Title
Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer (JCOG0702): Results for the group with PTV ⩾ 100 cc

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Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer (JCOG0702): results for the group with PTV ≥ 100cc.

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

Short running title: Dose escalation study of SBRT: JCOG 0702

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Previous presentation

This work was presented at the 57th Annual Meeting of the American Society for Radiation Oncology, October 18 – 21, 2015 in San Antonio, TX.
Abstract

Purpose: A dose escalation study to determine the recommended dose (RD) with stereotactic body radiation therapy (SBRT) for peripheral T2N0M0 non-small cell carcinomas (NSCLC) was conducted. The results of the group with PTV $\geq$ 100 cc is reported in this paper.

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 maximum tolerated dose (MTD). Dose limiting toxicity (DLT) was Grade 3 or higher radiation pneumonitis (RP), and Grade 2 or higher RP was used as a surrogate DLT. The RD was equal to the MTD. The dose was prescribed at D$_{95}$ of the PTV.

Results: Thirteen patients were accrued. More patients should have been enrolled but we decided not to prolong the study period. No patients experienced Grade 3 RP. Two patients experienced Grade 2 RP at 50 Gy in 4 fractions. The predicted MTD was 50.2 Gy. The posterior probability of the Grade 2 RP frequency over 40% was 5.3% for the dose level of 50 Gy. The RD was determined to be 50 Gy.

Conclusions: The RD was determined to be 50 Gy in 4 fractions in this population.
Introduction

Stereotactic body radiotherapy (SBRT) for T1-2N0M0 non-small cell lung cancers (NSCLC) shows better overall survival (OS) than conventional radiotherapy [1-3]. Palma et al. reported improvements in the OS of patients with stage I NSCLC after the introduction of SBRT [1]. Nagata et al. reported that OS at 3 years was 59.9% for inoperable patients and 76.5% for operable patients, with SBRT using 48 Gy in 4 fractions for T1N0M0 NSCLC [2]. Chang et al. reported that there is a clinical equipoise between SBRT and surgery in a pooled analysis of 2 randomized trials comparing SBRT and surgery for stage I NSCLC [3]. The SBRT is commonly recognized as the standard therapy for medically inoperable patients with T1N0M0 and T2N0M0 NSCLC and may be an alternative for operable patients who refuse surgery. However, local control of SBRT for T2N0M0 NSCLC is poorer than with T1N0M0 NSCLC [4]. There can be a dose-response relationship between tumor size and the irradiated dose in SBRT [5-8], and Kestin et al. reported that higher doses are associated with better survival for T1-T2N0M0 NSCLC [5]. Guckenberger et al reported that a strong dose–response relationship was observed in NSCLC [6]. Onimaru et al. reported that the difference in the local control rates between 40 and 48 Gy in 4 fractions at the isocenter was larger with stage IB than with stage IA cancers [7]. Koshy et al. reported
that higher doses are associated with better survival in patients with T2N0M0 NSCLC [8]. It appears that dose escalation could be a method to improve the outcomes of SBRT for T2N0M0 NSCLC.

We conducted a phase I study to estimate the maximum tolerated dose (MTD) and to determine the recommended dose (RD) with SBRT for patients with peripheral T2N0M0 NSCLC (JCOG0702). The enrolled patients were stratified into 2 subgroups: a subgroup with PTV < 100 cc and one with PTV ≥ 100 cc, to assess the toxicities accurately considering the irradiated volume. This paper reports the results of the subgroup of patients with PTV ≥100 cc.
Patients and Methods

The eligibility and exclusion criteria, the radiotherapy methods and the study design for the group with PTV ≥ 100 cc are the same as those previously reported for the group with PTV < 100cc [9].

Patients

The major eligibility criteria were as follows: pathologically or cytologically proven NSCLC; peripheral T2N0M0 more than 3 cm in diameter (UICC 6th ed., 2002); the dose constraints of organs at risk (OARs) can be fulfilled; either "age ≥ 20 years and unfit for lobectomy as determined by the surgeon" or "age ≥ 70 years and refusing surgery"; no dyspnea on exertion that require stopping when ascending 1 flight of stairs or walking 1 city block (0.1 km); PaO2 ≥ 60 torr and FEV1.0 ≥ 700 mL; and written informed consent. The main exclusion criteria were as follows: apparent interstitial pneumonitis or pulmonary fibrosis on chest X-rays; active infectious diseases; continuous systemic steroid administration; intermittent or continual oxygenation; fever above 38°C; and uncontrolled cough without narcotics.

In the 6th edition of the UICC TNM classifications, a T2N0M0 tumor was defined as 1) a tumor size of more than 3 cm, or 2) a tumor involving the main bronchus,
2 cm or more distal to the carina, or 3) a tumor invading the visceral pleura, or 4) a tumor associated with atelectasis or obstructive pneumonia that extends to the hilar region but does not involve the entire lung.

**Radiotherapy**

A slice thickness of 1 to 3 mm around the primary tumor was required for the CT planning. The gross tumor volume (GTV) was the same as the primary tumor. The clinical target volume (CTV) was equal to the GTV. The internal target volume (ITV) was created from the CTV by adding a sufficient internal margin. The PTV was created from the sum of the ITV plus adding 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.

In principle, a multileaf collimator (MLC) was circumscribed around the PTV with a 5 mm distance. The distance between the PTV and the edge of the MLC was permitted to change only to fulfill the dose constraints of the OAR without compromising the dose covering 95% of the volume ($D_{95}$) of the PTV when the dose constraints of the OAR were violated. The central review of the treatment planning showed that the PTV included the ITV with set-up margin sufficiently and that there was no modification of the PTV to affect the lung irradiated dose.
The use of a heterogeneity correction, an algorithm equivalent to superposition algorithms was mandatory. The dose was prescribed at $D_{95}$ of the PTV. The fraction number was fixed at 4. The dose constraints of the OARs are as same as in the previous report [9].

Four to six MV X-rays were used, and verification of setup errors $< 5$ mm before each treatment delivery was mandatory. Image guided radiotherapy techniques such as CT on rail, 2 orthogonal kv fluoroscopic images with internal fiducial marker, ExacTrac (BrainLAB AG, Feldkirchen, Germany), or CBCT were permitted but not mandatory.

**Study Design**

The continual reassessment method (CRM) [10] was used to determine the dose level that 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 or higher 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 based on their prior knowledge of the distribution of Grade 3 RP, 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 is low, and further, a single occurrence would have a strong impact on the calculation of the assigned dose level. To resolve this, we used a Grade 2 or higher RP within 180 days of the start of the SBRT as the surrogate DLT, as 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, USA [11]. It would be difficult to diagnose low grade RP especially in patients with severe pulmonary comorbidities making it necessary to evaluate the RP based on the pre-treatment symptoms. Appendix 1 shows the RP grade based on the pre-treatment symptoms. The prior distribution of the dose-response curve and the MTD was calculated based on the expected frequency of the Grade 2 RP (Appendix 2). 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% and the threshold was determined as 40%. 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 till 65 Gy. The 40 Gy starting dose was determined based on the estimate that 40 Gy in 4 fractions at the D$_{95}$ of the PTV corresponds to 48 Gy in 4 fractions at the isocenter, a dose which is common practice in Japan; and the safety has been confirmed in a Phase I/II study [12]. The maximum dose level was determined as 65 Gy in 4 fractions at the D$_{95}$ 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, and this study was registered at the UMIN Clinical Trials Registry [http://umin.ac.jp/ctr/] as UMIN000001459.
**Statistical analysis**

The posterior distribution by the CRM was updated by the JCOG Data Center.

Overall survival (OS) was defined as the number of 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

Thirteen patients were accrued from Oct. 2008 to Apr. 2014. The median follow-up period for all the patients was 3.5 years (range 1.0 – 5.4 years).

Ages ranged from 76 to 86 years and the median age was 80 years. Eight patients were male and 5 patients were female. Eight patients with adenocarcinomas, 3 patients with squamous cell carcinomas, and 2 patients with NSCLC not specified. Tumor sizes ranged from 30.0 to 48.0 mm with a median of 36.0 mm. Tumor locations were as follows: right upper lobe 3 patients; right middle lobe 3 patients; right lower lobe 3 patients; left upper lobe 1 patient; and left lower lobe 3 patients. Performance status (ECOG) was 0 for 5 patients, 1 for 7 patients, and 2 for 1 patient. Nine patients had a smoking history. Four patients were unfit for lobectomy and 9 patients refused surgery. Table 1 shows the patient characteristics.

The numbers of patients at each dose level were 5 at 40 Gy, 3 at 45 Gy, and 5 at 50 Gy. More patients should have been assigned to the level of 50 Gy by CRM to attain the pre-planned rule. However, no more patients were enrolled during the study period because there were no patients with T2N0M0 NSCLC at the 3 institutions, violations of OAR dose constraints at 2 institutions, no indication to proceed with clinical trials due to difficulty in obtaining informed consent at 1 institution, and a conflict with a
replacement period of the Linac at 1 institution.

No patients experienced Grade 3 RP. Two patients assigned to 50 Gy experienced Grade 2 RP. Grade 1 RP occurred in 9 patients, of which 4 were assigned to 40 Gy, 2 to 45 Gy, and 3 to 50 Gy.

The expectation for the posterior distribution for Grade 2 RP at 40 Gy, 45 Gy, and 50 Gy were 13.2%, 18.6 %, and 25.5 %, respectively. Because the MTD was the dose level at which the expectation for a posterior distribution of Grade 2 RP was around 25% in the preplanned rule, we decided that the predicted MTD was 50.2 Gy (95% CI:41.5-63.5 Gy) although the lower and upper limits of the 95% CI for the expected MTD included the adjacent dose level. The posterior probability for a DLT (Grade 2 RP) frequency over 40% was 5.3% for the dose level of 50 Gy and 25.9% for the dose level of 55 Gy, respectively (Table 2).

The dose volume histogram (DVH) parameters are shown in Table 3. The mean lung dose was from 2.9 to 8.5 Gy for all patients; it was 6.4 Gy in the patients assigned to 50 Gy. The median isocenter doses were 47.9 Gy, 52.2 Gy, and 60.4 Gy in the patients assigned to 40 Gy, 45 Gy, and 50 Gy, respectively.

There were no Grade 3 or worse toxicities after 180 days. For Grade 2 toxicities, the toxicities, the number of patients, and the dose levels were as follows:
dermatitis in 1 patient at 40 Gy; hypoxia in 1 patient at 45 Gy, a fracture in 1 patient at 45 Gy and in 2 patients at 50 Gy; neuropathy in 1 patient at 45 Gy; dyspnea in 2 patients at 50 Gy; chest pain in 2 patients at 50 Gy; induration in 1 patient at 40 Gy; and fibrosis-deep connective tissue in 1 patient at 40 Gy (Table 4).

The OS at 3 years was 83.3 % (95% Confidence Interval 48.2 – 95.6%), and the PFS at 3 years 76.2% (42.7 – 91.7%) (Figure 1).
Discussion

The RD of SBRT in 4 fractions for peripheral T2N0M0 NSCLC with PTV $\geq$ 100 cc was determined as 50 Gy ($D_{95}$) in this study. We determined the RD based on the predefined rule that the MTD was the dose level at which the expectation of a posterior distribution of Grade 2 RP was around 25% and RD is equal to MTD.

The CRM is a Bayesian statistical method making it possible to reduce the number of patients receiving doses different from the MTD. Determining a prior distribution is an important issue in Bayesian statistics, and results are more likely to be affected by a prior distribution when sample size is very small. In addition, there is a possibility that the estimated prior distribution was very different from the true RP distribution. A uniform distribution is sometimes used as the prior distribution to avoid this disadvantage, but this gives rise to the further disadvantage of requiring unnecessarily many patients to be enrolled especially in cases where there is prior knowledge of the dose levels. We adopted a prior distribution determined using data obtained from 6 experts with their prior knowledge because a small number of patients is desirable for a phase I study.

The 95 % CI of the MTD (41.5 – 63.5 Gy) included adjacent dose levels (45 Gy, 55 Gy and 60 Gy). This means that more patients should have been assigned to the
dose level of 50 Gy so that the lower and upper limits of the 95% CI would not include these adjacent dose levels. However, we decided not to prolong the study period excessively because of worries about the study results becoming out-of-date due to advances in SBRT techniques. Based on the result that the posterior probability of the DLT (Grade 2 RP) frequency over the pre-determined threshold of 40% was 5.3% for 50 Gy, which is adequately low, the RD was determined to be 50 Gy. At the dose level of 50 Gy, Grade 2 RP occurred in two of five patients (40%), which corresponds to the threshold level. It is possible that the true MTD is higher than that determined in this study because of the early stopping of the study. However, this seems unlikely, considering that violation of dose constraints was one of the reasons that no more patients were accrued and the trial was terminated early.

We previously reported the results for patients with PTV < 100cc, and the RD was 55 Gy (D95) for these patients with PTV < 100 cc [9]. One of the reasons for the lower RD in this report may be the differences in the irradiated lung volume. The larger PTV in this study results in a larger irradiated lung volume. Many studies have shown that the tolerance dose for the lungs depends on the irradiated lung volume and that the tolerance dose decreases as the irradiated volume increases [11, 13, 14], consistent with the results of our study here. Another explanation is the difference in the prior
distribution between the group with PTV < 100 cc and the group with PTV ≥ 100 cc. Considering the irradiated lung volume, the 6 radiation oncologists predicted that the risk of RP would be higher in the group with PTV ≥ 100 cc. The RD is influenced by the prior distribution especially in a study of small sample size, so it could be expected that the RD in this study would be lower than that of the group with PTV < 100 cc.

No patients who violated the dose constraints to OARs were enrolled in this study, so it is unclear whether the RD of 50 Gy is feasible in the irradiation of all the patients with peripheral T2N0M0 NSCLC. The dose constraints of OAR other than the lungs were the same as a phase II study which evaluated the efficacy and the safety of SBRT using 48 Gy in 4 fractions for T1N0M0 NSCLC [2]. There were no Grade 3 or higher toxicities in serial organs like esophagus and trachea in the phase II study showing that the dose constrains of OAR were safe for these organs [2]. However, the dose constraints of the esophagus in this study (V_{40Gy} < 1cc), for example, may be conservative because Stephans et al. reported that no esophageal fistula was found in patients with esophageal 1-cc doses below 48 Gy [15]. At the same time, Tekatli et al. reported that 1 of the 2 patients treated with 35 – 40 Gy in 8 fractions at D_{0.5cc} of the esophagus experienced Grade 3 esophageal toxicity [16]. The esophageal dose constraint in our study seems to be biologically higher than a D_{0.5cc} equal to 40 Gy
considering the fractionation number. Further investigation is needed to evaluate the
tolerance dose of OAR in SBRT, but changes in dose constraints should be made with
great care because the toxicities in serial organs like the esophagus and trachea are
lethal [17, 18].

In conclusion, the RD of SBRT in 4 fractions for peripheral T2N0M0 NSCLC
with PTV ≥ 100 cc is determined as 50 Gy (D$_{95}$) using CRM. A Phase II study is needed
to evaluate the safety and efficacy of the RD of 50 Gy.
References


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

Figure 1. Overall survival data for the 13 participating patients.

Acknowledgements

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

Operations Office: Dr. Kenichi Miyamoto, 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. Onimaru has received personal fees from Janssen Pharmaceutical K.K. and personal fees from Shimadzu Corporation, unrelated to the submitted work.

Dr. Shirato has received grants from the Government of Japan, during the conduct of the study; grants from Hitachi, Ltd., grants from Jokoh, 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, unrelated to 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.
Years after registration

Proportion surviving

3-year %OS: 83.3% (95% CI 48.2-95.6%)
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Age</th>
<th>Median</th>
<th>80 y.o.</th>
<th>Range</th>
<th>76-86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>8</td>
<td>Female</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td>Adenocarcinoma</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous cell carcinoma</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC not specified</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>Median</td>
<td>36.0 mm</td>
<td>Range</td>
<td>30.0-48.0 mm</td>
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</tr>
<tr>
<td>Tumor volume</td>
<td>Median</td>
<td>104.7 cc</td>
<td>Range</td>
<td>100.0-270.4 cc</td>
<td></td>
</tr>
<tr>
<td>Tumor Location</td>
<td>RUL</td>
<td>3</td>
<td>RML</td>
<td>3</td>
<td>RLL</td>
</tr>
<tr>
<td>Performance status</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>2</td>
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</tbody>
</table>

RUL: Right Upper Lobe, RML: Right Middle Lobe, RLL: Right Lower Lobe, LUL: Left Upper Lobe, LLL: Left Lower Lobe.
Radiation Pneumonitis within 180 days

<table>
<thead>
<tr>
<th>Level 1 (40 Gy) N=5</th>
<th>Level 2 (45 Gy) N=3</th>
<th>Level 3 (50 Gy) N=5</th>
<th>Level 4 (55 Gy) N=0</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP Grade 1</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>RP Grade 2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>RP Grade 3</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

The expectation of posterior distribution for Grade 2 RP

<table>
<thead>
<tr>
<th></th>
<th>Level 1 (40 Gy)</th>
<th>Level 2 (45 Gy)</th>
<th>Level 3 (50 Gy)</th>
<th>Level 4 (55 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP Grade 2</td>
<td>13.2%</td>
<td>18.6%</td>
<td>25.5%</td>
<td>33.7%</td>
</tr>
<tr>
<td>Table 3</td>
<td>Median DVH Parameter (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level 1</td>
<td>Level 2</td>
<td>Level 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(40 Gy)</td>
<td>(45 Gy)</td>
<td>(50 Gy)</td>
<td></td>
</tr>
<tr>
<td>N=5</td>
<td></td>
<td>N=3</td>
<td>N=5</td>
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</tr>
<tr>
<td>Isocenter Dose of PTV (Gy)</td>
<td>47.9</td>
<td>52.2</td>
<td>60.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(45.8–50.5)</td>
<td>(51.0–57.5)</td>
<td>(57.7–62.5)</td>
<td></td>
</tr>
<tr>
<td>MLD (Gy)</td>
<td>5.3</td>
<td>5.0</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2.9–8.5)</td>
<td>(3.3–5.9)</td>
<td>(6.0–7.5)</td>
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</tr>
<tr>
<td>V₂₀ of Lung-PTV (cc)</td>
<td>258.0</td>
<td>224.3</td>
<td>377.0</td>
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<tr>
<td></td>
<td>(182.9–467.0)</td>
<td>(220.0–348.7)</td>
<td>(291.0–559.0)</td>
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<tr>
<td>V₁₀ of Lung-PTV (cc)</td>
<td>513.6</td>
<td>452.0</td>
<td>708.0</td>
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<tr>
<td></td>
<td>(365.2–791.1)</td>
<td>(430.4–1018.3)</td>
<td>(547.6–948.0)</td>
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</table>
Other Toxicities $\geq$ Grade 2 after 180 days

<table>
<thead>
<tr>
<th></th>
<th>Level 1 (40 Gy) N=5</th>
<th>Level 2 (45 Gy) N=3</th>
<th>Level 3 (50 Gy) N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Dermatitis</td>
<td>1(G2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-</td>
<td>-</td>
<td>2(G2)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>-</td>
<td>1(G2)</td>
<td>-</td>
</tr>
<tr>
<td>Chest pain</td>
<td>-</td>
<td>-</td>
<td>2(G2)</td>
</tr>
<tr>
<td>Fracture</td>
<td>-</td>
<td>1(G2)</td>
<td>2(G2)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>-</td>
<td>1(G2)</td>
<td>-</td>
</tr>
<tr>
<td>Induration</td>
<td>1(G2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fibrosis-deep connective tissue</td>
<td>1(G2)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

No Grade 3 or worse toxicities.