

ORIGINAL ARTICLE

Hypofractionated radiotherapy for medically inoperable stage I non-small cell lung cancer

Wei Jiang, Jian-Yang Wang, Jing-Bo Wang, Jun Liang, Zhou-Guang Hui, Xiao-Zhen Wang, Zong-Mei Zhou & Lu-Hua Wang

Department of Radiation Oncology, Cancer Hospital & Institute, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Keywords

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Correspondence

Lu-Hua Wang, Cancer Hospital & Institute, Chinese Academy of Medical Sciences, Panjiayuan Nanli #17, Chaoyang District, Beijing 100021, China.
Tel: +86 10 8778 8799
Fax: +86 10 8771 6559
Email: wlhwq@yahoo.com

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Abstract

Background: To investigate the clinical outcomes and toxicity of hypofractionated radiotherapy for medically inoperable stage I non-small cell lung cancer (NSCLC).

Methods: Patients treated with radiotherapy at a dose of 4–6 Gy per fraction using fixed-field intensity modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) at our hospital from June 2005 to December 2013 were analyzed. The total prescription doses ranged from 50–78 Gy with 4–6 Gy per fraction. The median follow-up period was 24 months.

Results: A total of 65 patients with stage I NSCLC were analyzed, including 43 primary NSCLC patients and 22 patients with recurrent or second primary NSCLC. An objective response (complete or partial response) was achieved at six months in 84.6% of patients. The three-year local control rate was 90.8%. Kaplan–Meier estimates of local failure-free, progression-free, overall, and cancer-specific survival rates at three years were 90.3%, 64.3%, 68.9%, and 88.8%, respectively. The rate of symptomatic radiation pneumonitis was 16.9%, and no grade 4–5 toxicity was observed.

Conclusion: Favorable local control and outcome was achieved with hypofractionated radiotherapy in patients with inoperable stage I NSCLC with acceptable toxicity. The most common schedule of 6 Gy × 12 fractions may be a promising regimen, and a prospective study is in process.

Introduction

Lung cancer is the primary cause of cancer death worldwide. Although the gold standard for treatment of early non-small cell lung cancer (NSCLC) remains surgery, it may not be practical as a result of coexisting medical comorbidities.¹ Stereotactic body radiation therapy (SBRT) provides a therapeutic strategy for such cases. Compared with conventional fractionated radiotherapy, SBRT has the ability to deliver a high biologically equivalent dose (BED) of more than 100 Gy, leading to local control (LC) rates of approximately 90%, which are comparable to those after surgery.^{2,3} The recommended dose fractionation regimens in most reports are 10–20 Gy per fraction.^{2,4} However, these regimens require advanced technique and strict quality assurance and control, which are not available in some cancer centres, particularly in developing countries. Under such circumstances, hypofractionated radiotherapy with an adapted dose regimen may be an alternative to compromise between tumor

control and the risk of adverse effects resulting from the potential inaccuracy of radiotherapy. The hypofractionated regimen may be more valuable/practical in central lung cancer in which higher doses of fractionation were reported to be intolerable.⁵

Moderate dose schedules have been reported to achieve comparable outcomes to surgery in several studies with relatively small numbers of patients. Duncker-Rohr *et al.* reported that 7 Gy × 5 led to favorable local progression-free survival (PFS) and overall survival (OS) rates of 95% and 65.4% at two years, respectively, and low toxicity for small primary or metastatic lung tumors.⁶ A recent study performed at MD Anderson Cancer Center attempted a regimen of 70 Gy in 10 fractions in clinically challenging cases, including those with centrally located lesions or lesions proximal to the chest wall, and observed two-year OS and LC rates of 66.9% and 96.2%, respectively.⁷

In our institution, hypofractionated radiotherapy with a dose fractionation scheme of 4–6 Gy per fraction has been

utilized for early stage NSCLC, particularly for central lesions. This study explores clinical outcomes and toxicity by retrospectively reviewing stage I or re-stage I NSCLC patients treated with hypofractionated radiotherapy in our hospital from 2005 to 2013.

Material and methods

Patients

Patients were selected according to the following inclusion criteria: (i) Stage I (T1a, T1b or T2a) primary or local recurrent NSCLC according to the 7th edition of the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) classification system;⁸ (ii) medically inoperable status or refusal of surgery; (iii) completion of hypofractionated radiotherapy; (iv) dose fractionation regimen of 4–6 Gy per fraction; and (v) consecutive treatment from June 2005 to December 2013. NSCLC was confirmed by pathology or cytology but not imperatively. Nineteen patients with repeated unsuccessful or declined biopsies were diagnosed according to signs of malignancy on positron emission tomography-computed tomography (PET-CT).

Second primary NSCLC was defined as a second tumor with a different pathologic type or occurring at least six months after the initial diagnosis and different from the initial site without evidence of progression at other sites of the body. Central tumors, defined as lesions within 2 cm of the bronchial tree or mediastinal structures, were not excluded.

Treatments

All cases assigned to receive hypofractionated radiotherapy were discussed by our multidisciplinary tumor board and patients signed informed consent for treatment.

All patients were treated with 6 MV linear accelerator-based hypofractionated radiotherapy. Immobilization was achieved with thermoplastic resin shells at the supine position. Treatment simulation was performed using various techniques, including four-dimensional (4D) CT at slice intervals of 3 mm in 10 phases spanning the respiratory cycle, PET/CT-simulation under free-breathing with 3.27-mm slice thickness, and helical CT imaging with slice thicknesses of 5 mm under free breathing.

The gross tumor volume (GTV) was delineated as the volume of a macroscopic tumor on pulmonary windows, and adjacent mediastinum or chest wall structures were avoided on soft tissue windows. The clinical target volume (CTV) was created by adding a 0.3–0.8 cm margin around the tumor as appropriate. In patients who underwent simulation with 4DCT, the internal target volume (ITV) was contoured in the maximum intensity projection dataset or the sum of the

GTVs in all 10 breathing phases. The planning target volume (PTV) was the CTV or ITV with a 0.3–0.5 cm expansion to account for residual tumor motion or set-up error.

All plans were created using adaptive convolve dose calculations with heterogeneity correction by Pinnacle³ v.9 treatment planning system software (Philips Medical Systems, Andover, MA, USA). A three-dimensional conformal radiation therapy (3DCRT) technique was used in two patients before October 2008 for three or four-beam planning. Afterwards, a fixed-field IMRT plan was generated using five to seven non-opposing coplanar beams, and the VMAT plan was delivered using two partial arcs.

The radiation dose was prescribed to 95% of the PTV under a risk-adapted fractionation scheme depending on the treating physician's discretion, 4–6 Gy dose fractions, five times per week. The linear-quadratic formula (with an assumed α/β of 10) was used for dose-fraction adjustments and dose constraints in normal tissues. Cone-beam CT was employed to ensure high-precision delivery.

Assessment of response and toxicity

All patients were monitored daily for acute toxicity during radiotherapy. Follow-up CT scans were performed at one to three months after treatment and then every three to four months during the first two years. ¹⁸F-fluorodeoxyglucose (FDG)-PET/CT imaging was required only when disease relapse was suspected. The evaluation of tumor response was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.⁹ An objective response (ORR) was defined as CR or PR.

Patterns of failure were classified as follows: local recurrence was defined as primary tumor recurrence, and regional recurrence was defined as recurrence in the mediastinum, hilum, supraclavicular fossa or the same lobe. Other sites of recurrence, including different lobes, contralateral lung, and metastatic lymph nodes in the neck or axilla, were defined as distant metastases.

Acute and late radiation-related toxicities were defined as adverse effects within and after six months of treatment completion, respectively, and assessed according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.¹⁰

Statistical analyses

Survival was calculated from the beginning of radiotherapy to the date of death or last assessment. The OS, PFS, cancer-specific survival (CSS), and LC rates were estimated by Kaplan–Meier method and the log-rank test was used for survival comparison between different groups. Variables

showing a P value < 0.2 in univariate analysis were selected for the multivariate Cox proportional hazard regression model (backward conditional stepwise).

Comparisons of failure rates stratified with BED and therapeutic objects were made using the Kaplan–Meier method and log-rank tests.

A value of $P < 0.05$ was considered statistically significant and all tests were two-sided. Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Table 1 summarizes the general characteristics of the study population. In total, 43 primary NSCLC, 15 second primary NSCLC, and seven recurrent NSCLC postoperative cases were included. Reasons for inoperability included advanced age in four, coexisting lung or cardiovascular comorbidities in 51, a history of previous lobectomy in nine patients, and synchronous primary NSCLC in one patient. Of the 65 patients enrolled in the analysis, the median age was 73 years (range, 44–91) and 14 patients (21.5%) had central diseases. The comorbidity rate was 87.7% (57/65) and 84.6% patients had Charlson Comorbidity Index (CCI) scores of more than three. Twenty-five patients (38.5%), with 72% of histological confirmed NSCLC had a double-primary cancer, including renal carcinoma, hypopharynx carcinoma, diffuse large B-cell lymphoma, and colorectal, gastric, cervical, prostate, tongue, and bladder cancers. Six patients, including two with recurrence and four with second primary cancer, had a history of thoracic radiotherapy, 11 months to 14 years prior to current treatment. Hypofractionated radiotherapy was delivered with a median total dose of 70 Gy (range, 48–78) in moderate fractionation (four to six Gy/fraction) daily, converted into a median BED of 105.6 Gy (range, 67.2–124.8). Six Gy \times 12 fractions was the most commonly used fractionation regimen (43.1%, $n = 28$). Patients were followed for a median of 24.3 months (range, 9.3–105.8), and none were lost to follow-up.

Tumor response and survival

In total, among the 65 patients, CR, PR, SD, and ORR were 10.8%, 46.2%, 40.0%, and 56.9% at three months, and 23.1%, 61.5%, 6.2%, and 84.6% at six months, respectively. The ORRs were 86.0%, 86.3%, and 71.5% in the patients with primary NSCLC, second primary NSCLC, and recurrent NSCLC at six months, respectively (as shown in Table 2). The three-year LC rates were 90.8%, 91.3%, and 91.3% for all patients, patients with primary or second primary NSCLC, and pathological or cytological confirmed patients, respec-

Table 1 Patient characteristics ($n = 65$)

Characteristic		Value (%)
Age (years)	≤ 75	42 (64.6%)
	> 75	23 (35.4%)
Gender	Male	52 (80.0%)
	Female	13 (20.0%)
KPS scale	≥ 90	42 (64.6%)
	60–80	23 (35.4%)
Smoking history	With	48 (73.8%)
	Without	17 (26.2%)
Charlson comorbidity index	0–2	10 (15.4%)
	3–4	16 (24.6%)
	≥ 5	39 (60.0%)
Histology	Squamous cell carcinoma	32 (49.2%)
	Adenocarcinoma	14 (21.5%)
	Others	2 (3.1%)
Tumor location	Unspecified	17 (26.2%)
	Peripheral	51 (78.5%)
T stage	Central	14 (21.5%)
	T1a	9 (13.8%)
Therapeutic object	T1b	25 (38.5%)
	T2a	31 (47.7%)
	Primary NSCLC	43 (66.2%)
Bi-primary cancer	Second primary NSCLC	15 (23.1%)
	Yes	7 (10.8%)
	No	25 (38.5%)
Prior thoracic radiotherapy	Yes	40 (61.5%)
	No	6 (9.2%)
GTV volume (mean \pm SD)	23.94 \pm 17.83	59 (90.8%)
PTV volume (mean \pm SD)	85.45 \pm 57.42	
Radiation technology	3DCRT	2 (3.1%)
	IMRT	53 (81.5%)
	VMAT	10 (15.4%)
BED	< 100	29 (44.6%)
	≥ 100	36 (55.4%)
Dose fractionation regimens	4 Gy \times 12-17f	11 (16.9%)
	5 Gy \times 10-15f	11 (16.9%)
	6 Gy \times 10-13f	43 (66.2%)

3DCRT, three-dimensional conformal radiation therapy; BED, biological equivalent dose; GTV, gross tumor volume; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky performance status; NSCLC, non-small cell lung cancer; PTV, planning target volume; SD, standard deviation; VMAT, volumetric modulated arc therapy.

tively. Figure 1 shows a typical case of primary NSCLC treated with hypofractionated radiotherapy.

The survival curve of the 65 patients is shown in Figure 2a. The three-year PFS rates were 64.3% and 57.1% in all and 46 histologically confirmed patients, respectively. Age (≤ 75 vs. > 75) was a prognostic factor of PFS ($P = 0.047$, hazard ratio [HR] 2.50, 95% confidence interval [CI] = 1.01–6.16). Patients who received radiotherapy for recurrent NSCLC had a significantly poorer PFS than those with primary NSCLC ($P = 0.047$, log-rank $P = 0.024$, Fig 2b).

Fourteen patients died during follow up. The OS rate at three years was 68.9%, with a median survival of 58.7 months,

Table 2 Tumor responses to radiotherapy at three and six months

	Primary NSCLC (n = 43)		Second primary NSCLC (n = 15)		Recurrent NSCLC (n = 7)	
	3 months	6 months	3 months	6 months	3 months	6 months
CR	2 (4.7%)	8 (18.6%)	4 (26.7%)	5 (33.3%)	1 (14.3%)	2 (28.6%)
PR	21 (48.8%)	29 (67.4%)	6 (40.0%)	8 (53.3%)	3 (42.9%)	3 (42.9%)
SD	20 (46.5%)	3 (7.0%)	5 (33.3%)	1 (6.7%)	1 (14.3%)	0 (0.0%)
PD	0 (0.0%)	3 (7.0%)	0 (0.0%)	1 (6.7%)	2 (28.6%)	2 (28.6%)

CR, complete response; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

and 66.7% in 46 patients with confirmed pathology or cytology. Cancer-specific survival at three years was 88.8% and 90.3% in all and histologically confirmed patients, respectively. Probably because of the limitations associated with the small cohort and short follow-up period, multivariate analysis failed to identify any independent prognostic factors associated with OS or CSS. Tumor stage, tumor location, existing comorbidity, target volume or BED had no significant impact on OS (Table 3).

Failure patterns

Post-treatment failure occurred in 23 patients (35.4%) during follow-up, including local failure in seven (10.8%), regional failure in eight (12.3%), and distant metastases in 11 (16.9%) patients. One patient was observed to suffer from all

types of failure patterns, and one had synchronous regional failure and distant metastasis.

Local recurrence was not observed in patients with T1a tumors. All seven patients with recurrent NSCLC experienced disease progression, and the three-year rate of regional failure (71.4%) was significantly higher than in patients with primary NSCLC (7.3% and 14.4% for primary and secondary, respectively, $P < 0.001$). BED ≥ 100 Gy led to a trend of better local control but was not significant (3-year local recurrence rates of 14.1% and 6.1% in BED < 100 Gy and ≥ 100 Gy, $P = 0.240$).

Toxicity

Hypofractionated radiotherapy was generally well tolerated and none of the toxicities interfered with treatment

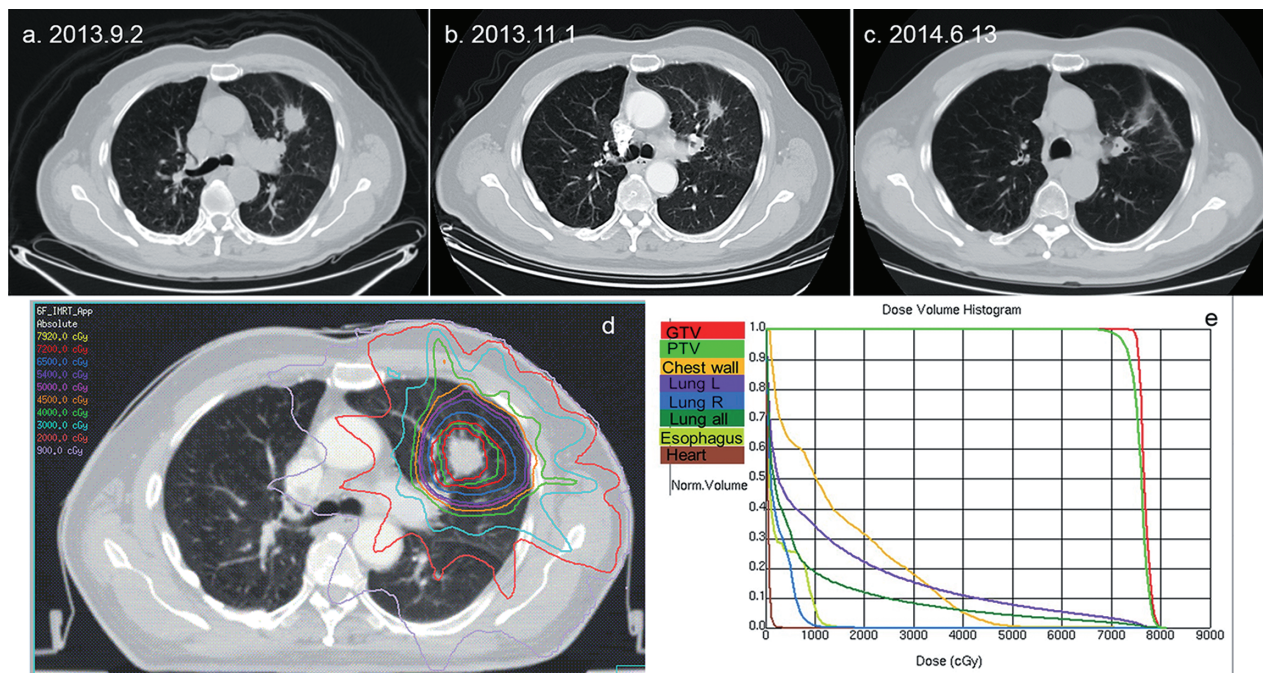


Figure 1 Tumor response and treatment plan of a patient who received hypofractionated radiotherapy with a dose of 72 Gy in 12 fractions. (a) Chest computed tomography (CT) pretreatment scan of a peripheral lesion in the left upper lobe. (b) Chest CT scan five weeks after radiotherapy showed marked regression of lesions. (c) Follow-up CT at nine months, revealing no definitive tumor with mild radiation-induced changes of cord-like shadows. (d) and (e) IMRT planning: Isodose distribution and dose-volume histogram. GTV, gross tumor volume; L, left; PTV, planning target volume.

Table 3 Survival analysis of stage I NSCLC after hypofractionated radiotherapy

Factors	PFS						OS						CSS					
	Univariate			Multivariate			Univariate			Multivariate			Univariate			Multivariate		
	N	PFS (%)	P	HR (95% CI)	P	3-year OS (%)	HR (95% CI)	P	3-year OS (%)	HR (95% CI)	P	3-year CSS (%)	HR (95% CI)	P	3-year CSS (%)	HR (95% CI)	P	
Overall	65	64.3	-	-	-	68.9	-	-	-	-	-	88.8	-	-	-	-	-	
Age (years)	42	73.3	0.081	1	0.047	76.5	0.041	0.196	1	0.196	0.093	89.6	0.093	1	89.6	0.093	0.246	
	23	46.3		2.50 (1.01-6.16)		54.3		2.15 (0.67-6.85)				89.4		3.02 (0.47-19.55)				
Gender	52	63.8	0.559	-	-	62.6	0.055	0.976	1	0.976	0.252	86.1	0.252	-	100	-	-	
	13	67.1				100		28.99 (0.11-7435.93)				100						
KPS scale	23	60.5	0.992	-	-	95.0	0.015	0.150	1	0.150	0.084	100	0.084	1	100	0.084	0.957	
	42	66.7				52.8		4.67 (0.57-38.04)				80.9		42199.0 (0.0-10 ¹⁷⁰)				
Smoking history	17	65.4	0.601	-	-	61.9	0.091	0.378	1	0.378	0.183	84.2	0.183	1	84.2	0.183	0.958	
	48	64.2				85.7		0.38 (0.05-3.25)				100		0.00 (0.0-10 ¹⁶⁵)				
Charlson score	10	70.0	0.996	-	-	88.9	0.385	-	-	-	0.538	100.0	0.538	-	100.0	-	-	
	16	64.3				86.7						93.3			93.3			
	39	63.6				59.5						84.7			84.7			
Histology	32	66.1	0.306	-	-	68.3	0.512	-	-	-	0.433	91.9	0.433	-	91.9	-	-	
	14	44.2				68.2						100			100			
	2	50.0				50.0						50.0			50.0			
	17	76.5				73.2						87.5			87.5			
Tumor location	51	64.0	0.695	-	-	65.6	0.724	-	-	-	0.298	86.8	0.298	-	86.8	-	-	
	14	68.8				91.7						100			100			
T stage	34	70.6	0.393	-	-	79.9	0.633	-	-	-	0.061	100	0.061	1	100	0.061	0.953	
	31	57.7				62.1						81.0		34992.7 (0.0-10 ¹⁷⁴)				
Therapeutic object	43	61.9	0.045	0.267 (0.08-0.86)	0.027	64.4	0.561	-	-	-	0.313	84.5	0.313	-	84.5	-	-	
	15	85.6		0.184 (0.04-0.86)	0.032	77.5						100			100			
Recurrence	7	42.9	0.047*	1	0.047*	NR						NR			NR			
Bi-primary cancer	25	75.3	0.589	-	-	72.6	0.600	-	-	-	0.465	90.0	0.465	-	90.0	-	-	
	40	58.8				67.9						87.8			87.8			
BED (Gy)	29	63.9	0.702	-	-	68.2	0.843	-	-	-	0.280	92.9	0.280	-	92.9	-	-	
	36	60.6				72.2						86.8			86.8			
GTV volume (mL)	37	66.1	0.970	-	-	77.2	0.383	-	-	-	0.288	92.9	0.288	-	92.9	-	-	
	28	61.8				59.9						85.4			85.4			

*Overall P value from conditional test. ADC, adenocarcinoma; BED, biological equivalent dose; CI, confidence interval; CSS, cancer-specific survival; GTV, gross tumor volume; HR, hazard ratio; KPS, Karnofsky performance status; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

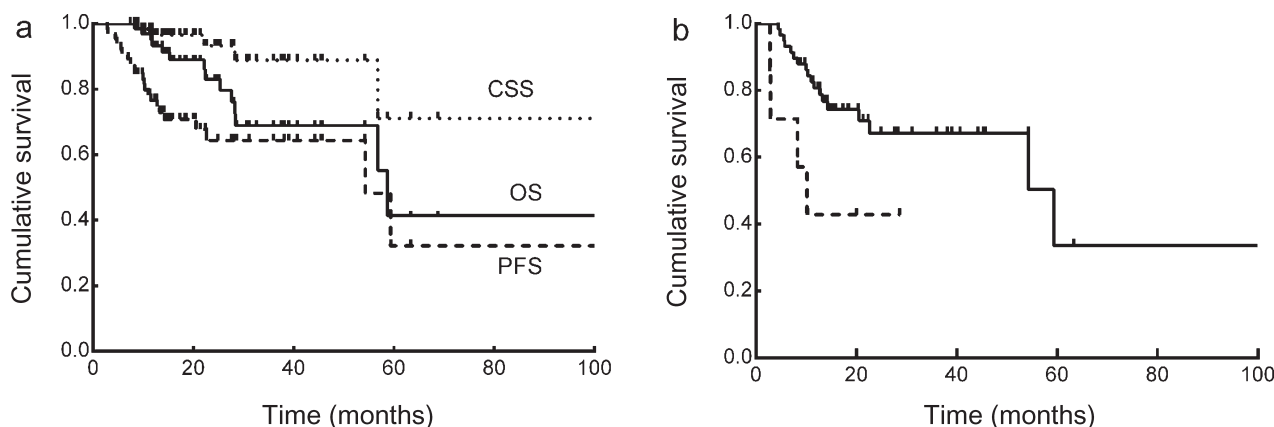


Figure 2 Kaplan–Meier survival curves of the enrolled patients. (a) Overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS) of all 65 patients. (b) PFS compared between patients with primary and recurrent NSCLC. — Primary NSCLC; - - - Recurrent NSCLC.

completion (as shown in Table 4). Symptomatic pneumonitis (grade 2 and above) occurred in 11 patients (16.9%); two of these patients (3.1%) experienced grade 3 cough and received corticosteroid therapy.

During the administration of radiotherapy, grade 1 (in 6 patients, 9.2%) and 2 (in 2 patients, 3.1%) esophagitis was observed. Two patients with tumors close to the chest wall reported grade 2 (6.2%) pain at 11 and 17 months after radiotherapy. No brachial neuralgia or cardiovascular toxicity was observed.

Patients with central lesions did not have greater overall grade 2 toxicity than those with peripheral lesions (28.6% for central lesions vs. 19.6% for peripheral lesions, $P = 0.470$).

Discussion

Stereotactic body radiation therapy has been reported to achieve 70% five-year OS for inoperable primary or recurrent NSCLC and plays an increasing role in the treatment of operable early NSCLC patients.^{2,11,12} However, when delivery of high dose SBRT is restricted as a result of radiation techniques or central lung cancers, hypofractionated stereotactic radiotherapy provides a therapeutic strategy/alternative. A

multi-institutional study reported encouraging outcomes with a five-year OS rate of 47.2%.¹³

Consistent with the above-mentioned Japanese study, our study yielded three-year LC and OS rates of 90.8% and 69.1%, respectively, with fractionation schedules of 4–6 Gy \times 10–17 fractions. Our results are comparable to those of previous studies, including the classic RTOG 0236 study of SBRT for NSCLC, which reported three-year LC and OS rates of 98% and 56%, respectively, for patients who received 60 Gy in three fractions.^{2,14,15} Another representative trial, JCOG 0403, was the first Phase II clinical trial for medically operable NSCLC.¹⁶ It demonstrated three-year OS and local PFS rates of 76% and 69%, respectively, for operable cases treated with 48 Gy in four fractions. Considering the inoperable patients in the present study, our results are promising, indicating efficiency from another perspective.

A BED has been accepted to be the most significant predictor of local control. A large multi-institutional retrospective review by Onishi *et al.* demonstrated that LC and survival rates in a group treated with BED ≥ 100 Gy were superior to those treated with a lower dose.¹³ An analysis of SBRT BED for lung tumors proposed that a BED >100 Gy is required to achieve a $>85\%$ LC rate.¹⁷ On the contrary, a meta-analysis

Table 4 Toxicity related to hypofractionated radiotherapy

Event	CTCAE Grade				
	I	II	III	IV	V
Radiation pneumonitis	28 (43.1%)	9 (13.8%)	2 (3.1%)	0	0
Central	6 (42.9%)	2 (14.3%)	1 (7.1%)	0	0
Peripheral	22 (43.1%)	7 (13.7%)	1 (2.0%)	0	0
Chest wall pain	4 (6.2%)	2 (3.1%)	0	0	0
Esophagitis	6 (9.2%)	2 (3.1%)	0	0	0
Brachial neuralgia	0	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events.

showed that OS was higher in the medium (83.2–106 Gy) or medium to high (106–146 Gy) BED groups than in the low (<83.2 Gy) or high (>146 Gy) BED.¹⁸ In our study, the BEDs in 95.4% of patients were at medium and medium to high ranges (84–124.8 Gy), and there was no significant difference in survival and local recurrence between patients treated with a BED of 100 or more and those treated with a BED of less than 100. These results reveal that a medium BED might also be reasonable to treat stage I NSCLC.

In the literature, tumor size has been proposed to be associated with outcome. Park *et al.* reported that patients with a tumor size of <3 cm had a LC rate of 96.2% at two years, superior to those with a tumor size \geq 3 cm of 50%.¹⁷ In our study, local recurrence was not observed in patients with T1a tumors; however, we noticed that a higher BED did not significantly improve local recurrence rate in patients with larger tumors ($P = 0.2$). The small cohort used in our study may be a potential limitation.

Treatment of NSCLC thoracic recurrence is a significant challenge for radiation oncologists. Retrospective analysis of SBRT for thoracic re-irradiation with median doses ranging from 40–80 Gy has recently been published.¹⁹ LC rates varied from 65–92%. The two-year PFS and OS were reported in ranges of 26%–64% and 29%–74%, respectively. Only seven recurrent NSCLC patients were included in our study, but all experienced disease progression. Comparing primary NSCLC patients, the regional failure rate was significantly higher under similar LC, demonstrating more aggressive behavior. The PFS rate was only 42.9% at three years, which was, nevertheless, favorable by contrast and consistent with previous reports. The ideal treatment regimen in recurrent NSCLC remains to be determined by larger studies.

Second primary lung cancers are also difficult to treat because of limited cardiopulmonary reserves after surgery or radiotherapy for an initial cancer. SBRT was reported to be promising treatment for early stage multiple primary lung cancer with limited toxicities, with four-year in-field LC and OS rates of 95.7% and 47.5%, respectively.²⁰ In the current study, hypofractionated regimens also performed well for second primary lung cancer; second primary lung cancer showed similar outcomes to first primary lung cancer.

Currently, dose fractionation regimens are very heterogeneous across centers. Although several prospective phase II–III dose escalation trials are ongoing to explore the optimal SBRT regimen for early stage NSCLC, such as RTOG0813, JCOG0702, and JROSG10-1, initial doses remain a large dose per fraction of 10–12.5 Gy. In this study, 6 Gy \times 12 fractions was the most commonly used schedule; a prospective clinical trial is in progress to explore this schedule. Although only 28 patients were included in our analysis, we established feasibility and safety and further results are expected.

There were some limitations to our study, most notably the short length of follow-up and the comparatively small

number of patients, which could potentially affect the interpretation of tumor control and prognostic parameters. Nonetheless, hypofractionated stereotactic radiotherapy yielded positive outcomes. Despite lacking long-term follow-up and a uniform treatment technique, the regimen showed promising efficacy and safety, suggesting it could be widely applied.

Conclusion

Hypofractionated radiotherapy provides a therapeutic alternative when it is unfeasible to administer high dose stereotactic radiotherapy. Favorable LC and outcomes were achieved with hypofractionated radiotherapy in inoperable patients with stage I NSCLC, with acceptable to mild toxicity. A prospective study is in progress to confirm whether 6 Gy \times 12 fractions could represent a promising treatment schedule.

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Disclosure

No authors report any conflict of interest.

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