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Evaluating the optimal radiation dose for definitive chemoradiotherapy for esophageal squamous cell carcinoma

A single institution experience

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Abstract

The optimal radiation dose for definitive chemoradiotherapy in inoperable esophageal squamous cell carcinoma (ESCC) has been long debated. In this study, we evaluated the effect of doses greater than the conventional radiation dose (50.4 Gy) on tumor control, tumor response, overall survival (OS), and disease-free survival (DFS).

The database of patients diagnosed with inoperable ESCC from 2007 to 2015 was obtained from the cancer registry of Chi-Mei Medical Center. All categorical variables were compared using Chi-squared test. The risk of OS and DFS were estimated using Cox proportional hazards regression, and Kaplan–Meier plots presented the trend of OS and DFS with log-rank tests used to compare differences. All significance levels were set at $P < .05$.

A total of 84 patients were retrospectively analyzed, with 42 (50%) receiving >50.4 Gy and 42 (50%) receiving ≤50.4 Gy (50%) concurrently with chemotherapy. Univariate and multivariate analysis revealed no significant differences between higher dose and conventional dose in OS ($P = .21$) and DFS ($P = .26$). Further dose analysis of <50, 50 to 50.4, 51 to 60, and >60 Gy showed no significant differences in OS or DFS. Higher doses conveyed no significant benefit on the failure pattern, either local regional failure or distant failure ($P = .42$). Major prognostic factors associated with better OS on multivariate analysis were stages I and II patients ($P = .03$) and radiation technique using arc therapy ($P = .04$). No acute toxicity of grade III or higher was recorded.

The results of our study show that providing higher than conventional radiation doses concurrent with chemotherapy for inoperable ESCC does not impact OS or DSF, nor does it improve locoregional failure or distant failure. Although tumor response might be improved by radiation doses >50.4 Gy, the impact on OS and DFS remain to be studied.

Abbreviations: BMI = body mass index, CCRT = concurrent chemoradiotherapy, CRT = chemoradiotherapy, CT = computed tomography, DFS = disease-free survival, EAC = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma, GE = gastroesophageal, Gy = Gray, IMRT = intensity-modulated radiation therapy, LRR = locoregional recurrence, NCDB = National Cancer Data Base, OS = overall survival, pCR = pathologic complete response, PET = positron-emission tomography, RECIST = Response Evaluation Criteria In Solid Tumors, SIB = simultaneous integrated boost.

Keywords: chemoradiotherapy, esophageal squamous cell carcinoma, radiation dose

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1. Introduction

Esophageal cancer is the 8th most common cancer and the 6th most common cause of cancer death, worldwide.[1] Global cancer statistics indicate an increasing incidence of esophageal cancers, but treatment outcomes remain poor.[2,3] In Taiwan, esophageal cancer is a leading cause of cancer death in males.[4] Unlike in the West, esophageal squamous cell carcinoma (ESCC) is more predominant than esophageal adenocarcinoma (EAC).[5–7] In previous studies, those with ESCC had significantly higher locoregional recurrence (LRR) rates but a lower hematogenous metastasis rate than patients with EAC after definitive chemoradiotherapy (CRT).[8,9] In addition, the pathologic complete response rate was significantly higher in patients with ESCC compared with patients with EAC after neoadjuvant CRT.[8] On the contrary, ESCC will sometimes manifest as oropharyngeal squamous cell carcinomas while EAC can manifest as gastric adenocarcinoma.[10] Furthermore, ESCCs are commonly located in the cervical and thoracic esophagus while EACs are located mostly at the gastroesophageal junction.[11] Whether the above factors indicate that ESCC will respond to treatment at higher than normal radiation doses remains unknown.

More than half of ESCCs are diagnosed in a late unresectable stage, with concurrent chemoradiotherapy (CCRT) as the

treatment of choice. Currently, the standard dose of definitive CCRT is 50 to 50.4 Gy (1.8–2.0 Gy/d), based on the landmark INT0123 (RTOG 9405) phase III trial.[12] In the INT0123 trial, 2-dimensional radiation was primarily used, unlike the intensity-modulated radiation therapy (IMRT) which has been the major radiation technique for the last decade. Aside from that, patients in the INT0123 trial were mostly in early stage (AJCC stages I–II) cancer and included those with both ESCC and EAC. In contrast to the West, in Asia ESCC is the dominant pathology and most cases diagnosed are unresectable due to advanced stage.[13,14] The optimal radiation dose for definitive CCRT in ESCC has long been debated. In our study, we evaluated whether doses greater than the conventional radiation dose ($\leq$50.4 Gy) can improve tumor control, tumor response, overall survival (OS), and disease-free survival (DFS) in patients with inoperable ESCC.

2. Materials and methods

2.1. Data source

We performed a retrospective analysis using patient data from the Chi-Mei Medical Center, a large regional medical center serving a population of more than 3 million. The variables included were patient demographics, cancer stage, and interventions received, including surgery, radiation therapy, and chemotherapy. Details related to radiation technique included arc vs IMRT, fraction size, treatment dose, and treatment field. Other clinical details included 1st day of radiation treatment, last day of radiation treatment, 1st day of failure, failure pattern, time of follow-up, personal history, comorbidity, morbidity, and mortality. We defined progress disease (PD) "local recurrence" regional recurrence and distant recurrence as treatment failure. Using Response Evaluation Criteria In Solid Tumors (RECIST) V1.1[15] criteria with images by computed tomography (CT) to evaluate tumor response of treatment. The definition of CR is disappearance of all target lesions and confirmed at 4 weeks. The definition of PR is at least a 30% decrease and confirmed at 4 weeks. The definition of SD is neither PR nor PD. The definition of PD is at least a 20% increase or no CR, PR, or SD documented before increase disease.

2.2. Study cohort

The database of patients diagnosed with ESCC from 2007 to 2015 was obtained from the cancer registry of Chi-Mei Medical Center. The inclusion and exclusion criteria are summarized in Figure 1. ESCC stages I to III was identified, and only unresectable patients receiving CCRT were included. Patients with incomplete data or those coded as receiving palliative care were excluded from the study.

2.3. Statistical analysis

Demographic characteristics were compared between patients receiving doses of $\leq$50.4 and >50.4 Gy. All categorical variable items for the 2 groups were compared using Chi-squared test (Table 1). The primary endpoint was DFS, defined as the time from the 1st day of radiation treatment until the 1st day of failure. The secondary endpoint was OS, defined as the time from the 1st

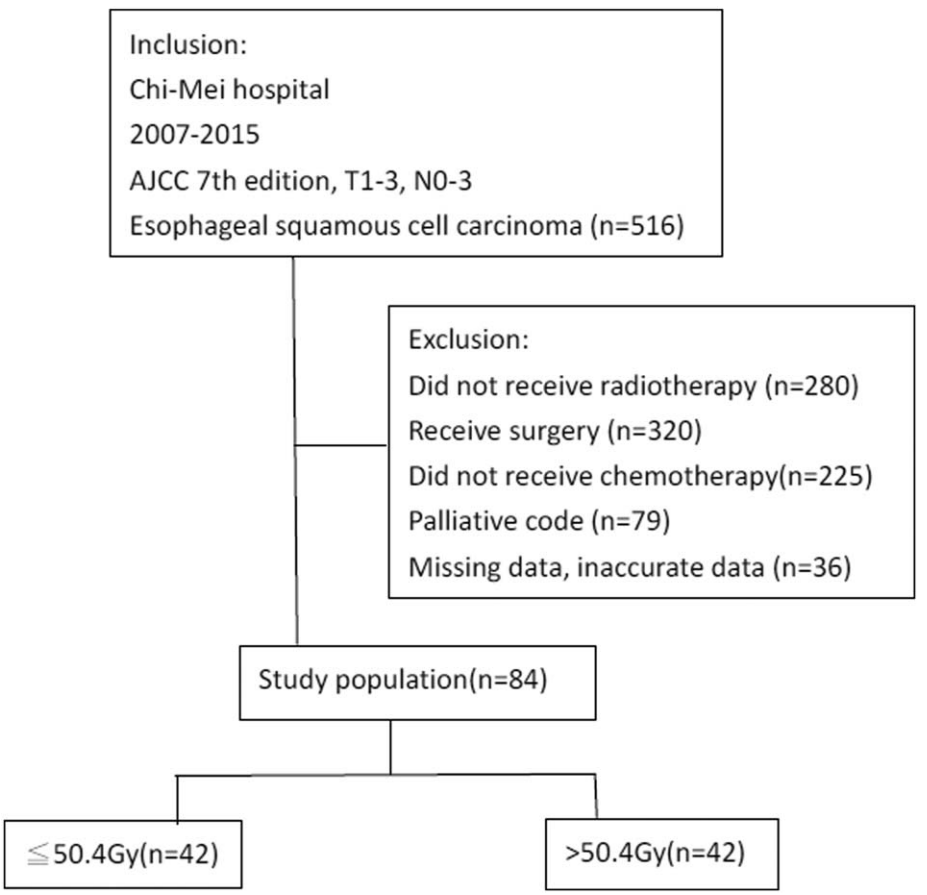

Figure 1. Study flow diagram.

Table 1

Patient characteristics and demographic data.

Variable	Radiation dose, Gy		*P*-value
	≤50.4	>50.4	
Patient total	N = 42	N = 42	
Age at diagnosis (y/o)			
Median (range)	54 (40–78)	57 (41–83)	.19
Sex			
Male	41 (97.6)	39 (92.9)	.30
Female	1 (2.4)	3 (7.1)	
ECOG			
0	26 (61.9)	31 (73.8)	.24
1–2	16 (38.1)	11 (26.2)	
Year of diagnosis			
2007–2009	2 (4.80)	9 (21.4)	.01
2010–2012	15 (35.7)	20 (47.6)	
2013–2015	25 (59.5)	13 (31.0)	
Tumor location			
Cervical/upper 3rd	14 (33.3)	24 (57.1)	.02
Middle 3rd	14 (33.3)	14 (33.3)	
Lower 3rd/cardinal	14 (33.3)	4 (9.5)	
T category (7th AJCC)			
1	2 (4.8)	6 (14.3)	.04
2	3 (7.1)	6 (14.3)	
3	31 (73.8)	18 (42.9)	
4	6 (14.3)	12 (28.6)	
N category (7th AJCC)			
0	6 (14.3)	11 (26.2)	.4
1	14 (33.3)	16 (38.1)	
2	11 (26.2)	8 (19)	
3	11 (26.2)	7 (16.7)	
Overall stage (7th AJCC)			
I–II	7 (16.7)	15 (35.7)	.04
III	35 (83.3)	27 (64.3)	
Radiotherapy field			
T	5 (11.9)	7 (16.7)	.53
T + N	37 (88.1)	35 (83.3)	
Radiation modality			
IMRT	27 (64.3)	35 (83.4)	.04
Arc	15 (35.7)	7 (16.7)	
Smoking			
Non	6 (14.3)	8 (19)	.55
Yes	36 (85.7)	34 (70.9)	
Alcohol			
Non	7 (16.7)	13 (31)	.12
Yes	35 (83.3)	29 (69)	
Betal nut			
No	23 (54.8)	27 (64.3)	.37
Yes	19 (45.2)	15 (35.7)	
Mean follow time (mo)	19.38	27.08	.06

ECOG = Eastern Cooperative Oncology Group.

day of radiation treatment until the date of death. Kaplan–Meier plots were drawn to present the trends for OS and DFS with the log-rank test used to compare the differences between groups (Figs. 2 and 3). Univariate and multivariate analyses were performed using the Cox hazards proportional regression model to determine potential confounding factors (Appendix 1, http://links.lww.com/MD/C633). The hazard ratio of OS and DFS for the 2 groups was determined using multivariate Cox regression, adjusted for age, sex, Eastern Cooperative Oncology Group (ECOG) score, tumor location, overall stage, radiation field, radiation modality, smoking, alcohol use, betel nut exposure and double primary cancer (Table 2). Failure patterns and tumor treatment response between the 2 groups were also compared using the Chi-squared test (Tables 3 and 4). We further stratified the groups by tumor location and tumor AJCC stage, using the log-rank test to compare OS and DFS (Tables 5 and 6). All statistical significance levels were set as 2-sided, with $P \leq .05$. Statistical analyses were performed using SPSS, version 22 (IBM Corp, Armonk, NY).

3. Results

3.1. Patient characteristics and demographics

We identified 84 patients, stages I to III ESCC who received definitive CCRT from 2007 to 2015 at Chi-Mei Medical Center (Fig. 1). The demographic characteristics and tumor-specific and treatment-related data are listed in Table 1. Half, or 42 patients, received CCRT ≤50.4 Gy (median: 49.5 Gy, range 44–50.4 Gy) with IMRT and 42 received CCRT >50.4 Gy (median: 61.8 Gy, range 52.2–70 Gy) with IMRT. The mean follow-up time after the 1st day of radiation therapy was 23.2 months (standard deviation, 19 months). The 2 groups did no differ significantly in age, sex, ECOG score, staging, radiotherapy field, smoking, alcohol drinking, betel nut chewing, double cancer, or mean follow-up time. The percentage of patients receiving a higher radiation dose decreased steadily from 81.8% in 2007 to 2009 to 34.2% in 2013 to 2015 while the incidence of ESCC rose over the same period. Of those receiving the higher radiation dose, 66.7% received it at the cervical/upper 3rd thoracic esophagus. Fewer patients (40%) received the higher radiation dose at the middle, lower 3rd thoracic, and/or cardinal esophagus. Locally advanced esophageal carcinoma was predominant in this study; 73.8% of all cases were diagnosed at stage III. However, the group receiving higher radiation doses had a lower proportion of locally advanced stage cancers (40%).

The multivariate Cox regression analysis indicated that advanced AJCC clinical stage (>stage III) was a statistically significant independent predictor of poor outcomes in ESCC (Appendix 1, http://links.lww.com/MD/C633). Major prognostic factors associated with better OS on multivariate analysis were stages I and II cancer ($P = .03$) and the use of arc therapy ($P = .04$) (Appendix 1, http://links.lww.com/MD/C633).

3.2. Survival outcome

The median and 2-year OS for patients treated with ≤50.4 Gy was 12.6 months and 54.8% compared with 23.9 months and 57.1% for those treated with >50.4 Gy ($P = .06$). Neither OS nor DFS differed significantly by radiation dose, according to univariate and multivariable Cox regression (Table 2, Figs. 2 and 3). When dose levels were further subdivided into <50, 50 to 50.4, 51 to 60, and >60 Gy, differences in OS or DFS remained without statistical significance between the 4 groups (Table 7).

3.3. Failure pattern and clinical tumor response

Failure pattern, including local-regional failure and distant failure ($P = .42$), showed no statistically significant differences by radiation dose (Table 3). However, those receiving the higher dose (>50.4 Gy) had a higher complete response rate than those receiving the conventional radiation dose (≤50.4 Gy) ($P = .002$) (Table 4).

3.4. Subgroup analysis

Additional subgroup analyses were performed to examine OS and DFS by radiation dose according to tumor location and

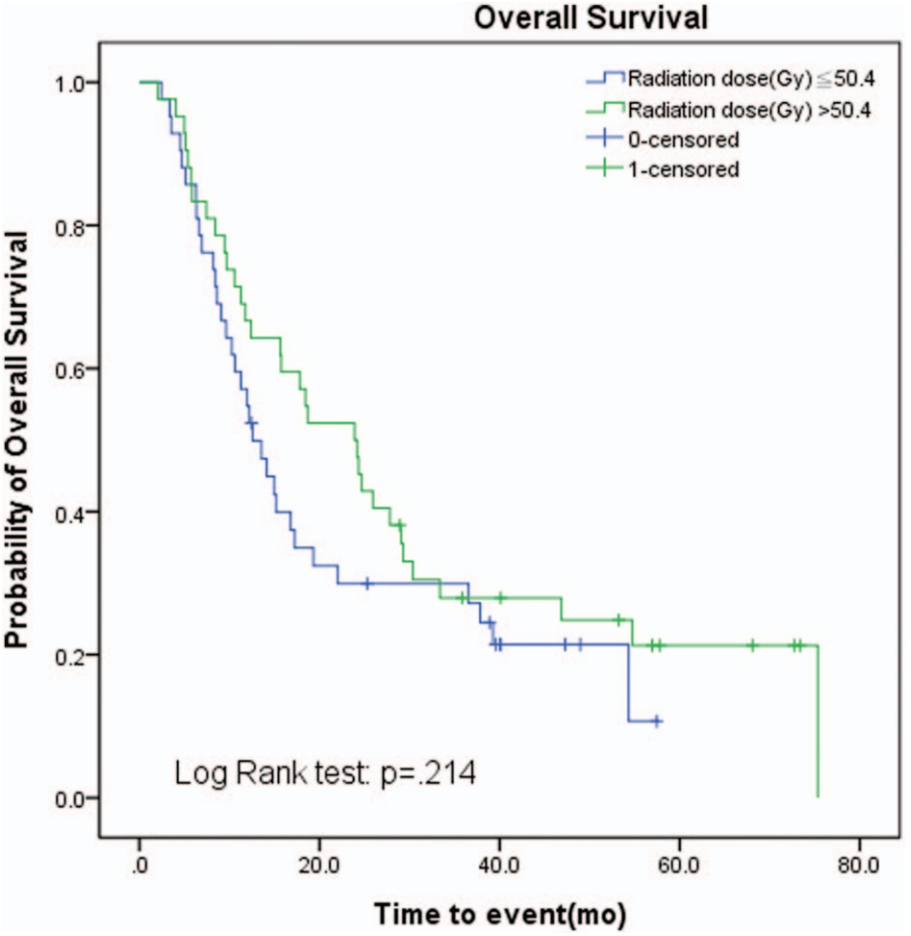

Figure 2. Kaplan–Meier curves of overall survival comparing by radiation dose at ≤50.4 Gy vs >50.4 Gy.

AJCC overall stage. OS and DFS showed no statistically significant difference between the groups when stratified by tumor location or AJCC overall stage (Tables 5 and 6).

3.5. Treatment-related morbidity and mortality

We reviewed all medical records but found neither treatment-related deaths nor more than grade III acute toxicity. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 to record the adverse reaction was used (Appendix 2, http://links.lww.com/MD/C633). All toxicities including radiation dermatitis "radiation esophagitis" dysphagia and cough were no difference between 2 groups. No dyspnea in all patients was noted. Fourteen patients had grade II radiation dermatitis in high-dose group and 4 patients in conventional dose group. One patient had grade II radiation esophagitis in high-dose group and 5 patients in conventional dose group. There was no grade II dysphagia in high-dose group but 1 patient in conventional dose group. There was no grade II cough in conventional dose group but 2 patients in high-dose group.

4. Discussion

Reports of rates of OS and DFS differ in esophageal cancers treated with CCRT.[16–18] However, previous studies differed widely in their histology and radiation technology. The current standard suggested dose for definitive CCRT, 50 to 50.4 Gy (1.8–2.0 Gy/d), was based on the landmark INT0123 (RTOG 9405) phase III trial.[12] However, this trial used primarily 2-dimensional radiation techniques. In addition, these patients were mostly in early stage cancer (AJCC stages I–IIB). Moreover, both ESCC and EAC were included in the trial. However, in Asia, locally advanced (stage III) ESCC is the primary diagnosis and IMRT is the major radiation technique. Therefore, higher radiation doses are possible and have been tried in various cancer centers with mixed outcomes. A 2016 retrospective analysis from the US National Cancer Data Base (NCDB) also supported the conclusions of INT0123, even though it included modern techniques like 3-dimentional radiotherapy and IMRT.[19] However, this study also had a mixed study group of ESCC (45.8%) and EAC (54.2%). Unlike the higher dose of 64.8 Gy in the INT0123 trial, higher doses in the NCDB were 55 to 60 Gy (17.8%) and >60 Gy (13.9%). In our study, we limited our patients to those with inoperable advanced ESCC with IMRT as the major radiation therapy technique. Patients receiving CCRT with radiation doses >50.4 Gy had no significant change in OS or DFS over those receiving conventional doses. Our results coincide with those from the 2 important US studies.[12,19]

In another trial from Chang et al[4] high-dose IMRT-based CCRT yielded more favorable survival outcomes in patients with advanced stage ESCC. However, the cut point for radiation therapy dose was set at 60 Gy rather than the standard 50.4 Gy.

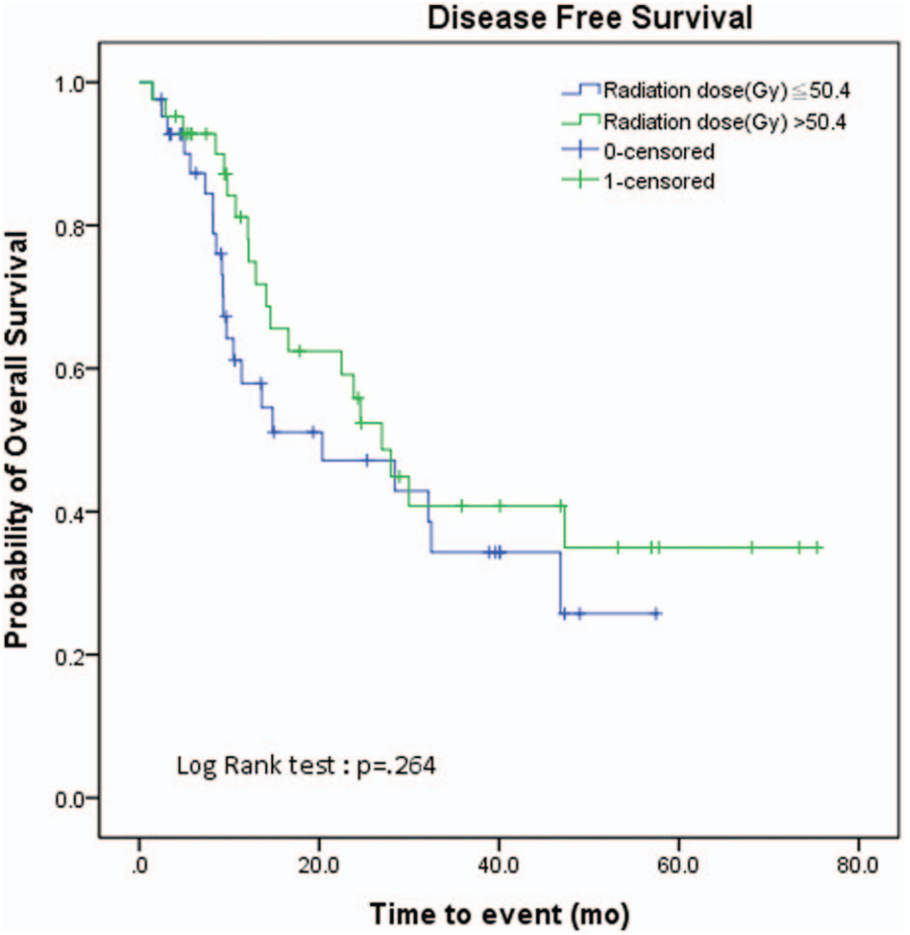

Figure 3. Kaplan–Meier curves of disease-free survival comparing by radiation dose at ≤50.4 Gy vs >50.4 Gy.

The relative higher dose (45–59.4 Gy) in the low-dose group (<60 Gy) may have skewed these results. In addition, the median dose of the high-dose group (>60 Gy) was 66.6 Gy and ranged from 60 to 72 Gy. The high dose was therefore higher than in the INT0123 trial, the NCDB study or our study. The authors did not mention the toxicity and complications at the relatively higher dose. A meta-analysis by Chen et al[20] reported that a dose of ≥60 Gy appeared to be better at improving OS and locoregional control, especially in Asian populations. However, most of these studies were retrospective, had few patients and differed significantly in many factors.

Welsh et al[21] explored the effect on local control of simultaneous integrated boost (SIB) to escalate the radiation dose in locally advanced esophageal cancer from a prospective phase I/II trial. The findings concluded that SIB with IMRT or IMRT improved local control; thus, dose escalation was expected to have same outcome. This study also had a smaller group receiving higher radiation (58.8 to 63 Gy) (n=38) compared to the conventional group (50.4 Gy) (n=97). In our study, the higher dose conveyed no benefit in local-regional control or distant control (P=.42). Higher radiation did not significantly impact OS, DFS, local-regional control, or distant control. However, improved tumor response was seen in radiation dose above 50.4 Gy (P=.002). An earlier study by Tong et al[22]

Table 2

The hazard ratio of overall survival and disease-free survival using the univariate and multivariable Cox regression between radiation dose (Gy) ≤50.4 and >50.4.

	Univariate HR (95% CI)	*P*-value	Adjusted* HR (95% CI)	*P*-value
Overall survival				
Radiation dose, Gy				
≤50.4	1.00 (Ref.)		1.00 (Ref.)	
>50.4	0.74 (0.45–1.22)	.24	0.61 (0.29–1.25)	.18
Disease-free survival				
Radiation dose, Gy				
≤50.4	1.00 (Ref.)		1.00 (Ref.)	
>50.4	0.70 (0.39–1.30)	.26	0.87 (0.36–2.09)	.76

CI=confidence interval, HR=hazard ratio.
* Adjusted by age, sex, Eastern Cooperative Oncology Group, diagnosis years, tumor location, overall stage, radiation field, radiation modality, smoking, alcohol, and betel nut.

Table 3

The distribution of failure pattern among different dose range.

	Local or regional	DM	*P*-value
Dose range, Gy			
≤50.4	13 (31)	9 (21.4)	.42
>50.4	8 (19)	12 (28.6)	

DM=distant metastatsis.

Table 4

The distribution of clinical tumor response and radiation dose range.

	Complete response	Partial response	Stable	*P*-value
Dose range, Gy				
≤50.4	0 (0)	35 (83.3)	7 (16.7)	.002
>50.4	9 (21.4)	22 (52.4)	11 (26.2)	

showed a positive correlation between OS and the histopathologic response after CCRT. Ma et al[23] reported that raising individualized dose levels has the potential to improve OS, as indicated by an increased rate of complete metabolic response by positron-emission tomography CT (PET-CT). Even though all our subjects had ESCC, we realized that the metabolic response could not substitute for histopathologic response. In this study, tumor response might be improved by escalating the radiation dose greater than 50.4 Gy. However, the impact of this increase on OS and DFS remains to be studied. Further studies are warranted to confirm the positive correlation between tumor complete response and DFS or OS.

Subgroup analyses by tumor location and AJCC stage showed no significant impact on DFS or OS in those receiving either radiation dose.

Major prognostic factors associated with better OS on multivariate analysis were stages I and II patients ($P=.03$) and radiation technique using arc therapy ($P=.04$) (Appendix 1, http://links.lww.com/MD/C633). Xu et al[24] found that, compared with step-and-shoot IMRT, volumetric arc therapy had better target conformity. Choi et al[25] found superior conformity index and conformation number in modulated arc therapy compared to step-and-shoot IMRT. These results may suggest that arc therapy be effective for esophageal cancer. However, OS was not affected by the use of this technique. In our study, we hypothesize that the better outcomes in the arc therapy group might be a result of better nutritional support. Arc therapy was started in our center in 2009, and in recent years, our center strictly monitors nutritional care for every esophageal cancer patient, as poor intake is a major cause of poor survival in this group of patients. A study by Sun et al,[26] comparing the nutritional parameters in 502 patients with ESCC, found that baseline nutritional status is predictive of OS in patients with ESCC. The median survival for patients with body mass index (BMI) <18.5 and BMI >24.9 were 19.2 and 51.6 months, while 5-year OSR were 25.2% and 48.1%, respectively. The authors concluded that BMI is a sensitive prognostic parameter for patients with ESCC. Treatment in patients with ESCC with low BMI should integrate the clinical modalities and individual nutritional support.

Table 5

Overall survival and disease-free survival using the log-rank test between radiation dose (Gy) ≤50.4 and >50.4 by tumor location stratification.

	Overall survival			Disease-free survival		
	Dose range, Gy			Dose range, Gy		
Tumor location	≤50.4	>50.4	*P*-value	≤50.4	>50.4	*P*-value
Cervical/upper 3rd	14	24	.89	14	24	.77
Middle 3rd	14	14	.94	14	14	.32
Lower 3rd/cardinal	14	4	.45	14	4	.08

Table 6

Overall survival and disease-free survival using the log-rank test between radiation dose (Gy) ≤50.4 and >50.4 by tumor stage stratification.

	Overall survival			Disease-free survival		
	Dose range, Gy			Dose range, Gy		
Tumor stage	≤50.4	>50.4	*P*-value	≤50.4	>50.4	*P*-value
Stages I–II	7	15	.32	7	15	.17
Stage III	35	27	.71	35	27	.69

Table 7

The hazard ratio of overall survival and disease-free survival among different radiation dose range (Gy).

	Overall survival			Disease-free survival		
Dose range (Gy)	Number of events	Adjusted* HR (95% CI)	*P*-value	Number of events	Adjusted* HR (95% CI)	*P*-value
<50	6	1.00 (Ref.)		6	1.00 (Ref.)	
50–50.4	36	1.264 (0.44–3.60)	.07	36	1.16 (0.34–3.91)	.81
51–60	17	1.182 (0.39–3.57)	.76	17	1.17 (0.32–4.26)	.81
>60	25	0.76 (0.25–2.27)	.62	25	0.60 (1.65–2.22)	.45

CI = confidence interval, HR = hazard ratio.

* Adjusted by age, sex, Eastern Cooperative Oncology Group, diagnosis years, tumor location, overall stage, radiation field, radiation modality, smoking, alcohol, and betal nut.

Our study has some limitations. First, there is the potential for selection bias inherent to retrospective analyses. Second, we did not consider the differences in chemotherapy regimens and course. Third, the conventional group did not have any complete tumor response. Stratified analysis of larger cohorts is needed to confirm our results. Fourth, the evaluation of tumor response was based on RECIST criteria but not uniformly done by the same evaluating tool, causing biases in the study. Lastly, the median dose in the high-dose group (61.8 Gy) was less than that in the INT0123 high-dose group (64.8 Gy).

5. Conclusion

In modern radiation technology, IMRT is the standard radiation therapy technique utilized in our major cancer center, allowing us to prescribe a higher dose with a better outcome and fewer complications. This concept has been used in various studies of locally advanced unresectable ESCC, although the outcomes remain controversial. Our study shows that a radiation dose greater than 50.4 Gy had no significant impact on OS, DFS, local regional control or distant control in ESCC with IMRT-based CRT. The conclusion coincides with the results of INT0123 (RTOG 9405) and the 2004 to 2012 NCDB study. However, in our study, tumor response might be improved by escalating the radiation dose higher than 50.4 Gy. Further randomized controlled trials are needed to confirm our conclusions and clarify the outcomes for higher radiation doses.

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