Hypofractionated Versus Conventionally Fractionated Radiotherapy After Chemo-immunotherapy in Locally Advanced or Advanced NSCLC: A Comparative Study of Efficacy and Toxicity

Siyi Yang
Tianjin Medical University Cancer Institute and Hospital
Yuntao Zhou
Tianjin Medical University Cancer Institute and Hospital
Hui Zhu
Tianjin Medical University Cancer Institute and Hospital
Xueping Huang
Lingcheng District People's Hospital of Dezhou City
Jialei Liu
Tianjin Medical University Cancer Institute and Hospital
Miao Yu
Tianjin Medical University Cancer Institute and Hospital
Lujun Zhao
Tianjin Medical University Cancer Institute and Hospital
Yongchun Song
Tianjin Medical University Cancer Institute and Hospital
Chengwen Yang
Tianjin Medical University Cancer Institute and Hospital
Chao Qu
Tianjin Medical University Cancer Institute and Hospital
Ningbo Liu
liuningbo@tjmuch.com
Tianjin Medical University Cancer Institute and Hospital

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Abstract

Background: Chemotherapy combined with immunotherapy (CIT) has reshaped the first-line treatment landscape for locally advanced and advanced non-small cell lung cancer (NSCLC).

However, the optimal radiotherapy (RT) fractionation regimen for patients who remain inoperable after neoadjuvant therapy has yet to be defined. This study aimed to systematically compare survival outcomes and toxicity between hypofractionated radiotherapy (HFRT) and conventionally fractionated radiotherapy (CFRT) following induction CIT.

Methods: In this retrospective analysis, 201 patients with locally advanced/advanced NSCLC receiving RT after CIT were divided into HFRT (45–54 Gy/15–18 fractions, n=69) and CFRT (60 Gy/30 fractions, n=132) groups. Overall survival (OS) was the primary endpoint; secondary endpoints included progression-free survival (PFS), locoregional PFS (LPFS), and toxicity. Multivariable Cox regression and propensity score matching adjusted for confounders. A novel endpoint—LPFS based on conventional PTV—directly compared “gross-tumor-only” versus elective-nodal irradiation.

Results: After a median follow-up of 26.2 months, adjusted analyses showed no significant differences in OS (HR=1.29, P=0.340), PFS, or LPFS between HFRT and CFRT. Exploratory analyses suggested trends favoring HFRT for PFS with consolidative immunotherapy (HR=0.58) and for OS/PFS in patients with high tumor burden (GTV ≥100 cm^3; HR=0.85 and 0.88). HFRT was associated with significantly lower rates of acute radiation pneumonitis, key hematologic toxicities, and grade ≥2 pulmonary fibrosis (17.19% vs. 32.81%, P=0.041). The “PGTV-only” strategy achieved locoregional control comparable to elective nodal irradiation (HR=1.063, P=0.765). All out-of-field nodal recurrences occurred with or after distant metastasis.

Conclusion: HFRT provides survival outcomes equivalent to CFRT after CIT, with a more favorable safety profile, supporting a “precision intensification” paradigm of target-volume de-escalation combined with hypofractionation.

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases[1]. Immune checkpoint inhibitors (ICIs) have significantly improved survival outcomes in patients with advanced disease[2,3]. For unresectable stage III or oligometastatic stage IV NSCLC, radiotherapy (RT) is a cornerstone local treatment[4,5]. Recent evidence confirms that adding definitive thoracic RT to first-line chemo-immunotherapy significantly improves survival in locally advanced NSCLC, underscoring its continued relevance in the immunotherapy era[6]. However, the optimal RT fractionation regimen within this multimodal paradigm is undetermined. Although hypofractionated RT (HFRT) is increasingly adopted in practice, robust comparative evidence on its efficacy and safety versus conventionally fractionated RT (CFRT) following chemotherapy combined with immunotherapy (CIT) remains limited and confounded. We compared

survival and toxicity between HFRT and CFRT post-CIT using multivariable regression and propensity score matching.

2. Methods

2.1. Study Population and Design

This single-center, retrospective cohort study included 201 patients with locally advanced or advanced NSCLC who remained unresectable after neoadjuvant therapy with chemotherapy plus a Programmed cell death protein 1(PD-1)/Programmed death-ligand 1(PD-L1) inhibitor. Between June 2020 and July 2025, all patients subsequently underwent radiotherapy at Tianjin Medical University Cancer Institute & Hospital. Key exclusion criteria were prior thoracic RT, missing baseline imaging, or concurrent active malignancies. Patients were stratified into HFRT (n = 69) or CFRT (n = 132) groups per multidisciplinary decision.

2.2. Treatment Protocols

All patients underwent induction therapy with chemotherapy (selected according to pathological type) combined with immune checkpoint inhibitors prior to RT. Patients underwent computed tomography (CT) simulation in the treatment position. The gross tumor volume (GTV) included the primary tumor and any PET-positive or pathologic lymph nodes. The planning gross tumor volume (PGTV) was generated by expanding the GTV by 5–8 mm.For patients receiving CFRT, the planning target volume (PTV) was defined to include the PGTV and high-risk nodal stations. For those receiving HFRT, treatment was delivered only to the PGTV without elective nodal coverage.

The prescription doses for the CFRT group were: (1) 60 Gy in 30 fractions to a conventional PTV (expanded from the GTV to include high-risk nodal stations); or (2) a simultaneous integrated boost with 60 Gy in 30 fractions to the PGTV and 54 Gy in 30 fractions to the PTV. For the HFRT group, the prescription dose was 45–54 Gy delivered in 15–18 fractions (3 Gy per fraction) to the PGTV. Both groups were treated once daily, five days per week. The administration of concurrent chemoradiotherapy (CCRT), immunotherapy during RT, and consolidative immunotherapy following RT were documented.

2.3. Data Collection and Study Endpoints

Patient demographics, clinicopathological characteristics, treatment details, and toxicity data were collected from the medical record system. The primary endpoint was overall survival (OS), defined as the time from RT initiation to death from any cause. Patients alive at the last follow-up were censored. Secondary endpoints included: (1) progression-free survival (PFS), defined as the time to radiologically confirmed disease progression (according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) or death; (2) locoregional progression-free survival (LPFS), defined as the time to in-field progression or death; and (3) treatment-related toxicity.

To compare locoregional control between “gross tumor only” and “elective nodal” irradiation strategies, a novel composite endpoint was defined: locoregional PFS based on the conventional PTV anatomical region (LPFS-conPTV). This endpoint adjudicated events using the standard conventional PTV region (encompassing primary site and involved nodal basin) as a unified reference for all patients. Endpoint events included progression at the primary site, within involved nodes, or new nodal progression within this region, as well as any-cause death. For HFRT patients with progression, failure patterns (in-field, mixed, out-of-field) were categorized, and the timing of out-of-field nodal progression relative to distant metastasis was analyzed.

Treatment-related toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, with a focus on grade ≥ 2 acute radiation pneumonitis, radiation esophagitis, pulmonary fibrosis, and hematologic toxicities.

2.4. Statistical Analysis

Statistical analyses were performed using R software (version 4.3.0). A two-sided $P < 0.05$ was considered statistically significant.

2.4.1. Comparison of Baseline Characteristics and Treatment Toxicity

Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on the normality of distribution. Comparisons between groups were performed using the independent t-test or Mann-Whitney U test, as appropriate. Categorical variables are presented as numbers (percentages) and compared using the Chi-square test or Fisher's exact test. Group comparisons of the incidence of treatment-related adverse events were also performed using the aforementioned tests, conducted separately in the overall cohort and the matched cohort.

2.4.2. Survival Analysis and Prognostic Factor Modeling

The Kaplan-Meier method was employed to estimate OS, PFS, LPFS, and the novel endpoint, LPFS-conPTV. Differences between groups were compared using the log-rank test. HRs were calculated with the CFRT group as the reference.

2.4.3. Strategy for Assessing the Effect of Fractionation

To control for confounding bias and accurately evaluate the independent effect of RT fractionation on survival outcomes, this study employed two complementary analytical strategies:

Nested Cox Model Analysis: A series of nested Cox proportional hazards models were constructed to sequentially adjust for demographic factors (age, sex), treatment covariates (CCRT, immunotherapy during RT, consolidative immunotherapy after RT), and tumor burden (GTV volume).The trajectory of changes in the hazard ratio (HR) corresponding to the fractionation regimen across this sequence of models was observed to assess and disentangle the influence of confounding factors.

Propensity Score Matching (PSM) Analysis: PSM with a caliper of 0.2 standard deviation was performed to reduce baseline imbalance. Matching variables included tumor GTV volume, Karnofsky Performance Status (KPS), age, pathological type, clinical stage, sex, smoking history, CCRT, concurrent immunotherapy, and consolidative immunotherapy after RT. Survival differences in the matched cohort were compared using the Kaplan–Meier method and log-rank test.

2.4.4. Subgroup Analysis and Interaction Testing

Exploratory subgroup analyses assessed effect heterogeneity across key covariates. For each covariate, a separate multivariable Cox model was fitted, including the treatment group, the dichotomized covariate, and their multiplicative interaction term. The P-value for interaction was used to formally test for heterogeneity across subgroups. All subgroup analyses were considered exploratory and hypothesis-generating.

3. Results

3.1. Patient Baseline Characteristics

The study cohort consisted of 201 patients, with 69 and 132 individuals assigned to the HFRT and CFRT groups, respectively. The overall cohort had a median age of 65 years, 84.1% were male, and 78.6% had a smoking history. Baseline clinico-pathological characteristics were well-balanced between the HFRT and CFRT groups (all $P > 0.05$; Table 1).

Table 1
Baseline Characteristics Table

Variables	Total (n = 201)	CFRT (n = 132)	HFRT (n = 69)	Statistic	*P*
Age, M (Q_1, Q_3)	65.00 (58.00, 69.00)	65.00 (57.00, 69.00)	66.00 (60.00, 70.00)	Z=-0.48	0.633
KPS, n(%)				χ^2=0.16	0.689
> 80	151 (75.12)	98 (74.24)	53 (76.81)		
≤ 80	50 (24.88)	34 (25.76)	16 (23.19)		
Pathological Type, n(%)				χ^2=1.15	0.563
Squamous cell carcinoma	134 (66.67)	89 (67.42)	45 (65.22)		
Adenocarcinoma	57 (28.36)	38 (28.79)	19 (27.54)		
Other	10 (4.98)	5 (3.79)	5 (7.25)		
Sex, n(%)				χ^2=0.65	0.420
Male	169 (84.08)	109 (82.58)	60 (86.96)		
Female	32 (15.92)	23 (17.42)	9 (13.04)		
Smoking, n(%)				χ^2=0.20	0.654
No	43 (21.39)	27 (20.45)	16 (23.19)		
Yes	158 (78.61)	105 (79.55)	53 (76.81)		
T, n(%)				χ^2=1.80	0.615
1	19 (9.45)	13 (9.85)	6 (8.70)		
2	57 (28.36)	39 (29.55)	18 (26.09)		
3	58 (28.86)	34 (25.76)	24 (34.78)		
4	67 (33.33)	46 (34.85)	21 (30.43)		
N, n(%)				χ^2=2.81	0.422
0	11 (5.47)	5 (3.79)	6 (8.70)		
1	15 (7.46)	11 (8.33)	4 (5.80)		
2	101 (50.25)	65 (49.24)	36 (52.17)		

Note: Data are presented as median (Q_1, Q_3) or n (%). Z: Mann-Whitney U test, χ^2: Chi-squared test. CFRT, conventionally fractionated radiotherapy; HFRT, hypofractionated radiotherapy; KPS, Karnofsky Performance Status; M, median; Q_1, first quartile; Q_3, third quartile; T, tumor; N, node; M, metastasis.

Variables	Total (n = 201)	CFRT (n = 132)	HFRT (n = 69)	Statistic	*P*
3	74 (36.82)	51 (38.64)	23 (33.33)		
M, n(%)				χ^2=1.03	0.311
0	143 (71.14)	97 (73.48)	46 (66.67)		
1	58 (28.86)	35 (26.52)	23 (33.33)		
Clinical Stage, *n* (%)				χ^2=3.38	0.496
IIIA	55 (27.36)	40 (30.30)	15 (21.74)		
IIIB	58 (28.86)	37 (28.03)	21 (30.43)		
IIIC	30 (14.93)	20 (15.15)	10 (14.49)		
IVA	47 (23.38)	30 (22.73)	17 (24.64)		
IVB	11 (5.47)	5 (3.79)	6 (8.70)		

Note: Data are presented as median (Q_1, Q_3) or n (%). Z: Mann-Whitney U test, χ^2: Chi-squared test. CFRT, conventionally fractionated radiotherapy; HFRT, hypofractionated radiotherapy; KPS, Karnofsky Performance Status; M, median; Q_1, first quartile; Q_3, third quartile; T, tumor; N, node; M, metastasis.

3.2. Survival Analysis

The median follow-up was 26.2 months. Median OS was not reached in the CFRT group and was 30.0 months (95% confidence interval [CI]: 23.03–not reached) in the HFRT group. Kaplan-Meier analysis showed a non-significant trend toward better OS with CFRT (HR = 1.529, 95% CI: 0.944–2.477, P = 0.082,Fig. 1). No significant disparity was observed in PFS (median CFRT 15.53 months vs. HFRT 13.67 months; HR = 1.018, 95% CI: 0.696–1.490, P = 0.926,,Fig. 1) or LPFS (median CFRT 18.53 months vs. HFRT 19.03 months; HR = 1.045, 95% CI: 0.702–1.555, P = 0.828,Fig. 1).

3.3. Efficacy Analysis After Adjustment for Confounding Factors

Although univariate analysis suggested a trend toward inferior OS with HFRT (HR = 1.529, P = 0.082), this difference attenuated upon adjustment for confounders. In nested Cox models, the HR for HFRT decreased from 1.53 (P = 0.084) in the unadjusted model to 1.29 (P = 0.340) after sequential inclusion of demographic factors, treatment patterns, and tumor burden (GTV) (Table 2).

Table 2
Nested Cox Proportional Hazards Models: Effect of HFRT vs. CFRT on OS

Model	Adjustment Variables	HR (95% CI)	P-value
Model 1	Unadjusted (Radiation fractionation only)	1.53 (0.94–2.48)	0.084
Model 2	Model 1 + Demographic factors (Age, Sex)	1.56 (0.96–2.52)	0.073
Model 3	Model 2 + Treatment patterns (CCRT, Immunotherapy during/after RT)	1.44 (0.86–2.41)	0.168
Model 4	Model 3 + Tumor burden (Total GTV volume)	1.29 (0.76–2.19)	0.340
Footnote: All models use CFRT as the reference group. HR, hazard ratio.			

PSM further confirmed this finding. In the matched cohort (64 patients per group), no significant difference in OS (HR = 1.070, 95% CI: 0.609–1.879; P = 0.815,Fig. 1) or PFS (HR = 0.765, 95% CI: 0.493–1.188; P = 0.231,Fig. 1), or LPFS (median: 15.53 vs. 19.03 months; Log-rank P = 0.390,Fig. 1) was observed between HFRT and CFRT. Collectively, multivariable and PSM analyses demonstrated comparable survival outcomes for the two fractionation regimens after accounting for baseline and treatment-related factors.

3.4. Locoregional Efficacy and Failure Pattern Characteristics

Using the novel endpoint “LPFS based on the anatomical region of the conventional PTV,” we directly compared locoregional control between the HFRT (PGTV-only) and CFRT (elective nodal irradiation) strategies. No significant difference was observed between the groups, with a median LPFS of 18.53 months (95% CI: 14.37–26.10) for CFRT and 17.90 months (95% CI: 11.10–30.27) for HFRT (HR = 1.063, 95% CI: 0.714–1.582; Log-rank P = 0.765,Fig. 2).

Among the 21 HFRT patients with progression, failure patterns included in-field (12/21, 57.1%,Fig. 3), mixed (6/21, 28.6%,Fig. 3), and isolated out-of-field progression (3/21, 14.3%,Fig. 3). Time-sequencing analysis revealed that all three isolated out-of-field events occurred after distant metastasis (Fig. 3). Thus, no instances of isolated nodal progression preceding or independent of systemic metastasis were observed.

3.5. Subgroup Analysis: Exploring Heterogeneity in the Efficacy of Fractionation Regimens

3.5.1 Subgroup Analysis Based on GTV

Using a cutoff of 100 cm³, no significant interaction between GTV and fractionation regimen was observed for OS (P-interaction = 0.163) or PFS (P-interaction = 0.162). In the multivariable model adjusted for GTV, the HR for OS was 0.85 (95% CI: 0.36–2.02) in patients with GTV ≥ 100 cm³ and 1.53 (95% CI: 0.70–3.31) in those with GTV < 100 cm³ (Fig. 4). For PFS, the corresponding HRs were 0.88 (95% CI: 0.40–1.91) and 0.90 (95% CI: 0.53–1.53), respectively (Fig. 5).

3.5.2 Subgroup Analysis Based on CCRT and Consolidative Immunotherapy Status

In subgroup analyses, no significant interaction was found between CCRT status and fractionation regimen for OS (P-interaction = 0.765) or PFS (P-interaction = 0.360). For OS, the adjusted HRs were 1.39 (95% CI: 0.79–2.43) and 3.80 (95% CI: 0.36–40.54) for patients not receiving and receiving CCRT, respectively, with the latter estimate being imprecise(Fig. 4). For PFS, a statistically significant interaction was observed with consolidative immunotherapy status (P-interaction = 0.017)(Fig. 5). Patients receiving consolidative immunotherapy showed a trend toward improved PFS with HFRT (HR = 0.58, 95% CI: 0.29–1.15), while no such trend was seen in those without it (HR = 1.44, 95% CI: 0.82–2.53). No significant interaction was found for OS regarding consolidative immunotherapy (P-interaction = 0.523), with HRs of 2.08 (95% CI: 0.81–5.34) and 1.32 (95% CI: 0.65–2.67) in patients with and without immunotherapy, respectively.

3.5.3 Exploratory Analysis Based on Clinical Stage, Performance Status, and Age

The interactions of clinical stage, KPS score, and age with the fractionation regimen did not show statistical significance for either OS or PFS (all P for interaction > 0.05). The hazard ratios for each subgroup after adjustment for the corresponding variable are detailed in in Fig. 4 and Fig. 5.

3.6 Treatment-Related Toxicity Analysis

Within the overall cohort (n = 201), grade ≥ 2 toxicities were significantly less frequent in the HFRT group. This included acute radiation pneumonitis (28.99% vs. 43.94%, P = 0.039), hemoglobin decrease (1.45% vs. 11.36%, P = 0.014), leukopenia (8.70% vs. 30.30%, P < 0.001), and thrombocytopenia (1.45% vs. 10.61%, P = 0.019). No significant difference was observed in acute radiation esophagitis (17.39% vs. 13.64%, P = 0.478), and the lower incidence of pulmonary fibrosis in the HFRT group (17.39% vs. 26.52%, P = 0.147) did not reach statistical significance (Supplementary Table 1).

In the PSM-matched cohort (n = 128), the incidence of grade ≥ 2 pulmonary fibrosis became significantly lower in the HFRT group (17.19% vs. 32.81%, P = 0.041). Other toxicities remained numerically lower with HFRT—acute pneumonitis (31.25% vs. 40.62%, P = 0.269), hemoglobin decrease (1.56% vs. 4.69%, P = 0.611), leukopenia (9.4% vs. 15.6%, P = 0.285), and thrombocytopenia (1.56% vs. 6.25%, P = 0.362)—though these differences were not statistically significant. Acute esophagitis incidence did not differ significantly between groups (18.75% vs. 10.94%, P = 0.214) (Table 3).

Table 3
Comparative Analysis of Treatment-Related Toxicities After Propensity Score Matching: HFRT vs. CFRT

Variables	Total (n = 128)	CFRT (n = 64)	HFRT (n = 64)	Statistic	*P*
Acute Radiation Pneumonitis ≥ Grade 2, n (%)				χ^2=1.22	0.269
No	82 (64.06)	38 (59.38)	44 (68.75)		
Yes	46 (35.94)	26 (40.62)	20 (31.25)		
Pulmonary Fibrosis ≥ Grade 2, n (%)				χ^2=4.17	**0.041**
No	96 (75.00)	43 (67.19)	53 (82.81)		
Yes	32 (25.00)	21 (32.81)	11 (17.19)		
Acute Radiation Esophagitis ≥ Grade 2, n (%)				χ^2=1.55	0.214
No	109 (85.16)	57 (89.06)	52 (81.25)		
Yes	19 (14.84)	7 (10.94)	12 (18.75)		
Bone Marrow Suppression (Hemoglobin) ≥ Grade 2, n (%)				χ^2=0.26	0.611
No	124 (96.88)	61 (95.31)	63 (98.44)		
Yes	4 (3.12)	3 (4.69)	1 (1.56)		
Bone Marrow Suppression (Leukocytes) ≥ Grade 2, n (%)				χ^2=1.14	0.285
No	112 (87.50)	54 (84.38)	58 (90.62)		
Yes	16 (12.50)	10 (15.62)	6 (9.38)		
Bone Marrow Suppression (Platelets) ≥ Grade 2, n (%)				χ^2=0.83	0.362
No	123 (96.09)	60 (93.75)	63 (98.44)		
Yes	5 (3.91)	4 (6.25)	1 (1.56)		

Note: Data are presented as number of patients (percentage). Group comparisons were performed using the Chi-square test.

4. Discussion

Our adjusted analyses show comparable survival outcomes between HFRT and CFRT following CIT. Exploratory analyses revealed favorable trends for HFRT in patients receiving consolidative immunotherapy or with high tumor burden (GTV ≥ 100 cm^3). Notably, using an innovative endpoint, this study first demonstrates that a “gross tumor-only” strategy yields locoregional control equivalent to elective nodal irradiation. The initially inferior OS with HFRT was likely due to selection bias, as it was more frequently used in patients with higher tumor burden or less fit for CCRT—an artifact clarified by multivariable and propensity score matching analyses. Our results align with a body of prior work: for instance, a PSM analysis in stage III NSCLC showed no difference in OS between HFRT and CFRT [7], and their efficacy was also comparable in limited-stage small cell lung cancer [8]. The efficacy of HFRT is also supported in other stages of NSCLC, including stage I [9]and stage IIB[10].

However, the value of this study lies in moving beyond a simple conclusion of "equivalence." Our multivariable analysis confirmed that tumor burden (GTV) is one of the strongest independent prognostic factors affecting survival, aligning with results from multiple studies[11–13]. This underscores that high tumor burden constitutes a critical bottleneck to achieving long-term disease control [14,15]. After multivariable adjustment, the initial survival disadvantage observed with HFRT disappeared, a finding likely explained by its higher baseline GTV and confirming comparable overall efficacy. Within the GTV ≥ 100 cm^3 subgroup, HFRT showed favorable trends in both OS (HR = 0.85) and PFS (HR = 0.88), suggesting a potential clinical benefit. Large tumor burden, associated with hypoxia and proliferative heterogeneity, theoretically requires a higher biologically effective dose (BED) for control. Shorter CFRT courses (typically ≤ 6 weeks) are associated with improved disease control, underscoring the need to limit treatment time to mitigate tumor repopulation[16].In contrast, radiobiological modeling in NSCLC suggests a low α/β ratio (approximately 4.0 Gy), indicating that increasing BED by elevating fraction size (as in HFRT) is a more efficient strategy than merely increasing total dose[17]. Thus, HFRT offers a dual radiobiological advantage: delivering a higher BED per fraction while avoiding protracted treatment courses that allow for tumor repopulation. This rationale is well established in the literature [18], and the clinical feasibility of such BED escalation via modern precision techniques has demonstrated acceptable toxicity and promising outcomes[19]. Consequently, our findings provide exploratory support for employing HFRT in patients with larger tumor burdens, though this warrants prospective validation.

Univariate analysis linked CCRT to improved OS (HR = 0.53, P = 0.039), consistent with prior studies[20,21]; however, this association lost significance after adjusting for GTV and consolidative immunotherapy (HR = 0.70, P = 0.275). Nested modeling suggested the observed survival trend may reflect higher CCRT use in the CFRT group rather than a fractionation effect. Notably, within the CCRT subgroup, HFRT showed a trend toward better PFS (HR = 0.18). Although this trend warrants cautious interpretation due to its wide confidence interval (0.02–1.45), its direction is consistent with a recent phase III trial reporting significantly improved PFS with HFRT versus CFRT in patients receiving concurrent chemotherapy (HR = 0.58, 95% CI 0.40–0.85, P = 0.003) [22]. Subgroup analysis revealed a significant interaction between consolidative immunotherapy and fractionation for PFS (P-interaction = 0.017), with HFRT showing a trend toward improved PFS in patients receiving immunotherapy (HR = 0.58). This

potential synergy was not observed for OS (HR = 2.08), possibly due to limited sample size, subsequent therapies, or insufficient follow-up. This potential synergy finds direct prospective validation in the GASTO-1091 trial, where consolidative nivolumab significantly improved PFS following a treatment backbone that included hypofractionated chemoradiotherapy (hypo-CCRT) [23]. This interaction aligns with a radiobiology framework in which hypofractionation promotes immunogenic cell death and reprograms the tumor microenvironment — key mechanisms for priming systemic anti-tumor immunity[24]. Mechanistically, experimental studies show HFRT promotes early CD8 + T-cell activation and PD-1 upregulation in NSCLC models, facilitating synergy with immune checkpoint inhibitors[25].This study provides clinical evidence positioning HFRT as the preferred RT option for combination with immunotherapy. Studies indicate severe CCRT toxicity in large tumors; Wiersma et al. reported 7.1% treatment-related mortality, a risk particularly high in patients with comorbidities[26].Given its favorable safety profile and the observed trend for improved PFS with consolidative immunotherapy, we propose the exploratory hypothesis that HFRT could enable safer CCRT and more effective bridging to immunotherapy in high-risk patients.Beyond clinical efficacy, HFRT offers notable socioeconomic advantages. By reducing the treatment course from the conventional 30 fractions to 15–18 fractions, it lowers direct medical costs and minimizes indirect financial burdens on patients, such as travel expenses and time away from work. Additionally, this condensed schedule optimizes healthcare resources. Thus, HFRT represents a cost-effective, patient-centric approach that enhances treatment convenience.

The novel endpoint "locoregional PFS based on the conventional PTV region" showed comparable locoregional control between "PGTV-only" and elective nodal irradiation after CIT (Log-rank P = 0.765, HR = 1.063), supporting target-volume de-escalation to improve the therapeutic ratio. Prior evidence from the chemotherapy era demonstrated that involved-field radiotherapy (IFRT) did not increase nodal failure risk compared to elective nodal irradiation (ENI), while reducing toxicity and maintaining efficacy—justifying dose escalation through target-volume reduction[27,28]. Leveraging CIT's high pathological response rates[29], this study focuses target-volume de-escalation on residual disease irradiation. Failure pattern analysis showed all out-of-field nodal recurrences coincided with or followed distant metastasis, suggesting they reflect systemic progression. This supports combining focused target-volume de-escalation with HFRT’s biologic potentiation in a “precision intensification” paradigm: maximally attacking refractory lesions while sparing systemically controlled areas and normal tissue to optimize the therapeutic ratio.

Based on the findings, treatment decisions for NSCLC patients receiving post-CIT radiotherapy should evolve from a simple HFRT vs. CFRT comparison to a multidimensional, risk-adaptive framework. This framework integrates tumor aggressiveness (e.g., GTV[30,31] and pathological subtype[32]), treatment intensity (e.g., CCRT [20,21]), and host-specific risks (e.g., treatment-related toxicity [33]). Within this model, HFRT emerges as a valuable strategic option due to its efficacy equivalence, favorable acute toxicity profile, and observed potential for synergistic benefit, offering a feasible pathway for patients who need to balance efficacy with safety (e.g., those with large tumor burden or CCRT intolerance).

Limitations and Future Perspectives

The retrospective, single-center design limits this study, as residual confounding and selection bias may persist despite statistical adjustments. The sample size also limits the power of subgroup analyses. Furthermore, the biological mechanisms underlying potential benefits of HFRT, such as immune-microenvironment interactions, remain unexplored. Consequently, the generalizability of our findings may be limited to similar patient populations treated at specialized cancer centers. Future multicenter prospective studies are warranted to validate these findings. Further research should also integrate novel biomarkers—such as radiomics and circulating tumor DNA—into risk prediction models to guide clinical decisions, thereby advancing radiotherapy for locally advanced NSCLC toward more precise and individualized modalities.

5. Conclusion

This study demonstrates that HFRT provides equivalent OS, PFS, and locoregional control compared to CFRT in patients with locally advanced or advanced NSCLC treated with CIT, while offering a superior safety profile with significantly lower risks of acute hematologic toxicity and radiation pneumonitis. Exploratory analyses revealed numerical trends favoring HFRT in specific subgroups, such as patients receiving consolidative immunotherapy or those with high tumor burden (GTV ≥ 100 cm^3). Through an innovative endpoint, this study provides the first clinical evidence in the CIT setting that a precise “gross tumor-only” target strategy yields locoregional control comparable to traditional elective nodal irradiation. These findings support HFRT combined with focused target volumes as a viable “toxicity-reducing and efficacy-enhancing”approach. Future work should focus on developing risk-adaptive frameworks to guide individualized RT in this evolving treatment paradigm.

Abbreviations

NSCLC
Non-small cell lung cancer
ICIs
Immune checkpoint inhibitors
RT
Radiotherapy
HFRT
Hypofractionated radiotherapy
CFRT
Conventionally fractionated radiotherapy
CIT
Chemotherapy combined with immunotherapy
PD-1
Programmed cell death protein 1

PD-L1
Programmed death-ligand 1
GTV
Gross tumor volume
PGTV
Planning gross tumor volume
PTV
Planning target volume
CCRT
Concurrent chemoradiotherapy
OS
Overall survival
PFS
Progression-free survival
LPFS
Locoregional progression-free survival
RECIST
Response Evaluation Criteria in Solid Tumors
CTCAE
Common Terminology Criteria for Adverse Events
LPFS-conPTV
Locoregional progression-free survival based on the anatomical region of the conventional PTV
PSM
Propensity score matching
KPS
Karnofsky Performance Status
HR
Hazard ratio
CI
Confidence interval
BED
Biologically effective dose

Declarations

Ethics approval and consent to participate

Ethics approval was waived The Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (No.bc20260586). Informed consent was waived by the ethics committee/Institutional Review Board of Tianjin Medical University Cancer Institute and Hospital. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The data are available from the corresponding author upon request.

Competing interests

The authors declare no competing interests

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Author contributions

Conceptualization: Siyi Yang, Yuntao Zhou, Chao Qu and Ningbo Liu; Methodology: Yuntao Zhou, Chengwen Yang, Chao Qu and Ningbo Liu; Formal analysis: Siyi Yang and Yuntao Zhou; Investigation: Siyi Yang, Hui Zhu, Xueping Huang, Jialei Liu and Miao Yu; Data Curation: Siyi Yang, Xueping Huang, Jialei Liu and Miao Yu; Visualization: Siyi Yang and Yuntao Zhou; Writing – Original Draft: Siyi Yang; Writing – Review & Editing: Chengwen Yang, Chao Qu and Ningbo Liu; Resources: Lujun Zhao and Yongchun Song; Supervision: Lujun Zhao, Chengwen Yang and Ningbo Liu; Project Administration: Hui Zhu and Yongchun Song; Funding Acquisition: Ningbo Liu

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Figures

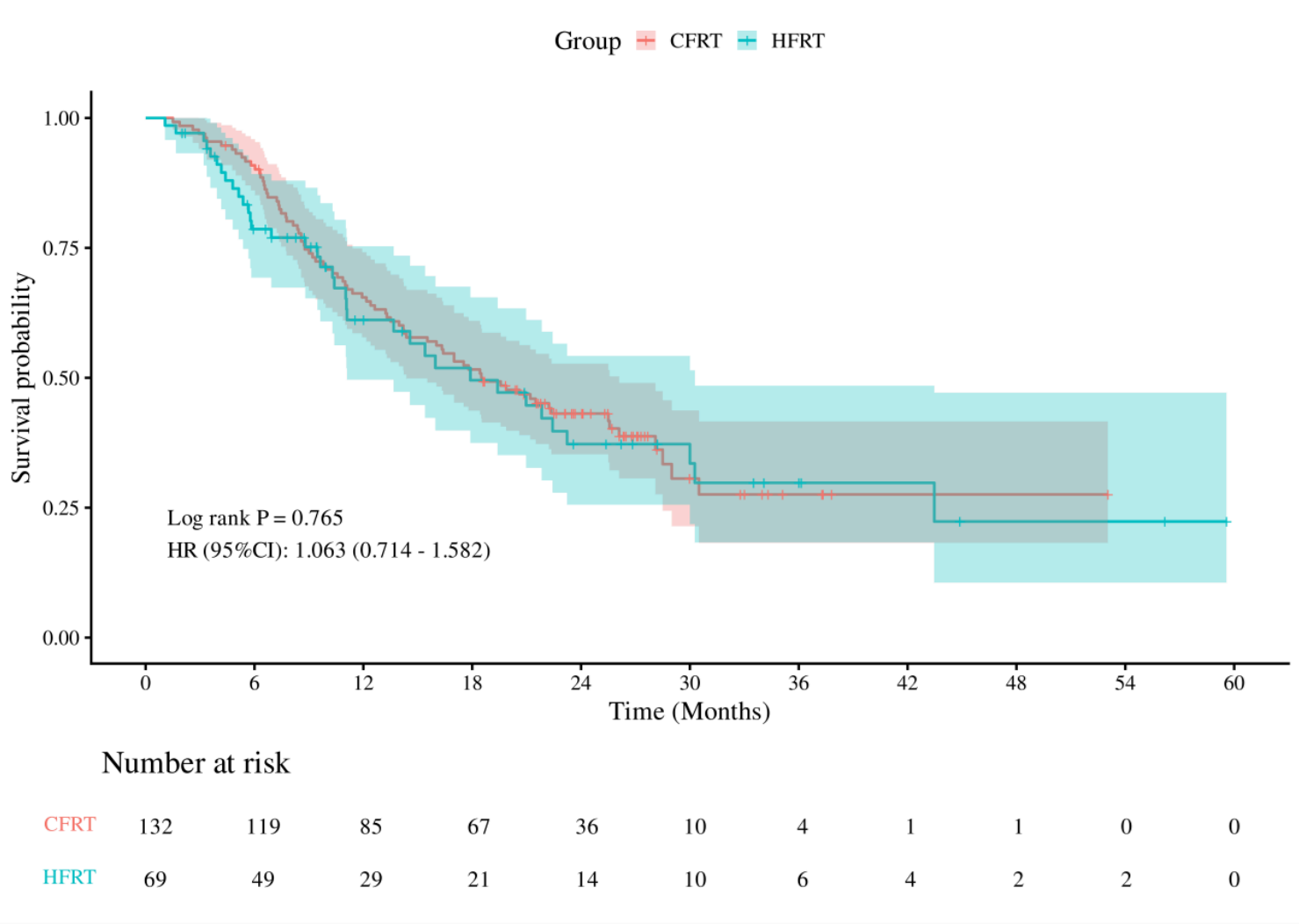

Figure 2

Kaplan–Meier curves comparing HFRT and CFRT for locoregional progression-free survival based on the anatomical region of the conventional PTV (Overall cohort).

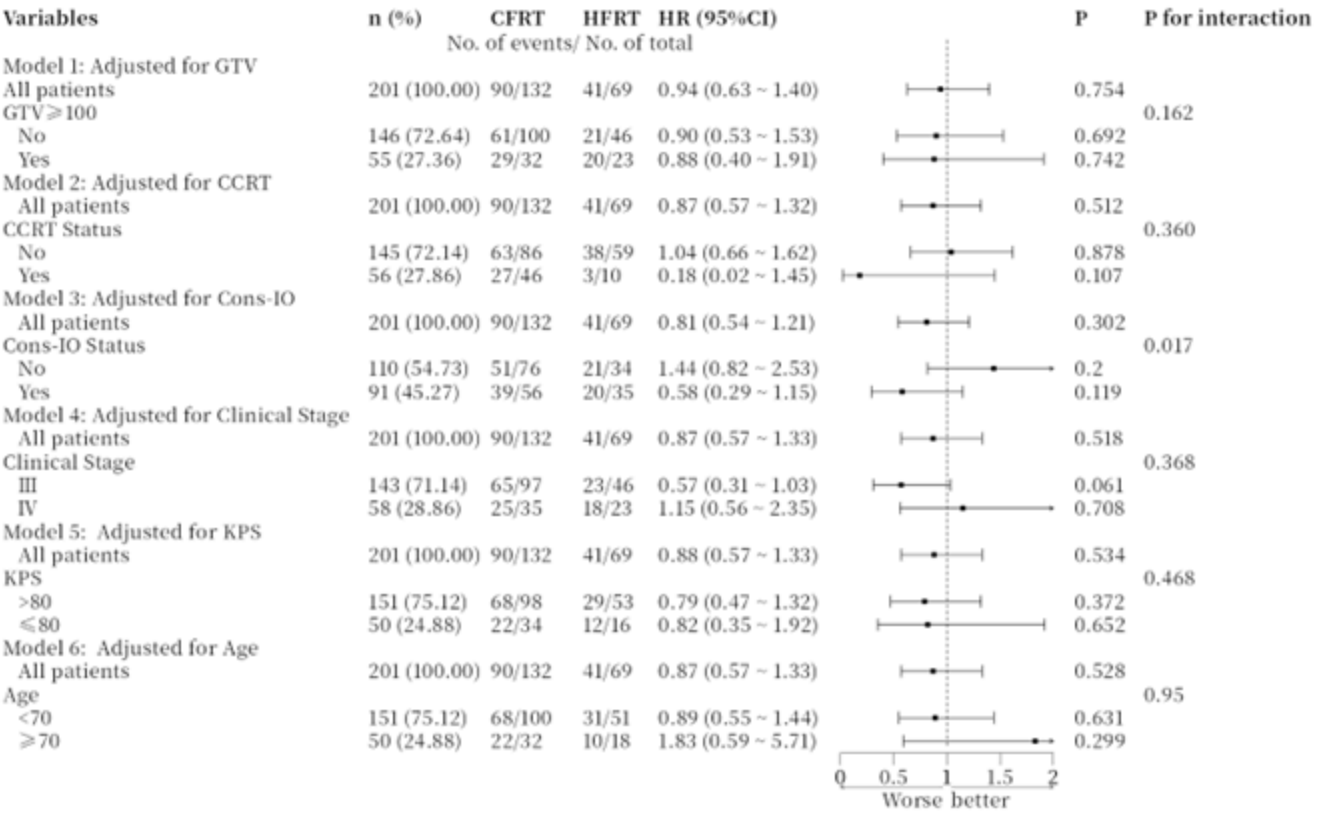

Figure 5

Forest plot for subgroup analysis of progression-free survival comparing HFRT to CFRT. Hazard ratios (95% CI) are shown for key subgroups; the dashed line indicates no difference (HR=1). P for interaction tests heterogeneity of treatment effect across subgroups.

Supplementary Files

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- SupplementaryTable.docx