ORIGINAL PAPER

Nagoya J. Med. Sci. **86**. 588–595, 2024
doi:10.18999/nagjms.86.4.588

Risk-adapted stereotactic body radiation therapy delivered in four fractions in patients with non-small cell lung cancer

Yutaka Masuoka[1], Takuhito Tada[1], Shogo Matsuda[1], Yoshikazu Hasegawa[2], Kentaro Ishii[3], Haruo Inokuchi[4] and Keiko Shibuya[4]

[1]*Department of Radiology, Izumi City General Hospital, Izumi, Japan*
[2]*Department of Medical Oncology, Izumi City General Hospital, Izumi, Japan*
[3]*Department of Radiation Oncology, Tane General Hospital, Osaka, Japan*
[4]*Department of Radiation Oncology, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan*

ABSTRACT

Risk-adapted stereotactic body radiation therapy is preferred over conventional radiotherapy at the authors' institution based on the hypothesis that even with a lower than recommended dose, stereotactic body radiation therapy would yield better local control than conventional radiotherapy. This retrospective study was performed to verify the hypothesis. Data from 34 patients with non-small cell lung cancer, who underwent risk-adapted stereotactic body radiation therapy delivered in 4 fractions between 2012 and 2018, were analyzed. The 3-year local control rate for patients receiving 42–44 Gy, 40 Gy, and 32–38 Gy was 80.8%, 75.0%, and 66.7%, respectively. The 3-year overall survival rate was 63.5%, 63.5%, and 40.0%, respectively. Three patients experienced grade 3 toxicities, with no toxicities > grade 3 observed. The results support the use of risk-adapted stereotactic body radiation therapy, both with a relatively high dose and a low dose.

Keywords: lung cancer, risk adapted, stereotactic body radiation therapy

Abbreviations:
SBRT: stereotactic body radiation therapy
OS: overall survival

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is an effective treatment modality for early-stage lung cancer. High doses, with a biologically effective dose > 100 Gy, have resulted in greater local control.[1-7] However, in patients with risk factors such as neighboring organs at risk, co-morbidities, and/or advanced ages, there is hesitation to perform SBRT using the recommended doses. At our institution, risk-adapted SBRT has been preferred over conventional radiotherapy for such patients. This preference is based on the hypothesis that even with a lower dose than that

Received: September 7, 2023; accepted: February 7, 2024
Corresponding Author: Yutaka Masuoka, MD
Department of Radiology, Izumi City General Hospital, 4-5-1 Wake-cho, Izumi 594-0073, Japan
Tel: +81-725-41-1331, Fax: +81-725-43-3350, E-mail: yutaka.masuoka@tokushukai.jp

recommended, SBRT would yield better local control than conventional radiotherapy. Therefore, we performed this retrospective study to verify our hypothesis.

MATERIALS AND METHODS

Patients

The present study was approved by the Institutional Review Board of Izumi City General Hospital (Izumi, Japan; reference number: 23-J08) and performed in accordance with the principles outlined in the 1964 Declaration of Helsinki and subsequent amendments.

This retrospective analysis included patients with histologically proven non-small cell lung cancer who underwent SBRT with a dose < 48 Gy. Patients with a tumor size > 5 cm, regional lymph node metastases, and distant metastases were excluded. Therefore, the clinical T-, N-, and M-stages were T1 or T2, N0, and M0 (Union for International Cancer Control [UICC] eighth edition), respectively, in all patients. In most patients, 18-F-fluorodeoxyglucose positron emission tomography/computed tomography was performed for staging.

Treatment

All patients were irradiated using stereotactic techniques. The gross tumor volume included only the primary tumor, with no consideration for a clinical target volume margin. Internal target volume margin and a 5 mm set up margin were added to generate the planning target volume. Patients were immobilized using a full-body vacuum bag system for position stabilization and consistency. Irradiation was performed with the patients under free breathing. X-ray fluoroscopy was used to assess motion of the target during the breath cycle and the internal target volume margin around the gross tumor volume.

Treatment was performed using 8 non-coplanar static beams with an energy of 6-MV, and a three-dimensional treatment planning system with heterogeneity correction calculation. Dose constraints for organs at risk were applied in accordance with those defined in the Japan Clinical Oncology Group study (JCOG0403).[8] In addition, the volume of the chest wall receiving more than 30 Gy was constrained[9] less than 30 cm^3. The dose (or slightly lower than that) was comprehensively prescribed based on risk factors emphasizing safety for the elderly patients. The dose was prescribed at the isocenter.

Statistical analyses

The primary endpoint of the analysis was local control, with other endpoints including overall survival (OS) and toxicity. Local control and OS were estimated using the Kaplan-Meier method. Toxicity data were graded in accordance with the Common Terminology Criteria for Adverse Events version 5.0.

RESULTS

Patient characteristics

Between October 2012 and February 2018, a total of 35 patients with non-small cell lung cancer underwent SBRT with a dose < 48 Gy at the authors' institution. One patient who underwent a 5-fraction regimen was excluded from the analysis. This retrospective analysis included data from the remaining 34 patients (2 of whom were operable), and all of whom underwent a 4-fraction regimen. Reasons for the dose modification included neighboring organs at risk,

comorbidities, post partial pneumonectomy status, and advanced age (≧ 85 years) in 27, 7, 7, and 6 patients, respectively (the reasons partly overlapped.). The organs at risk and the comorbidities are summarized in Table 1. The patients' pretreatment characteristics are summarized in Table 2, while details of the patient characteristics and risk factors are listed in Table 3. The prescribed dose was 42–44 Gy, 40 Gy, and 32–38 Gy for 12, 17, and 5 patients, respectively.

Table 1 Organs at risk and comorbidities

Variable	n
Organs at risk	
Chest wall	16
Heart	5
Hilum of the lung	4
Spinal cord	2
Stomach	1
Brachial plexus	1
Great vessel	4
Comorbidities	
Interstitial lung disease	4
Malignancy	2
Benign pleural effusion	1

Table 2 Patient characteristics

Characteristic	Value
Age (years)	
Range	61–92
Median	82
Sex	
Male	25
Female	9
Clinical stage	
T1a	1
T1b	10
T1c	8
T2a	11
T2b	4
Histology	
Squamous cell carcinoma	17
Adenocarcinoma	17
ECOG Performance status	
0	2
1	21
2	9
3	2

ECOG: Eastern Cooperative Oncology Group

Table 3 Patient characteristics and risk factors

Patient	Age	Sex	PS (ECOG)	Dose (Gy)	Location	Organs at risk	Other risk factors
1	83	M	1	44	RL	Chest wall	
2	81	F	1	40	LU	Chest wall	Malignancy
3	84	F	3	44	LU		Malignancy
4	85	M	1	34	LL	Chest wall, stomach	Super-old
5	76	M	1	40	LU	Chest wall	
6	83	M	1	32	LU	Heart	
7	77	M	0	40	LU	Great vessel	Amyloidosis
8	77	M	2	44	LL	Chest wall	ILD, post-surgery
9	83	F	2	40	RL	Chest wall	Post-surgery
10	74	F	0	40	RL	Hilum	Post-surgery
11	83	M	1	40	LL	Chest wall, great vessel	
12	83	M	1	40	RL	Chest wall	
13	72	M	1	40	RL	Chest wall	ILD
14	75	M	2	44	RU	Chest wall	Sarcoidosis
15	77	M	1	40	RL	Chest wall	ILD
16	81	M	2	40	LU		Post-RT
17	85	M	1	40	LL		Super-old
18	83	F	1	40	RL	Heart, great vessel, hilum	
19	85	F	2	44	RU		Super-old, HOT
20	92	M	3	34	RM	Hilum	Super-old, post-surgery
21	82	M	1	44	RL	Chest wall	
22	69	M	2	32	RL		ILD, post-surgery
23	70	M	1	40	RM	Heart	
24	67	M	2	40	LU	Hilum	
25	87	M	1	44	LU		Super-old
26	83	F	1	40	RU	Chest wall	
27	83	M	1	40	LU	Chest wall, heart	
28	82	M	1	40	LU, LL	Chest wall	
29	82	M	1	44	LU	Chest wall	
30	79	M	1	38	RL	Heart	Pleural effusion
31	87	F	2	44	RL		Super-old
32	61	M	1	44	LL	Esophagus, brachial plexus	Post-surgery
33	64	F	1	44	LU	Spine, great vessel	Post-surgery
34	81	M	2	42	RL	Spine	

PS: performance status
ECOG: Eastern Cooperative Oncology Group
RU: right upper lobe
RM: right middle lobe
RL: right lower lobe
LU: left upper lobe
LL: left lower lobe
ILD: interstitial lung disease
HOT: home oxygen therapy
RT: radiotherapy

Patient outcomes

The median clinical follow-up was 28.9 months. The 3-year local control rate for patients receiving 42–44 Gy, 40 Gy, and 32–38 Gy was 80.8%, 75.0%, and 66.7%, respectively (Fig. 1). The 3-year OS was 63.5%, 63.5%, and 40.0%, respectively (Fig. 2). At the time of analysis, 14 patients had died, of which, 6 had died from lung cancer while the remaining other 8 patients had died from intercurrent diseases.

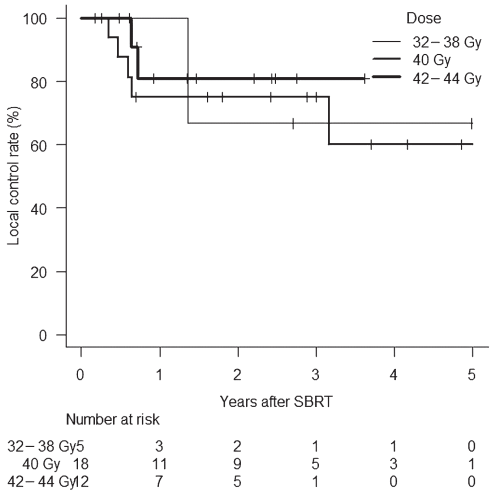

Fig. 1 Local control rate for the 42–44 Gy, 40 Gy, and 32–38 Gy cohorts
The 3-year local control rates were 80.8%, 75.0%, and 66.7% for the 42–44 Gy, 40 Gy, and 32–38 Gy cohorts, respectively.
SBRT: stereotactic body radiation therapy

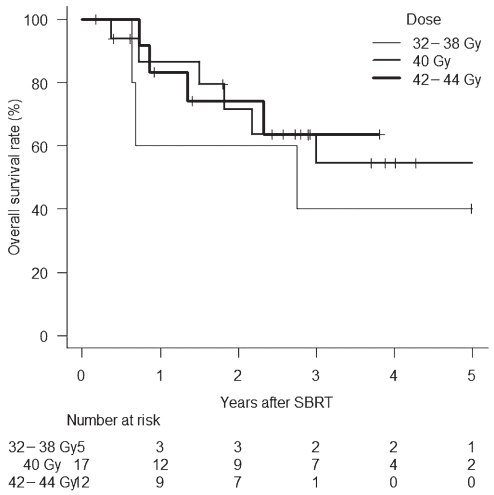

Fig. 2 Overall survival rate for the 42–44 Gy, 40 Gy, and 32–38 Gy cohorts
Three-year overall survival was 63.5%, 63.5%, and 40.0% for the 42–44 Gy, 40 Gy, and 32–38 Gy cohorts, respectively.
SBRT: stereotactic body radiation therapy

Three patients had experienced grade 3 toxicities, of which, 2 had pneumothorax and 1 had pneumonia. Toxicities > grade 3 were not observed, nor were there any rib fractures.

DISCUSSION

In Japan, SBRT with a dose of 48 Gy delivered in 4 fractions was often performed for patients with early-stage non-small cell lung cancer, both in clinical trials and in practical clinics.[8,10] In the JCOG0403 study, using a dose of 48 Gy delivered to the isocenter in 4 fractions, the 3-year OS rate was reported to be 59.9% and 76.5%, while the 3-year local control rate was 87.3% and 85.4% for the inoperable and operable populations, respectively.[8] On the other hand, in conventional radiotherapy using a high dose for patients with stage I–III, the 5-year loco-regional control rate was 49% even in patients receiving 92–103 Gy, while it was only 35% in those receiving 74–84Gy.[11] At our institution, the usual dose for conventional radiotherapy was 60–66 Gy in 30–33 fractions. Therefore, loco-regional control was estimated to be around 35% for patients with stage I disease because the clinical stage was considered to have a small impact on loco-regional control. Considering the difference in local control between SBRT and conventional radiotherapy, a considerable dose reduction was believed to be acceptable.

Although a decent number of studies regarding risk-adapted SBRT for centrally located lung tumors exist, the dose fraction scheme, which was lower than that used in the JCOG0403 study, was used in only few reports. Modh et al used a dose of 45 Gy in 5 fractions as the most common dose and reported a 2-year local failure rate of 21% and a 2-year OS of 64%.[12] Regnery et al treated patients with ultra-central lung tumors with a dose of 50 Gy in 10 fractions and reported a 2-year local failure rate of 26.9% and a 2-year OS of 54.9%.[13] Unger et al delivered a median dose of 35 Gy in 5 fractions using CyberKnife; however, the 1-year local control rate was disappointing 63% and the 1-year OS was 54%.[14] Kowalchuk et al prescribed a far lower dose, a median dose of 28 Gy in 4 fractions, and the treatment resulted in a 23-month local control of 64% and a median survival time of 24 months.[15] In the present study, the low-dose group (32–38 Gy) exhibited a 3-year local control rate of 66.7%, which was comparable with these reports using the low-dose scheme SBRT. In conventional radiotherapy, Kong et al reported a 5-year local control of 35% for patients receiving 74–84 Gy.[11] Therefore, the outcomes of SBRT using the low dose were not considered inferior to those of conventional radiotherapy when evaluated based on local control. Furthermore, SBRT offered the added benefit of a shortened treatment term compared to conventional radiotherapy.

In the relatively high-dose groups in the present study, the 3-year local control rate was 80.8% and 75.0%, and the 3-year OS rate was 63.5% and 63.5% for patients who received 42–44 Gy and 40 Gy, respectively. Although the local control rate was lower than that in the JCOG0403 study, the OS was not inferior. A decrease in local control, to a certain extent, may have a relatively small impact on OS. One possible explanation for the relatively favorable OS, despite lower local control, was that the dose modification would decrease the incidence of intercurrent deaths since the frequency of intercurrent deaths was considerably high in the JCOG study and other studies.[8,16-18] A dose of 40–44 Gy was considered an alternative for patients in whom there was hesitation to prescribe the recommended dose for SBRT.

Out of 34 patients, only 3 experienced grade 3 toxicities, with no toxicities > grade 3 observed. Therefore, the toxicity profile was considered to be acceptable.

Chang et al applied simultaneous integrated boost to prescribe an increased dose for gross tumor volume when a decreased dose was prescribed for the planning target volume.[19] Recently, in our institution, simultaneous integrated boost was introduced for risk-adapted SBRT when it

was deemed safe, as it was theoretically considered to improve local control. However, in this study, simultaneous integrated boost was not implemented in any patient.

In conclusion, risk-adapted SBRT yielded expected local control in comparison with conventional radiotherapy, both in the low-dose group and the relatively high-dose group. These findings supported that the choice of treatment was not only conventional radiotherapy but also risk-adapted SBRT when standard-dose SBRT was risky to be performed. However, our study was limited by the retrospective design and small sample size. Therefore, further data accumulation is required to draw a more definitive conclusion.

CONFLICT OF INTEREST

All authors have no conflict of interest.

REFERENCES

1 Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I non-small cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multi-institutional study. *Cancer*. 2004;101(7):1623–1631. doi:10.1002/cncr.20539.

2 Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol.* 2007;2(7 Suppl 3):S94–S100. doi:10.1097/JTO.0b013e318074de34.

3 Zimmermann FB, Geinitz H, Schill S, et al. Stereotactic hypofractionated radiotherapy in stage I (T1-2 N0 M0) non-small-cell lung cancer (NSCLC). *Acta Oncol.* 2006;45(7):796–801. doi:10.1080/02841860600913210.

4 Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys.* 2009;75(3):677–682. doi:10.1016/j.ijrobp.2008.11.042.

5 Guckenberger M, Wulf J, Mueller G, et al. Dose-response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4D dose calculation. *Int J Radiat Oncol Biol Phys.* 2009;74(1):47–54. doi:10.1016/j.ijrobp.2008.06.1939.

6 Zhang J, Yang F, Li B, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for stage I non-small-cell lung cancer? A meta-analysis. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e305–e316. doi:10.1016/j.ijrobp.2011.04.034.

7 Stahl JM, Ross R, Harder EM, et al. The effect of biologically effective dose and radiation treatment schedule on overall survival in stage I non-small cell lung cancer patients treated with stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 2016;96(5):1011–1020. doi:10.1016/j.ijrobp.2016.08.033.

8 Nagata Y, Hiraoka M, Shibata T, et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan clinical oncology group study JCOG0403. *Int J Radiat Oncol Biol Phys.* 2015;93(5):989–996. doi:10.1016/j.ijrobp.2015.07.2278.

9 Dunlap NE, Cai J, Biedermann GB, et al. Chest wall volume receiving > 30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;76(3):796–801. doi:10.1016/j.ijrobp.2009.02.027.

10 Ueki N, Matsuo Y, Shibuya K, et al. Difference in the dose-volume metrics with heterogeneity correction status and its influence on local control in stereotactic body radiation therapy for lung cancer. *J Radiat Res.* 2013;54(2):337–343. doi:10.1093/jrr/rrs084.

11 Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys.* 2005;63(2):324–333. doi:10.1016/j.ijrobp.2005.02.010.

12 Modh A, Rimner A, Williams E, et al. Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys*. 2014;90(5):1168–1176. doi:10.1016/j.ijrobp.2014.08.008.

13 Regnery S, Eichkorn T, Weykamp F, et al. Safety and efficacy of stereotactic body radiotherapy in ultra-central lung tumors using a risk-optimized fractionation scheme. *Clin Lung Cancer*. 2021;22(4):332–340. e3. doi:10.1016/j.cllc.2020.11.003.

14 Unger K, Ju A, Oermann E, et al. CyberKnife for hilar lung tumors: report of clinical response and toxicity. *J Hematol Oncol*. 2010;3:39. doi:10.1186/1756-8722-3-39.
15 Kowalchuk RO, Waters MR, Richardson M, Spencer K, Larner JM, Kersh CR. Low-dose hilar and mediastinal stereotactic body radiation therapy for non-small cell lung cancer: Analysis of outcomes in patients receiving one or multiple courses of treatment. *Thorac Cancer*. 2020;11(7):2005–2013. doi:10.1111/1759-7714.13501.
16 Videtic GM, Paulus R, Singh AK, et al. Long term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase II study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2019;103(5):1077–1084. doi:10.1016/j.ijrobp.2018.11.051.
17 Andratschke N, Zimmermann F, Boehm E, et al. Stereotactic radiotherapy of histologically proven inoperable stage I non-small cell lung cancer: Patterns of failure. *Radiother Oncol.* 2011;101(2):245–249. doi:10.1016/j.radonc.2011.06.009.
18 Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patient treated with stereotactic body radiotherapy. *J Clin Oncol.* 2009;27(20):3290–3296. doi:10.1200/JCO.2008.21.5681.
19 Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of the single-arm, prospective trial with prespecified comparison to surgery. *Lancet Oncol.* 2021;22(10):1448–1457. doi:10.1016/S1470-2045(21)00401-0.