Dose escalation of 3D radiotherapy is effective for esophageal squamous cell carcinoma: a multicenter retrospective analysis (3JECROG R-03)

Wencheng Zhang[1#], Jingjing Zhao[1#], Weiming Han[2], Hualei Zhang[1], Xin Wang[2], Chen Li[2], Junqiang Chen[3], Xiaomin Wang[4], Yidian Zhao[4], Xueying Qiao[5], Zhiguo Zhou[5], Chun Han[5], Shuchai Zhu[5], Wenbin Shen[5], Lan Wang[5], Xiaolin Ge[6], Xinchen Sun[6], Kaixian Zhang[7], Miaomiao Hu[7], Ling Li[7], Chongli Hao[7], Gaofeng Li[8], Yonggang Xu[8], Yadi Wang[9], Na Lu[9], Miaoling Liu[10], Shuai Qian[10], Zefen Xiao[2], Ping Wang[1], Qingsong Pang[1]

[1]Department of Radiation Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Tianjin, China; [2]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [3]Department of Radiation Oncology, Fujian Cancer Hospital/Fujian Medical University Cancer Hospital, Fuzhou, China; [4]Department 4th of Radiation Oncology, Anyang Cancer Hospital, Anyang, China; [5]Department of Radiation Oncology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China; [6]Department of Radiation Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [7]Department of Oncology, Tengzhou Central People's Hospital, Tengzhou, China; [8]Department of Radiation Oncology, Beijing Hospital, National Center of Gerontology, Beijing, China; [9]Department of Radiation Oncology, The Seventh Medical Center of PLA General Hospital, Beijing, China; [10]Department of Radiation Oncology, Affiliated Hospital of Hebei University, Baoding, China

Contributions: (I) Conception and design: Q Pang, P Wang, Z Xiao; (II) Administrative support: Q Pang, P Wang, Z Xiao; (III) Provision of study materials or patients: Q Pang, P Wang, Z Xiao, C Han; (IV) Collection and assembly of data: W Zhang, J Zhao, H Zhang; (V) Data analysis and interpretation: W Zhang, J Zhao, W Han; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Qingsong Pang, MD. Department of Radiation Oncology, Tianjin Medical University Cancer Institute and Hospital, Huanhu West Road, Hexi District, Tianjin, China. Email: pangqingsong@tjmuch.com; Ping Wang, MD. Department of Radiation Oncology, Tianjin Medical University Cancer Institute and Hospital, Huanhu West Road, Hexi District, Tianjin, China. Email: wangping@tjmuch.com; Zefen Xiao, MD. Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. Email: xiaozefen@sina.com.

Background: To evaluate the impact of radiation dose escalation on overall survival (OS) in patients with non-metastatic esophageal squamous cell carcinoma (ESCC) treated with radical radiotherapy.

Methods: The clinical data of ESCC patients treated with three-dimensional (3D) radiotherapy alone or chemoradiotherapy were collected from multiple institutes and retrospectively analyzed. Patients who received radiation dose ≥40 Gy were included. Radiation dose as a continuous variable was entered into the Cox regression model by using penalized spline regression to allow for a nonlinear relationship between radiation dose and OS to be identified. Patients were stratified into five groups according to EQD_2. The Kaplan-Meier method was used to assess the OS in different dose groups. Univariate and multivariate analyses were performed to evaluate the factors associated with OS.

Results: A total of 2,469 patients were included from 10 institutes across China. The median follow-up time was 58.3 months [95% confidence interval (CI): 56.4–60.2 months]. The median OS and PFS time were 24.3 months (95% CI: 22.5–26.2 months) and 18.0 months (95% CI: 16.4–19.6 months), respectively. The risk of death decreased sharply with a dose up to 60 to 62 Gy, before increasing slightly after the dose was elevated beyond 62 Gy. Multivariate analysis indicated that the chance of death was significantly decreased in patients who received radiotherapy doses of 60–62 Gy [P=0.028, hazard ratio (HR) 0.85, 95% CI: 0.73–0.98)], compared with those who received radiotherapy doses of 40–60 Gy.

Conclusions: Our results reveal radiation dose is a significant prognostic factor of survival for ESCC

patients. Higher radiation dose contributes to much more favorable survival outcomes for ESCC patients receiving radical radiotherapy by modern techniques, and 60 Gy or above might be the most optimal radiation dose.

Keywords: Esophageal squamous cell carcinoma (ESCC); overall survival (OS); radiation dose

Submitted Feb 15, 2020. Accepted for publication Aug 14, 2020.
doi: 10.21037/atm-20-4672
View this article at: http://dx.doi.org/10.21037/atm-20-4672

Introduction

Esophageal cancer (EC), as the seventh most frequently diagnosed cancer, was the sixth leading global cause of cancer-associated death in 2018 (1). Surgery is the primary option for treatment of EC at early stage. While accumulated evidence demonstrate that neoadjuvant concurrent chemoradiotherapy followed by surgery yield more favorable survival outcomes compared with surgery alone for EC, with acceptable adverse events (2,3). Unfortunately, due to EC having no obvious symptoms in its early stage, most patients are not eligible for curative surgery at the time of diagnosis. According to the results of the Radiation Therapy Oncology Group (RTOG)-8501 and RTOG 94-05, radical concurrent chemoradiotherapy (CCRT) to a total dose of 50.4 Gy has been accepted as the standard treatment for locally advanced inoperable EC (4,5).

The survival outcome and local control of the tumor of CCRT are still poor, and local failure occurs in about 50% patients, indicating that the standard radiation dose (50.4 Gy) is inadequate to achieve satisfactory tumor local control (4-7). Moreover, in East Asia, squamous cell carcinoma (SCC) is the predominant histological type of EC and differs from adenocarcinoma in epidemiology, tumor biology, radiation sensitivity, and patterns and sites of recurrence (7-9). With esophageal SCC (ESCC), the local regional recurrence rate is marginally higher (7). Thus, in clinic, a dose of 60 Gy is more preferred for the definitive CCRT for ESCC in China. However, some studies maintain that dose escalation may lead to high incidence of radiation-related toxicities, such as esophageal bleeding, perforation, fistula, etc, which is a challenge in the treatment for EC (10,11). Because of these factors, achieving a consensus on the optimal radiation dose for ESCC has been pursued in studies over many years (10-17).

In recent years, the remarkable development in radiation techniques has seen the application of three-dimensional (3D) treatment planning, including intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and helical tomotherapy, which exhibit significantly superior in dose distribution, in numerous countries. Compared to conventional RT techniques, a higher RT dose is selectively delivered to the tumor, while the surrounding normal tissue receives a lower dose (18,19). Consequently, with 3D radiation therapy, the incidence of radiation-induced toxicities might reduce, and the treatment tolerance might improve. The modern RT techniques provide favorable technical support for the treatment for EC. Several studies have suggested that, with the improvements in RT techniques, dose-escalated RT achieves better local tumor control and more favorable survival outcomes, but opposite arguments also exist (10,14-17). Whether dose escalation of 3D radiotherapy is safe and effective, especially for ESCC, is still a subject of debate.

Given the discrepancies on the optimal dose for ESCC, we investigated the clinical effects of the RT dose escalation using modern RT techniques to treat of patients with non-operable ESCC, based on a multi-center database provided by Jing-Jin-Ji Esophageal and Esophagogastric Cancer Radiotherapy and Oncology Group (3JECROG).

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4672).

Methods

Data source

Data, including patients' demographics, disease characteristics, treatment details, tumor control, and survival outcomes, were obtained from 10 medical centers in China. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of National Cancer Center/Cancer

Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 17-089/1345). Patient data was retrieved from hospital medical record system, so an informed consent form was not required. The patient's personal data has been secured.

Patient selection

All patients enrolled were confirmed as newly diagnosed ESCC without other cancers or distant metastases between January 2002 and December 2016. The included patients met the following eligibility criteria: (I) age ≥18 years old; (II) pathologically confirmed as ESCC; (III) inoperable tumor or refusing an operation; (IV) disease staging based on the sixth edition of the American Joint Committee on Cancer (AJCC 6th) tumor node metastasis (TNM) stage classification, clinical stage of TanyNanyM$_0$ or M$_1$ with only supraclavicular or abdominal lymph node metastasis; (V) Karnofsky (KPS) score ≥70; (VI) life expectancy ≥3 months; (VII) initially received definitive RT of 3D conformal radiotherapy (3D-CRT) or IMRT.

A total of 2,762 ESCC patients were identified as the initial study population and were excluded if they met the following criteria: (I) non-SCC histology or other coexisting primary tumors; (II) prior thoracic radiotherapy or surgery; (III) radiation dose <40 or >72 Gy; (V) unconventional dose fractional RT; (V) missing clinical data.

Finally, a total of 2,469 ESCC patients treated with definitive RT were enrolled for retrospectively analysis, and were categorized into 5 groups in terms of equivalent dose in 2 Gy fractions (EQD$_2$): group 1 (40 Gy ≤ EQD$_2$ <60 Gy, n=350), group 2 (60 Gy ≤ EQD$_2$ <62 Gy, n=1,435), group 3 (62 Gy ≤ EQD$_2$ <64 Gy, n=254), group 4 (64 Gy ≤ EQD$_2$ <66 Gy, n=230) and group 5 (66 Gy ≤ EQD$_2$ ≤72 Gy, n=200).

Variables

Patients received a total RT dose of 40–72 Gy (1.8–2.2 Gy/fraction). Because there was nonuniformity in the RT planning parameters collected from the different participating institutions, we used EQD$_2$ to balance the discrepancies in RT dose-fraction among the medical centers. To evaluate the biologically effective dose (BED) in diverse dose-fractions, the linear-quadratic (LQ) model was applied to estimate equivalent radiotherapy schedules. RT doses were converted into the equivalent dose in 2 Gy fraction (EQD$_2$) using an α/β=10 and calculated using the prescribed $EQD_2 = Nd\,(1 + d/\alpha/\beta) / [1 + 2/\alpha/\beta]$ (20,21).

Treatment and follow-up

All patients had received radiotherapy delivered by 3DCRT or IMRT techniques. Gross tumor volume (GTV) was defined as any visible primary tumor plus metastatic lymph nodes detected by CT, esophagogram, or endoscopy. The clinical target volume (CTV) was obtained by expanding the GTV to a margin to 3.0–5.0 cm at the long axis and 0.8–1.0 cm at the lateral axis. The planning target volume (PTV) was reached by CTV plus a margin of 0.5 cm. The planning GTV (PGTV) was reached by GTV plus a margin of 1.0 cm. The sequential boost or simultaneous integrated boost approaches had been prescribed as the dose of 40.0–72 Gy to PGTV in 1.8–2.2 Gy fraction. Concurrent chemotherapeutic regimens were platin-based, including 5-FU-cisplatin, paclitaxel-cisplatin, and oxaliplatin-capecitabine. The patients were followed up every three months during the first two years, every six months in the third and fourth years, and then on a once-yearly basis. The follow-up examinations included routine laboratory tests, neck/chest/abdomen CT scans, cervical/abdominal lymph node ultrasound, barium swallow, and/or PET/CT. If suspicious recurrent lesions were detected by imaging, biopsy was immediately applied.

Statistical analysis

The end points of this analysis were overall survival (OS), progression-free survival (PFS), local-regional failure-free survival (LRFFS), and distant metastasis-free survival (DMFS). These were defined as the time from the first treatment to the last follow-up or death by any cause, the first instance of any progression, local-regional recurrence, and tumor metastasis, respectively. The Kaplan-Meier method was used to assess the OS, PFS, LRFFS, and DMFS. Survival difference among groups with different doses was analyzed using the log-rank test. The Cox regression model was employed to perform univariate and multivariate analyses. All statistical analyses were carried out with SPSS software (version 24, IBM SPSS, CA, USA). Statistical significance was determined by a two-sided P value of <0.05.

The penalized spline (P-spline) fit in the Cox model allowed the nonlinear relationships of RT dose with the logarithm [ln hazard ratio (HR)] of mortality, disease progression, local-regional recurrence (LRR), or distant metastasis (DM), to be estimated based on the full Cox

regression model adjusted for all covariates. P-spline was applied using the smooth HR package in R, version 3.2.3. The dfmacox (degrees of freedom in multivariate additive Cox models) function in the smoothHR package was used to obtain the optimal number of degrees of freedom in the extended Cox-type additive multivariate analysis.

Results

Patient characteristics and treatment

A total of 2,469 patients were included in the study, of whom 65.4% (1,614/2,469) were less than 70 years old and 68.7% (1,696/2,469) were male (*Table 1*). According to AJCC 6th stage classification, 74.0% (1,828/2,469) of the patients were in stages III or IV.

In terms of treatment, 46.4% (1,145/2,469) patients received 3D-CRT, and 53.6% (1,324/2,469) patients received IMRT. CCRT was received by 43.7% (1,078/2,469) patients, and 17.5% (433/2,469) patients received adjuvant chemotherapy. RT EQD_2 was in the range of 40–72 Gy, with a median dose was 60 Gy. The patients were further stratified into five subgroups based on the RT dose. The median follow-up time was 58.3 months [95% confidence interval (CI): 56.4–60.2 months]. As of the date cutoff, the median OS and PFS time were 24.3 months (95% CI: 22.5–26.2 months) and 18.0 months (95% CI: 16.4–19.6 months), respectively.

Dose-dependent effect of RT dose on survival

To assess the dose-dependent effect, RT dose was entered as a continuous variable into the Cox regression using P-splines in smoothHR to allow for the nonlinear relationships between the RT dose and end points to be identified. As shown in *Figure 1*, the risk (ln HR) of death decreased sharply in the range of 60 to 62 Gy, and increased slightly when dose was elevated beyond 62 Gy. Similar tendencies could been seen in the dose-dependent effect of RT for PFS, LRFFS and DMFS, though they were not as constant enough compared with OS (*Figures S1-S3*). These results demonstrated the dose-dependent effect of RT dose on the survival and indicated that a dose ≥60 Gy was the optimal dose in treating inoperable ESCC.

Univariate analyses

The result of the univariate analysis indicated that improved OS was closely associated with age <70 years old, female sex, cervical/upper esophagus location, early (I–II) AJCC clinical stage, lower T stage, node negative status, GTV volume ≤53 cm^3, receiving IMRT, receiving CCRT or adjuvant chemoradiotherapy, and RT dose in the range of 60–62 and 62–64 Gy (*Table 2*).

Multivariable analyses

All factors with statistical significance in the univariate analysis were then included into the multivariate analysis. Multivariate cox regression analysis showed that age <70 years old, cervical/upper esophagus location, early (I–II) AJCC clinical stage, node negative status, GTV volume ≤53 cm^3, receiving CCRT, and a RT dose from 60–62 Gy were still associated with better survival outcomes (*Table 2*). Multivariate analysis indicated that the risk of death decreased significantly (HR: 0.85, 95% CI: 0.73–0.98, P=0.028) in patients who received an RT dose in the range of 60–62 Gy compared with patients who received 40–60 Gy, which suggested that RT dose was an independent factor associated with OS (*Table 2*). Furthermore, the 60–62 Gy group also exhibited improved PFS, LRFFS, and DMFS compared with the 40–60 Gy group (PFS, HR: 0.77, 95% CI: 0.67–0.90, P=0.001; LRFFS, HR: 0.83, 95% CI: 0.69–0.99, P=0.033; DMFS, HR: 0.74, 95% CI: 0.58–0.93, P=0.009) (*Tables S1-S3*). Overall, RT dose was a significant independent prognostic factor for OS, PFS, LRFFS, and DMFS.

Disease control and survival

The 1-, 2-, 3- and 5-year OS rates for the entire cohort were 73.1%, 50.4%, 41.1%, and 33.2%, respectively; PFS was 60.3%, 43.4%, 37.0%, and 32.2%, respectively; LRFFS was 70.5%, 56.8%, 50.6%, and 46.3%, respectively; and DMFS was 84.0%, 75.8%, 73.1%, and 69.7%, respectively. The median OS, PFS, and LRFFS were 24.35, 18.04, and 38.28 months, respectively. In the present study, the 3-year OS rates for the 40–60, 60–62, 62–64, 64–66, and 66–72 Gy groups were 34.6%, 42.0%, 47.6%, 37.2%, and 41.1%, and the median OS was 19.8, 24.1, 24.8, 30.8, 25.2, and 22.8 months, respectively. There were significant differences in OS (P=0.0044, *Figure 2A*), PFS (P=0.0003, *Figure 2B*), and DMFS (P=0.0033, *Figure 3A*), and a tendency toward statistical difference in LRFFS (P=0.0822, *Figure 3B*) among the dose groups.

Table 1 Patient, disease, and treatment characteristics

Characteristics	Total	40≤D[#]<60 Gy	60≤D[#]<62 Gy	62≤D[#]<64 Gy	64≤D[#]<66 Gy	66≤D[#]≤72 Gy
	2,469 (100.0%)	350 (14.2%)	1,435 (58.1%)	254 (10.3%)	230 (9.3%)	200 (8.1%)
Age at diagnosis, years						
<70	1,614 (65.4%)	230 (65.7%)	910 (63.4%)	176 (69.3%)	155 (67.4%)	143 (71.5%)
≥70	855 (34.6%)	120 (34.3%)	525 (36.6%)	78 (30.7%)	75 (32.6%)	57 (28.5%)
Median (range)	65 (30–90)	65 (35–90)	65 (30–90)	63 (39–88)	65 (36–87)	64 (34–84)
Sex						
Male	1,696 (68.7%)	255 (72.9%)	989 (68.9%)	159 (62.6%)	150 (65.2%)	143 (71.5%)
Female	773 (31.3%)	95 (27.1%)	446 (31.1%)	95 (37.4%)	80 (34.8%)	57 (28.5%)
Tumor location						
Cervical/upper	823 (33.3%)	83 (23.7%)	449 (31.3%)	104 (40.9%)	87 (37.8%)	100 (50.0%)
Middle	1,125 (45.6%)	158 (45.1%)	691 (48.2%)	104 (40.9%)	99 (43.0%)	73 (36.5%)
Lower/GEJ	521 (21.1%)	109 (31.1%)	295 (20.6%)	46 (18.1%)	44 (19.1%)	27 (13.5%)
AJCC clinical stage						
I–II	641 (26.0%)	71 (20.3%)	380 (26.5%)	78 (30.7%)	69 (30.0%)	43 (21.5%)
III–IV	1,828 (74.0%)	279 (79.7%)	1,055 (73.5%)	176 (69.3%)	161 (70.0%)	157 (78.5%)
T stage						
T1	35 (1.4%)	3 (0.9%)	20 (1.4%)	4 (1.6%)	4 (1.7%)	4 (2.0%)
T2	415 (16.8%)	50 (14.3%)	247 (17.2%)	47 (18.5%)	46 (20.0%)	25 (12.5%)
T3	910 (36.9%)	153 (43.7%)	555 (38.7%)	80 (31.5%)	61 (26.5%)	61 (30.5%)
T4	1,109 (44.9%)	144 (41.1%)	613 (42.7%)	123 (48.4%)	119 (51.7%)	110 (55.0%)
N stage						
N0	782 (31.7%)	88 (25.1%)	422 (29.4%)	102 (40.2%)	94 (40.9%)	76 (38.0%)
N1	1,687 (68.3%)	262 (74.9%)	1013 (70.6%)	152 (59.8%)	136 (59.1%)	124 (62.0%)
GTV volume, cm^3						
≤53	1,515 (61.4%)	170 (48.6%)	892 (62.2%)	178 (70.1%)	155 (67.4%)	120 (60.0%)
>53	954 (38.6%)	180 (51.4%)	543 (37.8%)	76 (29.9%)	75 (32.6%)	80 (40.0%)
Radiation modality						
3DCRT	1,145 (46.4%)	152 (43.4%)	655 (45.6%)	96 (37.8%)	142 (61.7%)	100 (50.0%)
IMRT	1,324 (53.6%)	198 (56.6%)	780 (54.4%)	158 (62.2%)	88 (38.3%)	100 (50.0%)
Radiation dose modality						
SB-IMRT/SIB-IMRT	873 (35.4%)	129 (36.9%)	418 (29.1%)	164 (64.6%)	68 (29.6%)	94 (47.0%)
Others	1,596 (64.6%)	221 (63.1%)	1,017 (70.9%)	90 (35.4%)	162 (70.4%)	106 (53.0%)
CCRT						
No	1,310 (53.1%)	190 (54.3%)	725 (50.5%)	127 (50.0%)	150 (65.2%)	118 (59.0%)
Yes	1,078 (43.7%)	151 (43.1%)	655 (45.6%)	115 (45.3%)	77 (33.5%)	80 (40.0%)
Unknown	81 (3.3%)	9 (2.6%)	55 (3.8%)	12 (4.7%)	3 (1.3%)	2 (1.0%)
Adjuvant CT						
No	1,955 (79.2%)	284 (81.1%)	1,109 (77.3%)	205 (80.7%)	188 (81.7%)	169 (84.5%)
Yes	433 (17.5%)	57 (16.3%)	271 (18.9%)	37 (14.6%)	39 (17.0%)	29 (14.5%)
Unknown	81 (3.3%)	9 (2.6%)	55 (3.8%)	12 (4.7%)	3 (1.3%)	2 (1.0%)

[#], equivalent dose in 2 Gy fractions (EQD_2). AJCC, American Joint Committee Cancer; GTV, gross tumor volume; 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; SB-IMRT, sequential boost-IMRT; SIB-IMRT, simultaneous integrated boost-IMRT; CCRT, concurrent chemoradiotherapy; CT, chemotherapy.

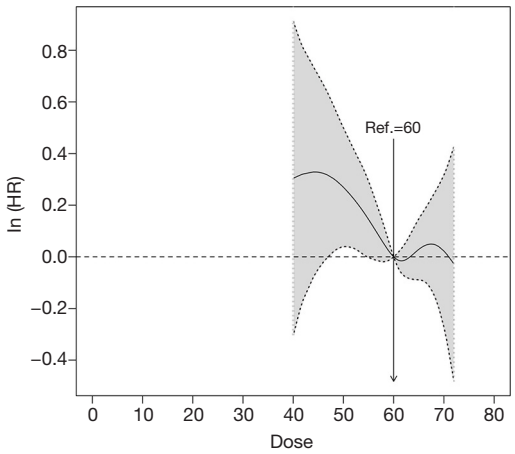

Figure 1 Estimated logarithm hazard ratios (HRs) (solid lines) with 95% confidence intervals (shading) for the association of RT dose in grays with OS. The effects of RT on the risk of mortality are modeled with a penalized spline (P-spline) expansion, with RT dose as a continuous covariate. A dose of 60 Gy (indicated by the vertical line), as the common cutoff value in clinical practice, was used as the reference value for calculating the HRs.

Discussion

Based on data sourced provided by 3JECROG, the association between RT dose (as a continuous covariate) and survival outcomes in ESCC was explored in this retrospective study (3JECROG R-03). RT dose was revealed to be an important prognostic factor for OS, PFS, LRFFS, and DMFS, and 60 Gy or above was the best optimal RT dose for patients who received radical radiotherapy delivered through modern RT techniques.

Our study showed that patients who received an RT dose of 60–62 Gy exhibited improved survival. However, the RTOG 9405 study demonstrated that high RT dose (64.8 Gy) was responsible for increased treatment-related mortality, and that no local control and survival benefit were observed compared with the standard dose arm (50.4 Gy) (5). The RTOG 9405 trial included patients with either SCC or adenocarcinoma, each of whom received conventional RT. The RT target varied in margin in different dose arms. Although more treatment-related deaths were observed in the high-dose arm (11 *vs.* 2), 7 of the 11 treatment-related

Table 2 Univariable and multivariable analysis of overall survival for all patients

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age at diagnosis, years						
<70	1.00	–	–	1.00	–	–
≥70	1.12	1.01–1.24	0.029	1.13	1.01–1.26	0.036
Sex						
Male	1.00	–	–	1.00	–	–
Female	0.86	0.78–0.96	0.008	0.93	0.83–1.04	0.194
Tumor location						
Cervical/upper	1.00	–	–	1.00	–	–
Middle	1.38	1.23–1.55	<0.001	1.27	1.12–1.43	<0.001
Lower/GEJ	1.35	1.18–1.56	<0.001	1.22	1.06–1.42	0.007
AJCC clinical stage						
I–II	1.00	–	–	1.00	–	–
III–IV	1.67	1.45–1.89	<0.001	1.23	1.01–1.49	0.041
T stage						
T1	1.00	–	–	1.00	–	–
T2	1.46	0.88–2.42	0.144	1.31	0.79–2.19	0.292
T3	1.73	1.05–2.84	0.031	1.34	0.81–2.23	0.260
T4	2.26	1.38–3.70	0.001	1.54	0.92–2.58	0.104

Table 2 *(continued)*

Table 2 *(continued)*

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
N stage						
N0	1.00	–	–	1.00	–	–
N1	1.52	1.36–1.70	<0.001	1.29	1.13–1.47	<0.001
GTV volume, cm^3						
≤53	1.00	–	–	1.00	–	–
>53	1.62	1.46–1.79	<0.001	1.37	1.23–1.53	<0.001
Radiation modality						
3DCRT	1.00	–	–	1.00	–	–
IMRT	0.87	0.78–0.96	0.005	1.00	0.89–1.12	0.989
Radiation dose modality						
SB-IMRT/SIB-IMRT	1.00	–	–	–	–	–
Others	1.02	0.92–1.14	0.677	–	–	–
CCRT						
No	1.00	–	–	1.00	–	–
Yes	0.84	0.76–0.93	0.001	0.86	0.77–0.97	0.013
Unknown	0.64	0.47–0.88	0.006	0.68	0.49–0.94	0.019
Adjuvant CT						
No	1.00	–	–	1.00	–	–
Yes	0.87	0.76–1.00	0.049	0.93	0.81–1.07	0.320
Unknown	0.68	0.50–0.93	0.014	0.68	0.49–0.94	0.019
EQD2, Gy						
40≤ $D^{\#}$ <60	1.00	–	–	1.00	–	–
60≤ $D^{\#}$ <62	0.78	0.68–0.91	0.001	0.85	0.73–0.98	0.028
62≤ $D^{\#}$ <64	0.70	0.57–0.86	0.001	0.82	0.67–1.02	0.070
64≤ $D^{\#}$ <66	0.87	0.71–1.06	0.165	1.01	0.82–1.24	0.940
66≤ $D^{\#}$ ≤72	0.89	0.72–1.11	0.297	0.98	0.79–1.22	0.840

$^{\#}$, equivalent dose in 2 Gy fractions (EQD_2). AJCC, American Joint Committee Cancer; GTV, gross tumor volume; 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; SB-IMRT, sequential boost-IMRT; SIB-IMRT, simultaneous integrated boost-IMRT; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; EQD_2, equivalent dose in 2 Gy fractions.

deaths occurred prior to a dose of 50.4 Gy being reached. In our study, we focused only on ESCC, which exhibits different biological characteristics and treatment response from adenocarcinoma. More importantly, all of the included patients were treated using modern RT techniques, including 3D-CRT and IMRT. These RT techniques dramatically reduced the incidence of toxicity because of more precise delivery RT dose to tumor and sparing the surrounding normal tissue.

A growing number of studies conducted recently have evaluated the effect of RT dose escalation on survival benefit in esophageal carcinoma by utilizing modern techniques (*Table 3*) (10,12,14-16,22). He *et al.* retrospectively assessed the treatment outcomes of 3D-CRT in ESCC patients. A high RT dose (>50.4 Gy) was found to significantly improve local tumor control compared with a low RT dose (≤50.4 Gy) (17.9% *vs.* 34.3%, P=0.024). However, there was no difference in five-year OS between the two groups

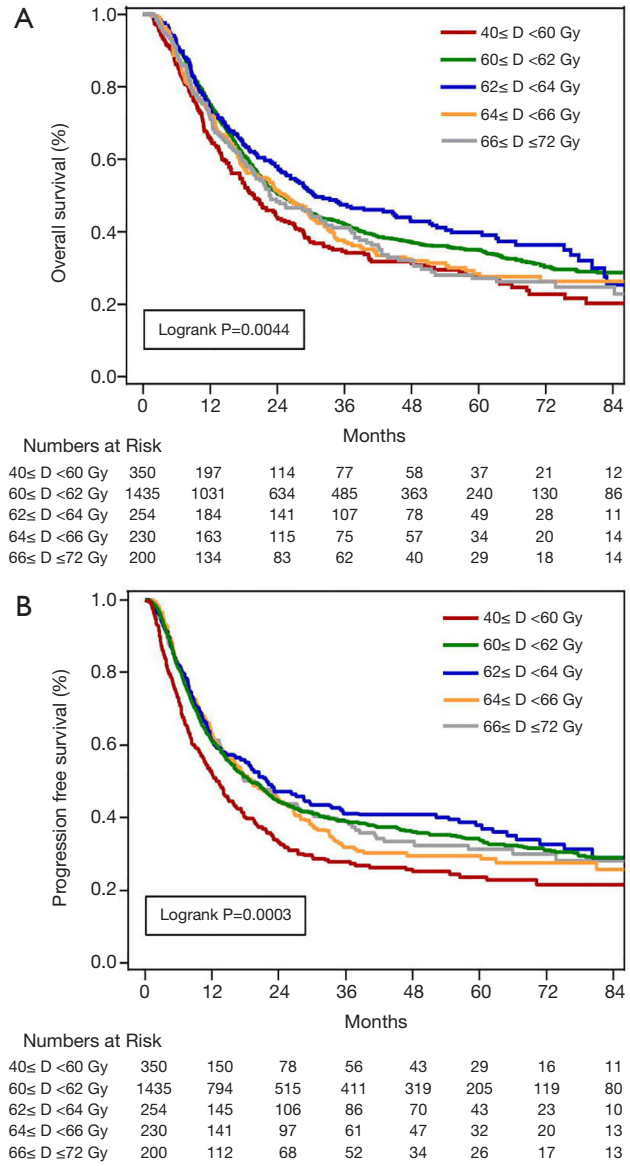

Figure 2 Kaplan-Meier curves comparing overall survival (OS) (A) and progression-free survival (PFS) (B). By EDQ2, there were significant differences in OS (P=0.0044) and PFS (P=0.0003).

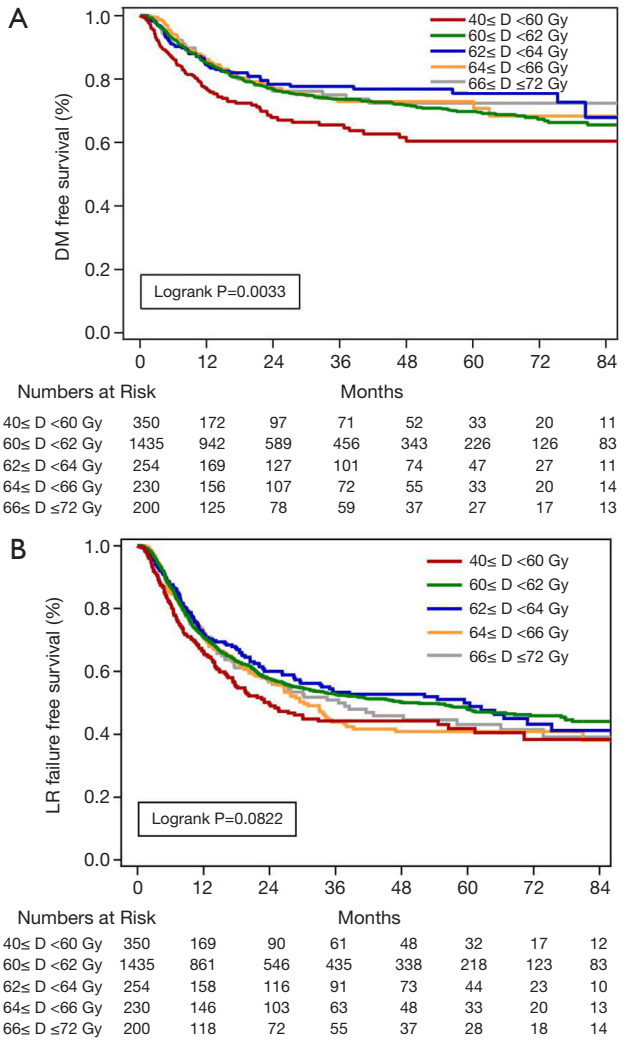

Figure 3 Kaplan-Meier curves comparing distant metastasis-free survival (A) and local-regional failure-free survival (B). By EDQ2, there were a tendency toward difference in (DMFS) (P=0.0033) and significant differences in distant metastasis-free survival LRFFS (P=0.0822).

(P=0.617) (10). Other retrospectively analyses of ESCC have also indicated that a higher RT dose results in more favorable survival outcomes (14-16). Consistently, a meta-analysis of 28 studies identified the clinical outcomes between high RT dose (≥60 Gy) and the conventional dose. The results suggested that CCRT with a high dose improved clinical outcomes compared with the conventional dose, especially in ESCC (17). As modern RT techniques were used in all studies mentioned above, treatment-related toxicity reached an acceptable level and no treatment-related deaths occurred. The survival rate in the high dose group was also increased with the use of 3D-CRT or IMRT compared with the use of 2D-RT (23). However, Ren *et al.* noted that an RT dose above 60 Gy significantly increased the incidence of conditions such as severe radiation esophagitis, radiation pneumonitis, hemorrhage, and fistula (16). The findings of this present multi-center respective study

Table 3 Studies regarding high-dose and conventional-dose radiotherapy for patients with esophageal carcinoma utilizing modern techniques

Authors	Radiation dosage (Gy)	No. of patients	Histology SCC	AC	others	LCR (%)	P value	OS	P value
Minsky *et al.* (5)	50.4	109	92	17	0	56 (LFR)	0.71	40 (2 years)	>0.05
	64.8	109	95	14	0	52		31	
Brower *et al.* (22)	50–50.4	3,821	1,489	2,211	121	–	–	42.8 (2 years)	0.53
He *et al.* (10)	>50.4	3,033	1,560	1,391	82	–	–	41.8	–
	≤50.4	137	137	0	0	34.3 (LFR)	0.02	33.0 (5 years)	0.62
Kim *et al.* (12)	>50.4	56	56	0	0	17.9	<0.01	41.7	0.04
	<60	120	117	3	0	50.3 (2 years)		22.3 (MST)	
	≥60	116	113	3	0	69.1		35.1	
Ren *et al.* (16)	50–50.4	190	190	0	0	29.8 (10 years)	0.03	24.0 (10 years)	0.001
	60	190	190	0	0	52.0		13.3	
Chang *et al.* (14)	<60	1,134	1,134	0	0	–	–	26.74 (2 years)	<0.01
	≥60	927	927	0	0	–	–	35.47	
Chen *et al.* (15)	50–50.4	324	324	0	0	–	–	14 (5 years)	<0.05
	≥60	324	324	0	0	–	–	22	

SCC, squamous cell carcinoma; AC, adenocarcinoma; LCR, local control rate; LFR, local failure rate; OS, overall survival; MST, median survival time.

support those of previous studies. Improved survival was found when RT dose was raised above 60 Gy. When the RT dose exceeded 64 Gy, the OS rate decreased. Treatment-related toxicity was most likely one of the most important factors leading to worse survival.

Despite radical radiotherapy treatment, owing to the high local recurrence rate, patients with locally advanced esophageal cancer usually have a poor prognosis (5,6). The LRR rate of ESCC is higher than that of esophageal adenocarcinoma (24,25). Several studies have verified that RT dose escalation benefits the local control rates, especially in ESCC (12,26-31). Zhang *et al.* investigated 69 patients with stage II–III unresectable esophageal cancer treated with CCRT. The patients in the high RT dose (>51 Gy) group had better 3-year local control rate (36% *vs.* 19%) and DFS (25% *vs.* 10%) than those in the low RT dose (≤51 Gy) group, although the OS was not significantly different between these two groups (13% *vs.* 3%, P=0.054) (26). Kim *et al.* found that patients in the high RT dose (≥60 Gy) group had significantly better 2-year LRC (69.1% *vs.* 50.3%, P=0.002), median PFS (16.7 *vs.* 11.7 months, P=0.029), and median OS (35.1 *vs.* 22.3 months, P=0.043) than the low RT dose group (12). Furthermore, RT doses of at least 60 Gy have been reported to improve OS and locoregional control, especially in Asian countries (32). A high RT dose (≥60 Gy) was recommended for locally advanced esophageal cancer in several Asian countries (33,34). These previous studies support our findings that RT ≥60 Gy exhibits better local control and OS benefits than RT dose <60 Gy.

There were some limitations to our analysis owing to the retrospective nature of this database cohort study. Firstly, a selection bias in various RT dose subgroups and chemotherapy regimens may have existed. Secondly, as half of the patients were stratified in the 60–62 Gy group, generalizability in the data analysis might have been affected. Thirdly, the RT biological effect on survival might have been affected by inconsistent fraction dose, dose rate, and overall treatment time (35). In the present study, we used EQD_2 to estimate equivalent RT schedules in various institutions. Larger-scale, prospective, randomized trials are needed to confirm our results. Currently, there are two ongoing Chinese clinical trials to compare high-dose RT (60–61.2 Gy) with the standard-dose (50–50.4 Gy) for the treatment of inoperable EC patients receiving CCRT using IMRT.

Conclusions

In conclusion, our results suggest RT dose to be a significant prognostic factor for survival in patients with locally advanced ESCC. Within a certain RT dose, higher RT dose yields more favorable survival outcomes for ESCC patients treated with definitive RT using modern techniques, and 60 Gy or above was the optimal RT dose.

Acknowledgments

Funding: This study was supported by the National Nature Science Foundation of China (81872462); and the Clinical Trial Supporting Foundation of Tianjin Medical University Cancer Institute & Hospital (Grant No.C1707).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4672

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-4672

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4672). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 17-089/1345). Patient data was retrieved from hospital medical record system, so an informed consent form was not required. The patient's personal data has been secured.

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Cite this article as: Zhang W, Zhao J, Han W, Zhang H, Wang X, Li C, Chen J, Wang X, Zhao Y, Qiao X, Zhou Z, Han C, Zhu S, Shen W, Wang L, Ge X, Sun X, Zhang K, Hu M, Li L, Hao C, Li G, Xu Y, Wang Y, Lu N, Liu M, Qian S, Xiao Z, Wang P, Pang Q. Dose escalation of 3D radiotherapy is effective for esophageal squamous cell carcinoma: a multicenter retrospective analysis (3JECROG R-03). Ann Transl Med 2020;8(18):1140. doi: 10.21037/atm-20-4672

Supplementary

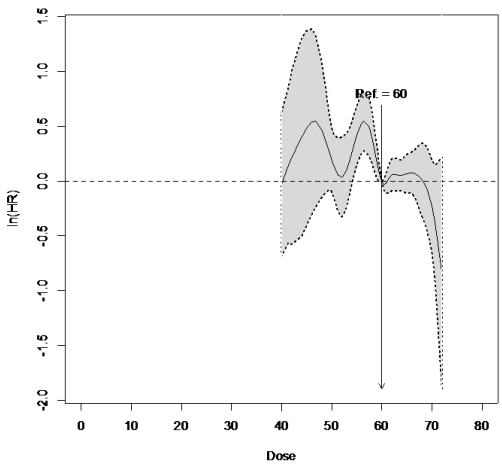

Figure S1 Dose-dependent effect of radiotherapy on progression-free survival.

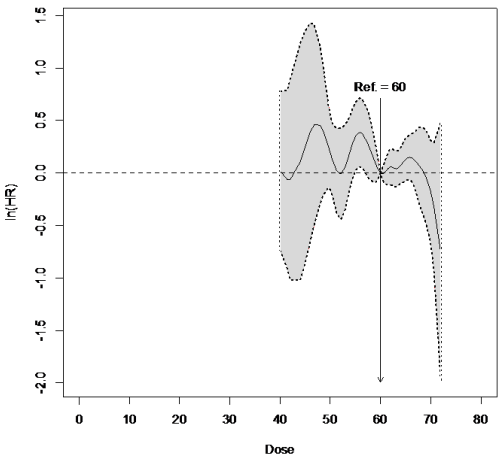

Figure S3 Dose-dependent effect of radiotherapy on local-regional control.

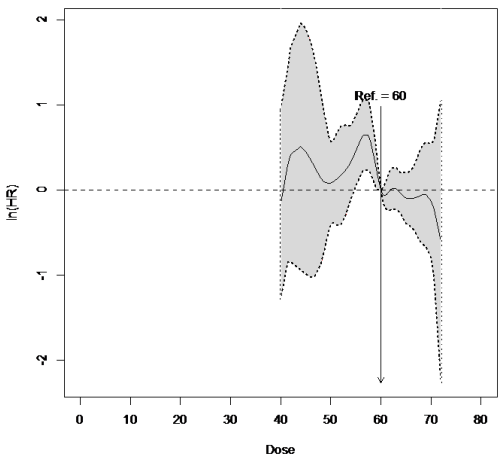

Figure S2 Dose-dependent effect of radiotherapy on distant metastasis.

Table S1 Univariable and multivariable analysis of progression–free survival for all patients

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age at diagnosis, years						
<70	1.00			–	–	–
≥70	1.05	0.94–1.16	0.398	–	–	–
Sex				–	–	–
Male	1.00			1.00		
Female	0.84	0.76–0.94	0.002	0.91	0.81–1.02	0.088
Tumor location						
Cervical/upper	1.00			1.00		
Middle	1.27	1.13–1.43	<0.001	1.19	1.06–1.34	0.003
Lower/GEJ	1.27	1.11–1.46	0.001	1.19	1.03–1.37	0.021
AJCC clinical stage						
I–II	1.00			1.00		
III–IV	1.63	1.44–1.84	<0.001	1.19	0.98–1.45	0.081
T Stage						
T1	1.00			1.00		
T2	1.42	0.84–2.40	0.188	1.23	0.73–2.09	0.431
T3	1.85	1.11–3.10	0.018	1.38	0.82–2.34	0.229
T4	2.19	1.31–3.65	0.003	1.48	0.87–2.54	0.151
N Stage						
N0	1.00			1.00		
N1	1.50	1.34–1.68	<0.001	1.28	1.11–1.46	<0.001
GTV volume, cm^3						
≤53	1.00			1.00		
>53	1.52	1.38–1.69	<0.001	1.30	1.16–1.45	<0.001
Radiation modality						
3DCRT	1.00			–	–	–
IMRT	1.00	0.90–1.10	0.925	–	–	–
Radiation dose modality						
SB-IMRT/SIB-IMRT	1.00			–	–	–
Others	0.96	0.86–1.07	0.474	–	–	–
CCRT						
No	1.00			–	–	–
Yes	1.00	0.90–1.11	0.962	–	–	–
Unknown	1.10	0.83–1.46	0.502	–	–	–
Adjuvant CT						
No	1.00			–	–	–
Yes	0.99	0.87–1.13	0.887	–	–	–
Unknown	1.10	0.83–1.45	0.501	–	–	–
EQD2, Gy						
40≤ D <60	1.00			1.00		
60≤ D <62	0.73	0.63–0.84	<0.001	0.77	0.67–0.90	0.001
62≤ D <64	0.68	0.55–0.83	<0.001	0.78	0.63–0.96	0.018
64≤ D <66	0.77	0.63–0.94	0.012	0.88	0.72–1.09	0.236
66≤ D ≤72	0.74	0.59–0.92	0.007	0.80	0.64–1.00	0.053

AJCC, American Joint Committee Cancer; GTV, gross tumor volume; 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; SB-IMRT, sequential boost-IMRT; SIB-IMRT, simultaneous integrated boost-IMRT; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; EQD_2, equivalent dose in 2 Gy fractions.

Table S2 Univariable and multivariable analysis of local-regional failure-free survival for all patients

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age at diagnosis, years						
<70	1.00			–	–	–
≥70	1.07	0.95–1.21	0.256	–	–	–
Sex						
Male	1.00			–	–	–
Female	0.93	0.82–1.05	0.229	–	–	–
Tumor location						
Cervical/upper	1.00			1.00		
Middle	1.23	1.08–1.41	0.002	1.19	1.04–1.37	0.012
Lower/GEJ	1.11	0.94–1.31	0.230	1.07	0.90–1.27	0.478
AJCC clinical stage						
I–II	1.00			1.00		
III–IV	1.40	1.22–1.62	<0.001	1.09	0.87–1.37	0.451
T stage						
T1	1.00			1.00		
T2	1.10	0.64–1.90	0.732	1.00	0.58–1.73	0.996
T3	1.36	0.80–2.32	0.258	1.14	0.66–1.98	0.637
T4	1.57	0.92–2.66	0.098	1.22	0.69–2.14	0.495
N stage						
N0	1.00			1.00		
N1	1.29	1.13–1.47	<0.001	1.16	0.99–1.35	0.074
GTV volume, cm^3						
≤53	1.00			1.00		
>53	1.38	1.23–1.56	<0.001	1.25	1.10–1.43	0.001
Radiation modality						
3DCRT	1.00			–	–	–
IMRT	0.90	0.88–1.11	0.856	–	–	–
Radiation dose modality						
SB-IMRT/SIB-IMRT	1.00			–	–	–
Others	0.95	0.84–1.08	0.462	–	–	–
CCRT						
No	1.00					
Yes	0.94	0.83–1.06	0.302	–	–	–
Unknown	1.11	0.81–1.53	0.528	–	–	–
Adjuvant CT						
No	1.00			–	–	–
Yes	1.06	0.91–1.24	0.443	–	–	–
Unknown	1.15	0.84–1.58	0.381	–	–	–
EQD2, Gy						
40≤ D <60	1.00			1.00		
60≤ D <62	0.79	0.66–0.94	0.009	0.83	0.69–0.99	0.033
62≤ D <64	0.76	0.60–0.97	0.027	0.84	0.66–1.07	0.154
64≤ D <66	0.89	0.70–1.13	0.319	0.98	0.77–1.17	0.864
66≤ D ≤72	0.85	0.66–1.10	0.226	0.91	0.45–1.13	0.454

AJCC, American Joint Committee Cancer; GTV, gross tumor volume; 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; SB-IMRT, sequential boost-IMRT; SIB-IMRT, simultaneous integrated boost-IMRT; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; EQD_2, equivalent dose in 2 Gy fractions.

Table S3 Univariable and multivariable analysis of distant metastasis-free survival for all patients

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age at diagnosis, years						
<70	1.00			–	–	–
≥70	0.95	0.80–1.14	0.589	–	–	–
Sex						
Male	1.00			1.00		
Female	0.80	0.66–0.96	0.014	0.87	0.72–1.05	0.153
Tumor location						
Cervical/upper	1.00			1.00		
Middle	1.35	1.11–1.64	0.003	1.22	1.00–1.49	0.050
Lower/GEJ	1.53	1.22–1.92	<0.001	1.41	1.11–1.79	0.005
AJCC clinical stage						
I–II	1.00			1.00		
III–IV	2.36	1.88–2.97	<0.001	1.65	1.16–2.33	0.005
T stage						
T1	1.00			1.00		
T2	3.45	0.85–14.06	0.084	2.81	0.69–11.49	0.150
T3	5.09	1.26–20.47	0.022	2.76	0.68–11.29	0.157
T4	6.10	1.52–24.52	0.011	2.96	0.72–12.18	0.133
N stage						
N0	1.00			1.00		
N1	2.10	1.71–2.57	<0.001	1.57	1.24–2.00	<0.001
GTV volume, cm^3						
≤53	1.00			1.00		
>53	1.71	1.45–2.02	<0.001	1.32	1.11–1.58	0.002
Radiation modality						
3DCRT	1.00			–	–	–
IMRT	0.95	0.81–1.13	0.565	–	–	–
Radiation dose modality						
SB-IMRT/SIB-IMRT	1.00			–	–	–
Others	1.06	0.89–1.26	0.537	–	–	–
CCRT						
No	1.00			–	–	–
Yes	1.02	0.86–1.21	0.816	–	–	–
Unknown	1.33	0.88–2.01	0.182	–	–	–
Adjuvant CT						
No	1.00			1.00		
Yes	0.83	0.66–1.05	0.119	0.82	0.65–1.03	0.094
Unknown	1.28	0.85–1.92	0.247	1.53	1.01–2.32	0.045
EQD2, Gy						
40≤ D <60	1.00					
60≤ D <62	0.67	0.53–0.84	0.001	0.74	0.58–0.93	0.009
62≤ D <64	0.59	0.42–0.82	0.002	0.72	0.51–1.01	0.056
64≤ D <66	0.63	0.45–0.88	0.008	0.78	0.55–1.10	0.151
66≤ D ≤72	0.62	0.43–0.89	0.010	0.72	0.49–1.04	0.080

AJCC, American Joint Committee Cancer; GTV, gross tumor volume; 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; SB-IMRT, sequential boost-IMRT; SIB-IMRT, simultaneous integrated boost-IMRT; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; EQD_2, equivalent dose in 2 Gy fractions.