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Stereotactic body radiotherapy to treat small lung lesions clinically diagnosed as primary lung cancer by radiological examination: A prospective observational study

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ABSTRACT

Objectives: Even with advanced image guidance, biopsies occasionally fail to diagnose small lung lesions, which are highly suggestive of primary lung cancer by radiological examination. The aim of this study was to evaluate the outcome of stereotactic body radiotherapy (SBRT) to treat small lung lesions clinically diagnosed as primary lung cancer.

Materials and methods: This is a prospective, multi-institutional observation study. Strict inclusion and exclusion criteria were determined in a nation-wide consensus meeting and used to include patients who were clinically diagnosed with primary lung cancer using precise imaging modalities, for whom further surgical intervention was not feasible, who refused watchful waiting, and who were highly tolerable of SBRT with informed consent. SBRT was performed with 48 Gy in 4 fractions at the tumor isocenter.

Results: From August 2009 to August 2014, 62 patients from 11 institutions were enrolled. Their median age was 80 years. The tumors ranged in size from 9 to 30 mm in diameter (median, 18 mm). The median follow-up interval was 55 months. The 3-year overall survival rate was 83.3% (95% confidence interval (CI) 71.1–90.7%) for all the patients and 94.7% (95% CI 68.1–99.2%) for the patients younger than 75 years. Local failure, regional lymph node metastases and distant metastases occurred in 4 (6.4%), 3 (4.8%) and 11 (17.7%) patients, respectively. Grades 3 and 4 toxicities were observed in 8 (12.9%) patients and 1 (1.6%) patient, respectively. No grade 5 toxicities were observed.

Conclusions: SBRT is safe and effective for patients with small lung lesions clinically diagnosed as primary lung cancer that satisfied the proposed strict indication criteria as previously reported. A prospective interventional study is required to ascertain if SBRT is an alternative strategy for these patients.

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1. Introduction

Pathological diagnosis is essential to treat primary lung cancer. However, biopsy occasionally fails to diagnose small lung lesions that are highly suggestive of primary lung cancer. Additionally, biopsy and diagnostic surgery are often not feasible due to medical complications or are refused by elderly patients. Recently, Detillon et al. showed that the mortality rate is 6.0% for patients 80 years or older who received surgical lung cancer resection [1]. Damhuis et al. reported that postoperative mortality increased with age: 1.7% for patients < 60 years old versus 9.4% for patients of 80 years or older using data from the Rotterdam and Thames Cancer registries and a prediction model [2]. Occasionally physicians recommend watchful waiting until the nodule grows. In patients who receive watchful waiting, those with cancer are at high risk of tumor progression.

Stereotactic body radiation therapy (SBRT) with a high local dose has been applied to peripheral lung cancers and provides excellent survival benefit for both operable and inoperable cases [3,4]. We have previously described a national retrospective SBRT study of patients with clinically diagnosed primary lung cancer by radiological examination in 12 institutions [5]. The study showed that the 3-year overall survival rate (OS) was 89.8% and that the grade 2 or higher pulmonary adverse reaction rate was 3.4% in patients with a tumor diameter ≤ 20 mm. To confirm these results, strict eligibility and exclusion criteria were made, and a prospective, nation-wide, multi-institutional SBRT observational study was performed. This is the final report describing that study.

2. Materials and methods

2.1. Study design and participants

The eligibility and exclusion criteria for SBRT to treat primary lung cancer clinically diagnosed by radiological examination were determined at the nation-wide consensus meeting attended by pulmonologists, radiologist, and oncologist from institutes in JCOG 0403 [4] and JCOG0702 [6,7]. All of the following criteria were required for a patient to be eligible: (a) tumor diameter was ≤30 mm; (b) biopsy by bronchoscope or CT was attempted once or more but failed to diagnose the lesion; the biopsy was refused or was unable to be performed because of medical complications; either the (c1) tumor size was enlarged on sequential CT examination and fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) was also positive, or (c2) for a ground-glass nodule (GGN) with a negative FDG PET, the pure GGN tumor size was 10 mm or larger and enlargement on sequential CT examination, or a GGN had the appearance of a solid component; (d) surgery was contraindicated or refused; (e) watchful waiting was refused; (f) the Eastern Cooperative Oncology Group performance status was 0–2; (g) patient age was ≥20 years; (h) dose constrains of all organs at risk were expected to be fulfilled; (i) there was no history of irradiation to the thorax; (j) PaO2 ≥ 60 Torr (under room air); (k) forced expiratory volume 1.0 ≥ 700 ml; and (l) written informed consent was obtained.

The rationale for the (c2) criterion where a pure GGN tumor size 10 mm or larger and enlargement on sequential CT examination is following. When the nation-wide consensus meeting mentioned above was held, this subgroup had been recognized to have a high frequency of bronchioloalveolar carcinoma or invasive adenocarcinoma, sampling error on percutaneous biopsy, and false negative PET findings and was recommended to be surgically resected, as reviewed by Godoy and Naidich afterwards [8]. In fact, Lim et al. recently confirmed that 39% of pure GGN 10 mm or larger by CT were invasive adenocarcinomas by pathology [9].

Exclusion criteria were as follows: (a) apparent interstitial pneumonia or pulmonary fibrosis on the chest film; (b) active infectious disease; (c) synchronous or metachronous cancer within 2 years; (d) pregnancy; (e) severe psychological disorder; (f) continuous systemic steroid administration; or (g) continuous O_2 inhalation. Patients were excluded if they had any of these conditions.

2.2. Procedures

All the patients were irradiated using SBRT techniques. Three-dimensional treatment planning was performed using non-coplanar static ports or dynamic arcs. The clinical target volume was exactly the same as the gross tumor volume. Various techniques using breathing control or gating methods and immobilization devices were utilized to reduce internal margins. The internal margin, which varies by technique, and a 5 mm setup margin were added to create the planning target volume (PTV).

A total dose of 48 Gy at the isocenter was administered in 4 fractions over 4–8 days, which is the same as the schedule used in JCOG0403 [4]. X-rays of 4–6 MV were allowed. A heterogeneity correction calculation was used. The position of the multileaf collimator sets was usually the PTV plus a 5 mm margin such that the PTV was mostly covered by the 80% isodose line. The dose constraints of the organs at risk were the same in JCOG0403.

The primary endpoint was 3-year OS. Secondary endpoints included OS, progression-free survival (PFS), local control rate (LC), toxicity and patterns of failure. OS was defined as the time from the date of registration to the date of death due to any cause and censored at the date of the last follow-up for surviving patients. PFS included local failures, regional lymph node failures, distant metastases and all deaths as events and was censored at the last date without any events. LC included only local failures as events and was censored at the last date without local failure.

Patients were followed up with basic CT examinations at 2, 4, 6, 9 and 12 months after treatment and every 6 months thereafter for at least 3 years until the end of the study. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Distinguishing between residual tumor tissue and radiation fibrosis was difficult; therefore, the Response Evaluation Criteria in Solid Tumor (RECIST) were not used in this study. Local failure was considered to have occurred when enlargement of the local tumor continued for > 6 months on follow-up CT scans or was confirmed histologically. FDG-PET/CT was recommended when local failure was suspected, but this was not mandatory. Absence of local failure was defined as locally controlled disease. No chemotherapy was allowed after SBRT until recurrence. After confirmation of any failures, salvage treatment was allowed.

2.3. Statistical analysis and ethical considerations

Because the 3-year OS was 78% in patients with a tumor diameter ≤30 mm in the national retrospective SBRT study mentioned above [5], we estimated that the 3-year OS for patients in this prospective observation study would be 80%. The sample size was determined to be 62 by a precision basis so that the 95% confidence interval (CI) for the estimated 3-year OS would be ± 10% around the expected value of 80%.

OS, PFS and LC were calculated using the Kaplan-Meier method. The log-rank test was used to calculate statistical significance between differences. Multivariate analysis was performed using a Cox proportional hazards regression model. A value of $p < 0.05$ was considered statistically significant. All the analyses were performed with SAS release 9.4 (SAS Institute, Cary, NC).

The study protocol was accepted by 11 institutions in Japan in July 2009. Nine of the 11 were involved in JCOG 0403 [4] and JCOG 0702 [6,7]; therefore, the SBRT quality control (QA) was completed already [10]. For the other 2 institutions, we added a survey for their QA program for SBRT and accepted them. The patients were recruited from August 2009 to August 2014, and the data were analyzed in August

Table 1
Patient characteristics.

Characteristic	Value
Age (years)	
Median	80
Range	61–91
Gender (n)	
Male	40
Female	22
Performance status	
0	44
1	15
2	3
Smoking (n)	
Yes	19
No	43
Reason for pathological unproven	
Nondiagnostic biopsy undergone	33
Biopsy refused	19
Biopsy impossible due to medical complications	9
Other	1
Ground-glass nodule	
Yes	15
No	47
Tumor size (mm)	
Median	18
Range	9–30
Tumor site (n)	
Upper lobe	35
Middle lobe	1
Lower lobe	26
Medical condition (n)	
Operable	43
Inoperable	19
Forced expiratory volume 1.0 (ml)	
Median	1645
Range	740–2890

2017.

3. Results

3.1. Survival and local control

Sixty-two patients from 11 institutions were enrolled. Their median age was 80 years. The tumor sizes ranged from 9 to 30 mm in diameter (median 18 mm). Patient characteristics are shown in Table 1.

Of the 62 patients, 14 died; 8 of these deaths were from causes unrelated to lung cancer. Thus, the proportion of primary cancer death was 42.9% (6/14). The median follow-up was 55 months and ranged from 12 to 90 months. For patients with a follow-up period less than 36 months, four patients were lost to follow-up at 12, 18, 20 and 25 months after the treatment.

The 3-year OS was 83.3% (95% CI 71.1–90.7%) (Fig. 1). The 3-year PFS and LC were 69.7% and 93.5% (Fig. 1), respectively. Univariate analysis showed that only age (< / ≥80) was a prognostic factor for OS (p = .039, Fig. 2); thus, no other parameters were significant prognostic factors for OS (Table 2). There were no significant differences in operable (n = 43) or inoperable (n = 19), GGN (n = 15) or non-GGN (n = 47), or tumor size larger (n = 27) or smaller than (n = 35) 20 mm. Age (< / ≥80) remained a significant prognostic factor for OS even in multivariate analysis (HR 1.020-11.276, p = .046). Additionally, the 3-year OS for patients younger than 75 years with a median age of 68 years was 94.7% (95% CI 68.1–99.2%). However, for patients 75 years or older with a median age of 82 years, the 3-year OS was 78.0% (95% CI 62.0–88.0%) (Fig. 2). Univariate analysis showed that age (< / ≥ 75) was a prognostic factor for OS (p = .021) as well.

A total of 14 failures were observed. Local failure, regional lymph node metastases and distant metastases occurred in 4 (6.4%), 3 (4.8%) and 11 (17.7%) patients, respectively. The combination of failure patterns is shown in Table 3. Those with distant metastases include 9 patients with pleural dissemination, 3 in the lung, 2 in the liver and 1 in the brain and muscle.

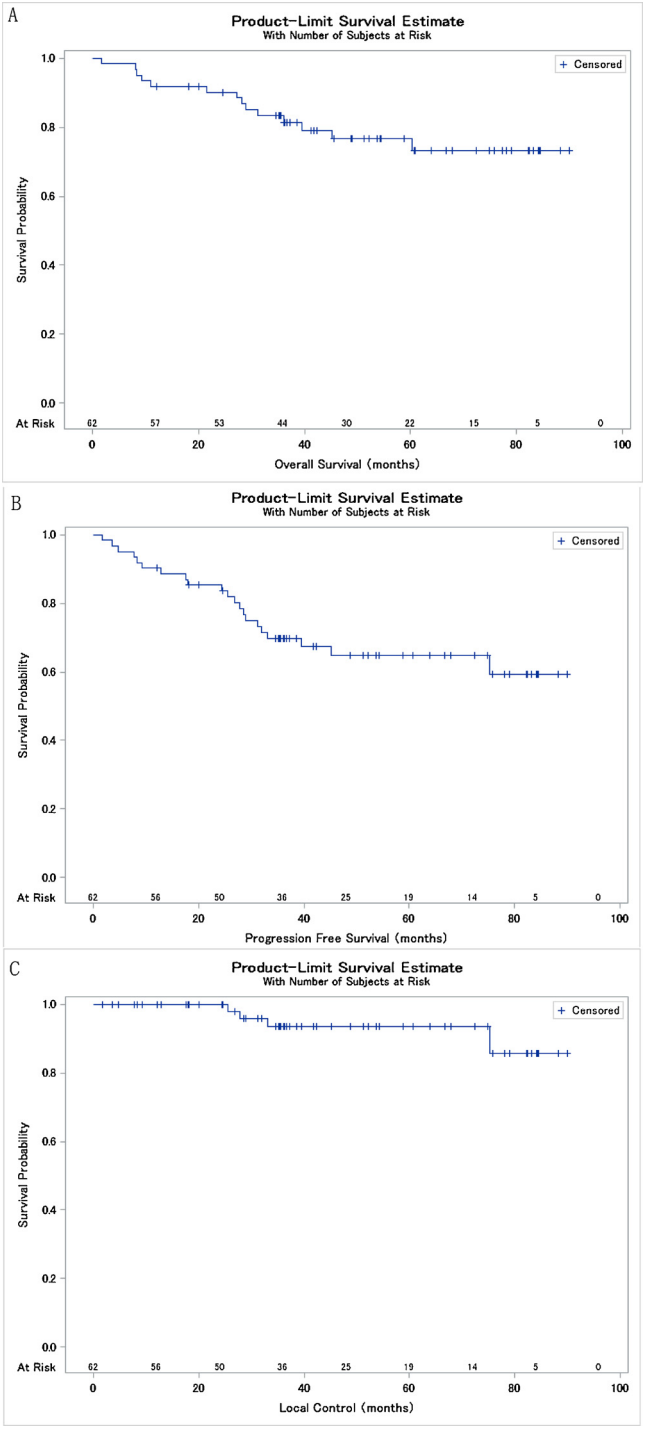

Fig. 1. Kaplan-Meier curve of the overall survival rate (A), progression-free survival (B), and local control rate (C) for all the patients.

3.2. Toxicities

Acute (≤56 days) and late (≥57 days) toxicities were prospectively observed and evaluated. No acute toxicities grade 3 or higher occurred. Grade 3 and 4 late toxicities were observed in 8 (12.9%) and 1 (1.6%) patients, respectively. No grade 5 toxicities were observed. Details

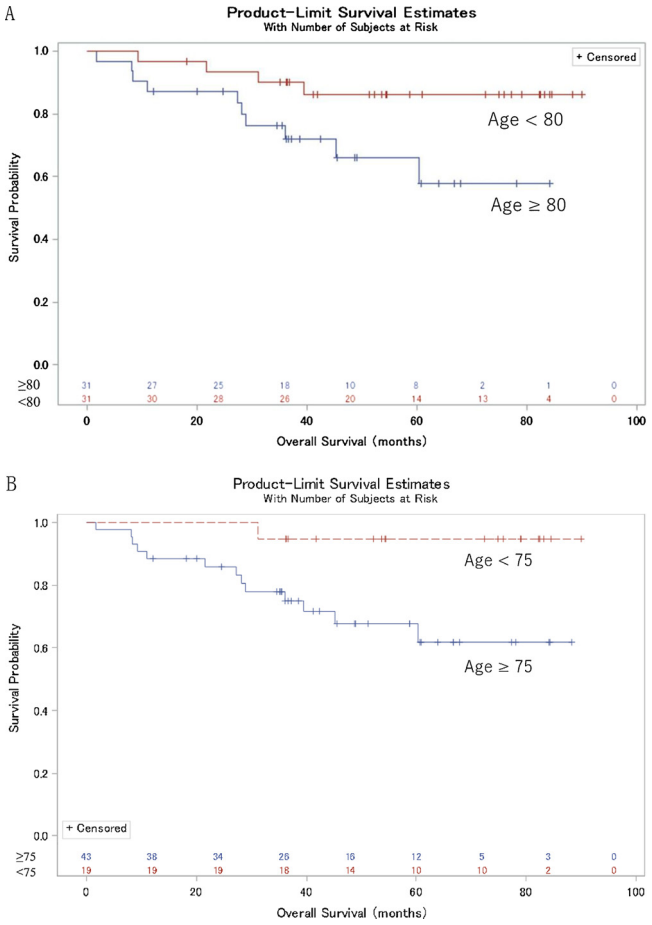

Fig. 2. Kaplan-Meier curve of the patients older and younger than 80 years old. Significant differences were observed (p = .046) between the two groups (A). Kaplan-Meier curve of the patients older and younger than 75 years old. Significant differences were observed (p = .021) between the two groups (B).

regarding late toxicities are shown in Table 4. There was grade 3 dyspnea in 7 (11.2%) patients, radiation pneumonitis in 3 (4.8%) patients and hypoxia in 2 (3.2%) patients. There was grade 4 dyspnea in 1 (1.6%) patient, radiation pneumonitis in 1 (1.6%) patient, and hypoxia in 1 (1.6%) patient. No other late adverse effects of grade 3 or higher were observed.

4. Discussion

The results of this study should be carefully evaluated because GGNs are included. A GGN with a solid component is known to exhibit similar results as stage I non-small cell lung cancer (NSCLC) after surgery. Noguchi et al. showed in 1995 that surgery for GGNs 2 cm or smaller with a solid component resulted in a 5-year OS of 74.8%, with a 3-year OS of approximately 80% [11]. In 2013, Asamura et al. recommended major surgical resection for patients with GGNs ≤30 mm with a consolidation to a tumor ratio > 0.5 by CT based on achieving a 5-year OS of 88.9%, with a 3-year OS of 94% for patients under 75 years old with a median age of 62 years [12]. Regarding pure GGNs without a solid component, Godoy and Naidich recommended surgical resection for pure GGNs 10 mm or larger [8]. Lim et al. recently confirmed that 39% of pure GGNs 10 mm or larger by CT are invasive adenocarcinomas by pathology [9]. Regarding pure GGNs without a solid component, because we added GGN enlargement by sequential CT for pure GGN 10 mm or larger in the inclusion criteria, the incidence of invasive cancer may be higher in this study. Consequently, there were no significant differences between the outcomes of patients with GGNs and those with non-GGN tumors in this study. The 3-year OS for patients under 75 years old with a median age of 68 years was 94.7% (95% CI 68.1–99.2%), which is consistent with the estimated 3 year-OS in a surgical study by Asanuma et al. These findings, in addition to

Table 2
Univariate and multivariate analyses for overall survival.

Variable	n	OS at 3yrs (%)	OS at 5yrs (%)	UVA p value	MVA HR (95% CI)	p value
Age (years)						
≥80	31	76·2	66·0	0·039*	3·392	0·046*
< 80	31	86·2	86·2		(1·020 – 11·276)	
Gender						
Female	22	77·3	77·3	0·662	0·265	0·205
Male	40	86·7	75·6		(0·034 – 2·061)	
Performance status						
0	44	83·9	77·7	0·486	0·984	0·982
1/2	18	82·1	74·6		(0·245 – 3·953)	
Smoking						
No	19	74·4	68·2	0·147	6·45	0·107
Yes	43	87·6	80·7		(0·668 – 62·283)	
Reason for pathological unproven						
Other	29	78·0	72·4	0·678	1·733	0·351
Nondiagnostic biopsy undergone	33	87·7	80·2		(0·546 – 5·502)	
Ground-glass nodule						
No	47	80·0	74·5	0·272	2·166	0·367
Yes	15	93·3	84·0		(0·404 – 11·598)	
Tumor size (mm)						
≥20	27	76·6	72·4	0·541	1·678	0·429
< 20	35	88·4	79·9		(0·466 – 6·050)	
Medical condition						
Inoperable	19	78·2	78·2	0·892	1·023	0·973
Operable	43	85·6	76·8		(0·274 – 3·819)	

Abbreviations: UVA = univariate analysis, MVA = multivariate analysis, HR = hazard ratio.
* Significant (p < 0·05).

Table 3
Patterns of failure.

Pattern	Value (n)
Local only	3
Local + LN	0
Local + distant	1
Local + LN + distant	0
LN only	0
LN + distant	3
Distant only	7
Total	14

Abbreviation: LN = lymph node.

Table 4
Late toxicities.

Toxicity	Value (n)
Grade3 (n = 8, 12.9%)	
Dyspnea	3
Pneumonitis	1
Dyspnea + Pneumonia	2
Dyspnea + Hypoxia	2
Grade4 (n = 1, 1.6%)	
Dyspnea + Hypoxia + Pneumonitis	1
Grade5 (n = 0)	0
Total	9

Abbreviation: LN = lymph nod.

recommendations by Asanuma et al. and Godoy and Naidich, suggest that the GGN inclusion criteria in this study were reasonable.

We adapted positive FDG PET results as eligibility criteria for non-GGN. Before the introduction of FDG PET in the 1990s, the percentage of malignant disease for solitary lung nodules detected by plain chest X-ray or CT examination was 50–75% [13–16]. However, a meta-analysis in 2001 by Gould et al. showed that FDG-PET has 77.8% specificity, 96.8% sensitivity, and 91.2% accuracy for diagnosing primary lung cancer [17]. By adding tumor enlargement by sequential CT examination and a positive FDG PET examination in the inclusion criteria, the likelihood of invasive cancer should be higher than 77.8% in this study.

There were 12.9% grade 3 and 1.6% grade 4 late toxicity events in our series. JCOG0403 showed 10.6% grade 3 and 1.9% grade 4 late toxicities in inoperable patients and 8.9% grade 3 and 1.2% grade 4 toxicities in total after SBRT for pathologically proven stage I NSCLC [4]. The similarity between our study and JCOG0403 is reasonable, as we used the same technology. Sawabata et al. also reported that after surgical resection of NSCLC, postoperative complications grade 4 or higher were observed in 4.5% in 11,663 operable patients with 0.4% operative death (death within 30 days) and 0.4% hospital death (death after 30 days or more) treated during 2004 in Japan [18]. For operable patients who refuse surgery, grade 4 or higher late toxicity after SBRT was suggested to be lower than the surgical series, although the latter included patients with higher clinical stages. Solaini et al. reported that the risk of complications after surgical biopsy ranges from 3.3–13.4%, although its severity varies [19]. Considering that the median age was 80 years and the medial forced expiratory volume 1.0 (ml) was 1645 ml distributed from 740 to 2890 ml in total, this study suggested that SBRT has a risk of adverse reaction nearly equal to biopsy for patients with inoperable tumors.

It would be informative to compare the results of this study with the results of pathologically proven SBRT patients. In the JCOG0403 study, in which SBRT was used for pathologically proven T1N0M0 non-small cell lung cancer, the 3-year overall survival rate (OS) was 76.5% (95% CI 64.0–85.1%) for operable patients and 59.9% (95% confidence interval 49.6–68.8%) for inoperable patients [4]. The 83.3% (95% CI 71.1–90.7%) 3-year OS in this study seems to be superior to that of the JCOG0403 study, but it must be noted that the distribution of the ECOG performance status of the patients was better in this series than that in JCOG0403; 71% of the patients had PS 0 in this series vs 39% of operable patients in JCOG0403 and 61% of inoperable patients in JCOG0403.

There is no reliable data describing the outcome after watchful waiting for the same patient cohort patients. As a reference, a study using the Surveillance Epidemiology and End Results (SEER) database in the USA showed that the OS for no treatment (n = 291) in patients 80 years or older with Stage I NSCLC was 28.9% (95% CI 23.3–34.7%) at 2 years [20]. However, the medical condition of the patients might have been considerably different from this study. As another reference, the 3-year OS was estimated to be 91% in patients with a median age of 67 years with clinical Stage IA NSCLC (n = 6295) who had received surgery in Japan in 2004 [18]. Chang et al. reported the outcome of SBRT and lobectomy for operable stage I NSCLC [21]. The 3-year OS was 95% in the SBRT group with a median age of 67 years and 79% in the surgery group with a median age of 67 years. The present results for patients younger than 75 years old are similar to the Japanese surgical study and Chang et al.'s study on age distribution as well as treatment outcome. For patients 75 years or older, the 3-year OS was 78.0% (95% CI 62.0-88.0%) with a median age of 82 years in the present study. Miyazaki et al. recently reported that SBRT treatment and surgery exhibit similar results for patients 80 years or older with Stage I NSCLC using propensity score matching [22]. Taremi et al. reported results using SBRT for medically inoperable lung cancer regardless of pathological confirmation [23] and observed no significant differences in OS among patients with pathologically confirmed cancer. In fact, recent reports regarding SBRT often contain patients with small lung lesions clinically diagnosed as primary lung cancer without a precise definition of diagnostic criteria [23–26]. This study confirmed that OS after SBRT in patients with small lung lesions clinically diagnosed as primary lung cancer is similar to OS after surgery and SBRT in patients with pathologically proven stage IA NSCLC.

In patterns of failure analysis, distant metastases were the most frequently observed event, which was similar to the adverse events observed in JCOG0403 [4]. Distant metastases were observed in 17.7% of patients, whereas local failure and regional lymph node metastases observed in 6.4% and 4.8% of patients, respectively. The low local and regional relapse rate in addition to the low adverse reaction rates in this study suggested that a total dose of 48 Gy at the isocenter administered in 4 fractions only to the primary tumor is sufficient. Additional treatment to reduce distant metastasis is an issue requiring discussion.

Patients with solid tumors 10 mm or smaller were generally ineligible for this study because of the inclusion criteria. In fact, only one patient with a lesion smaller than 10 mm (9 mm) entered this study because of positive FDG PET results and enlargement by sequential CT examination. A more sophisticated non-invasive diagnostic method is required for lesions 10 mm or less in diameter because FDG-PET/CT has a lower sensitivity and specificity for small lesions [27–30].

5. Conclusions

SBRT to treat small lung lesions clinically diagnosed as primary lung cancer is effective and safe as long as strict eligibility and exclusion criteria are adapted. This treatment can be considered an alternative treatment option to watchful waiting or open surgery for patients with small lung lesions clinically diagnosed as primary lung cancer by radiological examination. A prospective interventional study is required to confirm our findings.

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Conflicts of interest

Dr. Shirato reports personal fees from Astra Zeneca, grants from Ministry of Health, Labour and Welfare, Japan, grants from Japan Agency for Medical Research and Development (AMED), grants from Ministry of Education, Culture, Sports, Science and Technology, Japan, during the conduct of the study; grants from Shimadzu Corporation, grants from Hitachi Ltd, outside the submitted work; In addition, Dr. Shirato has a patent US6307914 B1 licensed to Hitachi co ltd., and a patent US6307914 B1 with royalties paid to Mitsubishi heavy industries and Milestone payment from Olympus co ltd. for the development of a medical appliance through endoscope, EP 1588670 A4; from Medikit co ltd. for the development of a medical appliance through a needle. Dr. Nagata reports grants from Japan Agency for Medical Research and Development (AMED), outside the submitted work. Dr. Kinoshita reports grants from AstraZeneca, personal fees from Novartis, personal fees from Bristol-Myers Squibb, personal fees from Taiho Pharmaceutical, personal fees from Chugai Pharmaceutical, outside the submitted work. Dr. Inoue and Katoh reports grants from Ministry of Education, Culture, Sports, Science and Technology, Japan, during the conduct of the study. Dr. Inaba reports grants from Elekta,Japan, outside the submitted work. All other authors have nothing to disclose.

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References

[1] D.D.E.M.A. Detillon, E.J. Veen, Postoperative outcome after pulmonary surgery for non-Small cell lung cancer in elderly patients, Ann. Thorac. Surg. 105 (2018) 287–293.

[2] R. Damhuis, A. Coonar, P. Plaisier, et al., A case-mix model for monitoring of postoperative mortality after surgery for lung cancer, Lung Cancer 51 (2006) 123–129.

[3] R. Timmerman, R. Paulus, J. Galvin, et al., Stereotactic body radiation therapy for inoperable early stage lung cancer, JAMA 303 (2010) 1070–1076.

[4] Y. Nagata, M. Hiraoka, T. Shibata, 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. 93 (2015) 989–996.

[5] T. Inoue, S. Shimizu, R. Onimaru, et al., Clinical outcomes of stereotactic body radiotherapy for small lung lesions clinically diagnosed as primary lung cancer on radiologic examination, Int. J. Radiat. Oncol. Biol. Phys. 75 (2009) 683–687.

[6] R. Onimaru, H. Shirato, T. Shibata, et al., 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), Radiother. Oncol. 116 (2015) 276–280.

[7] R. Onimaru, H. Onishi, T. Shibata, et al., 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, Radiother. Oncol. 122 (2017) 281–285.

[8] M.C.B. Godoy, D.P. Naidich, Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management, Radiology 253 (2009) 606–622.

[9] H.J. Lim, S. Ahn, K.S. Lee, et al., Persistent pure ground-glass opacity lung nodules ≥ 10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications, Chest 144 (2013) 1291–1299.

[10] T. Nishio, H. Shirato, M. Ishikawa, 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), J. Radiat. Res. 55 (2014) 600–607.

[11] M. Noguchi, A. Morikawa, M. Kawasaki, et al., Small adenocarcinoma of the lung: histologic characteristics and prognosis, Cancer 75 (1995) 2844–2852.

[12] H. Asamura, T. Hishida, K. Suzuki, et al., Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201, J. Thorac. Cardiovasc. Surg. 146 (2013) 24–30.

[13] K. Shaffer, Role of radiology for imaging and biopsy of solitary pulmonary nodules, Chest 116 (1999) 519S–522S.

[14] D.M. Libby, C.I. Henschke, D.F. Yankelevitz, The solitary pulmonary nodule: update 1995, Am. J. Med. 99 (1995) 491–496.

[15] P.E. O'Reilly, J. Brueckner, J.F. Silverman, Value of ancillary studies in fine needle aspiration cytology of the lung, Acta Cytol. 38 (1994) 144–150.

[16] M.J. Mack, S.R. Hazelrigg, R.J. Landreneau, et al., Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule, Ann. Thorac. Surg. 56 (1993) 825–830.

[17] M.K. Gould, C.C. Maclean, W.G. Kuschner, et al., Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis, JAMA 285 (2001) 914–924.

[18] N. Sawabata, E. Miyaoka, H. Asamura, et al., Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade, J. Thorac. Oncol. 6 (2011) 1229–1235.

[19] L. Solaini, F. Prusciano, P. Bagioni, F. di Francesco, D.B. Poddie, Video-assisted thoracic surgery (VATS) of the lung: analysis of intraoperative and postoperative complications over 15 years and review of the literature, Surg. Endosc. 22 (2008) 298–310.

[20] A.K. Ganti, V. Shostrom, M. Alorabi, et al., Early stage non e small-cell lung cancer in octogenarian and older patients: a SEER database analysis, Clin. Lung Cancer 17 (2016) 285–291.

[21] J.Y. Chang, S. Senan, M.A. Paul, 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. 16 (2015) 630–637.

[22] T. Miyazaki, T. Yamazaki, D. Nakamura, et al., Surgery or stereotactic body radiotherapy for elderly stage I lung cancer: a propensity score matching analysis, Surg. Today 47 (2017) 1476–1483.

[23] M. Taremi, A. Hope, M. Dahele, et al., Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients, Int. J. Radiat. Oncol. Biol. Phys. 416 (2011) 1–7.

[24] A. Takeda, N. Sanuki, E. Kunieda, et al., Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm, Int. J. Radiat. Oncol. Biol. Phys. 73 (2009) 442–448.

[25] D. Palma, O. Visser, F.J. Lagerwaard, J. Belderbos, B.J. Slotman, S. Senan, 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. 28 (2010) 5153–5159.

[26] P. Baumann, J. Nyman, M. Hoyer, 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. 27 (2009) 3290–3296.

[27] H. Nomori, K. Watanabe, T. Ohtsuka, et al., Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images, Lung Cancer 45 (2004) 19–27.

[28] S.L. Aquino, E.F. Halpern, L.B. Kuester, A.J. Fischman, FDG-PET and CT features of non-small cell lung cancer based on tumor type, Int. J. Mol. Med. 19 (2007) 495–499.

[29] J.J. Erasmus, H.A. MacApinlac, Low-sensitivity FDG-PET studies: less common lung neoplasms, Semin. Nucl. Med. 42 (2012) 255–260.

[30] V. Ambrosini, S. Nicolini, P. Caroli, et al., PET/CT imaging in different types of lung cancer: an overview, Eur. J. Radiol. 81 (2012) 988–1001.