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Radiotherapy with S-1 for the treatment of esophageal squamous cell carcinoma 75 years or older

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Abstract

Objective Explore the efficacy and safety of involved-field irradiation (IFI) combined with S-1 as definitive concurrent chemoradiotherapy (dCRT) for locally advanced elderly esophageal squamous cell carcinoma (ESCC), under the premise of intensity-modulated radiotherapy (IMRT).

Methods We designed a prospective single-arm phase II study. The study enrolled 91 patients aged 75 to 92 years. Eligible participants had histologically confirmed squamous cell carcinoma, stage II to IV disease based on the 8th edition of the American Joint Committee on Cancer (AJCC). All elderly patients (EPs) received dCRT with S-1. which was administered orally twice daily for 28 days. The radiotherapy dose was 61.2 Gy delivered in 34 fractions or 50.4 Gy delivered in 28 fractions. The primary endpoint was 2-year overall survival (OS), and the secondary endpoints were progression-free survival (PFS), local control rate (LCR), and safety.

Results From July 2017 to July 2021, we enrolled EPs with ESCC who were treated at the Jiangsu Cancer hospital. As of August 1, 2023, the median follow-up of surviving EPs was 31.4 months (IQR: 25.2 to 72.6 months). 83 patients (91.2%) completed the whole course of treatment. The 2-year OS rate was 59.2%, and the PFS rate was 43.7%. The most common grade 1 to 2 adverse effects (AEs) were radiation esophagitis (79.1%), and then were radiation pneumonia (46.2%). Anemia (41.8%) was the most common of grade 1 to 2 hematologic toxicity. The incidence of grade 3 or above AEs was 24.2%, and the incidence of leukopenia was the highest (11.0%). There was not one death due to treatment-related toxicity. In a subgroup analysis of radiotherapy doses, we found no statistically significant differences in PFS ($P=0.465$) and OS ($P=0.345$) in EPs with ESCC who received 50.4 Gy and 61.2 Gy, and that patients in the 50.4 Gy group had lower dermatitis ($P=0.045$) and anemia ($P=0.004$).

Conclusions IF-IMRT combined with S-1 is a promising regimen for elderly ESCC. And the radiotherapy dose of 50.4 Gy remains the standard dose for EPs with ESCC undergoing CCRT.

Keywords Elderly, Esophageal squamous cell carcinoma, Involved-field irradiation, Intensity-modulated radiotherapy, S-1

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Introduction

Esophageal cancer is the sixth leading cause of cancer-related death worldwide [1]. The median age at diagnosis is 68 years old [2]. Most elderly patients (EPs) with esophageal cancer are excluded from large clinical studies due to chronic diseases, organ function decline, or poor nutritional status [3]. As the aging of the population in our country continues and the mortality rate of elderly patients with esophageal cancer rises, it is very important to study and standardize the treatment strategies for patients with esophageal cancer. The RTOG 85−01 [4] study established definitive concurrent chemoradiotherapy (dCRT) as the standard treatment for locally advanced inoperable esophageal cancer. However, up to 42% of patients in the study (26% of patients in the dCRT group who are 70 years old or older) stopped treatment due to high toxicity. Because of the great toxicity of dCRT, most EPs with ESCC currently only receive radiotherapy or palliative care only [5].

Elective nodal irradiation (ENI) has traditionally been the standard radiotherapy approach for esophageal cancer. However, this method has been associated with a significant incidence of radiation-related toxicity, primarily due to the extensive volume of tissue exposed to radiation. Several retrospective [6] analyses have indicated that Eps with esophageal cancer who underwent ENI in conjunction with double-agent intravenous chemotherapy not only poor treatment adherence but also alarming treatment-related mortality rates ranging from 13 to 18%. This highlights the need for alternative, less toxic, and more effective treatment strategies for this patient population. Recent studies have highlighted that involvement-field irradiation (IFI) [7, 8] can reduce radiotherapy-related toxicity without compromising patients survival by minimizing the volume of tissue exposed to radiation. S-1 [9], a third-generation new fluorouracil, is not only endowed with both anti-cancer and radiosensitizing effects but also boasts high efficiency, low toxicity, and ease of administration. Studies [10] have demonstrated that S-1 is as effective and safe as intravenously administered fluorouracil in gastric cancer patients. This opens up new possibilities for CCRT in EPs with ESCC. Building on these findings, we have designed a phase II study (ESO-Nanjing4) to investigate the combination of IFI and oral S-1 chemotherapy in ESCC, with the aim of verifying the efficacy and safety of this treatment regimen.

Inclusion and exclusion criteria

Inclusion criteria, (1) participants must be 75 years of age or older; (2) a definitive diagnosis of squamous cell carcinoma; (3) an Eastern Cooperative Oncology Group (ECOG) performance status ranging from 0 to 2; (4) no prior treatment received at the initial consultation; (5) ineligibility for surgical intervention or a voluntary refusal of intravenous chemotherapy, with stage II to IV disease based on the 8th edition of the TNM; (6) no serious hematologic cardiac, pulmonary, hepatic, or renal dysfunctions, nor any immune deficiencies; (7) a projected survival period exceeding 3 months; (8) no evidence of a second primary tumor at other sites prior to treatment, or a second primary tumor that has remained stable for over 5 years.

Exclusion criteria, (1) complete obstruction of the esophagus resulting in an inability to ingest food; (2) severe esophageal ulcers, perforation, or vomiting of blood; (3) current involvement in other clinical trials; (4) a history or presence of interstitial lung disease; (5) incapacitating seizures or a loss of consciousness due to mental disorders; (6) any condition that, in the opinion of the research team, makes the patient unsuitable for this trial.

Following approval from the Jiangsu Cancer hospital's ethics committee, all participants in the study signed have provided their informed consent willingly engaging in the research process (Fig. 1).

Radiotherapy regimen

IMRT was delivered using a linear accelerator with 6MV photons. Patients are positioned supine, with an appropriate headrest selected based on the curvature of the neck, and their hands are raised and crossed to hold their elbows. After being fixed with a thermoplastic body mold, a CT simulation localization scan is performed, with the range extending from the cricoid cartilage to below the diaphragm, with a slice thickness of 5 mm. Due to the long time period covered by this study, dose prescription varied to some extent. The gross tumor volume (GTV) included the primary tumor and involved lymph nodes. In general, the clinical tumor volume (CTV), GTV is extended up and down by 3 cm, and it is not released outside all around. There is no CTV in metastatic lymph nodes. Planned tumor volume (PTV), CTV was placed 1 cm around and above and below, and one side of the spinal cord can be modified as appropriate to avoid high doses of radiation to the spinal cord (Supplementary File 1). The evaluation of the quality of a treatment plan is conducted using tools such as the Dose-Volume Histogram (DVH) and isodose curves. Position verifications were executed at least weekly using kV images or Cone Beam Computer Tomography (CBCT). Dose constraints to the organs at risk are as follows: maximum dose in the spinal cord ≤ 45 Gy; mean lung dose (MLD) ≤ 13 Gy, lung V20 ≤ 28%, lung V30 ≤ 18%; mean heart dose (MHD) < 36 Gy, heart V30 ≤ 45%. Principle of radiotherapy suspended, patients with neutrophil (ANC) $< 1.0 \times 10^9$/L (or white blood cell $< 2 \times 10^9$/L, when ANC was not available), or platelet (PLT) $< 50 \times 10^{12}$/L discontinue radiotherapy. Radiotherapy can be

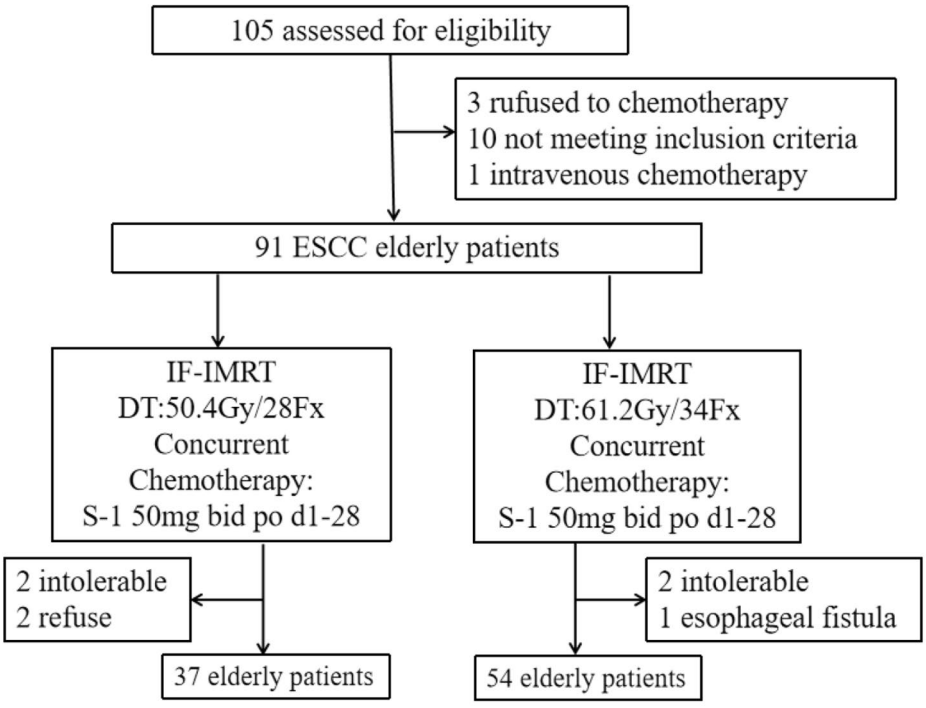

Fig. 1 91 elderly patients with ESCC underwent IF-IMRT and S-1 with concurrent chemotherapy

postponed for up to 2 weeks, otherwise, it should be discontinued in principle, unless the investigator deems it necessary to continue radiotherapy.

Chemotherapy regimen

On the first day of radiotherapy, all patients take S-1 orally (50 mg bid.), once half an hour after breakfast and once half an hour after dinner, continuously for 4 weeks, followed by a rest period of 2 weeks, with 6 weeks constituting one treatment cycle. After the completion of concurrent chemoradiotherapy, patients proceed with two additional cycles of consolidation chemotherapy. During chemotherapy, if a patient is unable to swallow S-1 capsules, the powder inside the capsules can be dissolved in water for consumption. All patients should receive the planned dosage of S-1. If necessary, the dosage of S-1 may be adjusted based on the patient's hematologic toxicity or other toxicities. Should the chemotherapy be delayed by two weeks or longer, the patient should discontinue the oral intake of S-1. Following the conclusion of concurrent chemoradiotherapy, EPs then engage in two cycles of consolidative chemotherapy. In instances where EPs have difficulty swallowing S-1 capsules, the contents can be dissolved in water for easier ingestion. It is imperative that all EPs adhere to the prescribed dosage of S-1. Adjustments to the S-1 dosage may be warranted in response to hematologic or other toxicities experienced by the patient. If there is a delay of two weeks or more in the chemotherapy schedule, the patient must cease taking S-1 orally.

Follow-up and data collection

The primary endpoint was a 2-year OS. Secondary endpoints were PFS, LCR, and safety. OS was defined as the last follow-up time from the start of treatment to death from any cause or to the end of the study; PFS was the time from the onset of treatment to disease progression or death; Local control time refers to the time between initiation of radiation therapy and recurrence of esophageal lesions or lymph nodes in the radiotherapy target. All EPs document AEs utilizing the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Acute toxicities are evaluated from the commencement of radiotherapy through to three months post-treatment. Follow-up visits were planned at 4 weeks and 10 weeks and every 3 months thereafter for the first year, every 6 months for the second year, and annually from years 3 to 5. We acquired the following clinical characteristics via electronic medical records and telephone follow-up, including age; sex; tumor site; tumor length, stage; ECOG performance status; the lowest point of the absolute lymphocyte count (ALC) (from examination reports within two months of concurrent chemoradiotherapy); and parameters of the DVH: MHD, MLD, heart V30 and lung V20, and lung V5.

Sample size calculation and statistical methods

In previous studies, the 2-year radiotherapy OS for Eps who received radiotherapy alone was 16% [4], and our study is expected to increase the 2-year OS of Eps to 36%. The enrollment period was 48 months, and the last enrolled patient was followed up for 2 years, for a total study period of 60 months. Under the test level $\alpha=0.05$ (two-sided test), 80% power, considering the shedding rate of 10%, the minimum sample size was calculated as 91 cases.

Data entry and statistical analysis with SPSS17.0 software. Categorical variables were descriptively analyzed by frequency and proportion. Median and inter-quartile range (IQR) were used to summarize continuous variables. X-tile 3.6.1 software (Yale University, New Haven, CT, USA) was used to determine the best critical value of pretreatment ALC nadir (ALCmix). On this basis, the receiver operating characteristics (ROC) curve was used to determine the cut-of points for dosimetric parameters with ALCmix as the state variable. The Kaplan-Meier method calculates the patient's OS and plots the survival curve. Cox proportional hazards regression analysis was used to calculate the risk ratio and 95% CI. The Pearson chi-square test or Fisher's exact test was used to compare treatment effects, toxic side effects, and other categorical variables between subgroups. $P\leq0.05$ was statistically significant. The study was performed in accordance to the declaration of Helsinki in its latest version and was approved by our independent ethics committee. All patients gave written informed consent prior to treatment initiation.

Table 1 Characteristics of 91 elderly patients with ESCC

Characteristic	*N* (%)
Age(y)	
≤ 78	46(50.5%)
> 78	45(49.4%)
Sex	
Male	63(69.2%)
Female	28(30.7%)
Stage (AJCC, 8th)	
II	36(39.5%)
III	42(46.1%)
IVa	13(14.2%)
T stage	
T2	41(45.0%)
T3	38(41.7%)
T4	12(13.1%)
N stage	
N0	8(8.7%)
N1	71(78.0%)
N2	11(12.0%)
N3	1(1.0%)
Tumor location	
Upper (< 25 cm)	20(21.8%)
Middle (25 ~ 30 cm)	58(63.7%)
Lower (> 30 cm)	13(14.2%)
Tumor length, cm	
≤ 4	40(43.9%)
> 4	51(56.0%)
ECOG score	
0 ~ 1	88(96.7%)
2	3(3.2%)
Smoking history	
Former or current	46(50.5%)
Never	45(49.4%)
Drinking history	
Former or current	37(40.7%)
Never	54(59.3%)
Radiation dose	
50.4 Gy	37(40.7%)
61.2 Gy	54(59.3%)

Results

Clinical data and treatment completion

The characteristics of the 91 patients are listed in Table 1. The median age is 78 years old (range, 75 to 92 years old). The median length of esophageal tumors was 4.5 cm (range, 2.0 to 9.0 cm). 29.7% of patients had a family history of tumors; 47 patients (51.6%) had diabetes and hypertension chronic diseases. 88 patients (96.7%) completed the full course of radiotherapy, of which 36 patients received 50.4 Gy, 52 patients received 61.2 Gy. Reasons for prematurely stopping RT were poor physical condition (3.3%) and the formation of a tracheoesophageal fistula (1.1%) (initially diagnosed with T4b, CT showing tumor invasion of the trachea), respectively. 86 patients (94.5%) completed two cycles of chemotherapy, 4 patients received only one cycle due to intolerance, and one patient discontinued S-1 due to tracheoesophageal fistula. 84 patients (92.3%) completed the entire course of dCRT, as shown in Fig. 1. 9 patients, due to difficulty in swallowing during chemotherapy, dissolved the powder from the capsules in water for consumption, respectively.

Survival situation

As of August 1, 2023, the median follow-up time of surviving patients was 31.4 months (IQR: 25.2 to 72.6 months), and no patients were lost to follow-up. 61 patients (67.0%) died, including 28 (30.8%) patients due to esophageal tumors, 7 (7.7%) patients due to tumor-related complications, and 26 patients (28.6%) due to other diseases and/or accidents. The median OS was 30.2 months (IQR: 12.3 to 75.4 months), and the 2-year OS rate was 59.2%, and 3-year and 5-year OS were 44.8% and 26.3%. The median PFS was 19.1 months, and the 2-year PFS was 43.7%, and 3-year and 5-year PFS were 32.6% and 20.2% (Fig. 2).

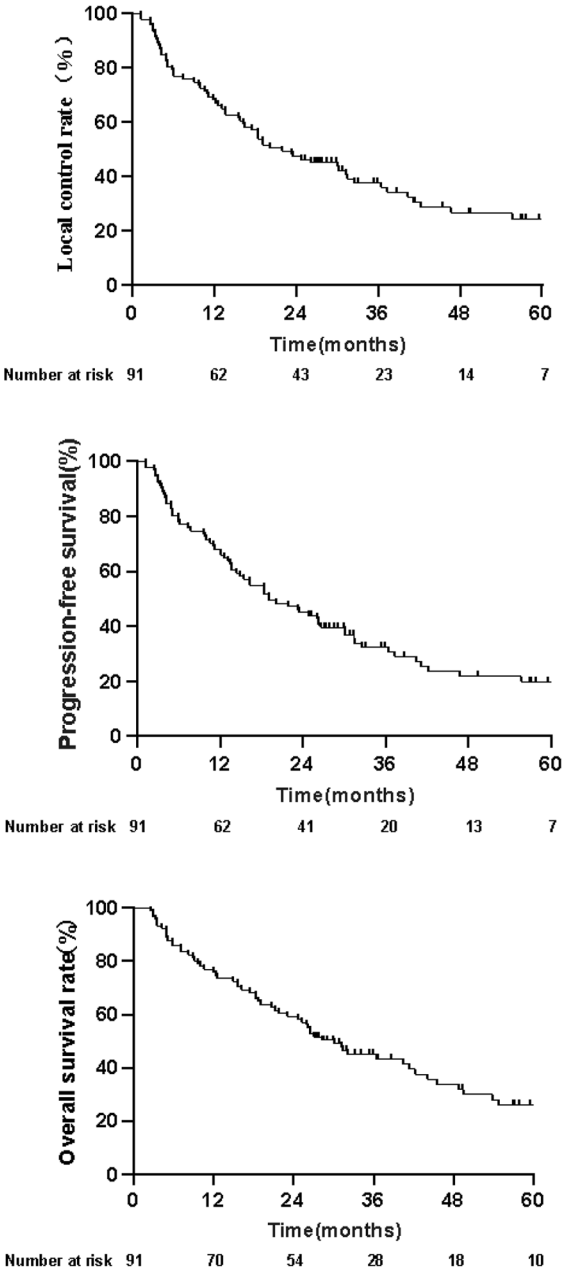

Fig. 2 IF-IMRT combined with S-1 concurrent chemotherapy in the treatment of LCR, PFS, and OS in elderly patients with ESCC

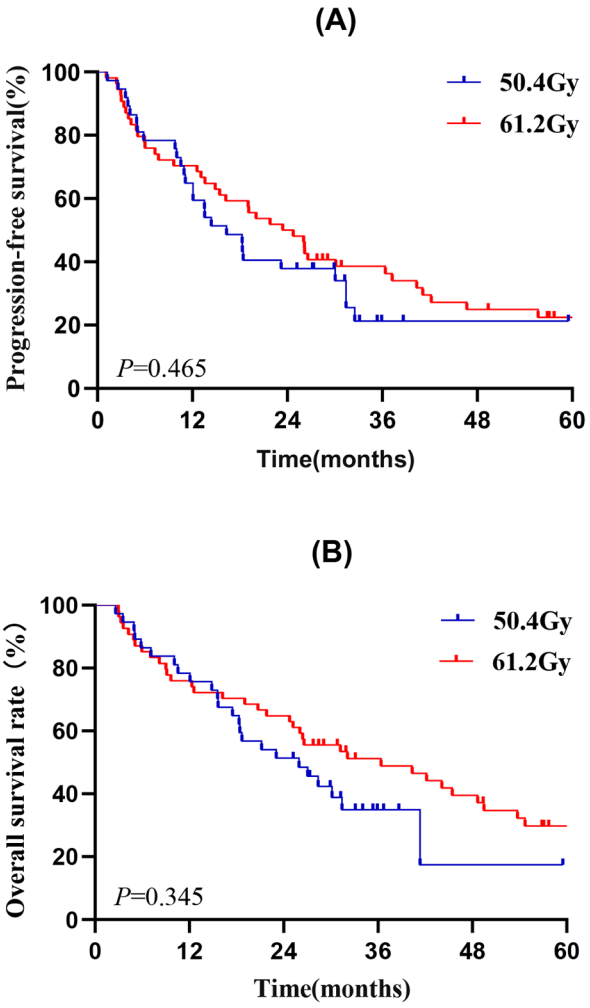

Fig. 3 Elderly patients with ESCC received PFS and OS in different radiotherapy dose subgroups

In a post-hoc analysis of patients receiving different doses of radiotherapy, PFS was no longer in the 61.2 Gy subgroup than in the 50.4 Gy subgroup (the median PFS, 24.7 months vs. 16.3 months; HR=1.26 [95% CI, 0.76 to 2.09]; *P*=0.465). We also observed the same results in OS (the median OS, 26.0 months vs. 36.4 months, HR=1.37 [95% CI, 0.80 to 2.35]; *P*=0.345, Fig. 3).

The univariate analysis and multivariate results as shown in Table 2. The results showed that the older, a decrease in ALCmix, an increase in heart V30, and an increase in lung V20, all of which were negatively correlated with survival in EPs. We include variables with a p-value less than or equal to 0.1 in the univariate analysis into the multivariate analysis. The multivariate analysis revealed that ALCmix, heart V30, and lung V20 were the pivotal determinants of patient outcomes.

Treatment failure mode

38 patients (41.8%) had regional recurrence, including 32 patients (35.2%) within the irradiation field and 6 (6.6%) outside the irradiation field. Among the recurrent outside the irradiation field, 4 patients had intra-abdominal lymph node metastasis, and 2 patients had supraclavicular lymph node metastasis. Distant metastases occurred in 12 patients (13.2%), including 3 patients (3.3%) liver metastases, 8 patients (8.8%) lung metastases, and 1 patient (1.1%) pleural metastasis. Of the 48 patients who failed treatment, 3 patients (3.3%) had both local recurrence and distant metastases.

Table 2 Univariate analysis and multivariate analysis of the factors associated with OS

Baseline characteristics	Univariate analysis		Multivariate analysis	
	P- value	HR (95% CI)	*P*- value	HR (95% CI)
Age, years (≤ 78 vs. > 78)	0.011#	0.51(0.300-0.858)	0.102	0.63(0.357–1.098)
Sex (male vs. female)	0.060	0.46(0.209–1.032)	0.001#	0.35(0.182–0.660)
ECOG score (0–1 vs. 2)	0.453	0.64(0.200-2.052)	-	-
Tumor length, cm (< 5 vs. ≥ 5)	0.468	0.79(0.419–1.492)	-	-
Clinical stage (II vs. III)	0.946	0.98(0.569–1.694)	-	-
Clinical stage (II vs. IV)	0.932	0.98(0.670–1.444)	-	-
T stage (T1-2 vs. T3-4)	0.700	0.91(0.543–1.507)	-	-
N stage (N0-1 vs. N2-3)	0.074	0.35(0.108–1.108)	0.084	0.35(0.108–1.151)
Treatment discontinuation (no vs. yes)	0.500	0.71(0.255–1.947)	-	-
ALCmix, $*10^9$/L (≤ 0.51 vs. > 0.51)	0.023#	0.42(0.799–0.887)	0.034#	0.44(0.207–0.941)
Heart V30, % (≤ 38.01 vs. > 38.01)	0.013#	0.42(0.211–0.830)	0.006#	0.34(0.158–0.735)
MHD, Gy (≤ 13.04 vs. > 13.04)	0.805	0.93(0.531–1.635)	-	-
Lung V5, % (≤ 45.89 vs. > 45.89)	0.511	0.83(0.473–1.452)	-	-
Lung V20, % (≤ 26.46 vs. > 26.46)	0.040#	0.45(0.214–0.966)	0.019#	0.39(0.179–0.858)
MLD, Gy (≤ 13.04 vs. > 13.04)	0.062	0.56(0.300-1.031)	0.139	0.61(0.320–1.173)

Abbreviation: ALCmix, absolute lymphocyte count nadir; MHD, mean heart dose; MLD, mean lung dose; #, the p-value was less than 0.05 and statistically significant

Table 3 The mode of treatment failure

Failure site	*N* (%)			*P*-value
	50.4 Gy(*N* = 37)	61.2 Gy(*N* = 54)	Total(*N* = 91)	
Regional recurrence	18(48.6%)	20(37.0%)	38(41.8%)	0.270
Within the irradiation field	16(43.2%)	16(29.6%)	32(35.2%)	0.182
Outside the irradiation field	2(5.4%)	4(7.4%)	6(6.6%)	1.000
Distant metastasis	5(13.5%)	7(13.0%)	12(13.2%)	0.939
Lung	4(10.8%)	4(7.4%)	8(8.8%)	0.852
Liver	1(2.7%)	2(3.7%)	3(3.3%)	0.791
Pleura	0	1(1.9%)	1(1.1%)	0.305

Table 4 Adverse effects in 91 elderly patients with ESCC treated with IF-IMRT combined with S-1

Adverse effects	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	15(16.4%)	15(16.4%)	8(8.7%)	2(2.1%)
Neutropenia	10(10.9%)	13(14.2%)	3(3.2%)	1(1.0%)
Thrombocytopenia	23(25.2%)	3(3.2%)	3(3.2%)	0
Anemia	36(39.6%)	2(2.1%)	1(1.0%)	0
Fever	2(2.1%)	0	0	0
Hiccup	5(5.4%)	1(1.0%)	0	0
Acid reflux	21(23.0%)	0	0	0
Esophagitis	24(26.3%)	48(52.7%)	4(4.3%)	0
Pneumonitis	31(34.0%)	11(12.0%)	0	0
Dermatitis	13(14.2%)	0	0	0

A post-hoc analysis, the rates for all failure were 59.5% and 48.1% in the 50.4 Gy and 61.2 Gy subgroups, respectively, including locoregional failure in 48.6% vs. 37.0%, distant metastasis in 13.5% vs. 13.0%, and both locoregional and distant failure in 3.1% versus 2.5%, respectively; these values were not significantly different (Table 3).

Adverse effects

The most common grade 1 to 2 AE was radiation esophagitis (70.2%). 42 patients (46.0%) developed grade 1 to 2 radiation pneumonitis; The most common hematologic toxicity was a decrease in leukocytes (44.0%). The incidence of grade 3 and above AEs were 24.2%, including 10 (11.0%) leukopenia, 4 (4.4%) neutrophilia, 4 (4.4%) radiation esophagitis, 3 (3.3%) thrombocytopenia, and 1 (1.1%) hemoglobin decrease. All patients had improved AEs after symptomatic treatment, and there were no deaths of treatment-related toxicity (Table 4).

A post-hoc analysis indicated that severe AEs (grade 3 or higher) were documented in 18.9% of patients within the 50.4 Gy treatment subgroup and in 20.4% of patients

within the 61.2 Gy treatment subgroup (P=0.846). However, the prevalence of radiation-induced dermatitis was notably elevated in the subgroup receiving 61.2 Gy compared to the subgroup treated with 50.4 Gy (5.4% vs. 20.4%, P=0.045, Table 5).

Discussion

Our study suggested that 75 years old or older ESCC patients receiving single-agent S-1 combined with IF-IMRT were significantly higher in local control, survival rate, and well tolerated. Furthermore, the survival rates among patients undergoing 50.4 Gy dose radiotherapy were comparable to those receiving 61.2 Gy, while the frequency of adverse events was significantly lower in the 50.4 Gy cohort.

With the extension of life expectancy and the aggravation of population aging, the cancer burden of EPs in China is increasing [11]. As the principal therapeutic approach for patients with ESCC, enhancing the precision of radiotherapy targeting and mitigating the toxicity to target organs and adjacent tissues presents a formidable challenge. Compared with conventional radiation therapy, IMRT reduces cardiac and pulmonary exposure and toxicity and prolongs survival [12]. Owing to the unique "skipping" metastatic behavior of lymph nodes in esophageal tumors, the application of prophylactic lymph node irradiation may effectively curtail local recurrence or distant metastasis in patients [13]. Target volume delineation during the precise RT for EC includes IFI and ENI. ENI has a larger range of irradiation field, which increases the incidence of grade 3 or higher radiation esophagitis and radiation pneumonitis [14, 15]. In the study by Chen et al. [16], it was observed that patients aged 75 years or older with ESCC who received IF-IMRT in combination with S-1 achieved a 2-year OS rate of 54.3%. The incidence of radiation esophagitis of grade 3 or higher was notably low, at only 3.8%. The predominant patterns of treatment failure were local recurrence and distant metastasis within the irradiated field, with almost no instances of lymph node recurrence in the irradiated areas. In our study, the 2-year OS rate was 59.2% in 91 patients, which is broadly similar to the results of the two studies above. In summary, IF-IMRT is recommended for EPs with locally advanced ESCC, especially those with chronic diseases such as heart and lung, who receive radical CCRT.

EPs were at increased risk of toxicity to intravenous chemotherapy compared with younger patients due to increasing age and decreasing bone marrow reserve [17]. As shown in the relevant clinical studies in Table 6, we can observe that the toxicity of dual-agent intravenous chemotherapy combined with radiotherapy for EPs with ESCC is greater than that of single-agent chemotherapy combined with radiotherapy [9, 18–23]. Although some retrospective studies [20, 24] showed that EPs receiving fluorouracil and cisplatin rarely develop serious AEs and death from related causes, these patients may be carefully screened, and most of these patients also receive lower doses of chemotherapy or radiotherapy. S-1/capecitabine oral chemotherapy combined with radiotherapy appears to be more appropriate for EPs with ESCC [25]. S-1 is a third-generation novel fluorouracil oral anticancer drug consisting of tigafluoride, gemstone, and acrylamide potassium [26]. Meta-analysis showed that for EPs with esophageal cancer, S-1 combined with radiotherapy could achieve more satisfactory efficacy and better tolerated [27]. Moreover, Xu et al. [28] conducted a randomized, open-label, phase-clinical trial in 23 centers in China. This study included 298 patients with locally advanced ESCC aged 70 to 85 years. The 2-year OS in the radiotherapy group combined with S-1 was significantly higher than that in the radiotherapy alone group (53.2% vs. 35.8%, P=0.002). Grade 3 or above were more patients in the concurrent chemoradiotherapy group than in the radiotherapy alone group (95% vs. 27%, P=0.010). Similarly, our study further supports the efficacy of S-1. Interestingly, S-1 [29] is an oral fluoropyrimidine derivative similar to capecitabine, but there have been few studies of single-agent capecitabine in combination with radiotherapy in EPs with ESCC. A large multicenter randomized phase III study by Jia and colleagues [23] included 246 patients with ESCC who were assessed as not tolerating surgery or unwilling to undergo surgery.

Table 5 Comparison of the safety of radiotherapy dose 50.4 gy and 61.2 gy in elderly patients with ESCC

Adverse effects	50.4 Gy(n=37)			61.2 Gy(n=54)			P-value
	Grade 1~2	Grade 3	Grade 4	Grade 1~2	Grade 3	Grade 4	
Leukopenia	13(35.1)	3(8.1)	1(2.7)	17(31.5)	5(9.3)	1(2.0)	0.752
Neutropenia	8(21.6)	1(2.7)	0	15(27.8)	2(3.7)	1(2.0)	0.355
Thrombocytopenia	13(35.1)	2(5.4)	0	13(24.1)	1(2.0)	0	0.142
Anemia	23(62.2)	0	0	17(31.5)	1(2.0)	0	0.004#
Esophagitis	22(59.5)	0	0	42(77.8)	0	0	0.060
Pneumonitis	14(37.8)	0	0	28(51.9)	0	0	0.249
Dermatitis	2(5.4)	0	0	11(20.4)	0	0	0.045

Table 6 Clinical research on radiotherapy combined with single-drug/double-drug chemotherapy for the treatment of esophageal squamous cell carcinoma in the EPs

Study	Sample size	Study type	Age(year)	stage	Treatment	Completion rate (%)	mOS(months)	2-year OS rate (%)	AEs (grade ≥ 3) (%)
Liu (2022) [9]	34	prospective	72–80	II-III	RT vs. CCRT: IF-IMRT (50–60 Gy/25–30 F) + S-1	100	23.0 vs. 27.0	47.1 vs. 58.8	1.4 vs. 5.8
Wang (2017) [18]	56	retrospective	70–87	II-IV	CCRT: RT (54.0 Gy/27–30 F) + S-1 + cisplatin	67.9	18.2	45.6	55.4
S E Anderson (2007) [16]	25	retrospective	66–88	II-III	CCRT: RT (50.4 Gy/28F) + 5-FU + mitomycin	88.0	35.0	64.0	36.0
Xing (2014) [20]	75	retrospective	65–74	I-IV	CCRT vs. SCRT: RT (54.0–60 Gy/30–33 F) + capecitabine + cisplatin	68.9 vs. 96.7	15.7 vs. 11.6	60.2 vs. 45.3	45.2 vs. 17.2
Huang (2019) [21]	271	retrospective	65–89	I-IV	RT vs. RT (40–74 Gy) + docetaxel/ platinum/5-FU vs. RT (40–74 Gy) + platinum + 5-FU/paclitaxel/docetaxel	NA	15.6 vs. 28.8 vs.27.8	39.0 vs. 59.0 vs.57.0	8.5 vs. 26.3 vs.45.8
Hulshof (2021) [22]	260	prospective	34–90	I-IVb	RT (50.4 Gy) + PC vs. RT (61.6 Gy) + PC	93.1 vs. 87.7	25.7 vs. 24.6	50.8 vs. 40.8	55.0 vs. 63.6
Jia (2024)[23]	246	prospective	61–71	II-IV	RT (50 Gy/25F) + capecitabine vs. RT + XELOX vs. RT + PF	100	40.9 vs. 41.9 vs.35.4	75.0 vs. 66.7 vs. 70.9	28.8% vs.36.5%, vs.45.7%

Abbreviation: mOS: median OS; AEs: adverse events; RT: radiotherapy; CCRT: concurrent chemoradiotherapy; SCRT: sequential chemoradiotherapy; IF-IMRT: involved-field intensity-modulated radiotherapy; F: fractions; XELOX: capecitabine + oxaliplatin; PF: fluorouracil plus cisplatin

They were randomly divided into groups receiving radiotherapy combined with capecitabine, radiotherapy combined with capecitabine plus oxaliplatin (XELOX), and radiotherapy combined with 5-fluorouracil plus cisplatin (PF). The median age of the patients in the capecitabine group was 66 years old. In capecitabine, XELOX, and PF arms, the 2-year OS rate was 75%, 66.7%, and 70.9% (capecitabine vs.PF: $P=0.637$; XELOX vs.PF: $P=0.444$); the mOS was 40.9, 41.9 and 35.4 months. The incidence of grade ≥ 3 AEs during the entire treatment was 28.8%, 36.5%, and 45.7%, respectively. The higher 2-year OS rate in this study may be attributed to the advances in radiotherapy techniques, fewer Eps, comprehensive supportive care, and high treatment compliance. In conclusion, the results of these clinical trials [26, 27, 30, 31] suggest that EPs can tolerate S-1 combine with radiotherapy, and this treatment can be used as a standard treatment regimen for radical chemoradiotherapy in elderly esophageal cancer. However, capecitabine is also likely to be an alternative option for locally advanced EPs with ESCC.

Radiation in a dose of 50 Gy combined with dCRT is the standard therapy for patients with localized carcinoma of the esophagus who are selected for nonsurgical treatment, on the basis of the Intergroup trial RTOG 85 − 01 [4, 32]. However, the locoregional failure rate after dCRT was high (35–45%), which was also demonstrated in several other large dCRT series [33]. The dose of 50 Gy is relatively low compared with radiation doses used in curative dCRT schemes for other carcinomas, such as lung cancer and head and neck cancer, and higher OS rates are achieved in these tumors [34–36]. The randomized RTOG INT 0123 trial [37] compared CRT using a high dose (64.8 Gy) with a standard dose (50.4 Gy), combined with chemotherapy. There was no significant difference in 2-year OS (31% vs.40%) between the high- and standard-dose arms. The ARTDECO study [22], a total of 260 patients with esophageal cancer were enrolled and randomly assigned to high-dose (64.8 Gy) and standard-dose (50.4 Gy). The results showed no difference in OS ($P=0.220$) and grade ≥ 3 AE ($P=0.150$) between the two groups, and the increase in radiotherapy dose did not improve the local control rate of patients. Presently, the NCCN guidelines, the Japanese esophageal cancer guidelines, the CSCO esophageal cancer guidelines, and several clinical studies have not made a dosing for radical chemoradiotherapy in EPs with esophageal cancer [38]. Several randomized studies and meta-analysis showed that 50–50.4 Gy doses should be used as the standard dose in patients receiving concurrent chemoradiotherapy [39–41]. Due to the large time span of our study, the standard

radiotherapy dose for dCRT for esophageal cancer changed during the trial, so we made appropriate adjustments. Results from different dose subgroups showed no significant difference in PFS and OS, but EPs who received 61.2 Gy were more likely to develop radiation dermatitis. Moreover, the rates of local and distant recurrence were the same in the two subgroups. Advances in radiotherapy technology and the determination of standard doses of radiotherapy have reduced the occurrence of AEs, but intra-field recurrence remains the most common type of progression after radical chemoradiotherapy [42, 43]. Zhao et al. [44] are conducting a study to screen patients who would benefit from increased radiotherapy dose based on SUV values shown on PET/CT, to improve local control and more precise individualized treatment. However, some patients have been resistant to radiotherapy, so the combination of new drugs may be more likely to improve the LCR and survival of patients. At present, multiple phase II studies have confirmed the efficacy and safety of immunization combined with radical chemoradiotherapy in the treatment of locally advanced esophageal cancer [45, 46]. Therefore, dose escalation of radical chemoradiotherapy, combination of new drugs, and exploration of prognostic markers will provide more precise treatment for patients with locally advanced ESCC.

Notably, our univariate analysis showed that age was one of the prognostic factors affecting ESCC patients, while multivariate results showed that gender was one of the independent factors for prognosis, and tumor length, clinical stage, and ECOG score were also generally associated with prognosis [47–49]. It may be that 42.6% of EPs died from chronic diseases and decreased physiological function contributed to our results showing a bias of prognostic factors.

Limitations

There were some limitations to our study. First, this was a small, single-center, prospective study with no separate radiotherapy control group. Second, in our study, patients received different doses of radiotherapy, which may have led to some deviations in the survival and safety of patients, although there was no statistically significant difference in subgroup analysis. In addition, we did not comprehensively assess the health status and quality of life after treatment in elderly patients, which may be a key factor in influencing whether patients can complete treatment, and can better assess the safety of IFI in combination with S-1.

Conclusion

In our study, the efficacy of IF-IMRT combined with S-1 in the treatment of EPs with ESCC aged 75 years or older was commendable. In EP with advanced ESCC CCRT with S1 is feasible with primising outcome and acceptable toxicity. Furthermore, we recommend a radiation dose of 50.4 Gy as the standard dose for CCRT.

Supplementary Information

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Supplementary Material 1

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Author contributions

Jinjun Ye had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Dayong Gu and Tian Wang contributed equally to this work. Concept and design: Jinjun Ye, Dayong Gu. Acquisition, analysis, or interpretation of data: Yiyu Guo, Ying Fang, Wei Chen, Qiang Wang, Rongrong Zhang. Drafting of the manuscript: Dayong Gu, Tian Wang. Critical revision of the manuscript for important intellectual content: Jinjun Ye, Tian Wang, Ying Liu. Statistical analysis: Tian Wang, Haifeng Shi, Daguang Wu. Obtained funding: Jinjun Ye. Administrative, technical, or material support: Zhi Zhang, Guoren Zhou.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics committee of the Jiangsu Cancer Hospital, reference number ChiTR1900020876.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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