biopsy can be hazardous (1). Therefore, it is a matter of debate whether the use of radiotherapy should be used when the residual tumor is still small as the primary treatment or should be reserved as a potential salvage treatment for the residual tumor enlarged (3).

Stereotactic radiosurgery (SRS) has been proven useful for reducing unnecessary irradiation to the normal tissue surrounding meningiomas and provides an excellent local control rate (LCR) for small to mid-size skull base meningiomas (3,4). Three-dimensional conformal radiotherapy (3D-CRT) and fractionated stereotactic radiotherapy (FSRT) are expected to be useful for further reducing the possibility of late adverse reactions, even for relatively large tumors (5,6). Although there were several precise reports from a few institutions about the long-term outcome after FSRT (5–8), we are still short of knowledge about the treatment results of FSRT with the median follow-up longer than 60 months for intracranial meningioma.

We began using FSRT 15 years ago for patients with intracranial skull base meningiomas, principally for patients who were inoperable, who had residual tumors with some components of high mitotic index or high MIB-1 index, who experienced relapse of the tumor. In this study, we retrospectively reviewed our long-term results for FSRT of intracranial skull base benign meningiomas in order to investigate the usefulness and prognostic factors of this treatment.

PATIENTS AND METHODS

Patients

The outcome of 27 patients with intracranial skull base benign meningiomas treated with FSRT at Hokkaido University Hospital between May 1994 and February 2009 was retrospectively reviewed. Our treatment policy was to apply FSRT principally for those patients with intracranial skull base meningiomas who were inoperable, who had residual tumors or who experienced relapse of the tumor.

The patients' characteristics are summarized in Table 1, which were classified by the treatment category. In our cases, diagnosis was based on pathological examinations in 17 patients and radiological characteristics in 10 patients. The tumor was located at lateral structures in 17 (anterior fossa in 2, middle-lateral sphenoid wing in 8 and cerebellopontine angle and posterior fossa in 7 patients) and at central structures in 10 patients (cavernous sinus and tuberculum sellae in all 10 patients). The median tumor volume was 9.1 (range: 1.1–86.1) cc in all benign meningiomas. The median tumor volume in the initial treatment group was smaller than that in the salvage treatment group (6.3 vs. 12.3 cc), but there was no significant difference statistically ($P = 0.139$; Mann–Whitney test).

In this study, 11 patients were treated with FSRT alone as the initial treatment: 1 after biopsy (Simpson's grade V) and 10 after radiological diagnosis. Radiotherapy was used as a part of the initial treatment after incomplete excision in 4 patients and as a salvage treatment for tumor recurrence after surgery in 12 patients. The number of surgical procedures before FSRT was 1, 2 and 3 in 10, 5 and 1 patients, respectively. Patients who received open biopsy or surgery were classified according to Simpson's grade (9). Simpson's grade II (complete removal and coagulation of dual attachment) and IV (subtotal resection) surgery before radiotherapy was performed in 1 and 15 patients, respectively. Only one patient received biopsy (Simpson's grade V).

Table 1. Patients' characteristics

Factors	Initial treatment group	Salvage treatment group	Total
Total	15	12	27
Diagnosis			
Pathological diagnosis	5	12	17
Radiological diagnosis	10	0	10
Sex			
Male	1	6	7
Female	14	6	20
Age			
Mean (range)	60.3 (18–78)	45.5 (14–72)	53.7 (14–78)
Tumor cite			
Lateral	11	6	17
Central	4	6	10
Gross tumor volume			
Median (range) (cc)	6.3 (1.1–58.9)	12.3 (2.5–86.1)	9.1 (1.1–86.1)
Simpson's grade			
I	0	0	0
II	0	1	1
III	0	0	0
IV	4	11	15
V	1	0	1
Radiotherapy alone	10	0	10

Radiation Therapy Method

The gross tumor volume (GTV) was taken as the gross tumor shown on computed tomography (CT) with or without magnetic resonance imaging (MRI). The clinical target volume (CTV) was equal to the GTV, post-operative tumor bed or both in this study. The planning target volume (PTV) was 2–3 mm geometric expansion of the CTV. In delineating GTV, MRI co-registered with CT was used in 18 recent patients, and only the CT information was used for the remaining 9 patients.

Treatment planning systems were Focus or Xio (CMS Japan, Japan). A dose calculation algorithm used for the

skull base meningiomas was the Clarkson method or the convolution method. Stereotactic radiotherapy was carried out by using a 6 or 10 MV linear accelerator (LINAC) (2100C: Varian, Palo Alto, CA, USA; EXL15DP: Mitsubishi, Japan) with an in-house developed LINAC-based SRT system. Three-dimensional non-coplanar, single isocenter and the technique using multileaf collimator (MLC) were used. Three to eight static non-coplanar ports with the conformal fields were used in general. The width of these leafs was 5–10 mm at the isocenter. The dose was prescribed at the isocenter and defined as 100% in the dose distribution profile. MLCs were opened to cover PTV by a 90–95% isodose shell. The maximum dose point was always situated near the isocenter with the dose <110% (Fig. 1).

Patients were fixed by using a thermo-plastic mask and a custom-made head rest system. The dose to the optic chiasm was limited to ≤46 Gy. The total dose was 48–54 Gy in 26 cases and 32 Gy in 1 case using 2.0 Gy as the daily dose. When these radiation schedules were converted into the biological equivalent dose (BED) using an α/β ratio of 2.0 Gy, the median BED dose was 82.0 Gy (range: 52–90 Gy).

Follow-up and Statistical Analyses

The median follow-up time was 90 months (range: 21–209 months) after initial treatment, surgery or FSRT. The median follow-up time was 63 months (range: 19–154 months) after FSRT. More than 70% of patients were followed longer than 36 months after FSRT. Patients were periodically monitored by physical as well as radiographic examination in Hokkaido University Hospital and related hospitals. Local tumor progression (PD) was scored when the maximum diameter of the tumor increased 2 mm or more and partial reaction was scored when the diameter decreased 2 mm or more. The LCR was defined as no change or decrease of the tumor volume in the anatomical region consistent with the PTV of the treatment planning image. When more than 80% of the relapsed tumor volume was outside of the PTV, the recurrence was defined as out of field (10). In-field (>95% of the relapsed tumor volume in the PTV), marginal (20–95% of the relapsed tumor volume in the PTV), and out-of-field (less than 20% of the relapsed tumor volume in the PTV) recurrence were defined in this study.

Statistical analyses were conducted by using commercially available software (SPSS v18; IBM Inc., Chicago, IL). The overall survival (OS) and LCR were calculated from the date of the initiation of radiotherapy using the Kaplan–Meier method, and statistical evaluations were carried out by the log-rank test.

RESULTS

The OS, progression-free survival (PFS) and LCR at 5 years after initial treatment were 95.7 [95% confidence interval (CI): 87.3–100], 91.6 (80.4–100) and 95.5 (86.9–100)%.

The OS, PFS and LCR at 5 years after FSRT were 96.2 (88.8–100), 84.6 (67.7–100) and 88.6 (72.9–100)%.

Partial response was achieved in two benign patients, and the other patients with local control experienced no change of tumor volume. Three (11%) patients experienced in-field recurrence. These tumors had received Simpson's grade IV surgical resection. One patient had progression disease out of irradiation field. The recurrent cases were observed at the posterior fossa (at 55 and 81 months) in two patients, and at the cavernous sinus and tuberculum (at 19 and at 27 months) in two patients. These four recurrent cases are summarized in Table 2. No marginal recurrence was observed.

Univariate analyses were performed on OS, PFS and LCR after FSRT for patients with benign meningioma (Table 3). The female patients had significantly better PFS ($P = 0.009$) and LCR ($P = 0.04$) than the male patients. The 5-year OS, PFS and LCR after FSRT were all 100% for the benign meningiomas with a tumor volume of <9.1 cc and these parameters were 91.7 (76.0–100), 68.2 (37.2–99.2) and 75.8 (45.2–100)% for the tumors >9.1 cc, respectively. The difference was significant in PFS ($P = 0.022$) and LCR ($P = 0.044$) (Fig. 2).

In this study, the 11 patients who received FSRT alone had 100% OS, 88.9% PFS and 100% LCR at 5 years, respectively. The OS, PFS and LCR of patients who received FSRT with or without surgery as the initial treatment ($n = 15$) were 100, 91.7 and 100%, whereas those of patients who received FSRT for relapse ($n = 12$) were 90.9, 68.2 and 68.2%, respectively. The LCR was significantly worse in patients who received FSRT for a relapsed tumor ($P = 0.01$). A higher biological radiation dose, BED, was paradoxically associated with a lower PFS and LCR. The median tumor volume was larger (11.0 vs. 6.7 cc) and the ratio of patients with relapsed tumor was higher (7/11 vs. 5/16) in the higher

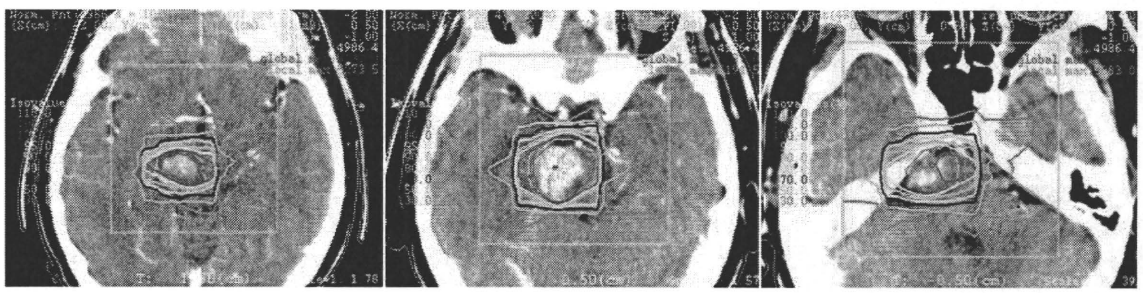

Figure 1. Dose distribution of FSRT for an intracranial benign meningioma. FSRT, fractionated stereotactic radiotherapy.

Table 2. The characteristics of patients with skull base benign meningioma who experienced tumor recurrence after FSRT either in-field or out-of-field

No.	Age	Sex	Primary site	Gross tumor volume (cc)	Simpson's grade	FSRT for relapsed tumor	Dose/fraction (Gy/fraction)	Local control	Recurrent site	Relapse (months)	Survival times	Final status
1	78	M	Cavernous sinus	58.9	Grade V	No	54 Gy/27fr	NC	Out-of-field	27	27	Alive
2	35	M	Cerebellopontine angle	9.75	Grade IV	Yes	54 Gy/27fr	PD	In-field	81	81	Alive
3	51	M	Cerebellopontine angle	13.9	Grade IV	Yes	44 Gy/ 22fr + 10 Gy/ 4fr	PD	In-field	55	55	Alive
4	58	F	Tuberculum sellae	24.9	Grade IV	Yes	54 Gy/27fr	PD	In-field	19	20	Death

FSRT, fractionated stereotactic radiotherapy; NC, no change; PD, progression of disease.

Table 3. The univariate analysis of prognostic factors after FSRT in patients with skull base benign meningiomas

Factor	5-year OS (95% CI)	*P* value	5-year PFS (95% CI)	*P* value	5-year LCR (95% CI)	*P* value
Age						
>60 ($n = 11$)	100	0.429	87.5 (64.6–100)	0.703	100	0.219
≤60 ($n = 16$)	93.8 (81.8–100)		82.0 (58.1–100)		82.0 (58.1–100)	
Gender						
Female ($n = 20$)	95.0 (85.4–100)	0.584	94.7 (84.7–100)	0.009	94.7 (84.7–100)	0.04
Male ($n = 7$)	100		55.6 (7.0–100)		66.7 (13.4–100)	
Gross tumor volume						
<9.1 cc ($n = 14$)	100	0.28	100	0.022	100	0.044
≥9.1 cc ($n = 13$)	91.7 (76.0–100)		68.2 (37.2–99.2)		75.8 (45.2–100)	
Planning method						
With MRI fusion ($n = 18$)	94.1(82.9–100)	0.467	86.5 (69.1–100)	0.229	93.8 (81.8–100)	0.473
Without MRI fusion ($n = 9$)	100		87.5 (64.6–100)		87.5 (64.6–100)	
Treatment for recurrence						
No ($n = 15$)	100	0.243	91.7 (76.0–100)	0.102	100	0.013
Yes ($n = 12$)	90.9 (73.8–100)		68.2 (27.6–100)		68.2 (27.6–100)	
Biological effective dose (Gy) ($\alpha/\beta = 2$)						
≥85 ($n = 11$)	90.9 (73.8–100)	0.243	60.6 (21.8–99.4)	0.006	68.2 (27.6–100)	0.013
<85 ($n = 16$)	100		100		100	

OS, overall survival; CI, confidence interval; PFS, progression-free survival; LCR, local control rate; MRI, magnetic resonance imaging.

dose group than the lower dose group, although the difference did not reach the level of statistical significance.

No adverse event was observed in the follow-up period. No optical injury, temporal lobe injury or hydrocephalus, or symptoms related to radiotherapy were observed.

DISCUSSION

The median dose used in the present study is 48–54 Gy with daily dose of 2.0 Gy. It is lower than the dose used in the Heiderberg study (5,7), in which the mean radiation dose was 56.8 Gy (± 4.4 Gy), and higher than the dose used in the French study (8), in which 45 Gy with daily dose of 1.8 Gy was used. Since a dose–response curve for normal tissues and tumor changes rapidly at the dose range from 40 to 60 Gy with 1.8–2 Gy fractional dose, our results add new biological data for the meningioma and surrounding normal tissue with the long follow-up.

We found that the OS and LCR were 100% at 5 years after FSRT alone for patients with benign skull base meningioma who received FSRT as the initial treatment. This is consistent with a recent article by Korah et al. (6) in which the 8-year LCR was 94% after radiotherapy alone for

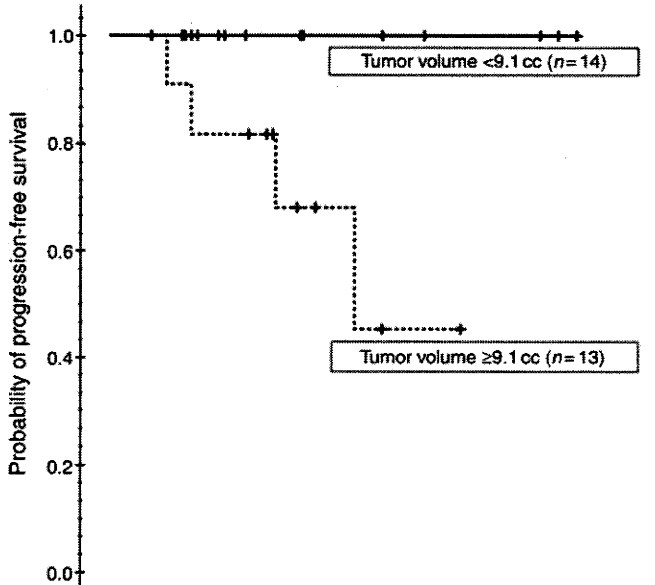

Figure 2. Progression-free survival curves according to the tumor volume. The patients were divided at a median volume of 9.1 cc.

42 patients. Lee et al. (10) also reported a 96.9% LCR at 5 years after SRS alone for 83 patients with cavernous sinus meningiomas. Other series have also suggested a high LCR after radiotherapy alone for benign meningiomas (4,5,11).

After incomplete surgical resection of Simpson's grade III or IV, the recurrence rate of meningiomas is high without radiotherapy (12,13). The recurrence rates for skull base meningioma are especially high, because total resection is much more difficult at this site than at other sites (12,14,15). Adjuvant FSRT immediately after subtotal resection has been suggested to reduce the recurrence rate without lowering the complication rate compared with previous radiotherapy (1,16,17). Previous reports have suggested that radiotherapy for recurrent meningioma is more difficult than radiotherapy used as the initial treatment (14,18). Condra et al. (1)reported that the cause-specific survival was better in patients who received radiotherapy immediately after subtotal resection than those who did not receive radiotherapy. Milker-Zabel et al. (5) also found that patients treated for recurrent meningioma showed a trend toward decreased PFS compared with patients treated with primary therapy, after biopsy or after subtotal resection ($P < 0.06$) in 179 patients with benign or atypical meningiomas.

Our results also suggested that better LCR were obtained for patients who received FSRT with or without surgery as the initial treatment than for those who received FSRT for relapsed tumors. However, the number of patients who were surgically treated and had residual tumor in our institution is uncertain. A small amount of residual benign meningioma after total or subtotal removal often does not enlarge or become symptomatic. Therefore, there is a possible bias that delayed irradiation was given for a poor prognosis group with a tendency of enlargement and irradiation was not required at all for the majority of patients in a good prognosis group. Precise selection criteria for the early irradiation after surgery are warranted to reduce the unnecessary irradiation for the good prognosis group.

The poorer outcome for recurrent meningioma is likely due to the progressive nature of some meningiomas or a mixed component of atypical meningioma (4,19,20). Meningiomas have been reported to obtain radioresistance or a component of malignant transformation as a natural course of the disease (20–23).

Considering that relapsed meningiomas often contain a progressive component, the treatment policy of applying radiotherapy only in the case of relapsed tumors causes a selection bias in the treatment outcome. The progressive nature of some meningiomas may also result in a leading bias with the treatment policy. Our study showed that the 5-year OS was 96.3% after any initial treatment and 88.2% after FSRT for the same patients' group. We summarized the previous studies of SRS and FSRT in Table 4 and found that our results contained the largest proportion of the relapsed tumors in these series. The tendency for the outcome to be better in the series with a lower proportion of relapsed tumors was not negligible. The lack of these biases may partly explain the excellent results in the group that received radiotherapy alone. The present study suggested that the selection bias and leading bias must be held in mind when we compare the treatment results of radiotherapy among different institutions or compare it with surgical series.

This study showed that the tumor volume was a significant prognostic factor as reported previously (5,22). We summarized the previous studies of SRS and FSRT which discriminated the tumor volume of benign tumors from atypical and malignant meningiomas (Table 4). The median tumor volume was 10 cc less in the majority of studies (4,10,11,24–29). The 5-year PFS and LCR values were more than 90% in these series. This study showed that our results of FSRT for tumors <9.1 cc (median) were as good as those in the previous studies. However, for the total patient group, including patients with larger tumors, the 5-year PFD and LCR were 84.6 and 88.6%, respectively. This finding is consistent with the results of Subach et al., who reported a mean tumor volume of 13.7 cc and a reduction of 5-year LCR to 86% (24).

Conventional 3D-CRT was reported to achieve excellent results in 1980s–early 1990s when CT and MRI images had 5 mm slice thickness and very precise fixation did not make sense. However, in the late 1990s, treatment planning using images with 1–2 mm thickness began to require precise fixation of the skull. Although there is no randomized studies to compare 3D-CRT and FSRT, FSRT can reduce the dose to the critical part of brain tissue with higher certainty than conventional 3D-CRT in the era of 1–2 mm slice thickness of the medical images. There are two recent reviews comparing different radiotherapy techniques such as 3D-CRT, SRS

Table 4. Previous studies of stereotactic radiosurgery and fractionated stereotactic radiotherapy for skull base benign meningioma in which the median or mean tumor volume was described for benign tumors

Institution	SRS or FSRT	No. of patients	Tumor volume median (range) (cc)	Recurrent cases (%)	Follow-up period median (range) (months)	PFS	LCR
Mayo Clinic (30)	SRS	88	10 (2.3–30)	>3 (3%)	35 (12–83)	95.0%	—
University of Pittsburgh (24)	SRS	60	13.7[a] (0.8–56.8)	>13 (21%)	35[a] (12–101)	—	86.7%
University of Pittsburgh (10)	SRS	155	6.5 (0.5–52.4)	Unknown	39[a] (2–145)	—	93.1%
University Hospital, Verona (25)	SRS	111	8.1[a] (1–20)	0 (0%)	48.2 (12.1–82.5)	96.0%	97.0%
CHU La Timone (4)	SRS	32	2.28[a] (0.25–60)	2 (6%)	56[a] (24–118)	100.0%	—
University of Pittsburgh (26)	SRS	219	5.0 (0.47–56.5)	0 (0%)	29 (2–164)	—	93%
Medical University Graz (28)	SRS	200	6.5 (0.38–89.8)	Unknown	94.8 (60–144)	98.5%	—
Seoul National University (11)	SRS	63	6.3[a] (0.5–18.4)	1 (2%)	77[a] (48–112)	90.2%	—
University of Pittsburgh (29)	SRS	168	6.1 (0.3–32.5)	35 (21%)	72 (–254)	91.0%	97% (at 10 years)
University of California (27)	FSRT	45	14.5 (1.4–65.66)	8 (31%)	36 (12–53)	97.4% (3 years)	—
Hokkaido University (9.1 cc>)	FSRT	14	4.7 (1.1–9.0)	4 (28.6%)	79.0 (27–154)	100.0%	100.0%
Hokkaido University (all cases)	FSRT	27	9.1 (1.1–86.1)	12 (44.4%)	63.0 (19–154)	84.6%	88.6%

SRS, stereotactic radiosurgery.
[a]Mean.

and FSRT (30,31). Elia et al. (30) summarized that FSRT has toxicity equivalent to that of SRS, despite its biased use for larger meningiomas with more complicated volumes. Minniti et al. (31) recommended SRS only for tumors <3 cm away more than 3 mm from the optic pathway because of the high risk of long-term neurological deficits.

Selch et al. (27) reported an encouraging 3-year PFS of 97% after FSRT for patients with a median tumor volume of 14.5 cc using a dose fractionation schedule similar to that in our study. Milker-Zabel et al. (5) have published results of FSRT for 179 skull base meningiomas, achieving 90.5 and 89% recurrence-free survival rates for benign meningiomas and atypical meningiomas, respectively, and using a median dose of 57.6 Gy (range: 45–68 Gy). Their results were excellent considering that the median target volume was as large as 33.6 cm^3 (1–412.6 cm^3) and as many as 141 (44.5%) cases of recurrent disease were included. Eight (4.4%) patients developed new clinical symptoms, such as reduced vision, trigeminal neuralgia and intermittent tinnitus located at the side of the irradiated meningioma after FSRT in their series. The slightly higher dose used in their study might have been the reason for the better tumor control with a little higher complication rate compared with our study. Korah et al. (6) used FSRT, 3D-CRT and SRS for 9, 11 and 22 patients, respectively, and among these, only 1 patient treated with SRS developed a symptomatic radiation-related neurological complication. There were no late adverse reactions in our series (27). Considering that a lower complication rate is an extremely important issue for patients with benign tumors, FSRT is one of the initial treatment options for patients with intracranial skull base meningioma which locate very close to the critical portion of normal brain tissues.

However, in our relapse cases, the LCR was low. We consider that the 2–3 mm PTV margin was sufficient with our FSRT technique by adding MLC margin to cover the PTV with 90–95% isodose line. However, it is not deniable that the high relapse rate of the larger tumors may also be explained by the small PTV margins used in our study. Goldsmith et al. (32) reported that the PFS rate in the group treated with a minimum tumor dose of >52 Gy was better than the group treated with ≤52 Gy (93 vs. 65%; $P = 0.04$). When FSRT was used for treating the case of the tumor located near the organ at risk (OAR), we must have reduced the margin for PTV to exclude the OAR from the high-dose area. Thus, the dose concentration for the tumor was gotten worse than an ideal dose distribution. Intensity-modulated radiotherapy (IMRT) is expected to increase the therapeutic ratio by reducing the dose to normal tissue because IMRT can deliver the prescription dose to the targets without worsen the dose concentration. For improvement of the LCR of those relapse cases, IMRT with a fractionated schedule will be more appropriate than simple FSRT to increase the dose for these tumors without increasing the dose to the surrounding normal tissue (33–36). However, higher radiation dose to the rest of the body and higher cost to the patient must be taken into account for each patient to use IMRT.

In conclusion, the long-term outcome suggests that FSRT is a safe and effective treatment for intracranial skull base benign meningioma, especially for those who have tumors <9.1 cc or would receive FSRT with or without surgery as the initial treatment.

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Conflict of interest statement

None declared.

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学術

綜　説

高精度放射線治療について

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はじめに

近年の放射線照射技術の進歩は目覚ましい。15年前に最先端とされていた脳病変に対する定位放射線照射は保険収載以降、急速に普及し既に通常治療の一部になろうとしている。また肺癌のような体幹部病変に対する定位照射も、開発後わずか数年で保険収載され多くの施設で行われるようになった。危険臓器に隣接した比較的大きなターゲットに線量分布を合わせ込む特殊照射技法－強度変調放射線治療－はこの10年間で瞬く間に普及し、更に放射線治療計画時や照射時に先端画像技術を用いることで精度を上げる画像誘導下放射線治療技術も治療計画ソフトや照射機械に標準的に装備されるようになり、その進歩は留まるところを知らない。一方でこれら新技術に関するエビデンスの蓄積は遅々として進んでいない。本稿では今、俄に脚光を浴びている高精度放射線治療について紹介し、その現状に関し私論を交えて概説する。

高精度放射線治療の概説

脳定位放射線照射（Stereotactic irradiation, STI）の基本的考え方

脳定位放射線照射は、古典的には定位脳手術と同じようなフレームを頭蓋骨に観血的ピン固定することで（**図1-a**）位置再現精度を1mm以下に抑え、複数の放射線束を病変に集中して照射する方法のことを意味する。正式には大線量を1回で照射する方法を定位手術的照射（Stereotactic radiosurgery, SRS）、数回の分割を加えて照射する方法を定位放射線治療（Stereotactic radiotherapy, SRT）に分けて定義されるが、最近は両者を併せて定位照射と略称で呼ばれることも多い。脳定位照射の始まりはラルス・レクセルがガンマナイフを開発した1967年まで遡る。1990年以降、国内でも定位照射が行われるようになったが、2000年ころまでは一部の教育的機関で施行されてきたに過ぎない。最近になりプラスチックシェルのような非侵襲的固定具の進歩や（**図1-b**）、また後述する画像誘導照射技術（Image-guided radiation therapy：IGRT）などがライナックに標準的に搭載され（**図2**）、比較的容易にできるようになったこと、保険収載されたことなどが相俟って施行施設が急速に増加している。

脳定位照射の適応となるのは、病変部位と正常組織の境界がはっきりした疾患である。神経鞘腫や髄膜腫に代表される良性腫瘍（**図3-a**）、転移個数が1個の転移性脳腫瘍（**図3-b**）[1),2)]、手術が難しい脳深部に局在するような動静脈奇形（**図3-c**）は脳定位照射の適応として認知されている。これは定位照射が通常照射と異なり高線量域と低線量域の境界が非常にシャープであり、病変と正常部の境界が不明瞭な疾患に用いた場合に再発率

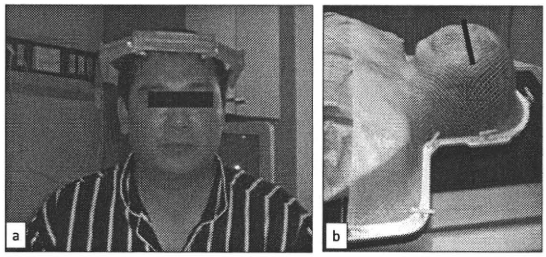

図1　脳定位照射における固定具：観血的ピン固定を伴った定位照射用フレーム（a）、熱可塑性プラスチックシェル（b）

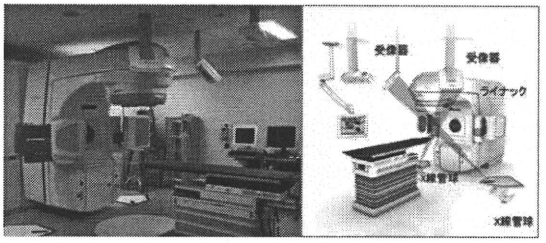

図2　新潟大学に導入された高精度放射線治療機械（ノバリスTX）：画像誘導（IGRT）機能、0.1mmの精度で6軸補正が可能な天板など最新の機能が搭載されている

が高まる可能性があることが主たる理由である。従って、グリオーマやジャーミノーマ[3]、中枢神経原発悪性リンパ腫は定位照射の良い適応とは言えない。

観血的ピン固定を伴うSRSはフレームを長期間装着することができないという技術的制約がある。そのため1回、もしくは数回で照射を終わらせる必要があった。脳定位照射の有害反応として重要なのは放射線脳壊死である。これは照射後半年以降に発症することから晩期障害に分類され、その発生因子として1回線量の多寡が重要な意味を持つ。通常の放射線照射では晩期有害反応のリスクを低下させるため1回線量を抑え、数週間に分けて照射する分割照射法が用いられる。SRSは物理的線量分布を腫瘍に限局させれば1回照射のデメリット（晩期有害反応発生リスク）は補えるという仮定のもとに成り立つ治療法であるが、現実的には2cmを超える腫瘍では晩期障害のリスクが高まることから投与線量を低く抑える必要があり、また3cmを超える腫瘍では合併症発生率を許容範囲内（3-5%以内）に抑えたうえで腫瘍制御を得るような満足すべき線量投与ができない。このあたりが1回照射を用いたSRSの限界点であることを理解しておく必要がある。現在は非侵襲的固定具や後述する画像誘導技術を用いることで、観血的フレーム装着を行わなくとも十分な位置再現精度が得られるようになったことから、短期分割を用いたSRTの役割が増すであろう[4-7]。

体幹部定位照射（Stereotactic-body radiation therapy, SBRT）

脳で発達した定位照射技術を体幹部疾患に適応拡大したのが体幹部定位照射である。体幹部病変は頭蓋内とは異なり、腫瘍や正常構造は静的ではなく、呼吸や蠕動に代表されるような様々な動きによる影響を受ける。そのため体幹部疾患に線量分布の辺縁fall-offが急峻な定位照射技術を用いるためには様々な工夫が必要となる。その先駆けとなったのが動体追跡照射装置である[8]。これは病変の近傍に埋め込まれた金マーカーを照射中に透視で追跡し、金マーカーが適切な場所に来た時のみ照射用のX線を照射するという装置である。その後、胸壁、腹壁の動きと腫瘍の位置座標情報を同期させて照射する方法も普及してきたが、それぞれのモダリティーに一長一短があり、各施設で試行錯誤している段階と言える。

現在、適応と考えられているのは早期肺癌（**図3-d**）や肝腫瘍である。特に年齢や葉切除を受けた場合の残存肺機能の問題のため手術非適応となった早期肺癌への定位照射は日本と米国で急速に広まってきた。国内複数施設が協力しておこなった遡及的研究におけるステージⅠの5年生存率が70-80%程度であり[9]、これらの症例が呼吸機能や年齢を理由に手術適応とならなかった症例を対象にした治療成績であることを考えると驚異的な数字といえる。本治療法はJCOG（Japan Clinical Oncology Group）やRTOG（Radiation Therapy Oncology Group）といった日米の主な臨床研究機関で前向き試験が行われ、現在その最終解析結果を待っているところである。

強度変調放射線治療（Intensity-modulated radiation therapy, IMRT）

定位放射線照射が比較的小さな病変を対象としているのに対し、強度変調放射線治療は一般的に比較的大きく、リスク臓器が入り組むように近接している場合に用いられる。この場合のリスク臓器とは前立腺癌における直腸や尿管、頭頸部癌における耳下腺と脊髄、脳腫瘍における視交叉や脳幹である。このような状況で腫瘍に十分な線量を維持し、かつリスク臓器の線量を低減するためには線量曲線に複雑な凹凸を作る必要がある。頭蓋

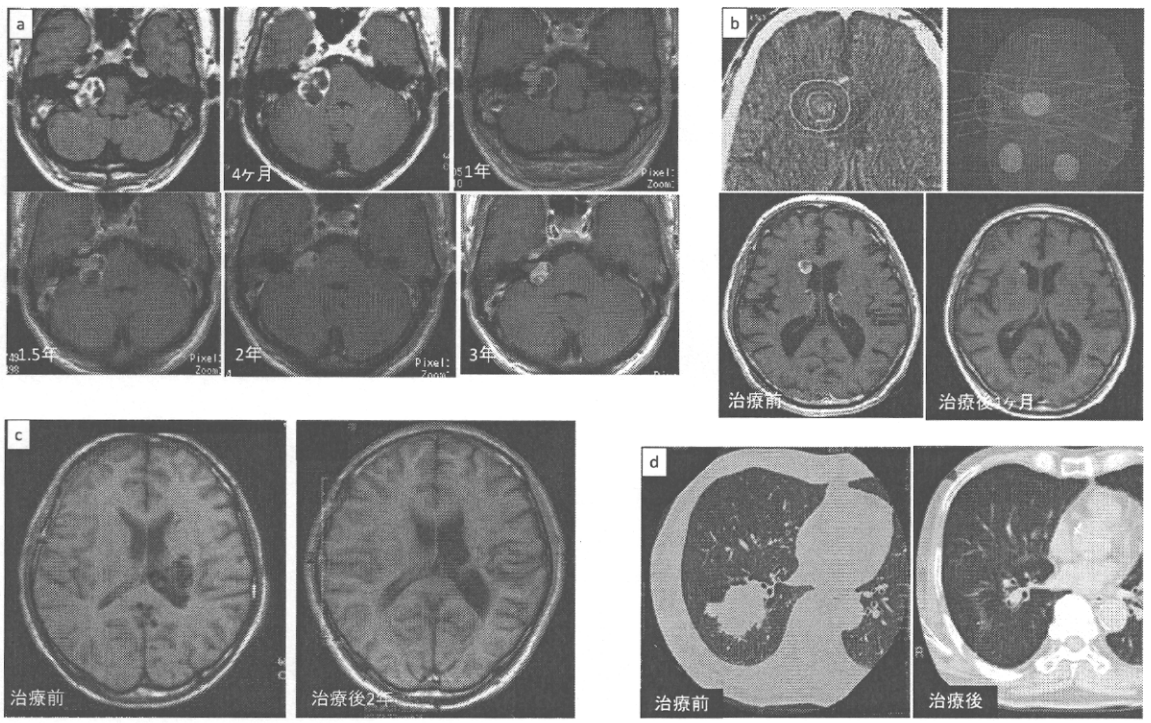

図3　定位照射の代表的疾患における治療前後の画像変化：聴神経鞘腫（a）、転移性脳腫瘍（b）、脳動静脈奇形（c）、非小細胞肺癌（d）

内病変では頭頂側からビーム入射が可能であるためIMRTは必ずしも必要ではないが、体軸に垂直な断面からしか入射できない体幹部病変で、線量分布に2カ所以上の凹を作る必要がある場合が良い適応となる。**図4**に代表的疾患におけるIMRTの線量分布を示す。最も広く使われているのは前立腺癌である（**図4a**）。前立腺癌の場合はすぐ背側に位置する直腸がリスク臓器であり、IMRTを含む外照射の最大の欠点は3-5％で起こる直腸出血である。これも晩期に分類される障害であり、照射終了後8か月以降に発生する。この発生リスクを低減させるためには一定以上の線量が照射される直腸体積を下げることが鍵となる。特に線量に依存したPSA非再発率の低下が期待できる中～高等度リスク群ではとりわけ重要となる。また確立された方法とは言えないが、前立腺中心部を貫く様に位置する尿道線量を抑えることもIMRTでは可能となる。頭頸部癌、特に放射線治療での高い治癒率が証明されている上咽頭癌では、耳下腺をはじめとした唾液腺線量を下げることが難治性口腔内乾燥の程度を抑えるために重要となる（**図4b**）[10,11]。脳病変では大きな体積と複雑な形状を持ち、視交叉、視神経、眼球、脳幹、内頸動脈などのリスク臓器に近接した頭蓋底腫瘍は良い適応と考える（**図4c**）。

IMRTを行うためにはマルチリーフコリメータ（MLC）が必要である。一方向からのビーム内でMLCを出し入れすることでモザイク状の線量分布を作り、この様なビームを複数組み合わせることではじめて複雑な形状をもった線量分布を得ることが可能となる（**図5**）。このような計算は人間の頭脳では不可能であり、あらかじめ治療計画用CTの上で照射ターゲットとリスク臓器を囲み、それぞれに対して最低線量と最高線量を規定して、それに従った線量分布をコンピュータに作成させる方法がとられる。ただし、この線量分布作成の部分がブラックボックスになってしまうため、できあがった分布が本当に正しいのか、患者に用いても大丈夫なのかを精密に検証する必要がある。これは従来の診療放射線技師や放射線腫瘍医の業務範疇を大幅に超えており、安全にIMRTを行うためには品質管理を専らの業務とする職種

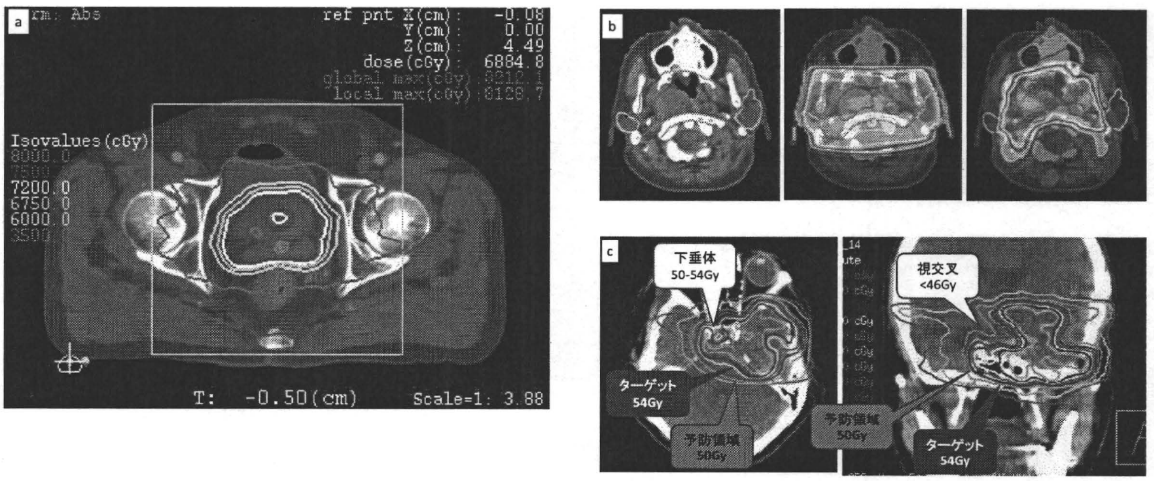

図4　強度変調放射線治療の線量分布：前立腺癌（a）、上咽頭癌（b）、頭蓋底髄膜腫（c）

（医学物理士や品質管理士）が必須となる。もともと医学物理士が常在し、日常の品質チェックを行ってきた欧米では大きな問題とはならなかったが、医師と技師のみで照射する体制が染みつき医学物理士が認知されているとは言えない日本において、この状況を改善するのは容易ではない。最近になり幾つかの大学では医学部に医学物理士養成コースが設立され、徐々にではあるが成果を挙げつつある。

画像誘導放射線治療（Image-guided radiation therapy, IGRT）

これは画像情報をフル活用した放射線治療のことを意味し、①治療計画用CTにプラスアルファとしてMRIやPETなどを用いることで治療計画時の情報量を増し、照射ターゲットの形状と放射線を照射したくない領域の形を正確に把握し放射線治療計画をより精密にするという考え方、②ライナックに装着された透視画像装置などを用いて、患者が実際に治療台に寝ている状態で画像取得し、これとあらかじめ治療計画用CTで撮像されていた画像と合わせ込むことで位置再現精度を高める方法が含まれている。

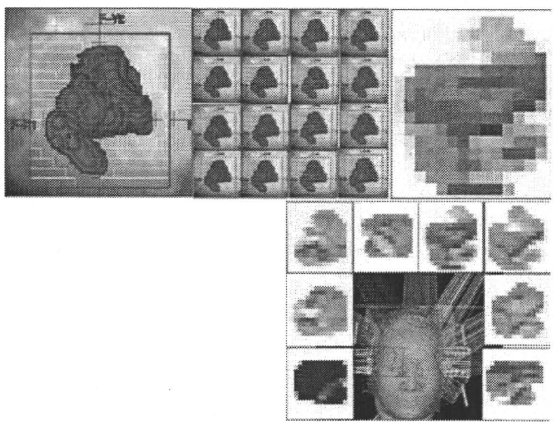

図5　強度変調照射の原理

①の例としてこれまで我々が行ってきた取り組みを示す。1999年にMRIと治療計画用CTをfusionさせる装置を開発し、脳腫瘍に対する放射線治療の計画に用いてきた。その結果、骨のアーチファクトが強い後頭蓋窩に位置する病変や造影される病変周囲にみられる浮腫を照射ターゲットとするようなグリオーマでは、異なる観察者間におけるターゲット体積のバラツキを約40％から15％程度まで低下させることができることが示唆された[12]。また脳磁図やfunctional MRI、拡散強調MR画像で描出された錐体路の情報を治療計画に統合することで、錐体路部が脳壊死のリスクである15Gy以上照射される体積を有意に減らせることも示された[13]。現在、画像診断手法の進歩は日進月歩であり、例えば放射線抵抗性である低酸素領域の情報を治療計画に取り込み、その部位の線量をSRIやIMRTなどの照射法を用いることで増加させる試みなどがされており、今後も研究領域としても興味深い領域である。②について

は、例えば7月から新潟大学において稼働を開始した高精度照射装置（図2）には、直交する二軸の透視装置を用いて骨構造を合わせ込む機能、ライナックに装着されたCTを見ながら臓器で合わせ込む機能、赤外線マーカーを用いることで呼吸サイクルに同期した照射をする機能、IGRTで計測されたずれを6軸方向で0.1mmの精度で補正する天板など現時点で考えられる最先端の機能が搭載されていることから、物理的精度の高い照射への期待が高まっている。

高精度放射線治療に関するエビデンス（結語にかえて）

脳定位照射が世界に普及してから既に20年が経過しようとしている。しかしながら現在のところ無作為割り付け試験に基づいたレベル1エビデンスは転移性脳腫瘍と膠芽腫に限られる。転移性脳腫瘍に関する無作為割り付け試験としては、全脳照射単独治療群と全脳照射＋定位照射併用群を比較した試験（RTOG9508）と定位照射単独治療と定位照射＋全脳照射併用群を比較した試験（JROSG99-1）がある。前者では孤立性脳転移では全脳照射に定位照射を加えることで頭蓋内腫瘍制御率のみならず全生存率も向上する可能性が示された[1]。また本邦で行われた後者の研究では定位照射単独治療は全脳照射併用治療と比べて全生存率に差はないものの、頭蓋内腫瘍再発率は約3倍高く、認知機能温存期間も短い傾向にあることが示された[2),14)]。膠芽腫に関しては、60Gyの通常照射にSRSを加えても再発率、再発様式、生存率のいずれもメリットはないということが示された[15)]。現在のところ脳定位照射の当初のコンセプトである「脳手術に置き換わる治療法」であることを証明した研究は存在しない。これは脳定位照射の良い適応とされ、既に標準治療に組み込まれた感のある脳神経由来の神経鞘腫や脳動静脈奇形についても同様であり、この仮説を証明するような臨床研究デザインの難しさを物語っている。体幹部定位照射については国内においてはJCOG放射線治療グループが主体で第Ⅱ相臨床試験を立ち上げ、現在検証している段階であり、まだ開発から10年も経過していない未熟な技術であることを熟知した上で行うべきである。強度変調放射線治療に関しても、無作為割り付け試験は上咽頭癌で二つ[10),11)]、乳癌で二つ[16),17)]あるに過ぎない。いずれも有害反応の程度をエンドポイントとして評価できる様にデザインされた研究である。前者については、強度変調放射線治療によって口腔乾燥症の程度を改善させることが証明されたが、後者では明確な結論を得るに至らなかった。

このように、新技術は常に大きな期待を背負って誕生するものであるが、そのメリットを証明するのは概して困難なものである。我々臨床医は過度な期待を持つことなく科学者としての冷静な眼をもって評価、検証していくという姿勢をもち続けることが大切であろう。これは新規薬剤を扱った臨床研究などにも当てはまることである。

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CLINICAL INVESTIGATION

RELATIONSHIP BETWEEN DISEASED LUNG TISSUES ON COMPUTED TOMOGRAPHY AND MOTION OF FIDUCIAL MARKER NEAR LUNG CANCER

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Purpose: For lung cancer patients with poor pulmonary function because of emphysema or fibrosis, it is important to predict the amplitude of internal tumor motion to minimize the irradiation of the functioning lung tissue before undergoing stereotactic body radiotherapy.

Methods and Materials: Two board-certified diagnostic radiologists independently assessed the degree of pulmonary emphysema and fibrosis on computed tomography scans in 71 patients with peripheral lung tumors before real-time tumor-tracking radiotherapy. The relationships between the computed tomography findings of the lung parenchyma and the motion of the fiducial marker near the lung tumor were investigated. Of the 71 patients, 30 had normal pulmonary function, and 29 had obstructive pulmonary dysfunction (forced expiratory volume in 1 s/forced vital capacity ratio of <70%), 6 patients had constrictive dysfunction (percentage of vital capacity <80%), and 16 had mixed dysfunction.

Results: The upper region was associated with smaller tumor motion, as expected ($p = .0004$), and the presence of fibrosis ($p = .088$) and pleural tumor contact ($p = .086$) were weakly associated with tumor motion. The presence of fibrotic changes in the lung tissue was associated with smaller tumor motion in the upper region ($p < .05$) but not in the lower region. The findings of emphysema and pulmonary function tests were not associated with tumor motion.

Conclusion: Tumors in the upper lung region with fibrotic changes have smaller motion than those in the upper region of the lungs without fibrotic changes. The tumor motion in the lower lung region was not significantly different between patients with and without lung fibrosis. Emphysema was not associated with the amplitude of tumor motion. © 2010 Elsevier Inc.

Lung tumor motion, lung fibrosis, emphysema, real-time tumor-tracking radiotherapy.

INTRODUCTION

Focused, high-dose radiotherapy has been increasingly indicated for inoperable peripheral lung cancers (1–3). Inoperable patients with such tumors often have moderate to severe pulmonary function impairment from morphologic changes of the diseased lung such as pulmonary emphysema, inflammatory changes, and fibrosis with or without previous thoracic surgery. It is crucial to minimize the irradiation volume of the functioning lung tissue for these patients. Accordingly, it is important to predict the amount of tumor motion from the clinical and radiologic findings before treatment to determine adequate internal margins for the clinical tumor volume during radiotherapy for these patients.

Previous studies have shown that simple pulmonary function, as assessed by such parameters as vital capacity and forced vital capacity, does not have predictive value for tumor motion (4, 5). In addition, these simple tests have recently been shown to be inadequate for the assessment of obstructive disease, and more precise criteria for pulmonary function have been recommended (6). However, the morphologic changes of the lung tissue around the tumor, as measured using high-resolution computed tomography (CT), which has

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been shown to be useful for the evaluation of obstructive, inflammatory, and fibrotic changes of the lung, might be useful for predicting tumor motion (7, 8). Therefore, in the present study, we compared two parameters with respect to their efficacy in predicting tumor motion: the global standard of pulmonary function in the presence of obstructive lung disease and the morphologic changes of the diseased lung around the tumor. These two parameters were compared with the trajectory of the fiducial marker near the tumor, as measured during real-time tumor-tracking radiotherapy (RTRT), which has been shown to be useful for estimating the amplitude of the tumor (9–12).

METHODS AND MATERIALS

After inserting a fiducial marker near the lung cancer, a planning CT scan was performed while the patients held their breath at the end of expiration. We used an RTRT system that can track a gold marker in the patient's body during actual irradiation of the therapeutic beam as previously reported (9, 10). The patients were asked to relax on the treatment table, and no additional method was used to control the patient's respiration during actual RT. The advantage of RTRT is that the motion of the fiducial marker can be automatically detected using a pattern recognition method during delivery of the treatment beam every 0.033 s (9). The linear accelerator was gated to irradiate the tumor only when the fiducial marker was within gating window, usually ±2.0 mm from its planned position. Therefore, even if the magnitudes of tumor motion between the CT plan, initial setup, and during treatment were different, we would not need to replan or expand/contract the internal margin at different points during treatment. The treatment time could be prolong if the tumor motion magnitude has increased because the linear accelerator must wait longer for the fiducial marker to come into the gating window at the end of exhalation. If the baseline of the tumor motion changes during RT, we adjusted the table position for the trajectory of the marker position to come into the gating window (10).

Three to four fiducial markers with a diameter of 1.5 mm were inserted through a bronchial fiberscope near the lung tumor (11). The coordinates of one of the markers nearest to the tumor were recorded in the log files at intervals of 0.033 s using the RTRT system (12). To measure marker movement, the log files of the RTRT system were analyzed using a previously described computer program (10).

In the present study, the x, y, and z directions were consistent with the left–right, craniocaudal, and anteroposterior directions, respectively. We assumed that the motion of fiducial markers nearest to the tumor, usually within 1 cm of the tumor boundary, was the actual tumor motion in the x, y, and z directions. The amplitude of the fiducial marker differed from patient to patient and also fluctuated within the same patient during treatment. Therefore, we randomly sampled the respiratory cycles from each patient. The mean ± standard deviation (SD) of the sampling numbers of the respiratory cycle was 79 ± 53 for 1 patient. The variations in the sampling numbers of the respiratory cycle resulted from the treatment time length, not researcher preference. We first measured the mean amplitude and SD of the amplitude during treatment for each patient to represent our data series. Because it is important to know the distance the actual tumor is likely to move in the thoracic space during RT, we also measured the maximal three-dimensional amplitude during treatment for each patient.

The three-dimensional maximum movement was estimated from the following formula using the mean ± SD of the amplitude along each direction:

$$\text{Estimated three} - \text{dimensional maximal movement(in mm)} = \sqrt{x^2 + y^2 + z^2}$$

Thus, each patient had only one "estimated three-dimensional maximal movement."

Chest CT images were acquired to plan the RT for all patients within 1 week after the insertion of the gold markers and within 1 week before the start of RT. We used a four-detector acquisition high-resolution CT (Aquilion Multi Toshiba, Tokyo, Japan) to evaluate the morphologic changes in the lung tissue. In all cases, we scanned the entire lung in the exhale position. Contrast medium was not used for the chest CT scan. All scan data were reconstructed using 1 × 1 × 1-mm voxels.

Two board-certified diagnostic radiologists independently interpreted the CT images to assess the presence of fibrotic changes. Grossly speaking, a diagnosis of fibrotic changes was made when nonsegmental reticular abnormalities and ground-glass attenuation were observed in the lung parenchyma (Fig. 1). The percentage of low attenuation volume (%LAV) was used to quantify the pulmonary emphysema objectively (13–15). The %LAV was calculated as the area under the curve (AUC) under the cutoff line low attenuation value at −950 Hounsfeld units divided by the total AUC using the Virtual Place Advanced software package (AZE, Tokyo, Japan) and workstation according to the following formula: %LAV = 100 × AUC of under −950 Hounsfeld units/total AUC of total CT density distribution.

The tumor location was categorized into two groups as follows: the upper region ($n = 41$), for tumors restricted to the right or left upper lobes without lingual segment; and the lower region ($n = 30$), for tumors involving the middle and right lower lobe and tumors in the lingual segment and left lower lobe. The presence of pleural contact of the tumor, which could be a sign of tumor fixation to the chest wall and a reduction in tumor motion, was also diagnosed using the same CT scan. The maximal tumor diameter on the transaxial CT planes was defined as the tumor size.

The pulmonary functions and body mass index of all patients were assessed before RT. The ratio of forced expiratory volume in 1 s to forced vital capacity ($FEV_1/FVC \times 100 = FEV_1/FVC$) and the percentage of vital capacity (%VC) were evaluated (6).

JMP, version 7.0.1 (SAS Institute Japan, Tokyo, Japan) was used for statistical analysis. Because the estimated three-dimensional maximal movement does not necessarily have a normal distribution, we used the median of the estimated three-dimensional maximal movement in the following analysis and used a nonparametric statistical analysis. The correlation coefficient (Spearman's correlation coefficient using the rank test) was calculated between the effects of various factors and the estimated three-dimensional maximal tumor movement. The Mann-Whitney U test was used to compare the median values between the two groups. A probability value of $<.05$ was considered statistically significant.

RESULTS

A total of 71 patients (52 men and 19 women) treated between 2001 and 2006 were entered into the present study (Table 1). All the patients underwent stereotactic, hypofractionated, high-dose, small-field irradiation using the RTRT system. The median patient age was 73 years (range,

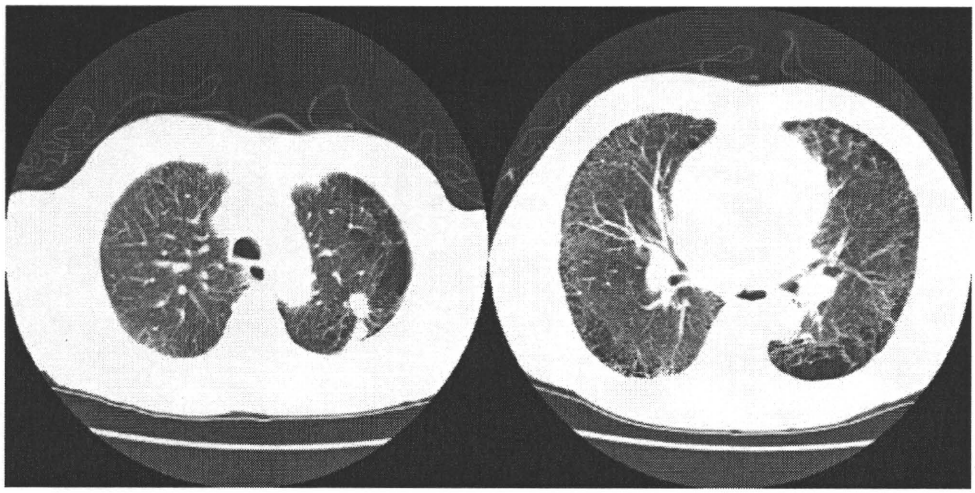

Fig. 1. Example of lung tumor in left upper region of patient with fibrotic changes in lung. Mean ± standard deviation amplitude in *x*, *y*, and *z* directions was 2.4 ± 0.3, 4.1 ± 0.8, and 2.8 ± 0.2 cm, respectively. Tumor was treated with real-time radiotherapy and controlled well.

36–85). Of the 71 patients, 56 had primary lung cancer and 6 had metastatic lung tumor from other organs; for 9 patients, the etiology was unknown. The maximal tumor diameter was 0.5–7.4 cm (median, 2.7). Four patients had previously undergone surgical lobectomy. No patient had thoracic nodal involvement, as determined from the radiologic examinations.

Of the 71 patients, 20 had normal pulmonary function, 29 had obstructive pulmonary dysfunction (FEV_1/FVC ratio <70%), 6 had constrictive dysfunction (%VC <80%), and 16 had mixed dysfunction. The mean ± SD for the FEV_1/FVC ratio and %VC was 62.5% ± 16.9% and 94.9% ± 25.7%, respectively. A significant negative correlation was found between the FEV_1/FVC ratio and log %LAV (correlation coefficient, −0.494; p <.0001), confirming that the %LAV has morphometric value for pulmonary emphysema (Fig. 2).

The mean ± SD of the mean amplitude among the 71 patients was 3.7 ± 4.6, 6.7 ± 6.2, and 4.4 ± 4.8 mm along the right–left, craniocaudal, and anteroposterior direction, respectively. The mean ± SD of the amplitudes among the 71 patients was 1.2 ± 2.2, 1.8 ± 2.8, and 1.1 ± 1.5 mm along the right–left, craniocaudal, and anteroposterior direction, respectively.

The mean ± SD of the amplitude of the fiducial marker among the 71 patients was 0.2–32.1, 0.2–31.2, and 0.5–34.8 mm along the right–left, craniocaudal, and anteroposterior direction, respectively. The estimated three-dimensional maximal movement was calculated using these data for each patient. The median of the estimated three-dimensional maximal movement of the 71 patients was 11.9 mm (range, 1.79–50.38).

The relationship between each factor and the estimated three-dimensional maximal movement, which we used as the surrogate for tumor motion in the present study, is listed in Table 2. The presence of fibrosis was weakly associated with tumor motion, but this association did not reach statistical significance (p = .088). Pulmonary emphysema, as estimated by the %LAV, was not associated with tumor motion. The median of the estimated three-dimensional maximal movement in the lower regions of the lung was significantly larger than that in the upper regions, as was expected (p = .0004). The presence of pleural contact of the tumor was weakly associated with tumor motion, but this association did not reach statistical significance (p = .086). Tumor size was not associated with tumor motion. The body surface area and the results of the pulmonary function tests, FEV_1/FVC ratio and %VC, also were not associated with tumor motion. The median of the estimated three-dimensional maximal movement in the four postoperative patients was smaller than that of the patients without previous surgery (p = .001).

Next, we examined the influence of fibrotic changes on tumor motion in the upper region and the lower region (Fig. 3). In the upper region, the tumor motion was significantly less in the lungs with fibrotic changes than in those without fibrotic changes (p <.05). In the lower region, no significant influence of fibrotic changes on tumor motion was found.

An estimated three-dimensional maximal movement of >20 mm was seen in 10 patients. In contrast to the general tendency of smaller tumor motion in the upper region, 6 of the 10 tumors with >20 mm of movement were located in the upper region.

The combination of FEV_1/FVC ratio and log %LAV was not effective for predicting tumor motion (Fig. 2). The combination of the %VC and $\%FEV_1$/FVC ratio was also ineffective (Fig. 4).

DISCUSSION

Fibrotic or emphysematous changes of lung tissue are known to produce dynamic changes in respiratory function. Hyperinflation of the lung can affect the motion of the diaphragm (16) and can result in so-called paradoxical motion (17). Pleural adhesion of lung cancer can also be associated

Table 1. Patient characteristics

Characteristic	Value
Gender *(n)*	
Male	52
Female	19
Age (y)	
Median	75
Range	36–85
Body surface area (m^2)	
Median	1.57
Range	1.22–2.19
Postoperative lung *(n)*	
Yes	4
No	67
Pulmonary function test results	
FEV_1/FVC	
Median	63.0
Range	31.4–96.0
%VC	
Median	95.3
Range	40.1–153.8
Morphologic changes in lung	
Presence of fibrosis *(n)*	
Yes	27
No	44
%LAV	
Median	0.4
Range	0.0–45.2
Histopathologic diagnosis *(n)*	
Adenocarcinoma	35
Squamous cell carcinoma	20
Large cell carcinoma	1
Metastasis	6
Unknown	9
Tumor location *(n)*	
Upper	41
Lower	30
Right	39
Left	32
Right upper	21
Right lower	18
Left upper	15
Left lower	17
Tumor size (mm)	
Median	27
Range	5–74
Pleural contact *(n)*	
Yes	49
No	22
Nodal involvement *(n)*	
Yes	71
No	0

Abbreviations: FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; %VC = percentage of vital capacity; %LAV = percentage of low attenuation volume.

with restricted tumor motion (10). Cardiopulmonary function also affects the tumor mobility and respiration patterns to a certain degree because of the difference in cardiac beat, ejection fraction, and tidal volume (10).

Our results have demonstrated that tumor motion is significantly smaller in the upper region of lungs with fibrotic changes compared with those without fibrosis. In the lower lung region, the presence of fibrosis did not significantly

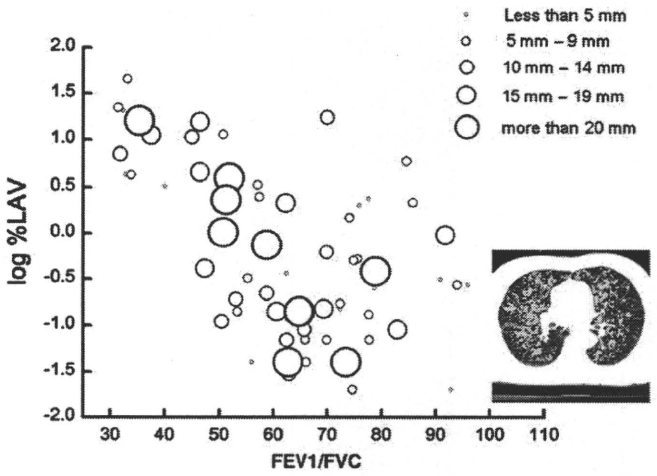

Fig. 2. Distribution of tumor motion according to forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio and log percentage of low attenuation volume (%LAV). Blue area in computed tomography image indicates area for which computed tomography value was lower than threshold of −950 Hounsfeld units and used for estimation of %LAV. Circle sizes indicate estimated three-dimensional maximal movement of tumors in lung with log (%LAV) value in patients with FEV_1/FVC value.

influence tumor motion, probably because the motion in this region is affected dominantly by the motion of the diaphragm. In contrast, of the 10 tumors with an estimated three-dimensional maximal movement of >20 mm, 6 were located in the upper lung region. This conflicting finding suggests the difficulty in predicting the internal margin for individual patients (16).

It is well known that the amount of diaphragmatic motion often decreases in patients with an emphysematous lung (17). Tumors in the normal lung move mostly in a craniocaudal direction because of diaphragmatic motion (18). We, therefore, hypothesized that pulmonary emphysema could be a cause of reduced tumor motion. We are certain that the %LAV is a reasonable parameter to estimate the severity of emphysema,

Table 2. Relationship between each factor and tumor motion

Variable	Correlation coefficient	*p*
Body surface area	0.128	0.296
Postoperative lung (yes vs. no)	4.67	.001
Pulmonary function tests		
FEV_1/FVC	−0.157	.196
%VC	0.162	.184
Morphologic changes in lung		
Presence of fibrosis (yes vs. no)	0.088	
%LAV	0.021	.858
Tumor characteristics		
Tumor location		
Upper or lower	0.0004	
Right or left	0.326	
Right upper or right lower	0.026	
Left upper or left lower	0.057	
Tumor size	−0.021	.859
Presence of pleural contact (yes vs. no)	0.086	

Abbreviations as in Table 1.

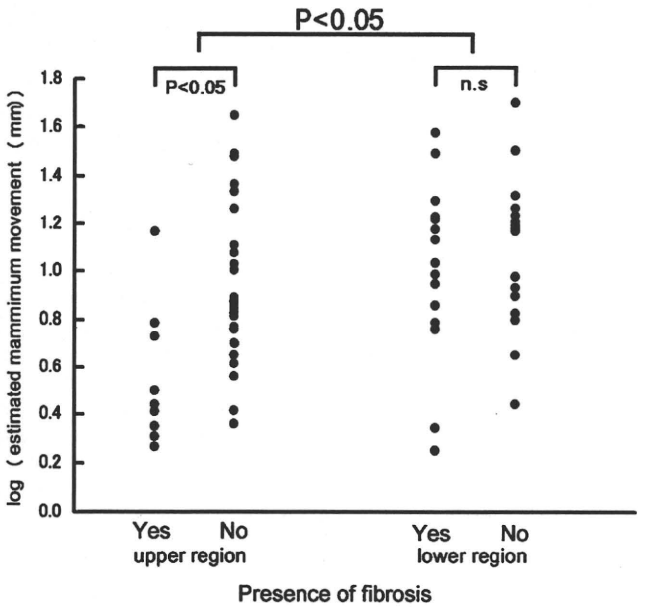

Fig. 3. Relationship between tumor motion and presence of fibrosis by region. Black symbols indicate fibrotic tumors; white symbols, nonfibrotic tumors. Significant difference found in amount of tumor motion in upper region between tumors with and without fibrosis and between tumors in upper and lower regions. No significant relationship found between tumor motion and presence of fibrosis in lower region tumors.

because the %LAV was significantly associated with the FEV_1/FVC ratio in the present study. Such an association has also been suggested by other investigators (13, 15). However, the results from the present study showed no significant reduction in tumor motion with an increase in the %LAV. Recent studies have shown that the diaphragm sometimes exhibits so-called paradoxical motion. (17, 19). Emphysema can cause complex tumor motion, resembling the complex motion of the diaphragm, rather than simply causing a reduction in tumor motion.

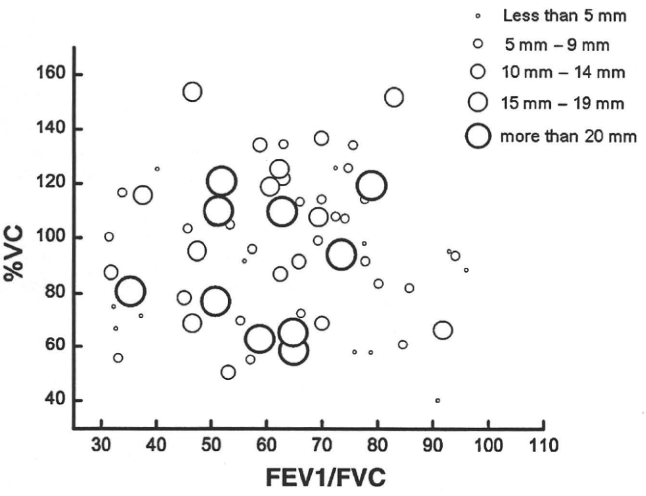

Fig. 4. Distribution of tumor motion according to forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio and percentage of vital capacity (%VC). No statistically significant correlation found between FEV_1/FVC ratio and %VC.

We have previously shown that neither the VC alone nor the FEV_1 alone is associated with tumor motion (5). However, pulmonologists have suggested that the %VC and the FEV_1/FVC ratio should be used instead of the VC and FEV_1 to assess its pathologic meaning (6). We, therefore, used these combined parameters in the present study; however, we found that these variables still had no significant value for predicting tumor motion, even in this form.

The present results have suggested the usefulness and limitation of CT assessment before RT. Moreover, as we had previously published (18), the speed and amplitude of the tumor motion was variable, even in the same patient on different treatment days. Thus, the assessment of tumor motion on the initial treatment day might not be applicable on the second treatment day. A stereotactic body frame and rhythm generators were shown to not be useful in reducing these uncertainties in a recent study (20). Image-guided RT using onboard cone-beam CT (21), four-dimensional cone-beam CT guidance (22), a margin model based on the internal motion (23), or gating using external signals (24) have been useful to reduce daily setup error and lung motion uncertainties to some extent; however, these all have limitations for intrafractional variations in tumor motion.

The treatment results of RTRT for Stage T1N0M0 non–small-cell lung cancer were encouraging using 48 Gy in four fractions (25). In RTRT, as long as the position of the marker relative to the tumor mass is not different from its planned position at the end of the exhalation phase, any irregularity in the tumor trajectory will not affect the accuracy of irradiation. Therefore, we have not customized the margins for each patient when using the RTRT system. We used 5-mm planning target volume margins in RTRT to cover the possible residual errors such as discrepancies in the respiratory phase between the planning stage and the actual treatment, minor displacements of the fiducial marker, and shrinkage of the tumor during the 1-week treatment period. However, when we could not insert fiducial markers near the tumor, we used an individualized internal margin for each tumor by taking CT scans at three different respiratory phases (26). From the findings in the present study, we would be able to reduce the internal margin for tumors in the upper lobe with fibrotic changes but not for tumors in the upper lobe without fibrotic changes when treating patients without fiducial markers. In RTRT, using a treatment time >1 week might require replanning or margin expansion/contraction, because the distance between the tumor and fiducial marker could be different from its planned position.

CONCLUSION

The tumor location remained an important parameter, as expected, but tumor motion >20 mm was seen as often in the upper region as in the lower region. Although conventional static CT images and pulmonary function tests were still inadequate for predicting the internal margins, fibrotic changes in the lung and pleural contact of the tumor were

weakly associated with tumor motion. In particular, fibrotic changes in the lung were associated with tumor motion in the upper region. The presence of emphysema, as estimated by the %LAV on the CT scans, was not associated with tumor motion. At present, we do not have a simple method to predict the tumor motion using pulmonary pretreatment tests and CT images to avoid the potential for target volume miscoverage. The results of the present study have suggested an additional guide for avoiding miscoverage of the target volume and a caution for simple stratification of patients into those with upper and lower lung region tumors in the determination of the internal margin.

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PHYSICS CONTRIBUTION

EVALUATION OF THE EFFECTIVENESS OF THE STEREOTACTIC BODY FRAME IN REDUCING RESPIRATORY INTRAFRACTIONAL ORGAN MOTION USING THE REAL-TIME TUMOR-TRACKING RADIOTHERAPY SYSTEM

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Purpose: To evaluate the effectiveness of the stereotactic body frame (SBF), with or without a diaphragm press or a breathing cycle monitoring device (Abches), in controlling the range of lung tumor motion, by tracking the real-time position of fiducial markers.

Methods and Materials: The trajectories of gold markers in the lung were tracked with the real-time tumor-tracking radiotherapy system. The SBF was used for patient immobilization and the diaphragm press and Abches were used to actively control breathing and for self-controlled respiration, respectively. Tracking was performed in five setups, with and without immobilization and respiration control. The results were evaluated using the effective range, which was defined as the range that includes 95% of all the recorded marker positions in each setup.

Results: The SBF, with or without a diaphragm press or Abches, did not yield effective ranges of marker motion which were significantly different from setups that did not use these materials. The differences in the effective marker ranges in the upper lobes for all the patient setups were less than 1mm. Larger effective ranges were obtained for the markers in the middle or lower lobes.

Conclusion: The effectiveness of controlling respiratory-induced organ motion by using the SBF+diaphragm press or SBF + Abches patient setups were highly dependent on the individual patient reaction to the use of these materials and the location of the markers. They may be considered for lung tumors in the lower lobes, but are not necessary for tumors in the upper lobes. © 2010 Elsevier Inc.

Organ motion, Body frame, Real-time tracking, Effective range.

INTRODUCTION

The risk of radiation-induced lung complications may be minimized if intrafractional tumor motion caused by respiration during irradiation can be accurately accounted for. Various approaches to the management of respiratory motion in radiation therapy are comprehensively discussed in the American Association of Physicists in Medicine (AAPM) Report 91 (1). These include the accurate tracking of organ and tumor motion during treatment and methods by which the motion may be restricted or dampened.

Motion tracking may be accomplished by taking two sets of fluoroscopic images of the tumor itself, other anatomical structures, or fiducial markers placed near the tumor (2–4). Ideally, the function of real-time tracking is to determine the full range of tumor motion, as well as its trajectory during treatment from these fluoroscopic images taken at high frequency. At present, this is only possible in a few centers that have facilities dedicated for this purpose, such as the real-time tumor-tracking radiation therapy system developed at Hokkaido University Hospital (5, 6).

Restriction of respiration, on the other hand, can be achieved by using patient immobilization and by applying abdominal pressure. In extracranial stereotactic irradiation, Lax *et al.* (7), Herfarth *et al.* (8), and Negoro *et al.* (9) have reported the effectiveness of an abdominal press in reducing respiratory-induced tumor movement in stereotactic conformal radiation therapy of body tumors. Alternatively, an

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Conflict of interest: This study was conducted in cooperation with Elekta Oncology Systems, Japan.

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air-injected blanket has also been suggested for abdomen compression and fixation (10) to reduce breathing-induced organ motion.

In this study, we evaluated the effectiveness of a body frame and its combination with a diaphragm press in restricting the range of lung tumor motion by tracking the three-dimensional real-time position of fiducial gold markers embedded near the tumor. We also investigated the effect on respiratory-induced organ motion of using the stereotactic body frame (SBF) together with a breathing cycle monitoring device (Abches), which was used to self-regulate the patient's breathing cycle.

MATERIALS AND METHODS

The real-time tumor-tracking radiotherapy system

The three-dimensional trajectories of fiducial markers near or at tumor sites were tracked via the real-time tumor-tracking radiotherapy (RTRT) system at the Radiotherapy Department of Hokkaido University Hospital (5, 6, 11, 12). This fluoroscopy-based system is composed of two pairs of an X-ray source and image intensifier and an image acquisition and recognition unit that is interfaced with a linear accelerator to perform gated-irradiation. The positions of the gold markers were acquired every 0.033 s.

Body frame, diaphragm press, and breathing cycle monitor

For patient immobilization, we used Elekta's SBF (Elekta Oncology Systems) (13, 14). The same body frame was used in an earlier investigation on respiratory tumor movement and setup error verification using X-ray simulator images (7, 9, 15). The SBF is made from a rigid material formed into a half-hexagonal shell that wraps around the patient's torso. Because of the restricted space inside the shell, the patient's arms had to be positioned outside the shell by raising them above the head. Patient fixation inside the body frame was accomplished by means of a vacuum pillow, the size of which was chosen to ensure that it could provide an exact fit to the patient's body contour.

An additional accessory to the SBF was a frame that supports a pentagonal plastic plate that can be placed against the patient's abdomen to restrict the diaphragm motion. The pressure applied by the plate was regulated depending on the tolerance of each patient and was used only in the part of our measurements where its effectiveness to control motion from respiration was evaluated.

A breathing cycle monitor (commercially available as Abches [APEX Medical Inc., Tokyo, Japan]) was also used in combination with the body frame to investigate whether self-regulated breathing can reduce the amplitude of respiratory-induced tumor and organ motion. As shown in Fig. 1, the Abches consists of two extended arms, one for detecting abdominal movement and the other for detecting chest movement, and a respiration range indicator visible to the patient through a mirror attached to the head during the measurement.

Patient demographics

The patient population for this study was composed of 16 males and 3 females who were scheduled to undergo radiation therapy using the RTRT system in our hospital between 2006 and 2008. Table 1 shows the characteristics of the cohort for this study. The patients' ages ranged between 59 and 85 years (mean, 76 years). Fourteen patients had T1 lung cancer, whereas 5 had T2 and 1 had T3. No patient had lymph nodes irradiation and none of the patients had metastasis. Four patients had partial lung resection before the irradiation.

Table 1. Characteristics of the cohort for this study

Parameters	Number of patients
Sex	
Male	16
Female	3
Age range	59–85 (mean, 76)
Gold marker locations	
Upper right lobe	5
Middle lobe	1
Lower right lobe	4
Upper left lobe	6
Lower left lobe	3
Cancer classification	
T1N0M0	13
T2N0M0	5
T3N0M0	1

The locations of the gold markers were judged based on where they appeared in the computed tomography images of the patient. We classified the sample population into "upper lobe" or "middle or lower lobe" patients according to the location of gold markers in the lungs, because it has been reported that the relative locations in

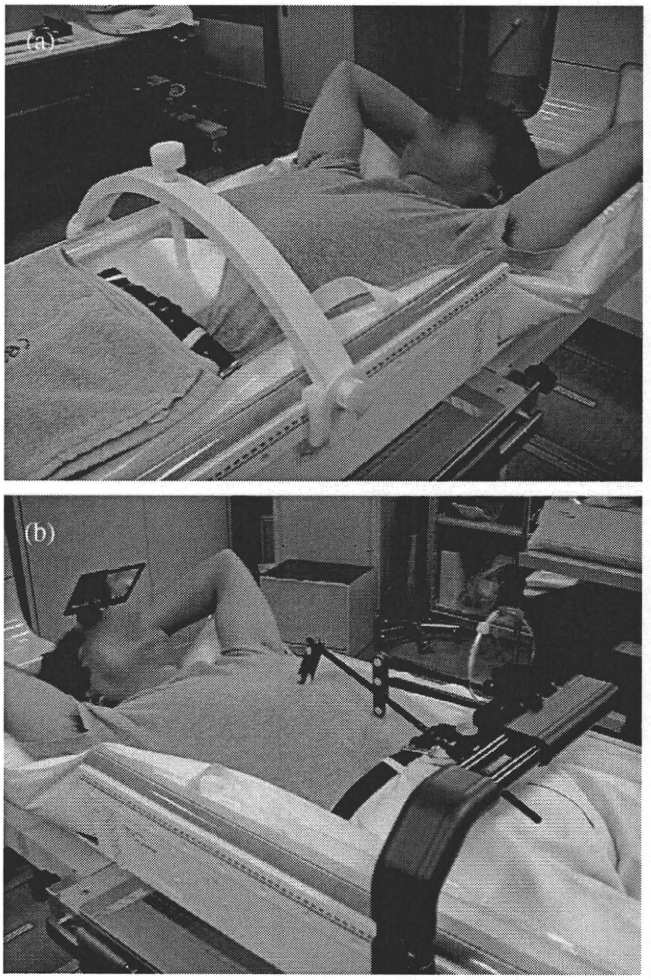

Fig. 1. Patient set-ups using the (a) stereotactic body frame (SBF)+diaphragm press (left) and the (b) SBF + Abches (right).