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CLINICAL INVESTIGATION **Lung**

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

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Purpose: To retrospectively analyze the clinical outcomes of stereotactic body radiotherapy (SBRT) for patients with Stages 1A and 1B non–small-cell lung cancer.

Methods and Materials: We reviewed the records of patients with non–small-cell lung cancer treated with curative intent between Dec 2001 and May 2007. All patients had histopathologically or cytologically confirmed disease, increased levels of tumor markers, and/or positive findings on fluorodeoxyglucose positron emission tomography. Staging studies identified their disease as Stage 1A or 1B. Performance status was 2 or less according to World Health Organization guidelines in all cases. The prescribed dose of 50 Gy total in five fractions, calculated by using a superposition algorithm, was defined for the periphery of the planning target volume.

Results: One hundred twenty-one patients underwent SBRT during the study period, and 63 were eligible for this analysis. Thirty-eight patients had Stage 1A (T1N0M0) and 25 had Stage 1B (T2N0M0). Forty-nine patients were not appropriate candidates for surgery because of chronic pulmonary disease. Median follow-up of these 49 patients was 31 months (range, 10–72 months). The 3-year local control, disease-free, and overall survival rates in patients with Stages 1A and 1B were 93% and 96% ($p = 0.86$), 76% and 77% ($p = 0.83$), and 90% and 63% ($p = 0.09$), respectively. No acute toxicity was observed. Grade 2 or higher radiation pneumonitis was experienced by 3 patients, and 1 of them had fatal bacterial pneumonia.

Conclusions: The SBRT at 50 Gy total in five fractions to the periphery of the planning target volume calculated by using a superposition algorithm is feasible. High local control rates were achieved for both T2 and T1 tumors.

Stereotactic body radiotherapy, Lung cancer, Superposition algorithm.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) for patients with early non–small cell lung cancer (NSCLC) is now being investigated in prospective studies (1, 2). Historically, numerous clinical trials of lung tumor treatment were carried out with dose calculation by using the Clarkson algorithm or without heterogeneity correction.

We have carried out SBRT since 2001 with dynamic conformal arc therapy calculated by using the multigrid (MG) superposition algorithm (3). In this retrospective study, we analyzed the clinical outcomes of patients with Stage 1 NSCLC who were irradiated with a dose of 50 Gy total in five fractions to the periphery of the planning target volume (PTV), calculated by using the superposition algorithm.

METHODS AND MATERIALS

Eligibility criteria

The retrospective study population consisted of patients who had undergone SBRT with intent to cure at either the Tokyo Metropolitan Hiroo General Hospital (Tokyo. Japan; from Dec 2001 to Nov 2004) or the Ofuna Chuo Hospital (Kamakura, Japan; from Feb 2005 to May 2007).

All patients underwent appropriate staging studies identifying their disease as Stage IA or IB. Histopathologic or cytologic confirmation of cancer was required by using either biopsy or cytologic examination in Group A. For cases without histopathologic or cytologic confirmation, *i.e.*, Group B, tumor marker level increase or standardized uptake value positivity on fluorodeoxyglucose positron emission tomography (FDG-PET) was required. As a tumor marker, we monitored carcinoembryonic antigen (<5.0 ng/mL), carbohydrate antigen 19–9 (<40 U/mL), sialyl lex-i antigen (<40

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U/mL), squamous cell carcinoma related antigen CYFRA cytokeratin 19 fragment (<1.5 ng/mL), and CYFRA (<3.4 ng/mL) levels. In all subjects, performance status was 2 or less according to World Health Organization guidelines. Patients with previous radiation to the lung or mediastinal region were excluded.

Treatment methods

Our techniques for immobilization and planning have been described in detail (4–6). We performed 10-arc dynamic conformal stereotactic radiotherapy with or without additional static conformal ports. The three-dimensional radiation treatment planning system (XiO, Version 4.2 or 4.3; CMS, St. Louis, MO) was used at both institutions. Radiation doses were calculated by using an MG-superposition algorithm with heterogeneity correction. The prescribed dose was 10 Gy/fraction × five (50 Gy total) to the PTV periphery. Gross tumor volume was defined as the visible tumor on computed tomography (CT) images using a CT number window level of −600 and width of 1,500. All series equated the gross tumor volume to the clinical target volume (CTV). To account for breathing motion–induced changes in tumor position, a long-scan-time CT (LSTCT; 6–8 s/slice) was performed to delineate the internal target volume (ITV) directly (5). For the PTV, individualized treatment margins of 6–8 mm were applied around the ITV. The treatment dose was prescribed to the periphery of the PTV, which corresponded to 80% of the maximum dose (Fig. 1).

Evaluation

All patients were followed up monthly on an outpatient basis with chest X-ray examinations during the first 6 months. Follow-up CT scans were performed at 1 and 3 months after SBRT and thereafter at 3-month intervals during the first 2 years, even in the absence of clinical symptoms. Subsequently, follow-up interviews and CT scans were obtained at 4–6-month intervals. Our follow-up procedures were previously described in detail (6). If there was a possibility that local treatment or systemic therapy would be required for suspected tumor recurrence, FDG-PET was performed to assess the extent of locally recurrent lesions and detect distant metastases. Biopsy or surgery was performed, if necessary. Toxicity was graded using Version 3 of the National Cancer Institute-Common Toxicity Criteria.

Statistical analysis

Follow-up started from the date of the first SBRT to determine median follow-up and time-to-event estimates as outcome data. Control and survival rates were calculated by using Kaplan-Meier analysis with SPSS 15.0 (SPSS Inc., Chicago, IL). Log-rank test was used to compare control or survival between the subsets of patients analyzed. Differences were regarded as statistically significant at $p < 0.05$.

RESULTS

One hundred twenty-one patients with primary NSCLC were treated with SBRT. Eight of these patients were treated without histopathologic or cytologic confirmation, tumor marker level increase, or positive findings on FDG-PET. Twenty-eight patients were treated for postoperative recurrence or with palliative intent, and 31 were treated on an irregular schedule (*i.e.*, reduced total dose of 40 Gy or 10 fractions) because their tumors were located in the central lung or near critical organs or because of poor pulmonary function. Therefore, 63 patients were included in this analysis and 58 were excluded. Patient characteristics are listed in Table 1. In Groups A and B, 30 and 8 patients had Stage 1A, and 22 and 3 had Stage 1B, respectively. Forty-nine patients were not appropriate candidates for surgery because of chronic pulmonary disease, advanced age, or other chronic illnesses, whereas the remaining 14 were surgical candidates but had chosen SBRT although their physicians and the authors fully explained that surgery is the standard therapy for these stages.

Median follow-up for the 49 living patients was 31 months (range, 10–72 months). Local recurrence developed in 2 Group A and 1 Group B patient. The 3-year local control, regional recurrence-free, distant metastasis-free, and disease-free survival rates in patients with Stages 1A and 1B were 93% and 96% ($p = 0.86$; Fig. 2), 82% and 94% ($p = 0.37$), 87% and 89% ($p = 0.35$), and 76% and 77% ($p = 0.83$; Fig. 3), respectively.

The 3-year overall survival (OAS) rates were 90% and 63% ($p = 0.09$; Fig. 4), and 3-year cause-specific survival (CSS) rates were 100% and 81% ($p = 0.10$; Fig. 5) in patients with Stages 1A and 1B, respectively. The 3-year OAS rates

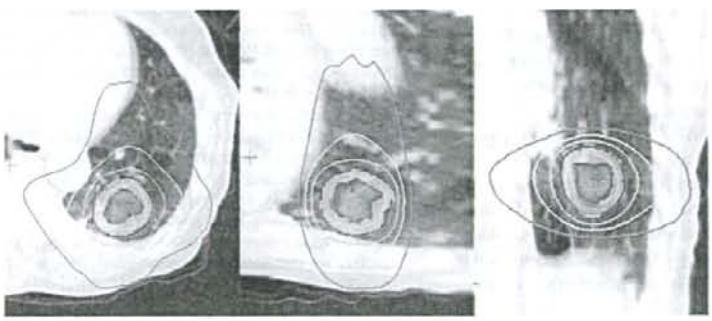

Fig. 1. Axial, sagittal, and coronal images of treatment planning computed tomography (CT). The inner area enclosed by a bold line corresponds to the internal target volume (ITV) directly visualized by long-scan-time CT. The outer area enclosed by a bold line corresponds to the planning target volume derived from the ITV and a 6–8mm margin. The isodose lines from outer to inner represent 20%, 40%, 60%, and 80% of the maximal dose.

Table 1. Patient and tumor characteristics

	Group A	Group B
Patients (*n*)	52	11
Age (y)	78 (56–91)	78 (66–87)
Gender		
Men	32	8
Women	20	3
Operability		
Operable	13	1
Inoperable	39	10
T Classification		
T1	30	8
T2	22	3
Histologic type		
Adenocarcinoma	35	
Squamous cell cancer	14	
Unclassified NSCLC	3	
Tumor marker		4
SUV positive		9

Abbreviations: NSCLC = non-small-cell lung cancer; SUV = standardized uptake value.

were 91% and 77% ($p = 0.31$), and the 3-year CSS rates were 91% and 94% ($p = 0.66$) in operable and inoperable patients, respectively. Eight and five recurrences were identified in patients with Stage 1A and Stage 1B, respectively (Fig. 6).

All patients were treated, and no acute toxicity was observed. Grades 2 and 3 radiation pneumonitis were identified in 1 and 2 patients, respectively. The Grade 2 pneumonitis occurred 4 months after SBRT; the patient was given oral steroid therapy, and pneumonitis resolved by 6 months. One of the patients with Grade 3 who developed pneumonitis 1 month after SBRT was given oral steroid therapy and pneumonitis resolved by 6 months. In the remaining patient, pneumonitis developed 3 months after SBRT. Although oral steroid and oxygen therapies initially provided relief, the patient developed fatal bacterial pneumonia 8 months after SBRT at the site of radiation pneumonitis. We considered SBRT to have possibly contributed to the events leading to the death (Grade 5).

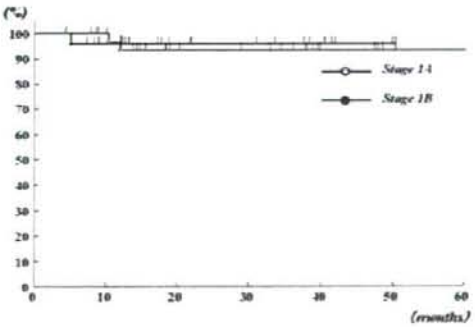

Fig. 2. Local control rates for patients with Stages 1A ($n = 38$) and 1B ($n = 25$) treated with stereotactic body radiotherapy.

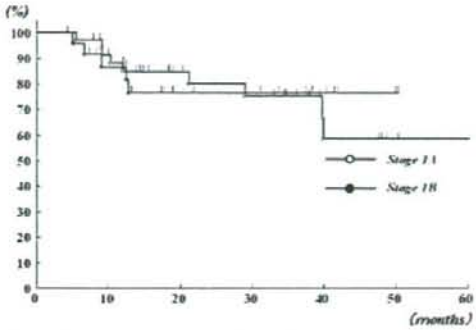

Fig. 3. Disease-free rates for patients with Stages 1A ($n = 38$) and 1B ($n = 25$) treated with stereotactic body radiotherapy.

DISCUSSION

A number of prospective Phase II studies have been conducted exploring SBRT treatment of patients with lung tumors. In the Radiation Therapy Oncology Group (RTOG) 0236 study of patients with inoperable primary lung cancer, the prescribed dose was 60 Gy in three fractions at the PTV periphery (2). In the Japan Clinical Oncology Group (JCOG) 0403 protocol, the total dose of 48 Gy at the isocenter in four fractions was prescribed for patients with T1N0M0 primary lung cancer (1).

Relationship between tumor size and total SBRT dose

Some reports (7–9) have shown the local control rate of T1 tumors to be significantly higher than that of T2 tumors with SBRT. Baumann *et al.* (7) treated 141 patients with 30–48 Gy/two to four fractions. They found local failure to be more frequent for T2 (13%) than T1 tumors (3%). Onimaru *et al.* (8) treated 41 patients with 40 Gy/four fractions or 48 Gy/four fractions. A significant difference was seen in local control between patients with T1 and T2 tumors and between 40 and 48 Gy. They also showed a significant difference in

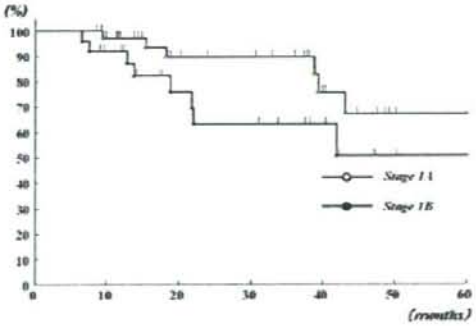

Fig. 4. Overall survival rates for patients with Stages 1A ($n = 38$) and 1B ($n = 25$) treated with stereotactic body radiotherapy.

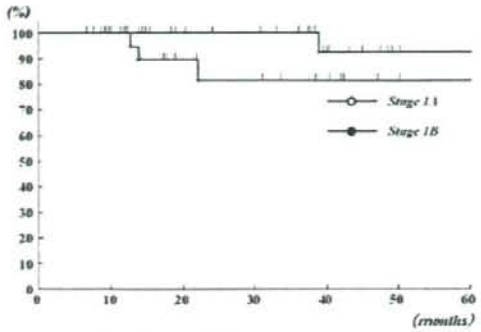

Fig. 5. Cause-specific survival rates for patients with Stages 1A (n = 38) and 1B (n = 25) treated with stereotactic body radiotherapy.

local control between 40 and 48 Gy in patients with Stage IB, but not those with Stage IA. Koto *et al.* (9) treated patients with 45 Gy/three fractions or 60 Gy/eight fractions. The 3-year local control rates were 77.9% (T1) and 40.0% (T2). However, the 3-year local control rate was as high as 96% for both T1 and T2 tumors in our series. These findings suggest that higher doses may contribute to better local control.

Analysis of the biologically effective dose

Table 2 lists methods, treatment factors, and results obtained in this analysis. The biologically effective dose assuming α/β ratios of 10 Gy (BED10) for 50 Gy total in five fractions was 141 Gy. A Japanese multi-institutional retrospective survey showed that a BED10 greater than 100 Gy resulted in significantly better survival and local control than a BED10 less than 100 Gy when SBRT was used to control Stage I NSCLC (10). The range of BED10 in the studies by Onimaru *et al.* (8) and Koto *et al.* (9), which suggested different control rates by tumor volumes, as mentioned, were 80–106 Gy and 105–113 Gy, respectively. These results suggested their treatment regimens to be effective in patients with T1 tumors, while failing to provide adequate control of T2 tumors. Therefore, a BED10 of 100 Gy seems sufficient to control T1 tumors. However, a BED10 greater than 120 Gy, possibly as high as 140 Gy, may be required to control T2 tumors.

PTV definition

Other factors that influence local control are the definition of PTV and the calculation algorithm used. In planning CT, we directly delineate the visualized ITV on an LSTCT (6–8 s/slice) with respiratory motion reduced to less than 10 mm with or without abdominal pressure (5). Recently, we delineated the visualized ITV on a maximum intensity projection image fused with planning CT for more precise visualization (11). Then we added 6–8 mm as a margin to generate the PTV. We adjusted the dose distribution to ensure that 80% of the maximum dose encompassed the PTV. As a result, a prescribed dose of 50 Gy total in five fractions to the

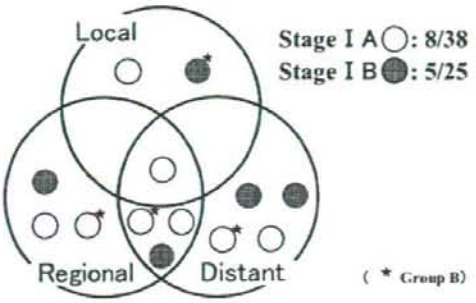

Fig. 6. Recurrence distribution. Eight and five recurrences were identified in patients with Stages 1A (n = 38; white circle) and 1B (n = 25; black circle), respectively. Two (one each, Stages 1A and 1B) were only local recurrences. Three (Stage 1A, one; Stage 1B, two) were only regional recurrences. Four (Stage 1A, two; Stage 1B:, two) were only distant metastases. Three (Stage 1A, two; Stage 1B, one) had combinations of regional recurrence and distant metastases. The other patient (Stage 1A) had combinations of local, regional, and distant recurrence or metastasis. Circles with * indicate cases without pathologic confirmation (Group B).

PTV periphery essentially corresponds to D95 (the minimal dose delivered to 95% of the target volume; data not shown). Giraud *et al.* (12) showed that the CTV margin must be increased to 8 and 6 mm for adenocarcinoma and squamous cell carcinoma to cover 95% of microscopic extension, respectively. However, in our series, the ITV visualized by using LSTCT or maximum intensity projection does not include a CTV margin. We use a CT scanner and a linear accelerator installed in the same treatment suite that share a common table/couch (13). For every treatment, we identify the isocenter position by means of LSTCT with a 2-mm thickness and 1-mm pitch and set it to the isocenter position of the linear accelerator automatically. Therefore, setup error is very small. We then add 6–8 mm as a CTV margin plus a setup margin to the ITV to generate the PTV.

Calculation algorithm and SBRT

In previous SBRT studies, tissue heterogeneity has often not been accounted for during dose calculation. Heterogeneity correction was not used in RTOG 0236 (2). Recently, the RTOG physics committee released recommendations for appropriately accounting for heterogeneity in a planning system. The RTOG 0618 will require calculation taking heterogeneity into account. In the JCOG 0403 study, tissue heterogeneity was accounted for in the dose calculation, and the Clarkson or convolution algorithm was used. However, novel algorithms using the dose kernel of model-based calculation with shapes expanded to correspond with heterogeneity around the calculation point, such as the superposition algorithm, lead to more precise simulation than conventional algorithms (14, 15).

Haedinger *et al.* (16) compared the pencil-beam and collapsed-cone (CC) algorithms for SBRT. They showed that

Table 2. Protocols for stereotactic body radiotherapy

	Our Study	RTOG0236 (2)	JCOG0403 (1)	Onimaru *et al.* (8)	Koto *et al.* (9)
n	63	—	—	41	31
Prescribed dose (Gy/fractions)	50/5	60/3	48/4	40–48/4	45/3; 60/8
Reference point	PTV periphery	PTV periphery	Isocenter	Isocenter	Isocenter
Calculation algorithm	SP	PB	CL/Conv	CL/SP	BPL
Heterogeneity	Yes	No	Yes	Yes	Yes
Dose at isocenter (Gy/fractions)	62.5/5	67–100/3	48/4	40–48/4	45/3; 60/8
BED10 at isocenter	141	211–426	106	80–106	113/105
3-y LC in T1 (%)	93	—	—	67	78
3-y LC in T2 (%)	96	—	—	31	40

Abbreviations: RTOG = Radiation Therapy Oncology Group; JCOG = Japan Clinical Oncology Group; PTV = planning target volume; BED10 = biologically effective dose assuming α/β ratios of 10 Gy; LC = local control; SP = superposition; PB = pencil-beam; CL = Clarkson; BPL = Batho power low; Conv = convolution.

the average PTV dose coverage decreased by 7.1% and the monitor units calculated to achieve the prescribed dose were 5.4% greater with the CC algorithm. Kunieda *et al.* (17), studying nine small lung tumors, showed that the isocenter dose obtained by using the Fast Fourier Transform convolution algorithm was 7–12% higher than the dose obtained by using the MG-superposition algorithm.

Fogliata *et al.* (15) indicated that algorithms based on pencil-beam convolutions showed a systematic deficiency in managing the presence of heterogeneous media. Conversely, "advanced" algorithms in which electron transport is considered indicated good agreement with respect to the Monte Carlo simulation observed. In particular, CC and MG-superposition indicated fairly similar results for the normal lung model. The MG-superposition for XiO is substantially a CC algorithm implementing a speed utility in which the convolution is performed on a coarse grid when no gradients in density of fluence are present (3, 15).

Miften *et al.* (18) reported that the MG-superposition model predicts a dose closer to that of the Monte Carlo simulation, and it estimates the dose build-down and build-up near tissue interfaces and penumbra broadening more precisely than the Clarkson model (18), which overestimates the dose in the lung. Therefore, the actual doses at the PTV periphery are underestimated when calculated using the Clarkson algorithm, and this may result in inadequate dose distribution at the PTV periphery. In the MG-superposition algorithm, a density-scaling method based on O'Connor's theorem (19) is used to scale the kernels by calculating the average density along the straight-line path between the dose deposition and the interaction voxels (3). However, differences in the calculated dose of 10% or more among various algorithms have been reported (14, 20). For this reason, the MG-superposition algorithm is preferred to the Fast Fourier Transform convolution or Clarkson algorithm, which can result in underdosage of the lung tumor by almost 10% (3, 14, 18).

We have used the MG-superposition algorithm for the XiO radiation treatment planning system in planning SBRT of the lung since 2001. Our protocol involves prescribing a dose to the periphery of the PTV. Therefore, the dose we administered was apparently higher than the corresponding dose calculated by using the Clarkson algorithm, and the dose distribution at the PTV periphery is more sufficient.

Dose–volume and toxicity in SBRT

Radiation pneumonitis higher than Grade 1 was observed in 3 patients (5%) in this series. The toxicity rate was low (10, 21, 22), and SBRT seemed to be feasible. However, 1 patient developed fatal bacterial pneumonia associated with radiation pneumonitis. Four patients in the study by Timmerman *et al.* (2) also experienced fatal bacterial pneumonia, and they concluded that their regimen should not be used for patients with tumors near the central airways because of excessive toxicity. In the patient with Grade 5 toxicity in our study, a tumor 5.3 cm in diameter was located at the periphery of the left segment 6 and showed extensive attachment. We speculate that this was a relatively large tumor located not far from the central area, which might have caused the fatal toxicity.

Survival in Stage I primary lung cancer

The 3-year OAS and CSS rates were 90% and 100% in patients with Stage 1A and 63% and 81% in patients with Stage 1B. The 3-year OAS and CSS rates in operable patients were 91% and 91%, and those in inoperable patients were 77% and 94%, respectively. In the study by Nagata *et al.* (23), the 3-year OAS rates in patients with Stages 1A and 1B were 83% and 72%, respectively. In the study by Uematsu *et al.* (24), the respective 3-year OAS rates in patients with Stage 1 and operable patients were 66% and 86%. In the investigation conducted by Onishi *et al.* (10), the 3-year OAS rate in patients with a BED10 greater than 100 was 88%. These SBRT results are consistent among different studies. Conversely, The Japanese Joint Committee of Lung Cancer Registry investigated prognosis in 6,644 patients who underwent resection for non–small-cell cancer histologic type (25). The 5-year survival rates for patients with clinical Stages 1A (n = 2,423) and 1B (n = 1,542) were 72% and 50%, and the 3-year survival rates for those with clinical Stages 1A (n = 2,423) and 1B (n = 1,542) were 82% and 63%, respectively. According to these results, the outcomes of SBRT may be equivalent to those of surgery. Of course, longer follow-up and more experience with SBRT are needed. In conducting prospective trials comparing survival in operable patients undergoing

SBRT vs. surgery, many other factors will be considered, including pain, length of hospital stay, cost-effectiveness, recurrence site, and salvage therapy with local and systemic therapy.

Significance of omission of mediastinal treatment in SBRT

The role of mediastinal lymph node dissection (MLND) in the staging and treatment of patients with NSCLC remains controversial. In a prospective randomized trial, significantly higher survival rates after MLND were indicated in comparison to mediastinal lymph node sampling in patients with Stage 1 NSCLC (82% vs. 57%) (25). Conversely, Izbicki *et al.* (26, 27) reported that MLND did not influence disease-free survival or OAS in patients with NSCLC. A randomized breast cancer study found that internal mammary node (IMN) removal did not improve survival. The IMN dissection confirmed IMN metastases in 20.5% of patients. However, only 4% of patients had IMN recurrence in the no-dissection group (28, 29).

In SBRT, we ruled out mediastinal lymph node involvement by using enhanced CT and PET-CT. However, the respective accuracy, sensitivity, and specificity of CT were reported to be 70%, 69%, and 69%, and even those of PET/CT were only 85%, 84%, and 84% for evaluating preoperative nodal staging (30). Konaka *et al.* (31) retrospectively reviewed data from 171 patients undergoing resection of peripheral clinical T1N0M0 carcinoma smaller than 2 cm in diameter. Lymph node metastases were noted in 18% of patients (6% N1, 12% N2) and were more frequently associated with tumors 1.5–2.0 cm than with those less than 1.5 cm in diameter (31). Therefore, more frequent mediastinal metastasis was suspected in patients with clinical T2N0M0. In our study, 3-year regional recurrence-free rates in patients with Stages 1A and 1B were 82% and 94%, respectively. After a longer follow-up, more frequent hilar and mediastinal metastasis may occur. Therefore, we must pay close attention to future results, keeping in mind that pathologic metastasis does not always induce visible metastasis, as in the study of IMN dissection in patients with breast cancer (28, 29).

Diagnosis of primary lung cancer and indications for SBRT

We analyzed 11 patients without histopathologic or cytologic confirmation who were given a diagnosis of primary lung cancer based on tumor marker level increase and/or standardized uptake value positivity on FDG-PET (Group B). In Group B, local recurrence alone, regional recurrence alone, both regional and distant metastasis, and distant metastasis alone occurred in 1 patient each. One patient died of primary lung cancer. These rates were not substantially different from those of Group A. However, indications for SBRT in patients lacking histopathologic or cytologic confirmation are controversial. In Group B patients, we attempted transbronchoscopic lung biopsy and/or CT-guided biopsy, but were unable to confirm the malignancy because of failure to obtain an adequate biopsy specimen. Currently, the numbers of very early-stage lung cancers detected by means of CT screening are increasing (32). They include small and ground glass opacity lesions, which are difficult to confirm by means of biopsy. Lagerwaard *et al.* (33) reported outcomes of SBRT for patients with Stage 1 NSCLC. Pathologic confirmation of malignancy was obtained in only 31% of their patients. Patients lacking pathologic confirmation were required to have a new or growing lesion that showed CT characteristics of malignancy and FDG-PET uptake before being accepted for SBRT, and the probability of malignancy was calculated retrospectively (34, 35). Methods of diagnosis or criteria for identifying primary lung cancer other than histopathologic or cytologic confirmation may be needed in the future.

CONCLUSION

The SBRT for primary lung cancer with a dose of 50 Gy total in five fractions to the periphery of the PTV calculated by using a superposition algorithm is feasible. The results of this study indicate that high local control rates are achievable for T2 and T1 tumors and the 3-year OAS rate with SBRT may be equivalent to that of surgery.

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