

Clinical results of accelerated hypofractionated radiotherapy for central-type small lung tumours

Y. Hatayama MD PhD,* M. Aoki MD PhD,* H. Kawaguchi MD PhD,* K. Hirose MD PhD,[†] M. Sato MD PhD,* H. Akimoto MD,* M. Tanaka MD,* I. Fujioka MD,* K. Ichise MD,* S. Ono MD PhD,* and Y. Takai MD PhD[†]

ABSTRACT

Purpose We evaluated the efficacy and toxicity of accelerated hypofractionated radiotherapy (AHYPOF-RT) for central-type small lung tumours.

Methods Between November 2006 and January 2015, 40 patients with central-type small lung tumours underwent AHYPOF-RT delivered using 10 MV X-rays and a coplanar 3-field technique. The number of fractions ranged from 24 to 28, with a fraction size of 2.5–3 Gy. A total dose of 69–75 Gy to the isocentre of the planning target volume was administered to each patient. Cumulative survival and local control rates were calculated using the Kaplan–Meier method.

Results The 27 men and 13 women enrolled in the study had a median age of 79 years (range: 60–87 years). The tumour stage was T1a in 9 patients, T1b in 17 patients, and T2a in 14 patients, with a median size of 26.5 cm (range: 11–49 cm). The median follow-up period was 23 months. A complete response was achieved in 3 patients (7.5%), and a partial response, in 17 patients (42.5%). The overall 2-year and 3-year local control rates were 87.3% and 81.8% respectively; the 2-year and 3-year overall survival rates were 78.9% and 66.7% respectively. Grade 3 pneumonitis occurred in 3 patients; no other severe adverse events (≥grade 3) were observed in any patient.

Conclusions Accelerated hypofractionated radiotherapy using a fraction size of 2.5–3 Gy was highly safe and can be a more effective treatment option than conventional radiotherapy for patients with central-type small lung tumours.

Key Words Lung tumours, central type; radiotherapy; accelerated hypofractionation

Curr Oncol. 2017 Aug;24(4):e285-e289

www.current-oncology.com

INTRODUCTION

Lung cancer is one of the most common causes of cancer death in Japan. The standard treatment for patients with stage I non-small-cell lung cancer is surgical, which has a 5-year overall survival (OS) rate of approximately 50%–70%^{1–3}. However, the number of medically inoperable stage I non-small-cell lung cancers has been increasing because of complications and older age at the time of diagnosis. Stereotactic body radiotherapy (SBRT) for medically inoperable stage I non-small-cell lung cancers and small solitary metastatic lung tumours has recently become more widespread in Japan and countries in Europe. However, the

criteria for the application of radical radiotherapy (RT) to those lung cancers have not been established.

The 5-year OS rate for small central-type lung cancers after conventional RT is only 15%–22%^{4–6}. In addition, patients treated with conventional RT eventually develop local recurrence and distant metastasis, which lead to death, even if the initial disease is stage I. According to the literature with respect to RT using conventional fractionation, dose escalation is an important factor for local control that influences survival in patients with stage I disease⁴. In facilitating dose escalation by focusing the beam on the tumour, SBRT has been reported to have excellent treatment results^{7–13}. However, an increase in adverse events has been

Correspondence to: Yoshiomi Hatayama, Department of Radiology and Radiation Oncology, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562 Japan.
E-mail: yonoki2005@gmail.com ■ DOI: <https://doi.org/10.3747/co.24.3500>

reported after SBRT with a large fraction size for central lesions that are close to the trachea, bronchus, hilum of the lung, pulmonary artery, esophagus, aorta, or heart.

To improve local control and survival rates, and to reduce adverse events, we treated central-type stage I non-small-cell lung cancers (defined as those that are close to the trachea, bronchus, hilum of the lung, pulmonary artery, esophagus, aorta, or heart) and small solitary metastatic lung tumours with accelerated hypofractionated RT (AHypof-RT) using a fraction size of 2.5–3 Gy. The purpose of the present study was to evaluate the efficacy and toxicity of that dose of AHypof-RT for central-type small lung tumours.

METHODS

Patients

Between November 2006 and January 2015, 40 patients with central-type small (<5 cm) lung tumours underwent AHypof-RT at Hirosaki University Hospital and its affiliated hospitals. Written informed consent was obtained from all patients after they had received an explanation of clinical stage and prognosis, treatment goals, treatment schedule, other treatment options, and adverse events. The study was approved by the research ethics board of our institution.

The 27 men and 13 women enrolled in the study had a median age of 79 years (range: 60–87 years). Median follow-up time was 23 months (range: 2.5–87 months). The complete patient evaluation included physical examination, biopsy or cytology by bronchoscopy (or both), blood count, screening blood chemistry, electrocardiography, respiratory function tests, and blood gas analysis. Clinical TNM staging according to the 7th edition of the Union for International Cancer Control guideline was performed using any one or a combination of chest radiography, chest and abdominal computed tomography (CT), or combined positron-emission tomography–CT imaging.

Radiotherapy

We used a 3-dimensional RT planning procedure. Serial CT images at 2.5 mm intervals were obtained. After the CT imaging, the gross tumour volume was drawn; however, no significant clinical target volume margins were added to the gross tumour volume. The gross tumour volume margins between the clinical target volume and the planning target volume were 10 mm anteroposteriorly, 10 mm laterally, and 10 mm–15 mm craniocaudally. We used 10 mm in the craniocaudal direction for upper lung lesions and 15 mm in the craniocaudal direction for middle and lower lung lesions. We used 10 MV X-rays and a coplanar 3-field technique. Figure 1 shows a representative case of 3-dimensional RT planning for a central lung cancer.

Evaluation and Analysis

We evaluated local control, OS, and toxicity. Patients were seen for follow-up every 3 months for the first year and every 4–6 months thereafter. Local tumour response was evaluated using CT imaging and the Response Evaluation Criteria in Solid Tumors¹⁴. Local tumour control was defined as a lack of any significant tumour regrowth on follow-up CT imaging. Cumulative survival rates and local control rates were calculated using the Kaplan–Meier



FIGURE 1 Representative axial slice of 3-dimensional dose distributions for central lung cancer receiving a total dose of 72 Gy using 3 fixed coplanar beams. The gross tumour volume is shown in red, and the planning target volume, in green.

method. All analyses were performed using the Prism software application (version 5.0f; GraphPad Software, San Diego, CA, U.S.A.).

Treatment toxicities were evaluated for grade using the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events* (version 3.0). Acute and subacute toxicities were defined as those that occurred within 6 weeks and between 6 weeks and 6 months after RT; late toxicities were defined as those that occurred at 6 months or later.

RESULTS

Patient Characteristics

Table 1 summarizes the patient and RT characteristics. Tumour stage was T1a in 9 patients, T1b in 17 patients, and T2a in 14 patients, with an overall median size of 26.5 cm (range: 11 cm–49 cm). The histology was adenocarcinoma in 20 patients, squamous cell carcinoma in 11 patients, others in 2 patients, and unknown in 7 patients who had been clinically diagnosed. Clinical diagnosis of malignancy was based on increase in size on CT images or contrast uptake on combined positron-emission tomography–CT images. The number of RT fractions ranged from 24 to 28, with a fraction size of 2.5–3 Gy. A total dose of 69–75 Gy at the isocentre was administered to each patient. No patient received chemotherapy during RT.

Local Tumour Response

On CT imaging 3–6 months after treatment, a complete response (CR) was achieved in 3 patients (7.5%), and a partial response (PR), in 17 patients (42.5%). The response rate (CR + PR) was therefore 50% ($n = 20$ of 40). Stable disease was achieved in the other 20 patients (50%, Table 1). Figure 2 shows 1 representative patient. Imaging by CT before RT shows a left hilar tumour [Figure 2(A)], which had almost disappeared at 4 months after AHypof-RT [Figure 2(B)].

Survival and Local Tumour Control

For the 40 study patients overall, the 2-year and 3-year local control rates [Figure 3(A)] were 87.3% [95% confidence

TABLE I Patient characteristics

Characteristic	Value
Age (years)	
Median	79
Range	60–87
Sex [n (%)]	
Men	27 (67.5)
Women	13 (32.5)
Performance status [n (%)]	
0	25 (62.5)
1	12 (30)
2	3 (7.5)
Tumour diameter (cm)	
Median	26.5
Range	11–49
Histology [n (%)]	
Adenocarcinoma	20 (50)
Squamous cell carcinoma	11 (27.5)
Unclassified NSCLC	2 (5)
Clinically diagnosed	7 (17.5)
Radiotherapy dose [n (%)]	
72 Gy in 24 fractions	25 (62.5)
75 Gy in 25 fractions	13 (32.5)
70 Gy in 28 fractions	1 (2.5)
69 Gy in 23 fractions	1 (2.5)

NSCLC = non-small-cell lung cancer.

TABLE II Treatment response after radiotherapy

Response type	Patients [n (%)]
Complete	3 (7.5)
Partial	17 (42.5)
Stable disease	20 (50)

interval (CI): 69.6% to 95.1%] and 81.8% (95% CI: 60.5% to 92.3%) respectively. The 2-year and 3-year OS rates [Figure 3(B)] were 78.9% (95% CI: 58.3% to 90.1%) and 66.7% (95% CI: 42.5% to 82.6%) respectively.

Table III shows the sites of initial failure. During follow-up, local progression occurred in 3 patients (7.5%), and 7 patients developed distant metastasis. Carcinomatous pleurisy occurred in 2 patients, intrapulmonary metastasis developed in 2 patients, and lymph node metastasis developed in 2 patients. One patient developed local progression and distant metastasis simultaneously. So far, 8 patients have died. Cause of death was disease progression in 5 patients, interstitial pneumonia unrelated to lung irradiation in 1 patient, cerebral hemorrhage in 1 patient, and unknown in 1 patient.

Toxicities

Symptomatic radiation pneumonitis (*Common Terminology Criteria for Adverse Events* grade 2) was observed in 4

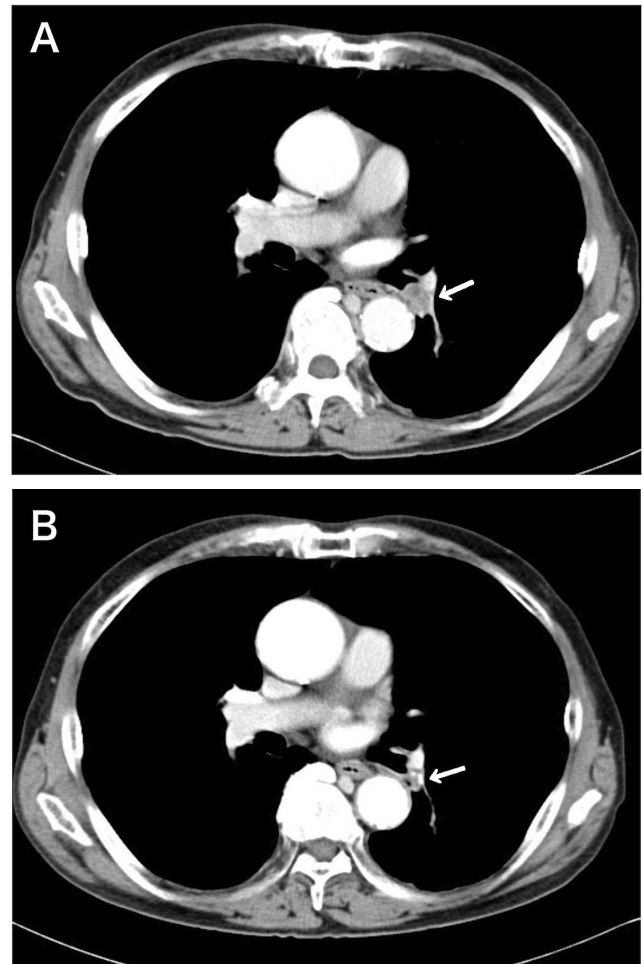


FIGURE 2 A 69-year-old man received a total dose of 72 Gy. (A) Representative computed tomography axial slice before radiotherapy shows a left hilar tumour (arrow). (B) At 4 months after radiotherapy, the tumour has almost disappeared.

patients (10%) 2–6 months after RT. At 6 months after RT, asymptomatic rib fracture within the field of irradiation was observed in 1 patient (2.5%) whose tumour was located on the dorsal side of the aorta and near the rib. No other severe adverse events ($\geq$ grade 3) have yet been observed in any of the patients.

DISCUSSION

The best responses of CR and PR were achieved in 3 (7.5%) and 17 patients (42.5%) respectively, for a total response rate of 50%. After RT, distinguishing residual tumour from radiation pneumonitis on CT imaging is usually difficult. In hindsight, we occasionally observed residual consolidation with a decrease in tumour size over time; tumours that exhibited that characteristic after RT should have been considered a CR or PR. The local response rate in our study population might therefore be higher than the 50% that was contemporaneously recorded.

The 2-year and 3-year OS rates in the present study were 78.9% and 66.7% respectively. The 3-year OS rate

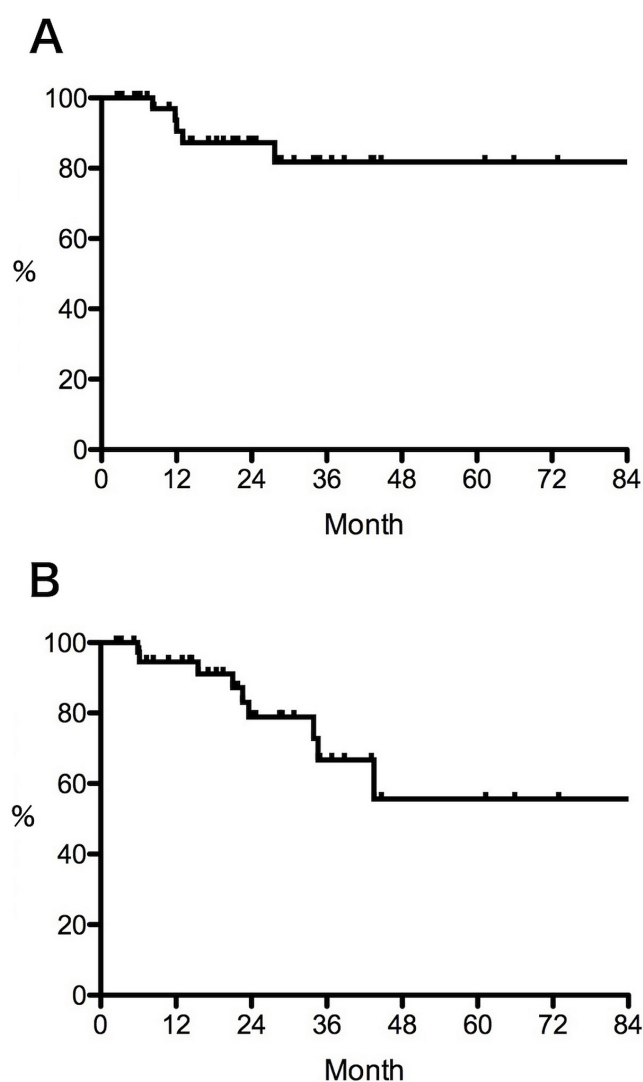


FIGURE 3 (A) Local control and (B) overall survival rates for 40 patients with small central lung tumours treated with accelerated hypofractionated radiotherapy at a fraction size of 2.5–3 Gy.

TABLE III Failure patterns after radiotherapy

Site of initial failure	Patients [n (%)]
Local	3 (7.5)
Distant	7 (17.5)
Carcinomatous pleurisy	2
Intrapulmonary metastasis	2
Lymph node	2
Bone	1

for patients with small lung cancers who received conventionally fractionated RT at a median dose of 60–66 Gy has previously been reported to be only approximately 34%^{4–6}, mainly because of primary disease progression in approximately 60% of patients. In contrast, because the RT fields included comprehensive lymph node regions in some

patients, grades 3–5 toxicities occurred in approximately 2% of patients⁴. Dose escalation in the involved field is therefore considered important in terms of providing longer survival without any increase in adverse effects. In the present study, AHypof-RT with a fraction size of more than 2 Gy facilitated dose escalation in the involved fields. As a result, the survival rate in our population was much better than has been reported for conventionally fractionated RT.

The 2-year and 3-year local control rates in our study were 87.3% and 81.8% respectively, and local recurrence was observed in only 3 patients (7.5%). The local control rates with SBRT for stage I primary lung cancer and small metastatic lung cancers have been reported to be 80%–97% in other studies^{7,10–13}.

Outcomes comparisons between SBRT and surgery have become available in recent years¹⁵. According to the clinical practice guidelines in Japan, the standard treatment for stage I non-small-cell lung cancer is lobectomy; SBRT is recommended for patients with inoperable disease. However, based on the excellent treatment results already described, SBRT has become increasingly commonly used in Japan even for operable disease. In the near future, SBRT—together with surgery—is expected to become the standard treatment even for operable disease^{13,15}.

In contrast, lethal complications have been reported after long-term follow-up in patients who underwent SBRT for central tumours that were located close to the mediastinum^{16,17}. Among those complications, radiation pneumonitis has been the most common; other reported causes are esophageal ulcers, lethal hemoptysis, and major airway stenosis^{10,18–20}. When performing SBRT for central tumours that are close to the mediastinal organs, it is necessary to pay attention to the relevant dose constraints. However, the dose constraints are not met in some plans. In the present study, we therefore sought a safer RT method for tumours located close to the mediastinum. To avoid severe complications to the mediastinal organs, we introduced a fraction size that is much less reduced than that used for SBRT. The low complication rates that we observed and the absence of any adverse events to the mediastinal organs indicate that our treatment method could be tolerable.

Limitations of our study are the small number of patients and the short follow-up period. Nevertheless, the results in this study—rates of local control and os—were as least as good as those reported in prior studies. Reports of AHypof-RT for small lung tumours have been few^{21–24}. In those studies, a total dose of 48–80.5 Gy in 12–35 fractions, with a fraction size of 2.3–4 Gy, was used in patients who underwent AHypof-RT. The local control and os rates after 2–3 years were 23.9%–40% and 35%–61% respectively—results that are inferior to ours. Most of the other reports included many cases of peripheral lesions; almost no reports of AHypof-RT before the present report have been limited to central lesions.

We introduced AHypof-RT for central-type small lung tumours to improve outcomes compared with conventional RT and to reduce toxicities compared with SBRT. Our report, which focuses solely on central-type tumours, shows some of the best results to date. Continued follow-up is needed to obtain long-term therapeutic and safety results of AHypof-RT for central-type small lung tumours. This simple method

of AHYPof-RT could possibly be an alternative to SBRT for central-type small lung tumours that are associated with a higher risk of complications to the mediastinal organs.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Department of Radiology and Radiation Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, and †Southern Tohoku BNCT Research Center, Koriyama, Japan.

REFERENCES

- Okada M, Nishio W, Sakamoto T, *et al.* Evolution of surgical outcomes for nonsmall cell lung cancer: time trends in 1465 consecutive patients undergoing complete resection. *Ann Thorac Surg* 2004;77:1926–30.
- Yoshino I, Yamaguchi M, Tagawa T, *et al.* Operative results of clinical stage I non-small cell lung cancer. *Lung Cancer* 2003;42:221–5.
- Alexiou C, Beggs D, Onyeaka P, *et al.* Pneumonectomy for stage I (T1N0 and T2N0) nonsmall cell lung cancer has potent, adverse impact on survival. *Ann Thorac Surg* 2003;76:1023–8.
- Sibley GS. Radiotherapy for patients with medically inoperable stage I nonsmall cell lung carcinoma: smaller volumes and higher doses—a review. *Cancer* 1998;82:433–8.
- Qiao X, Tullgren O, Lax I, Sirzén F, Lewensohn R. The role of radiotherapy in treatment of stage I non-small cell lung cancer. *Lung Cancer* 2003;41:1–11.
- Morita K, Fuwa N, Suzuki Y, *et al.* Radical radiotherapy for medically inoperable non-small cell lung cancer in clinical stage I: a retrospective analysis of 149 patients. *Radiother Oncol* 1997;42:31–6.
- Uematsu M, Shioda A, Suda A, *et al.* Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666–70.
- Nagata Y, Takayama K, Matsuo Y, *et al.* Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427–31.
- Onishi H, Araki T, Shirato H, *et al.* Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004;101:1623–31.
- Onimaru R, Shirato H, Shimizu S, *et al.* Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. *Int J Radiat Oncol Biol Phys* 2003;56:126–35.
- Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastasis: a systematic review. *J Thorac Oncol* 2010;5:1091–9.
- Baschnagel AM, Mangona VS, Robertson JM, Welsh RJ, Kestin LL, Grills IS. Lung metastases treated with image-guided stereotactic body radiation therapy. *Clin Oncol* 2013;25:236–41.
- 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;93:989–96.
- Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
- Chang JY, Senan S, Paul MA, *et al.* Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630–7. [Erratum in: *Lancet Oncol* 2015;16:e427]
- Nagata Y, Hiraoka M, Mizowaki T, *et al.* Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. *Int J Radiat Oncol Biol Phys* 2009;75:343–7.
- Timmerman R, McGarry R, Yiannoutsos C, *et al.* Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833–9.
- Rowe BP, Boffa DJ, Wilson LD, Kim AW, Detterbeck FC, Decker RH. Stereotactic body radiotherapy for central lung tumors. *J Thorac Oncol* 2012;7:1394–9.
- Joyner M, Salter BJ, Papanikolaou N, Fuss M. Stereotactic body radiation therapy for centrally located lung lesions. *Acta Oncol* 2006;45:802–7.
- Song SY, Choi W, Shin SS, *et al.* Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. *Lung Cancer* 2009;66:89–93.
- Yung T, Giuliani ME, Le LW, *et al.* Outcomes of accelerated hypofractionated radiotherapy in stage I non-small-cell lung cancer. *Curr Oncol* 2012;19:264–9.
- Cheung PC, Yeung LT, Basrur V, Ung YC, Balogh J, Danjoux CE. Accelerated hypofractionation for early-stage non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;54:1014–23.
- Urbanic JJ, Turrisi AT 3rd, Sharma AK, *et al.* Conformal high dose external radiation therapy, 80.5 Gy, alone for medically inoperable non-small cell lung cancer: a retrospective analysis. *J Thorac Oncol* 2006;1:112–19.
- Cheung PC, Mackillop WJ, Dixon P, Brundage MD, Youssef YM, Zhou S. Involved-field radiotherapy alone for early-stage non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2000;48:703–10.