



Title	Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer with PTV < 100 cc using a continual reassessment method (JCOG0702)
Author(s)	Onimaru, Rikiya; Shirato, Hiroki; Shibata, Taro; Hiraoka, Masahiro; Ishikura, Satoshi; Karasawa, Katsuyuki; Matsuo, Yukinori; Kokubo, Masaki; Shioyama, Yoshiyuki; Matsushita, Haruo; Ito, Yoshinori; Onishi, Hiroshi
Citation	Radiotherapy and oncology, 116(2), 276-280 <a href="https://doi.org/10.1016/j.radonc.2015.07.008">https://doi.org/10.1016/j.radonc.2015.07.008</a>
Issue Date	2015-08
Doc URL	<a href="http://hdl.handle.net/2115/62578">http://hdl.handle.net/2115/62578</a>
Rights	© 2015, Elsevier. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <a href="http://creativecommons.org/licenses/by-nc-nd/4.0/">http://creativecommons.org/licenses/by-nc-nd/4.0/</a>
Rights(URL)	<a href="http://creativecommons.org/licenses/by-nc-nd/4.0/">http://creativecommons.org/licenses/by-nc-nd/4.0/</a>
Type	article (author version)
File Information	manuscript+appendix.pdf



[Instructions for use](#)

**Phase I Study of Stereotactic Body Radiation Therapy for Peripheral T2N0M0**

**Non-Small Cell Lung Cancer with PTV < 100 cc using a Continual Reassessment**

**Method (JCOG0702)**

Rikiya Onimaru<sup>1</sup>, MD, PhD, Hiroki Shirato<sup>1</sup>, MD, PhD, Taro Shibata<sup>2</sup>, MSc, Masahiro Hiraoka<sup>3</sup>, MD, PhD, Satoshi Ishikura<sup>4</sup>, MD, PhD, Katsuyuki Karasawa<sup>5</sup>, MD, PhD, Yukinori Matsuo<sup>3</sup>, MD, PhD, Masaki Kokubo<sup>6</sup>, MD, PhD, Yoshiyuki Shioyama<sup>7</sup>, MD, PhD, Haruo Matsushita<sup>8</sup>, MD, PhD, Yoshinori Ito<sup>9</sup>, MD, and Hiroshi Onishi<sup>10</sup>, MD, PhD.

<sup>1</sup> Department of Radiation Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

<sup>2</sup> JCOG Data Center, Center for Research Administration and Support, National Cancer Center, Tokyo, Japan

<sup>3</sup> Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan

<sup>4</sup> Department of Radiology, Koshigaya Municipal Hospital, Koshigaya, Japan

<sup>5</sup> Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo,

Japan

<sup>6</sup> Department of Image-based Medicine, Institute of Biomedical Research and Innovation, Kobe, Japan

<sup>7</sup> Department of Clinical Radiology, Kyushu University Graduate School of Medicine, Fukuoka, Japan

<sup>8</sup> Department of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan

<sup>9</sup> Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

<sup>10</sup> Department of Radiology, University of Yamanashi Graduate School of Medical Science, Chuo, Japan

**Key Words: phase I study, continual reassessment method, non-small cell lung cancer (NSCLC), stereotactic body radiotherapy, SBRT.**

**Short running title:** A phase I study of SBRT: JCOG 0702

**Corresponding author:** Dr. Rikiya Onimaru, Department of Radiation Medicine, Hokkaido University Graduate School of Medicine, North 15 West 7, Kita-ku, Sapporo

060-8638, Japan. Tel: +81-11-716-1161 (Ext. 5977); Fax: +81-11-706-7876;

Email: ronimaru@pop.med.hokudai.ac.jp

### **Previous presentation**

This work was presented at the 55th Annual Meeting of the American Society for Radiation Oncology, September 22 – 25, 2013 in Atlanta, GA.

## Abstract

**Purpose:** To estimate the maximum tolerated dose (MTD) and to determine the recommended dose (RD) of stereotactic body radiation therapy (SBRT) for peripheral T2N0M0 non-small cell carcinoma (NSCLC) with target volume (PTV) < 100 cc.

**Materials and Methods:** The continual reassessment method (CRM) was used to determine the dose level that patients should be assigned to and to estimate the MTD. Dose limiting toxicity (DLT) was grade 3 radiation pneumonitis (RP) within 180 days after the start of SBRT, grade 2 RP was used as a surrogate DLT. The RD was equal to the MTD. The dose was prescribed at D<sub>95</sub> of the PTV.

**Results:** Fifteen patients were accrued. Only 1 experienced grade 2 RP at 60 Gy in 4 fractions. It was difficult to fulfill the dose constraints at 60 Gy in 4 fractions, and the maximum dose level assigned by CRM was changed to 55 Gy in 4 fractions. The lower limit of 95% of the credible interval exceeded the adjacent level, and the RD was determined as 55 Gy in 4 fractions.

**Conclusions:** The RD of SBRT for peripheral T2N0M0 NSCLC with PTV < 100 cc was determined to be 55 Gy in 4 fractions.

## **Introduction**

Stereotactic body radiation therapy (SBRT) for peripheral stage I non-small cell lung cancers (NSCLC) is recognized as a standard treatment for medically inoperable patients [1-6]. Nagata et al. reported that the overall survival (OS) for stage IA and IB NSCLC patients at 3 years were 83% and 72%, respectively [1]. Timmerman et al. reported 3-year results of RTOG 0236 where the OS for stage I patients at 3 years was 55.8% [2]. Baumann et al. reported that the OS for stage I patients at 3 years was 60% [3].

These SBRT results are an improvement over the historical controls of conventional fractionated radiotherapy with 17% to 55% OS at 3 years [7, 8]. A meta-analysis by Grutters et al. showed that the OS at 5 years for SBRT and conventional radiotherapy were 42.1% and 19.5%, respectively [4]. The introduction of SBRT in the treatment of elderly NSCLC patients is associated with an improvement in OS, as shown by Palma et al. in 2010 [5].

With these improvements there are however still unsolved issues in SBRT [6, 9]. One is the poorer clinical outcomes for peripheral T2N0M0 NSCLC than for T1N0M0 NSCLC. Onimaru et al. reported that the difference in the local control rate between 40 and 48 Gy in 4 fractions at the isocenter was larger with stage IB than with stage IA [10].

Baumann et al. reported that local failure increased in patients with T2 diseases compared with T1 diseases [3], and Onishi et al. found local disease recurrences of 9.7% for stage IA and 20.0% for stage IB [11].

The optimal dose for T2 may be different from the available dose which was determined in phase I trials for T1-2. If we escalate the dose for T2 tumors with larger PTV, attention must be paid to higher rates of late complications [9, 13]. Meta-analyses have suggested that too high BED may not be beneficial for survival [14, 15]. Therefore, a careful prospective dose finding study is needed for peripheral T2N0M0 NSCLC in SBRT, as Brada et al. have pointed out confounding data between tumor control and tumor volume] [9].

We conducted a multi-institutional phase I study to estimate the maximum tolerated dose (MTD) and to determine the recommended dose (RD) of SBRT for patients with peripheral T2N0M0 NSCLC (JCOG0702). The enrolled patients were stratified into two subgroups: those with PTV < 100 cc and those with PTV  $\geq$  100 cc, to assess the toxicities accurately according to the irradiated volume. This cut-off value was chosen to be able to enroll patients in the groups at the same pace, based on a survey of the number of T2N0M0 NSCLC patients treated with SBRT at the participating institutions, however the enrollment was more rapid in the

subgroup with PTV < 100cc and earlier than the subgroup with PTV  $\geq$  100 cc.

In this paper, we report the results of the subgroup of patients with PTV < 100 cc.



## **Patients and Methods**

### ***Patients***

The eligibility criteria were as follows: pathologically or cytologically proven NSCLC; peripheral T2N0M0 over 3 cm in diameter (UICC 6th ed., 2002) by chest X-ray, enhanced computed tomography (CT), and fluorodeoxyglucose-positron emission tomography (FDG-PET); no thoracic malignancy other than the primary cancer; the dose constraints of organs at risk (OARs) can be fulfilled by: either "age  $\geq$  20 years old and unfit for lobectomy as determined by the surgeon" or "age  $\geq$  70 years old and refusing surgery;" no irradiation history to the thorax; no history of chemotherapy other than endocrine therapy; ECOG- performance status (PS) 0–2; no dyspnea on exertion that require stopping walking during 1 flight of stairs or 1 city block (0.1 km); PaO<sub>2</sub>  $\geq$  60 torr and FEV<sub>1.0</sub>  $\geq$  700 mL; and written informed consent.

The exclusion criteria were as follows: apparent interstitial pneumonitis or pulmonary fibrosis on chest X-ray; active infectious diseases; double cancers within 2 years other than carcinoma in situ or mucosal cancer, T1N0M0 glottic cancer, stage I prostate cancer, and stage I breast cancer; pregnancy or lactation; severe psychological disorders; continuous systemic steroid administration; intermittent or continual oxygenation; fever above 38°C; uncontrolled cough without narcotics.

## ***Radiotherapy***

The slice thickness of the CT planning was 1 to 3 mm around the primary tumor. The gross tumor volume (GTV) was the primary tumor. The clinical target volume (CTV) was equal to the GTV. A sufficient internal margin was added to the CTV to make the internal target volume (ITV). The PTV was the sum of the ITV plus a setup margin (SM) of 5 mm. In principle, no modification of the PTV was permitted to fulfill the dose constraints of the OARs. The PTV had to include the ITV.

A Multileaf collimator (MLC) was circumscribed around the PTV with a 5 mm distance, in principle. Changes to the distance between the PTV and the edge of MLC were permitted only to fulfill the dose constraints of OAR without compromising the dose covering 95% of the volume ( $D_{95}$ ) of the PTV.

Heterogeneity corrections equivalent to superposition algorithms was mandatory. The voxel size in the dose distribution calculation was less than 2.5 mm. The dose was prescribed at  $D_{95}$  of the PTV. The fraction number was fixed at 4. The homogeneity index (HI) was defined as the ratio of the maximum dose in the PTV to the minimum dose in the PTV. An HI of above 1.6 was considered a deviation as it was expected that a homogeneous dose distribution would not be obtained with large tumors. The dose

constraints of the OARs including the spinal cord, esophagus, great vessels, trachea, and other organs are shown in Table 1.

Four to 6 MV X-ray was used. The overall treatment time was 4 to 8 days, and the treatment delivery was at the rate of 3 to 4 days per week. Verification of setup errors < 5 mm before each treatment delivery was mandatory.

A visiting survey of the 7 participating institutions was performed by the Japan Clinical Oncology Group (JCOG) Radiation Therapy Study Group/Medical Physics Working Group prior to the activation of the study. This survey ensured the accuracy of the delivered doses at the institutions participating in the study, using a lung phantom [16].

### ***Study Design***

The continual reassessment method (CRM) [17] was used to determine the dose level patients should be assigned to and to estimate the MTD. Toxicities including the dose limiting toxicity (DLT) were assessed based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Ver 3.0.

The DLT was grade 3 radiation pneumonitis (RP) within 180 days after the start of the SBRT. A prior distribution of the dose-response curve and the MTD was determined as

follows: 6 radiation oncologists estimated the dose-response curve and the MTD under the assumption that the DLT was grade 3 RP and the frequency of the DLT was 5% at the MTD. The parameters for the prior distribution were determined with a logistic dose-response model using the data obtained from the 6 radiation oncologists.

The frequency of the DLT at the MTD was expected to be 5%, which was low, and further, 1 occurrence would have a strong impact on the calculation of the assigned dose level. To resolve this, we used grade 2 or a higher RP within 180 days of the start of the SBRT as a surrogate DLT, since the 6 radiation oncologists expected the frequency of grade 2 RP at the MTD to be 25%, consistent with a previous study from the Netherlands and Michigan [18]. The prior distribution of the dose-response curve and the MTD was calculated based on the expected frequency of grade 2 RP. Appendix A shows the prior distribution of the dose-response curve for grade 2 RP. The pre-planned decision rule to determine the MTD and the recommended dose (RD) was as follows: The MTD was the dose level at which the expectation of a posterior distribution of grade 2 RP was around 25%. The lower and upper limits of the 95% credible interval (CI) for the predicted MTD level should not include the adjacent dose level. The RD was defined as being equal to the MTD.

The starting dose was 40 Gy in 4 fractions at the  $D_{95}$  of the PTV, and the dose

was increased in 5 Gy steps to 65 Gy. This starting dose was determined based on the estimate that 40 Gy in 4 fractions at the D<sub>95</sub> of the PTV corresponds to 48 Gy in 4 fractions at the isocenter, a dose which is commonly used in practice in Japan; its safety has been confirmed in a Phase I/II study.[1]. The maximum dose level was determined as 65 Gy in 4 fractions at the D<sub>95</sub> of the PTV before starting the trial. The dose level which patients were assigned to was calculated once a month using the CRM except with the first 5 patients, who were assigned to this starting dose.

Patient accrual was suspended to assess the DLT when a sufficient number of patients were enrolled at any dose level. Patient accrual was resumed when the number of patients needing a DLT assessment had decreased to 2 or less.

The study protocol was approved by the Japan Clinical Oncology Group (JCOG) Protocol Review Committee and the Institutional Review Board of each participating institution. Signed informed consent was obtained from each patient. This study was registered at the UMIN Clinical Trials Registry as UMIN000001459.

### ***Follow-up***

Patients were seen at 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, and 24 months after the start of the treatment. Chest X-rays were performed at 1, 3, and 5 months, and chest CT at 2, 4,

6, 9, 12, 18, and 24 months after the start of the treatment. When a patient showed grade 2 or higher RP, the information about the grade of RP of the patient and the patient accrual was shared among the participating institutions.

### ***Statistical analysis***

Posterior distribution by the CRM was updated by the JCOG Data Center. Overall survival (OS) was defined as days from the registration of the patient in the study till death from any cause, and it was censored at the last follow-up date when the patient was alive. The survival curve was estimated using the Kaplan-Meier method. All of the statistical analyses were carried out using the software program SAS, release 9.2 (SAS Institute, Cary, NC).

## Results

Fifteen patients from the 7 institutions were accrued from October 2008 to September 2012 in the PTV < 100 cc subgroup. The follow-up of the patients ranged from 0.9 to 4.5 years (median follow-up for all patients, 2.4 years). Eight patients were male and seven were female. The ages ranged from 71 to 88 years (median 81 years). The tumor sizes ranged from 31 mm to 39 mm (median 32 mm). The number of adenocarcinomas, squamous cell carcinomas, and large cell carcinomas was 10, 4, and 1, respectively. Eleven of the 15 patients had refused surgery. Other characteristics are shown in Table 2. The numbers of patients at each dose level were 5 at 40 Gy, 1 at 45 Gy, 3 at 50 Gy, 1 at 55 Gy, and 5 at 60 Gy. Due to the protocol deviation of the dose level at 40 Gy, one patient was excluded from the derivation of the posterior distribution of grade 2 RP to avoid underestimation of the toxicity.

Only 1 patient experienced grade 2 RP. This patient was treated with 60 Gy in 4 fractions at  $D_{95}$  of the PTV. The remaining 14 patients had Grade 1 or lower RP. Table 3 shows the number of patients who developed RP and their dose levels.

No patient was accrued in this study for more than 6 months from March 2011, when the assigned dose was 60 Gy. We interviewed each of the participating institutions to clarify the reasons for not enrolling patients, and found technical issues in fulfilling

the dose constraints of the OARs at 60 Gy. The numbers of patients who did not fulfill the dose constraint at a dose of 60 Gy after March 2011 were as follows by OAR: aorta, 4; pulmonary artery, 4; skin, 3; heart, 3; esophagus, 1; bronchus, 1; brachial plexus, 1; and spinal cord, 1. This suggests that no further dose escalation was feasible for the majority of eligible patients, and that accruing the minority who could fulfill the dose constraints would not be useful, considering the generalizability of the results of this study. To get around this, we decreased the maximum dose level assigned by the CRM from 60 Gy to 55 Gy in August 2012, and the lower limit of the 95% CI exceeded the adjacent level of 50 Gy. As a result, the RD was determined as 55 Gy at  $D_{95}$  of the PTV. At 55Gy, the tail probability of the posterior distribution that showed DLT to occur with a frequency above 25% was 8.0%. Appendix B shows the posterior distributions in terms of the estimated probability of grade 2 RP.

The other toxicities are summarized in Appendix C. There was no grade 3 or worse toxicity.

The dose volume histogram (DVH) parameters are shown in Table 4. The mean physical lung dose ranged from 3.0 to 7.0 Gy for all patients; it was 4.6 Gy in the one patient assigned 55 Gy.

The maximum dose for the patient treated with 55 Gy in 4 fractions at  $D_{95}$  was



66.8 Gy in 4 fractions. The biological effective dose (BED) was 174.9 Gy<sub>10</sub> for 66.8 Gy in 4 fractions assuming that the  $\alpha/\beta$  was 10 Gy for the tumor.

The median overall survival for all 15 patients was 2.6 years. The overall survival proportion was 39% (95% CI: 11.4%–67.1%) at 3 years, as shown in Figure 1. The proportion of 2 year survival for patients treated with 40 to 50 Gy and 55 to 60 Gy were 77.8% and 83.3%, respectively (Hazard ratio, 0.25 95%CI[0.03-2.05], p-value = 0.16).

## Discussion

In this study, the RD of SBRT for T2N0M0 NSCLC patients with PTV < 100cc was determined to be 55 Gy in 4 fractions at D<sub>95</sub> of PTV. The MTD could not be determined based on the pre-planned rules because of the limited number of patients assigned to the higher dose and no dose-limiting toxicity was observed. Five patients were assigned to the dose level of 60 Gy and only one developed Grade 2 RP, but we did not determine the RD as 60 Gy because the lower limit of the 95% CI for the predicted MTD did not exceed the adjacent dose level of 55 Gy. However, the lower limit of the 95% CI for the predicted MTD exceeded the dose level of 50 Gy based on the CRM, and finally 55 Gy was determined to be the RD based on the preplanned decision rules.

The dose constraints in this study may have been too conservative. However, we did not escalate the dose to OAR other than the lungs, because severe toxicity in serial organs like the esophagus, trachea, and large vessels due to SBRT can result in death [19-22]. Also, very high doses of irradiation to the heart and skin may cause serious complications such as coronary stenosis and skin necrosis, respectively [23-26]. We considered that it was not justified to increase the risk of severe toxicities other than RP for the participants subject to risks of severe RP. Dose escalation study of serial organs

need to be performed very carefully focusing on a specific organ with proper monitoring. It should also be kept in mind that the number of patients enrolled in a phase I study should be as small as possible in general, resulting in the number of patients to evaluate the safety of the dose constraints of every OAR to become too small.

The  $BED_{10}$  of the RD was 130.6  $Gy_{10}$ . Careful attention must be paid when using a  $BED_{10}$  at such a high dose-per-fraction schedule, because there have been controversies about comparing BEDs of different dose fractionation schedules with such high dose-per-fraction values [27, 28]. The differences in treatment methods among studies, such as the dose prescription, the normalization, and MLC fitting also make a simple comparison of BED values insufficient for a comparison and interpretation of the results of multiple studies.

We used CRM to determine the RD of the SBRT for T2N0M0 NSCLC in this trial, although the traditional 3 + 3 design is common in a phase I study. The CRM is a Bayesian approach and has advantages compared with the traditional 3 + 3 design. First, since the CRM uses all the data to determine the next dose level, the CRM can estimate the MTD more precisely than the traditional 3+3 design. We used the 95% CI and estimated the lower limit of the 95% CI of the MTD. We had to change the decision rule,

but were able to determine an RD based on the data with a statistical evaluation.

Second, rapid dose escalation is possible with the CRM. The DLT of radiotherapy sometimes needs to be observed over long terms, because some DLTs such as radiation pneumonitis occur 3 to 6 months after the completion of the radiotherapy. The need for a long observation period may necessitate long-term phase I studies in radiation oncology. With use of the CRM, the number of patients could be small because the dose levels are assigned to small numbers of patients (e.g., 1 or 2), so that the period of a study would be shorter when compared to traditional designs. In the present study, the rapid and safe dose escalation with the CRM was achieved with only one patient experiencing Grade 2 RP. However, the CRM also has disadvantages in that it is a complex method and that there is a need for a statistical expert to take part. The CRM appears to be an important method for phase I studies, but the advantages and disadvantages in its use should be considered carefully.

## Figure Legends

**Figure 1.** Overall survival for all 15 participating patients.

**Appendix A.** The prior distribution of the dose-response curve of grade 2 dose limiting toxicity and radiation pneumonitis. The horizontal axis shows the prescribed dose. The vertical axis shows the predicted percentage of the dose limiting toxicities (DLT) (%DLC). DLT is grade 2 radiation pneumonitis. The Median (dashed blue) and Logistic Curves (red) are not the same curve, but they nearly coincide and may appear to overlap.

### **Appendix B.**

The posterior distributions in terms of estimated probability of grade 2 dose limiting toxicity, radiation pneumonitis, for each dose level which are calculated from the results of the trial. The horizontal axis shows the predicted percentage of the dose limiting toxicities (DLT) (%DLC), grade 2 radiation pneumonitis. The vertical axis shows the probability density.

Dose level 1: 40Gy, 2: 45Gy, 3: 50Gy, 4: 55Gy, 5: 60Gy, 6: 65Gy,

The area under the curve of dose level 4 (55 Gy) from the 25 % to 100% in horizontal

axis (black area) shows where the probability of the percentage of grade 2 radiation pneumonitis at dose level 4 (55 Gy) is above 25 %.

### References

- [1] Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, 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.
- [2] Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA.* 2010;303:1070-6.
- [3] Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol.* 2009;27:3290-6.
- [4] Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruyscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol.* 2010;95:32-40.

[5] Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol.* 2010;28:5153-9.

[6] Louie AV, Palma DA, Dahele M, Rodrigues GB, Senan S. Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: Controversies, insights, and changing horizons. *Radiother Oncol.* 2015;114:138-47.

[7] Morita K, Fuwa N, Suzuki Y, Nishio M, Sakai K, Tamaki 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.

[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.

[9] Brada M, Pope A, Baumann M. SABR in NSCLC - The beginning of the end or the end of the beginning? *Radiother Oncol.* 2015;114:135-7.

[10] Onimaru R, Fujino M, Yamazaki K, Onodera Y, Taguchi H, Katoh N, et al. Steep dose-response relationship for stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy. *Int J Radiat Oncol Biol*

Phys. 2008;70:374-81.

[11] Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, 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.

[12] Kestin L, Grills I, Guckenberger M, Belderbos J, Hope AJ, Werner-Wasik M, et al. Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. *Radiother Oncol*. 2014;110:499-504.

[13] Bongers EM, Botticella A, Palma DA, Haasbeek CJ, Warner A, Verbakel WF, et al. Predictive parameters of symptomatic radiation pneumonitis following stereotactic or hypofractionated radiotherapy delivered using volumetric modulated arcs. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2013;109:95-9.

[14] Zhang J, Yang F, Li B, Li H, Liu J, Huang W, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. *International journal of radiation oncology, biology, physics*. 2011;81:e305-16.



[15] van Baardwijk A, Tome WA, van Elmpt W, Bentzen SM, Reymen B, Wanders R, et al. Is high-dose stereotactic body radiotherapy (SBRT) for stage I non-small cell lung cancer (NSCLC) overkill? A systematic review. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2012;105:145-9.

[16] Nishio T, Shirato H, Ishikawa M, Miyabe Y, Kito S, Narita Y, et al. Design, development of water tank-type lung phantom and dosimetric verification in institutions participating in a phase I study of stereotactic body radiation therapy in patients with T2N0M0 non-small cell lung cancer: Japan Clinical Oncology Group trial (JCOG0702). *Journal of radiation research*. 2014;55:600-7.

[17] Ishizuka N, Morita S. Practical Implementation of the Continual Reassessment Method. In: Crowley J, Ankerst DP, editors. *Handbook of Statistics in Clinical Oncology*. 2 ed. New York, NW: Chapman & Hall; 2006. p. 97-116.

[18] Seppenwoolde Y, Lebesque JV, de Jaeger K, Belderbos JS, Boersma LJ, Schilstra C, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. *Int J Radiat Oncol Biol Phys*. 2003;55:724-35.

[19] Onimaru R, Shirato H, Shimizu S, Kitamura K, Xu B, Fukumoto 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.

[20] Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, 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.

[21] Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic

body-radiation therapy. *The New England journal of medicine.* 2012;366:2327-9.

[22] Thomas E, Forbus WD. Irradiation injury to the aorta and the lung. *AMA archives of pathology.* 1959;67:256-63.

[23] Fajardo LF, Stewart JR, Cohn KE. Morphology of radiation-induced heart disease.

*Archives of pathology.* 1968;86:512-9.

[24] Kagan AR, Morton DL, Hafermann MD, Johnson RE. Evaluation and management

of radiation-induced pericardial effusion. *Radiology.* 1969;92:632-4.

[25] Nagata Y, Hiraoka M, Mizowaki T, Narita Y, Matsuo Y, Norihisa Y, 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.

[26] Duprez F, Berwouts D, Madani I, Bonte K, Boterberg T, De Gersem W, et al.

High-dose reirradiation with intensity-modulated radiotherapy for recurrent

head-and-neck cancer: disease control, survival and toxicity. *Radiother Oncol.*

2014;111:388-92.

[27] Guckenberger M, Klement RJ, Allgauer M, Appold S, Dieckmann K, Ernst I, et al.

Applicability of the linear-quadratic formalism for modeling local tumor control

probability in high dose per fraction stereotactic body radiotherapy for early stage

non-small cell lung cancer. *Radiother Oncol.* 2013;109:13-20.

[28] Andisheh B, Edgren M, Belkic D, Mavroidis P, Brahme A, Lind BK. A

comparative analysis of radiobiological models for cell surviving fractions at high doses.

*Technology in cancer research & treatment.* 2013;12:183-92.

## **Acknowledgements**

Data Center: Mr. Hidenobu Yamada and Ms. Chikako Aibara for data management, and Dr. Haruhiko Fukuda for study oversight.

Operations Office: Dr. Tomonori Mizutani, Dr. Junko Eba, and Dr. Kenichi Nakamura for support in the drafting of the manuscript. Supported in part by the National Cancer Center Research and Development Fund (grants 23-A-16, 23-A-21, and 26-A-4), Grants-in-Aid for Cancer Research (20S-5 and 20S-6), and a Health and Labour Sciences Research Grant for Clinical Research (20-020) from the Ministry of Health, Labour and Welfare of Japan.

## **Conflicts of Interest Statement**

Dr. Shirato has received grants from the Government, during the conduct of the study; grants from Hitachi, ltd., grants and personal fees from Mitsubishi Heavy Industries, Ltd., grants and personal fees from Shimadzu Corporation, grants and personal fees from Varian Medical Systems, Inc., and personal fees from Olympus Corporation, outside the submitted work. In addition, Dr. Shirato holds a patent US 6,307,914 with royalties paid.

Dr. Hiraoka reports grants from Varian Medical Systems, Inc. and grants from Mitsubishi Heavy Industries, Ltd., outside the submitted work.

Dr. Karasawa reports grants from Symbio Pharmaceuticals, outside the submitted work.

Dr. Matsuo has a patent pending with Mitsubishi Heavy Industries [pending].

Dr. Kokubo reports receipt of grants and personal fees from Mitsubishi Heavy Industries, Ltd., and grants from Elekta Japan, outside the submitted work.

**Table 1.** Dose Constraints Used

Organ at risk	Dose / fr.	Volume
Spinal cord	25 Gy / 4 fx	Max
Esophagus / Pulmonary artery	40 Gy / 4 fx 35 Gy / 4 fx	$\leq 1$ cc $\leq 10$ cc
Stomach / Small Intestine / Large intestine	36 Gy / 4 fx 30 Gy / 4 fx	$\leq 10$ cc $\leq 100$ cc
Trachea / Bronchus	40 Gy / 4 fx	$\leq 10$ cc
Other organ*	48 Gy / 4 fx 40 Gy / 4 fx	$\leq 1$ cc $\leq 10$ cc
Lung	$V_{20} \leq 37\%$	

Skin  $\leq 40\text{Gy}/4\text{fx}$  (if possible) \*Excluding rib, chest wall, liver, spleen.

$V_x$ , the volume irradiated  $\times$  Gy or greater.

**Table 2.** Characteristics of the 15 Patients with NSCLC

---

Age (year)	71–88 (median 81)	
Male/Female	8/7	
Tumor size	31–39 mm (median 32 mm)	
Histology	Adenocarcinoma	10
	Squamous cell carcinoma	4
	Large cell carcinoma	1
Location	Right upper lobe	8
	Right middle lobe	1
	Left upper lobe	5
	Left lower lobe	1
PS 0/1/2	8/5/2	
Smoking + / –	6/9	
Unfit for lobectomy/refusing surgery	4/11	

---

NSCLC, non-small cell lung cancer; PS, performance status.

**Table 3.** Radiation Pneumonitis (RP) within 180 Days

	40 Gy n=5	45 Gy n=1	50 Gy n=3	55 Gy n=1	60 Gy n=5
RP Grade 1	3	1	3	1	4
RP Grade 2	0	0	0	0	1
RP Grade 3	0	0	0	0	0

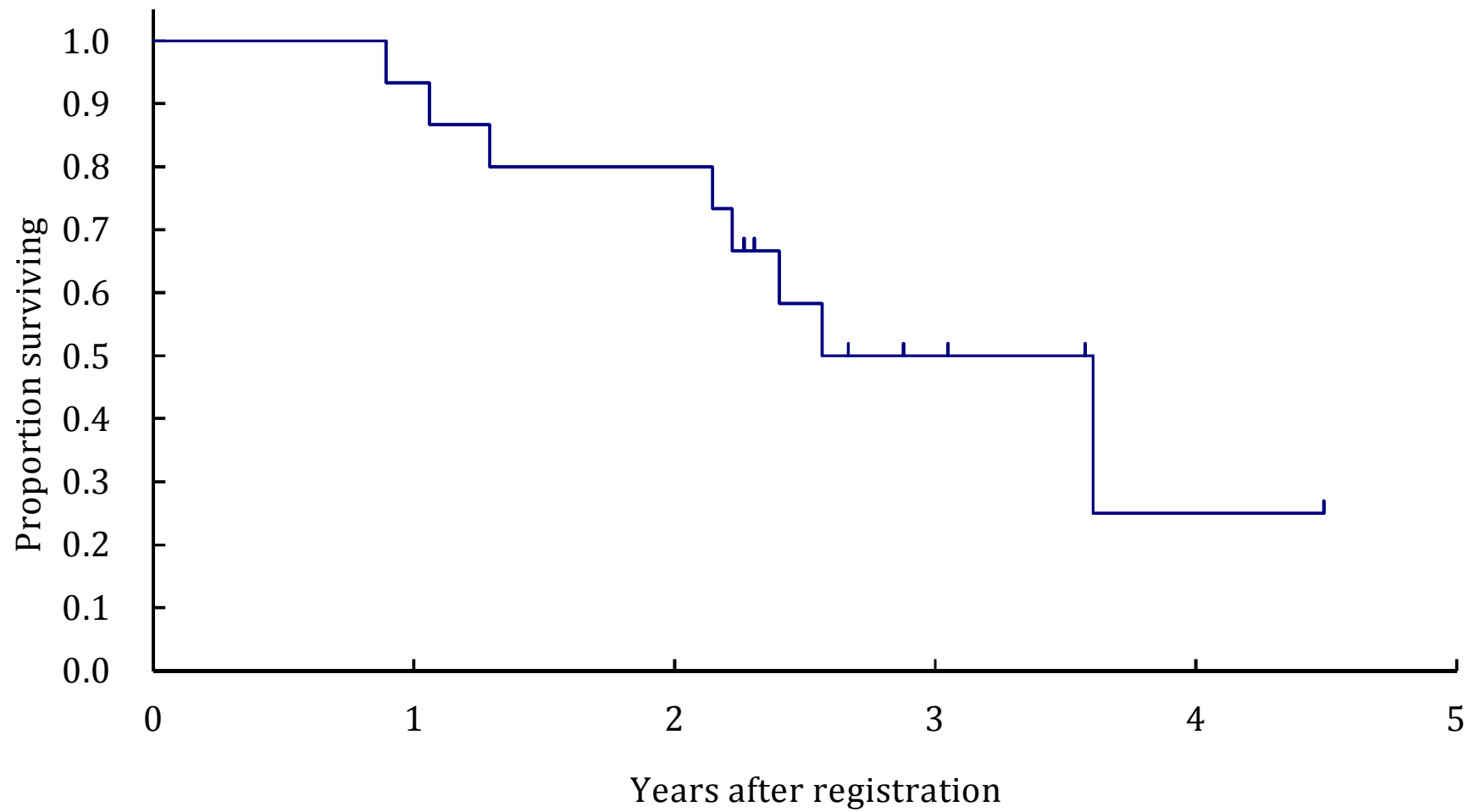


**Table 4.** Median DVH Parameters (range)

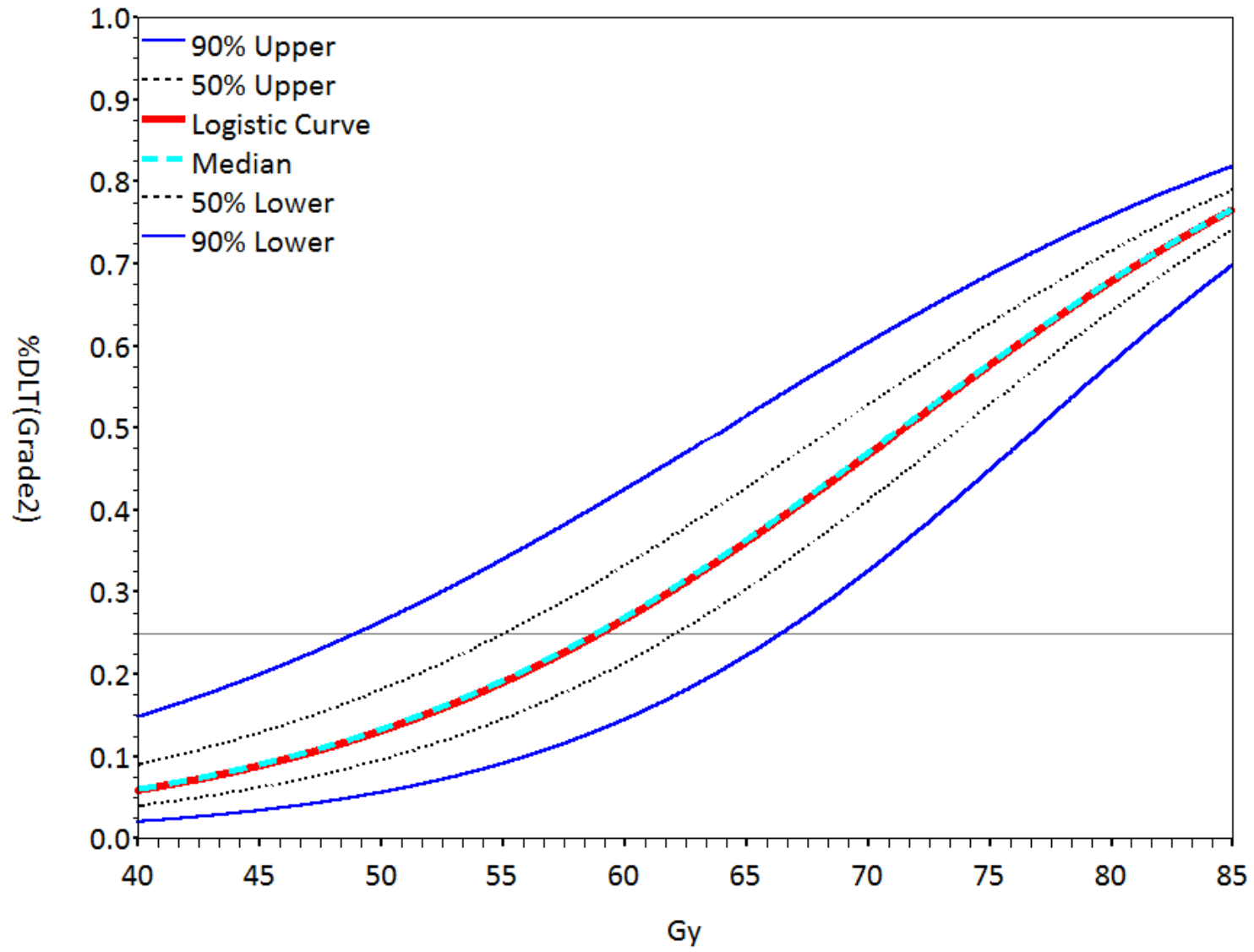
	40 Gy n=5	45 Gy n=1	50 Gy n=3	55 Gy n=1	60 Gy n=5
Isocenter Dose of PTV (Gy)	46.5 (45.3–51.9)	52.0	61.8 (58.7–62.2)	66.8	72.9 (67.7–75.1)
MLD (Gy)	3.5 (3.0–6.9)	3.4	5.5 (3.4–6.3)	4.6	4.6 (3.6–7.0)
V <sub>20</sub> of Lung-PTV (cc)	167.0 (141.7–215.3)	181.1	194.5 (173.5–367.7)	276.7	278.9 (188.1–302.2)
V <sub>10</sub> of Lung-PTV (cc)	401.6 (331.0–490.6)	376.9	374.2 (345.6–741.0)	534.1	419.5 (341.9–614.5)

MLD, mean lung dose; V<sub>x</sub>, the volume that receives x Gy or above.

**Figure 1.** Overall survival for all 15 participating patients.

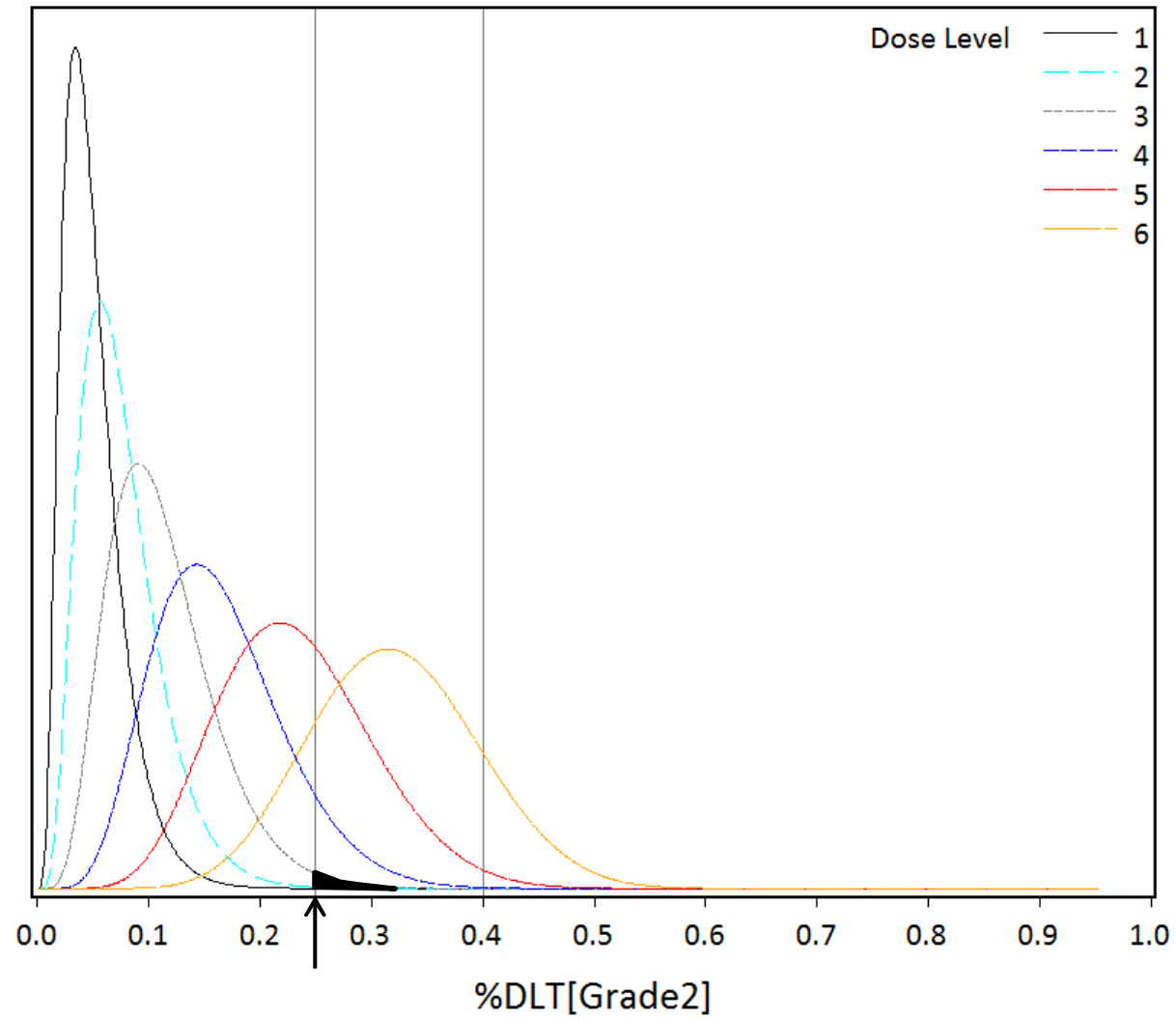


## Appendix A



## Appendix B

### Posterior distribution



Appendix C. Other Toxicities  $\geq$  Grade 2 after 180 Days

	40 Gy n=5	45 Gy n=1	50 Gy n=3	55 Gy n=1	60 Gy n=5
Cough	1 (G2)	–	1 (G2)	–	–
Dyspnea	2 (G2)	–	1 (G2)	–	1 (G2)
Hypoxia	1 (G2)	–	–	–	–
Chest pain	–	–	–	–	1 (G2)
Fracture	–	–	1 (G2)	–	2 (G2)
Brachial plexopathy	–	–	1 (G2)	–	–

G2, Grade 2.