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ORIGINAL ARTICLE

Concurrent chemoradiotherapyof different radiation doses and different irradiation fields for locally advanced thoracic esophageal squamous cell carcinoma: A randomized, multicenter, phase III clinical trial

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Abstract

Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced esophageal squamous cell carcinoma (ESCC). However, the optimal radiotherapy regimen, particularly in terms of total dose and planned range of irradiation field, remains unclear. This phase III clinical trial aimed to compare the survival benefits between different radiation doses and different target fields.

Methods: This trial compared two aspects of radiation treatment, total dose and field, using a two-by-two factorial design. The high-dose (HD) group received 59.4 Gy radiation, and the standard-dose (SD) group received 50.4 Gy. The

Abbreviations: HD, high dose radiation; SD, standard dose radiation; IFI, involved field radiation; ENI, elective nodal radiation; ESCC, esophageal squamous cell carcinoma; EC, esophageal cancer; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTCAE, Common Terminology Criteria for Adverse Events; CCRT, concurrent chemoradiotherapy; GTV, gross tumor volume; CTV, clinical target volume; CTVend, CTV of elective lymph nodes; PTV, planned target volume; OS, overall survival; mOS, median overall survival; PFS, progression-free survival; mPFS, median progression-free survival; LRFFS, locoregional failure-free survival; HR, hazard ratio; CI, confidence interval; ORR, objective response rate; SAE, severe adverse events; ECOG, Eastern Cooperative Oncology Group;; RTOG, Radiation Therapy Oncology Group; N.A., not available.

Jian Zhang, Minghao Li, Kaixian Zhang, Anping Zheng, Guang Li and Wei Huang contributed equally to this work.

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involved field irradiation (IFI) group and elective nodal irradiation (ENI) group adopted different irradiation ranges. The participants were assigned to one of the four groups (HD+ENI, HD+IFI, SD+ENI and SD+IFI). The primary endpoint was overall survival (OS), and the secondary endpoints included progression-free survival (PFS). The synergy indexwas used to measure the interaction effect between dose and field.

Results: The interaction analysis did not reveal significant synergistic effects between the dose and irradiation field. In comparison to the target field, patients in IFI or ENI showed similar OS (hazard ratio [HR] = 0.99, 95% CI: 0.80-1.23, p = 0.930) and PFS (HR = 1.02, 95% CI: 0.82–1.25). The HD treatment did not show significantly prolonged OS compared with SD (HR = 0.90, 95% CI: 0.72–1.11, p = 0.318), but it suggested improved PFS (25.2 months to 18.0 months). Among the four groups, the HD+IFI group presented the best survival, while the SD+IFI group had the worst prognosis. No significant difference in the occurrence of severe adverse events was found in dose or field comparisons.

Conclusions: IFI demonstrated similar treatment efficacy to ENI in CCRT of ESCC. The HD demonstrated improved PFS, but did not significantly improve OS. The dose escalation based on IFI (HD+IFI) showed better therapeutic efficacy than the current recommendation (SD+ENI) and is worth further validation.

KEYWORDS

clinical trial, concurrent chemoradiotherapy, elective nodal radiation, esophageal squamous cell carcinoma, high dose radiation, involved field radiation, overall survival, standard dose radiation

1 | BACKGROUND

Esophageal cancer (EC) rankssixth in cancer-associated deaths worldwide [1], and esophageal squamous cell carcinoma (ESCC) is the most common histological subtypeof EC in East Asia [2]. For unresectable locally advanced ESCC, the standard treatment is concurrent chemoradiotherapy (CCRT), which was established following the publication of the RTOG 85-01 clinical trial [3]. With the advancement of radiotherapy technology, the median overall survival (mOS) after CCRT has been improved from 14 months in RTOG 85-01 [3] to longer than 30 months in recent clinical trials [4–6].

The recommended dose of radiotherapy in CCRT of ESCCis 50.4 Gy (standard doseirradiation, SD) according to the RTOG 94-05 (INT 0123) trial [7, 8], but in the field of radiology it is considered that at least 60 Gy is necessaryto control local tumors [9, 10]. A high-dose (HD) radiation, i.e., 59.4 Gy, was often adopted in real-world practice [11, 12]. However, previous dose escalationtrials often failed to prove the benefits of HD radiationin OS [4, 6, 13, 14]. Due to the high rate of local control failure, there are still ongoing dose escalation trials being conducted in ESCC to determine the optimal dose using current radiotherapy technology [15].

On the other hand, given the high proportion of nodal micrometastasis and the high risk of regional nodal failure in ESCC, the current National Comprehensive Cancer Network (NCCN) guidelines recommendtargetingnot only the tumor-involved field (as involved field irradiation, IFI) but also the involved elective lymphnodes (as elective nodal irradiation, ENI) in radiotherapy [16]. ENI might havethe advantage of preventing regional nodal failure, especially for clinical N0 patients in whom the potential nodal micrometastasis might be undetectable in medical imaging. However, with developments in imaging technology in regard to pre-treatment evaluation and precision in radiotherapy, the necessity of ENI is being questioned due to its uncertain benefits and higher toxicity. There have been several phase III clinical trials designed to test the benefits of ENI in CCRT of ESCC, including the ongoing phase III clinical trial JCOG1904 [17], which only involved early patients (cT1bN0M0) to compare ENI and IFI, although the reported results are controversial [18–21].

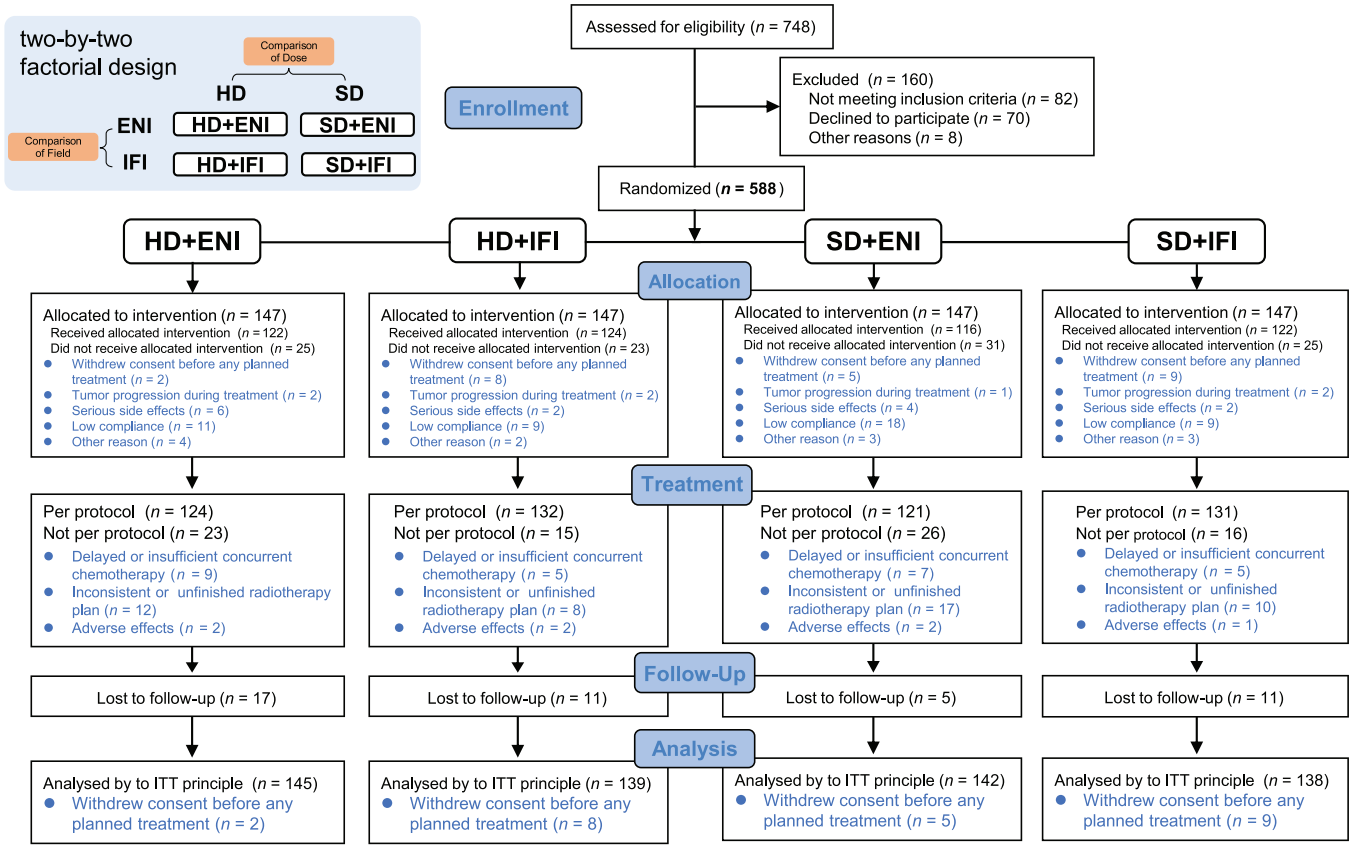

FIGURE 1 The CONSORT diagram of this clinical trial. Abbreviations: ENI, elective nodal radiation; HD, high dose radiation; IFI, involved field radiation; ITT, Intention-to-treat; SD, standard dose radiation.

In the era of immunotherapy for ESCC, the choice of expanding irradiation volume would be more critical to reduce lymphocytotoxicity in the draining lymph nodes [22].

To evaluate the potential interaction between radiation dose and volume, we designed and conducted this randomized, multicenter, phase III clinical trial, which implemented a two-by-two factorial design to simultaneously compare different total doses (SD or HD) and different target fields (ENI or IFI) in CCRT of ESCC. The recruitment stage started in July 2015 and ended in November 2020. The results provide updated evidence on the optimal pattern of radiotherapy in CCRT of ESCC.

2 | METHODS

2.1 | Design of the clinical trial

This multicenter, randomized, phase III clinical trial was registered in the Chinese Clinical Trial Registry (ChiCTR) with the registration number ChiCTR-IPR-15007172 and was approved by the ethics committee of Shandong Cancer Hospital and Institute (Jinan, Shandong, P. R. China) with the approval number of No. 201509008.

In this study, patients were divided into four treatment arms based on two independent variables (radiation dose and target field; Figure 1): (1) SD+ENI: patients receiving SD with ENI; (2) HD+ENI: patients receiving HD with ENI; (3) SD+IFI: patients receiving the SD with IFI; and (4) HD+IFI: patients receiving HD with IFI. For clarity, we combined the four treatment arms (HD+ENI, SD+ENI, HD+IFI, and SD+IFI) as different groups (HD, SD, IFI and ENI groups) for dose or field comparisons in the following part. The HD group consists of patients in two arms of HD+IFI and HD+ENI, the SD group of SD+IFI and SD+ENI, the ENI group of HD+ENI and SD+ENI, and the IFI group of HD+ IFI and SD+ IFI.

The patients were recruited from 31 centers, and all the initial evaluations and assignments were centralized at the Shandong Cancer Hospital and Institute. The participants were assigned to the four arms in a 1:1:1:1 ratio using block randomization, which was determined by a pre-established random sequence of assignments.

2.2 | Patients

The inclusion criteria were as follows: (1) aged 18 to 70 years old; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (3) life expectancy longer than 6 months; (4) histologically proven squamous cell carcinoma; (5) all lesions located in the thoracic part of the esophagus and the maximum length of tumor less than 10 cm; (6) stages II to IVa (6th Union for International Cancer Control [UICC]-tumor-node-metastasis [TNM] classification); (7) no prior antitumor treatment; and (8) provided signed informed consent.

The exclusion criteria were as follows: (1) a history of previous malignant tumor; (2) skip neoplastic lesions inthe esophagus; (3) pregnant or lactating; (4) had fertility but did not use contraception; (5) with serious comorbidity, including poorly controlled hypertension, a large area of myocardial infarction, cardiac function class II or higher, or severe diabetes, and severe emphysema or pulmonary fibrosis; (6) with psychiatric disease; (7) in activity of infectious diseases, such as community-acquired pneumonia or active hepatitis; (8) participated in other clinical trials; (9) used other anticancer drug therapy, including traditional Chinese medicine against tumors; (10) inserted esophageal stent prior to the trial; (11) high risk of esophageal perforation; and (12) history of organ transplantation.

2.3 | Definition of the irradiation target field

In this study, the gross tumor volume (GTV) was identified by multimodal imaging, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography/CT (PET/CT), gastrointestinal contrast, and esophagoscopy. The GTV is separated into GTV of the primary tumor (GTVp) and GTV of metastatic lymph nodes (GTVnd). Clinical metastatic lymph nodes were identified when the shortest axis of lymph nodes measured more than 1.0 cm in the intrathoracic and intra-abdominal regions, or more than 0.5 cm adjacent to the paraesophageal, tracheoesophageal sulcus, and supraclavicular regions, or when the nodes exhibited a significantly elevated standardized uptake value in PET/CT. The GTVnd region is only applicable to patients with clinically metastaticlymph nodes (cLN+).

We distinguished three parts of the clinical target volume (CTV). The CTV of the primary tumor (CTVp) represented the GTV with an extended margin (3cm craniocaudal margin expansion and a 0.5 cm lateral margin expansion). The CTV of metastatic lymph nodes (CTVnd) comprises the GTV with a lymph node extended margin (0.5 cm three-dimensional uniform expansion). The CTV of elective lymph nodes (CTVend) encompassed the predefined high-risk region of the draining lymph nodes [23, 24]. In accordance with the definition of GTVnd, the CTVnd was only defined in cLN+ patients, while the CTVend was defined in each ESCC primary tumor based on its location. The CTV in the IFI group included CTVp and CTVnd (in cLN+), while the CTV in the ENI group comprised CTVp, CTVnd (in cLN+), and CTVend. The planned target volume (PTV) was defined as the total CTV region plus a 0.5 cm radially expansion and a 0.5-0.8 cm craniocaudal margin expansion in all cases. All the expansions were adjusted when the anatomical barrier was considered.

2.4 | Treatments

The patients in the HD group and SD group received a total of 59.4 Gy and 50.4 Gy of intensity-modulated radiotherapy (IMRT), respectively.

Two cycles of Tegafur/gimeracil/oteracil (Tegio or S-1, 80 $mg{\cdot}m^{-2}{\cdot}day^{-1}$, oral) and cisplatin (DDP, 75 $mg{\cdot}m^{-2}{\cdot}cycle^{-1}$, injection, solution, intravenous) were administered concurrently with radiotherapy. The concurrent chemotherapy could be extended up to 28 $days{\cdot}cycle^{-1}$ if severe toxic reactions happened, but it had to be given in at least one cycle. The dose of DDP and S-1 could be adjusted to 75% of the planned dose but could not be less than 50%.

Radiologists generally reassess the GTV planning in CCRT of ESCC at around 40 Gy point. It is believed that 40 Gy should be enough for preventive irradiation; therefore, reduced preventive irradiation after 40 Gy might obtain equivalent treatment effects but less radiation-related toxicities. Therefore, the radiotherapy was conducted in two stages, which was also adopted in previous clinical trials, such as JCOG1904 [17], NCT01551589 [20], NCT00686114 [25], and UMIN000000856 [26].

In the first irradiation stage, all patients were given 41.4 Gy (1.8 Gy × 23 fractions) radiotherapy. In the second irradiation stage, the patients in the SD group were planned to receive 9 Gy (1.8 Gy × 5 fractions, 50.4 Gy in total), and the patients in the HD group were planned to receive 18 Gy (1.8 Gy × 10 fractions, 59.4 Gy in total). The IFI group and ENI groupused different CTVs in the first irradiation stage (41.4 Gy), while in the second irradiation stage (9 Gy or 18 Gy), the GTV was reassessed, and both IFI and ENI groups adopted CTV radiation without CTV end.

2.5 | Quality control of irradiation

To ensure the quality and homogeneity of radiotherapy across multiple centers, we conducted three quality control procedures. Firstly, we implemented a standardized protocol for CTVend contouring before the start of the clinical trial [23] and conducted seven training programs for clinicians in different cities from 2015 to 2018. Secondly, we collected and reassessed the radiotherapy plans of enrolled patients, especially on the irradiation fields, the dose-volume histograms, and the dose on the organs at risk in Shandong Cancer Hospital and Institute. Thirdly, with the assistance of the Shandong Cancer Quality Control Center (http://shandong.china-rt.cn/), we conducted quality control assessments of radiotherapy systems in the majority of the participating centers, which minimized the potential bias stemming from different radiotherapy equipment.

2.6 | Statistical analysis

The trial utilized a two-by-two factorial design with two independent comparisons (radiation dose and planned irradiation field). The primary endpoint was OS, and the secondary endpoints included progression-free survival (PFS), locoregional failure-free survival (LRFFS), objective response rate (ORR), and treatment toxicity.OS was defined as the period from randomization to death from any cause. PFS was defined as the period from randomization to disease progression, and it was censored if a patient had died without any evidence of progression. LRFFS was defined as the period from randomization to the time of local regional failure. ORR was defined as the percentage of patients with a confirmed complete response (CR) or partial response (PR) in short-term evaluation. The adverse reactions were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 criteria [27].

In the design stage of this trial, we estimated that the median survival time of all patients would beapproximately 2 years [28, 29], and we planned to achieve a median follow-up period of at least 4 years for all patients. For each of the two comparisons (radiation dose and irradiation field), under the condition of a 0.75 hazard ratio (HR) and a 0.025 (0.05/2) alpha level in a two-sided test, and an estimated 5% overall dropout rate, we needed 294 patients in each group (588 in total) to achieve 80% statistical power.

The final analysis was performed according to the intention-to-treat (ITT) principleonthe full analysis set (FAS). The ITT principle implied that all participants would be analyzed based on their original group assignment, regardless of the treatment they actually received. The FAS was defined as all the randomized patients, except those who withdrew their consent agreement before receiving any planned treatment.

The Kaplan-Meier survival curves were utilized to estimate the survival rate. The significance of survival comparisons wasassessed using the log-rank test, and the HR was calculated using the Cox proportional hazards model. The significance of categorical variables among groups, such as the adverse effects, was evaluated using the Fisher exact test. The synergy indexwas used to measure the interaction effect between dose and field in the Cox proportional hazards model. All the analyses and data visualization were conducted in R (version 4.2, R Core Team, https://www.R-project.org/) using the survival package (version 3.3).

3 | RESULTS

3.1 | Overview of the clinical trial

Of the 588 patients who were enrolled and randomized, 24 patients withdrew their consent before any planned treatment, and the remaining 564 patients (95.9% of 588) who proceeded with the treatment plan formed the FAS for all subsequent analyses (Figure 1). The planned treatments were fully compliedwith in 85.8% (484 out of 564) of the FAS. The per-protocol (PP) rates were similar in the HD group and SD group (86.8%*v.s.* 85.0%, $p = 0.630$). However, the IFI group had a higher PP rate than the ENI group (88.8% *v.s.* 82.9%, $p = 0.053$), suggesting better tolerance in the IFI group. The demographic characteristics of the FAS are summarized in Table 1.

The median follow-up time reached 64.6 months (range, 7.9-94.3 months, 95% CI: 61.2-69.5) up to April 2023. For all FAS patients, the median OS (mOS) was 31.2 months(95% CI: 27.5-39.4), and the median PFS (mPFS) was 20.9 months (95% CI: 17.5-25.8). The 1-year and 3-year OS rates were 78.5% (95% CI: 75.2-82.0) and 47.4%(95% CI: 43.4-51.7), respectively.

In the HD+ENI, SD+ENI, HD+IFI, and SD+IFI arms, the mOS was 27.2 months (95% CI: 22.1-25.8), 30.9 months (95% CI: 26.5-78.6), 46.3 months (95% CI: 28.6–not reached), and 28.3 months (95% CI: 24.7-36.8), respectively (Figure 2A), and the mPFS was 21.2 months (95% CI: 17.3-39.0), 21.0 months (95% CI: 13.5-32.8), 30.8 months (95% CI: 17.5–not reached), and 16.9 months (95% CI: 11.0-22.2), respectively (Figure 2B).

For exploratory purposes, we set the HD+IFI arm as the reference group and calculated the HR and nominal *p* value by Cox regression in the other three arms (Figure 2). The results indicated that the difference margins (measured by HR value) between SD+IFI and HD+IFI were 1.34 in OS and 1.51 in PFS. Of note, the pairwise comparisons

TABLE 1 Demographic characteristics of the FASpopulation.

Characteristic	HD+ENI ($n = 145$)	HD+IFI ($n = 139$)	SD+ENI ($n = 142$)	SD+IFI ($n = 138$)	p
Age (years)					
Median (25%-75%)	63 (57-67)	63 (58-67)	63 (58-67)	63 (59-66)	0.895
Tumor length (cm)					
Mean ± SD	5.81 ± 2.06	5.56 ± 1.96	5.55 ±2.01	5.34 ± 2.06	0.278
Sex, *n*(%)					
Female	38 (26.2)	33 (23.7)	37 (26.1)	38 (27.5)	0.910
Male	107 (73.8)	106 (76.3)	105 (73.9)	100 (72.5)	
ECOG score, *n*(%)					
0	47 (32.4)	52 (37.4)	58 (40.8)	51 (37.0)	0.528
1	98 (67.6)	87 (62.6)	84 (59.2)	87 (63.0)	
Location, *n*(%)					
Lower thorax	22 (15.2)	23 (16.5)	30 (21.1)	20 (14.5)	0.382
Middle thorax	71 (49.0)	53 (38.1)	60 (42.3)	60 (43.5)	
Upper thorax	52 (35.9)	63 (45.3)	52 (36.6)	58 (42.0)	
T stage, *n*(%)[a]					
T1	3 (2.1)	1 (0.7)	1 (0.7)	3 (2.2)	0.451
T2	15 (10.3)	25 (18.0)	16 (11.3)	14 (10.1)	
T3	95 (65.5)	91 (65.5)	99 (69.7)	91 (65.9)	
T4	32 (22.1)	22 (15.8)	26 (18.3)	30 (21.7)	
N stage, *n*(%)[a]					
N0	25 (17.2)	31 (22.3)	26 (18.3)	26 (18.8)	0.728
N1	120 (82.8)	108 (77.7)	116 (81.7)	112 (81.2)	
M stage, *n*(%)[a]					
M0	126 (86.9)	115 (82.7)	123 (86.6)	122 (88.4)	0.563
M1a	19 (13.1)	24 (17.3)	19 (13.4)	16 (11.6)	
TNM stage, *n*(%)[a]					
II	27 (18.6)	39 (28.1)	21 (14.8)	32 (23.2)	0.150
III	98 (67.6)	78 (56.1)	99 (69.7)	88 (63.8)	
IVA	20 (13.8)	22 (15.8)	22 (15.5)	18 (13.0)	
Smoking, *n*(%)					
No	77 (53.1)	71 (51.1)	85 (59.9)	86 (62.3)	0.187
Yes	67 (46.2)	67 (48.2)	57 (40.1)	51 (37.0)	
N.A.	1 (0.7)	1 (0.7)	0 (0)	1 (0.7%)	
Drinking, *n*(%)					
No	74 (51.0)	83 (59.7)	79 (55.6)	84 (60.9)	0.314
Yes	70 (48.3)	55 (39.6)	63 (44.4)	53 (38.4)	
N.A.	1 (0.7%)	1 (0.7%)	0	1 (0.7%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ENI, elective nodal radiation; HD, high dose radiation; IFI, involved field radiation; N.A., not available; SD, standard deviation; SD, standard dose radiation.

[a]assessed according to the 6th UICC-TNM staging system.

between the four arms were not part of the designed statistical tests of this clinical trial. In fact, due to the limited sample size in pairwise comparisons, even if we ignore the inflated cumulate type I error rate in multiple tests, the statistical power (around 55% in HR = 1.4 and total events = 170) still does not support us to obtain solid conclusions.

3.2 | Survival comparison

We accessed the significance of interactions between radiation dose and field using multiple Cox regression models with an interaction term (dose×field). The results (synergy index = 0.247, $p = 0.899$ in OS; synergy index = 0.458,

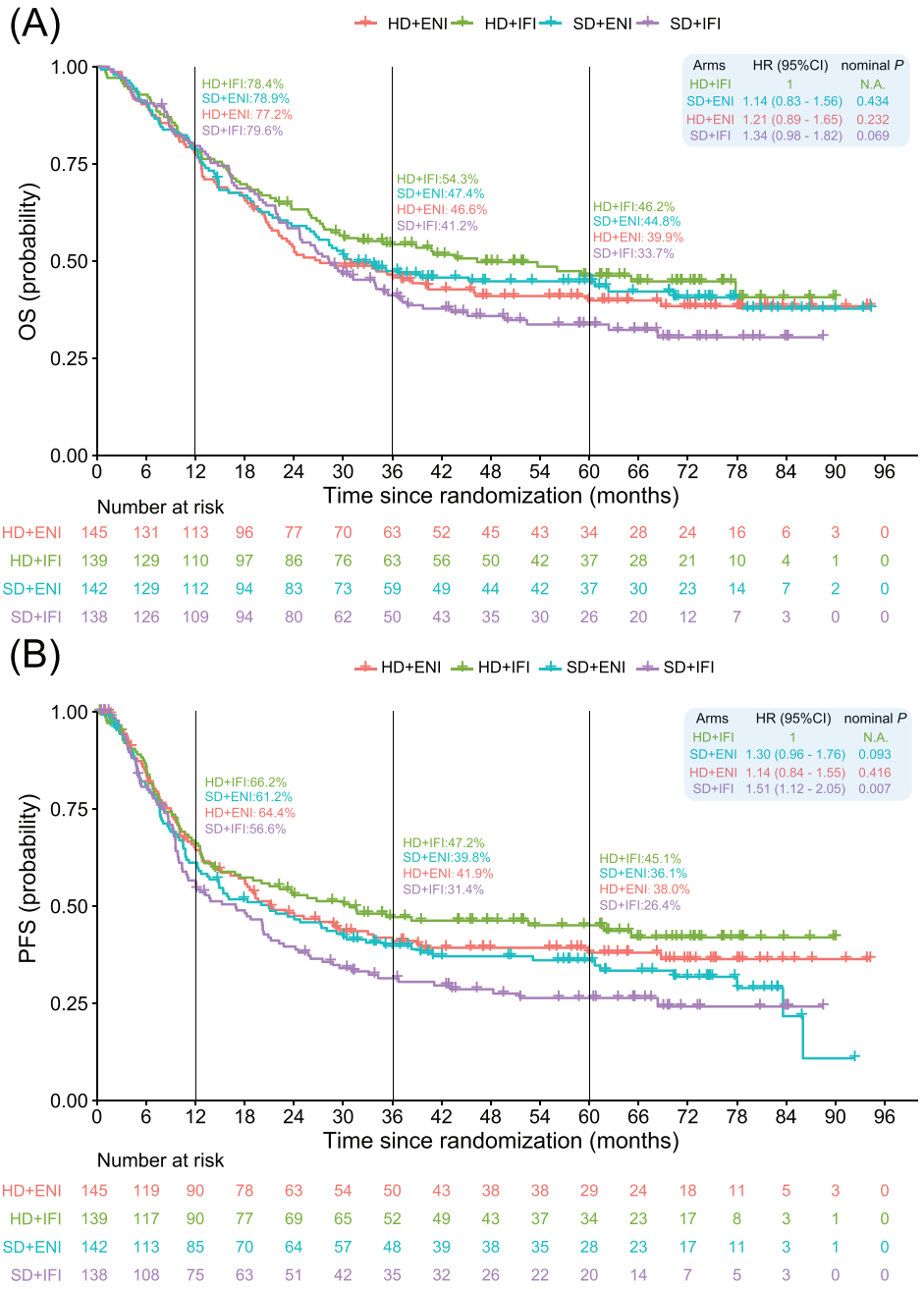

FIGURE 2 The survival plots in each treatment arm. TheOS (A) or PFS (B) survival curves in each treatment group. The survival rates of each arm at 12, 36 and 60 months are labeled in the plot. Abbreviations: CI, confidence interval; ENI, elective nodal radiation; HD, high dose radiation; HR, hazard ratio; IFI, involved field radiation; N.A., not available; OS, overall survival; PFS, progression-free survival; SD, standard dose radiation.

$p = 0.924$ in PFS) showed no significant synergistic effect between dose and field, indicating that the treatment efficacy of radiation dose and field is based more on their independent effects than the synergistic effects.

The comparisons of target fields (ENI *v.s.* IFI) indicated similar outcomes in OS (HR = 0.99, 95% CI: 0.80-1.23, $p = 0.930$), PFS(HR = 1.02,95% CI: 0.82–1.25, $p = 0.888$) and LRFFS(HR = 0.94,95% CI: 0.72–1.25, $p = 0.647$) (Figure 3A-C). The one-year cumulative local failure rate (or 1 minus one-year LRFFS) was numerically higher in the ENI group than in the IFI group (22.7% *v.s.* 19.2%, $p = 0.647$, Figure 3C. The ORR did not significantly vary between the ENI group and the IFI group (76.7% *v.s.* 77.6%, $p = 0.841$, Figure 4).

In the SD and HD groups, the mOS were 29.8 (95% CI: 26.5-36.8) and 36.0 (95% CI: 26.8-59.8) months,

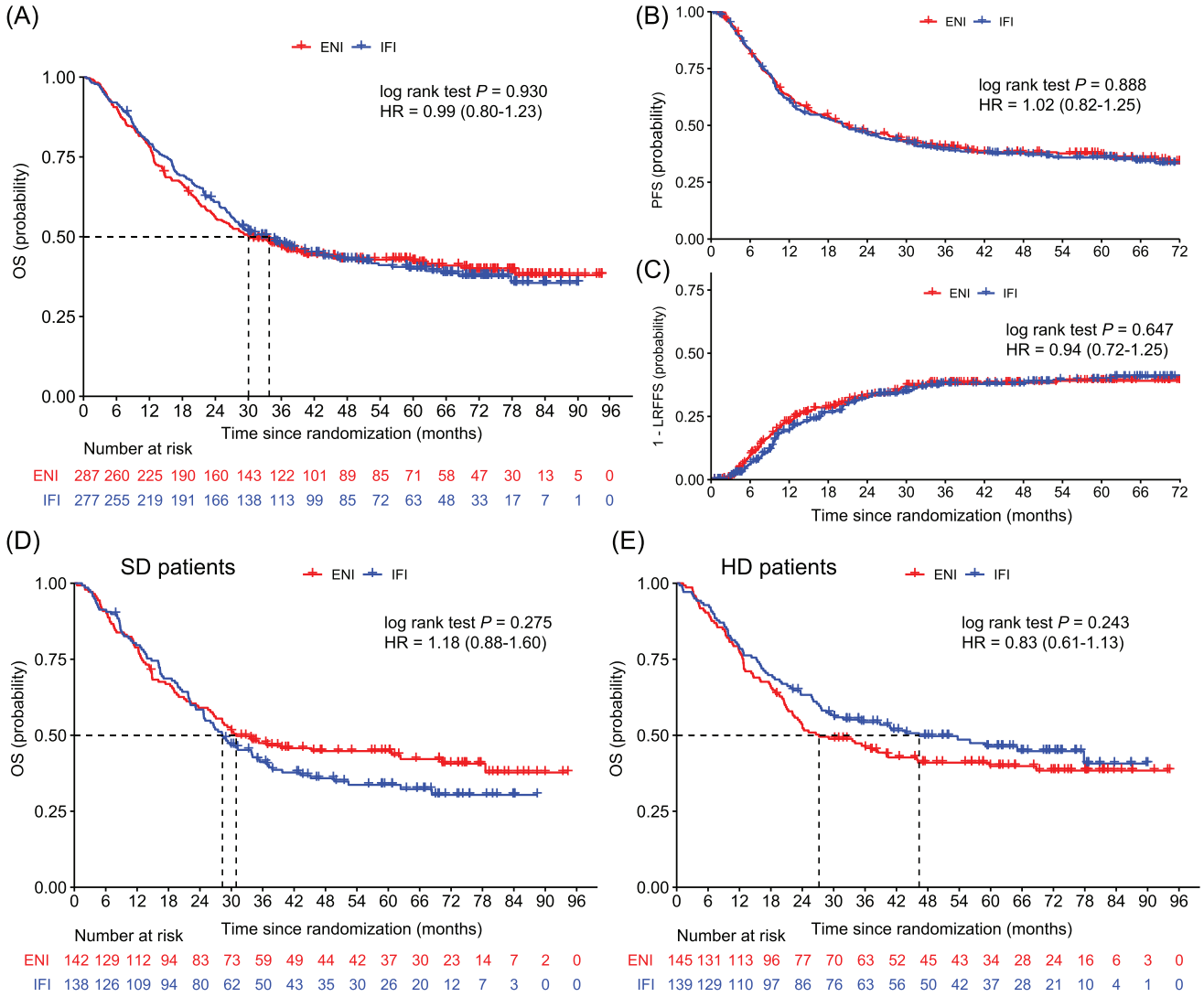

FIGURE 3 Survival comparison between IFI and ENI groups. (A) OS curves for comparison between the IFI and ENI groups. (B) PFS curves for comparison of the irradiation field.(C) the cumulative incidence curve of local-regional failure for comparison of the irradiation field. (D) OS curves for field comparison in SD patients. (E)OS curves for field comparison in HD patients. In (A), (D) and (E), the horizontal dashed lines are plotted to indicate the median survival rate (survival probability = 0.5), and the vertical dashed lines are plotted to show the median survival time in each group. Abbreviations: CI, confidence interval; ENI, elective nodal radiation; HD, high dose radiation; HR, hazard ratio; IFI, involved field radiation; LRFFS, locoregional failure-free survival; OS, overall survival; PFS, progression-free survival; SD, standard dose radiation.

respectively. The 1-year and 3-year OS rates were 79.3% (95% CI: 74.6%–84.2%) and 44.3% (95%CI: 38.8%–50.6%) in the SD group, 77.8% (95% CI: 73.1%–82.8%) and 50.4% (95% CI: 44.8%–56.6%) in HD patients. The mPFS was 18.0 months and 25.2 months in SD and HD patients. The prognostic benefit of HD was more significant in PFS (HR = 0.76, 95% CI: 0.62–0.94, $p = 0.012$) than in OS (HR = 0.90, 95% CI: 0.72–1.11, $p = 0.318$, Figure 5A-B).

The HD group also presented significantly improved local control, which suggested one-year cumulate local failure rates (or 1 minus one-year LRFFS) of 17.1% in the HD group and 24.9% in the SD group (nominal $p < 0.001$ in log-rank test, Figure 5C). The ORR did not significantly vary between the SD and the HD groups (74.0% *v.s.* 80.3%, $p = 0.088$, Figure 4).

3.3 | Exploratory analysis

In the exploratory subgroup analysis of target field comparison, the IFI presented slightly reduced mOS compared with ENI in SD patients (28.3 months *v.s.* 30.9 months, HR = 1.18, 95% CI: 0.88–1.60, Figure 3D and Figure 6A), while IFI suggested better mOS than ENI in HD patients

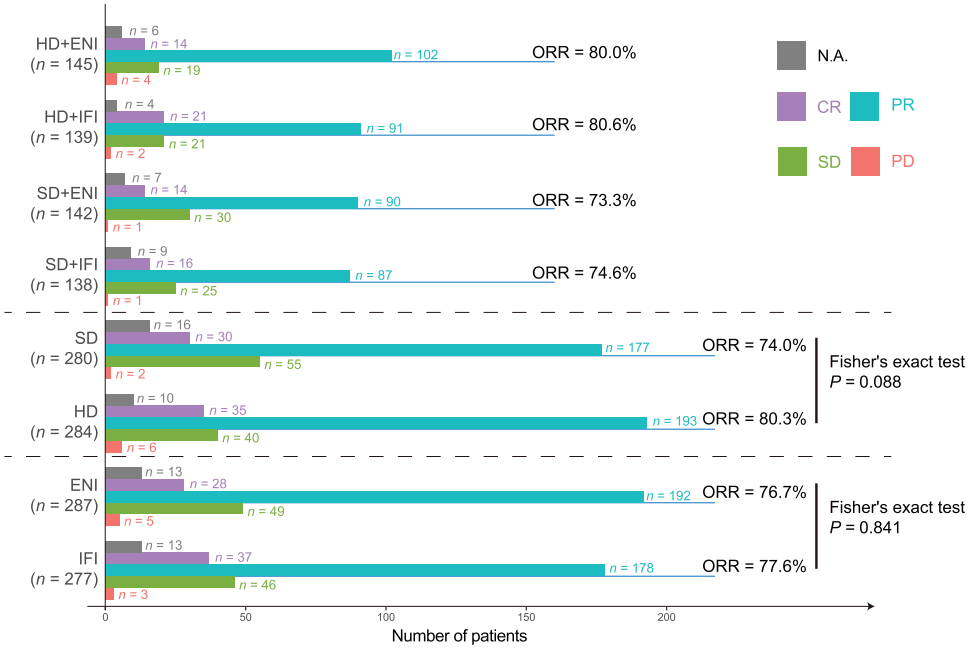

FIGURE 4 Comparisons of ORR among treatment groups. Abbreviations: ENI, elective nodal radiation; HD, high dose radiation; IFI, involved field radiation; N.A., not available; ORR, objective response rate; SD, standard dose radiation.

(46.3 *v.s.* 27.2 months, HR = 0.83, 95% CI: 0.61–1.13, Figure 3E and Figure 6A). For clinical cN0 patients ($n = 108$), ENI presented survival benefits (HR = 1.35, 95% CI: 0.78–2.32 in OS, HR = 1.42, 95% CI: 0.84–2.41 in PFS). These results did not reach statistical significance, possibly because of low statistical power (around 25% in HR = 0.7 and total events = 52) in this stratified analysis.

In the subgroup analysis of dose comparison, HD presented similar treatment efficacyin ENI patients compared with SD (HR = 1.07, 95% CI: 0.79–1.44, $p = 0.681$, Figure 5D) but suggested more benefits in IFI patients (46.3 *v.s.* 28.2 months in mOS, HR = 0.74, 95% CI: 0.54–1.01, $p = 0.058$, Figure 5E). HD irradiation also presented a higher therapeutic effect than SD irradiation in female patients ($n = 146$, HR = 0.64, 95% CI: 0.40-1.04), fully active patients (ECOG = 0, $n = 208$, HR = 0.66,95% CI: 0.45–0.97) and T4 tumors ($n = 110$, HR = 0.63,95% CI: 0.39–1.03, Figure 6B).

3.4 | Toxicity analysis

Atotal of 11 patients in the ITT group (1.95%) experienced grade 5 severe adverse events (SAEs, grade 3 or above), with 3 cases in the HD+ENI group, 3 in the HD+IFI group, 3 in the SD+ENI group, and 2 in the SD+IFI group. These events included 3 cases of pneumonitis, 3 cases of esophageal fistula, and 3 cases of esophageal hemorrhage.The percentage of patients experiencing one or more SAEswas 44.1%, 40.3%, 36.0%, and 37.0% in the HD+ENI, HD+IFI, SD+ENI, and SD+IFI groups, respectively ($p = 0.790$). The most frequent SAEs were white blood cell decrease (27.1% in all patients). We observed a higher rate of SAE (42.3% *v.s.* 36.4%, nominal $p = 0.380$), as well as more frequent hematological toxicities in HD group compared with SD group, although these differences did not reach statistical significance (Supplementary Table S1).

3.5 | Post-treatment analysis

We did not regulate the post-treatment regimen in this trial. However, post-treatment might influence the comparison of OS. Therefore, we summarized and analyzed the post-treatment in progressed patients (PFS events) within 2 years from randomization (Supplementary Table S2).

The relative proportions of post-treatment patients were similar within the four treatment arms (78.4% in SD+ENI, 76.7% in HD+ENI, 76.5% in SD+IFI, and 76.6% in HD+IFI), and the proportion of treatment regimen did not differ significantly ($p = 0.992$, Supplementary Table S2). However, in terms of the proportion to the ITT patients, patients in the HD+IFI arm had a lower post-treatment proportion (47/139, 33.8%) compared to the other three groups (58/142 [40.8%] in SD+ENI, 56/145 [38.6%] in HD+ENI, and 62/138 [44.9%] in SD+IFI). The HD+IFI arm had the lowest post-treatment proportion (35.3%) but presented the best mOS (46.3 months), while the SD+IFI arm with the highest

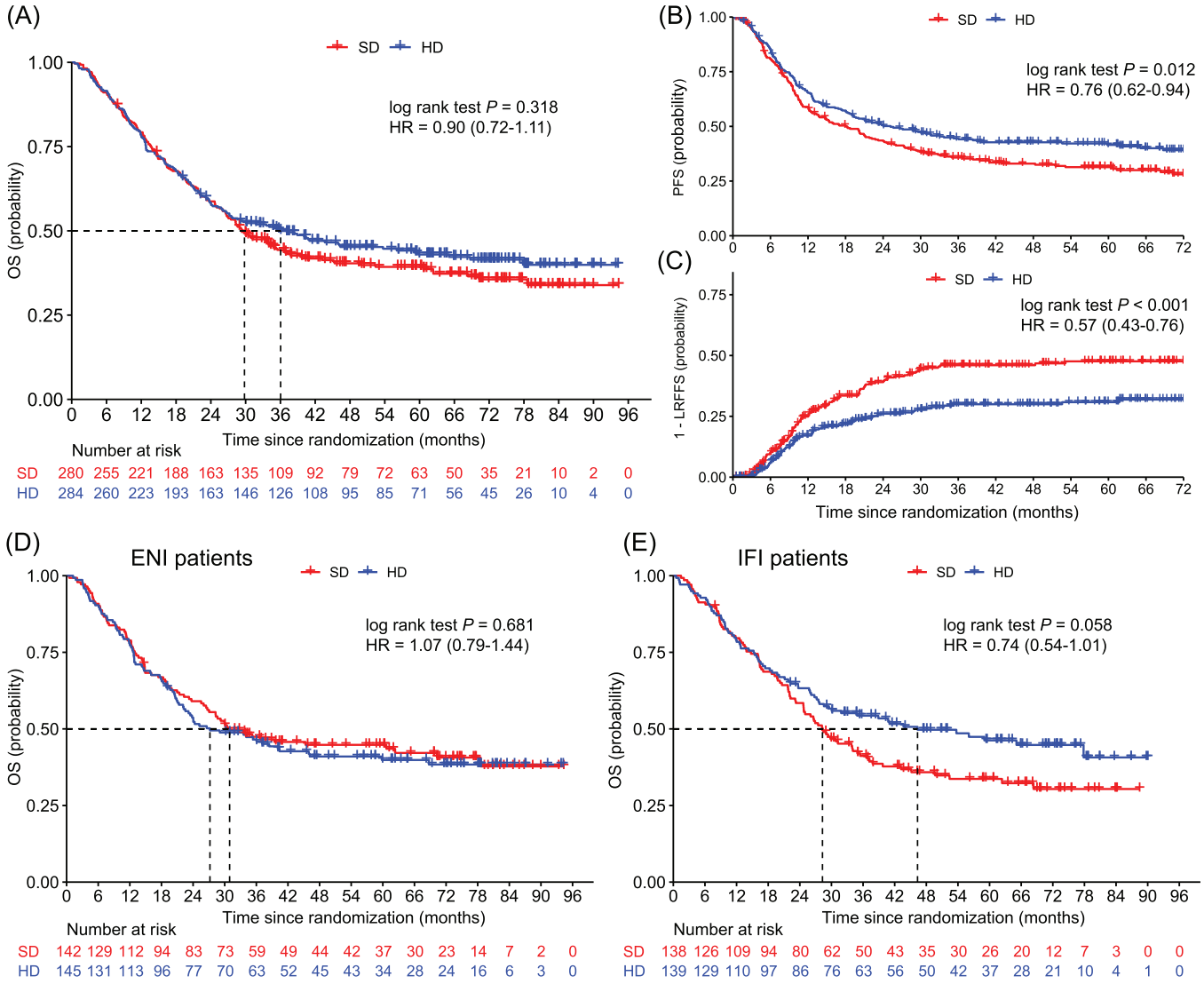

FIGURE 5 Survival comparison between HD and SD groups. (A) OS curves for comparison between the HD and SD groups. (B) PFS curves for comparison of the radiation dose.(C) the cumulative incidence curve of local-regional failure are used to compare the HD and SD groups. (D) OS curves for dose comparison in ENI patients. (E) OS curves for dose comparison in IFI patients. In (A), (D) and (E), the horizontal dashed lines are plotted to indicate the median survival rate (survival probability = 0.5), and the vertical dashed lines are plotted to show the median survival time in each group. Abbreviations: CI, confidence interval; ENI, elective nodal radiation; HD, high dose radiation; HR, hazard ratio; IFI, involved field radiation; LRFFS, locoregional failure-free survival; OS, overall survival; PFS, progression-free survival; SD, standard dose radiation.

post-treatment proportion (44.9%) and showed the worst mOS (28.3 months), which indicated that the differed post-treatments might reduce the differences in therapeutic effects in OS comparison.

4 | DISCUSSION

This multicenter phase III clinical trial simultaneously compared the radiation dose and target field in CCRT for ESCC using a two-by-two factorial design. The sample size and statistical power of this trial were larger than those of similar previous trials, but none of the two primary endpoints (OS comparisons in dose and field) reached statistical significance. The benefits of HD compared to SD were significant in PFS comparison (HR = 0.76, $p = 0.012$), while the survival differences between ENI and IFI groups were still slight in PFS (HR = 1.02, $p = 0.888$) and LRFFS (HR = 0.94, $p = 0.647$). The post-treatment analysis provides an explanation that the post-treatments after tumor progression could confound the first-line therapeutic effects in OS comparison.

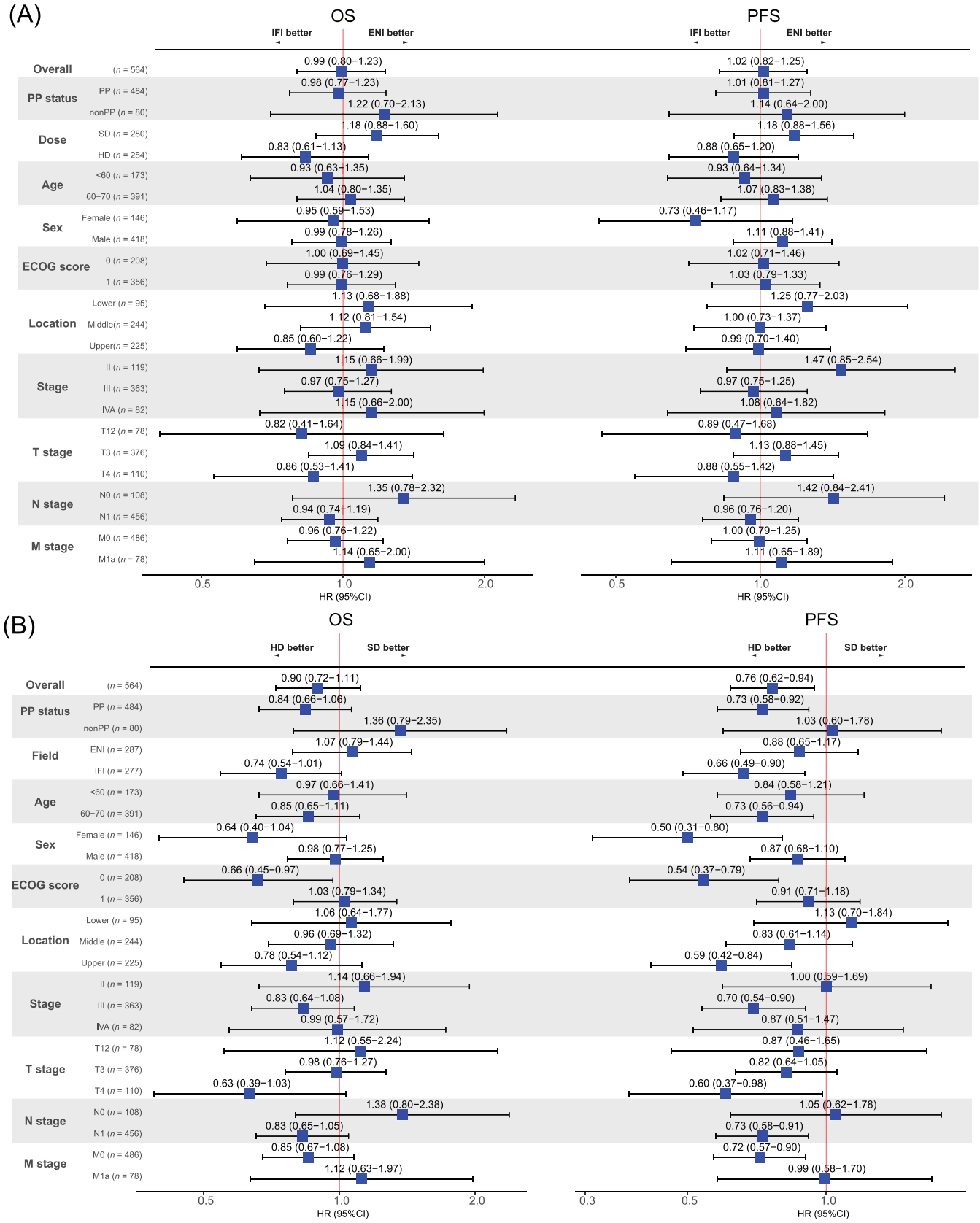

FIGURE 6 Exploratory subgroup analysis in OS and PFS. The forest plots presented HR with 95% CI in comparison tofield (A) or radiation dose (B) in OS (left panel) and PFS (right panel). Abbreviations: CI, confidence interval; ENI, elective nodal radiation; HD, high dose radiation; HR, hazard ratio; IFI, involved field radiation; OS, overall survival; PFS, progression-free survival; SD, standard dose radiation.

To reduce the heterogeneity of the enrolled patients, we excluded patients with cervical ESCC in this trial. The definitive chemoradiotherapy is the standard treatment for locally advanced cervical ESCC. Compared to thoracic ESCC, cervical ESCC has lower likelihood of undergoing surgery, and radiologists currently tend to administer higher doses of radiation (60-70 Gy) than the standard dose (50.4 Gy) [30]. We also excluded patients over 70 years old because they have a low tolerance to standard CCRT treatment. Recently, some clinical trials have specifically enrolled patients with ESCC who are older than 70 years, and have suggested that concurrent chemoradiotherapy with S-1 could be well-tolerated in this age group [31–33].

In this trial, the IFI presented slightly reduced OS compared with ENI (HR = 1.18) in SD patients, while IFI suggested better OS (HR = 0.83) in HD patients. Although these results were not statistically significant, the opposite trend implies that the IFI might be insufficient for patients with SD radiation and the ENI could bring extra benefits, while for HD radiation, IFI should be adequate and the expanded radiation volume of ENI bring extra damage instead of benefits. Among the four treatment arms, the HD+IFI combination demonstrated the best prognosis (mOS of 46.3 months, mPFS of 30.8 months) among the four groups, surpassing the currently recommended SD+ENI combination (mOS of 30.9 months, mPFS of 21.0 months). However, the pairwise comparisons between the four arms were not part of the designed statisticaltests. The planned sample size only supported two rigorous statistical comparisons of the primary endpoints. Although this trial was not solid enough for a recommendation, the HD+IFI is a promising radiation regimen to update the current practice and worth validation in further clinical trials.

Before our study, two phase III clinical trials (NCT01551589 [20] and NCT00686114 [25, 34]) comparing ENI to IFI in CCRT have been reported (Supplementary Table S3). The NCT01551589 [20] enrolled 228 patients in China and found similar OS and PFS between IFI and ENI. The NCT00686114 study enrolled a total of 352 participants and used a factorial design to compare both the irradiation field and the use of erlotinib in CCRT. In the study of NCT00686114, the ENI group suggested significantly better OS in ENI (HR = 0.74) than conventional field irradiation (equivalent to IFI in this study) [25, 34].

We noticed that the NCT00686114 trial [25, 34] included 42% cN0 patients, whereas cN0 patients only constituted 19.1% of enrolled patients inthis trial. In our exploratory subgroup analysis, the ENI presented survival benefits (HR = 0.74 in OS; HR = 0.70 in PFS) and improved local control in cN0 patients. The benefit of ENI in cN0 patients is still controversial [35–38]. The ongoing phase III clinical trial JCOG1904 [17], which compares ENI and IFI in cT1bN0M0 patients, might provide powerful evidence on this issue.

The standard-dose radiation was initially supported by the RTOG 94-05 trial [7] and subsequent large cohort-evidence [39]. The recently published phase III dose escalation trials (NCT01937208 [4], ARTDECO [13], and NCT02850991 [14]) consistently presented negative OS benefits in the escalated dose group. Although high-dose radiation might obtain better tumor control, as our results suggest, this improvement could not translate into significant prolonged OS. Notably, previous dose escalation trials often adopted ENI in CCRT. Our results indicate thatHD radiation was associated with better survival benefits in IFI, suggested promising resultsfor dose escalation trials based on IFI.

In the era of immunotherapy, radiotherapy has attracted considerable attention due to its immune activation effect [40]. The treatment efficacy of combined CCRT with immunotherapy in ESCC has been evaluated in ongoing phase III clinical trials such as NCT02409186 [41], RATIONALE 311 [42], and KEYNOTE-975 [43]. However, the conventional radiotherapy practice often results in robust immunosuppression in the tumor microenvironment and attenuates the efficacy of immunotherapy. In the view of radiobiology, the extend of lymphopenia during radiotherapy, which was significantly correlated with radiation volume, strongly affected the prognosis [44–46]. Preclinical studies have demonstrated that the ENI could significantly attenuate the adaptive antitumor immune responses due to its toxicity in draining lymph nodes [22, 47]. Compared with ENI, the IFI could ease treatment-related lymphopenia, especially in surrounding draining lymph nodes [48], and promote activation of antitumor immune reaction. Improved target volumes and fractions of dose in radiotherapy are called to enhance the system antitumor immune response [49]. Our results that the reduced target volumes regimen of IFI has similar treatment efficacy compared to the regimen with extra preventive lymph node irradiation of ENI, have provided reliable evidence in modification the current target volumes and promised better clinical benefits in radiotherapy–immunotherapy combinations.

Our study has some limitations. Firstly, we focused on ESCC and mainly recruited patients from Northern China. The geographical distribution of enrolled patients might limit the generalizability of our conclusion. Secondly, the staging criteria for ESCC have been updated since the start of this trial. According to the 8th UICC/AJCC stage [50], patients with positive M stage (n = 78 in this trial) should be classified as stage IVB and are no longer suitable for CCRT. Thirdly, the PET/CT scan is not mandatory in the trial, so only a small portion of enrolled patients have

PET/CT staging, which might result in missing some occult metastatic disease before treatment.

5 | CONCLUSION

IFI has similar treatment efficacy to ENI in CCRT of ESCC. HD irradiation has benefits in PFS but does not significantly improve OS. The dose escalation based on IFI (HD+IFI) showed better therapeutic efficacy than the current recommendation (SD+ENI) and is worth further validation.

AUTHOR CONTRIBUTIONS

Baosheng Li: designed the study and supervised all aspects of the work. *Jian Zhang and Minghao Li*: analyzed the data, prepared the figures and tables, and mainly wrote the manuscript. *Zhenjiang Li, Hongsheng Li and Zhongtang Wang*: collected and prepared the clinical information. *Kaixian Zhang, Anping Zheng, Guang Li, Wei Huang, Shaoshui Chen, Xiangming Chen, Xiaomin Li, Yanxing Sheng, Xinchen Sun, Liping Liu, Xiaowei Liu, Jie Li, Jun Wang, Hong Ge, Shucheng Ye, Qingsong Pang, Xianwen Zhang, Shengbin Dai, Richard Yu, Wendong Gu, Mingming Dai, GaowaSiqin, Yunwei Han, Xiaolin Ge, Xin Yuan, Yongjing Yang, Haiwen Zhu, Juan Pu, Lihua Dong, Xiangdong Sun, Jundong Zhou, Weidong Mao, Fei Gao, Haiqun Lin, Heyi Gong and Tao Zhou*: contributed to administration and supervision of the clinical trial. All authors reviewed and approved the final manuscript. The corresponding author takes full responsibility for the accuracy of all data and descriptions in this work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

CONSENT FOR PUBLICATION

All the authors provide consent for the publication of the manuscript.

DATA AVAILABILITY STATEMENT

The relevant data is available upon request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee of Shandong Cancer Hospital and Institute (No.201509008), and was registered in the Chinese Clinical Trial Registry (ChiCTR) with the registration number ChiCTR-IPR-15007172. All participants have consent agreements.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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