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Radiation Dose Escalation in Accelerated Hyperfractionated Radiotherapy for Stage III Non-small-cell Lung Cancer

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Abstract. *Aim: To identify clinical benefits of dose escalation in accelerated hyperfractionated radiotherapy (AH-RT) for stage III non-small-cell lung cancer (NSCLC) using propensity score-matched (PSM) analysis. Materials and Methods: Our study retrospectively examined 294 patients undergoing definitive radiotherapy [131 patients, conventional once-daily radiotherapy (OD-RT); and 163, AH-RT] who were followed-up for a median of 40.4 months. The impact of overall survival (OS), progression-free survival (PFS), and locoregional control (LRC) was investigated. Results: Pre-PSM, the median OS, PFS, and LRC durations were 23.1 vs. 39.9 (p=0.03), 8.9 vs. 13.5 (p<0.01), and 12.9 vs. 50.3 (p<0.01) months in the OD-RT and AH-RT groups, respectively. After-PSM (two matched groups of 144 patients), AH-RT was associated with better LRC [adjusted hazard ratio (aHR)=0.59, 95% confidence interval (CI)=0.33-0.99, p=0.04] and marginally better PFS (aHR=0.65, 95% CI=0.41-1.03; p=0.06), but not OS (aHR=0.75, 95% CI=0.46-1.24; p=0.26). Conclusion: After PSM analysis, dose escalation using AH-RT improved LRC and PFS in patients with locally advanced NSCLC. AH-RT can be a promising option for patients with advanced NSCLC.*

Non-small-cell lung cancer (NSCLC) is a major cause of death worldwide. The current standard of care for locally advanced NSCLC is definitive radiotherapy (RT), specifically concurrent chemoradiotherapy (CCRT) with a total of 60 Gy in 30 fractions (1,2). Despite advances in radiation technology, treatment outcomes remain poor (3-6). Treatment intensification using conventional dose escalation beyond 60 Gy with CCRT has been investigated in order to improve local control and survival (3-6). However, the Radiation Therapy Oncology Group (RTOG) study 0617 showed that dose escalation to 74 Gy with the once-daily radiotherapy (OD-RT) resulted in inferior local control and median survival, possibly due to the need for a prolonged radiation treatment time (7).

Uncertainty exists regarding appropriate dose fractionation to use for intermediate dose escalation (*i.e.* to total doses between 60 Gy and 74 Gy) with CCRT, and further investigations are required. Accelerated hyperfractionated radiotherapy (AH-RT), one approach to increasing RT intensity with shortened treatment time, can potentially improve local control and overall survival (OS) (8-10). A twice-daily AH-RT regimen of 64 Gy in 40 fractions with concurrent chemotherapy resulted in an excellent complete and partial response rate and median OS in a phase II study (11). Based on the previous study, we have treated selected patients with NSCLC using the AH-RT regimen. The objective of this study was to compare the locoregional control (LRC) and survival characteristics related to intermediate dose escalation in AH-RT using a propensity score-matched (PSM) pair analysis approach.

Materials and Methods

Patient population. After obtaining Institutional Review Board approval (no. 1606309044), retrospectively, consecutive patients with stage III NSCLC treated with definitive RT were reviewed. Before treatment, all patients gave written informed consent to use of their clinical information. Overall, 302 patients underwent treatment between November 2004 and June 2017, six with no histological evidence of malignancy and two diagnosed as having primary unknown lung cancer with mediastinum lymphadenopathy were excluded; 294 patients were included in the final cohort. In this non-randomized single-center study, decision of AH-RT regimen use was at the radiation oncologists' discretion.

This study was presented in part as an oral presentation at the 30th Annual Meeting of the Japanese Society for Radiation Oncology, Osaka, Japan in November 2017.

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Key Words: Radiation, non-small-cell lung cancer, chemoradiation, accelerated hyperfractionation, propensity score matching.

Baseline characteristics recorded included age, sex, Eastern Cooperative Oncology Group performance status (ECOGPS), treatment period, tumor size, clinical N classification, histology, epidermal growth factor receptor (*EGFR*) mutation status, chemotherapy regimen, CCRT, total number of chemotherapy cycles, RT dose, RT treatment time, RT technique, and delay in RT. The clinical stage and N classification were defined according to the TNM system of the Union for International Cancer Control (UICC), 6th (until March 2009) and 7th (after April 2009) editions (12, 13). Tumor size was measured on axial slice of pretreatment computed tomography (CT). Some differences occurred in definition between clinical stages IIIA, IIIB, and clinical T classification; therefore, these were excluded. Clinical N classification showed no differences between editions. RT treatment time was calculated using calendar days. Causes of death were confirmed from clinical records, whereas those lost to follow-up were tracked through telephone survey.

RT technique. Most patients were treated with 3-dimensional conformal RT. The planning technique was based on the International Commission on Radiation Units and Measurements, Publication 62 Reports (14). Gross tumor volume (GTV) was defined as primary tumor and metastatic nodes. Clinical target volume (CTV) consisted of elective (CTV1) and high-risk CTV (CTV2). CTV2 was calculated by adding a 5-mm margin to GTV, while CTV1 included CTV2 and elective nodal areas of the mediastinum. Each CTV was expanded by 5 mm to define the planning target volumes (PTV1 and PTV2). In the OD-RT regimen, the prescription dose was 60 Gy, conducted as 40 Gy/20 fractions for PTV1, and sequentially as 20 Gy/10 fractions for PTV2. For the AH-RT regimen, the prescribed doses were 64 Gy using 40 fractions administered twice daily over 4 weeks with concomitant boost technique (phase 1, 40 Gy/20 fractions for PTV1; phase 2, 24 Gy/20 fractions as the second daily fraction after a 6 h gap for PTV2). For both regimens, typical field arrangements consisted of four beams, usually anterior–posterior opposed fields for PTV1, and oblique opposed fields for PTV2.

Chemotherapy. Cisplatin (80 mg/m^2) on day 1 combined with vinorelbine (25 mg/m^2) on days 1 and 8 in 3-to 4-week intervals were delivered as concurrent and consolidation chemotherapy in 171 (58.2%) patients. Another chemotherapy regimen was administered largely for those with comorbidities and older age. The main second choice of chemotherapy regimen was carboplatin plus paclitaxel, which was administered to 57 patients (19%). Overall, four cycles of chemotherapy were administered, as far as possible. Total chemotherapy cycles, defined by the number of full-dose chemotherapy cycles used in CCRT and consolidation chemotherapy, excluded the number of weekly cycles of chemotherapy regimen and chemotherapy administered after recurrence.

Endpoints. The endpoints of this study were OS (time to death due to any cause), progression-free survival (PFS), and LRC; measured from the first day of treatment (including RT and chemotherapy). PFS was defined as at least 20% increase in the sum of target lesions diameters on CT, appearance of new lesions, or deaths resulting from primary NSCLC only; treatment-related deaths (counted as events and deaths from other causes) were censored. LRC was defined as absence of radiological progression of new lesions within the radiation field, and deaths from any cause without locoregional recurrence were censored.

Statistical analysis and PSM. In order to reduce selection bias, PSM methods were used. The propensity score (15) was estimated using a non-parsimonious multivariate logistic regression model with the use of AH-RT (dependent variable), and 10 baseline metrics (covariates). PSM used 1:1 matching protocol without replacement (nearest available method), with caliper width equal to 0.05 of logit of the propensity score standard deviation. Standard differences, estimated for all baseline covariates before and after matching to assess imbalance, if <10.0% for a given covariate, indicated a relatively small imbalance (15). The area under the curve showed the model performance to be 0.79 [95% confidence interval (CI)=0.74-0.84].

Sensitivity analyses were used to confirm the results of PSM analysis. Three other matched pairs (1:1 patient ratio), with sex, treatment period, and histology eliminated from the original 10 adjustment factors (no significant differences between OD-RT and AH-RT groups in the original cohort in these three factors) were generated. Univariate and multivariate analyses of datasets before matching were performed. Factors with $p<0.02$ in the univariate analysis were included in the multivariate analysis. Additionally, weighted Cox regression with inverse probability of treatment weighting (IPTW) and Cox proportional hazards model in pre-PSM cohort, adjusted with propensity score as a single covariate, were also conducted. IPTW approach compares outcomes in two pseudo-populations with and without exposure, with similar covariate distributions (15). Outcomes were estimated using Kaplan-Meier method and log-rank test. Cox proportional hazards model was used to determine hazard ratios, adjusted for matched design in PSM cohorts. Reported *p*-values are two-sided, while $p<0.010$ and $p<0.05$ were considered significant and marginally significant, respectively. All statistical analyses were performed using JMP Pro version 10 (SAS Institute Inc., Cary, NC, USA), EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), and a graphical user interface for R 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics before and after PSM are presented in Table I. Of 294 patients, 131 (44.6%) received treatment using OD-RT and 163 (55.4%), using AH-RT. In the pre-matching cohort, patients treated with OD-RT were more likely to be >70 years, with poor ECOG PS, larger tumor size, and higher N-classification. They tended to receive sequential CRT, and their total number of full-dose chemotherapy cycles were less than for AH-RT group. After PSM, baseline characteristics became generally comparable between groups (Table I), and all standard differences were confirmed to be <10.0%; indicating only small differences.

Median follow-up time was 40.4 (range=0.37-170.3) months. Before PSM, median OS, PFS and LRC for the OD-RT and AH-RT groups were 23.1 *vs.* 39.9 ($p=0.03$); 8.9 *vs.* 13.5 ($p<0.01$); and 12.9 *vs.* 50.3 ($p<0.01$) months, respectively (Figure 1). After PSM, the difference in LRC remained, with an adjusted hazard ratio (aHR) of 0.59 (95% CI=0.33-0.99; $p=0.04$). The difference in PFS remained marginally significant ($p=0.06$), while the difference in OS was lost after PSM ($p=0.26$) (Figure 2). Sensitivity analyses using PSM also demonstrated that LRC was significantly better for the AH-RT group when excluding sex

Table I. *Patient characteristics before and after propensity score matching (PSM).*

		Before PSM			After PSM		
		OD-RT (n=131)	AH-RT (n=163)	*p*-Value	OD-RT (n=72)	AH-RT (n=72)	*p*-Value
Age, years	Median (IQR)	66 (61-72)	63 (56-68)	<0.01	63 (58-68)	63 (56-70)	0.53
	<70, n (%)	82 (62.6)	132 (81)	<0.01	55 (76.4)	52 (72.2)	0.57
	≥70, n (%)	49 (37.4)	31 (19)		17 (23.6)	20 (27.8)	
Gender	Male	109 (83.3)	133 (81.6)	0.71	61 (84.7)	63 (87.5)	0.63
	Female	22 (16.8)	30 (18.4)		11 (15.3)	9 (12.5)	
ECOG PS	0	62 (47.3)	109 (66.9)	<0.01	36 (50)	38 (52.8)	0.74
	<1	69 (52.7)	54 (33.1)		36 (50)	34 (47.2)	
Treatment period	Up to 03/2009	61 (46.6)	72 (44.2)	0.68	33 (45.8)	31 (43.1)	0.74
	From 04/2009	70 (53.4)	91 (55.8)		39 (54.2)	41 (56.9)	
	Median (SD)	48.3 (22)	40.9 (19.3)	<0.01	46.0 (23.5)	42.8 (21.9)	0.42
Tumor size	<50 mm	69 (52.7)	114 (70.0)	<0.01	44 (61.1)	44 (61.1)	1.0
	≥50 mm	62 (47.3)	49 (30.0)		28 (38.9)	28 (38.9)	
	0/1/2/3	7/9/58/57	6/15/94/48	0.06	5/5/34/28	4/6/33/29	0.97
N-Classification	0-2	74 (56.5)	115 (70.6)	<0.01	44 (61.1)	43 (59.7)	0.87
	3	57 (43.5)	48 (29.4)		28 (38.9)	29 (40.3)	
Histology	SCC	55 (42)	62 (38)	0.8	31 (43.1)	32 (44.4)	0.97
	AC	67 (51.2)	89 (54.6)		36 (50)	35 (48.6)	
	NSCLC-NOS	9 (0.07)	12 (0.07)		5 (6.9)	5 (6.9)	
EGFR mutation	Yes	6 (4.6)	11 (6.8)	0.17	4 (5.6)	4 (5.6)	0.29
	No	48 (36.6)	74 (45.4)		25 (34.7)	34 (47.2)	
	Not assessed	77 (58.8)	78 (47.9)		43 (59.7)	34 (47.2)	
Chemotherapy regimen	CV	52 (39.7)	119 (73)	<0.01	42 (58.3)	40 (55.6)	0.88
	Other	79 (60.3)	44 (27)		30 (41.7)	32 (44.4)	
Chemoradiotherapy	Concurrent CRT	86 (65.6)	152 (93.3)	<0.01	42 (58.3)	40 (55.6)	0.74
	Sequential CRT	31 (23.7)	8 (4.9)		28 (38.9)	29 (40.3)	
	RT alone	14 (10.7)	3 (1.8)		2 (2.8)	3 (4.2)	
Total no. of chemotherapy cycle	0	13 (9.9)	3 (1.8)	<0.01	2 (3.5)	3 (4.1)	0.89
	1-2	55 (42)	52 (31.9)		30 (41.7)	31 (43.1)	
	≥3	63 (48.1)	108 (66.3)		40 (55.6)	38 (52.8)	
Radiation dose (Gy)	Median (range)	60 (58-66)	64 (61-64)	<0.01	60 (58-64)	64 (61-64)	<0.01
Radiation treatment time (days)	Median (IQR)	44 (43-48)	30 (29-33)	<0.01	44 (43-48)	29 (28-34)	<0.01
Treatment technique	3D-CRT	122 (93.1)	163 (100)	<0.01	72 (100)	72 (100)	1
	IMRT	9 (6.9)	0 (0)		0 (0)	0 (0)	
RT delay ≥7 days	Yes	32 (24.4)	34 (20.9)	0.47	18 (25)	17 (23.6)	0.85
	No	99 (75.6)	129 (79.1)		54 (75)	55 (76.4)	
Cause of death	Primary NSCLC	76 (89.4)	94 (84.7)		47 (88.7)	48 (82.8)	
	AE of the treatment	7 (8.2)	2 (1.8)		5 (9.4)	2 (3.4)	
	Other	2 (2.4)	15 (13.5)		1 (1.9)	8 (13.8)	

OD-RT: Once daily radiotherapy; AH-RT: accelerated hyperfractionated radiotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; SCC: squamous cell carcinoma; AC: adenocarcinoma; NSCLC-NOS: non-small-cell lung cancer not otherwise specified; *EGFR*: epidermal growth factor receptor; CV: cisplatin + vinorelbine; 3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiation therapy; AE: adverse event; IQR: interquartile range; SD: standard deviation.

(p=0.03), treatment period (p=0.01), and histology (p=0.02). These three analyses showed marginal difference in PFS and none in OS. Multivariate analyses, which included variables with p<0.2 at univariate analysis suggested sex (male *vs*. female: HR=1.54, 95% CI=1.04-2.34; p=0.03), total chemotherapy cycles (0-2 *vs*. ≥3 cycles: HR=1.34, 95% CI=1.02-1.09; p=0.04), and RT delay (0-6 *vs*. >7 days: HR=0.71, 95% CI=0.51-0.99; p=0.04) as significant prognostic variables of OS and treatment period (up to 03/2009 *vs*. from 04/2009: HR=1.49, 95% CI=1.1-2.0; p<0.01); N classification (0-2 *vs*. 3: HR=0.67, 95% CI=0.51-0.89; p<0.01) and total chemotherapy cycles (0-2 *vs*. ≥3 cycles: HR=1.78, 95% CI=1.33-2.34; p<0.001) of PFS; and treatment period (up to 03/2009 *vs*. from 04/2009: HR=1.55, 95% CI=1.09-2.2; p=0.01) and RT regimen (AH-RT *vs*. OD-RT, HR=0.63, 95% CI=0.44-0.89; p=0.01) of LRC (Tables II and III). The results of these sensitivity analyses consistently showed better LRC and PFS for the AH-RT group and no difference in OS (Table IV).

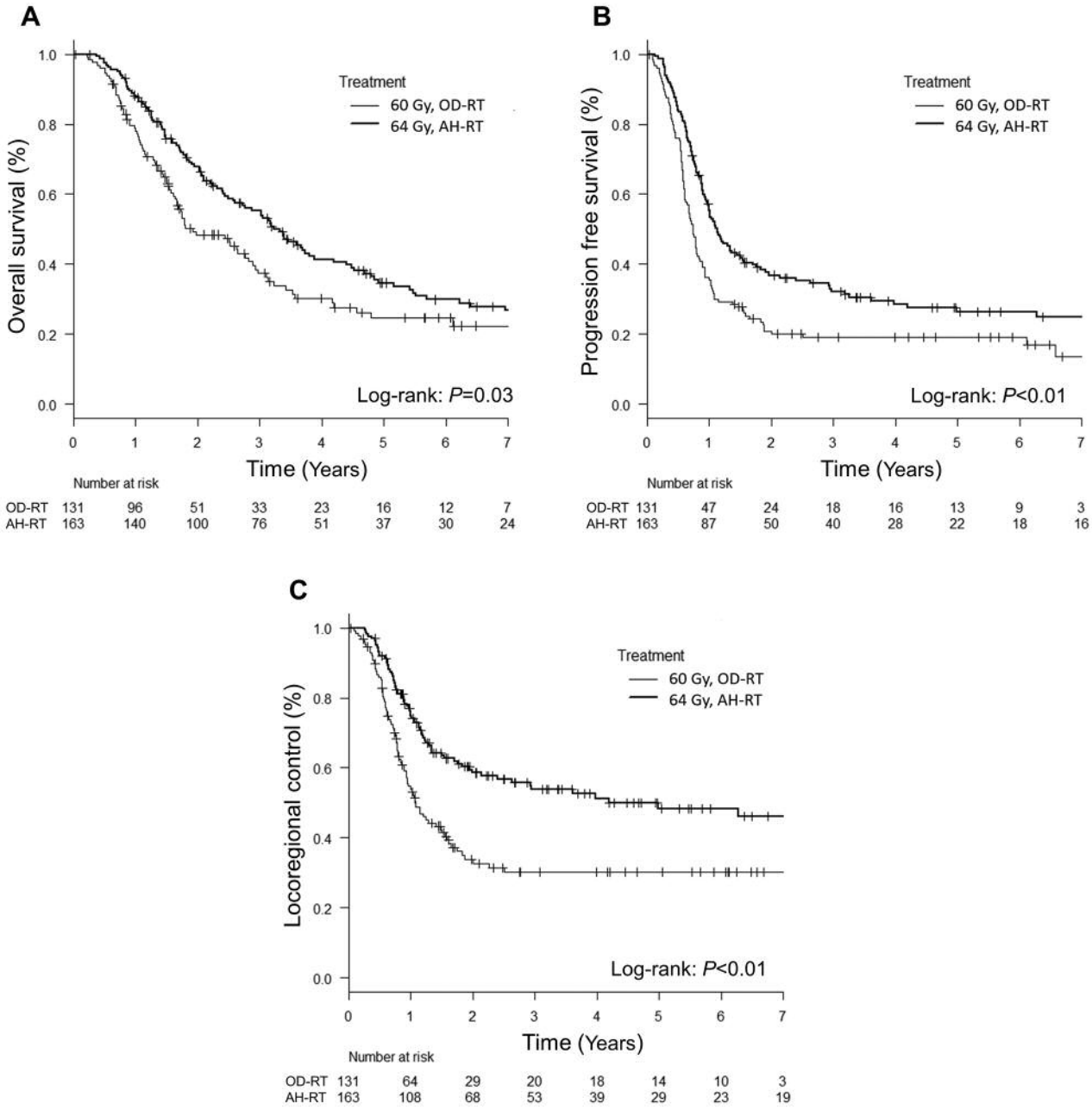

Figure 1. *Kaplan–Meier-estimates. A: Overall survival, B: progression-free survival, and C: locoregional control before propensity score matching in patients with stage III non-small-cell lung cancer according to therapy. OD-RT: Once-daily radiotherapy; AH-RT: accelerated hyperfractionated radiotherapy.*

During follow-up, 196 (66.7%) patients died. In the OD-RT group, more patients died from treatment-related adverse events (AEs). Nine patients died of other diseases in the OD-RT group, of which, seven, one, and one died from AEs, secondary cancer, and cardiac event, respectively. In the AH-RT group, two, nine, and two patients died from AE, secondary cancer, and cerebrovascular events; and one patient from each group died of Parkinson's disease, cardiac event, Nocardia pneumonia, and unknown causes, respectively. The nine deaths from AEs consisted of both radiation and infection-related pneumonia, except for one patient who died of multiple organ failure.

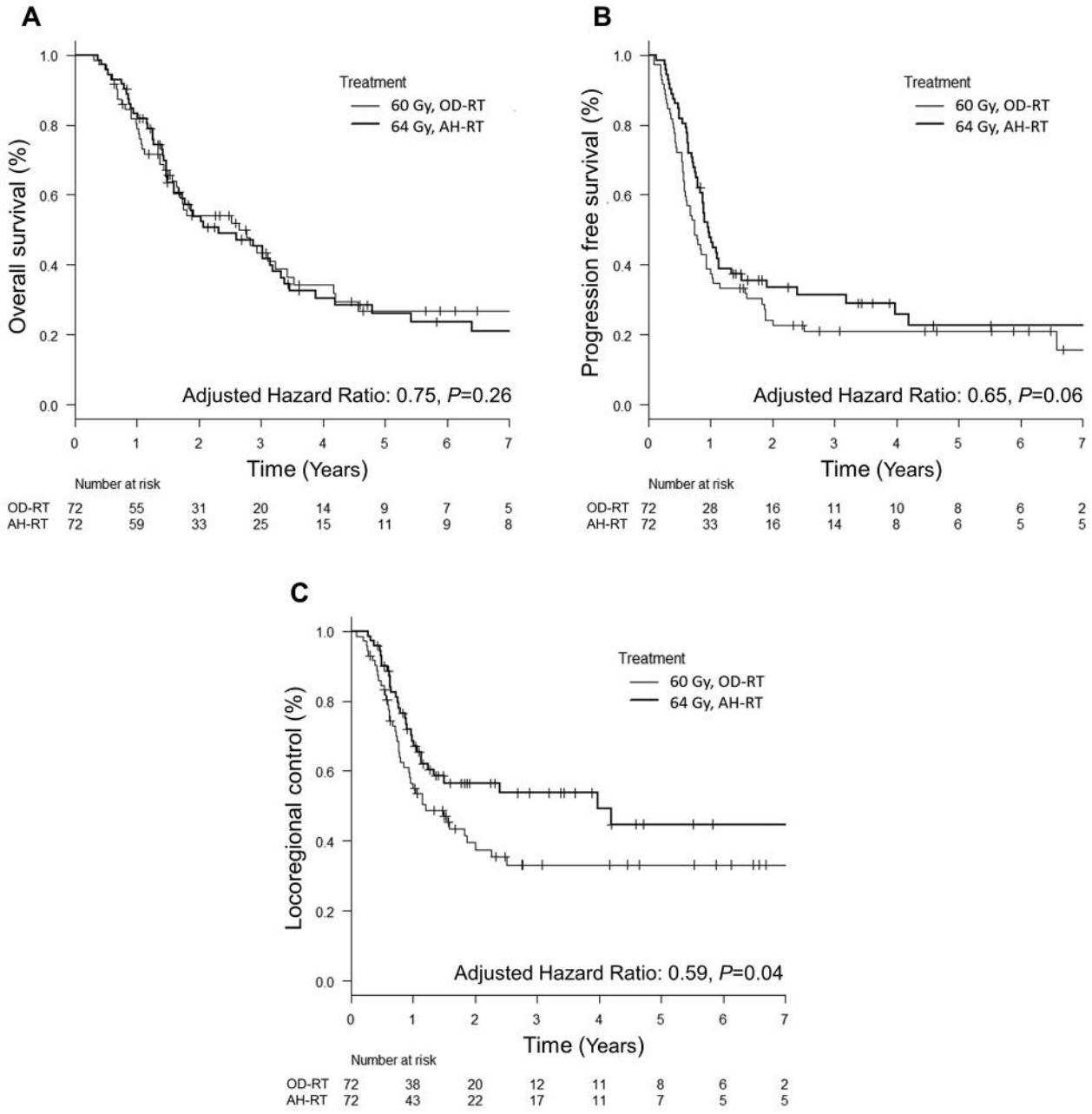

Figure 2. *Kaplan–Meier-estimates. A: Overall survival, B: progression-free survival, and C: locoregional control after propensity score matching in patients with stage III non-small-cell lung cancer according to therapy. OD-RT: Once-daily radiotherapy; AH-RT: accelerated hyperfractionated radiotherapy.*

Discussion

Propensity matched-pair analysis presented in this study showed association of dose escalation using AH-RT with LRC and PFS, but not OS. This finding was robustly confirmed by several sensitivity analyses. Treatment using AH-RT provided a means of RT intensification, which has the potential to improve OS (9). Series of continuous AH-RT trials have shown significant benefit of this modality in improving local control and OS, and confirmed the importance of RT treatment time as a factor in CRT for NSCLC (9, 16). Prolonging RT treatment time can negatively affect LRC and OS in patients with lung cancer (17). The radiobiological underpinning for this might be the accelerated repopulation of surviving tumor

Table II. *Impact of variables on overall survival (OS), progression-free survival (PFS), locoregional control (LRC) for 294 patients at univariate analyses.*

		OS			PFS			LRC		
Factor	Comparison	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	≥70 *vs.* <70 Years	1.65	1.2-2.24	<0.01	1.2	0.88-1.61	0.23	1.3	0.9-1.84	0.15
Gender	Male *vs.* female	1.57	1.07-2.41	0.03	1.12	0.79-1.63	0.53	1.26	0.83-2.0	0.3
Treatment period	Up to 03/2009 *vs.* from 04/2009	1.14	0.85-1.52	0.35	1.3	0.99-1.69	0.06	1.53	1.11-2.11	<0.01
ECOG PS	≥1 *vs.* 0	1.29	0.97-1.71	0.09	1.29	0.98-1.68	0.06	1.23	0.89-1.7	0.2
Histology	AC *vs.* other	0.87	0.66-1.16	0.37	1.05	0.81-1.37	0.72	0.83	0.61-1.15	0.27
Tumor size	<50 *vs.* ≥50 mm	0.85	0.64-1.14	0.24	0.93	0.71-1.23	0.61	0.79	0.57-1.09	0.15
N-Classification	0-2 *vs.* ≥3	0.89	0.67-1.2	0.46	0.65	0.5-0.86	<0.01	0.78	0.57-1.09	0.14
Chemotherapy regimen	CV *vs.* other	0.66	0.5-0.89	<0.01	0.85	0.65-1.11	0.22	0.82	0.59-1.13	0.22
CRT	Concurrent *vs.* other	0.62	0.45-0.89	<0.01	0.72	0.53-1.02	0.05	0.54	0.37-0.79	<0.01
Total no. of chemotherapy cycles	0-2 *vs.* ≥3	1.66	1.24-2.21	<0.01	1.64	1.25-2.14	<0.01	1.31	0.95-1.81	0.1
RT regimen	AH *vs.* OD	0.73	0.55-0.97	0.02	0.63	0.48-0.83	<0.01	0.52	0.38-0.71	<0.01
RT delay	<7 *vs.* ≥7 Days	0.66	0.49-0.92	0.01	0.73	0.55-1.00	0.04	0.75	0.52-1.09	0.12

ECOG PS: Eastern Cooperative Oncology Group performance status; AC: adenocarcinoma; CV: cisplatin + vinorelbine; CRT: concurrent chemoradiotherapy; RT: radiotherapy; OD: once-daily; AH: accelerated hyperfractionation.

Table III. *Impact of variables on overall survival (OS), progression-free survival (PFS), locoregional control (LRC) for 294 patients at multivariate analyses including factors with p<0.02 in the univariate analysis.*

		OS			PFS			LRC		
Factor	Comparison	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	≥70 *vs.* <70 Years	1.28	0.89-1.81	0.17	-	-	-	1.06	0.72-1.56	0.75
Sex	Male *vs.* female	1.54	1.04-2.39	0.03	-	-	-	-	-	-
Treatment period	Up to 03/2009 *vs.* from 04/2009	-	-	-	1.49	1.1-2.0	<0.01	1.54	1.09-2.2	0.01
ECOG PS	≥1 *vs.* 0	1.26	0.94-1.69	0.11	1.27	0.96-1.67	0.09	-	-	-
Histology	AC *vs.* other	-	-	-	-	-	-	-	-	-
Tumor size	<50 *vs.* ≥50 mm	-	-	-	-	-	-	0.84	0.61-1.67	0.29
N-Classification	0-2 *vs.* ≥3	-	-	-	0.67	0.51-0.89	<0.01	0.86	0.62-1.2	0.35
Chemotherapy regimen	CV *vs.* other	0.91	0.64-1.29	0.58	-	-	-	-	-	-
CRT	Concurrent *vs.* other	0.73	0.49-1.14	0.16	1.0	0.67-1.49	0.95	0.78	0.5-1.23	0.28
Total no. of chemotherapy cycles	0-2 *vs.* ≥3	1.39	1.02-1.9	0.04	1.78	1.33-2.38	<0.01	1.28	0.9-1.82	0.17
RT regimen	AH *vs.* OD	0.98	0.71-1.38	0.92	0.75	0.56-1.01	0.06	0.63	0.44-0.9	0.01
RT delay	<7 *vs.* ≥7 Days	0.71	0.51-0.99	0.04	0.84	0.62-1.16	0.29	0.81	0.56-1.19	0.27

ECOG PS: Eastern Cooperative Oncology Group performance status; AC: adenocarcinoma; CV: cisplatin + vinorelbine; CRT: concurrent chemoradiotherapy; RT: radiotherapy; OD: once-daily; AH: accelerated hyperfractionation.

clones, which commences about 28 days after RT initiation (18). Therefore, an AH-RT regimen with 4-week RT treatment time may be more efficient than the standard 6-week regimen. The biologically effective dose for early-responding tissue, widely accepted for comparison of different RT regimens (18), was 74.9 Gy in this study (64 Gy/40 fractions/28 days), 66.2 Gy for the standard dose (60 Gy/30 fractions/30 days), and 79.3 Gy for the high dose used in the RTOG-0617 study (74 Gy/37 fractions/51 days). Considering the high dose (74 Gy) failed to improve local control and OS, LRC improvement in the current AH-RT regimen was possibly due to both shortened RT treatment time and moderate dose escalation. Although a recent study showed that better local control of advanced NSCLC can lead to improved OS (19), an OS advantage for the AH-RT group was not seen in the current study. We believe this was due to potential deviation in administration of salvage therapy, including EGFR tyrosine-kinase inhibitors or immunotherapy, which was not considered in this PSM, and

Table IV. *Summary of sensitivity analysis comparing accelerated hyperfractionated radiotherapy (AH-RT) with once daily radiotherapy (OD-RT): Cox regression models for overall survival, progression free survival, and locoregional control rate.*

	Overall survival			Progression-free survival			Locoregional control rate		
AH- *vs*. OD-RT	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Unadjusted Cox model	0.73	0.55-0.97	0.03	0.63	0.48-0.83	<0.01	0.52	0.38-0.72	<0.01
PSM cohort*	0.75	0.46-1.24	0.26	0.65	0.41-1.03	0.06	0.59	0.33-0.99	0.04
PSM excluding sex*	0.71	0.43-1.2	0.2	0.63	0.4-1.02	0.06	0.56	0.32-0.96	0.03
PSM excluding treatment period*	0.84	0.51-1.41	0.52	0.67	0.42-1.08	0.09	0.50	0.51-0.88	0.01
PSM excluding histology*	0.72	0.42-1.23	0.22	0.67	0.41-1.08	0.09	0.52	0.29-0.92	0.02
Cox model adjusted for variables with $p<0.2$ in univariate analysis	0.98	0.71-1.38	0.92	0.75	0.56-1.02	0.06	0.63	0.44-0.9	0.01
IPTW	0.99	0.7-1.41	0.97	0.74	0.53-1.03	0.08	0.69	0.46-1.05	0.07
Cox model adjusted for PS	1.01	0.72-1.43	0.93	0.76	0.56-1.04	0.08	0.63	0.43-0.91	0.01

HR: Hazard ratio; 95% CI: 95% confidence interval; PS: Eastern Cooperative Oncology Group performance status; PSM: propensity score matching; IPTW: inverse probability of treatment weighting. *Adjusted for matched design in the PSM cohorts.

the relatively large number of deaths from other causes in the AH-RT group. One other variable in the multivariate analysis, treatment period, may also be a surrogate for difference in staging, including the 6th and 7th UICC editions, and the improvement of the modality used for staging, especially the use of positron-emission tomography/CT, which can positively affect clinical outcomes (20). The N classification (0-2 *vs*. 3) and number of chemotherapy cycles were strong predictors of metastatic disease, as reported in previous studies (2, 21). Sex may be a surrogate for genetic background, including EGFR mutations or Ifestyle and environmental factors, as previously reported (22). RT delay was associated with poorer OS in multivariate analysis. We consider that RT delay may be a surrogate for the presence of complications or poor general patient condition because it did not worsen LRC and PFS.

Critical treatment-related AEs were observed in some patients. Out of nine deaths due to treatment-related AEs, eight were due to lung events, while deaths from cardiac events were observed in two. RTOG-0617 hypothesized that higher heart dose in the high-dose group (74 Gy) might be responsible for the poor clinical result. However, they had no data on the true cause of death (7). In this study, cause of death was confirmed, showing that few of patients died of cardiac events compared with lung events in this cohort (2 *vs*. 8 patients). The relationship between cardiac events and CRT was not detected. Although the result might change when OS improves by immunotherapy combined with conventional CRT, which has demonstrated promising clinical benefit in advanced lung cancer (23), our findings showed that dose constraint to the lung should have more priority than that to the heart in current CRT without immunotherapy.

A Iimitation of our study includes its retrospective design, which might have introduced selection bias into the dataset. Despite the PSM approach, the possibility of unaccounted bias persisted. Because of the long observation period, staging modalities, clinical care for AEs, and salvage therapy, were altered. In addition, EGFR data were lacking for half of the patients. Therefore, salvage treatment after recurrence including EGFR (TKI) might explain some, or all, of the observed difference. The strength of our study includes the relative homogeneity of the RT regimen. Data on cause of death were obtained for most patients.

In conclusion, our PSM analysis of patients with locally advanced NSCLC undergoing CCRT with AH-RT compared with conventional OD-RT revealed improved LRC and PFS in the AH-RT group, but no superiority in OS. The number of deaths due to cardiac events was small; therefore, reducing the RT dose to the lung should be prioritized over that to the heart. Regarding the fact that shortened RT treatment time and moderate dose escalation may be needed for advanced NSCLC, the AH-RT regimen can be a promising option instead of moderate dose escalation using OD-RT. Additional studies may be required to confirm the present results.

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Conflicts of interest

The Authors declare no conflict of interest in regard to this study.

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