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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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Abstract

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.

A total of 90 inoperable ESCC patients with locally advanced stages of II-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.

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%, $P = .008$) and OS (1-year OS 57.5% vs 39.5%; 2-year OS 31.4% vs 15.8%, $P = .007$). 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; $P = .021$), but not for PFS (HR: 0.56; 95% CI: 0.31–1.02; $P = .058$). There was no significant difference in treatment-related toxicities of grade ≥3 between the 2 groups ($P = .402$).

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.

Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy, CRT = chemoradiotherapy, CT = chest computed tomography, CTV = clinical target volumes, DMFS = distant metastasis free survival, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, IMRT = intensity-modulated radiotherapy, LCR = local control rate, LRC = locoregional control, OS = overall survival, PFS = progression free survival.

Keywords: dose, esophageal squamous cell carcinoma, inoperable, intensity-modulated radiotherapy, radiotherapy

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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 authors have no conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. 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 recommend chemoradiotherapy (CRT) as the standard treatment for locally advanced EC patients with the radiation dose of 50 to 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 to 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. Since the LCR remained low in EC, there are increasing debate on the optimal radiation dose. For instance, Zhang et al. reported that >51 Gy (high dose) had significantly better LCR than ≤51 Gy (lower dose) in EC patients treated with 2-dimensional radiotherapy or 3-dimensional conformal radiotherapy (3DCRT) ($P = .01$).[6] However, whether higher dose would be more favorable was not clear. Hurmuzlu et al retrospectively analyzed 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.[7]

As intensity-modulated radiotherapy (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. conducted a study with 676 nonrandomized EC patients to estimate the survival effects of 3DCRT and IMRT.[8] 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 first retrospectively compared radiation dose ≥60 Gy versus <60 Gy in 2061 thoracic esophageal squamous cell carcinoma treated with IMRT.[9] 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%, $P < .0001$). However, Chang et al only included patients at relatively earlier stages of IA-IIIC.[9] 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 II-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.

2. Methods

2.1. Patient selection and pre-treatment evaluation

The study flow diagram is shown in Figure 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-CT, bone and abdomen CT, and brain magnetic resonance imaging were performed to evaluate distant and retroperitoneal lymph node metastasis prior to treatment.

2.2. Treatment approaches

Patients were treated 5 days per week at 1.8 to 2.0 Gy/fraction, one fraction/day. The total radiation dose ranged from 40 to 70 Gy (median: 64 Gy). The gross target volumes were delineated based on CT results, including gross tumor volumes (GTVt) and gross nodal tumor volumes. 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 gross nodal tumor volumes. 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 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 planning target volume. Concurrent chemotherapies were platinum-based regimens.

2.3. 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

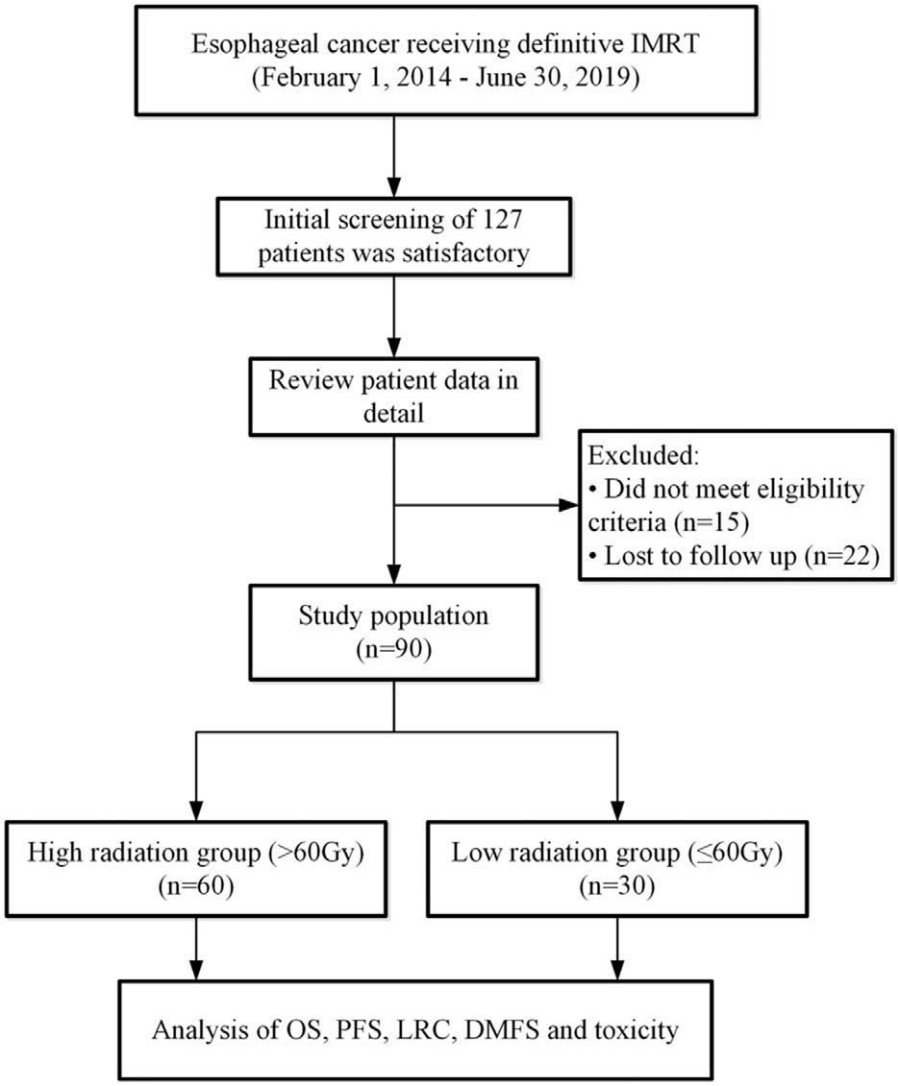

Figure 1. Study flow diagram. DMFS = distant metastasis free survival, IMRT = intensity-modulated radiotherapy, LRC = locoregional control, OS = overall survival, PFS = progression free survival.

years 3–5, and annually thereafter. Tumor response and nodal disease were evaluated with repeated CT, barium swallow, and endoscopy. Magnetic resonance imaging or positron emission tomography-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.

2.4. Statistical analysis

The Pearson's Chi-Squared 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 $P < .05$ considered statistically significant. The analyses were conducted using IBM SPSS statistics software version 25.0 and GraphPad Prism 6.

3. Results

3.1. 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 $\leq$60 Gy radiation doses (low dose), and the other 60 received $>$60 Gy radiation doses (high dose). The median

Table 1

Patient, disease, and treatment characteristics (N = 90).

Characteristic	Lower dose group (≤60 Gy) number (%)	Higher dose group (>60 Gy) number (%)	*P* value
Age (y)			.666
Median (range)	65.5 (46–87)	69.0 (47–86)	
Gender			.764
Male	26 (86.7%)	49 (81.7%)	
Female	4 (13.3%)	11 (18.3%)	
Tumor location			.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)			.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			.004
cT2	6 (20%)	8 (13.3%)	
cT3	3 (10%)	27 (45.0%)	
cT4	21 (70%)	25 (41.7%)	
Clinical N stage			.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			.139
II	3 (10%)	7 (11.6%)	
III	4 (13.3%)	19 (31.7%)	
IVA	23 (76.7%)	34 (56.7%)	
Hemoglobin (g/L)			.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%)	
Treatment regimen			.456
Radiotherapy	16 (53.3%)	27 (45%)	
CRT	14 (46.7%)	33 (55%)	

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 ($P > .05$). A larger proportion of patients in the high dose group had cT3 ($P = .004$), but the clinical TNM stage had no statistically significant difference between the 2 groups ($P = .139$).

3.2. 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).

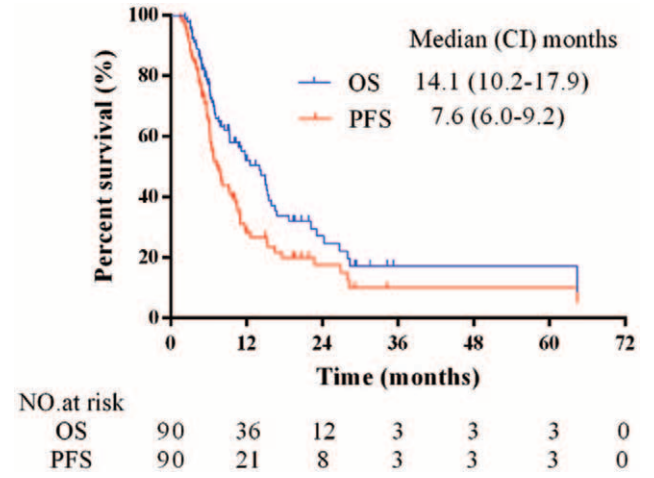

Figure 2. Kaplan–Meier plot of OS and PFS in the 90 ESCC patients. CI = confidence interval, OS = overall survival, PFS = progression free survival.

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%, $P = .007$). 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%, $P = .008$). 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.

3.3. 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 ($P < .05$) (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 ($P < .05$) (Table 3).

One-year OS rates according to total radiation dose were shown in Figure 4. The relationship between total radiation dose and OS rate showed a positive correlation for a total radiation dose ranging between 40 and 65 Gy. However, 1-year OS rates decreased when patients received a total radiation dose ranging between 66 and 70 Gy.

3.4. 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 ($P = .402$). 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 radio-

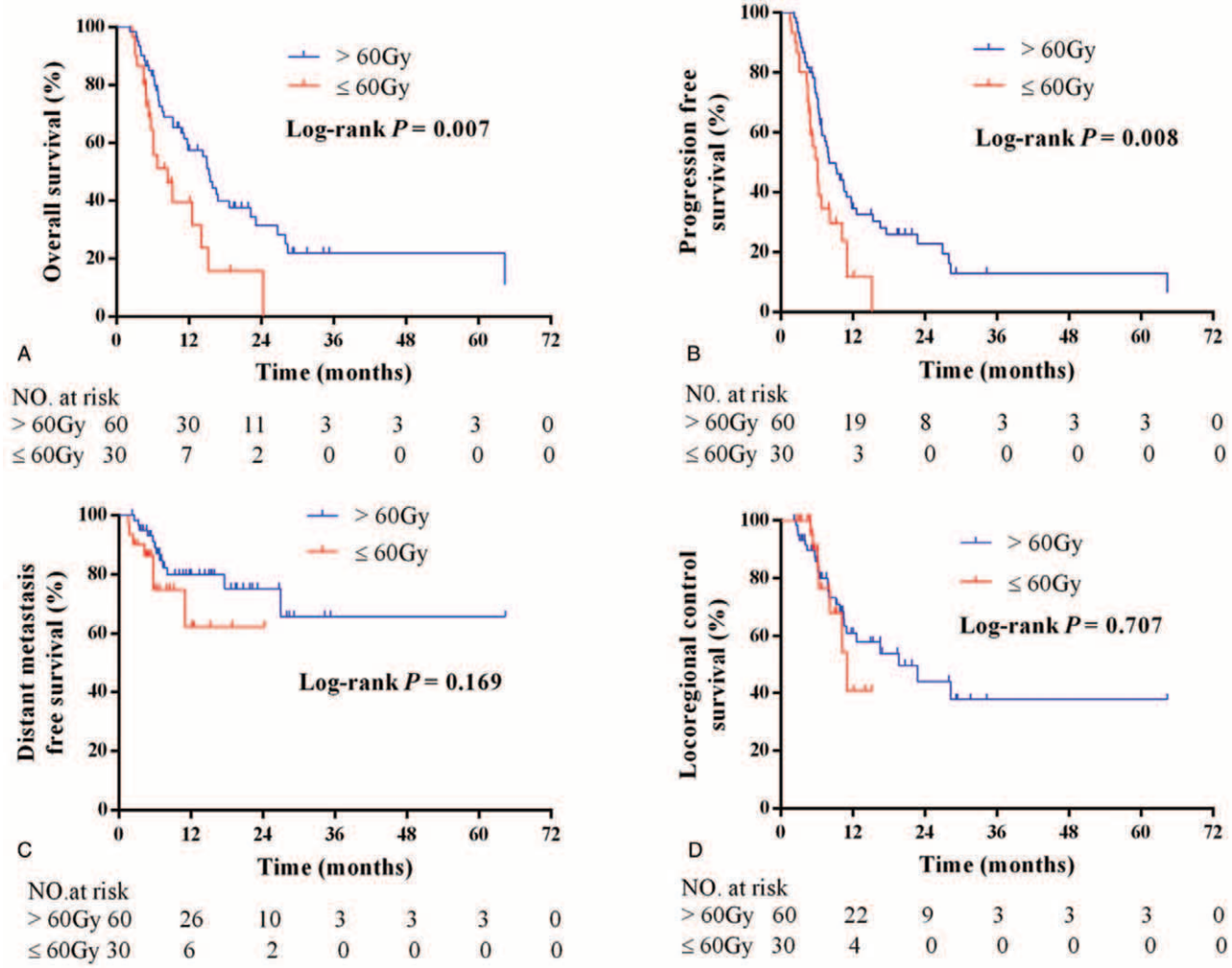

Figure 3. Log-rank comparisons of all patients grouped on the high (>60 Gy) versus low dose group (≤60 Gy) for (A) OS, (B) PFS, (C) DMFS, and (D) LRC. DMFS = distant metastasis free survival, LRC = locoregional control, OS = overall survival, PFS = progression free survival.

dermatitis occurred in 4 patients in the high dose group and 1 patient in the low dose group. Moreover, 2 patients in the high dose group had grade ≥3 fistula, while none in the low dose group (Table 4).

4. 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 established concurrent CRT as the standard therapeutic strategy for EC patients.[11] Shortly afterwards, the RTOG9405 study identified an optimal dose of concurrent CRT at 50.4 Gy for EC patients.[5] 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-IVA). The OS and PFS of patients were better in the high dose group

Table 2

Multivariate Cox analysis and forest plots indicating the independently prognostic factors of PFS. PFS = progression free survival, HR = hazard ratio, CI = confidence interval.

	PFS		
Variable	**HR**	**95% CI**	***P* value**
Age (≥70 vs <70 y)	1.40	0.81–2.42	.229
Gender (Male vs Female)	0.73	0.35–1.51	.391
Tumor location			.549
Upper thoracic vs Cervical esophagus	0.64	0.24–1.69	.362
Middle thoracic vs Cervical esophagus	0.67	0.25–1.80	.425
Lower thoracic vs Cervical esophagus	0.98	0.37–2.59	.963
Tumor length (≥5 vs < 5 cm)	2.29	1.05–4.99	**.037**
Clinical T stage			.133
cT3 vs cT2	2.27	0.69–5.88	.092
cT4 vs cT2	2.33	0.99–5.26	.051
Clinical N stage			.183
cN1 vs cN0	1.71	0.49–5.96	.403
cN2 vs cN0	1.48	0.40–5.52	.562
cN3 vs cN0	3.67	1.02–13.28	**.047**
Clinical TNM stage			.932
III vs II	0.86	0.29–2.53	.785
IVA vs II	1.02	0.34–3.04	.977
Hemoglobin (≥132.1 vs <132.1g/L)	0.46	0.24–0.90	**.023**
Radiation dose (>60 vs ≤60 Gy)	0.56	0.31–1.02	.058

Table 3

Multivariate Cox analysis and forest plots indicating the independently prognostic factors of OS. OS = overall survival, HR = hazard ratio, CI = confidence interval.

	OS		
Variable	**HR**	**95% CI**	***P* value**
Age (≥70 vs <70 y)	1.36	0.72–2.57	.344
Gender (Male vs Female)	0.94	0.41–2.16	.886
Tumor location			.375
Upper thoracic vs cervical esophagus	0.64	0.20–2.02	.445
Middle thoracic vs cervical esophagus	0.82	0.26–2.61	.737
Lower thoracic vs cervical esophagus	1.27	0.42–3.80	.673
Tumor length (≥5 vs <5 cm)	1.81	0.78–4.19	.169
Clinical T stage			**.030**
cT3 vs cT2	3.13	1.19–8.33	**.020**
cT4 vs cT2	3.12	1.27–7.69	**.013**
Clinical N stage			.362
cN1 vs cN0	1.60	0.40–6.45	.509
cN2 vs cN0	1.00	0.23–4.32	1.000
cN3vs cN0	2.58	0.68–9.72	.162
Clinical TNM stage			.178
III vs II	3.02	0.87–10.52	.082
IVA vs II	2.85	0.81–10.01	.102
Hemoglobin (≥132.1 vs <132.1g/L)	0.36	0.16–0.79	**.012**
Radiation dose (>60 vs ≤60 Gy)	0.44	0.22–0.89	**.021**

than the low dose group in our study ($P<.05$). Previous studies also indicated that increased radiotherapy dose improved the therapeutic effects of CRT on EC patients, as shown in Table 5.[6,9,12–16] The higher radiation doses resulted in significantly better OS ($P<.05$).[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%, $P=.007$). However, Suh et al reported that higher doses (≥60 Gy) had higher 2-year LCR (69% vs 32%, $P<.01$) and 2-year PFS rate (47% vs 20%, $P=.01$).[13] The median OS of the high and low dose groups were 28 and 18 months, respectively ($P=.26$). Zhang et al reported that >51 Gy had significantly better LCR than ≤51 Gy in EC patients with clinical stages II or III ($P=.01$).[6] Our study also suggested a persistent trend toward better LRC in the high dose group ($P=.707$). In addition to Chang et al, the other 6 studies did not consider the possible effects of the radiation technique on patients (Table 5). 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 PFS.

Although patients in the high dose group (>60 Gy) exhibited significantly better OS than those in the low dose group (≤60 Gy)

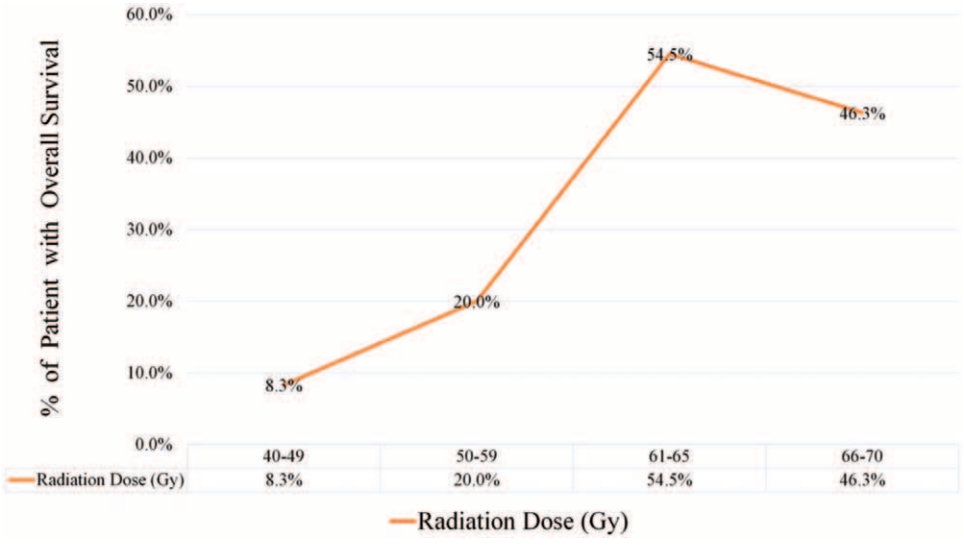

Figure 4. Percentage of patients with 1-year OS rates after treatment as a function of radiation dose.

Table 4

Treatment-related toxicities of grade ≥3 occurred in 18 patients.

Treatment-related toxicities	High dose group (>60 Gy)	Low dose group (≤60 Gy)
Hematologic toxicity	5	3
Radiation esophagitis	3	0
Radiodermatitis	4	1
Radiation pneumonitis	2	0

($P = .007$). As shown in Figure 4, we presented the percentage of patients with 1-year OS rates after treatment as a function of radiation dose. The 1-year OS rates increased with the increase of radiation dose, but decreased when the radiation dose increased to a certain value. The highest 1-year OS rates was 54.5% when ESCC patients received a total radiation dose ranging between 60 and 65 Gy. However, 1-year OS rates decreased when ESCC patients received a total radiation dose ranging between 66 and 70 Gy. It was worthing point out that this may be related to the increase of radiation dose, the increase of radiotherapy treatment-related toxicity. IMRT has replaced conventional radiation therapy since the beginning of the 21st century due to its distinct advantages on dose control and target delineation. The target volume delineation for patients receiving IMRT was determined using guidelines 62 and 83 of the International Commission on Radiation Units.[17,18] The prescribed dose was 68 to 70 Gy to the gross target volume of the nasopharynx.[19] It has been reported that 5-year OS rate is only about 15% after conventionally fractionated 60 Gy in locally advanced non-small cell lung cancer. However, patients in locally advanced non-small cell lung cancer have demonstrated improved outcomes in dose escalation trials.[20] IMRT treatment guidelines for gastric cancer patients recommend an overall dose of 45 to 50.4 Gy.[21] In our study, our work suggested that the optimal dose of IMRT for ESCC patients is 60 to 65 Gy. A carefully designed dose-escalation randomized prospective trial would be next required to confirm this conclusion.

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 is based on the depth of tumor invasion into surrounding tissues, which is different from most solid tumors depending on tumor length.[10] 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; $P = .037$). Currently, increasing researches explore the relationship between tumor length and EC prognosis. Eloubeidi et al retrospectively analysed 10,441 patients with EC in SEER database and found that tumor length was an independent factor for prognosis.[22] 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.[23] 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.[24–27] 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.[28] Other studies also confirmed that IMRT decreased the radiation doses to protect the normal tissues, such as lungs, heart and thyroid.[9,29–32] In our study, no patient died of treatment-related toxicity. No significant difference existed between the high and the low dose groups on treatment-related toxicities of grade ≥3, including hematologic toxicity, radiation esophagitis, radiodermatitis and fistula ($P = .402$).

It should be noted that there were several limitations in this study. First, it was a retrospective study in a single institution, which inevitably resulted in a selection bias and treatment

Table 5

High versus low dose group radiotherapy for esophageal cancer. 2DRT = two-dimensional radiotherapy, 3DCRT = three-dimensional conformal radiotherapy, SCC = squamous cell carcinoma, AC = adenocarcinoma, MST = median survival time, OS = overall survival.

Author	Year	Study design	No. of patients	Clinical stage	Radiation dose	Radiation technology	Pathology (SCC/AC)	OS	*P* value
Zhang[6]	2005	Retrospective	69	II-III	>51 Gy ≤ 51 Gy	2DRT/ 3DCRT	47/20 2Unknown	13% (3 y) 3%	.054
Wang[12]	2006	Retrospective	35	I-III	>50 Gy < 50 Gy	2DRT/ 3DCRT	31/4	29% (5 y) 0%	.002
Suh[13]	2014	Retrospective	126	II-III	≥60 Gy < 60 Gy	2DRT/ 3DCRT	117/6 3Unknown	52.4% (2 y) 45.2%	.26
He[14]	2014	Retrospective	193	I-IV	≥ 50.4 Gy < 50.4 Gy	3DCRT	193/0	41.7% (5 y) 33.0%	.617
Kim[15]	2016	Retrospective	236	II-III	≥60 Gy < 60 Gy	3DCRT/ IMRT	230/6	35.1 mo (MST) 22.3 mo	.043
Chang[9]	2017	Retrospective	2061	IA-IIIC	≥ 60 Gy < 60 Gy	IMRT	-	35.47% (2 y) 26.74%	<.0001
Deng[16]	2017	Retrospective	137	I-III	≥59.4 Gy 50–50.4 Gy	3DCRT/ IMRT	137/0	30% (3 y) 24%	.037

heterogeneity. Second, the number of patients included in this study was relatively small. In the future, a large-scale randomized prospective trial is required to further confirm the conclusion.

5. Conclusion

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

Author contributions

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