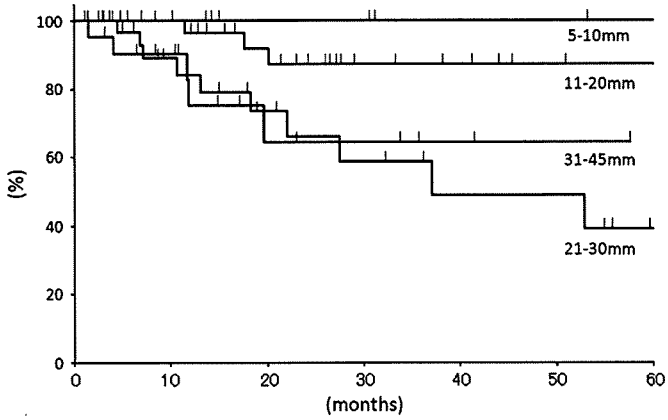

Fig. 1. Kaplan-Meier curve of overall survival rates for the patients with a tumor size (diameter) of 5 to 10 mm (n = 11), 11 to 20 mm (n = 47), 21 to 30 mm (n = 35), and 31 to 45 mm (n = 22).

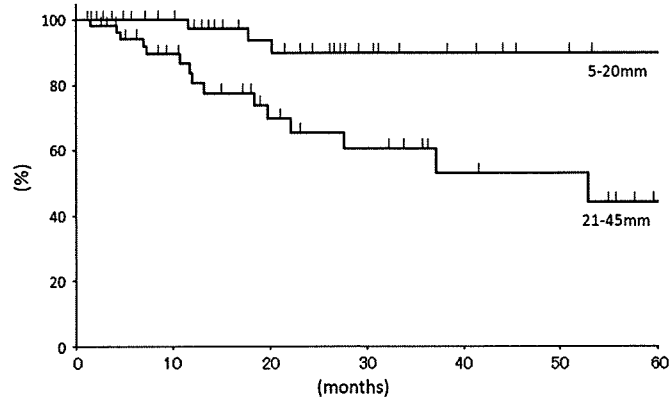

Fig. 2. Kaplan-Meier curve of overall survival rates for the patients with a tumor size (diameter) of 5 to 20 mm (n = 58) and 21 to 45 mm (n = 57). A statistically significant difference was found ($p < 0.0005$) between the two groups.

Ethical considerations

Use of SBRT was approved for Stage I lung cancer by the ethics committee in each institution. Clinically diagnosed Stage I lung cancer was not included in the ineligibility criteria at each institution. Written informed consent to receive SBRT was obtained from all patients. This retrospective study was approved by the ethics committee of each institution and was performed in accordance with the 1975 Declaration of Helsinki, as revised in 2000.

Statistical analysis

Overall survival rates were calculated from the first day of treatment using the Kaplan-Meier method. The log-rank test was used to calculate statistically significant differences. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Survival

We separated the patients into four groups by tumor size at its maximum diameter, consisting of the 5 to 10 mm (Group A; n = 11), 11 to 20 mm (Group B; n = 47), 21 to 30 mm (Group C; n = 35), and 31 to 45 mm (Group D; n = 22) groups. The 3-year and 5-year overall survival rates were both 100% for Group A, both 87.2% for Group B, 58.7% and 48.9% for Group C, and both 64.5% for Group D (Fig. 1). When we excluded the 11 patients whose follow-up period was <4 months, there was no apparent difference in these results; 3-year and 5-year overall survival rates were both 100% for Group A, both 87.2% for Group B, and 58.7% and 39.2% for Group C, and both 67.7% for Group D.

The 3-year and 5-year overall survival rates were both 89.8% for patients with a tumor size ≤20 mm (n = 58) compared with 60.7% and 53.1% for patients with a tumor size >20 mm (n = 57) (p <0.0005; Fig. 2). According to medical operability, the 3-year and 5-year overall survival rates for operable patients (n = 43) were both 88.4%, compared with 67.0% and 60.9% for inoperable patients (n = 72) (Fig. 3). According to BED, the 3-year and 5-year overall survival rates for the patients with BED <100 Gy (n = 17) were both 71.8%, compared with 76.6% and 61.9% for the patients with BED ≥ 100 Gy (n = 98) (Fig. 4).

Local tumor response and distant metastases

Local progression occurred in 2 patients (3.4%) with a tumor size ≤20 mm and in 3 patients (5.3%) with a tumor size >20 mm. Lymphatic and distant metastasis were observed in 3 patients (5.2%) and 6 patients (10.3%) with a tumor size ≤20 mm and in 6 patients (10.5%) and 10 patients (17.5%) with a tumor size >20 mm, respectively. For the patients with BED <100 Gy, no local progression occurred.

Toxicities

Pulmonary adverse effects were graded according to the Common Toxicity Criteria for Adverse Events version 3.0. In brief, radiation pneumonitis was graded as follows: Grade 1, asymptomatic, radiologic findings only; Grade 2, symptomatic, not interfering with activities of daily life (ADL); Grade 3, interfering with ADL, O2 indicated; Grade 4, life-threatening, ventilatory support indicated; and Grade 5, death.

Of patients with a tumor size ≤20 mm in diameter, Grade 2 pulmonary complications were observed in 2 patients (3.4%), whereas no patients experienced Grade 3 to 5 toxicities. In patients with a tumor size >20 mm, Grades 2, 3, and 5 pulmonary toxicities were observed in 5 patients (8.8%), 3 patients (5.3%), and 1 patient (1.8%), respectively. A Grade 5 pulmonary complication occurred in 1 patient with interstitial pneumonia, which resulted in acute worsening from SBRT after 1.5 months. One case of radiation pleuritis, one case of intercostal neuralgia, and one case of rib fracture were observed, but these patients' symptoms were controlled easily by conservative treatment. Grade 2 pulmonary toxicity occurred in 3 cases (17.6%) in patients with BED <100 Gy and in 8 cases (8.2%) in patients with BED ≥100 Gy.

DISCUSSION

There is no doubt that pathologic diagnosis is the most accurate diagnosis for lung tumors. When possible, clinicians

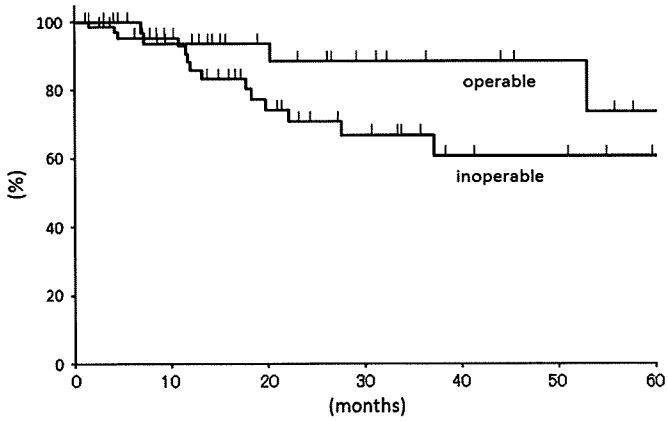

Fig. 3. Kaplan-Meier curve of overall survival rates for operable (n = 43) and inoperable (n = 72) patients. No statistically significant difference was found (p = 0.07) between two groups.

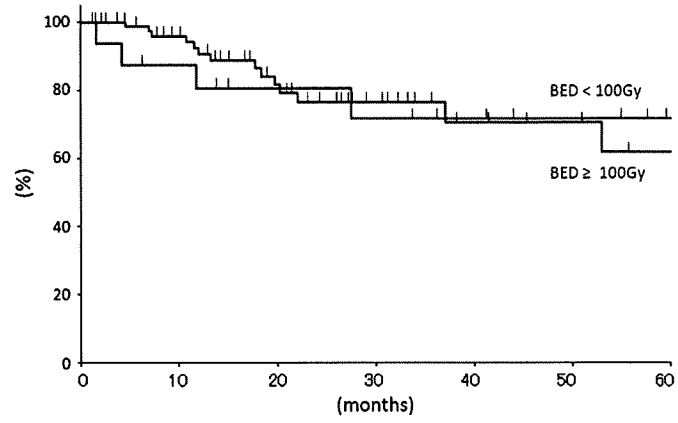

Fig. 4. Kaplan-Meier curve of overall survival rates for the patients with a biologic effective dose (BED) <100 (n = 17) and a BED ≥100 (n = 98). No statistically significant difference was found (p = 0.95) between the two groups.

should persuade patients to receive pathologic confirmation before SBRT and to receive surgical resection if they are operable. However, as we have observed in this retrospective study, for patients with poor respiratory function, pathologic confirmation of the small lung lesions is often difficult or life threatening and occasionally abandoned by pulmonologists and thoracic surgeons. Therefore, it is extremely important to find a subset of patients who would benefit from SBRT instead of the conventional strategy of watchful waiting or elective surgical resection.

In patients with clinically diagnosed lung cancer ≤20 mm in diameter, the 3-year survival rate was 89.8% in our series. Although the median follow-up is still short, the 5-year survival rate was projected to be 89.8% for these patients. Because of the very low complication rate for these patients, SBRT for inoperable patients highly likely to have Stage I lung cancer with tumors ≤20 mm in diameter may be justifiable. However, the excellent survival rates for those patients with tumors ≤20 mm may be partly caused by the inclusion of nonmalignant lesions in the radiation-treated patients. The clinical implications of the high local control rate depend on the accuracy of clinical/radiologic diagnosis for small lung lesions and are to be carefully evaluated in a prospective study.

Median follow-up period 14 months was relatively short, including 11 patients whose follow-up period was <4 months. However, 3- and 5-year survival data were not impacted so much by them because follow-up period of the other patients was much longer.

Onishi *et al.* reported that the patients treated with BED <100 Gy had a tendency to have worse clinical outcomes than those treated with larger dose in SBRT (1). In this study, there were only 17 patients who received BED <100 Gy. There was no significant difference in overall survival rates between those treated with BED <100 Gy and those treated with BED≥100Gy, probably because of the small number of the patients who received BED <100 Gy.

Improvement of clinical/radiologic diagnosis of small lung tumors is essential if SBRT is used for clinically diagnosed Stage I lung cancer. Before the introduction of FDG-PET, the percentage of benign diseases in the solitary lung nodules detected by plain chest X-ray or CT was reported to be 25% to 50%, which is obviously too high (9–12). However, improvement of imaging modalities has made it possible to diagnose small peripheral lung cancer much more precisely than before. There were recent reports that FDG-PET and PET/CT showed 88% to 96.8% sensitivity, 77% to 77.8% specificity, and 91.2% accuracy in diagnosis of primary lung cancer (13, 14). A combination of positive FDG-PET findings, enlargement of the nodule on CT image, and negative laboratory tests for worsening of inflammatory diseases would reduce the false-positive diagnosis of Stage I lung cancer. However, Nomori *et al.* reported that lung nodules that were <10 mm in size or that showed ground-glass opacity on CT image cannot be evaluated accurately by FDG-PET (15). Therefore, for solid round tumors ≤10 mm and those with ground-glass appearance, watchful waiting would be the preferable choice at present, and improvement in diagnostic imaging is warranted. In addition, even if small lung lesions are highly suggestive of primary lung cancer on clinical/radiologic examination, the possibility of small-cell lung cancer (SCLC), for which it is better to be given additional chemotherapy, cannot be excluded. Some tumor markers such as neuron-specific enolase or progastrin-releasing peptide are shown to have relatively high sensitivity and specificity for SCLC (16). Tumor marker screening has the potential to reduce the inclusion of SCLC, although the tumor size may be too small to detect marker elevation.

Recently video-assisted thoracoscopic surgery (VATS) for lung cancer has become a safe and common procedure. In comparison with open surgery, VATS is less invasive and is associated with less morbidity and mortality (17). However, a recent review showed that VATS still has a 3.3% to 13.4% complication rate for surgical biopsy and a 7.7% to 36.6% complications rate for lobectomy (17). In 567 patients with peripheral NSCLC ≤20 mm who were operable as evaluated by cardiopulmonary function tests and had no history of previously treated cancer, the complication rate was reported to be 6.6% for sublobar resection and 7.3% for lobar

resection with 1 operative death (18). In the present SBRT study, for patients with a peripheral lung tumor ≤20 mm who were often inoperable based on cardiopulmonary function tests and who could have a history of previously treated cancer, only 3.4% (2 of 58) experienced Grade 2 pulmonary complications and none experienced Grade 3 to 5 complications. Therefore, although the comparison of the complication between surgery and SBRT is difficult, SBRT can be regarded as a safer treatment than lobectomy using VATS and as safe as biopsy using VATS for patients with a tumor size ≤20 mm. On the contrary, for patients with a tumor size >20 mm, Grade 2, 3, and 5 pulmonary complications were observed in 8.8% (5 of 57), 5.3% (3 of 57), and 1.8% (1 of 57) of study patients, respectively. Because the risk of SBRT is not minimal for these patients, the indication of SBRT for clinically diagnosed Stage I lung cancer with a tumor >20 mm should be very carefully evaluated by members of the cancer board in each institution.

It is important to state that our study does not give any guidance for inoperable patients whose tumors are highly suggestive of benign lesions but that cannot be definitely determined not to be malignant, as this study looks only at those with tumors highly suggestive of malignant lesions. Patients with benign pulmonary lesion such as hamartoma, granulomatous inflammation, and focal fibrosis may require pathologic confirmation because these patients sometimes have tumors highly suggestive of benign lesions but that cannot be definitely determined not to be malignant. At present, it is obvious that VATS should be recommended for operable patients with tumors that are highly suggestive of benign lesions but that cannot be definitely determined not to be malignant, as VATS gives us pathologic confirmation.

CONCLUSION

In conclusion, in clinically diagnosed Stage I lung cancer patients with a tumor ≤20 mm in diameter, SBRT was reasonably safe in this retrospective study. The clinical implications of the high local control rate depend on the accuracy of clinical/radiologic diagnosis for small lung lesions and are to be carefully evaluated in a prospective study.

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SBRT of lung cancer

Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy ☆

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ABSTRACT

Purpose: We evaluated the relationship between the mean lung dose (MLD) and the incidence of radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT), and compared this with conventional fractionated radiation therapy (CFRT).
Materials and methods: For both SBRT ($n = 128$) and CFRT ($n = 142$) patients, RP grade $\geqslant 2$ was scored. Toxicity models predicting the probability of RP as a function of the MLD were fitted using maximum log likelihood analysis. The MLD was NTD (Normalized Total Dose) corrected using an α/β ratio of 3 Gy.
Results: SBRT patients were treated with 6–12 Gy per fraction with a median MLD of 6.4 Gy (range: 1.5–26.5 Gy). CFRT patients were treated with 2 Gy or 2.25 Gy per fraction, the median MLD was 13.2 Gy (range: 3.0–23.0 Gy). The crude incidence rates of RP were 10.9% and 17.6% for the SBRT and CFRT patients, respectively. A significant dose–response relationship for RP was found after SBRT, which was not significantly different from the dose–response relationship for CFRT ($p = 0.18$).
Conclusion: We derived a significant dose–response relationship between the risk of RP and the MLD for SBRT from the clinical data. This relation was not significantly different from the dose–response relation for CFRT, although statistical analysis was hampered by the low number of patients in the high dose range.

Stereotactic body radiation therapy (SBRT) for pulmonary lesions is becoming more widely used following the first clinical experiences described by Blomgren et al. in 1995 [1]. Collaboration of Japanese radiation departments resulted in the publication of encouraging outcomes among stage I lung cancer patients after SBRT [2,3]. In addition, SBRT proved to be an effective treatment for metastases in lung and liver with high tumour control rates being achieved [4,5]. With respect to healthy tissue injury, Timmerman et al. [6] observed a significantly higher toxicity for centrally located tumours compared to peripherally located tumours using similar irradiation schedules. In an analysis of Lagerwaard et al. [7], lowering the fraction dose for centrally located tumours resulted in similar toxicity for central and peripheral tumours. A recent review of Brock et al. [8] evaluating SBRT studies showed limited toxicity, whereas a large heterogeneity of treatment techniques, dose parameters and clinical endpoints is observed between these studies. To extend the applicability of SBRT, knowledge of the dose–toxicity relationship is necessary. However, dose–response evaluations are hampered by the restricted dose range and (consequently) the low number of toxicity events following SBRT. Moreover, the influence of larger fraction dose, shorter overall treatment time and differences in dose distribution on the existing radiobiological models is rather unknown. In addition, patients receiving pulmonary SBRT are a select group of patients with a high comorbidity.

Radiation pneumonitis (RP) is a serious complication which was fatal after SBRT in three of the 25 patients in a recent study of Yamashita et al. [9] after 48 Gy in four fractions. The incidence of RP requiring clinical intervention ranges from 0% to 29% after SBRT [9–14]. Unfortunately, no predictive model to assess the probability of RP is available for SBRT.

The goal of our study was to evaluate the relation between the radiation dose and the occurrence of RP after SBRT. In addition,

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since the relation between lung dose and radiation pneumonitis (RP) is extensively evaluated for CFRT (e.g. [15]), we compared the dose relationship of SBRT and CFRT patients.

Materials & methods

Patients

SBRT patients were irradiated with hypofractionated schedules at the Department of Radiation Medicine of the Hokkaido University School of Medicine, Sapporo, Japan. Clinical data and treatment plans were retrievable for 128 patients treated between April 1998 and December 2005. Follow-up was performed at the outpatient clinic of the Department of Radiation Medicine. Irradiation regimens were 35 Gy in four fractions, 40 Gy in four fractions, 48 Gy in eight fractions, 60 Gy in eight fractions and 48 Gy in four fractions. A subgroup of these patients with a schedule of 40 and 48 Gy in four fractions (n =41) was previously described in a tumour dose–response study [16]. The approach to define appropriate doses and margins for the SBRT patients can be described as a continuous reassessment approach which was dependent on tumour control and toxicity. This has been accurately described previously [16]. Patients with a schedule of 35 Gy in four fractions, 48 and 60 Gy in eight fractions (irradiated before 2000) and patients treated for multiple targets were treated in a similar manner.

Ninety-five SBRT patients were irradiated on one single target. The treatment schedule, diagnosis of RP and the MLD of these patients are listed out in Table 1. Thirty-three patients received irradiations on multiple targets. For 20 patients, the initial radiation treatment consisted of multiple targets that were successively treated (Table 2). For 13 patients, a new treatment plan was made sometime after the initial treatment because of additional pulmonary lesions (Table 3). No time-related recovery of lung tissue was taken into account for these 13 patients. These 33 patients received an individually adapted (i.e. restricted) dose schedule. For all plans (and summed plans in case of re-irradiations), a maximum dose of 46 and 60 Gy (recalculated into 2 Gy per fraction with an α/β ratio of 2 Gy) for the spinal cord and oesophagus, respectively, was allowed. A total dose of 60 Gy/8fr or equivalent dose calculated using LQ model with an α/β ratio = 2 Gy was allowed as maximum dose in the lung.

Patients with a conventional dose per fraction (CFRT) schedule were treated at the Department of Radiation Oncology of the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, The Netherlands. We updated our previous analysis (with 106 patients) by Seppenwoolde [17] to a total of 142 patients. Our update included 86 patients of the dose escalation (DE) study of Belderbos et al. [17]) (with 88 patients). For two patients included in this study, dose data were lost. Of the 58 non-DE patients included in the Seppenwoolde study, we excluded two patients, whose treatment was interrupted and not finished. Therefore, we were able to include 86 patients of the DE study (who were irradiated to a dose of 60.8 and 94.5 Gy with 2.25 Gy per fraction), and 56 patients who were irradiated with a dose of 70 Gy in 2 Gy per fraction.

For both SBRT and CFRT patients, three dimensional (3-D) treatment plans were made. To correct for the effect of dose per fraction, the local dose was converted to the 2 Gy equivalent Normalized Total Dose (NTD) [18] using the linear quadratic (LQ) model [19] with an α/β ratio of 3 Gy. The α/β ratio of 3 Gy was used because in coventional schemes this commonly used [20] and detailed analysis revealed that for SBRT this was the best value to correct for the dose per fraction evaluating RP (data not shown). For the 33 SBRT patients irradiated on multiple lesions, individual plans were summed after NTD corrections and image registration had been performed. From the 3-D dose data, the MLD was calculated as the average corrected dose over the total lung volume (based on CT) excluding the gross tumour volume.

For the SBRT plans, a convolution superposition algorithm for tissue density heterogeneity was used. For the CFRT patients, the inhomogeneity correction was performed using the equivalent-path length (EPL) inhomogeneity correction. The MLD_{EPL} was converted to the MLD according to convolution superposition algorithm using the conversion factor determined by De Jaeger et al. ($MLD = 0.64(MLD_{EPL})^{1.10}$) [21].

The dose–response relationship in the lungs between RP and MLD was modelled by a sigmoid-shaped relation according to Lyman [22] using the TD_{50} representing the dose for a 50% complication probability. The slope of the dose–response relationship is proportional to the reciprocal value of $m \cdot TD_{50}$. Using this model and parameter values, the normal tissue complication probability (NTCP) (i.e. RP) can be calculated from the MLD [23].

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{\infty}^{t} e^{\frac{-x^2}{2}} dx \text{ with } t = \frac{\mathrm{MLD} - \mathrm{TD}_{50}}{m \cdot \mathrm{TD}_{50}}$$

Radiation pneumonitis (RP) was prospectively scored for both SBRT and CFRT patients and was classified according to the NCI-CTC (CTC 2.0) or SWOG criteria. Grade 2 RP was scored for both SBRT and CFRT after steroids had been prescribed for RP symptoms. Grade 3 RP was scored after oxygen was required, and grade 4 was scored for assisted ventilation. Grade 5 was scored after death due to RP.

None of the included SBRT patients who were scored with RP grade 2 used steroids for other pulmonary morbidities than for RP before or after the irradiation. For the CFRT patients, information on pre-treatment use of steroids was not available. For all patients, the diagnosis and grade of RP were determined by the radiation oncologist and by a pulmonologist experienced in the diagnosis of RP.

Statistics

By maximizing the logarithm of the likelihood function of a dataset containing N patients

$$\ln(L) = \ln\left(\prod_{i=1}^{N} L_i\right) = \sum_{i=1}^{N} \ln(L_i)$$

$$= \sum_{i=1}^{N} [\mathrm{ep}_i \ln(P_i) + (1 - \mathrm{ep}_i) \ln(1 - P_i)],$$

Table 1
The total dose, fraction dose, median tumour volume, median MLD, and the incidence of RP for each treatment schedule of the SBRT patients.

Number of patients	Total dose (Gy)	Fraction dose (Gy)	Median tumour volume (cm^3)	Median MLD (Gy)	Number of RP
3	35	8.75	32.8	5.1	1
29	40	10	15.9	5.4	2
15	48	6	12.0	5.5	0
39	48	12	7.7	7.0	4
9	60	7.5	2.6	3.5	0
20	≥2 successively treated lesions		19.5	10.1	5
13	≥2 treated lesions (minimum time interval of 2.8 months)		30.6	7.5	2

Table 2
Treatment schedule, number of irradiated targets, diagnosis of RP, and the MLD of SBRT patients with multiple targets incorporated in one single treatment plan.

Pt	Number of targets	D 1 (Gy)	fr 1	D 2 (Gy)	fr 2	D 3 (Gy)	fr 3	RP	MLD (Gy)
1	2	48	8	48	12				5.5
2	2	40	4	35	4			+	8.0
3	2	48	8	48	8				16.1
4	2	48	4	48	4			+	15.8
5	2	48	4	48	8			+	19.2
6	2	40	4	40	4				17.0
7	2	48	4	48	4				11.0
8	2	40	4	40	4				11.0
9	2	40	4	40	4				8.9
10	2	35	4	35	4				3.7
11	2	35	4	45	15				6.4
12	2	60	8	60	8				4.5
13	2	40	4	50	16				6.9
14	2	48	4	40	8				11.1
15	2	48	8	48	8				10.7
16	2	48	4	60	8			+	10.3
17	2	48	4	48	4				6.9
18	2	48	8	48	8			+	16.2
19	3	40	4	40	4	48	8		5.3
20	3	40	8	35	4	35	4		7.1

Table 3
Treatment schedule, time between subsequent treatments, diagnosis of RP and the MLD of SBRT patients with multiple targets incorporated in different treatment plans.

Pt	Number of treatments	D 1 (Gy)	fr 1	D 2 (Gy)	fr 2	Time 2 (mths)	D 3 (Gy)	fr 3	Time 3 (mths)	D 4 (Gy)	fr 4	Time 4 (mths)	RP	MLD (Gy)
1	2	48	8	30	8	13.3								7.6
2	2	35	4	40	4	9.8								8.9
3	2	40	4	30	8	8.3							+	7.5
4	2	40	4	35	4	4.4								9.2
5	2	60	8	40	4	2.8								8.6
6	3	48	8	35	8	6.3	48	8	6.7				+	18.1
7	3	48	4	30	10	1.4	48	8	13.2					20.6
8	3	60	8	60	8	0.6	60	8	9.1					9.7
9	3	48	8	25	5	0.1	25	5	16.9					8.4
10	4	60	8	40	4	0.7	48	8	10.8	25	5	15.7		13.3
11	4	60	8	35	4	9.7	35	4	9.7	35	4	9.7		10.6
12	4	40	4	40	4	0.1	40	4	0.6	40	4	3.3		26.5
13	4	60	8	48	8	0.0	48	8	21.5	35	4	28.8		13.5

where P_i ($i = 1, \ldots, N$) represents the NTCP of a patient i, and ep_i is the binary outcome (0 = no RP, 1 = RP), the parameters TD_{50} and m of the NTCP model were estimated. Ninety-five percent confidence intervals around m and TD_{50} were calculated using a profile likelihood approach [22]. For each parameter, the confidence interval includes a certain value if twice the difference of the log likelihood evaluated at the maximum likelihood estimate and at the value of interest does not exceed the quantile of a chi-square (χ^2) distribution with one degree of freedom [24]. To determine the confidence interval of the NTCP curve, a similar approach was performed, however, this test was performed with two degrees of freedom.

To test the difference between the fitted NTCP model of SBRT and CFRT, the data of both models were pooled. The NTCP model based on the pooled data (i.e. one TD_{50} and one m) was compared to the NTCP model, whereby the dataset-specific optimized parameters of SBRT and CFRT were included in a two degree of freedom likelihood ratio test [22].

We also compared the empirical incidence of RP across datasets for several non-overlapping dose intervals using Fisher's exact test.

The Hosmer–Lemeshow goodness-of-fit test [25] was used to estimate the goodness of the fit of the fitted NTCP model. Patients were divided into 10 equal bins in increasing order of the estimated NTCP. The χ^2 test statistic was calculated by

$$\chi^2_{HL} = \sum_{i=1}^{10} \frac{(O_i - N_i \cdot \overline{NTCP_i})^2}{N_i \cdot \overline{NTCP_i} \cdot (1 - \overline{NTCP_i})}$$

where N_i is the total number of patients in the ith group, O_i is the total number of events in the ith group, and $\overline{NTCP_i}$ is the mean calculated NTCP in the ith group. The test statistic is compared to a χ^2 distribution with eight degrees of freedom (by definition of the Hosmer–Lemeshow goodness-of-fit test). The null hypothesis is that there is no difference between the observed and expected values of RP. (i.e. large values of χ^2 (and small p values) indicate a lack of fit by the model).

A two-tailed $p < 0.05$ was considered to be statistically significant.

Results

Radiation pneumonitis

Median follow-up was 16.1 months for the SBRT patients and was 13.0 months for the CFRT patients. All 39 events occurred within 6.2 months following treatment for both SBRT and CFRT within a similar time frame. Within this period, four SBRT patients and 18 CFRT patients were censored (Fig. 1).

For SBRT, the crude incidence of RP grade 2 or higher was 10.9% (14 events in the group of 128 patients). Only one SBRT patient was diagnosed with grade 3 RP. Three SBRT patients included in the analysis, received oxygen within the first year after irradiation, and were not scored as having RP because of the uncertainty of diagnosis (one patient had cardiac problems, one patient had a

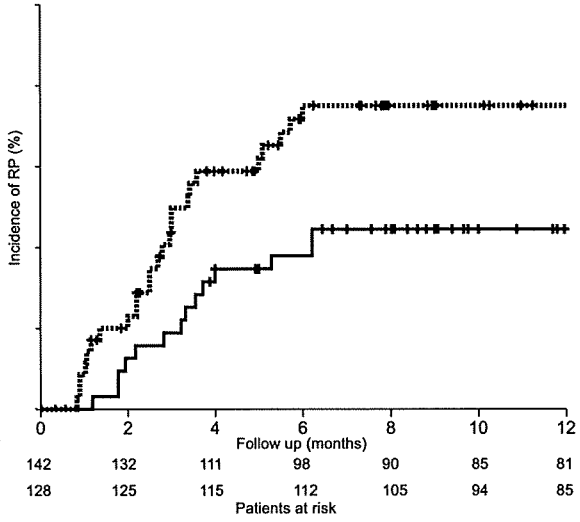

Fig. 1. The incidence of RP as a function of the follow-up (months). Vertical axis: one minus the cumulative RP-free survival. Censored patients are indicated by crosses. The follow-up is given in months on the horizontal axis.

medical history of receiving oxygen before treatment and one patient had fibrosis and tumour progression).

For CFRT, the crude incidence of RP was 17.6% (25 events in the group of 142 patients). Four CFRT patients experienced a grade 3 RP, and one patient died due to pulmonary toxicity (grade 5 RP).

Tumour volume and mean lung dose

The median MLD for SBRT was 6.4 Gy (range: 1.5–26.5 Gy). The median tumour volume of the SBRT patients was 9.6 cm^3 (range: 0.2–106.9 cm^3). For CFRT patients, the median MLD was 13.2 Gy (range: 3.0–23.0 Gy) and the median tumour volume was 61.2 cm^3 (range: 3.8–789.9 cm^3).

Normal tissue complication probability

SBRT

For SBRT, the observed incidence of RP as a function of the MLD is plotted in Fig. 2a. The error bars represent the 68% confidence interval (CI) of the observed incidence in 4 Gy dose bins. The observed number of RP and the total number of patients within each dose bin are indicated. The solid line represents the best fit of the NTCP model based on the MLD. The best parameter values of the NTCP model were TD_{50} = 19.6 Gy (95% CI: 16.0–30.0 Gy) and m = 0.43 (95% CI: 0.33–0.59). The dashed lines represent the 68% CI of the fitted curve.

CFRT

For CFRT, the observed incidence of RP as a function of the MLD is plotted in Fig. 2b. The optimal fit of the NTCP model using MLD resulted in a TD_{50} of 28.6 Gy (95% CI: 21.5–125.0 Gy) and in an m value of 0.56 (95% CI: 0.39–0.99).

SBRT versus CFRT

Both the SBRT model and the CFRT model fitted the clinical data well (χ^2_{HL} = 8.27, p = 0.41 and χ^2_{HL} = 4.36, p = 0.82, respectively).

A comparison of the dose-specific observed RP incidence between SBRT and CFRT revealed that there was no significant difference for any of the six dose ranges covering 4 Gy each. However, RP occurred more frequently in the two highest dose ranges for SBRT compared to CFRT, but this difference was not significant (Table 4). Importantly, lower numbers of patients were included in the higher dose ranges for both SBRT and CFRT, limiting the power of statistical comparison of these particular high dose groups.

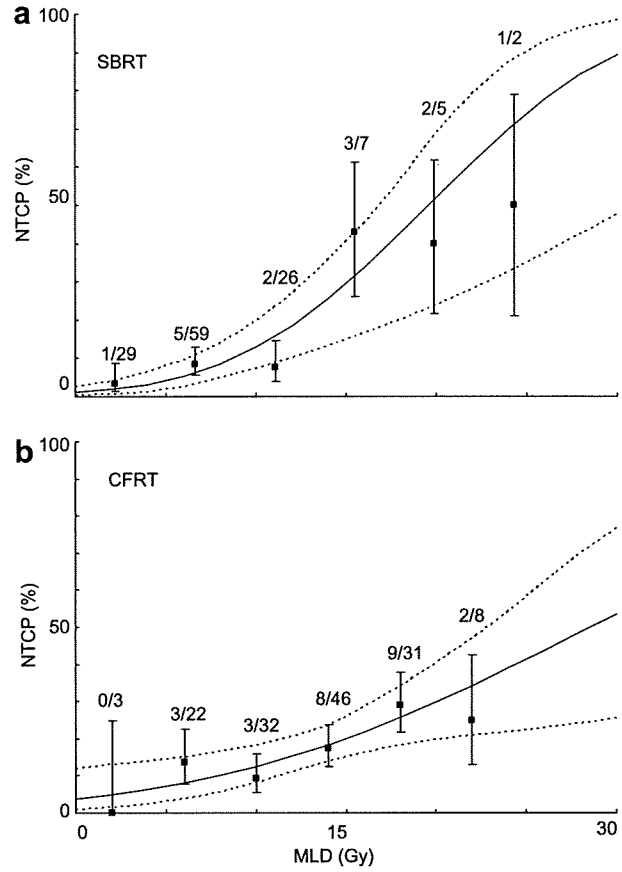

Fig. 2. (a and b) The incidence of grade ⩾2 RP of SBRT (2a)- and CFRT (2b)-irradiated patients as a function of the MLD. The error bars represent the 68% confidence intervals (CIs) of the observed incidence. The solid lines represent the probability of RP according to the NTCP model with the optimized parameters m and TD_{50}. The dotted lines represent the 68% CI of the fitted NTCP curve.

Table 4
Incidence of RP by MLD range and treatment type (SBRT and CFRT).

Dose bin (Gy)	SBRT Number of RP events/total number of patients	CFRT Number of RP events/total number of patients	p-value Fisher's exact test
0–4	0/23 (0%)	0/3 (0%)	0.99
4–8	4/60 (7%)	3/22 (14%)	0.38
8–12	4/28 (14%)	3/32 (9%)	0.70
12–16	1/8 (13%)	4/46 (9%)	0.99
16–20	4/7 (57%)	9/31 (29%)	0.20
20–28	1/2 (50%)	2/8 (25%)	0.46

On evaluating the whole dose range, the NTCP curve of SBRT is steeper for the high dose range suggesting an increased risk for RP after SBRT compared to CFRT for patients with a higher MLD. However, there was no statistical evidence that the fitted NTCP model (with the parameters m and TD_{50}) differed between SBRT and CFRT (p = 0.37, likelihood ratio test). Again, we would like to stress that the statistical power was limited due to lower number of patients in the high dose range.

The optimal fit of the SBRT and CFRT together resulted in a TD_{50} of 24.4 Gy (95% CI: 21.0–32.0 Gy) and in m of 0.49 (95% CI: 0.42–0.61) (Fig. 3).

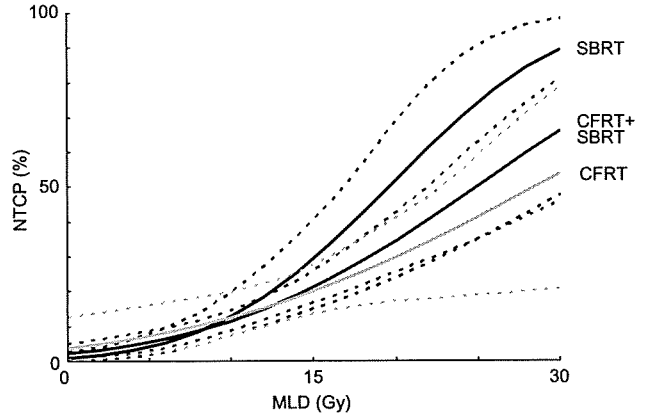

Fig. 3. Fitted NTCP curves (solid lines) and their 68 % confidence intervals (CI) intervals (dashed lines) as a function of the MLD for SBRT (dark grey), CFRT (black) and combined data (light grey) (coloured version available online).

Discussion

A significant relationship between the MLD and the incidence of RP following SBRT was observed. Moreover, the NTCP model fitted the SBRT data well. We observed no significant difference between the NTCP models predicting RP in SBRT and CFRT patients. Furthermore, no significant difference between SBRT and CFRT was observed in the incidence of RP in any dose range. Nevertheless, an increased risk for SBRT in higher dose ranges was suggested by both the NTCP model fit and the observed RP incidences. However, because fewer patients were available in the high dose range no firm conclusions can be made concerning these differences.

At the Department of Radiation Medicine of the Hokkaido University School of Medicine, different SBRT dose schedules have been used since 1998. The first applied schedule was 35 Gy in four fractions which was escalated to 48 Gy in four fractions. Between these schedules, interim doses of 40 Gy in four fractions and 48 and 60 Gy in eight fractions were given. In addition, tumours located near to critical structures were more fractionated than peripheral tumours. The absence of severe toxicity strengthened the approach of re-treating patients with tumour recurrence or irradiating multiple lesions sequentially. Consequently, a dose–response analysis could be performed with a dose range similar to the dose range of the CFRT. The comparison of SBRT with CFRT was performed with an update of previously evaluated NKI-AVL CFRT patients. As expected, the m and TD_{50} for these CFRT patients were similar to a previous publication [18] and the meta-analysis of Semenenko and Li [15].

Previous SBRT studies reported a 0% to 29% incidence of RP grade 2 or higher [3,9–14,26]. Unfortunately, only a limited number of studies reported dose parameters to describe the lung dose. Yamashita et al. [9] reported a high incidence of RP grade 2 or higher in seven of the 25 patients treated with 48 Gy in four fractions. The mean MLD was only 4.3 Gy (ranging from 1.72 Gy to 5.85 Gy). However, for the calculation of the lung dose, which was not NTD corrected, not only the tumour volume was subtracted from the total lung volume, but also an extra margin surrounding the tumour was subtracted, resulting in an underestimation of the lung dose. Nagata et al. [13] reported a 4% incidence of RP grade 2 in patients treated with 48 Gy in four fractions with a mean V20 (percentage volume of the whole lung receiving more than 20 Gy) in this patient group of only 4.5%. In the study by Ng et al. [26], no RP grade 2 or higher was observed. However, this study included only 20 patients with 80% of the patients having a V20 < 20% (GTV ranged from 4.27 to 74 cm^3).

The clinical applicability of our results in relation to other SBRT schedules may be questionable as many institutions in Europe and the USA use fraction doses of 18 Gy or 20 Gy. In our study, 48 Gy in four fractions was the most commonly used fractionation schedule having eight different beam angles (i.e. 1.5 Gy per beam). For fraction doses of 18 Gy, at least 12 different beam angles are used [6], which also results in 1.5 Gy per beam. Therefore, the major part of the lung tissue will receive equivalent doses per fraction. Moreover, in the 18 Gy or 20 Gy per fraction schedule, the percentage of lung tissue receiving the highest proportion of the dose is small because smaller dose planning margins of 5 to 10 mm around the tumour are used [6] (most of our patients had 11 to 13 mm margins [16]). Therefore, large deviations in the lung tissue response of these hypofractionated schedules are not expected.

Because the collaboration encompassed two different radiotherapy departments, a lot of effort was invested in standardizing methods for dose planning and dose calculation between the patient groups. A recent study by Gershkevish [27] showed that deviations between different treatment planning systems decrease with the use of more advanced calculation algorithms. For all patients included in this analysis, the superposition or collapsed cone algorithm was used for treatment planning. The clinical variability in the prescribing of steroids between the two institutes was limited as only patients who were diagnosed by both radiotherapists and pulmonologists experienced with the diagnosis of radiation pneumonitis were included. Patients were excluded if the diagnosis of RP was hampered or was accompanied by pulmonary comorbidity (e.g. infection, tumour progression, and previous use of oxygen). Nevertheless, the uncertainties of including patients from two different institutes should be taken into account, and a similar one single-institute validation would be of interest.

We observed a similar time frame for RP occurrences in both SBRT and CFRT; RP occurred several weeks to 6 months after irradiation as both Guckenberger et al. [10] and Yamshita et al. [9] reported for SBRT, and as Graham et al. [28] reported for CFRT. Further toxicity may be observed with a longer follow-up. In the study by Timmerman et al. [6], four of the six treatment-related deaths occurred after 12 months. Four of the patients suffered from a bacterial pneumonia, and one patient experienced tumour recurrence adjacent to the carina. Evidently, both short- and long-term toxicity may conceivably be obscured by pulmonary comorbidity or tumour progression. Therefore, these patients, who are often suffering from pulmonary comorbidities, should be intensively followed up by both radiation oncologists and pulmonologists.

For lung cancer patients or patients with pulmonary metastases, the critical prognostic importance of controlling RP risks must be balanced not only against the patient's physical condition, but also against tumour control. A strong consequential component between acute and long-term pulmonary toxicity after lung irradiation is observed in animal studies [29,30]. Consequently, even though grade 2 RP might not be life threatening, it may substantially contribute to a cascade of pulmonary deterioration in patients with pulmonary comorbidity. Moreover, a long-term dose-dependent progressive decline of pulmonary function is observed in patients treated with CFRT [31] with MLD up to 21.9 Gy (mean MLD 13.9 Gy). In a recently published SBRT phase II study [32], no relationship was observed between toxicity and lung dose. In this study, a mean MLD of 7 Gy for 60 patients was found. Our retrospective study encompassed a larger dose range for a larger number of patients, but no pulmonary function data or follow-up CTs were evaluated. A prospective study with a large dose range with long-term follow-up should reveal the predictability of any radiation-induced toxicity after hypofractionated schedules.

To date, there are no clinical data available which compare the prognosis (survival) of lung cancer patients experiencing clinically

relevant radiation-induced toxicity versus non-symptomatic patients. With regard to the optimal treatment, the clinical evaluation of the risk of tumour recurrence and of the probability of toxicity is a matter of concern in a patient group with a poor tumour-related prognosis and a high incidence of comorbidity. Our retrospective evaluation can serve as a guideline estimating the probability of RP for the clinical decision making (i.e. staying on the safe side for pulmonary compromised or palliative patients and accepting a higher risk of toxicity for curable patients without pulmonary comorbidities). Nevertheless, prospective studies are needed to reveal the relation of short- and long-term toxicity and tumour control.

Time-related recovery of lung tissue was not taken into account in our patients who had received multiple treatment schemes. A mouse study by Terry et al. [33] showed that irradiation-induced lung injury tissue could (partly) recover, suggesting an early target cell depletion and regeneration which was dependent on the size of the initial injury (i.e. dose). For a single dose of 10 Gy, less recovery was observed than for 6 Gy. Clinical studies evaluating toxicity after re-irradiations for lung cancer patients are limited due to poor prognosis. Okamoto et al. [34] studied 34 lung cancer patients re-irradiated because of a local recurrence. The large number of patients (19 patients, i.e. 56%) experiencing grade 2 or higher RP suggest limited (or no) time-related recovery. Moreover, from the long-term survivors (20–58 months after re-irradiation) 71% of the patients experienced a grade 2 RP. However, no lung dose characteristics were reported, and RP risk estimating could therefore not be performed.

To predict normal tissue complication probabilities (NTCPs) after radiotherapy treatment, the delivered dose has to be recalculated into a biological-effective dose using a mathematical model (linear quadratic model) [35,36] derived from in vitro and animal studies [37]. The clinical applicability of this model is a historical cornerstone in assessing tumour doses and dose tolerance of normal tissues in conventional fractionation schemes. In contrast, no study validated the clinical applicability of the LQ model for hypofractionation. For NSCLC cell lines and animal iso-effect data modifications of the LQ model were proposed showing an improved description of the dose response relation using these models [38,39]. Further evaluation concerning the LQ model and potential modifications of the LQ model to calculate the biological-effective dose in clinical setting for hypofractionated schedules is therefore warranted.

Although there were numerous limitations in our study, we were able to show a relationship between the lung dose and the incidence of RP for SBRT that was not significantly different from CFRT.

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Materials/Methods: Thirty-seven consecutive patients with breast cancer were treated on a helical tomotherapy unit. During simulation, kVCT images were obtained for treatment planning. These were fused with daily MVCT scans, and after setup based on skin marks and laser alignment, the necessary shifts were carried out. The magnitude of daily shifts (mm) was retrospectively obtained from the daily image fusions and the breast volume was obtained from the treatment plan. A total of 873 fusion scans were reviewed. Random error for absolute and directional daily shifts was evaluated for correlation to breast volume. Variation of setup over time was also evaluated.

Results: Mean random shift for all patients in the lateral, longitudinal, and vertical directions was 2.7 (SD 2.0), 3.1 (SD 1.5) & 3.2 (SD 2.6) mm, respectively. Mean absolute distance shifted was 6.0 (SD 3.5) mm. Based on Pearson's product-moment coefficient, there was no significant correlation between mean absolute or mean directional daily shift and breast volume (0.08, 0.08, 0.22, & 0.14 respectively). There was no correlation between set up variation and time course.

Conclusions: In this cohort, there is no correlation between breast volume and degree of daily shift. In our experience, larger breasts still make for a more difficult set up; this is not explained by volume alone. It is possible that another parameter such as breast density or overall shape correlate to set up variation; this is a course of our future investigations. There is no correlation between time course and setup variation. Therefore, setup variation does not improve or degrade with repeated treatment setups.

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2911 An Online Correction Strategy for Interfraction Variations Utilizing Couch Translation and Couch, Gantry, and Collimator Rotation

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Purpose/Objective(s): The online correction strategy for interfractional variations commonly used in IGRT uses couch translation with three degrees of freedom (3DOF). This strategy fails to correct for organ rotation and deformation. The purpose of this study was to evaluate a new strategy that utilizes the standard couch in conjunction with gantry and collimator rotation.

Materials/Methods: The correction scheme consists of standard 3-degree translation and 3-degree rotation achieved by isocentric couch (yaw), gantry (roll) and collimator (pitch) rotation angles for each beam of the RT plan. This scheme was implemented in a prototype software tool (AT2, Siemens) that is capable of registering a treatment CT set with the planning CT by optimizing the corrective adjustments using either the standard couch translation only (3DOF), the standard couch translation plus a common isocenteric couch rotation for all beams (4DOF), or the standard couch translation plus a common isocenteric couch rotation and gantry and collimator rotation for each beam (TCGC). Sample daily CT data collected for prostate and head and neck cancer patients treated with daily CT-guided IMRT on a combination of a standard linac and CT-on-rails (CTVision, Siemens) were used to evaluate the new strategy. A treatment planning system (Panther, Prowess) was used to generate dose distributions of original IMRT plan based on the planning CT, and the plans based on the CT of the day with the adjustments obtained from AT2 for the 3DOF, 4DOF, and TCGC schemes. Various dose-volume parameters for prostate, PTV, and normal structures were used to measure the dosimetric advantages of the new strategies.

Results: For the prostate cases evaluated, the PTV D95 for the 4DOF and TCGC methods had negligible and 1-3% improvement, respectively, over that for the 3DOF method. The rotational adjustments were below 4 degrees. For the head and neck case, the PTV D98 increased by 2% by using 4DOF and TCGC schemes. The maximum doses to the cord and the parotid glands for the TCGC scheme was reduced by 5% and 8%, respectively, compared to 3DOF scheme. Up to 5 degree collimator rotation was required for the TCGC scheme.

Conclusions: The TCGC online correction scheme, combining the 3-degree couch translations and couch, gantry, and collimator rotations, can improve the current method to account for interfractional variations. This correction strategy, not requiring a robotic couch, can be implemented on conventional couches and linacs.

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2912 Can the Real-time Tumor-tracking Radiotherapy Give the Planned Dose to the Tumor? DVH Analysis Based on Measured Real-time Tracking Data

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Purpose/Objective(s): Benefit of gated stereotactic body radiotherapy (SBRT) for peripheral lung tumors were evaluated by dose volume histogram (DVH)-based analysis using the actual internal trajectory of fiducial markers near the tumor as precisely detected by real-time tumor tracking (RTRT) system.

Materials/Methods: The subjects for this study consisted of four patients with stage I non-small cell lung cancer that were grouped according to those whose planning target volumes (PTV) were set to CTV+5mm and to CTV+7mm, respectively. Two irradiation regimens were evaluated for each patient, namely, with RTRT (gated) and without RTRT (non-gated) irradiation. The PTV prescribed dose was set to 40Gy ($D_{95\%}$ = 40Gy) in 4 fractions. All dose calculations were performed using the superposition algorithm in the XiO (CMS) treatment planning system. The trajectory of the fiducial marker nearest to the tumor was assumed to be consistent with the actual tumor trajectory. Shifted CTV ROIs were created from the original planned CTV by shifting the latter at 1mm resolution following the entire range of AP, LR, and SI tumor motion measured by the RTRT system. Position probabilities of the shifted CTVs were determined from the RTRT data, and the DVHs for each shifted CTV were then calculated. The total DVH accounting for CTV motion was the cumulative convolution of the shifted CTV position probability and its corresponding DVH. Multiple full-dose DVHs for the same patient were generated by using the tracking data of each beam and applying them to all the beams in a single fraction. V_{40Gy} and V_{42Gy} (normalized volume of the CTV with dose $\leq$ 40Gy and 42Gy,

respectively) were analyzed for gated and non-gated irradiation. $D_{99\%}$ (absolute dose covering 99% of the CTV) for each patient was also compared.

Results: Slight significant difference was found in the V_{40Gy} of the CTV between the gated and non-gated irradiations, and the average V_{42Gy} of the CTV non-gated cases was 92.18 ± 5.49 %, while that of the gated irradiation was 96.47 ± 3.16%. In terms of $D_{99\%}$, the average value for the gated case was 42.29 ± 0.60Gy and 40.49 ± 2.03Gy for the non-gated case. The DVHs for the gated cases had higher coverage dose and smaller variation compared to the non-gated cases. This means that complication probability for risk organs can possibly be made smaller by reducing the internal margin.

Conclusions: We confirmed that the CTV was adequately covered by the prescribed dose with smaller dose fluctuation in RTRT-gated irradiation. The results demonstrate that the dose delivery with the RTRT-gated irradiation was more precise and accurate than SBRT without RTRT. This will be essential to the accurate dose delivery in IMRT even in the presence of organ motion.

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2913 Improved Immobilization Reduces Interfractional Setup Error for Head and Neck Patients

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Purpose/Objective(s): Delivery of head and neck (HN) intensity modulated radiotherapy (IMRT) requires accurate and consistent patient immobilization to maximize precision of delivery of tumor dose and avoidance of critical structure dose. This study tests whether interfractional patient setup reproducibility could be improved by replacing the combination of standard thermoplastic head-frame and plastic headrest with a mask that extends to include the shoulders and a custom-molded headrest (AccuForm). Spatial differences in patient positioning with the head-neck-shoulder-frame with AccuForm (HNSF-A) technique were compared to those with the standard head-frame (HF) technique.

Materials/Methods: Setups were evaluated from twenty-two patients treated between December 2006 and May 2008 and included 6 HNSF-A and 16 HF with 10 oropharynx, 6 larynx, 4 unknown primary, 2 oral cavity cancers. Pretreatment mega-voltage cone beam (MVCB) computed tomography (CT) images from the beginning, middle, and end of treatment course were aligned to the C2 vertebral body on the planning CT images. The offset distance between the C7 vertebral body on the two image sets was then measured in the right-left (RL), anterior-posterior (AP), and cranio-caudal (CC) directions. The process was then reversed, aligning the image sets at C7 and measuring the offset distances at C2. An unpaired *t*-test was used to compare differences in mean offsets between the HNSF-A and HF techniques.

Results: For all disease sites, the mean offset distance at C7 in the AP direction was 4.4 mm for HF vs. 2.3 mm for HNSF-A when aligned at C2 and 4.2 mm at C2 for HF vs. 2.4 mm for HNSF-A with alignment at C7. These differences were both statistically significant ($p < 0.001$, 95% CI of 1.0-3.0 mm). The greatest difference was observed for oropharynx and oral cavity setups. The mean offset distance in the AP direction was 7.0 mm for HF vs. 2.3 mm for HNSF-A (at C7, aligned at C2) and 6.4 mm for HF vs. 2.4 mm for HNSF-A (at C2, aligned at C7). These differences between the setups for HF and HNSF-A were also statistically significant ($p < 0.001$, 95%CI of 3.0 - 6.0 mm). In contrast, the setup distances measured in the RL and CC directions did not significantly differ between the two immobilization devices.

Conclusions: This study shows that residual position errors inside the thermoplastic mask can have a significant effect on the setup of HN patients, potentially adversely affecting the spinal cord dose. The average vertical offset of 7 mm shows that although the HF setup adequately controls yaw effects, it does not accurately reproduce the pitch of the head. Therefore if PTV margins of 5 mm or less are being used, the extended mask, and the custom molded headrest are required. We recommend that whenever volumetric imaging is available a similar setup study be conducted to assess PTV margins.

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2914 Do Interventions for Prostate Cancer Intrafraction Motion Make a Difference?

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Purpose/Objective(s): Real-time electromagnetic tracking allows continuous motion measurement of prostate during radiation therapy, but it is unclear whether interventions would result in any measurable difference of prostate location during radiation therapy.

Materials/Methods: 63 patients with localized prostate cancer who opted for primary IMRT were enrolled on an IRB approved prospective multi-institutional clinical study. Patients underwent intraprostatic implantation of transponders and were treated with IMRT to the prostate and proximal SV using a posterior PTV margin of 3 mm and anterior/lateral/superior/inferior margins of at least 3mm. Treatment goals were to ensure that the isocenter position was within 2mm of the planned isocenter position, and interventions (after initial localization) during therapy such as couch-realignments and beam pauses were aimed at ensuring this. Following localization, data was collected on prostate position during beam-on as well as when the beam was off.

Results: Beam-on data was available for 25 patients. For 24 of the 25 patients, the percentage of time spent within the planned 2 mm while the beam was on ranged from 97-100%, with a mean of 99%. The corresponding percentages for positions during beam off were 76-100% with a mean of 94%. One patient was an outlier, and his prostate remained within the 2mm only 69% during beam on time and 64% during beam off. The difference between beam on and beam off ranged from 0-24%, with a mean of 5%. Five of the twenty-four patients had differences between beam on and beam off of greater than 10%.

Conclusions: An aggressive intervention regimen for prostate intrafraction motion using real-time electromagnetic tracking ensured radiation therapy delivery to within 2mm of planned isocenter for 96% of patients. The difference between the prostate position during beam on and beam off was minimal for most patients, but was meaningful for 21% of patients.

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III期非小細胞肺癌に対する化学放射線療法

新たな戦略と仮説の検証に向けて

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■ はじめに（III期非小細胞肺癌の標準治療）

切除不能III期非小細胞肺癌（NSCLC）に対する標準治療として，現在広く受け入れられている治療方法は，シスプラチンを含む同時併用化学放射線療法である[1]。併用される化学療法レジメンとしては，従来は標準用量の投与が可能な，cisplatinを含む第2世代の抗癌剤との併用（mitomycin + vindesine + cisplatin：MVP，cisplatin + etoposide：PEなど）が標準とされてきたが，最近では，vinorelbine，paclitaxel，docetaxel，irinotecan，pemetrexedなどの第3世代の抗癌剤との併用が数多く研究されている。

これまでは，併用される抗癌剤の組み合わせに関する研究が多く，放射線治療の最適化に関する研究は限られており，30年以上にわたり標準的な放射線の線量は60～63Gy程度にとどまっていた。本稿では，III期NSCLCの治療成績向上のための方向性，特に治癒の鍵を握る放射線治療の最適化に関する問題点や今後の課題について触れてみたい。

❶ 放射線治療における未解決の問題

III期NSCLCの治療において，局所制御率を上げることはいまだに大きな課題である。Le Chevalierらによる報告では，標準的な照射後の気管支鏡下生検による検討で，病理学的な局所・領域遺残・再発率は80%にも及び[2]，60Gy程度の線量は局所制御には不十分である。近年では，放射線治療の至適照射方法について，特に最適な標的体積の設定，線量増加についての検討が進められている。

❷ 標的体積の設定

臨床標的体積（clinical target volume：CTV）あるいは計画標的体積（planning target volume：PTV）をいかに設定するかは，三次元放射線治療計画における大きな課題のひとつである。International Commission on Radiation Units and Measurements（ICRU）の報告であるICRU50およびICRU62の定義では，微視的進展を考慮して肉眼的腫瘍体積（gross tumor volume：GTV）にマージンをつけてCTVとし，CTVに呼吸性移動やセットアップエラーを考慮したマージンをつけてPTVとすることとなっている。70例のNSCLC手術標本をもとに腫瘍辺縁からの微視的進展の距離を検討したGiraudらの報告によると，腫瘍の辺縁の微視的進展の平均は，腺癌では2.69mm，扁平上皮癌

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〔索引用語：肺癌，化学放射線療法，臨床試験〕

では1.48mmであり，95%の微視的進展をCTVに含めるためには，CTVマージンとしてそれぞれ8mmおよび6mmが必要とされている[3]。

このようにして決められたCTVにさらにマージンが加えられたPTVに根治的な高線量を投与する規定が，現在多くの臨床試験で採用されつつあるが，このことは，微視的進展が予想される部位にもGTVと同様の線量を投与することを意味している。このような規定で作成された治療計画は，従来行われてきた方法よりも広い照射野となり，効果および毒性のバランスの観点から果たして最適であるかは不明であり，臨床試験の結果を待つ必要がある。また，GTVと微視的進展を考慮する部位とでは明らかに存在する腫瘍量，すなわち制御に必要な線量は異なることが予想されるため，CTVマージンへは予防的な線量で十分，あるいは後述の予防照射同様にCTVマージンそのものを省略するアプローチも検討する価値があると考えられる。

また，III期NSCLCへの強度変調放射線治療（IMRT）の適応が検討されはじめたこともあり，標的体積の定義はより厳密化，複雑化している。PTVについても，単にCTV周囲に各施設共通の一律なマージンをつけるのではなく，治療計画CTの撮影方法や各施設の患者固定精度などを考慮した個別化がされるようになった。さらにIMRTでは，従来の標的基準点処方と異なり，PTVやリスク臓器（planning risk volume：PRV）等を規定し，その線量体積ヒストグラム（dose volume histogram：DVH）評価による線量処方がなされるため，従来とは異なる治療計画の記載・記録方法が必要とされるようになった。ASTROでは，IMRTにおける標的体積の定義，線量処方や記録方法についてのガイドラインを作成しており[4]，記録方法の標準化が図られている。

❸ 縦隔リンパ節領域に対する予防照射は必要か?

従来，III期NSCLCに対する放射線治療では，縦隔・肺門などのリンパ節領域に対し40Gy程度の予防的リンパ節照射（elective nodal irradiation：ENI）を行い，その後原発巣と転移リンパ節へ絞ったブースト照射として20Gy程度を追加することが標準とされてきた[5]。その背景には，ENIの概念が導入された時代にはまだCTが導入されておらず，縦隔リンパ節腫大の有無は胸部単純X線撮影あるいは断層撮影に頼らざるを得ず，偽陰性割合が高かったこと，また手術所見から領域リンパ節転移の頻度が高かったことなどがある。しかし現在ではPETの臨床導入に伴いリンパ節転移の診断精度が向上したこと，ENIを行いながら原発巣への線量を増加することは肺臓炎，食道炎といった有害事象の増加により困難であることなどからENIの見直しが図られるようになった[6-8]。これらのレトロスペクティブな報告では，肺臓炎，食道炎といった有害事象とともに，照射体積外の領域リンパ節再発も少なかったとされているが，いずれもステージング手法の違い，多数の打ち切り例，短い観察期間，イベントの定義など種々の問題点を抱えており，ENIの省略により照射野外再発が増加する危険性は否定できない。少なくともIII期NSCLCの治療において線量増加を伴わない場合にENIを省略することは慎重であるべきと考えられ，今後の臨床試験の結果を待つ必要がある。

❹ 治療強度の増強

局所進行NSCLCに対する標準線量が60Gyとなったのは，30年以上前に実施されたRTOG 7310試験の結果による（表1）[9]。しかし，その後の長期

表1　RTOG 7310の結果

線量	患者数	奏効割合（%）	生存期間中央値（月）	局所再発（%）
40Gy /10分割（2週間休止）	97	46	8.3	44
40Gy /20分割	103	48	10.3	52
50Gy /25分割	91	66	9.4	42
60Gy /30分割	85	65	10.8	33

経過観察の結果ではいずれの群も70%以上の局所領域再発が認められていること，また，この試験はコバルトを用いた2次元放射線治療であり，近年の画像診断技術，放射線治療技術においてもなお60Gyが標準であるかは再検討の必要がある。

1990年代より種々の線量増加試験が行われてきたが，米国で実施された複数のI/II相試験の結果，carboplatinとpaclitaxelの同時併用下では74Gyが推奨線量とされている[10-13]。これらの臨床試験で観察された生存期間は期待が持てるものであるが，症例数が限られていること，PET導入によるstage migrationおよび患者選択バイアスなどもあり，従来の60Gyよりも治療成績が向上しているか否かは判断できない。現在RTOGで実施されている第III相試験の結果を待ちたい。

❺ 線量処方と線量計算アルゴリズム

近年の治療計画装置の進歩により，より正確な線量分布計算が可能となったが，標的基準点の取り方，線量計算アルゴリズムの選択により，従来の不均質補正なしで計算された治療とは実際に投与される線量が大きく変化することがある。また現状では不均質補正の有無，線量計算アルゴリズムの統一がなされておらず，無視できない施設間のばらつきが生じている。

図1はsuperposition法で不均質補正を行う際に，標的基準点の取り方による線量分布の相違を示したものである。A）原発巣および転移リンパ節を含めたPTV中心，B）原発巣のGTV中心，C）縦隔予防照射（ENI）領域中心のいずれに標的基準点を置くかにより，線量分布の変化がみられる。このケースでモニターユニット（MU）値を比較すると，PTV中心（AP：113，PA：100），GTV中心（AP：103.5，PA：103.4），ENI中心（AP：107.7，PA：117.8）であり，10%を越える相違が認められ，標的基準点の取り方に関する標準化が必要である。

一方，これらの標的基準点への処方に対して，IMRTの導入に伴い線量体積ヒストグラム（dose-volume histogram：DVH）にもとづいたPTVの95%体積に投与される線量（D95）で規定する動きも出てきた。例えば，化学療法の併用タイミングと多分割照射の有効性を検証した第III相試験（RTOG 9410）の結果，不均質補正なしの63Gyは標準的線量と認識されているが，現在進行中の線量増加の有効性を検証する第III相試験（RTOG0617）の標準治療群では，superposition法，不均質補正あり，PTVのD95に60Gyの処方を行うこととなっている。見かけ上の総線量は下がっているようにみえるが，実際に投与される線量は原発巣中心で68Gy前後となり，従来の不均質補正なしの63Gy処方に相当するとの判断が示されている。不均質補正ありで原発巣中心を標的基準点として60Gyを投与する計画を立てた場合とは10%以上の相違が生じ，これらの違いについての十分な理解が必要である。

❻ 新たな戦略

これまで治療成績の向上が得られてきたとはいえ，III期NSCLCの治療成績はいまだ不良であり，今後も新たな仮説とその検証が必要である。1968年～2002年の間にRTOGが行った57の第III相試験のレビューがあるが，71%の臨床試験では標準治療がそのまま標準治療として残っている。全治療患者（n＝12734）を用いたメタアナリシスでは，有効性のオッズ比は1.01（99% CI，0.96～1.07）であり，新しい試験治療と標準治療はほぼ同等であった一方で，治療関連死のオッズ比は1.76（99% CI，1.01～3.07）と試験治療で高く，新しい治療が優れている可能性は高くないことが示された[14]。例えば，前述のRTOG 9410では，照射単独で予想された多分割照射の優位性が化学療法併用下では証明されなかった。また，化学療法併用下で線量増加を試みたRTOG L-0117でも，照射単独データから期待された線量増加は不可能であり，至適線量は74Gyにとどまっている[15]。また，有名な理論に，腫瘍および正常組織の線量反応関係がある。Hypothetical modelでは，腫瘍の方が正常組織より低い線量で死滅し，一定の線量で100%の腫瘍制御割合となっているが（図2A），実際に観察される腫瘍制御割合は一定の線量でプラトーに達し，毒性を考慮すると不十分なレベルに止まっていることも少なくない（図2B）。

これらのことから，理論のみで新たな治療を導入することは危険であり，臨床試験の結果を謙虚に受け止めつつ検証を重ねていく姿勢が重要である。既成

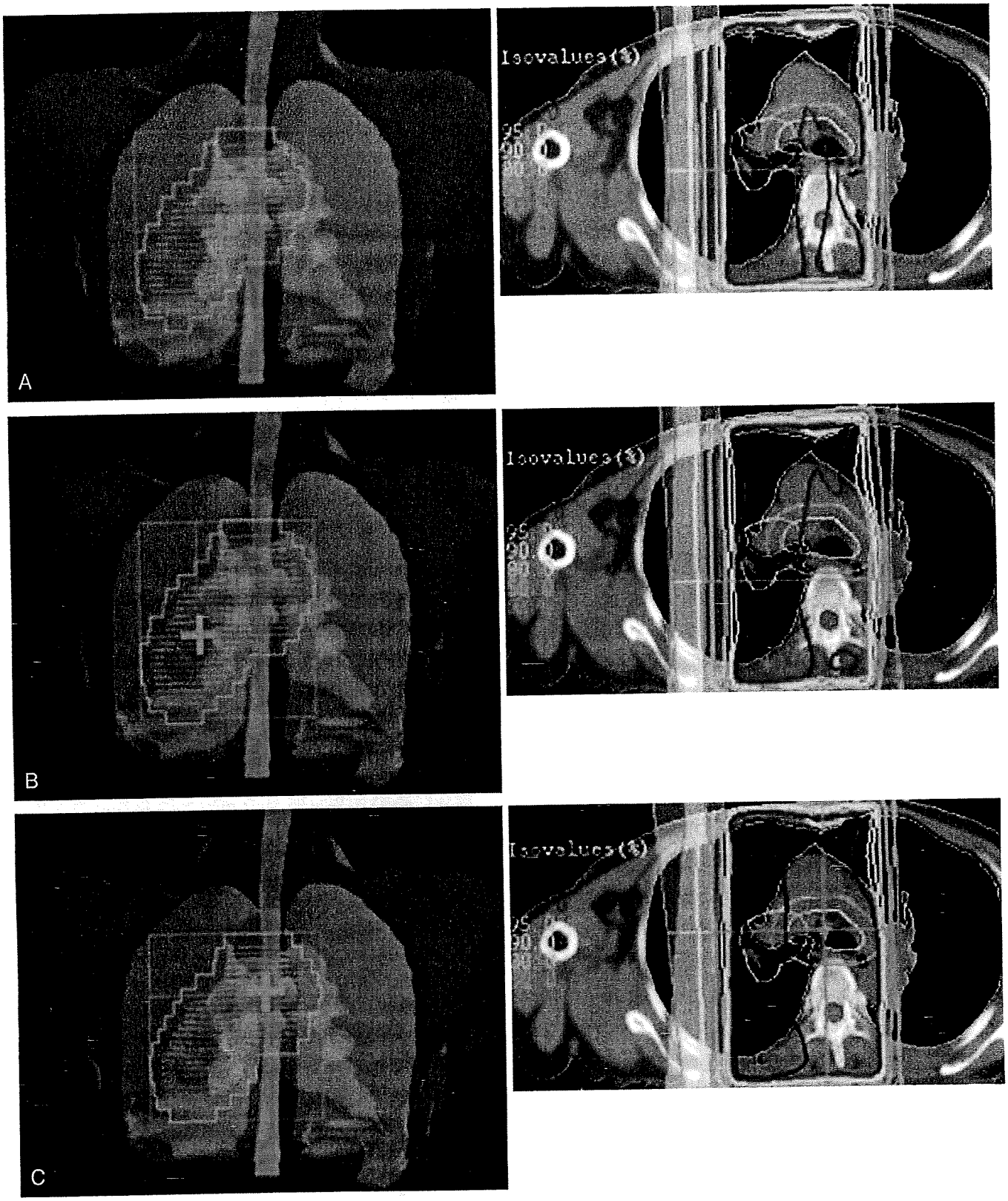

図1　標的基準点の取り方による線量分布の相違
A　原発巣および転移リンパ節を含めたPTV中心　B　原発巣のGTV中心　C　縦隔予防照射（ENI）領域中心

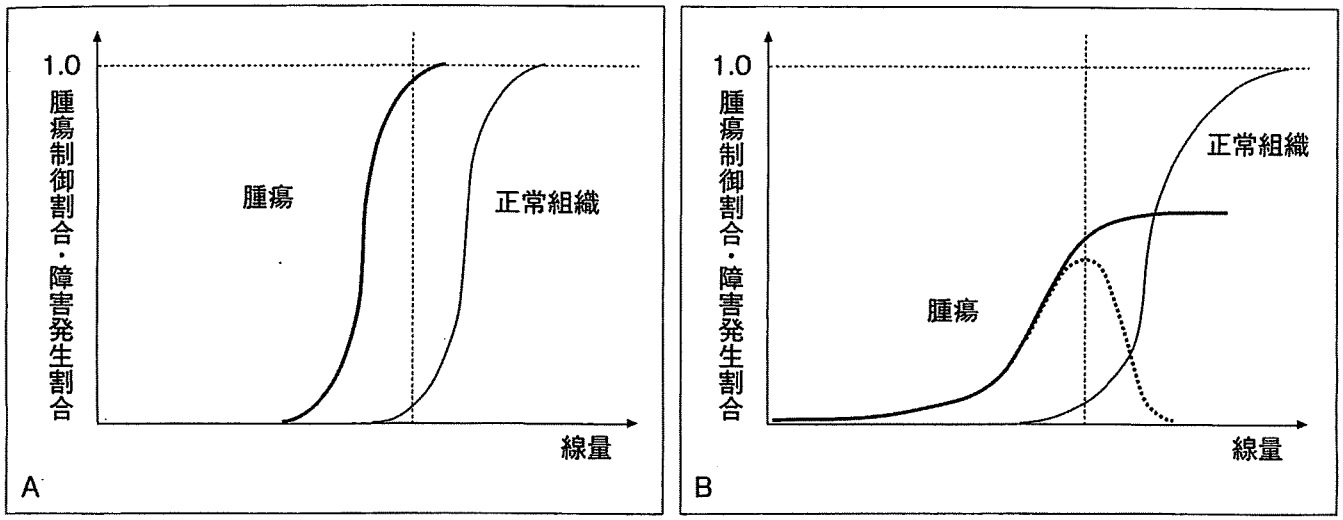

図2　腫瘍および正常組織の線量反応関係
A　仮説モデル　B　毒性を考慮した腫瘍制御

概念（ドグマ）に囚われていると，ブレイクスルーの芽を摘みかねない危険がある。日々の診療のなかから，あるいはレトロスペクティブな解析から新たな治療戦略（仮説）を掘り起こすことも重要である。例えば，リスク別，腫瘍サイズ別に個別化した線量増加が効果的である，あるいは放射線治療の quality の向上により生存率が向上する，といった仮説も検証する価値があろう。現在 III 期 NSCLC に対する新たな治療開発には閉塞感も感じられるが，今まさに自由な発想による仮説とその検証が求められている。

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Summary

Future strategies in chemoradiotherapy for stage III non-small cell lung cancer

The outcome of standard treatment for stage III non-small cell lung cancer, concurrent chemoradiotherapy, is still dismal. Recent researches in radiotherapy have been focusing on dose escalation and target volume definition. Future clinical trials to test hypotheses from different points will be necessary to further improve the survival.

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Radiotherapy quality assurance review in a multi-center randomized trial of limited-disease small cell lung cancer: the Japan Clinical Oncology Group (JCOG) trial 0202

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Abstract

Background: The purpose of this study was to analyze the radiotherapy (RT) quality assurance (QA) assessment in Japan Clinical Oncology Group (JCOG) 0202, which was the first trial that required on-going RT QA review in the JCOG.

Methods: JCOG 0202 was a multi-center phase III trial comparing two types of consolidation chemotherapy after concurrent chemoradiotherapy for limited-disease small cell lung cancer. RT requirements included a total dose of 45 Gy/30 fx (bis in die, BID/twice a day) without heterogeneity correction; elective nodal irradiation (ENI) of 30 Gy; at least 1 cm margin around the clinical target volume (CTV); and interfraction interval of 6 hours or longer. Dose constraints were defined in regards to the spinal cord and the lung. The QA assessment was classed as per protocol (PP), deviation acceptable (DA), violation unacceptable (VU), and incomplete/not evaluable (I/NE).

Results: A total of 283 cases were accrued, of which 204 were fully evaluable, excluding 79 I/NE cases. There were 18 VU in gross tumor volume (GTV) coverage (8% of 238 evaluated); 4 VU and 23 DA in elective nodal irradiation (ENI) (2% and 9% of 243 evaluated, respectively). Some VU were observed in organs at risk (1 VU in the lung and 5 VU in the spinal cord). Overall RT compliance (PP + DA) was 92% (187 of 204 fully evaluable). Comparison between the former and latter halves of the accrued cases revealed that the number of VU and DA had decreased.

Conclusion: The results of the RT QA assessment in JCOG 0202 seemed to be acceptable, providing reliable results.

Introduction

Quality assurance (QA) and quality control are an integral part of multi-center clinical trials involving radiotherapy (RT). Several reports have shown that failure to adhere to the treatment protocol deteriorated the outcome in clinical trials [1-5]. To provide reliable results in clinical trials, it is important to keep each treatment as uniform as possible. In addition, a QA program is indispensable for patient safety, preventing increased or unexpected toxicity, and ensuring a certain effect.

In 1999, Japan Clinical Oncology Group (JCOG) trial 9812 was started to evaluate whether RT with carboplatin would result in longer survival than RT alone in elderly patients with unresectable stage III non-small cell lung cancer; however, due to excessive serious adverse events, the trial was terminated early when 46 patients were registered. By retrospective RT QA review, a protocol violation was revealed in 60% of the cases [6].

JCOG 0202 was a multi-center phase III trial comparing two types of consolidation chemotherapy after concurrent chemoradiotherapy for limited-disease small cell lung cancer (Figure 1).

The primary endpoint of JCOG 0202 was overall survival and the secondary endpoints included disease-free survival and the toxicity profile of each treatment. This trial was the first in JCOG to require on-going RT QA to improve the quality of clinical trials. This is a retrospective evaluation of the protocol compliance of JCOG 0202.

Methods

Study design and RT requirements

After enrolling in this trial, patients received cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1–3, with concurrent RT. Patients were randomized after chemoradiotherapy and received either 3 cycles of the same chemotherapy of cisplatin and etoposide every 3 weeks, or cisplatin 60 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1, 8 and 15 every 4 weeks.

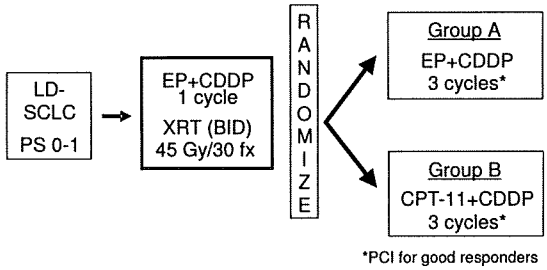

Figure 1
Schema of JCOG 0202. Abbreviations. LD-SCLC, limited-disease small cell lung cancer; PS, performance status; EP, etoposide; CDDP, cisplatin; XRT, thoracic radiotherapy; BID; bis in die/twice a day; CPT-11, irinotecan; PCI, prophylactic cranial irradiation.

RT requirements included a total dose of 45 Gy in 30 fractions (bis in die, BID/twice a day) with an interfraction interval of over 6 hours. For treatment planning, both conventional 2-dimensional (2-D) X-ray simulation and 3-dimensional (3-D) CT simulation were allowed. PET scanning was not required in RT planning. Gross tumor volume (GTV) was defined as the primary tumor demonstrated by CT scan as well as metastatic lymph nodes measuring 1 cm or greater in short axis. In this trial, the clinical target volume (CTV) for the primary tumor and metastatic lymph nodes was created without adding any margins to GTV. CTV also included a regional (elecitve) nodal area which consisted of ipsilateral hilum and bilateral mediastinal (pretracheal, paratracheal, tracheobroncheal, and subcarinal) lymph nodes. Contralateral hilar lymph nodes were not included in the CTV. The planning target volume (PTV) was created by adding margins at the discretion of radiation oncologists (typically 0.5–1 cm for lateral margin and 1–2 cm for cranio-caudal margin, depending on respiratory motion and patient fixation). A dose of 30 Gy was prescribed at the center of the PTV, including elective nodal irradiation (ENI), followed by a boost dose of 15 Gy to the primary tumor and metastatic lymph nodes. Tissue heterogeneity correction was not used for monitor unit calculation, because if heterogeneity correction was required and different calculation algorithms were allowed, inter-institutional variation of the delivered dose would have been significant, and the convolution-superposition algorithm was not available in some participating institutions at the beginning of this trial.

Dose constraints were defined in regard to the dose to the spinal cord and the lung. The dose to the spinal cord was kept at ≤ 36 Gy. A posterior spinal shield was not allowed. The percentage of normal lung volume minus PTV receiving 20 Gy or greater (V_{20}) was kept ≤ 35%. In 2-D planning, the field size was limited to ≤ half of the ipsilateral lung (for upper lobe tumors, ≤ 2/3).

Quality assurance review

For initial QA review, copies of pre-treatment diagnostic chest X-ray and CT, simulation and portal films, worksheets for monitor unit calculation of the prescribed dose, and RT charts with the record of the irradiated time were collected. Information on the initial RT plan was required to be sent to the QA review center within 7 days after the start of RT. Information on the total course of RT, including the boost treatment plan, was required to be sent within 30 days after completion of RT. These were reviewed periodically at least twice a month by the RT