Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 2, pp. 374–381, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.06.043

CLINICAL INVESTIGATION **Lung**

STEEP DOSE–RESPONSE RELATIONSHIP FOR STAGE I NON–SMALL-CELL LUNG CANCER USING HYPOFRACTIONATED HIGH-DOSE IRRADIATION BY REAL-TIME TUMOR-TRACKING RADIOTHERAPY

RIKIYA ONIMARU, M.D., PH.D.,* MASAHARU FUJINO, M.D.,* KOICHI YAMAZAKI, M.D., PH.D.,† YUYA ONODERA, M.D., PH.D.,* HIROSHI TAGUCHI, M.D.,* NORIO KATOH, M.D.,* FUMIHIRO HOMMURA, M.D., PH.D.,† SATOSHI OIZUMI, M.D., PH.D.,† MASAHARU NISHIMURA, M.D., PH.D.,† AND HIROKI SHIRATO, M.D., PH.D.*

Departments of *Radiation Medicine and †First Internal Medicine, Hokkaido University School of Medicine, Sapporo, Japan

Purpose: To investigate the clinical outcomes of patients with pathologically proven, peripherally located, Stage I non–small-cell lung cancer who had undergone stereotactic body radiotherapy using real-time tumor tracking radiotherapy during the developmental period.

Methods and Materials: A total of 41 patients (25 with Stage T1 and 16 with Stage T2) were admitted to the study between February 2000 and June 2005. A 5-mm planning target volume margin was added to the clinical target volume determined with computed tomography at the end of the expiratory phase. The gating window ranged from ±2 to 3 mm. The dose fractionation schedule was 40 or 48 Gy in four fractions within 1 week. The dose was prescribed at the center of the planning target volume, giving more than an 80% dose at the planning target volume periphery.

Results: For 28 patients treated with 48 Gy in four fractions, the overall actuarial survival rate at 3 years was 82% for those with Stage IA and 32% for those with Stage IB. For patients treated with 40 Gy in four fractions within 1 week, the overall actuarial survival rate at 3 years was 50% for those with Stage IA and 0% for those with Stage IB. A significant difference was found in local control between those with Stage IB who received 40 Gy vs. 48 Gy ($p = 0.0015$) but not in those with Stage IA ($p = 0.5811$). No serious radiation morbidity was observed with either dose schedule.

Conclusion: The results of our study have shown that 48 Gy in four fractions within 1 week is a safe and effective treatment for peripherally located, Stage IA non–small-cell lung cancer. A steep dose–response curve between 40 and 48 Gy using a daily dose of 12 Gy delivered within 1 week was identified for Stage IB non–small-cell lung cancer in stereotactic body radiotherapy using real-time tumor tracking radiotherapy. © 2008 Elsevier Inc.

Real-time tumor-tracking radiotherapy, Stereotactic radiotherapy, Lung cancer.

INTRODUCTION

External beam radiotherapy (RT) using rather a conventional fractionation and total dose has been the standard treatment for Stage I non–small cell lung cancer (NSCLC) in patients who are medically inoperable (1–4). Sibley (5) reviewed clinical data and found that the overall survival rates at 3 years ranged from 17% to 55% using a conventional radical dose and treatment time in conventional RT.

Recently, stereotactic body RT (SBRT) using a high focal dose within a short period for peripheral lung tumors has been reported to produce high local control rates. This treatment has been indicated for Stage I NSCLC and has resulted in survival rates at least as great as those after conventional RT. Hof *et al.* (6) reported a 64% 2-year overall survival rate with a single dose of SBRT. Uematsu *et al.* (7) reported a 66% 3-year overall survival rate. Nagata *et al.* (8) reported an 83% and 72% 3-year overall survival rate for patients with Stage IA and Stage IB, respectively. Onishi *et al.* (9) summarized the results of a Japanese series retrospectively and reported a 47% 5-year overall survival rate. A study from Sweden also showed a 55% 3-year overall survival rate with a high local control rate of 80% (10).

These observations have strongly suggested a steep dose–response curve for the control of NSCLC and resultant survival (11, 12). However, no sufficient dose-response data at the dose level beyond the conventional radiation dose have been available. We have seen high local control rates in retrospective surveys of SBRT for Stage I NSCLC in Japanese

Reprint requests to: Rikiya Onimaru, M.D., Ph.D., Department of Radiation Medicine, Hokkaido University School of Medicine, Sapporo, Japan. Tel: (+81) 11-716-1161, ext. 5977; Fax: (+81) 11-706-7876; E-mail: oni@radi.med.hokudai.ac.jp

Received Feb 4, 2007, and in revised form June 25, 2007. Accepted for publication June 25, 2007.

institutions, but the retrospective nature of the analyses, wide range of dose fractionation, and use of different techniques have prevented us from drawing a dose–response relationship with confidence (9).

We have developed a real-time tumor-tracking RT (RTRT) system and have reported on its reliability and possible uncertainty between 1999 and 2005 (13–17). The appropriate clinical target volume (CTV) margin to cover the gross tumor volume (GTV) and the planning target volume (PTV) margin for the CTV were both critical subjects related to technical developments. During this development stage, we performed a simultaneous dose-finding phase I-II study of high-dose focal irradiation for patients with peripheral NSCLC (18). These confounding variables made it difficult to perform a simple dose-escalation study for the same category of patients. The clinical protocols have had to be revised several times because of the technical and conceptual developments of SBRT during this period.

In this study, we analyzed the clinical outcomes of patients with Stage I NSCLC who underwent SBRT through the RTRT system during this developmental period to shed a light on the dose–response curve of Stage I NSCLC.

METHODS AND MATERIALS

Patients

Between February 2000 and June 2005, 41 patients were diagnosed with pathologically proven Stage I NSCLC and underwent SBRT using the RTRT system at Hokkaido University Hospital. Patients with peripheral tumors, which were located in the lung peripheral to the secondary bronchus, were included. The patient characteristics are given in Table 1. Three patients had a Karnofsky performance status of ≤70. The clinical stage according to the TNM classification of Malignant Tumors, version 6 (19), is given in Table 1. Of the 41 patients, 25 had Stage T1N0M0 and 16 had T2N0M0. The number of medically inoperable patients was 35. The reasons for inoperability were poor lung function in 11 patients, a history of cardiac disease in 9, a history of other cancer in 7, poor renal function in 2, poorly controlled schizophrenia in 1, and old age in 11. No patients received chemotherapy before confirmation of recurrence or metastasis. Follow-up examinations were performed every 3 months in the first year, every 4 months in the second year, and every 6 months thereafter. Patients were examined in the outpatient clinic at the Department of Radiation Oncology and Department of Respiratory Internal Medicine at Hokkaido University Hospital. Acute and late radiation reactions were assessed using the Common Terminology Criteria Adverse Effects, version 3.0. The median follow-up period for patients who were still alive at the last follow-up was 27 months (range, 9–62 months).

Table 1. Patient characteristics

Characteristic	Value
Age (y)	
Median	76
Range	52–85
Gender (*n*)	
Male	28
Female	13
KPS	
Median	90
Range	50–90
T stage (*n*)	
T1	25
T2	16
Pathologic finding	
Adenocarcinoma	30
SCC	10
Large	1
Tumor size (cm)	
Median	2.7
Range	1.0–7.0
Dose (Gy)	
40	13
48	28
Margin	
Wide	31
Narrow	10
Calculation algorithm	
Clarkson	31
Superposition	10

Abbreviations: KPS = Karnofsky performance status; SCC = squamous cell carcinoma.

Radiotherapy

Treatment plans were made using Focus (CMS, St Louis, MO) or XiO (CMS). The RT planning system was changed in April 2004 from Focus to XiO in our institute. The beam energy was 6 MV for 25 patients who were treated after June 2003 when the new RTRT system was installed. Before that, 10- and 4-MV X-rays were available and used for 12 and 4 patients, respectively, with the prototype RTRT system. The 4-MV X-rays were used for small tumors in that period. The dose was prescribed at the center of the PTV. Four to six non–coplanar ports were used. All ports were treated in the same day. The dose fractionation schedule was four fractions within 1 week for all patients.

After insertion of gold markers by bronchoscopy near the tumor (18), a planning computed tomography (CT) scan was taken with the patients in the supine position. Patients were asked to hold their breath at the end of expiration, the point at which a previous study had showed the variation in tumor position was minimal (16). The slice thickness of the planning CT scan was 2 mm near the tumor. The GTV was measured as the portion of the tumor that was visible on CT and whose display conditions were a window width of −700 Hounsfield units and a window level of −1,000 to 1,500. The CTV was equal to the GTV for narrow margin or a 6–8-mm margin to the GTV for a wide margin, after Giraud *et al.* (20) reported the necessity of adding these margins to cover 95% of the tumor. We added a 6-mm CTV margin for squamous cell carcinoma and 8 mm for adenocarcinoma and large cell carcinoma when we used the wide margin in this study. Elective nodal irradiation was not performed.

Usually, the PTV margin is larger in the craniocaudal direction for SBRT, considering that the tumor motion is greater in the craniocaudal direction than in the lateral and anteroposterior directions (8, 21, 22). However, no increase in the PTV margin for the craniocaudal direction was used in this study because the RTRT can reduce the size of the margin for respiratory movement. The PTV was set as the CTV plus a 5-mm margin three-dimensionally throughout the study period. Thus, in patients treated with the narrow margin, the GTV-PTV margin was 5 mm and in patients treated with the wide margin, the GTV-PTV margin was 11 mm for squamous cell carcinoma and 13 mm for adenocarcinoma. The leaf margin to the PTV was 2–5 mm for inclusion of the PTV in an 80% isodose line in dose

distribution. Inhomogeneity was corrected by the Clarkson method in the initial half and by the superposition method in the latter half of the study period. The gating window ranged from ±2 to 3 mm for the lateral, craniocaudal, and anteroposterior directions isotropically.

In our working hypothesis, the appropriate total dose would be 40–48 Gy in four fractions within 1 week. Assuming an α/β ratio of 10 for tumor, 40 Gy in four fractions within 1 week would be equivalent to a conventional radiation dose of 67 Gy using 2-Gy daily fractions. The regimen of 48 Gy in four fractions within 1 week represented a tumor dose equivalent to the standard dose used in non-gated SBRT in Japan (8). The biologically effective dose assuming α/β ratios of 10 Gy (BED_{10}) of 40 Gy in four fractions within 1 week and 48 Gy in four fractions within 1 week was 80 Gy and 105.6 Gy, respectively.

We adapted the continual reassessment approach rather than the serial escalation approach to investigate the appropriate dose and GTV-PTV margin. Because apparently many confronting biases existed owing to the technical and conceptual developments during this period, a strict Bayesian approach was abandoned, and a simple principle was used to determine the levels of dose and margin. First, we started at 40 Gy with a narrow margin. Second, when a local relapse was detected without serious adverse effects, we increased the dose to 48 Gy with a wide margin. Third, the dose was then decreased to 40 Gy, keeping the wide margin when a Grade 3 adverse effect without tumor relapse was detected. Finally, the dose was again increased to 48 Gy with a narrow margin when a local relapse was detected in the third group of patients. Before the relapses or radiation pneumonitis were detected, the same dose and margin had been used for patients sequentially entered into the study.

Using this strategy, between February 2000 and October 2001, 40 Gy with a narrow margin was used for 8 patients. Between November 2001 and May 2004, 48 Gy with a wide margin was used for 26 patients. Between June 2004 and November 2004, 40 Gy with a wide margin was used for 5 patients, and between December 2004 and June 2005, 48 Gy with a narrow margin was used for 2 patients.

As a whole, of 25 patients with Stage T1 tumors, 7 received 40 Gy, 5 with a narrow margin and 2 with wide margin; 18 received 48 Gy, 2 with a narrow margin and 16 with a wide margin. Of 16 patients with Stage T2 tumors, 6 received 40 Gy, 3 with a narrow margin and 3 with a wide margin, and 10 patients received 48 Gy, none with a narrow margin and 10 with a wide margin.

Statistical analysis

The overall actuarial survival (OAS) and cause-specific survival (CSS) rates were calculated from the first day of treatment using the Kaplan-Meier method. Deaths from causes other than lung cancer were counted as censored cases to calculate the CSS. The local control rate was also calculated from the first treatment day. If a tumor was not larger than that on the pretreatment CT scan, it was judged to be controlled. Deaths were counted as censored to calculate the local control rate.

The log–rank test was used to calculate the statistically significant differences in OAS, CSS, and local control rates between T stage (T1 vs. T2), dose (40 vs. 48 Gy), and margin status (narrow vs. wide margin). Stepwise Cox regression multivariate analyses of these covariates were also performed to determine whether the covariates were prognostic for OAS and local control.

The difference of monitor unit (MU) calculated by Clarkson and superposition was re-examined in 19 patients whose plans were available for recalculation. The mean ± standard deviation of MUs calculated by Clarkson and superposition was $(14.5 \pm 1.1) \times 10^2$ MU and $(15.0 \pm 1.1) \times 10^2$ MU, respectively, to give the same dose to the center of the PTV. The difference was statistically significant using a paired t test ($p < 0.001$).

The Statistical Package for Social Sciences, version 11.0 (SPSS, Chicago, IL), was used for statistical analysis.

RESULTS

The OAS rate for all patients at 2 and 3 years was 64% and 47%, respectively. The OAS rate at 3 years for 48 Gy in four fractions within 1 week and 40 Gy in four fractions within 1 week was 53% and 27%, respectively. The CSS rate for all patients at 2 and 3 years was 73% and 53%, respectively. The CSS rates at 3 years for 48 Gy in four fractions within 1 week and 40 Gy in four fractions within 1 week was 77% and 27%, respectively. The local control rate for all patients at 2 and 3 years was 73% and 57%, respectively.

In patients treated with 48 Gy in four fractions within 1 week, the OAS and CSS rate at 3 years was 82% and 88% for those with Stage IA and 32% and 50% for those with Stage IB, respectively (Fig. 1). In patients treated with 40 Gy in four fractions within 1 week, the OAS and CSS rate at 3 years was 50% and 68% for those with Stage IA and 0% and 0% for those with Stage IB, respectively (Fig. 1).

A significant ($p = 0.0011$) difference was found in the OAS between those with Stage T1 ($n = 25$) and Stage T2 ($n = 16$; Fig. 2a). No significant difference was found in OAS between those receiving 40 Gy ($n = 13$) and 48 Gy ($n = 28$), those with a narrow margin ($n = 10$) and a wide margin ($n = 31$), or the Clarkson algorithm ($n = 31$) and superposition algorithm ($n = 10$).

Significant differences were found in CSS between those with Stage T1 and T2 ($p = 0.0059$) and between those receiving 40 Gy and 48 Gy ($p = 0.0327$; Fig. 2c,d). The margin and calculation algorithms did not influence CSS.

A significant difference was seen in local control between those with Stage T1 and T2 ($p = 0.0373$) and between those receiving 40 and 48 Gy ($p = 0.0042$; Fig. 3a,b). Subset analysis showed a significant difference in local control between 40 and 48 Gy in those with Stage IB ($p = 0.0015$) but not those with Stage IA ($p = 0.5811$; Fig. 3c,d). The margin and calculation algorithms did not influence local control.

In 28 patients treated with 48 Gy, the OAS was better for those with Stage IA ($p = 0.0366$) but not CSS ($p = 0.1994$) or local control ($p = 0.9494$) compared with those with Stage IB.

Cox regression analysis examined whether the covariates were associated with OAS and local control. T stage (T1 vs. T2), dose (40 vs. 48 Gy), margin status (narrow vs. wide), and calculation algorithm (Clarkson vs. superposition) were the initial covariates. Of these, T stage was significant for OAS and T stage and dose were significant for local control (Table 2).

No serious radiation morbidity was observed using either dose schedule. Regarding acute radiation morbidity, 2 patients had radiation pneumonitis requiring steroid therapy without continuous oxygenation within 90 days from the last day of RTRT. Their symptoms were relieved by the

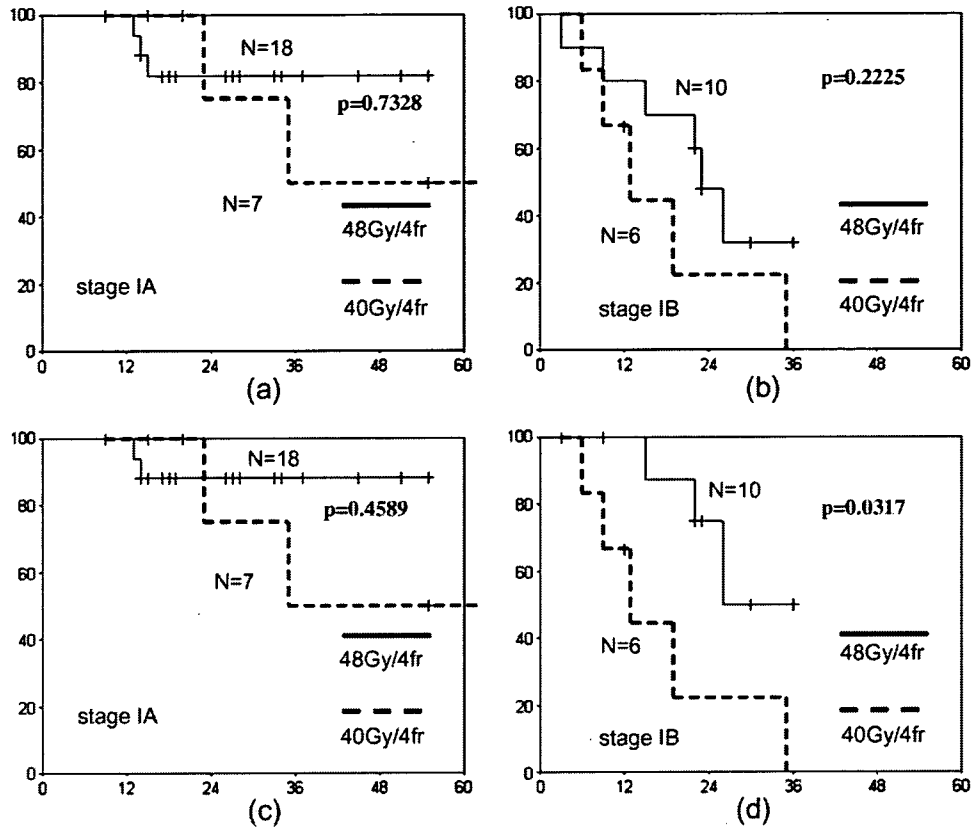

Fig. 1. (a) Overall actuarial survival (OAS) of Stage IA non–small-cell lung cancer (NSCLC) treated with 40 Gy and 48 Gy in four fractions. (b) OAS of Stage IB NSCLC treated with 40 Gy and 48 Gy in four fractions. (c) Cause-specific survival (CSS) of Stage IA NSCLC treated with 40 Gy and 48 Gy in four fractions. (d) CSS of stage IB NSCLC treated with 40 Gy and 48 Gy in 4 fractions.

steroids. Nine patients had late radiation morbidities. Radiation pneumonitis occurred in 4 patients. Of these 4 patients, 1 had received 40 Gy and 3 had received 48 Gy. All 4 had been treated with a wide margin. One patient who had received 48 Gy with a wide margin and one who had received 40 Gy with a wide margin needed house oxygenation therapy, corresponding to Grade 3 morbidity in Common Terminology Criteria Adverse Effects, version 3.0. Both patients had had poor lung function before RT, and one had had pleural effusion after local recurrence as the cause of the oxygen insufficiency. Four patients experienced chest wall pain from radiation pleuritis. Their symptoms were controlled by nonsteroidal anti-inflammatory drugs. Pleural effusion not related to tumor recurrence developed in 3 patients and was well managed conservatively. No significant relationship was observed between the adverse effects and radiation morbidity.

DISCUSSION

To reduce the adverse effects of hypofractionated RT, it is essential to avoid serial-structure organs (*i.e.*, spinal cord, esophagus, main bronchus, and large vessels at the pulmonary hilum and mediastinum) and to reduce the treated volume of parallel-structure organs (23). These goals can be achieved using the concept of SBRT to improve the setup accuracy and X-ray beams focused on tumors. Several image-guided radiotherapy techniques, such as diagnostic CT in the treatment room or megavoltage cone-beam CT, could be useful to reduce interfractional setup errors and to avoid serial-structure organs. The present study showed that SBRT using the RTRT system was equally effective as, but not more effective than, treatment of Stage I NSCLC as SBRT without RTRT using the same prescribed dose, 48 Gy in four fractions for either Stage T1 or T2. The possible benefit of the RTRT system for improving the tumor control rate might appear in situations in which the intrafractional internal organ motion is so large that, when RTRT is used, the actual absorbed dose is greater in the tumor and lower in the normal tissue (24).

Because most Stage I NSCLC disease requires a small PTV, irrespective of the treatment method, no difference was apparent in the adverse effects between our series and other SBRT series. Hof *et al.* (6) reported that no major clinical symptom associated with radiation morbidities was seen with single-dose stereotactic RT of 19–26 Gy. Nagata *et al.* (8) reported that no morbidities of Grade 3 or greater developed after treatment with 48 Gy in four fractions. Our results of 2 patients requiring continuous oxygenation intake was compatible with other investigators' reports on SBRT. Although we should be cautious about these results because of the small number of patents in this series, there seems to be no apparent difference in the occurrence of morbidity compared with other nongated SBRT studies (8, 25).

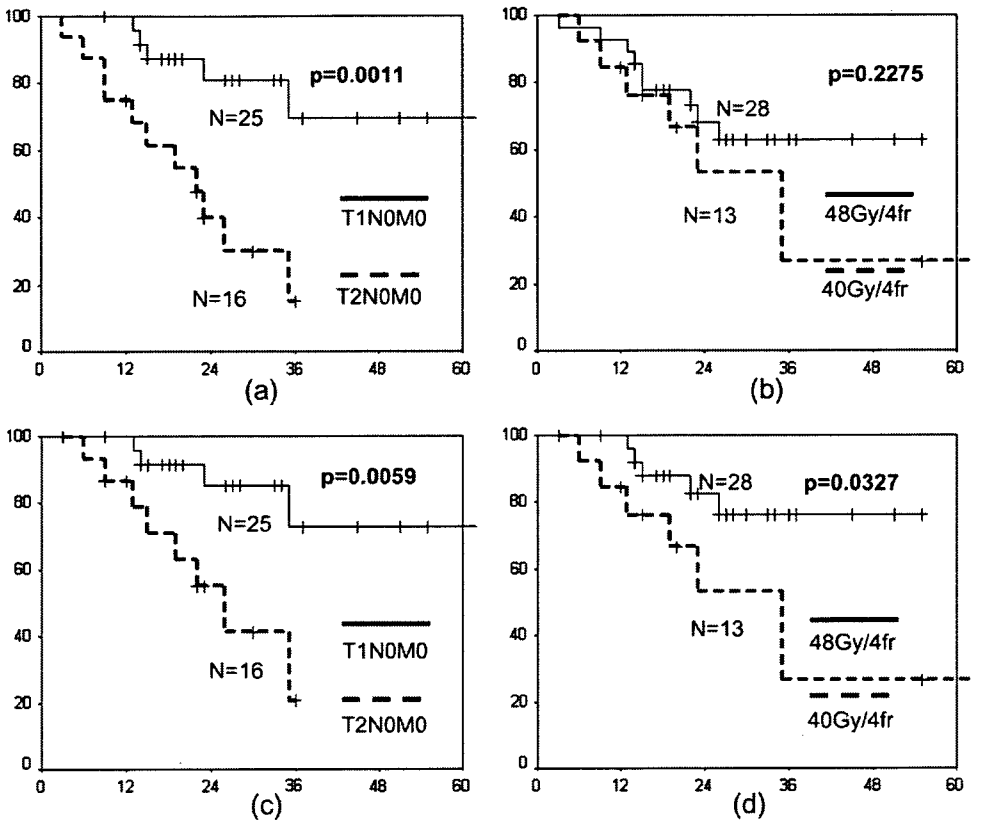

Fig. 2. (a) Overall actuarial survival (OAS) of Stage IA (T1N0M0) and IB (T2N0M0) non–small-cell lung cancer (NSCLC), with significant difference between Stage T1 and T2 (p = 0.0011). (b) OAS of patients treated with 40 Gy and 48 Gy in four fractions. (c) Cause-specific survival (CSS) of those with Stage IA (T1N0M0) and IB (T2N0M0) NSCLC, with significant difference between Stage T1 and T2 (p = 0.0059). (d) CSS of patients treated with 40 Gy and 48 Gy in four fractions, with significant difference between 40 and 48 Gy (p = 0.0059).

Much greater doses would be tolerable for peripheral lung tumors. McGarry *et al.* (25) reported the 72 Gy in three fractions is the maximal tolerance dose for tumors >5 cm. The biologically effective dose assuming α/β ratios of 2 Gy (BED_2) of 72 Gy in three fractions is 936 Gy, much greater than that of 48 Gy in four fractions (336 Gy). However, Fowler *et al.* (26) have shown that we must be careful when increasing the dose and volume in terms of late morbidity with hypofractionated RT. We are planning to start a dose-escalation study for Stage IB NSCLC using a strict stratification for PTV according to the precise prediction of radiation pneumonitis. The possible benefit of using the RTRT system to reduce adverse effects might be seen in a dose-escalation study of tumors with large respiratory motion, such as those in the lower lung field or tumors with large diameters (27).

In this study we were unable to find differences in clinical outcome between a narrow CTV margin and a wide CTV margin. This was possibly because the many confounding prognostic parameters, such as T stage and prescribed dose, masked the difference between the narrow and wide margins. This matter could be answered by a study in which the margin is decreased intentionally using the same CT scanner, dose, and calculation algorithm. However, the rapid improvement in advanced imaging modalities prevented us ethically from use of the same CT scanner. Once we applied the newer and better imaging quality available with CT scanning, the significance of the GTV and CTV margins changed considerably. The uncertainty in the delineation of the GTV in SBRT for NSCLC should be investigated more carefully in accordance with the advances in imaging modalities. We are still not certain that a narrow margin is as good as a wide margin because of the heterogeneity of the patients in this study. We are now using the wide margin and 48 Gy because of the low incidence of adverse effects with the wide margin in the present study.

The superposition algorithm resulted in greater MU for the same prescription dose than with the Clarkson algorithm, but no difference in clinical outcomes was apparent in our series for either tumor control or adverse effects. Because the superposition algorithm is known to have a smaller discrepancy from the measurement in lung tissue, we are now using it in the clinic. However, because of the small number of patients in this study, a careful dose-finding study of the superposition algorithm is still warranted.

In this study, we found a steep dose–response relationship in local control rates between 40 and 48 Gy for Stage I NSCLC. As stated, the BED_{10} of 40 Gy in four fractions within 1 week and 48 Gy in four fractions within 1 week was 80 Gy and 105.6 Gy, respectively. Our results agreed with those of the dose-escalation study at the University of Wisconsin that a total BED_{10} of 90–100 Gy is necessary for

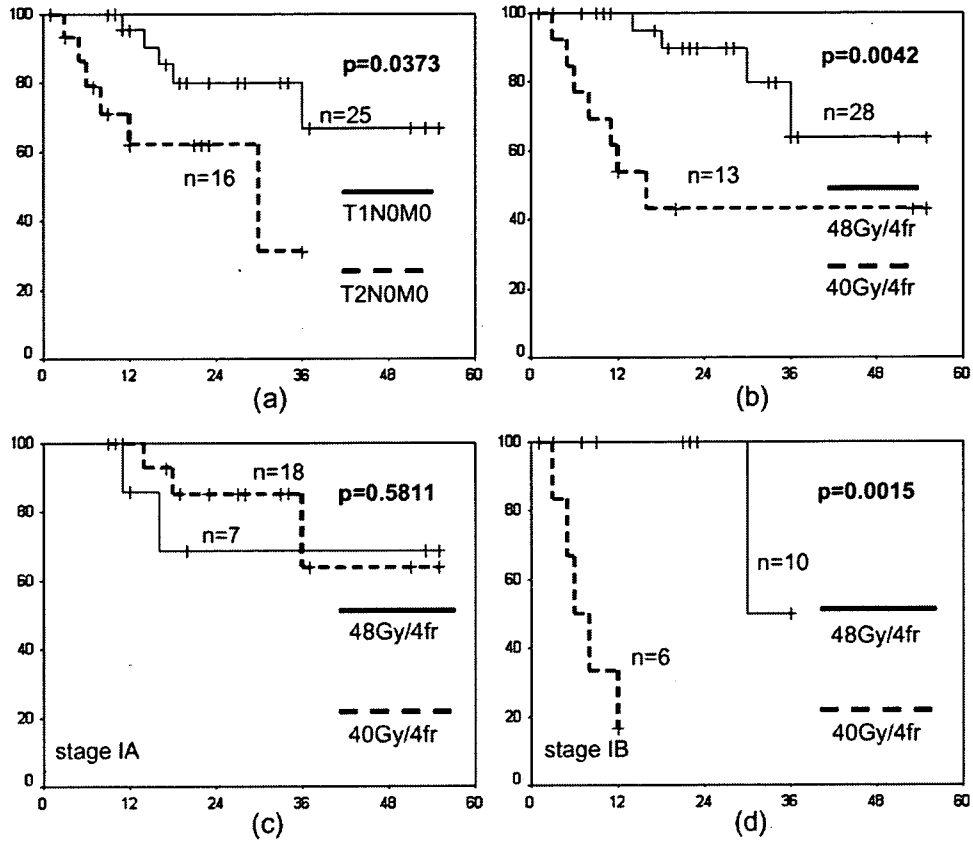

Fig. 3. (a) Local control rate of Stage IA (T1N0M0) and IB (T2N0M0) non–small-cell lung cancer (NSCLC), with significant difference between T1 and T2 ($p = 0.0373$). (b) Local control rate of patients treated with 40 Gy and 48 Gy in four fractions, with significant difference between 40 and 48 Gy ($p = 0.0042$). (c,d) Local control subset analysis. Subset analysis showed significant difference in local control between (d) those receiving 40 and 48 Gy with Stage IB ($p = 0.0015$) but (c) not those with Stage IA ($p = 0.5811$).

Stage I NSCLC control (12). A Japanese multi-institutional retrospective survey has also shown that a BED >100 Gy results in significantly better survival and local control than a BED of <100 Gy for Stage I NSCLC control using SBRT (9). In particular, a large difference was found in local control between 40 and 48 Gy for Stage T2 tumors. A dose of 40 Gy in four fractions within 1 week was strongly suggested to be insufficient for the treatment of Stage IB NSCLC. The number of patients was too small to conclude that 48 Gy in four fractions within 1 week was sufficient for Stage T2 tumors. The small number of patients also prevented finding the difference in the local control rate between those receiving 40 Gy in four fractions within 1 week and 48 Gy in four fractions within 1 week for Stage IA patients.

The 3-year overall survival rate was 55% in the series of Nyman *et al.* (10), 56% in a Japanese experience from 13 institutions (8, 9), and 66% in the series of Uematsu *et al.* (7). The survival rate for those with Stage I NSCLS in our series at 3 years, 47%, was somewhat lower than that in these previous series. One probable reason was that our study was a phase I-II study and included patients treated with the 40 Gy in four fractions within 1 week, for which the BED_{10} was equivalent to conventional RT, 67 Gy in 2-Gy fractions. Sibley *et al.* (5) found that the OAS rates at 3 years ranged from 17% to 55% using conventional RT (median dose, 60–66 Gy) for inoperable Stage I NSCLC. The OAS rate for those receiving 40 Gy in four fractions within 1 week in our study was 27%, within the range of conventional RT. The OAS rate for those receiving 48 Gy in four fractions within 1 week in our study was 53%, consistent with previous studies of SBRT.

Table 2. Cox proportional hazard model

Covariate	B	Standard error	Wald	df	*p*	Exp(B)
T stage	−1.653	0.700	5.582	1	0.018	0.210
Dose	2.003	0.705	8.074	1	0.004	7.409

Nagata *et al.* (8) reported a 3-year OAS and CSS rate of 72% and 83% for 32 patients with Stage IA, and 71% and 72% for 13 patients with Stage IB, respectively, using 48 Gy in four fractions within 2 weeks in their nongated SBRT study. In our series for Stage IA patients treated with 48 Gy, the OAS and CSS rate at 3 years was 82% and 88%, respectively, both greater than the rate reported by Nagata *et al.* (8). However, for those with Stage IB, the OAS and CSS rate at 3 years was 32% and 50%, respectively, both lower than in their series. The apparent difference between the series of Nagata *et al.* (8) and our series of patients with Stage IB was that they included only patients with tumors <4 cm in diameter and we included those with larger

tumors ≤7.0 cm. The small number of patients prevented a meaningful comparison for tumors <4 cm in diameter in Stage IB in our series. The low local control rate for those with Stage IB receiving 48 Gy in four fractions within 1 week in our series can be explained by the diameter of the tumor, although the number of patients was also too small to draw conclusions.

We used the BED based on the linear-quadratic model to define the dose fractionation schedule (9). It might be inappropriate to use the linear-quadratic model to compare the biologic effects of such a large dose per fraction with a 2-Gy daily dose, although Fowler *et al.* (26) reported that the linear-quadratic model fitted the radiation response of epithelial tissues ≤23 Gy/fraction. Tumor proliferation was neglected in our study, and more work is required to answer the question about the linearity between the biologic response and the BED.

A tumor size of >3 cm, or Stage IB, was shown to be a poor prognostic factor for peripheral Stage I NSCLC. This is consistent with the findings of previous studies of surgery (28, 29), conventional RT (30), and SBRT (31). In conventional RT, contradictory results have been reported by Firat *et al.* (32) and Ball *et al.* (33). The T stage did not have a statistically significant effect on the OAS of patients treated with a median dose of 61.2 Gy in the study by Firat *et al.* (32), and Ball *et al.* (33) reported that T stage was not a prognostic factor in patients treated with 60 Gy in 30 fractions within 3 or 6 weeks. The dose used in conventional RT might be insufficient to control even T1 tumors. Thus, there might have been no difference between T stages in prognosis in their series. The small number of patients in our study made it difficult to compare the OAS rate and local control rate between Stage IA and IB patients who received the same dose and margin with the same technological background.

Because we have used gated RT with the RTRT system, the dose distribution in the lung might have been different from that of nongated RT in which organ motion could blur the absorbed dose. If RT with the RTRT system can be performed perfectly, as planned, the dose distribution in the lung should be very close to the static irradiation (13). In nongated RT, the dose at the periphery of the PTV would be sufficient to eradicate microscopic tumor cells located around the GTV but lower than the dose producing radiation pneumonitis. In contrast, the dose at the periphery of the PTV might be too low to eradicate the microscopic tumor cells but great enough to produce radiation pneumonitis in nongated RT. These various possible situations would blur the dose–response curve of tumor control and adverse effects of nongated RT for tumors in motion. In other words, gating is a confounding factor when the clinical outcomes of RTRT are compared with other SBRT methods.

CONCLUSION

A steep dose–response curve between 40 and 48 Gy using a daily dose of 12 Gy delivered within 1 week was identified for local control of Stage I NSCLC, especially for Stage IB NSCLC, using SBRT with the RTRT system. We found that 48 Gy in four fractions within 1 week is a safe and effective treatment for Stage IA NSCLC, achieving an 81.9% and 88.2% OAS and CSS rate, respectively, at 3 years after treatment. Because we have used gated RT with the RTRT system, the dose distribution in the lung could be different from that with nongated RT, for which organ motion could blur the absorbed dose. Our study has confirmed that hypofractionated high-dose RT using a dose beyond that of conventional RT is a logical step forward to treat NSCLC, as long as the adverse effects are tolerable.

REFERENCES

1. Morita K, Fuwa N, Suzuki Y, *et al.* Radical radiotherapy for medically inoperable non-small cell lung cancer in clinical stage I: A retrospective analysis of 149 patients. *Radiother Oncol* 1997;42:31–36.
2. Gauden S, Ramsay J, Tripcony L. The curative treatment by radiotherapy alone of stage I non-small cell carcinoma of the lung. *Chest* 1995;108:1278–1282.
3. Krol ADG, Aussems P, Noorduk EM, *et al.* Local irradiation alone for peripheral stage I lung cancer: Could we omit the elective regional nodal irradiation? *Int J Radiat Oncol Biol Phys* 1996;34:297–302.
4. Lagerwaard FJ, Senan S, van Meerbeeck JP, *et al.* Has 3-D conformal radiotherapy (3D CRT) improved the local tumour control for stage I non-small cell lung cancer? *Radiother Oncol* 2002;63:151–157.
5. Sibley GS. Radiotherapy for patients with medically inoperable stage I nonsmall cell lung carcinoma: Smaller volumes and higher doses—A review. *Cancer* 1998;82:433–438.
6. Hof H, Herfarth KK, Münter M, *et al.* Stereotactic single-dose radiotherapy of stage I non–small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2003;56:335–341.
7. Uematsu M, Shioda A, Suda A, *et al.* Computed tomography-guided frameless stereotactic radiotherapy for stage I non–small-cell lung cancer: A 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666–670.
8. Nagata Y, Takayama K, Matsuo Y, *et al.* Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427–1431.
9. Onishi H, Araki T, Shirato H, *et al.* Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma. *Cancer* 2004;101:1623–1631.
10. Nyman J, Johansson A, Hultén U. Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer–Mature results for medically inoperable patients. *Lung Cancer* 2006;51:97–103.
11. Martel MK, Ten Haken RK, Hazuka MB, *et al.* Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. *Lung Cancer* 1999;24:31–37.
12. Mehta M, Scrimger R, Mackie R, *et al.* A new approach to dose escalation in non–small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2001;49:23–33.
13. Shirato H, Shimizu S, Kitamura K, *et al.* Four-dimensional treatment planning and fluoroscopic real-time tumor tracking

radiotherapy for moving tumor. *Int J Radiat Oncol Biol Phys* 2000;48:435–442.
14. Imura M, Yamazaki K, Shirato H, *et al.* Insertion and fixation of fiducial markers for setup and tracking of lung tumors in radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1442–1447.
15. Seppenwoolde Y, Shirato H, Kitamura K, *et al.* Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;53:822–834.
16. Shirato H, Suzuki K, Sharp GC, *et al.* Speed and amplitude of lung tumor motion precisely detected in four-dimensional setup and in real-time tumor-tracking radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;64:1229–1236.
17. Shirato H, Harada T, Harabayashi T, *et al.* Feasibility of insertion/implantation of 2.0-mm-diameter gold internal fiducial markers for precise setup and real-time tumor tracking in radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;56:240–247.
18. Harada T, Shirato H, Ogura S, *et al.* Real-time tumor-tracking radiation therapy for lung carcinoma by the aid of insertion of a gold marker using bronchofiberscopy. *Cancer* 2002;95:1720–1727.
19. Sobin LH, Wittekind CH, editors, for the International Union Against Cancer. TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss; 2002.
20. Giraud P, Antoine M, Larrouy A, *et al.* Evaluation of microscopic tumor extension in non–small-cell lung cancer for three-dimensional conformal radiotherapy planning. *Int J Radiat Oncol Biol Phys* 2000;48:1015–1024.
21. Uematsu M, Shioda A, Tahara K, *et al.* Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: A preliminary experience. *Cancer* 1998; 82:1062–1070.
22. Timmerman R, Galvin J, Michalski J, *et al.* Accreditation and quality assurance for Radiation Therapy Oncology Group: Multicenter clinical trials using stereotactic body radiation therapy in lung cancer. *Acta Oncol* 2006;45:779–786.
23. Withers HR, Taylor JM, Maciejewski B. Treatment volume and tissue tolerance. *Int J Radiat Oncol Biol Phys* 1988;14: 751–759.
24. Shimizu S, Shirato H, Kagei K, *et al.* Impact of respiratory movement on the computed tomographic images of small lung tumors in three-dimensional (3D) radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;46:1127–1133.
25. McGarry RC, Papiez L, Williams M, *et al.* Stereotactic body radiation therapy of early-stage non–small-cell lung carcinoma: Phase I study. *Int J Radiat Oncol Biol Phys* 2005;63: 1010–1015.
26. Fowler JF, Tome WA, Fenwick JD, *et al.* A challenge to traditional radiation oncology. *Int J Radiat Oncol Biol Phys* 2004; 60:1241–1256.
27. Onimaru R, Shirato H, Fujino M, *et al.* The effect of tumor location and respiratory function on tumor movement estimated by real-time tracking radiotherapy (RTRT) system. *Int J Radiat Oncol Biol Phys* 2005;63:164–169.
28. Naruke T, Tsuchiya R, Kondo H, *et al.* Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: The Japanese experience. *Ann Thorac Surg* 2001;71:1759–1764.
29. Gajra A, Newman N, Gamble GP, *et al.* Impact of tumor size on survival in stage IA non-small cell lung cancer: A case for subdividing stage IA disease. *Lung Cancer* 2003;42:51–57.
30. Kupelian PA, Komaki R, Allen P. Prognostic factors in the treatment of node-negative non–small-cell lung carcinoma with radiotherapy alone. *Int J Radiat Oncol Biol Phys* 1996; 36:607–613.
31. Beitler JJ, Badine EA, El-Sayah D, *et al.* Stereotactic body radiation therapy for nonmetastatic lung cancer: An analysis of 75 patients treated over 5 years. *Int J Radiat Oncol Biol Phys* 2006;65:100–106.
32. Firat S, Bousamra M, Gore E, *et al.* Comorbidity and KPS are independent prognostic factors in stage I non–small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;52:1047–1057.
33. Ball D, Smith J, Wirth A, *et al.* Failure of T stage to predict survival in patients with non–small-cell lung cancer treated by radiotherapy with or without concomitant chemotherapy. *Int J Radiat Oncol Biol Phys* 2002;54:1007–1013.

Radiotherapy and Oncology 85 (2007) 429–434
www.thegreenjournal.com

Lung cancer SBRT

A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer

Masashi Koto[a,*], Yoshihiro Takai[a], Yoshihiro Ogawa[a], Haruo Matsushita[a], Ken Takeda[a], Chiaki Takahashi[a], Keith R. Britton[a], Kei-ichi Jingu[a], Kenji Takai[a], Masatoshi Mitsuya[a], Kenji Nemoto[b], Shogo Yamada[a]

[a]*Department of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan,* [b]*Department of Radiation Oncology, Yamagata University Graduate School of Medicine, Yamagata, Japan*

Abstract

***Background and purpose*: The outcome of stage I non-small cell lung cancer (NSCLC) patients treated with conventional radiotherapy is inferior to that of patients treated surgically. We aimed to evaluate the clinical outcome of stereotactic body radiotherapy (SBRT) in the treatment of stage I NSCLC.**

***Materials and methods*: We performed SBRT for 31 stage I NSCLC patients. Of these, 20 were medically inoperable, and 11 refused surgery. Nineteen tumours were T1-stage masses, and 12 tumours were T2. Median tumour size was 25 mm. SBRT was administered as 45 Gy/3 fractions; however, when the tumour was close to an organ at risk, 60 Gy/8 fractions were used. These doses were prescribed at the centre of the tumours.**

***Results*: The median duration of observation for all patients was 32 months (range, 4–87 months). In 9 of the 31 cases, local recurrence was observed. The 3-year local control rates of T1 and T2 tumours were 77.9% and 40.0%, respectively. The 3-year overall and cause-specific survival rates were 71.7% and 83.5%, respectively. Although the symptoms improved with medical treatment, 5 patients developed acute pulmonary toxicity ⩾grade 2.**

***Conclusions*: SBRT is safe and effective for stage I NSCLC patients. However, a more intensive treatment regimen should be considered for T2 tumours.**

Keywords: Stereotactic body radiotherapy; Non-small cell lung cancer; Stage I; Phase II study; On-board imaging

Since 1998, lung cancer has been the leading cause of cancer death in Japan. In recent years, the number of cases diagnosed at an early stage has increased. This is most likely due to the widespread use of computed tomography (CT) screening [26]. Many lung cancers, however, continue to be detected at an advanced stage. Presently, the first treatment choice for early-stage lung cancer is surgical resection. However, non-small cell lung cancer (NSCLC) frequently occurs in people with an extensive smoking history and other smoking-related diseases, including coronary disease and chronic obstructive pulmonary disease. Accordingly, such patients may be declared medically inoperable and may be referred for radiotherapy. The local tumour control rate for such patients has been 30–60% [12,21,25], which is inferior to that achieved by surgical resection that has a local tumour control rate higher than 90% [15]. Recently, hypofractionated stereotactic radiotherapy, in particular stereotactic body radiotherapy (SBRT), has achieved excellent tumour control in stage I NSCLC [19,22,32]. However, there are insufficient clinical data to determine the optimal SBRT dose and delivery method. In 1998, we initiated a phase II study using SBRT for stage I NSCLC. The aim of this study was to evaluate the local control, survival, and toxicity of SBRT for stage I NSCLC.

Materials and methods

Patient eligibility

All patients included in this study had histological or cytological diagnoses of NSCLC and were staged as Union International Contre le Cancer (UICC) stage IA or IB (up to 5 cm) after appropriate staging studies. All the patients had either a medical contraindication to surgery or refused surgery. Further, all had a performance status of ⩽2 according to the World Health Organization guidelines. Patient eligibility was not restricted on the basis of tumour location, unless a part of the oesophagus, heart, main bronchi, hilus, or skin would be exposed to high-dose radiation of >20 Gy/3 fractions or >40 Gy/8 fractions. For the spinal cord, the restrictive dose was <15 Gy/3 fractions or <30 Gy/8 frac-

0167-8140/$ - see front matter doi:10.1016/j.radonc.2007.10.017

tions. If the treatment plan included these organs in the high-dose areas, the patients were treated with conventional radiotherapy or modified SBRT with a moderate irradiation dose; these patients were excluded from this study. The present study was approved by the Tohoku University Hospital Institutional Review Board, and informed consent was obtained from all patients.

Radiotherapy

The tumours were fluoroscopically observed prior to treatment planning. In cases in which tumour identification was impossible by imaging in 2 directions, a gold marker (Hakko guiding marker system) sized 3.0 × 0.8 mm was transcutaneously inserted in or around the tumour under CT guidance to maintain accuracy and reproducibility throughout the treatment period.

Patients were immobilised in the supine position with an individually fashioned half-body vacuum cast [27]. Both the upper extremities were immobilised in the raised position unless the tumour was located at the apex of the lung, in which case both the upper extremities were immobilised beside the body.

The criterion for using a respiratory-gated system was if fluoroscopic imaging revealed that the tumour moved more than 15 mm. Using the respiratory-gated irradiation system with active breathing control that we developed reduced the range of tumour movement to <5 mm [13].

To determine the extent of tumour movement and establish an individual internal margin (IM), all patients were placed in a simulator for fluoroscopic examination just prior to CT scanning for treatment planning. Serial CT scans were performed at intervals of 3 mm in the target area and 5 mm in the remaining area. When the range of tumour movement was >1 cm, a CT scan with an acquisition time of 4 s that included internal motion was performed to accurately define the IM. When this type of CT scanning was performed, the breathing rate was confirmed to be >15 breaths/min. In the case of respiratory-gated irradiation, CT images for treatment planning were obtained using the respiratory-gated system.

Gross tumour volume (GTV) was defined as the visible extent of the tumour on the CT image at the lung window. The clinical target volume (CTV) was set equal to the GTV. The internal target volume (ITV) was defined by adding the IM to the CTV corresponding to the tumour movement. For CT scanning with an acquisition time of 4 seconds, the ITV was set equal to the CTV. The planning target volume (PTV) was determined by allowing for a set-up margin of 5 mm beyond the ITV.

Treatment planning was performed with non-coplanar multi-dynamic arcs and/or multi-static beams by using a three-dimensional radiotherapy treatment planning system (CADPLAN and Eclipse, Varian Medical Systems, Palo Alto, CA). The modified Batho power law was used as the tissue heterogeneity correction algorithm. The target reference point dose was defined as the centre of the tumour, and the PTV was encompassed by the minimum 90% dose line of the reference point dose. The high-dose area should not include the risk organs previously described. X-rays of 6 MV were used in all treatments.

SBRT requires stricter patient positioning and tumour reproducibility than conventional radiotherapy. This methodology is essential for avoiding the cold regions in the tumour and hot regions in the risk organs. At our institute, SBRT has been performed since 2000 using a unique on-board imaging system, namely, the dual fluoroscopy and flat panel system (DFFP) [28,29,34] to verify the tumour or the implanted gold marker (Fig. 1). This system comprises two conventional diagnostic X-ray tubes that have been mounted directly onto the gantry of the accelerator (Clinac 23EX, Varian Medical Systems, Palo Alto, CA) and two sets of amorphous-silicon (a-Si) flat panel X-ray sensors (PaxScan 2520, Varian Medical Systems, Palo Alto, CA) that are mounted opposite the X-ray tubes. The focal spots of the tubes are located ±45° to the accelerator target, and two sets of a-Si flat panel are located at a gantry position of ±135°on retractable arms that extend from the lower part of the accelerator gantry. The accuracy and stability of this system have been discussed in previous reports [28,29]. The patient's treatment position was confirmed in three perpendicular directions at each treatment session using this system, and the set-up and inter-fractional errors were corrected (less than 1 mm). Before introducing this system, the patient's treatment position was verified using portal films in two directions at each treatment session.

The patients were treated with a radiation schedule of 45 Gy/3 fractions/1 week. However, when the tumour was close to a risk organ, a schedule of 60 Gy/8 fractions/2 weeks was used to reduce the risk of serious toxicity due to set-up error or internal movement.

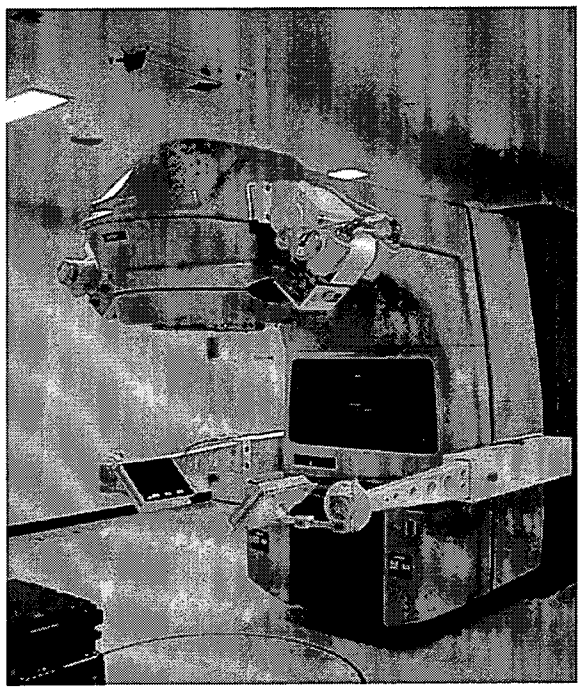

Fig. 1. Dual fluoroscopy with an amorphous-silicon flat panel (DFFP) system.

Follow-up

The first examination, including a clinical examination and CT scanning, was performed 4–6 weeks after treatment to assess the pulmonary reaction. Thereafter, the patients underwent follow-up examinations every 3 months for 2 years following treatment. After 2 years, the follow-up examinations were performed every 3–6 months.

Statistics

Follow-up was determined from the date of the first SBRT to determine the median follow-up and Kaplan–Meier time-to-event estimates of survival and local control data.

Results

Patients

Between March 1998 and December 2004, 34 patients with stage I NSCLS were registered with this study. However, 3 patients were excluded due to dose constraints related to the heart, hilus, and oesophagus, respectively. We treated 31 patients with stage I NSCLC with hypofractionated high-dose SBRT at Tohoku University Hospital (Table 1). Of the 31 patients, 20 were medically inoperable and 11 refused surgery. Further, 25 patients were men and 6 were women. Their median age was 77 years (range, 60–83 years). Their histologies were squamous cell carcinoma (15 patients), adenocarcinoma (12 patients), large cell carcinoma (2 patients), and unclassified NSCLC (2 patients). The median tumour size was 25 mm. Based on the UICC-based TNM classification system, 19 tumours were T1 masses, and 12 were T2. We treated 20 patients with a radiation schedule of 45 Gy/3 fractions/1 week, and 11 patients with a schedule of 60 Gy/8 fractions/2 weeks. The minimal and maximal PTV percent doses per fraction were 90.0% and 109.9%, respectively. The percent doses to 95% of the PTV were 95.8 ± 1.1% (mean ± standard deviation). The respiratory-gated system was used for only 2 patients. The others were irradiated with normal breathing. The median internal motions of the tumours under normal breathing were 11 mm (range, 0–15 mm), 1 mm (range, 0–5 mm), and 3 mm (range, 0–12 mm) in cranio-caudal, medial–lateral, and anterior–posterior directions, respectively. Of the 31 patients, 9 received a gold marker since their tumours were not fluoroscopically observed.

Table 1
Patient and tumor characteristics

Patient's characteristics	
Patients (*n*)	31
Age	
Range	60–83
Median	77
Gender	
Male	25
Female	6
Indication	
Refuse operation	11
Medically inoperable	20
Performance status	
0	18
1	10
2	3
Tumour characteristics	
Histology	
Squamous cell carcinoma	15
Adenocarcinoma	12
Large cell carcinoma	2
Unclassified NSCLC	2
T classification	
T1	19
T2 (≤5 cm)	12
Tumour size (mm)	
Range	10–48
Median	25
Tumour site	
Peripheral	30
Central	1
Radiotherapy	
Prescribed dose	
45 Gy/3 fractions/1 week	20
60 Gy/8 fractions/2 weeks	11
PTV (cm^3)	
Range	4.3–156.9
Median	62.4
Respiratory-gated irradiation	
Yes	2
No	29

PTV, planning target volume.

Local control and patterns of failure

All tumours showed partial or complete response to the SBRT, although it was difficult to determine if the tumour disappeared completely due to the pulmonary fibrosis that developed around it. Of the 31 patients, 9 showed evidence of local recurrence (Table 2). The 3-year local control rates for T1 and T2 tumours were 77.9% and 40.0%, respectively (Fig. 2). The median time to recurrence was 16.2 months (range, 12.7–27.6 months). Local recurrence was defined as local progression that was 1.5 times the dimensions of the original tumour. Some patients underwent positron emission tomography examination to distinguish a local recurrence from localised pulmonary fibrosis due to SBRT.

The recurrence patterns are shown in Table 3. Of the 9 patients with local recurrence, 6 had isolated local failures and the other 3 had simultaneous nodal and/or distant failures. Isolated distant metastases developed in 5 patients.

Survival

All the patients tolerated SBRT very well. The median follow-up period from the time of completion of SBRT was 32 months (range, 4–87 months). Of the 31 patients, 7 died of NSCLC and 5 of intercurrent causes. Of the 7 patients who died with NSCLC, 1 died of an isolated local disease, 1 of a local disease and regional lymph node metastases, 2 of local disease and distant metastases, and 3 of distant metastases. The 3-year overall survival rates were 71.7%, and the cause-specific survival rates after 3 years were 83.5% (Fig. 3).

Table 2
Characteristics of 9 patients with local recurrence

Age (Sex)	Operability	Tumour size (mm)	Histology	PTV (cm^3)	Prescribed dose	Period after treatment (months)
74 (Man)	Yes	35	Adeno	49.7	60 Gy/8 Fr	27.6
66 (Woman)	No	40	SqCC	155.3	60 Gy/8 Fr	24.7
73 (Man)	No	15	Adeno	39.9	45 Gy/3 Fr	22.5
82 (Man)	No	32	SqCC	89.5	45 Gy/3 Fr	12.6
71 (Man)	Yes	23	Adeno	54.5	45 Gy/3 Fr	16.2
80 (Man)	No	22	SqCC	78.7	45 Gy/3 Fr	12.7
80 (Man)	Yes	48	SqCC	156.9	60 Gy/8 Fr	17.0
60 (Man)	No	25	Large	86.6	45 Gy/3 Fr	15.4
82 (Man)	No	35	SqCC	111.7	60 Gy/8 Fr	15.9

PTV, planning target volume; Adeno, adenocarcinoma; SqCC, squamous cell carcinoma; Large, large cell carcinoma; Fr, fractions.

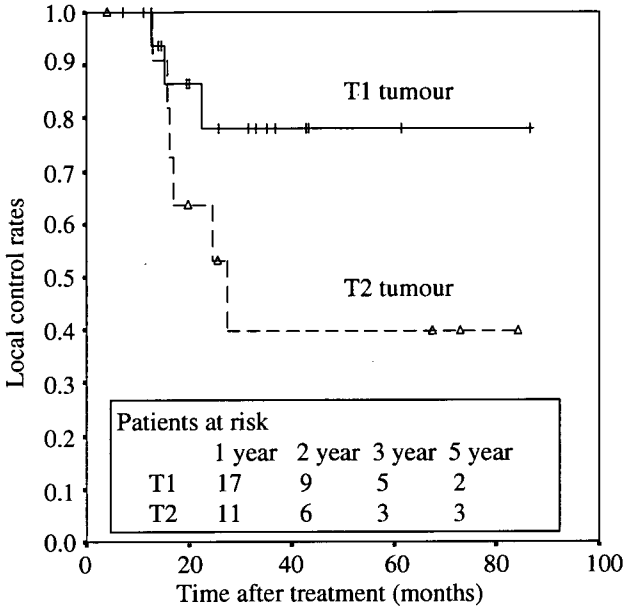

Fig. 2. Local control rates of T1 tumours (n = 19) and T2 tumours (n = 12) treated with stereotactic body radiotherapy. Patients at risk for local failure are given for 1-, 2-, 3-, and 5-year time periods.

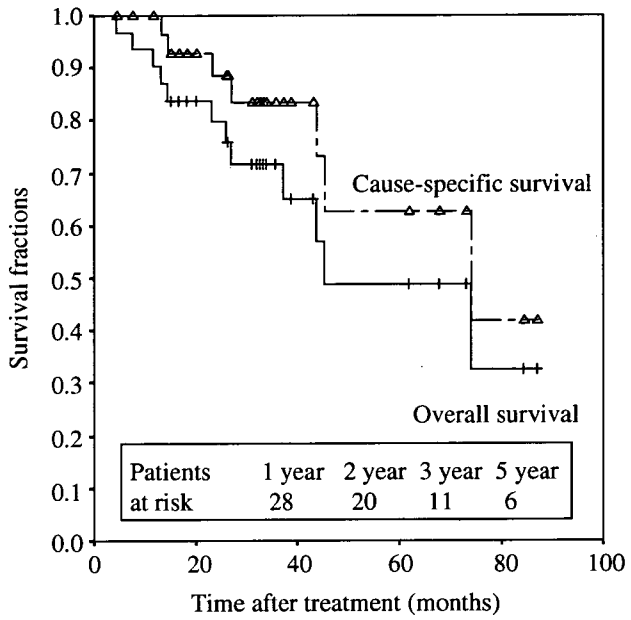

Fig. 3. Overall and cause-specific survival rates in 31 stage I non-small cell lung cancer patients. Patients at risk for failure are given for time periods up to 5 years.

Table 3
Patterns of failure

		T1	T2
Total	31	19	12
Recurrence	14	7	7
Isolated local	6	3	3
Local + L/N	2	0	2
Local + distant	1	0	1
Isolated distant	5	4	1
No recurrence	17	12	5

L/N, regional lymph node.

Toxicity

Acute adverse events were graded using the National Cancer Institute's Common Toxicity Criteria for adverse events version 3.0. Grade 1 acute pneumonitis developed in 24 patients. Grade 2 acute pneumonitis developed in 3 patients, and grade 3 in 1 patient. Two patients did not develop radiation-induced pneumonitis. Patients with grade 2 pneumonitis improved immediately after receiving steroid treatment. The patient with grade 3 acute pneumonitis was treated with oxygen before SBRT due to severe emphysema and needed to increase the flow of oxygen after SBRT. One patient with a tumour that invaded a sub-bronchus needed oxygen treatment temporally due to obstruction in the right upper bronchus that was estimated to be grade 3. No grade 2 or greater toxicity was observed outside the lungs.

Discussion

The optimum protocol of SBRT for NSCLC has not been established, although several protocols and clinical results have been previously reported [16,19,32]. When we de-

signed this protocol, 2 clinical results of SBRT had been reported for stage I NSCLC [1,31]. Both reported excellent local control rates of >90% using 50 Gy/5 fractions [31] and 60 Gy/8 fractions [1]. We calculated biologic effective dose (BED) as $nd[(1 + d/\alpha/\beta)$, where n is the number of fractions, d is the fraction size, and α/β is assumed to be 10 Gy; 50 Gy/5 fractions and 60 Gy/8 fractions were equal to BEDs of 100 Gy and 105 Gy, respectively. Therefore, we used 45 Gy/3 fractions and 60 Gy/8 fractions in this study that were equal to BEDs of 113 Gy and 105 Gy, respectively.

Onishi et al. [22] recently concluded that a BED of $\geqslant$100 Gy was necessary for optimal control in their retrospective multi-institutional study. Hoyer et al. [9] and Baumann et al. [2] reported that SBRT with a BED similar to ours resulted in favourable local control compared with conventional radiotherapy; however, Baumann et al. [2] also showed that the local control rate of T1 tumours was significantly higher than that of T2 tumours. In our study, the local control rate for T1 tumours was 77.9%. Therefore, SBRT at 45 Gy/3 fractions or 60 Gy/8 fractions for T1 tumours is more effective than conventional radiotherapy. However, for T2 tumours, the local control rate was 40.0%, which was lower than expected. However, verification by the log-rank test showed no significant difference between the local control rate of T1 and T2 tumours ($p = 0.111$). Wada et al. [33] analysed the tumour control rate of 42 pulmonary or liver tumours treated with SBRT at 45 Gy/3 fractions and concluded that the tumour control rate for tumours >3 cm in diameter was significantly lower than that for tumours with diameters <3 cm. Fowler et al. [5] suggested that the increase in the hypoxic cell population in lung tumours might correlate with the irradiation dose needed for tumour control. They reported that 3 doses of 23 Gy are required to reduce the surviving population to 10^{-11} if 1% of tumour cells is hypoxic. The increase in the hypoxic cell population due to tumour growth might decrease the control rate of T2 tumours after SBRT. Regarding the total dose of SBRT for NSCLC, it has also been suggested that the total dose delivered in 3 fractions to achieve 80% local control is between a marginal dose of 50 and 72 Gy [16]. Timmerman et al. [30] also reported that the maximal tolerated dose for stage I NSCLC is a marginal dose of more than 60 Gy administered in 3 fractions. In a review of 156 patients with stage I NSCLC, Sibley et al. [25] reported that high-dose radiotherapy showed better local control and survival rates than low-dose radiotherapy. A more intensive treatment regimen should be considered for T2 tumours because no severe toxicity occurred in this study.

Conventional radiotherapy for stage I NSCLC has been reported to achieve a 6–30% 5-year overall survival rate [8,11,12,14,17,21,23,25]. The actual overall survival rate in our study exceeded that reported with conventional radiotherapy; in our study, we achieved 3- and 5-year overall survival rates of 71.7% and 48.9%, respectively, although the median follow-up period was 32 months. In contrast, the 5-year survival rate for stage I patients after surgery has been reported to be approximately between 50% and 80% [4,7,18,20]. Most of our patients were of advanced age (median age, 77 years) and were contraindicated for surgery due to severe complications. Five intercurrent deaths (16.1% of all patients) occurred. These patients died as a result of cerebral infarction, arrhythmia, traffic accident, non-pathological femoral neck fracture or bacterial pneumonia of the non-irradiated lung.

It is reported that the incidence of pneumonitis $\geqslant$grade 3 is less than 10% for patients with stage I NSCLC administered a total dose of 60–70 Gy by conventional fractionation or hyperfractionation [11,24]. However, the rate of grade 3 or higher pneumonitis in SBRT is 5% or less [19,22]. Further, in the present study, only 1 patient (4.3%) developed grade 3 acute pneumonitis. However, the patient with grade 3 acute pneumonitis was not treated with steroids because there was no obvious radiological reason for the shortness of breath. The shortness of breath may have been caused by emphysema progression and not by the SBRT. However, Fujino et al. [6] examined the risk factors for symptomatic radiation pneumonitis ($\geqslant$grade 2) in 156 patients with stage I NSCLC after SBRT and determined that pre-treatment pulmonary function tests (percent vital capacity, forced expiratory volume in 1 second) and dose volume statistics (the percent of the total lung volume exceeding 20 Gy, total dose, BED, dose per fraction, peripheral dose) were not predictive of pneumonitis requiring steroid intake.

One patient developed grade 3 pulmonary toxicity due to an obstruction in the upper bronchus. The upper bronchus was included in the PTV because the tumour was located on and invaded the upper sub-bronchus. Although we excluded patients with a lung tumour on the hilus or main bronchus, SBRT must be carefully administered for patients with a lung tumour at the bronchus level.

The accuracy of tumour verification is crucial for SBRT because hypofractionated high-dose radiation is used and the organ at risk is often close to the tumour. In our study, all tumours were strictly verified. Patients were immobilised in the supine position with an individually fashioned half-body vacuum cast. Skin markers were also referred to for the verification. The X-ray images in 2 directions from a DFFP system were compared with CT planning pictures in the same 2 directions. Verification of the patient's treatment position was performed at each treatment session. Abdominal pressures or respiratory patterns cause interfractional errors for lung tumours when verification is performed on the basis of bone structure [10]. However, it became possible to achieve accurate tumour positioning and reproducibility by using the DFFP system. Britton et al. [3] reported that uncertainty regarding the motion of the prostate could be considerably decreased with daily use of the DFFP system. Therefore, we set a 5-mm set-up margin which appeared to be adequate to overcome set-up errors in our treatment. This system also permitted us to observe the pattern of tumour movement immediately before treatment; this was useful in confirming the coverage of the IM.

In conclusion, current data support the use of SBRT for stage I NSCLC. SBRT for T1 tumours administered in 45 Gy/3 fractions or 60 Gy/8 fractions is safe and effective. However, an appropriate treatment protocol is required, particularly for T2 tumours. Further works regarding SBRT will be necessary.

* **Corresponding author. Masashi Koto**, Department of Radiation Oncology, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aobaku, Sendai 980-8574, Japan. *E-mail address:* koto@rad.med.tohoku.ac.jp

Received 28 February 2007; received in revised form 15 October 2007; accepted 16 October 2007; Available online 26 November 2007

References

[1] Arimoto T, Usubuchi H, Matsuzawa T, et al. Small volume multiple non-coplanar arc radiotherapy for tumors of the lung, head and neck and the abdominopelvic region. In: Lemke HU, editor. CAR'98 computer assisted radiology and surgery. Tokyo: Elsevier; 1998. p. 257–61.

[2] Baumann P, Nyman J, Lax I, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. Acta Oncol 2006;45:787–95.

[3] Britton KR, Takai Y, Mitsuya M, Nemoto K, Ogawa Y, Yamada S. Evaluation of inter- and intrafraction organ motion during intensity modulated radiation therapy (IMRT) for localized prostate cancer measured by a newly developed on-board image-guided system. Radiat Med 2005;23:14–24.

[4] Flehinger BJ, Kimmel M, Melamed MR. The effect of surgical treatment on survival from early lung cancer Implications for screening. Chest 1992;101:1013–8.

[5] Fowler JF, Tome WA, Fenwick JD, Mehta MP. A challenge to traditional radiation oncology. Int J Radiat Oncol Biol Phys 2004;60:1241–56.

[6] Fujino M, Shirato H, Onishi H, et al. Characteristics of patients who developed radiation pneumonitis requiring steroid therapy after stereotactic irradiation for lung tumors. Cancer J 2006;12:41–6.

[7] Gail MH, Eagan RT, Feld R, et al. Prognostic factors in patients with resected stage I NSCLC A report from the Lung Cancer Study Group. Cancer 1984;54:1802–13.

[8] Gauden S, Ramsay J, Tripcony L. The curative treatment by radiotherapy alone of stage I non-small cell carcinoma of the lung. Chest 1995;108:1278–82.

[9] Hoyer M, Roed H, Traberg A, et al. Prospective study on stereotactic radiotherapy of limited-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;66:S128–35.

[10] Hugo G, Vargas C, Liang J, Kestin L, Wong JW, Yan D. Changes in the respiratory pattern during radiotherapy for cancer in the lung. Radiother Oncol 2006;78:326–31.

[11] Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Hyperfractionated radiotherapy alone for clinical stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1997;38:521–52.

[12] Kaskowitz L, Graham MV, Emami B, Halverson KJ, Rush C. Radiation therapy alone for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1993;27:517–23.

[13] Koto M, Takai Y, Nemoto K, et al. Evaluation of intrafractional movement of lung tumor under active breathing control (ABC), and morbidity of lung after respiratory-gated stereotactic radiotherapy using ABC device [Abstract]. Radiology 2004;233:178.

[14] Krol AD, Aussems P, Noordijk EM, Hermans J, Leer JW. Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation? Int J Radiat Oncol Biol Phys 1996;34:297–302.

[15] Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109:120–9.

[16] McGarry RC, Papiez L, Williams M, Whitford T, Timmerman RD. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. Int J Radiat Oncol Biol Phys 2005;63:1010–5.

[17] Morita K, Fuwa N, Suzuki Y, et al. Radical radiotherapy for medically inoperable non-small cell lung cancer in clinical stage I: a retrospective analysis of 149 patients. Radiother Oncol 1997;42:31–6.

[18] Mountain CF. A new international staging system for lung cancer. Chest 1986;89:225S–33S.

[19] Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005;63:1427–31.

[20] Naruke T, Goya T, Tsuchiya R, Suemasu K. Prognosis and survival in resected lung carcinoma based on the new international staging system. J Thorac Cardiovasc Surg 1988;96:440–7.

[21] Noordijk EM, vd Poest Clement E, Hermans J, Wever AM, Leer JW. Radiotherapy as an alternative to surgery in elderly patients with resectable lung cancer. Radiother Oncol 1988;13:83–9.

[22] Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623–31.

[23] Sandler HM, Curran Jr WJ, Turrisi 3rd AT. The influence of tumor size and pre-treatment staging on outcome following radiation therapy alone for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1990;19:9–13.

[24] Sibley GS. Radiotherapy for patients with medically inoperable Stage I non-small cell lung carcinoma: smaller volumes and higher doses – a review. Cancer 1998;82:433–8.

[25] Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 1998;40:149–54.

[26] Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351:1242–5.

[27] Takai Y, Mituya M, Nemoto K, et al. Simple method of stereotactic radiotherapy without stereotactic body frame for extracranial tumors. Nippon Igaku Hoshasen Gakkai Zasshi 2001;61:403–7.

[28] Takai Y, Mitsuya M, Nemoto K, et al. Development of a new linear accelerator with dual X-ray fluoroscopy using amorphous silicon flat panel X-ray sensors to detect a gold seed in tumor at real treatment position [Abstract]. Int J Radiat Oncol Biol Phys 2001;51:381.

[29] Takai Y, Mitsuya M, Nemoto K, et al. Development of a real-time tumor tracking system with dmlc with dual X-ray fluoroscopy and amorphous silicon flat panel on the gantry of linear accelerator [Abstract]. Int J Radiat Oncol Biol Phys 2002;54:193–4.

[30] Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946–55.

[31] Uematsu M, Shioda A, Tahara K, et al. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients. Cancer 1998;82:1062–70.

[32] Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys 2001;51:666–70.

[33] Wada H, Takai Y, Nemoto K, Yamada S. Univariate analysis of factors correlated with tumor control probability of three-dimensional conformal hypofractionated high-dose radiotherapy for small pulmonary or hepatic tumors. Int J Radiat Oncol Biol Phys 2004;58:1114–20.

[34] Wong J. Methods to manage respiratory motion in radiation treatment. American Association of Physicists in Medicine (AAPM). Medical physics monograph No. 29. In: Jatinder R Palta, Rockwell Mackie T, editors. Intensity modulated radiation therapy, the state of the art. Madison WI: Medical Physics Publishing; 2003. p. 682–5.

Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 5, pp. 1417–1423, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.05.054

CLINICAL INVESTIGATION **Esophagus**

TEMPORAL CHANGE IN BRAIN NATRIURETIC PEPTIDE AFTER RADIOTHERAPY FOR THORACIC ESOPHAGEAL CANCER

KEIICHI JINGU, M.D.,* KENJI NEMOTO, M.D.,† TOMOHIRO KANETA, M.D.,‡ MINAKO OIKAWA, M.D.,§ YOSHIHIRO OGAWA, M.D.,* HISANORI ARIGA, M.D.,* KEN TAKEDA, M.D.,* TORU SAKAYAUCHI, M.D.,* KEISUKE FUJIMOTO, M.D.,* KAKUTARO NARAZAKI, M.D.,* YOSHIHIRO TAKAI, M.D.,‖ EIKO NAKATA, PH.D.,‖ HIROSHI FUKUDA, M.D.,¶ SHOKI TAKAHASHI, M.D.,‡ AND SHOGO YAMADA, M.D.*

Departments of *Therapeutic Radiology, ‡Diagnostic Radiology, §Cardiovascular Internal Medicine, and ‖Radiological Technology, Course of Health Sciences, Tohoku University School of Medicine, Sendai, Japan; ¶Department of Nuclear Medicine and Radiology, Division of Brain Science, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan; and †Department of Therapeutic Radiology, Yamagata University School of Medicine, Yamagata, Japan

Purpose: To investigate the relationships of plasma levels of brain natriuretic peptide (BNP) with abnormal ^{18}F-fluorodeoxyglucose (FDG) accumulation in the myocardium corresponding to irradiated fields and temporal changes in BNP, which is used as an index of heart remodeling, after radiotherapy for the mediastinum.

Materials and Methods: Brain natriuretic peptide concentrations were measured before and after radiotherapy for thoracic esophageal cancer, and the change in BNP concentration after radiotherapy was investigated. Moreover, FDG accumulation in the myocardium was investigated in patients who had undergone FDG positron emission tomography less than 14 days before or after measurement of BNP concentration, and the Mann-Whitney *U* test was used to detect significant difference between BNP concentrations in patients with and without abnormal FDG accumulation corresponding to the irradiated field.

Results: There was significant difference between the levels of BNP in patients without abnormal FDG accumulation in the irradiated myocardium and in patients with abnormal FDG accumulation ($p < 0.001$). The levels of BNP in the 9–24 months after radiotherapy group and in the >24 months after radiotherapy group were significantly higher than the levels in the before radiotherapy group, immediately after radiotherapy group, 1–2 months after radiotherapy group, and control group.

Conclusions: The level of BNP was significantly increased more than 9 months after the start of radiotherapy and was significantly higher in patients who had high FDG accumulation corresponding to the irradiated field. The results of this study indicate that BNP concentration might be an early indicator of radiation-induced myocardial damage. © **2007 Elsevier Inc.**

Radiation-induced myocardial damage, Brain natriuretic peptide, MMP-3, FDG-PET, Esophageal cancer.

INTRODUCTION

Outcomes of treatment of malignant tumors have recently improved owing to improvements in techniques of radiotherapy and to the synergic effect of concurrent chemoradiotherapy, and the number of long-surviving patients with esophageal cancer has therefore been increasing (1, 2). Some clinical and pathologic studies have revealed radiation-induced myocardial damage in the late phase. We have also reported heart-related deaths after radiotherapy for early esophageal cancer (3). We have also reported that high accumulation in the base of the left ventricle corresponding to the irradiated field in ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) was often found in patients after irradiation of the mediastinum and that such findings were radiation-induced microcirculation injury of the myocardium and indicated the possibility that FDG-PET could detect myocardial damage before completion of interstitial fibrosis (4, 5). Because many patients with such abnormal FDG accumulation showed a high plasma concentration of brain natriuretic peptide (BNP), we have been interested in the abnormalities of BNP after radiotherapy.

Brain natriuretic peptide is an endogenous peptide produced by the heart as a nonactive 108-amino-acid hormone (6–8). BNP concentration has already become a widely accepted index of heart failure or heart remodeling. Brain natriuretic peptide is released from the heart in response to volume

Reprint requests to: Keiichi Jingu, M.D., Department of Therapeutic Radiology, Tohoku University School of Medicine, Seiryo-machi 1-1, Aoba-ku, Sendai 980-8574, Japan. Tel: (+81) 22-717-7312; Fax: (+81) 22-717-7316; E-mail: kjingu-jr@rad.med.tohoku.ac.jp

Conflict of interest: none.

Received Dec 17, 2006, and in revised form May 9, 2007. Accepted for publication May 11, 2007.

expansion and pressure overload, and it is thought that BNP has a cardioprotective effect (9). To our knowledge, however, there has been no report on the relationship of radiation-induced myocardial damage and plasma BNP.

Matrix metalloproteinases (MMPs) are a group of zinc-dependent enzymes that have high affinity for extracellular matrix components. These proteinases play a central role in many biologic processes, such as embryogenesis, wound-healing angiogenesis, and tissue remodeling, and in disease states, such as cancer and atherosclerosis. Twenty-three MMP genes have been identified in humans. Matrix metalloproteinase-3 (MMP-3) has a wide range of degrading capabilities, including capabilities to degrade collagen types III–V and IX, proteoglycans, laminin, and fibronectin. Matrix metalloproteinase-3 might also activate other members of the MMP family, making it a key player in matrix remodeling. The possibility that MMP-3 may be an index of heart remodeling has been reported (10–13).

In the present study, we retrospectively investigated temporal changes in plasma levels of BNP and MMP-3, which are already used as indices of heart remodeling, after radiotherapy for the mediastinum. We also investigated the relationships between abnormal FDG accumulation in the myocardium suggesting radiation-induced myocardial damage in the late phase and plasma levels of BNP and MMP-3.

METHODS AND MATERIALS

Plasma BNP and MMP-3 were measured in a resting state before and after radiotherapy for thoracic esophageal cancer. Patients with severe renal dysfunction were excluded because it is known that BNP concentration is elevated in patients with renal dysfunction. Considering the possibility of BNP being increased by right ventricular load due to radiation-induced lung interstitial change, the serum concentration of Krebs von den Lungen-6 (KL-6), which is used as an index of lung interstitial change, was also measured.

We investigated the correlations between number of months after radiotherapy and BNP, MMP-3, and KL-6 concentrations using scatter diagrams.

The data were classified according to time after radiotherapy into six groups (before radiotherapy, immediately [<1 month] after radiotherapy, 1–2 months after radiotherapy, 3–8 months after radiotherapy, 9–24 months after radiotherapy, and more than 24 months after radiotherapy), and temporal responses after radiation therapy were investigated using the median values of BNP, MMP-3, and KL-6 concentrations in each group. As a control group, BNP, MMP-3, and KL-6 concentrations in 13 patients with cancer who had undergone radiotherapy for organs other than the mediastinum were measured more than 24 months after radiotherapy. In the case of there being more than one value for the same patient in one group, the highest value was used for analysis. Multiple pair-wise comparisons were performed with the Steel-Dwass test.

Correlations between BNP, MMP-3, and KL-6 concentrations were analyzed by Pearson's correlation method.

Moreover, we retrospectively investigated FDG accumulation in the myocardium of patients who had undergone FDG-PET less than 14 days before or after measurement of BNP and/or MMP-3 concentrations, and we used the Mann-Whitney U test to detect significant differences in BNP and/or MMP-3 concentrations between patients with and without abnormal FDG accumulation corresponding to the irradiated field. Statistical significance was defined as a p value of <0.05 in the present study. Commercial software (SPSS 11.0 for Windows; SPSS, Chicago, IL) was used for all calculations.

Informed consent was obtained from all patients, and the study was carried out in compliance with the Helsinki Declaration.

Radiotherapy

We mainly used 10-MV photons from a linear accelerator. The daily fractional dose of radiotherapy was 2.0 Gy, administered 5 days per week. Irradiation was performed using anterior–posterior opposing fields until approximately 40 Gy and then using oblique opposing fields to avoid the spinal cord. Total irradiated prescription dose for the center of gross target volume ranged from 60 to 70 Gy (median, 60 Gy). The target volume was localized for radiotherapy in all patients by CT planning. Dose distribution was calculated by CADPLAN or ECLIPSE (Varian Medical Systems, Palo Alto, CA) with Batho power law correction.

The base of the left ventricular myocardium in all patients was irradiated with 40 Gy by anterior–posterior opposing fields. In patients with middle–lower thoracic esophageal cancer, the basal posterior and inferior of left ventricular myocardium was further irradiated with 20–30 Gy by oblique opposing fields (Figs. 1a and 1b).

Chemotherapy

All of the patients who underwent concurrent chemoradiotherapy received a combination of cisplatin or nedaplatin and 5-fluorouracil, with the expectation of not only an antitumor effect of chemotherapy itself but also a synergetic effect of chemoradiotherapy.

FDG-PET

Positron emission tomography scans were performed 1 h after administration of FDG at a dose of 3.1 MBq/kg using a Biograph PET/CT scanner or ECAT EXACT HR$^+$ PET scanner (Siemens, Hoffman Estates, IL) under the condition of more than 4 h of fasting. Emission scans were performed for 2 min per position. Attenuation corrections were also performed. For semiquantitative analysis of increased FDG uptake lesions and normal myocardium, the maximal standard uptake value (SUV) based on body weight (in grams) was calculated and converted into a value based lean body mass: SUV = tissue activity concentration (Bq/mL)/[administered activity (Bq)/weight (g)]. Cases with higher FDG uptake in the myocardium corresponding to the irradiated field than in other areas were diagnosed as positive findings with agreement of more than two nuclear medicine physicians (Fig. 1c). There were some patients with diffuse high FDG uptake in the myocardium even under the condition of more than 4 h of fasting. In those cases, we could not determine the abnormal focal FDG accumulation. Such patients were enrolled into the group without abnormal FDG accumulation in this study.

RESULTS

Plasma BNP concentrations were measured in 197 patients (179 male, 18 female; median age, 66 years; age range, 48–84 years), plasma MMP-3 concentrations were measured in 168 patients (147 male, 21 female; median age, 66 years; age range, 48–85 years), and serum KL-6 concentrations were measured in 165 patients (141 male, 24 female; median age, 66 years; age range, 48–85 years). The median value of BNP concentrations was 53.4 pg/mL (range, 3.9–585.8 pg/mL), that of MMP-3 concentrations was 56.05 ng/mL (range, 16.9–250.5 ng/mL), and that of KL-6 concentrations

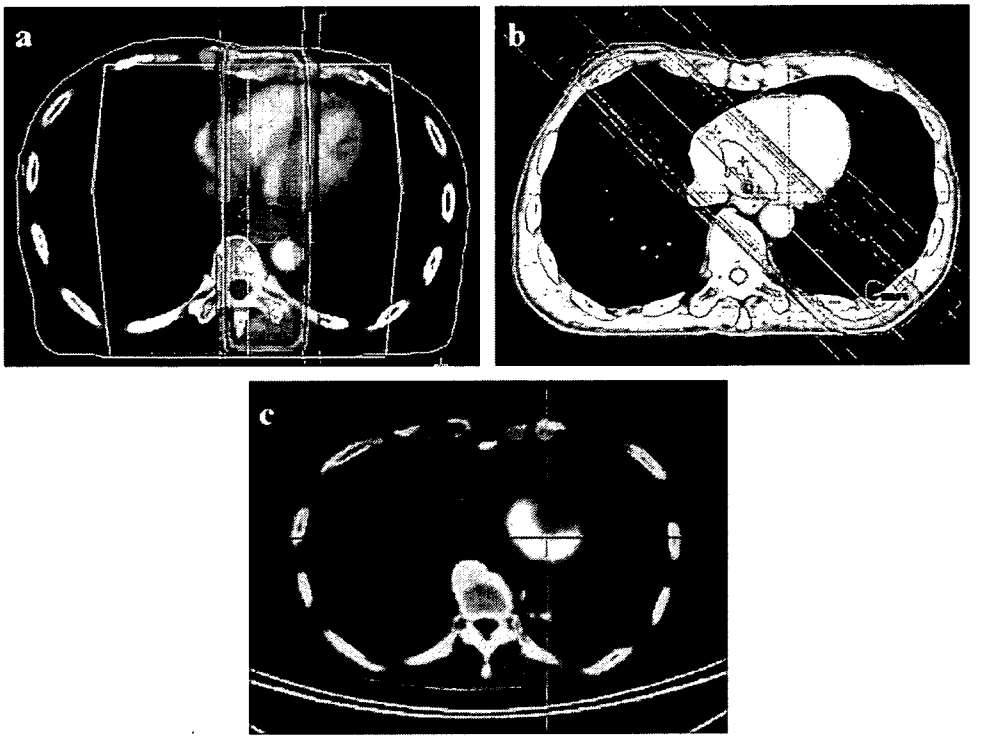

Fig. 1. (a) Dose-distribution axial image by anterior–posterior opposing fields, (b) dose-distribution axial image by oblique opposing fields, and (c) ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT axial image of a patient who had received radiotherapy for lower thoracic esophageal cancer. The base of the left ventricular myocardium in all patients was irradiated with 40 Gy by anterior–posterior opposing fields. In patients with middle–lower thoracic esophageal cancer, the basal posterior and inferior of left ventricular myocardium was further irradiated with 20–30 Gy by oblique opposing fields. On FDG-PET/CT, FDG accumulation was increased in the base of the septum and postinferior wall of the left ventricle, corresponding to the irradiated field.

was 168.0 U/mL (range, 100–933 U/mL). The characteristics of the patients in the present study are shown in Table 1.

Among the 197 patients in whom BNP concentrations were measured, 90 patients underwent FDG-PET within 14 days before or after examination of plasma BNP concentration. There was a significant difference between the BNP level in patients without abnormal FDG accumulation in the irradiated myocardium (72 patients) and that in patients with abnormal FDG accumulation (18 patients) (BNP in patients without abnormal FDG accumulation [mean ± SD]: 61.337 ± 78.577 pg/mL; BNP in patients with abnormal FDG accumulation: 155.978 ± 115.279 pg/mL; $p < 0.001$, Mann-Whitney U test) (Fig. 2a). The 18 patients with abnormal FDG accumulation in the myocardium corresponding to the irradiated field underwent FDG-PET at a median of 17.0 (mean ± SD, 21.5 ± 17.8) months after radiotherapy. FDG-PET scans were performed in 20 patients before radiotherapy in the present study, and none of those patients showed abnormal accumulation in the myocardium.

We performed similar investigations of MMP-3 and KL-6 concentrations, and we found a significant difference between the MMP-3 concentration (59.312 ± 37.6676 ng/mL) in patients without abnormal FDG accumulation in the irradiated myocardium (67 patients) and that (98.911 ± 60.791 ng/mL) in patients with abnormal FDG accumulation (9 patients) ($p = 0.025$, Mann-Whitney U test) (Fig. 2b), but there was no significant difference between KL-6 concentrations (KL-6 in patients without abnormal FDG accumulation: 177.097 ± 79.2044 U/mL; KL-6 in patients with abnormal FDG accumulation: 195.750 ± 95.2302 U/mL; $p = 0.603$, Mann-Whitney U test).

The BNP, MMP-3, and KL-6 concentrations were not significantly correlated with total irradiated dose (≤64 Gy or >64 Gy), history of heart disease including hypertension (yes or no), the main legion of the gross tumor volume (upper thoracic esophagus, middle thoracic esophagus, lower thoracic esophagus, or mediastinal lymph node), or concurrent chemotherapy (yes or no).

Scatter diagrams and regression lines between BNP, MMP-3, and KL-6 concentrations and number of months from the start of radiotherapy were drawn (Fig. 3), and weak but significant correlations were found between plasma levels of BNP and MMP-3 and number of months from the start of radiotherapy (BNP = 56.878 + 1.612 × months, $r = 0.377$, $p < 0.001$; MMP-3 = 59.231 + 0.678 × months, $r = 0.300$, $p < 0.001$). However, there was no significant correlation between serum level of KL-6 and number of months from the start of radiotherapy.

There was a significant correlation only between BNP and MMP-3 (Pearson correlation coefficient = 0.295, $p < 0.001$) among BNP, MMP-3, and KL-6.

The level of BNP in the more than 24 months after radiotherapy group was significantly higher than the levels in the

Table 1. Patient characteristics

Characteristic	BNP	MMP-3	KL-6
Gender			
Male	179	147	141
Female	18	21	24
Age (y)			
Median	66	66	66
Range	48–84	48–85	48–85
Stage			
0	3	3	2
I	56	35	34
IIA–B	31	30	32
III	54	49	49
IVA–B	23	22	20
Postoperative recurrence	29	28	27
Main legion of GTV			
Ut	23	22	25
Mt	113	86	71
Lt	32	32	42
Mediastinal lymph node	29	28	27
No. of months after start of radiotherapy			
Median	5	3.25	3
Range	0–144	0–144	0–144
Prescribed total irradiated dose (Gy)			
≤60	62	56	60
61–66	36	35	40
70	98	77	65
Concurrent chemotherapy			
Yes	158	142	139
No	39	26	25
Abnormal FDG uptake in myocardium			
Yes	18	9	8
No	72	67	62
Unexamined	107	92	95
History of cardiovascular disease			
Yes	53	44	50
No	144	124	115

Abbreviations: BNP = brain natriuretic peptide; MMP-3 = Matrix metalloproteinase-3; KL-6 = Krebs von den Lungen-6; Ut = upper thoracic esophagus; Mt = middle thoracic esophagus; Lt = lower thoracic esophagus; FDG = ^{18}F-fluorodeoxyglucose.

Values are number of patients, unless otherwise noted.

before radiotherapy group, immediately after radiotherapy group, 1–2 months after radiotherapy group, 3–8 months after radiotherapy group, and control group, and the level of BNP in the 9–24 months after radiotherapy group was also significantly higher than the levels in the before radiotherapy group, 1–2 months after radiotherapy group, and control group. However, there was no significant difference among any groups in terms of MMP-3 or KL-6 levels (Fig. 4). The number of patients, age, and BNP, MMP-3, and KL-6 concentrations in each group are shown in Table 2.

DISCUSSION

In our experience, plasma BNP and MMP-3 concentrations increased in many patients who had undergone radiotherapy for the mediastinum. Although increases in the BNP and MMP-3 concentrations had been suspected to reflect remodeling of heart tissue, it is not known whether increases in these concentrations are actually induced by irradiation of the myocardium. Although there are some reports of a correlation between atrial natriuretic peptide (ANP) and radiotherapy (14–16), to our knowledge there is no report on BNP in radiation-induced heart disease. Meinardi *et al.* (17) reported that BNP concentration increased after chemoradiotherapy for breast cancer, though they stated that the increase in BNP concentration was induced by chemotherapy. The body distribution of BNP is different from that of ANP. Although both BNP and ANP remain in existence slightly in the central neural system, ANP is mainly secreted from the atrium and BNP is mainly secreted from the ventricle. The plasma ANP concentration is affected by volume disturbance and body position. Many studies have shown that BNP levels in plasma is more sensitive, specific, and important than ANP as a predictor of cardiac dysfunction in various cardiovascular diseases, such as congestive heart failure, acute myocardial infarction, and essential hypertension (18, 19). We investigated the levels of plasma BNP in patients who underwent radiotherapy for thoracic esophageal cancer, and the results showed that BNP in patients who had undergone irradiation of the heart increased with time.

However, because the present study is a retrospective study using unpaired data, the detailed changes in BNP and MMP-3 after radiotherapy, especially more than 24 months after radiotherapy, are not clear. Prospective studies on changes in biochemical markers after radiotherapy for the mediastinum are necessary.

In the present study, a significant correlation between BNP and MMP-3 was found. There have been few reports on the relationships between BNP and MMP-3. However, some studies have shown that MMP-3 is also secreted at heart remodeling, and the results of the present study are consistent with the results of those previous studies (10–13).

Furthermore, because significant increases in BNP and MMP-3 concentrations were found in patients with abnormal FDG accumulation in the myocardium, the results of this study are also consistent with our past hypothesis that high FDG accumulation in the myocardium corresponding to the irradiated field indicates metabolic change of the myocardium caused by radiation-induced microcirculation disorder (5). Although some patients in the present study had breathlessness and/or chest pain, reduction in left ventricular ejection fraction on ultrasonography has rarely been observed. However, because a kinetic disorder might occur after heart remodeling, radiation oncologists must carefully follow-up patients with such findings.

Heart remodeling is a structural change of the myocardium due to various diseases of the cardiovascular system. Clinical as well as experimental studies have suggested that left ventricular remodeling is an important contributory event in the progression to end-stage congestive heart failure. Although it works as a vicarious mechanism in the early stage, increase in stiffness of the myocardium with protraction of relaxation caused by cardiomyocyte hypertrophy or interstitial fibrosis occurs in the delayed stage, and an

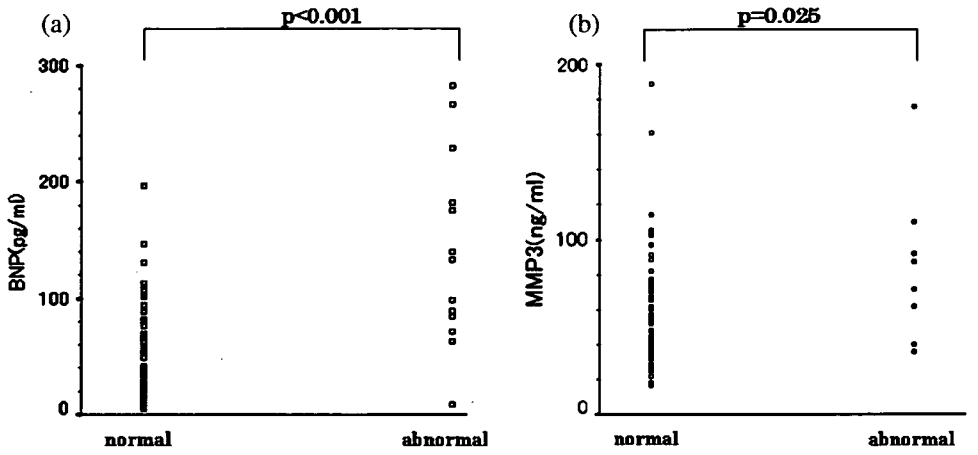

Fig. 2. Scatter diagrams of plasma brain natriuretic peptide (BNP) (a) and serum matrix metalloproteinase-3 (MMP-3) (b) levels in patients without or with abnormal ^{18}F-fluorodeoxyglucose (FDG) accumulation in the irradiated myocardium. There were significant differences between BNP levels and between MMP-3 levels in patients without abnormal FDG accumulation in the myocardium corresponding to the irradiated fields and in patients with abnormal FDG accumulation in the myocardium (Mann-Whitney *U* test).

extended functional disorder or contraction failure may occur. Therefore, excessive remodeling induces acceleration of heart failure in a morbid state, and it is important to control such remodeling. It is thought that actions of natriuretic peptides, including BNP, and their receptor systems are endogenous mechanisms by which heart remodeling is inhibited. Suppression of heart remodeling might prevent symptomatic radiation-induced myocardial damage; the basic research and clinical applications are expected.

Some drugs used in antineoplastic chemotherapy have induced the development of myocardial lesions. Furthermore, it is clear that radiation-induced injury of the heart may be enhanced by some of those compounds. This is particularly true of anthracyclines and specifically of doxorubicin.

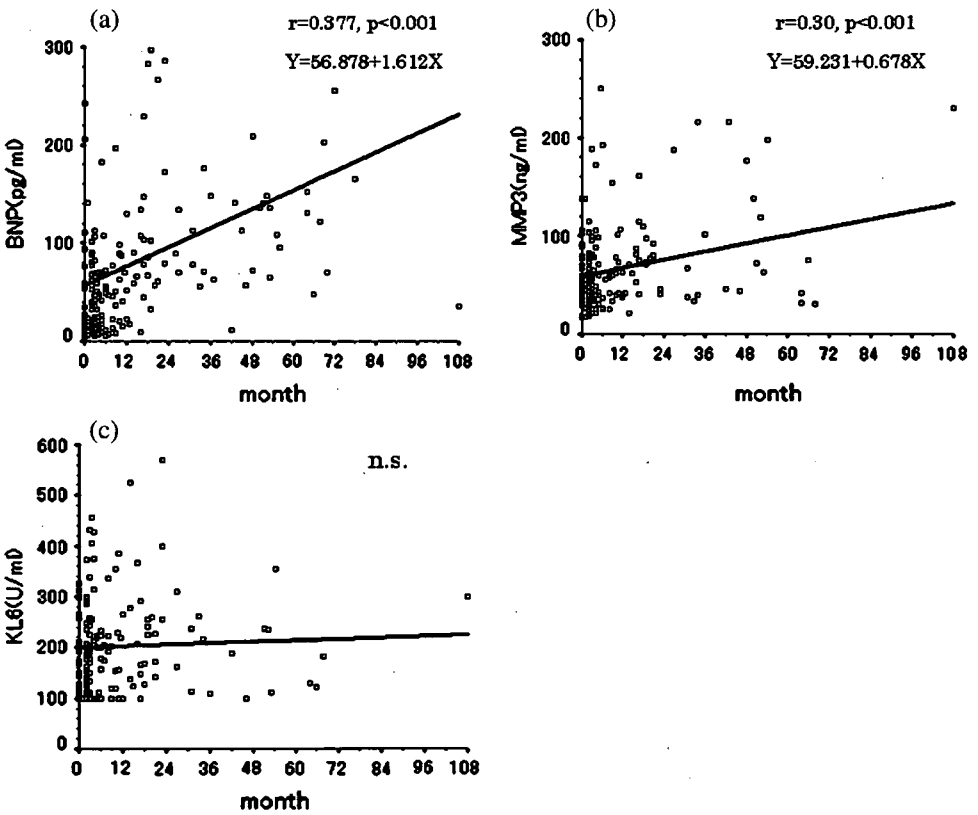

Fig. 3. Scatter diagrams and regression lines between brain natriuretic peptide (BNP) (a), matrix metalloproteinase-3 (MMP-3) (b), and Krebs von den Lungen-6 (KL-6) (c) concentrations and number of months from the start of radiotherapy. There were weak but significant correlations between plasma BNP and MMP-3 concentrations and number of months from the start of radiotherapy. However, there was no significant correlation between serum KL-6 concentration and number of months from the start of radiotherapy.

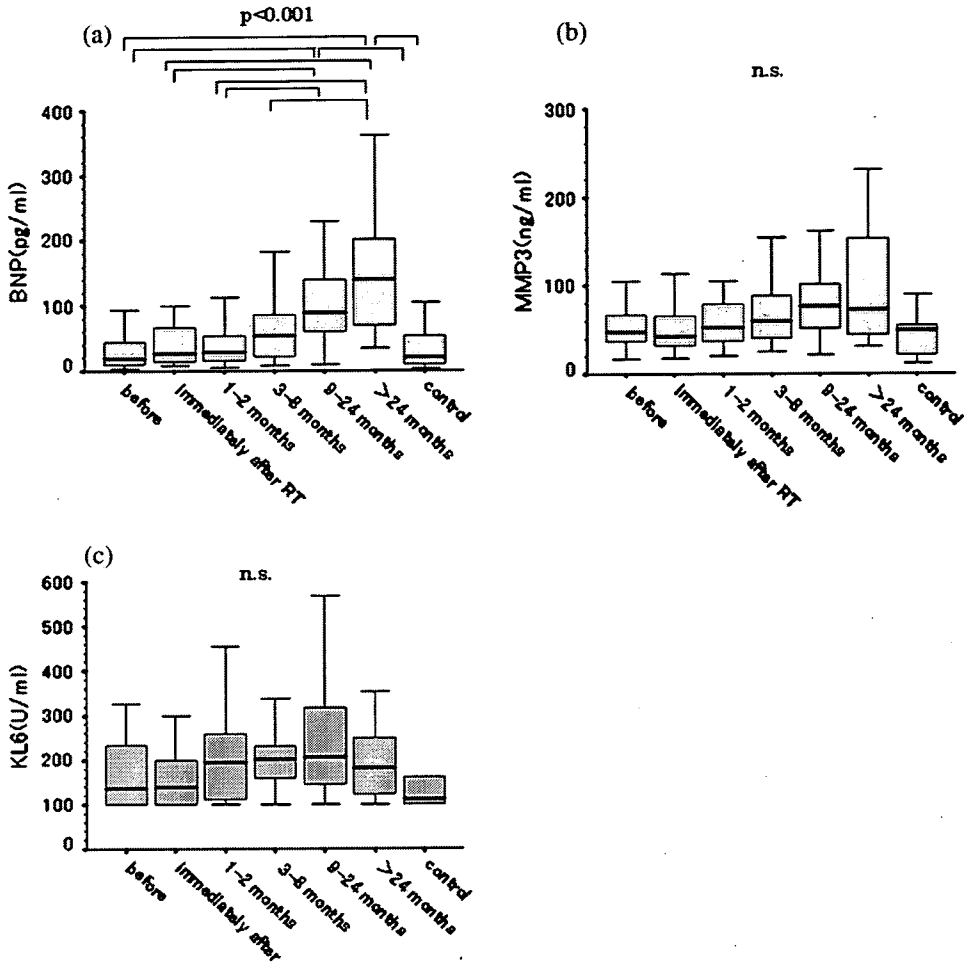

Fig. 4. Box plot of brain natriuretic peptide (BNP) (a), matrix metalloproteinase-3 (MMP-3) (b), and Krebs von den Lungen-6 (KL-6) (c) levels. The level of BNP in the more than 24 months after radiotherapy group was significantly higher than the levels in the before radiotherapy group, immediately after radiotherapy group, 1–2 months after radiotherapy group, 3–8 months after radiotherapy group, and control group, and the level of BNP in the the 9–24 months after radiotherapy group was also significantly higher than the levels in the before radiotherapy group, 1–2 months after radiotherapy group, and control group. However, there was no significant difference among any groups in terms of MMP-3 or KL-6 levels (Steel-Dwass test).

Table 2. Number of patients, age, and BNP, MMP-3, and KL-6 concentrations in each group

		After radiotherapy					
Group	Before RT	<1 mo	1–2 mo	3–8 mo	9–24 mo	>24 mo	Control
BNP							
No.	35	30	24	25	19	25	13
Age (y)	65.4 (50–84)	64.3 (48–83)	66.1 (48–84)	67.6 (48–84)	69.3 (54–82)	67.6 (58–78)	65.2 (46–87)
Concentration (pg/mL)	39.15 ± 54.05	61.32 ± 98.57	38.65 ± 30.63	92.27 ± 125.96	116.24 ± 90.48	160.49 ± 108.33	37.24 ± 41.26
MMP-3							
No.	35	27	24	19	16	16	13
Age (y)	65.3 (48–85)	65.3 (50–85)	66.1 (48–84)	67.7 (48–84)	69.5 (54–82)	66.9 (58–78)	65.2 (46–87)
Concentration (pg/mL)	54.15 ± 26.49	50.52 ± 24.98	60.76 ± 36.96	79.14 ± 59.40	79.16 ± 34.89	99.58 ± 69.18	65.77 ± 44.27
KL-6							
No.	36	36	29	21	15	15	13
Age (y)	66.0 (48–85)	67.0 (50–85)	66.3 (48–85)	69.8 (48–84)	70.3 (54–82)	66.1 (58–76)	65.2 (46–87)
Concentration (pg/mL)	186.19 ± 147.72	166.75 ± 72.15	231.79 ± 137.29	256.05 ± 189.17	250.73 ± 149.46	196.27 ± 82.39	165.23 ± 114.08

Abbreviations as in Table 1.
Values are number, median (range), or mean ± standard deviation.