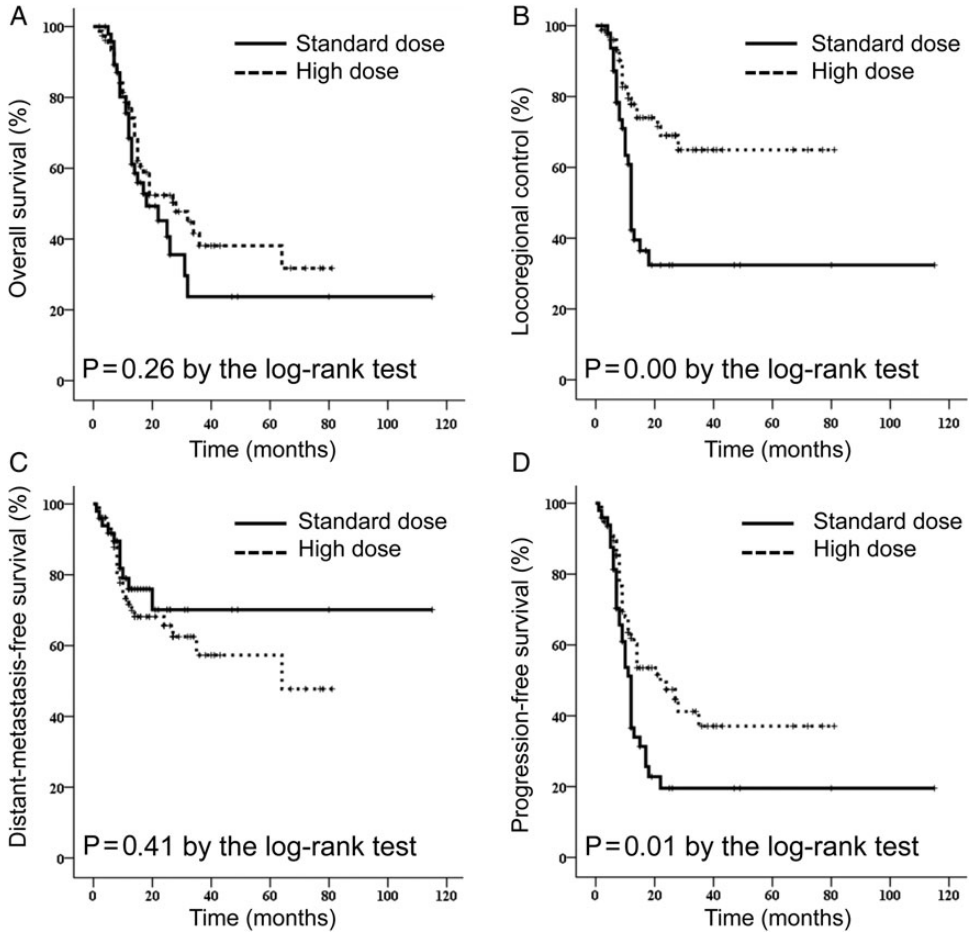

Figure 1. Kaplan–Meier plot of (A) overall survival, (B) locoregional control (LRC), (C) distant metastasis-free survival and (D) progression-free survival, according to radiation dose.

of intensities of chemotherapy between the groups was compared using independent samples *t*-tests. Survival was analyzed using the Kaplan–Meier estimates, and the log-rank test was used to assess the equality of the survival function across groups. Prognostic factors of survival were analyzed by univariate and multivariate analyses using Cox's proportional hazards model.

RESULTS

Patient Characteristics and Clinical Profile

Of the 126 patients included in our study, 49 received radiation doses of <60 Gy (standard-dose group) and 77 received radiation doses of ≥ 60 Gy (high-dose group). The median radiation dose received by the standard-dose group was 54 Gy (range, 45–59.4 Gy) while that of the high-dose group was 63 Gy (range, 60–75.6 Gy). Pretreatment patient and tumor characteristics of the two groups are listed in Table 2. There were no statistically significant differences in age, gender, performance status, histologic subtype, tumor location or tumor size between the two groups. However, the proportion of Stage III patients was higher in the high-dose group than in the standard-dose group (88 versus 65%, $P < 0.01$).

Table 3. Patterns of treatment failure

Failure pattern	No. of patients (%)		*P* value
	Standard dose ($n = 49$)	High dose ($n = 77$)	
Local recurrence	27 (55)	20 (26)	<0.01
Central failure	20 (41)	12 (16)	<0.01
Marginal failure	2 (4)	2 (3)	0.64
Outfield failure	5 (10)	6 (8)	0.75
Distant metastasis	11 (22)	26 (34)	0.23
Total	34 (69)	38 (49)	0.03

Survival and Disease Control

For surviving patients, the median follow-up times of the standard-dose group and the high-dose group were 28 months (range, 14–115) and 38 months (range, 15–81), respectively. Of 65 patients who died after completion of radiotherapy,

54 patients (43%) died from disease progression, eight patients (6%) from treatment-related mortality and three patients (2%) from other causes (two from cardiac failure and one from falling down injury). Median OS for the high- and the standard-dose groups was 28 and 18 months, respectively. Two-year OS rates for the high- and the standard-dose groups were 52.4 and 45.2%, respectively ($P = 0.26$) (Fig. 1A). However, the high-dose group had a significantly better 2-year local control rate (69 versus 32%, $P < 0.01$) and PFS (47 versus 20%, $P = 0.01$) than the standard-dose group, as shown in Fig. 1B and D. Two-year distant metastasis-free survival (DMFS) rate was not significantly different between the two groups (66% in the high-dose group versus 70% in the standard-dose group, $P = 0.41$) (Fig. 1C).

The complete, partial and no-response rates in the standard-dose group were 39, 53 and 8%, respectively, while these rates were 53, 42 and 5%, respectively, in the high-dose group. The complete response rate was greater in the high-dose group than the standard-dose group, but this result was not statistically significant ($P = 0.14$).

Patterns of Failure

Locoregional failure rates for the high- and standard-dose groups were 26 and 55%, respectively ($P < 0.01$). The central failure rate for the high-dose group was significantly lower than the standard-dose group (16 versus 41%, $P < 0.01$). Marginal failure rates and outfield failure rates for the groups were not significantly different. The rate of distant metastasis for all patients was 29%, and it was 34 and 22% for the high- and standard-dose groups, respectively; however this difference was not statistically significant ($P = 0.23$). These data are shown in Table 3.

Treatment-related Toxicities

Nine patients (18%) in the standard-dose group and 18 patients (23%) in the high-dose group developed late radiation pneumonitis, and incidences of radiation pneumonitis were not different between the groups ($P = 0.66$). Of nine patients who showed radiation pneumonitis in the standard-dose group, three, four one and one patient experienced Grade 1, 2, 4 and 5 radiation pneumonitis, respectively. In the high-dose group, eight, five, three and two patients showed Grade 1, 2, 3 and 4 radiation pneumonitis, respectively. The incidences of Grade $\geq$3 radiation pneumonitis in the standard-dose group and the high-dose group were 4 and 6%, respectively. This difference was not statistically significant ($P = 0.71$).

Frequencies of post-radiotherapy esophageal stenosis in both two groups were 29%, respectively. When incidences of

Table 4. Univariate analysis of prognostic factors

Factor	Locoregional control			Progression-free survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age $\geq$60 years	0.86	0.44–1.65	0.64	0.98	0.57–1.69	0.95	0.96	0.55–1.70	0.90
Male gender	5.21	0.71–38.4	0.10	2.92	0.92–9.35	0.07	3.92	0.96–16.1	0.06
KPS 90–100 (versus 60–80)	0.75	0.42–1.34	0.33	0.57	0.35–0.91	0.02	0.42	0.25–0.70	<0.01
Tumor in lower thoracic	0.75	0.36–1.56	0.45	0.8	0.45–1.44	0.47	0.60	0.31–1.18	0.14
Squamous cell type	0.88	0.31–2.46	0.81	0.92	0.40–2.12	0.84	0.69	0.30–1.60	0.39
Stage II (versus Stage III)	0.58	0.25–1.37	0.21	0.62	0.32–1.21	0.16	0.50	0.24–1.04	0.07
Radiation dose $\geq$60 Gy	0.36	0.2–0.64	<0.01	0.55	0.35–0.88	0.01	0.76	0.46–1.25	0.27
Tumor size >5 cm	1.05	0.59–1.87	0.87	1.15	0.72–1.82	0.56	1.40	0.86–2.29	0.18

CI, confidence interval.

Table 5. Multivariate analysis of prognostic factors

Factor	Locoregional control			Progression-free survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Male gender	5.18	0.70–38.5	0.13	2.70	0.83–8.70	0.10	3.17	0.76–13.3	0.11
KPS 90–100 (versus 60–80)	0.64	0.35–1.16	0.14	0.54	0.33–0.88	0.01	0.40	0.24–0.68	<0.01
Stage II (versus Stage III)	0.35	0.15–0.86	0.02	0.47	0.23–0.94	0.03	0.39	0.18–0.85	0.02
Radiation dose $\geq$60 Gy	0.25	0.13–0.46	<0.01	0.40	0.24–0.65	<0.01	0.47	0.27–0.81	0.01

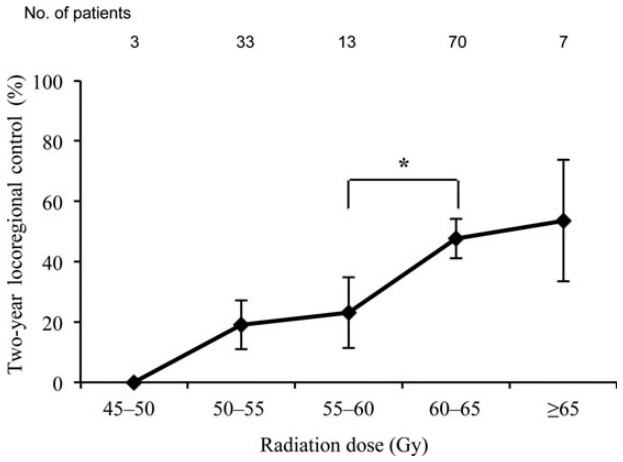

Figure 2. Two-year LRC rates according to total radiation dose. Error bars show standard error. *$P < 0.05$ in log-rank test.

Grade 3 or higher radiotherapy-related toxicities including esophageal stenosis, hemorrhage and fistula were compared between the two groups, four (8.2%) radiotherapy-related toxicities were observed in the standard-dose group versus eight (10.4%) in the high-dose group ($P = 0.75$). Grade 5 radiotherapy-related toxicities occurred in one patient (2.1%) in the standard-dose group and in three patients (3.9%) in the high-dose group ($P = 1.00$).

There were two treatment-related death (4%) in the standard-dose group and six treatment-related deaths (7.8%) in the high-dose group. Of these seven treatment-related deaths, three patients were due to chemotherapy-related toxicity, and one patient was due to radiation pneumonitis. Of the remaining four deaths, three patients occurred due to esophageal bleeding, and one due to tracheoesophageal fistula.

Prognostic Factors

The results of univariate analysis for LRC, PFS and OS are summarized in Table 4. High-dose radiotherapy (≥60 Gy) significantly affected both LRC and PFS. Good performance status [Karnofsky performance status (KPS) 90–100] was a favorable prognostic factor that affected PFS and OS. In multivariate analysis (Table 5), the high-dose radiotherapy (≥60 Gy) was a significant prognostic factor for improved LRC, PFS and OS. Stage II disease was also a significantly favorable prognostic factor for LRC, PFS and OS. Good performance status (KPS 90–100) was a significant prognostic factor for improved PFS and OS.

Dose–response Relationship

Two-year LRC rates according to total radiation dose are shown in Fig. 2. The relationship between total radiation dose and LRC rate showed a positive correlation for a total radiation dose ranging between 45 and 65 Gy. However, patients who received 65 Gy or higher radiotherapy did not show a significant improvement in LRC.

DISCUSSION

In the present study, we compared treatment outcomes between high-dose radiotherapy (≥60 Gy) and standard-dose radiotherapy (<60 Gy) in the setting of CCRT for Stages II–III esophageal cancer. We demonstrated that high-dose radiotherapy improved LRC and PFS without a significant increase in treatment-related mortalities or toxicities. Furthermore, in multivariate analysis, high-dose radiotherapy was a significant prognostic factor for improved LRC, PFS and OS. However, distant metastasis was more frequent in the high-dose group than the standard-dose group despite the improved LRC of the high-dose group, although this difference was not statistically significant. The reason of higher distant metastasis rate in the high-dose group is unclear. However, higher proportion of Stage III patients in the high-dose group may have contributed, in part, to higher distant metastasis in the high-dose group, because intensity of chemotherapy was not lower in the high-dose group than the standard-dose group.

Although NCCN esophageal cancer guidelines recommend radiation doses of 50 or 50.4 Gy for definitive CCRT, radiation dose escalation for treating esophageal cancer should be studied further. The NCCN esophageal cancer radiation dose recommendations are based on the results of the RTOG trial 94-05. RTOG trial 94-05 compared treatment response to CCRT using 64.8 versus 50.4 Gy radiotherapy in patients with Stages I–III squamous cell carcinoma (85%) or adenocarcinoma (15%) (14). This trial failed to show that high-dose radiotherapy with concurrent chemotherapy had any advantages over standard-dose radiotherapy with concurrent chemotherapy. Treatment-related deaths were more frequent in the high-dose arm than the standard-dose arm, and patients in the high-dose arm tended to have a worse prognosis. However, 7 of the 11 deaths in the high-dose arm occurred in patients who received 50.4 Gy or less; therefore, high-dose radiation was not responsible for the increased mortality in this group. The potential benefits of high-dose radiotherapy for esophageal cancer should, therefore, not be ignored based only on this study. The standard-dose arm in RTOG 94-05 had similar treatment outcomes as the standard-dose group in the present study with regard to median survival (18 versus 18 months) and 2-year survival rate (40 versus 45.2%). In contrast, the high-dose arm in RTOG 94-05 showed a worse prognosis than the high-dose group in the present study (the median survival, 13 versus 28 months).

In Japan, CCRT was introduced in the early 1990s, and the regimen of 60 Gy radiotherapy in 30 fractions with a 2-week planned break is widely used (17–20). The Japan Clinical Oncology Group (JCOG) 9906 trial was a Phase II study to evaluate the efficacy of CCRT with cisplatin and 5-FU for Stages II–III esophageal squamous cell carcinoma. Patients were treated with radiotherapy as described above, and the median survival and 3-year survival rates were 29 months and 44.7%, respectively (20). These survival results are comparable to the survival results obtained for patients in our high radiation dose group.

A recent randomized clinical trial comparing surgery alone with chemoradiation followed by surgery in patients with T1N1 or T2-3N0-1 esophageal cancer showed that demonstrated preoperative chemoradiotherapy improved survival among patients with potentially curable esophageal or esophagogastric junction tumor (7). In this study, chemoradiation followed by surgery showed excellent outcomes with median OS of 49.4 months. However, two randomized clinical trials and a recent meta-analysis, which compared chemoradiation alone with chemoradiation followed by surgery failed to benefit of surgery on OS, while addition of surgery to chemoradiation improved local control (21–23).

Due to retrospective nature of the current study, there are several limitations to this study. First limitation of this study is the possibility of underestimating treatment-related toxicities. Second limitation is unbalance of patient characteristics between the groups. Proportion of Stage III patients was higher in the high-dose group than the standard-dose group and as a result, the effect of high-dose radiotherapy on DMFS and OS could not be exactly identified. Third limitation is that dosages and cycles of chemotherapy were various according to patients. Although mean doses of 5-FU and cisplatin were not significantly different between the groups, the possibility that the intensity of chemotherapy could influence the outcomes of the groups cannot be excluded. Moreover, we could not analyze the role of maintenance chemotherapy, because it is possible that the patients with good performance status or showing good treatment response received maintenance chemotherapy. Therefore, we did not analyze the effect of maintenance chemotherapy on prognosis. However, despite these limitations, radiotherapy of 60 Gy or higher with concurrent chemotherapy produced better LRC and PFS without significant increase of treatment-related toxicities.

In conclusion, high-dose radiotherapy of 60 Gy or higher with concurrent chemotherapy is an effective treatment option for Stages II–III esophageal cancer. It improves LRC and PFS and may also improve the survival of Stages II–III esophageal cancer patients. Therefore, radiation dose escalation in the setting of CCRT for esophageal cancer deserves future randomized clinical trials.

Conflict of interest statement

None declared.

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