

Intensity-modulated radiotherapy with more than 60 Gy improved the survival of inoperable patients with locally advanced esophageal squamous cell carcinoma: a population-based real-world study

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Research

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Abstract

Background

Intensity-modulated radiotherapy (IMRT) is widely applied during the treatment of esophageal squamous cell carcinoma (ESCC), but the optimal radiation dose still lacks a consensus. The aim of this study was to explore the optimal radiation dose for inoperable locally advanced ESCC patients treated with IMRT in a real-world clinical setting.

Methods

A total of 90 inoperable ESCC patients with locally advanced stages of I-IVA treated with IMRT in our institute between February 1, 2014 and June 30, 2019 were included in this retrospective study. Sixty patients had received > 60 Gy (high dose group) and 30 patients had received ≤ 60 Gy (low dose group). The median radiation dose was 66 Gy (range: 61–70 Gy) and 50.2 Gy (range: 40–60 Gy), respectively. Concurrent chemotherapies were platinum-based regimens.

Results

The median progression free survival (PFS) and overall survival (OS) of all patients were 7.6 and 14.1 months, respectively. Patients in the high dose group exhibited a significantly better PFS (1-year PFS 34.6% vs 22.8%; 2-year PFS 11.9% vs 0%, $P = 0.008$) and OS (1-year OS 57.5% vs 39.5%; 2-year OS 31.4% vs 15.8%, $P = 0.007$). The median PFS in the high and low dose groups were 8.1 and 6.1 months, and the median OS were 15.4 and 8.5 months, respectively. Multivariate Cox analysis showed that radiation dose (> 60 Gy vs ≤ 60 Gy) was independently prognostic factor for OS (HR: 0.44; 95% CI: 0.22–0.89; $P = 0.021$), but not for PFS (HR: 0.56; 95% CI: 0.31–1.02; $P = 0.058$). There was no significant difference in treatment-related toxicities of grade ≥ 3 between the 2 groups ($P = 0.402$).

Conclusion

This retrospective study confirmed that higher radiation dose (> 60 Gy) resulted in better survival outcomes for inoperable patients with locally advanced ESCC treated with IMRT.

Introduction

Esophageal cancer (EC) is the sixth most common cause of cancer death in the world [1, 2]. In Eastern Europe and Asia, the main types of pathology in EC patients are esophageal squamous cell carcinoma (ESCC) [3]. Most ESCC patients are at advanced stages when diagnosed, resulting in poor life quality. National Comprehensive Cancer Network (NCCN) recommend chemoradiotherapy (CRT) as the standard treatment for locally advanced EC patients with the radiation dose of 50-50.4 Gy [4]. This recommendation is based on the RTOG9405 prospective randomized clinical trial results. In this prospective phase III randomized controlled trial [5], 109 patients were included in the high (fluorouracil + cisplatin + 64.8 Gy) and low dose groups (fluorouracil + cisplatin + 50.4 Gy). There was no significant difference in the median overall survival (OS) (13.0 vs 18.1 months), 2-year OS rate (31% vs 40%) or local control rate (LCR) (56% vs 52%) between the 2 groups. Therefore, lower radiation dose at 50-50.4 Gy was recommended.

Although the RTOG9405 study suggested no significant advantage in the high dose group, it was based on 2-dimensional radiotherapy (2DRT). Since the LCR remained low in EC, there are increasing debate on the optimal radiation dose. For instance, Zhang et al. [6] reported that > 51 Gy (high dose) had significantly better LCR than ≤ 51 Gy (lower dose) in EC patients treated with 2DRT or 3-dimensional conformal radiotherapy (3DCRT) ($P = 0.01$). However, whether higher dose would be more favorable was not clear. Hurmuzlu et al. [7] retrospectively analysed 46 EC patients at stages IIA-III, and

found that high dose (66 Gy)-related toxicities were significantly increased and the survival rates were not improved compared with the low dose.

As IMRT delivers higher dose within the tumor and protect the critical organs around the tumor better, it is widely used to treat EC and improves efficacy. Lin et al. [8] conducted a study with 676 nonrandomized EC patients to estimate the survival effects of 3DCRT and IMRT. The results suggested significantly lower risk of dying, lower risk of cardiac death, higher rates of OS, higher rates of locoregional control (LRC) after IMRT than 3DCRT. Whether higher dose delivered by IMRT could improve clinical outcomes reemerge as an important question in esophageal cancer treatment. In such setting, Chang et al. [9] firstly retrospectively compared radiation dose ≥ 60 Gy versus < 60 Gy in 2061 thoracic esophageal squamous cell carcinoma (TESCC) treated with IMRT. The 2-year OS rate of the high dose group (≥ 60 Gy) was significantly higher than that in the low dose group (< 60 Gy) (35.47% vs 26.74%, $P < 0.0001$). However, Chang et al. [9] only included patients at relatively earlier stages of IIA-III C. The cervical EC was not investigated in this study. Moreover, the database used for this study failed to provide detailed information of the patients, such as tumor length, clinical N stage and clinical T stage, as well as progression free survival (PFS), LRC and distant metastasis free survival (DMFS).

In our institution, definitive radiotherapy with or without chemotherapy has long been the preferred approach for the cervical EC patients. In this retrospective study, we initially explored the optimal radiation dose for ESCC patients at locally advanced stages of III-IVA with IMRT, and provided detailed information of clinicopathological, OS, PFS, LRC and DMFS. This finding prompted us that higher radiation dose > 60 Gy would be necessary for inoperable locally advanced ESCC patients treated with IMRT in a real-world clinical setting.

Methods

Patient selection and pre-treatment evaluation

The study flow diagram is shown in Fig. 1. A total of 90 patients with pathologically confirmed inoperable ESCC and without known metastases were recruited from the Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University from February 1, 2014 to June 30, 2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Zhongnan hospital of Wuhan University (2020105-1), and the requirement for informed consent was waived because of the retrospective nature of the research. Cancer stages were determined based on the AJCC/UICC 8th edition [10]. The inclusion criteria were as follows: (a) patients with pathologically confirmed ESCC; (b) inoperable patients treated with radiotherapy or CRT using IMRT technique; (c) patients with complete data of clinicopathological information, radiation dose, and serum hemoglobin levels; (d) patient without clinical evidence of distant or retroperitoneal lymph node metastasis; (e) patient without coexisting malignancies.

Pre-treatment evaluation included a medical history collection and physical examination, focusing on performance status and a history of dysphagia. Laboratory studies included a complete blood cell count and blood chemistries. Barium swallow, chest computed tomography (CT) and transesophageal endoscopic ultrasonography were performed to assess the clinical T and N stages. Positron emission tomography (PET)-CT, bone and abdomen CT, and brain magnetic resonance imaging (MRI) were performed to evaluate distant and retroperitoneal lymph node metastasis prior to treatment.

Treatment approaches

Patients were treated 5 days per week at 1.8-2.0 Gy/fraction, one fraction/day. The total radiation dose ranged from 40 to 70 Gy (median: 64 Gy). The gross target volumes (GTV) were delineated based on CT results, including gross tumor volumes (GTVt) and gross nodal tumor volumes (GTVn). The clinical target volumes (CTV) consisted of the CTVn and CTVt. The CTVt was defined by a 0.5- to 1-cm radial margin expansion and a 3- to 4-cm proximal and distal margin expansion around the GTVt. The CTVn was defined by a 0.5- to 1-cm expansion around the GTVn. The CTV should not

cover normal tissues and organs at risk, such as the spinal cord and vertebral body, and minimize the dose to the heart and lungs. The planning target volume (PTV) was the CTV plus a uniform 0.5-cm expansion margin. For both the low (≤ 60 Gy) and high dose (> 60 Gy) groups, prescribed dose was given to the PTV. Concurrent chemotherapies were platinum-based regimens.

Follow-up and evaluation

Follow-up was conducted by outpatient review, inpatient review and telephone contact. The last follow-up time was December 17, 2019, and the median follow-up time was 14.1 months (range: 2.2–64.4 months). Follow-up examinations were performed every 3 months in the first 2 years, every 6 months in years 3–5, and annually thereafter. Tumor response and nodal disease were evaluated with repeated CT, barium swallow, and endoscopy. MRI or PET-CT was also performed if clinically necessary. Treatment-related toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). LRC was defined as the period from the date of diagnosis to the date of the first evidence of locoregional disease progression or recurrence. DMFS was defined as the period from the date of diagnosis to the date of the first evidence of distant metastasis. PFS was defined as the period from the date of diagnosis to the date of any treatment failure (including distant metastasis, locoregional disease progression or recurrence) or death from any cause. OS was defined as time from diagnosis to death from any cause.

Statistical analysis

The Pearson's chi-square test was used to compare categorical variables. Rank-Sum test was used to compare continuous variables without Gaussian distribution. T test was used to compare continuous variables with Gaussian distribution. The Kaplan-Meier method with log-rank test was used to analyse survival outcomes between groups. The optimal cut-off was defined as the hemoglobin value with the smallest P-value of log-rank tests. Univariable and multivariable Cox regression analyses were performed to explore prognostic factors. All statistical tests were two-sided with a $P < 0.05$ considered statistically significant. The analyses were conducted using IBM SPSS statistics software version 25.0 and GraphPad Prism 6.

Results

Patient characteristics

A total of 90 ESCC patients at Zhongnan Hospital of Wuhan University between February 1, 2014 and June 30, 2019 were included in this retrospective study. Among the patients, 30 received ≤ 60 Gy radiation doses (low dose), and the other 60 received > 60 Gy radiation doses (high dose). The median radiation dose was 66 Gy (range: 61–70 Gy), and the median fraction size was 2 Gy (range: 1.8–2.0 Gy) in the high dose group. The median radiation dose was 50.2 Gy (range: 40–60 Gy), and the median fraction size was 2 Gy (range: 1.8–2.0 Gy) in the low dose group. Patients' clinicopathological characteristics, disease information and treatment profiles were shown in Table 1. No statistically significant difference was found between the 2 groups in age, gender, tumor location, tumor length, clinical N stage, clinical TNM stage, hemoglobin or treatment regimens ($P > 0.05$). A larger proportion of patients in the high dose group had cT3 ($P = 0.004$), but the clinical TNM stage had no statistically significant difference between the two groups ($P = 0.139$).

Table 1
Patient, disease, and treatment characteristics (N = 90)

Characteristic	Lower dose group (≤ 60 Gy) number (%)	Higher dose group (> 60 Gy) number (%)	<i>P</i> value
Age (y)			0.666
Median (range)	65.5 (46–87)	69.0 (47–86)	
Gender			0.764
Male	26 (86.7%)	49 (81.7%)	
Female	4 (13.3%)	11 (18.3%)	
Tumor location			0.949
Cervical esophagus	3 (10%)	8 (13.3%)	
Upper thoracic	11 (36.7%)	19 (31.7%)	
Middle thoracic	7 (23.3%)	15 (25%)	
Lower thoracic	9 (30%)	18 (30%)	
Tumor length (cm)			0.520
Median (range)	6.3 (2.3–12)	5 (2–12)	
< 5	8 (26.7%)	20 (33.3%)	
≥ 5	22 (73.3%)	40 (66.7%)	
Clinical T stage			0.004
cT2	6 (20%)	8 (13.3%)	
cT3	3 (10%)	27(45.0%)	
cT4	21 (70%)	25 (41.7%)	
Clinical N stage			0.432
cN0	2 (6.6%)	6 (10%)	
cN1	6 (20%)	16 (26.7%)	
cN2	5 (16.7%)	15 (25%)	
cN3	17 (56.7%)	23 (38.3%)	
Clinical TNM stage			0.139
II	3 (10%)	7 (11.6%)	
III	4 (13.3%)	19 (31.7%)	
IVA	23 (76.7%)	34 (56.7%)	
Hemoglobin (g/L)			0.129
Median (range)	112.9 (71.4-164.3)	125.6 (91.6-151.2)	
≥ 132.1	5 (16.7%)	19 (31.7%)	
< 132.1	25 (83.3%)	41 (68.3%)	

Characteristic	Lower dose group (≤ 60 Gy) number (%)	Higher dose group (> 60 Gy) number (%)	<i>P</i> value
Treatment regimen			0.456
Radiotherapy	16 (53.3%)	27 (45%)	
CRT	14 (46.7%)	33 (55%)	

Outcomes

The last follow-up time for the 90 patients was December 17, 2019, with a median follow-up of 14.1 months (range: 2.2–64.4 months). In our study, the median PFS was 7.6 months and the 1-, 2-, and 3-year PFS rates were 28.2%, 17.5% and 10.0% respectively. The median OS was 14.1 months and the 1-, 2-, and 3-year OS rates were 52.0%, 27.1% and 17.2%, respectively (Fig. 2).

We performed Log-rank comparisons between groups to investigate the impacts of radiation doses on OS, PFS, DMFS and LRC (Fig. 3). Patients in the high dose group exhibited significantly better OS than those in the low dose group (1-year OS 57.5% vs 39.5%; 2-year OS 31.4% vs 15.8%, $P = 0.007$). The median OS of patients in the high and lower dose groups were 15.4 months (95%CI: 13.4–17.4 months) and 8.5 months (95%CI: 4.7–12.3 months), respectively. Patients in the high dose group exhibited significantly better PFS than those in the low dose group (1-year PFS 34.6% vs 22.8%; 2-year OS 11.9% vs 0%, $P = 0.008$). The median PFS of the 2 groups were 8.1 months (95%CI: 5.4–10.7 months) and 6.1 months (95%CI: 4.9–7.4 months), respectively. Although no statistically significant difference was found, a persistent trend was noted toward better LRC and DMFS in the high dose group.

Prognostic analysis

In the multivariate Cox regression analysis, tumor length (≥ 5 vs < 5 cm), clinical N stage (cN3 vs cN0) and hemoglobin (≥ 132.1 vs < 132.1 g/L) were identified as prognostic factors for PFS ($P < 0.05$) (Table 2). Multivariate Cox analysis demonstrated that clinical T stage (cT3 vs cT2, cT4 vs cT2), hemoglobin (≥ 132.1 vs < 132.1 g/L) and radiation dose (> 60 vs ≤ 60 Gy) were independently prognostic factors for OS ($P < 0.05$) (Table 3).

Table 2
Multivariate Cox analysis and forest plots indicating the independently prognostic factors of PFS.

Variable	PFS		P value
	HR	95% CI	
Age (≥ 70 vs < 70 y)	1.40	0.81–2.42	0.229
Gender (Male vs Female)	0.73	0.35–1.51	0.391
Tumor location			0.549
Upper thoracic vs Cervical esophagus	0.64	0.24–1.69	0.362
Middle thoracic vs Cervical esophagus	0.67	0.25–1.80	0.425
Lower thoracic vs Cervical esophagus	0.98	0.37–2.59	0.963
Tumor length (≥ 5 vs < 5 cm)	2.29	1.05–4.99	0.037
Clinical T stage			0.133
cT3 vs cT2	2.27	0.69–5.88	0.092
cT4 vs cT2	2.33	0.99–5.26	0.051
Clinical N stage			0.183
cN1 vs cN0	1.71	0.49–5.96	0.403
cN2 vs cN0	1.48	0.40–5.52	0.562
cN3 vs cN0	3.67	1.02–13.28	0.047
Clinical TNM stage			0.932
IA vs II	0.86	0.29–2.53	0.785
IIA vs II	1.02	0.34–3.04	0.977
Hemoglobin (≥ 132.1 vs < 132.1 g/L)	0.46	0.24–0.90	0.023
Radiation dose (> 60 vs ≤ 60 Gy)	0.56	0.31–1.02	0.058
Abbreviations: PFS, progression free survival; HR, hazard ratio; CI, confidence interval.			

Table 3
Multivariate Cox analysis and forest plots indicating the independently prognostic factors of OS.

Variable	OS		
	HR	95% CI	P value
Age (≥ 70 vs < 70 y)	1.36	0.72–2.57	0.344
Gender (Male vs Female)	0.94	0.41–2.16	0.886
Tumor location			0.375
Upper thoracic vs Cervical esophagus	0.64	0.20–2.02	0.445
Middle thoracic vs Cervical esophagus	0.82	0.26–2.61	0.737
Lower thoracic vs Cervical esophagus	1.27	0.42–3.80	0.673
Tumor length (≥ 5 vs < 5 cm)	1.81	0.78–4.19	0.169
Clinical T stage			0.030
cT3 vs cT2	3.13	1.19–8.33	0.020
cT4 vs cT2	3.12	1.27–7.69	0.013
Clinical N stage			0.362
cN1 vs cN0	1.60	0.40–6.45	0.509
cN2 vs cN0	1.00	0.23–4.32	1.000
cN3 vs cN0	2.58	0.68–9.72	0.162
Clinical TNM stage			0.178
Ⅰ vs Ⅱ	3.02	0.87–10.52	0.082
ⅠA vs Ⅱ	2.85	0.81–10.01	0.102
Hemoglobin (≥ 132.1 vs < 132.1 g/L)	0.36	0.16–0.79	0.012
Radiation dose (> 60 vs ≤ 60 Gy)	0.44	0.22–0.89	0.021
Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval.			

Toxicity

There was no treatment-associated death. Treatment-related toxicities of grade ≥ 3 occurred in 18 patients, with 14 in the high dose group and 4 in the low dose group ($P = 0.402$). Grade ≥ 3 hematologic toxicity occurred in 5 patients in the high dose group while 3 patients in the low dose group. There were 3 patients with grade ≥ 3 radiation esophagitis in the high dose group, and none in the low dose group. Grade ≥ 3 radiodermatitis occurred in 4 patients in the high dose group and 1 patient in the low dose group. Moreover, 3 patients in the high dose group had grade ≥ 3 fistula, while none in the low dose group.

Discussion

In this retrospective study including 90 inoperable ESCC patients receiving IMRT, we found higher radiation doses brought significantly better PFS and OS than lower radiation doses (≤ 60 Gy). In addition, a persistent trend toward better LRC and

DMFS in the high dose group was also observed. Meanwhile, no additional grade ≥ 3 treatment-related toxicities were present in the high dose group. These results suggested that IMRT at a radiation dose > 60 Gy would be necessary and safe for inoperable patients with locally advanced ESCC. Our work contributed to explore the optimal dose of IMRT for ESCC patients.

The RTOG8501 study [11] established concurrent CRT as the standard therapeutic strategy for EC patients. Shortly afterwards, the RTOG9405 study [5] identified an optimal dose of concurrent CRT at 50.4 Gy for EC patients. However, there is still a lack of consensus on the optimal radiotherapy dose for locally advanced EC. First, although there were more deaths in the high dose group than the low dose group (11 vs 2), 7 of the 11 patients in the higher dose group died before the radiotherapy dose reached 50.4 Gy. Therefore, higher risk of death might not result from the higher radiation doses [5]. Second, more than 60% EC patients in the RTOG9405 trial were at early clinical stages. Third, higher distant metastasis rate might result from the higher proportion of stage III patients in the high dose group. Fourth, both squamous cell carcinoma (85%) and adenocarcinoma (15%) were included in the RTOG9405 study, which might have different optimal radiation dose since ESCC was more sensitive to radiotherapy. Fifth, the lower fluorouracil dose in the high dose group of RTOG9405 trial might impact the prognosis. Finally, patients received conventional rather than modern radiotherapy techniques in the RTOG9405 trial. The radiotherapy technology has been improved over the last decades, and the recommended radiation dose should be updated accordingly.

Our study aimed to investigate the efficacy of IMRT at the high dose (> 60 Gy) compared with the low dose (≤ 60 Gy) for inoperable ESCC patients with advanced clinical stages (II-III A). The OS and PFS of patients were better in the high dose group than the low dose group in our study ($P < 0.05$). Previous studies also indicated that increased radiotherapy dose improved the therapeutic effects of CRT on EC patients, as shown in Table 4 [6, 9, 12–16]. The higher radiation doses resulted in significantly better OS ($P < 0.05$) [9, 12, 15, 16]. In our study, we also found that the higher radiation doses increased OS rates compared with the lower doses (1-year OS 57.5% vs 39.5%; 2-year OS 31.4% vs 15.8%, $P = 0.007$). However, Suh et al. [13] reported that higher doses (≥ 60 Gy) had higher 2-year LCR (69% vs 32%, $P < 0.01$) and 2-year PFS rate (47% vs 20%, $P = 0.01$). The median OS of the high and low dose groups were 28 and 18 months, respectively ($P = 0.26$). Zhang et al. [6] reported that > 51 Gy had significantly better LCR than ≤ 51 Gy in EC patients with clinical stages II or III ($P = 0.01$). Our study also suggested a persistent trend toward better LCR in the high dose group ($P = 0.707$). In addition to Chang et al., the other 6 studies did not consider the possible effects of the radiation technique on patients (Table 2). Our data indicated that the higher radiation doses of IMRT might improve the PFS of inoperable patients with locally advanced ESCC. This finding complements previous studies reported by Chang et al. which failed to provide detailed information of the patients, as well as progression free survival (PFS).

Table 4
High versus low dose group radiotherapy for esophageal cancer.

Author	Year	Study design	No. of patients	Clinical Stage	Radiation dose	Radiation technology	Pathology (SCC/AC)	OS	Pvalue
Zhang [6]	2005	Retrospective	69	Ⅱ-Ⅲ	> 51 Gy ≤ 51 Gy	2DRT/ 3DCRT	47/20 2Unknown	13% (3y) 3%	0.054
Wang [12]	2006	Retrospective	35	Ⅱ-Ⅲ	> 50 Gy < 50 Gy	2DRT/ 3DCRT	31/4	29% (5y) 0%	0.002
Suh [13]	2014	Retrospective	126	Ⅱ-Ⅲ	≥ 60 Gy < 60 Gy	2DRT/ 3DCRT	117/6 3Unknown	52.4% (2y) 45.2%	0.26
He [14]	2014	Retrospective	193	Ⅱ-Ⅲ	≥ 50.4 Gy < 50.4 Gy	3DCRT	193/0	41.7% (5y) 33.0%	0.617
Kim [15]	2016	Retrospective	236	Ⅱ-Ⅲ	≥ 60 Gy < 60 Gy	3DCRT/ IMRT	230/6	35.1 mons (MST) 22.3 mons	0.043
Chang [9]	2017	Retrospective	2061	ⅡA-ⅢC	≥ 60 Gy < 60 Gy	IMRT	-	35.47% (2y) 26.74%	<i>cript</i> > 0.0001
Deng [16]	2017	Retrospective	137	Ⅱ-Ⅲ	≥ 59.4 Gy 50-50.4 Gy	3DCRT/ IMRT	137/0	30% (3y) 24%	0.037
Abbreviations: 2DRT, two-dimensional radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; MST, median survival time; OS, overall survival.									

EC tumor length was included in the TNM staging system until 1987. For EC patients, the current clinical T stage of UICC/AJCC edition 8 [10] is based on the depth of tumor invasion into surrounding tissues, which is different from most solid tumors depending on tumor length. However, in our study, the multivariate Cox regression analysis showed that tumor length (≥ 5 vs < 5 cm) was identified as a prognostic factor for PFS (HR: 2.29; 95% CI: 1.05–4.99; P = 0.037). Currently, increasing researches explore the relationship between tumor length and EC prognosis. Eloubeidi et al. [17] retrospectively analysed 10,441 patients with EC in SEER database and found that tumor length was an independent factor for prognosis. The longer the tumor length, the deeper the tumor infiltration, and the more lymph node metastasis. Serum hemoglobin levels were used as indicators of the patient's nutritional status in our study. Patients with hemoglobin ≥ 132.1 g/L had better OS and PFS. Hemoglobin is the main oxygen carrier in erythrocytes, as a marker of nutritional, immunity and tumor-

tolerance [18]. Retrospective studies confirmed that patients with lower hemoglobin values had poorer prognosis in cervical cancer, ovarian cancer, non-small cell lung cancer, and head and neck tumors [19–22]. In our study, the optimal cut-off was defined as the hemoglobin value with the smallest P-value of log-rank tests. Patients with hemoglobin levels < 132.1 g/L should be concerned and the patients' hemoglobin levels should be raised before treatment. Our data identified critically prognostic factors in inoperable patient with locally advanced EC with IMRT. Additional studies are still required for validation.

IMRT becomes increasingly popular since it improves target conformality and decreases treatment-related toxicity [23]. Other studies also confirmed that IMRT decreased the radiation doses to protect the normal tissues, such as lungs, heart and thyroid [9, 24–27]. In our study, no patient died of treatment-related toxicity. No significant difference between the high and the low dose groups on treatment-related toxicities of grade ≥ 3 , including hematologic toxicity, radiation esophagitis, radiodermatitis and fistula ($P = 0.402$).

It should be noted that this study had several limitations. First, it was a retrospective study in a single institution, which inevitably resulted in a selection bias and treatment heterogeneity. Second, the number of patients included in this study is relatively small. In the future, a large-scale randomized prospective trial is required to further confirm the conclusion.

Conclusion

Higher radiation dose (> 60 Gy) of IMRT performed better survival outcomes for inoperable patients with locally advanced ESCC.

Abbreviations

IMRT: Intensity-modulated radiotherapy; ESCC: Esophageal squamous cell carcinoma; PFS: Progression free survival; OS: Overall survival; EC: Esophageal cancer; NCCN: National Comprehensive Cancer Network; CRT: Chemoradiotherapy; LCR: Local control rate; 2DRT: 2-dimensional radiotherapy; 3DCRT: 3-dimensional conformal radiotherapy; TESCC: Thoracic esophageal squamous cell carcinoma; DMFS: Distant metastasis free survival; CT: Computed tomography; (PET)-CT: Positron emission tomography; MRI: Brain magnetic resonance imaging; GTV: Gross target volumes; GTVt: gross tumor volumes; GTVn: Gross nodal tumor volumes; CTV: Clinical target volumes; PTV: Planning target volume

Declarations

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Not applicable.

Author Contributions

Conception and design of the work: Wei Zhang, Jing Yu, Yan Gong and Conghua Xie. Acquisition, analysis and interpretation of data: Wei Zhang, Jing Yu, Jing Hu, Jie Li, Wen Ouyang, Junhong Zhang. Final approval of the final version and agreement to be accountable for all aspects of the work: all authors.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Zhongnan hospital of Wuhan University (2020105-1), and the requirement for informed consent was waived because of the retrospective nature of the research.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. *Gastroenterology*. 2018;154:360-73.
2. Luo HS, Huang SF, Xu HY, Li XY, Wu SX, Wu DH. A nomogram based on pretreatment CT radiomics features for predicting complete response to chemoradiotherapy in patients with esophageal squamous cell cancer. *Radiat Oncol*. 2020;15:249.
3. Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol*. 2013;19:5598-606.
4. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019;17:855-83.
5. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, 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;20:1167-74.
6. Zhang Z, Liao Z, Jin J, Ajani J, Chang JY, Jeter M, et al. Dose-response relationship in locoregional control for patients with stage II-III esophageal cancer treated with concurrent chemotherapy and radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;61:656-64.
7. Hurmuzlu M, Monge OR, Smaaland R, Viste A. High-dose definitive concomitant chemoradiotherapy in non-metastatic locally advanced esophageal cancer: toxicity and outcome. *Dis Esophagus*. 2010;23:244-52.
8. Lin SH, Wang L, Myles B, Thall PF, Hofstetter WL, Swisher SG, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2012;84:1078-85.
9. Chang CL, Tsai HC, Lin WC, Chang JH, Hsu HL, Chow JM, et al. Dose escalation intensity-modulated radiotherapy-based concurrent chemoradiotherapy is effective for advanced-stage thoracic esophageal squamous cell carcinoma.

Radiother Oncol. 2017;125:73-9.

10. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. *J Thorac Oncol.* 2017;12:36-42.
11. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr., Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA.* 1999;281:1623-7.
12. Wang S, Liao Z, Chen Y, Chang JY, Jeter M, Guerrero T, et al. Esophageal cancer located at the neck and upper thorax treated with concurrent chemoradiation: a single-institution experience. *J Thorac Oncol.* 2006;1:252-9.
13. Suh YG, Lee IJ, Koom WS, Cha J, Lee JY, Kim SK, et al. High-dose versus standard-dose radiotherapy with concurrent chemotherapy in stages II-III esophageal cancer. *Jpn J Clin Oncol.* 2014;44:534-40.
14. He L, Allen PK, Potter A, Wang J, Chang JY, Gomez DR, et al. Re-evaluating the optimal radiation dose for definitive chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Oncol.* 2014;9:1398-405.
15. Kim HJ, Suh YG, Lee YC, Lee SK, Shin SK, Cho BC, et al. Dose-response relationship between radiation dose and loco-regional control in patients with stage II-III esophageal cancer treated with definitive chemoradiotherapy. *Cancer Res Treat.* 2017;49:669-77.
16. Deng Y, Bian C, Tao H, Zhang H. Improved survival with higher radiation dose for esophageal squamous cell carcinoma patients treated with definitive chemoradiotherapy. *Oncotarget.* 2017;8:79662-9.
17. Eloubeidi MA, Desmond R, Arguedas MR, Reed CE, Wilcox CM. Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status. *Cancer.* 2002;95:1434-43.
18. Sun P, Zhang F, Chen C, Bi X, Yang H, An X, et al. The ratio of hemoglobin to red cell distribution width as a novel prognostic parameter in esophageal squamous cell carcinoma: a retrospective study from southern China. *Oncotarget.* 2016;7:42650-60.
19. Dunst J, Kuhnt T, Strauss HG, Krause U, Pelz T, Koelbl H, et al. Anemia in cervical cancers: impact on survival, patterns of relapse, and association with hypoxia and angiogenesis. *Int J Radiat Oncol Biol Phys.* 2003;56:778-87.
20. Kim JH, Lee JM, Ryu KS, Lee YS, Park YG, Hur SY, et al. The prognostic impact of duration of anemia during chemotherapy in advanced epithelial ovarian cancer. *Oncologist.* 2011;16:1154-61.
21. Langendijk H, de Jong J, Wanders R, Lambin P, Slotman B. The importance of pre-treatment haemoglobin level in inoperable non-small cell lung carcinoma treated with radical radiotherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiother Oncol.* 2003;67:321-5.
22. Lambin P, Ramaekers BL, van Mastrigt GA, Van den Ende P, de Jong J, De Ruyscher DK, et al. Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. *Cochrane Database Syst Rev.* 2009:Cd006158.
23. Deng W, Lin SH. Advances in radiotherapy for esophageal cancer. *Ann Transl Med.* 2018;6:79.
24. Wang D, Yang Y, Zhu J, Li B, Chen J, Yin Y. 3D-conformal RT, fixed-field IMRT and RapidArc, which one is better for esophageal carcinoma treated with elective nodal irradiation. *Technol Cancer Res Treat.* 2011;10:487-94.
25. Haefner MF, Lang K, Verma V, Koerber SA, Uhlmann L, Debus J, et al. Intensity-modulated versus 3-dimensional conformal radiotherapy in the definitive treatment of esophageal cancer: comparison of outcomes and acute toxicity. *Radiat Oncol.* 2017;12:131.
26. Kole TP, Aghayere O, Kwah J, Yorke ED, Goodman KA. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer. *Int J Radiat Oncol Biol Phys.* 2012;83:1580-6.
27. Park JM, Wu HG, Kim HJ, Choi CH, Kim JI. Comparison of treatment plans between IMRT with MR-linac and VMAT for lung SABR. *Radiat Oncol.* 2019;14:105.

Figures

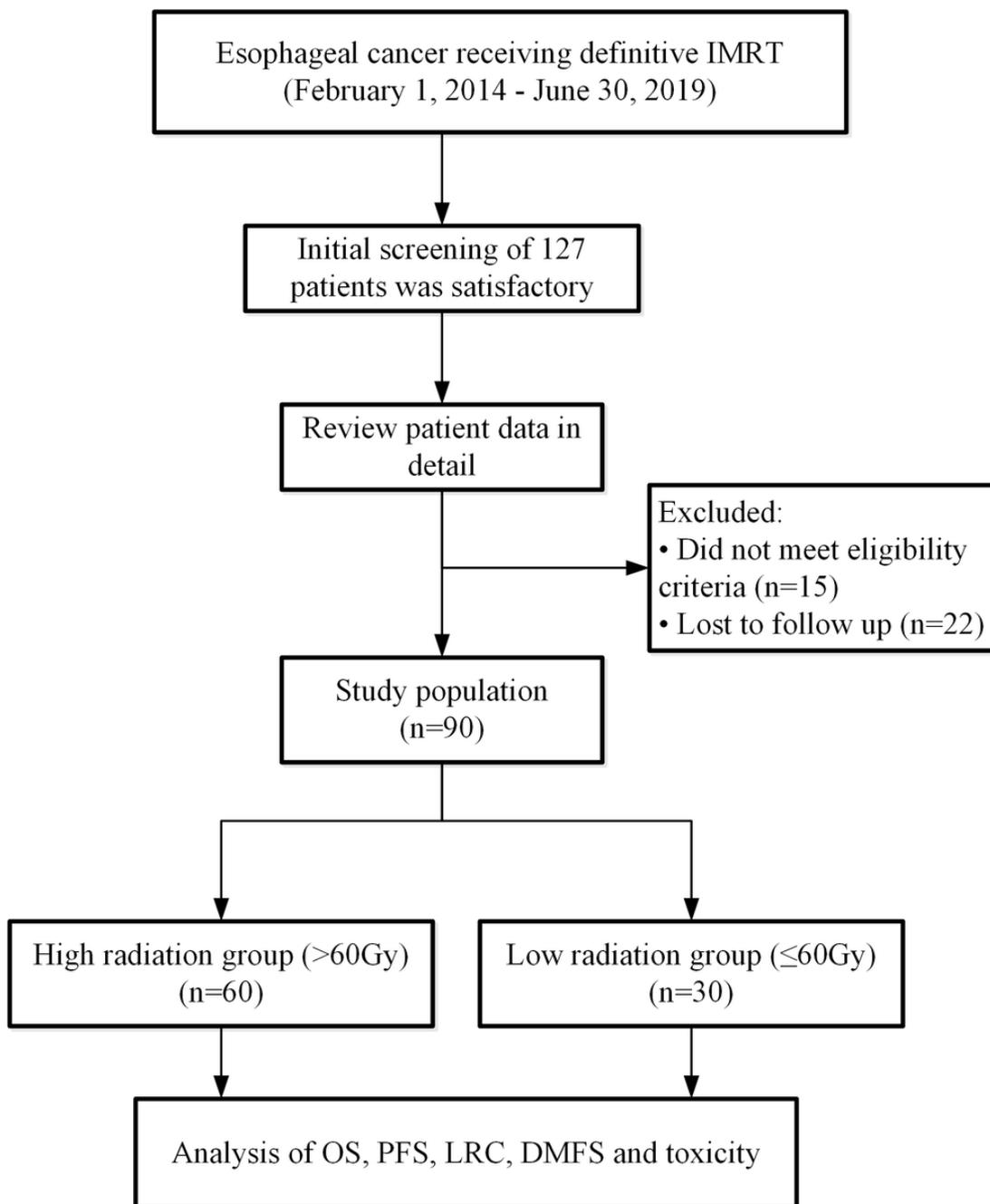
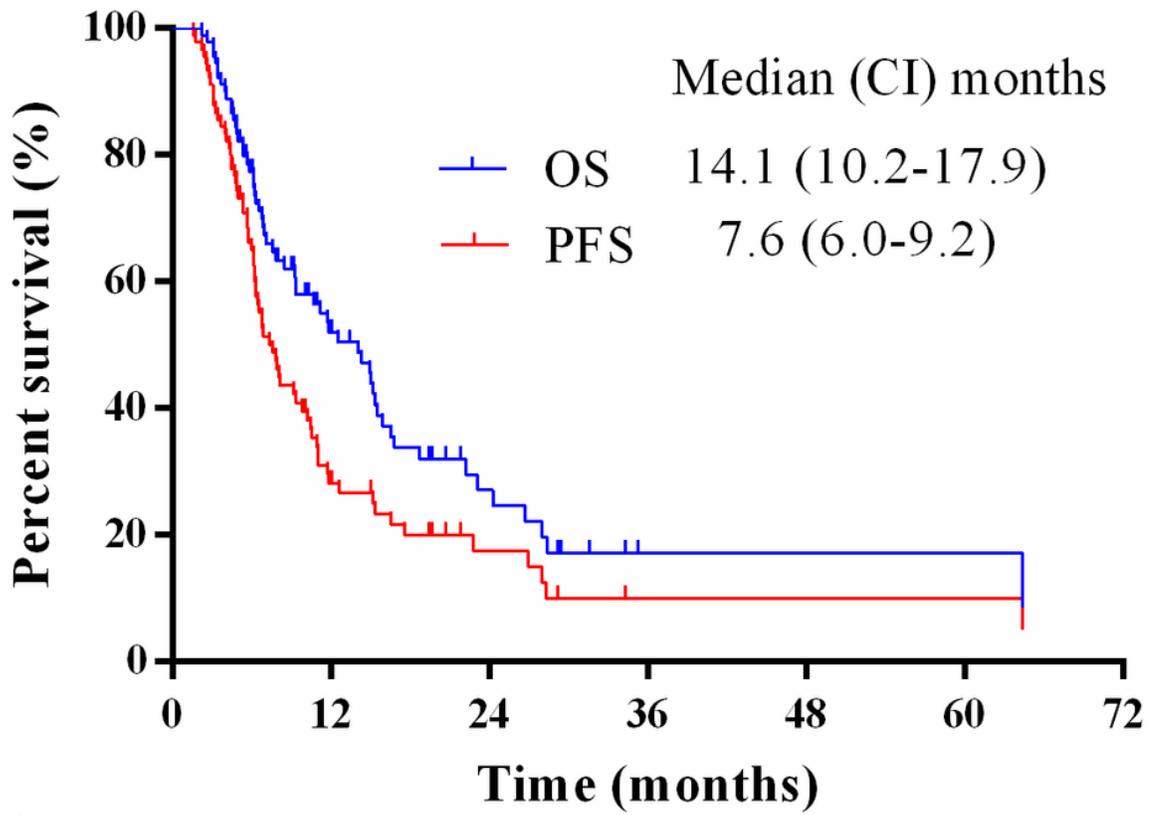


Figure 1

Study flow diagram. IMRT, intensity-modulated radiotherapy; OS, overall survival; PFS, progression free survival; DMFS, distant metastasis free survival; LRC, locoregional control.



NO.at risk	0	12	24	36	48	60	72
OS	90	36	12	3	3	3	0
PFS	90	21	8	3	3	3	0

Figure 2

Kaplan-Meier plot of OS and PFS in the 90 ESCC patients. OS, overall survival; PFS, progression free survival; CI, confidence interval.

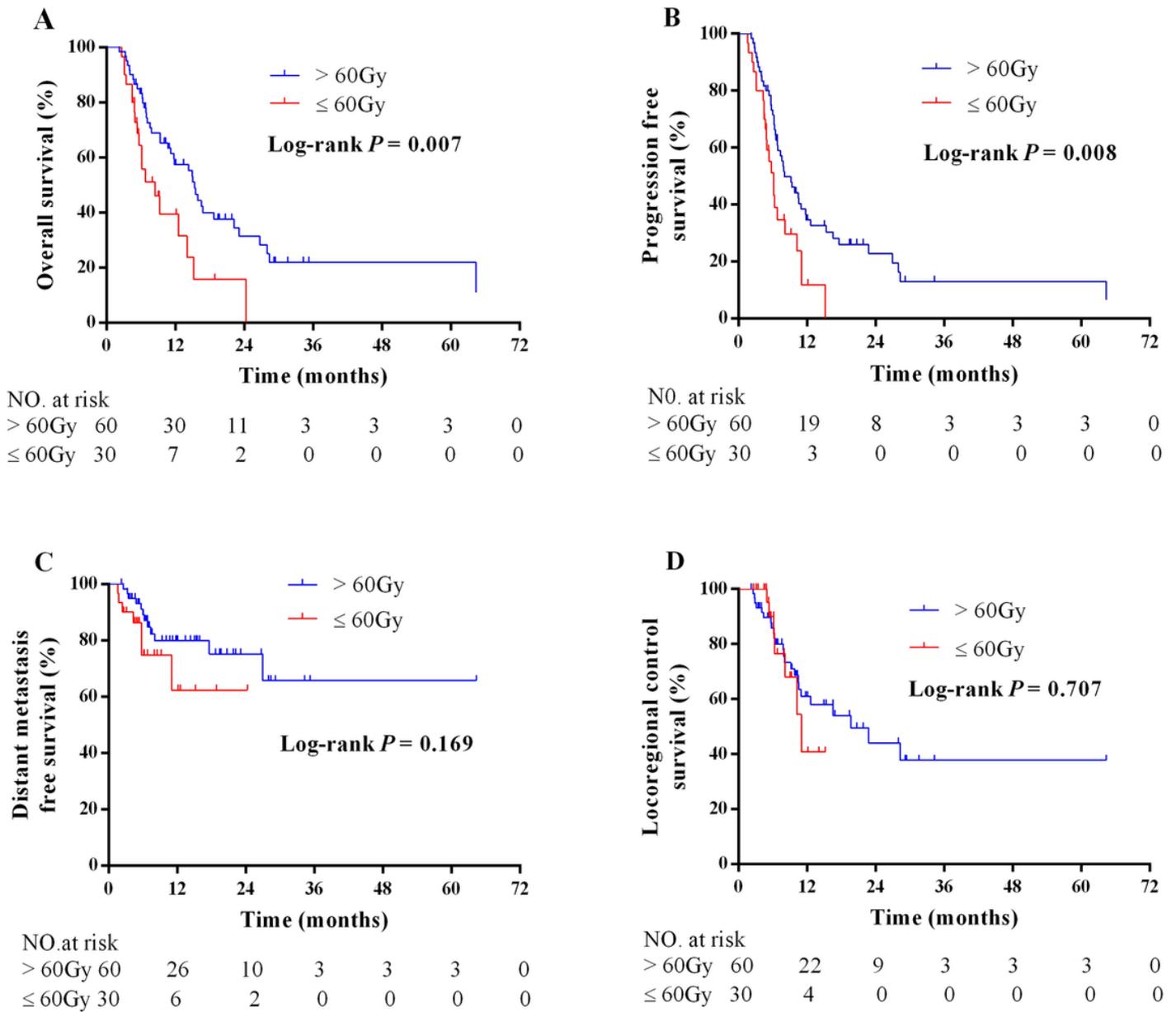


Figure 3

Log-rank comparisons of all patients grouped on the high (> 60 Gy) vs low dose group (\leq 60 Gy) for (A) OS, (B) PFS, (C) DMFS and (D) LRC. OS, overall survival; PFS, progression free survival; DMFS, distant metastasis free survival; LRC, locoregional control.

Supplementary Files

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