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CLINICAL INVESTIGATION

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

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Purpose: To review treatment outcomes for stereotactic body radiotherapy (SBRT) in medically operable patients with Stage I non–small-cell lung cancer (NSCLC), using a Japanese multi-institutional database.

Patients and Methods: Between 1995 and 2004, a total of 87 patients with Stage I NSCLC (median age, 74 years; T1N0M0, $n = 65$; T2N0M0, $n = 22$) who were medically operable but refused surgery were treated using SBRT alone in 14 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. Total dose was 45–72.5 Gy at the isocenter, administered in 3–10 fractions. Median calculated biological effective dose was 116 Gy (range, 100–141 Gy). Data were collected and analyzed retrospectively.

Results: During follow-up (median, 55 months), cumulative local control rates for T1 and T2 tumors at 5 years after SBRT were 92% and 73%, respectively. Pulmonary complications above Grade 2 arose in 1 patient (1.1%). Five-year overall survival rates for Stage IA and IB subgroups were 72% and 62%, respectively. One patient who developed local recurrences safely underwent salvage surgery.

Conclusion: Stereotactic body radiotherapy is safe and promising as a radical treatment for operable Stage I NSCLC. The survival rate for SBRT is potentially comparable to that for surgery. © **2010 Elsevier Inc.**

Stereotactic body radiotherapy, Lung cancer, Non–small-cell, Operable, Stage I.

INTRODUCTION

With the popularization of computed tomography (CT) screening, lung cancers are increasingly detected at an early stage. For patients with Stage I (T1 or 2, N0, M0) non–small-cell lung cancer (NSCLC), resection of the set of full lobar and systemic lymph nodes represents standard treatment. Five-year overall survival rates for clinical Stage IA and IB treated surgically are approximately 60–75% and 40–60%, respectively (1–3). However, a proportion of patients who meet the criteria for surgery refuse such intervention for various reasons. Radiotherapy offers a therapeutic alternative in such cases, but the effects of conventional radiotherapy in patients with Stage I NSCLC are unsatisfactory, with local control rates of approximately 50% during a short 5-year survival period in 15–30% of patients (4–7). Survival rates for conventional radiotherapy for a statistically sufficient number of cases of operable Stage I NSCLC have not been reported, because most

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patients receiving radiotherapy are inoperable. The poor local control rates with conventional radiotherapy have been attributed to doses of conventional radiotherapy that are too low to control the tumor. Mehta *et al.* (8) provided a detailed theoretical analysis of NSCLC responses to radiotherapy and a rationale for dose escalation. They concluded that higher biologically effective doses (BED) irradiated during a short period must be administered to achieve successful local control of lung cancer. To provide a higher dose to the tumor without increasing adverse effects, three-dimensional conformal radiotherapy techniques have been used, and better local control and survival have recently been reported (9–11). Over the last decade, hypofractionated high-dose stereotactic body radiotherapy (SBRT) has been actively performed for early-stage lung cancer, particularly in Japan (12–17). We have previously reported preliminary results for a Japanese multi-institutional review of 257 patients with Stage I NSCLC treated with SBRT (18). The results showed that local control and survival rates were better with BED $\geq$100 Gy than with <100 Gy, and survival rates were much better for medically operable patients than for medically inoperable patients. These results were encouraging, but the duration of follow-up for the study was somewhat short (median, 38 months), and we have not presented a detailed analysis of medically operable patients as a distinct subgroup. Although the standard therapy for operable Stage I NSCLC remains surgery, the effect of SBRT on medically operable patients is an issue of great concern. We provide herein detailed and matured results of SBRT (BED $\geq$100 Gy) for medically operable patients with Stage I NSCLC, using a retrospectively collected Japanese multi-institutional database.

PATIENTS AND METHODS

Eligibility criteria

All patients who satisfied the following eligibility criteria were retrospectively collected from 14 major Japanese institutions in which SBRT for lung cancer was actively performed: (*1*) identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdominal CT, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging; (*2*) histopathologic confirmation of NSCLC; (*3*) medically operable cancer but selection of SBRT after refusal to undergo surgery. Medical operability was discussed within the multidisciplinary tumor board of each institution according to respiratory function, age, and complicating diseases. Basic cutoff values for medical operability were World Health Organization performance status $\leq$2, pressure of arterial oxygen $\geq$65 mm Hg, predicted postoperative forced expiratory volume in 1 s $\geq$800 mL, no heart failure requiring pharmacotherapy, no diabetes requiring insulin, no severe arrhythmia, and no history of cardiac infarction. Positron emission tomography was not essential in the staging procedures.

Patients were informed of the concept, methodology, and rationale of this treatment, which was performed in accordance with the 1983 revision of the Declaration of Helsinki.

Table 1. Patient characteristics

Number (14 institutions)	87
Male	63
Female	24
Age (y), median (range)	74 (43–87)
ECOG performance status	
0	51
1	30
2	6
Histology	
Adenocarcinoma	54
Squamous cell carcinoma	25
Other	8
Stage	
IA	64
IB	23
Tumor diameter (mm), median (range)	25 (7–50)
IA	21
IB	39
Chronic lung disease	
Positive	38
Negative	49

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
Values are number unless otherwise noted.

Patient characteristics

A summary of patient pretreatment characteristics is given in Table 1. From April 1995 to March 2004, a total of 87 medically operable patients with primary NSCLC were treated using hypofractionated high-dose SBRT in 14 major Japanese institutions. Each of these 87 cases was judged medically operable, and surgery was initially recommended, but the patients declined surgery and selected SBRT as a radical treatment. Pathology of all tumors was confirmed as NSCLC by transbronchial or CT-guided percutaneous biopsy. The 14 participating institutions were these: Hokkaido University; Kyoto University; Cancer Institute Hospital; Tokyo Metropolitan Komagome Hospital; Kitasato University; Tohoku University; Hiroshima University; Tokyo Metropolitan Hiroo Hospital; Sapporo Medical University; Institute of Biomedical Research and Innovation; International Medical Center of Japan; Tenri Hospital; Kitami Red Cross Hospital; and Yamanashi University.

Treatment methods

Although the techniques to accomplish stereotactic methods differed among these institutions, all "stereotactic radiotherapy techniques" fulfilled the following five requirements: (*1*) reproducibility of the isocenter (setup error $\leq$5 mm), as confirmed by image guidance for every fraction; (*2*) respiratory motion (internal margin) suppressed using as much as possible, to <5 mm; (*3*) slice thickness on CT $\leq$3 mm for three-dimensional treatment planning; (*4*) irradiation with multiple noncoplanar static ports or dynamic arcs; and (*5*) single high dose $\geq$5 Gy.

Gross target volume (GTV) was delineated on CT images displayed with a lung window level. Clinical target volume (CTV) marginally exceeded GTV by 0–5 mm as judged by the individual radiation oncologist. Internal margin was

calculated and set around the CTV by 2–5 mm according to the individual measurements for respiratory motion of each institution. Internal margin caused by respiratory motion was reduced by gating, tracking, breath-hold technique, or abdominal compression. Planning target volume (PTV) comprised the CTV, a proper internal margin measured in each patient, and a 5-mm safety margin. The total margin between PTV and GTV was thus 7–15 mm. The irradiated port marginally exceeded PTV by 3–5 mm to secure the surface dose of PTV. Dose calculation was performed using the Clarkson algorithm and heterogeneity correction. A total dose of 45–72.5 Gy (mean, 58.7 Gy) at the isocenter in 3–10 fractions with single doses of 6.25–15 Gy was administered with 6-MV X-rays within 20% heterogeneity in the PTV dose. Minimum dose in the PTV corresponded to 85–95% of the prescribed dose in most cases. Typical dose/fractionation schedules were 75 Gy in 10 fractions for 42 patients and 48 Gy in 4 fractions for 38 patients. In principal, patients were treated on consecutive days, but some patients were treated every other day. No chemotherapies were administered before or during radiotherapy.

To compare the effects of various treatment protocols with different fraction sizes and total doses, BED was utilized in a linear-quadratic model (19). Biologically effective dose was here defined as $nd(1 + d/\alpha/\beta)$, with units of Gy, where n is fractionation number, d is daily dose, and α/β is assumed to be 10 for tumors. Biologically effective dose was not corrected with values for tumor doubling time or treatment term. Biologically effective dose was calculated at the isocenter in this study. Median calculated BED was 116 Gy (range, 100–141 Gy).

No restriction was placed on whether the tumor was located peripherally or centrally in the lung, but dose for the spinal cord was limited. Biologically effective dose limitation for spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity). Doses for other organs were not restricted.

Evaluation

The objectives of this study were to retrospectively evaluate toxicity, local control rate, and survival rate. Follow-up examinations were performed 4 weeks after treatment first, then patients were seen every 1–3 months. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors by CT (20). Chest CT (slice thickness, 2–5 mm) was usually obtained every 2 to 3 months for the first year and repeated every 4–6 months thereafter. Complete response indicated that the tumor had completely disappeared or was judged to have been replaced by fibrotic tissue. Partial response was defined as a ≥30% reduction in maximum cross-sectional diameter. Distinguishing between residual tumor tissue and radiation fibrosis was difficult. Any suspicious residual confusing density after radiotherapy was considered evidence of partial response, so actual complete response rate may have been higher than presented herein. Distinguishing between local recurrence and inflammatory change was also difficult. Here, local recurrence was considered to have occurred only when enlargement of the local tumor continued for >6 months on follow-up CT, obviously positive findings were identified on positron emission tomography, or histologic confirmation was acquired. Findings on CT were interpreted by two radiation oncologists in each case. Absence of local recurrence was defined as locally controlled disease. Lung, esophagus, bone marrow, and skin were evaluated using version 2 of the National Cancer Institute–Common Toxicity Criteria.

Statistical analysis

Cumulative rates of progression-free status at local, regional lymph node, and distant sites and survival were calculated and drawn using Kaplan-Meier algorithms, with day of treatment as the starting point. Subgroups were compared using log–rank statistics. Values of $p < 0.05$ were considered statistically significant. Statistical calculations were conducted using StatView version 5.0 software (SAS Institute, Cary, NC).

RESULTS

All patients completed treatment without obvious complaints. Median durations of observation for all patients and survivors as of final follow-up were 55 and 63 months, respectively.

Local tumor response

Complete response was achieved in 28 patients (32.2%), and partial response was seen in 43 patients (49.4%).

Toxicity

Radiation-induced pulmonary complications of National Cancer Institute–Common Toxicity Criteria (version 2.0) Grade 0, 1, 2, and 3 were noted in 21 (24.1%), 61 (70.1%), 4 (4.6%), and 1 patient (1.1%), respectively. Rib fracture and Grade 3 dermatitis were observed in 4 (4.6%) and 3 patients (3.4%), respectively. All tumors bordered the chest wall. Grade 3 radiation-induced esophagitis was produced in 1 patient, in whom the tumor slightly bordered the esophagus. Maximum esophageal dose in this case was 30 Gy in 5 fractions. No vascular, cardiac, or bone marrow complications had been encountered as of last follow-up. In total, Grade 3 toxicities were identified in 8 patients (9.2%).

No definite second malignancies were found during follow-up, but 1 patient died of acute myelogenous leukemia 3.7 years after completing SBRT.

Recurrence

Local recurrence, lymph node metastases, and distant metastases occurred in 8 (9.2%), 13 (14.9%), and 19 cases (21.8%), respectively.

Cumulative local progression–free rate curves according to stage are shown in Fig. 1. Cumulative local progression–free rate after 5 years was 86.7% (95% confidence interval [CI], 78.3–94.9%) for total cases. Cumulative local progression–free rate at 5 years was 92.0% (95% CI, 83.8–99.6%)

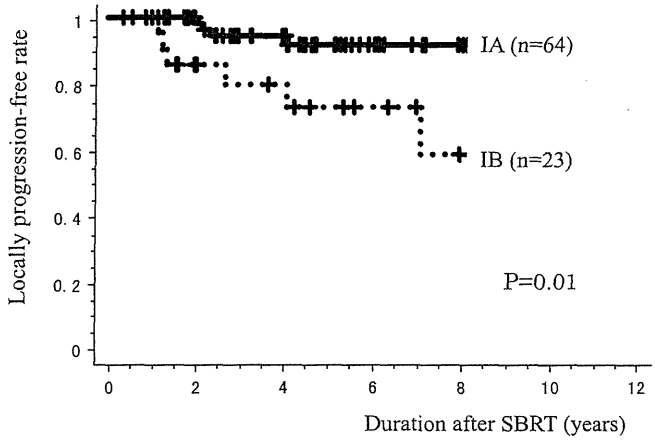

Fig. 1. Cumulative local progression–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

for the Stage IA subgroup, significantly superior ($p = 0.01$) to that for the Stage IB subgroup (73.0%; 95% CI, 52.2–93.7%). Five-year local progression–free rates were not significantly different between adenocarcinoma (80.9%; 95% CI, 68.7–93.1%) and squamous cell carcinoma (95.5%; 95% CI, 86.7–100.0%). One patient who developed local recurrence underwent surgery and has remained healthy for more than 3 years after operatively. The operation method was upper lobectomy and mediastinal lymphadenectomy, and they were performed safely without any trouble.

Cumulative curves of regional lymph node and distant metastases–free rates according to stage are shown in Figs. 2 and 3, respectively. The 5-year lymph node metastasis–free rate and distant metastasis–free rate for total cases was 85.3% (95% CI, 77.6–93.0%) and 75.1% (95% CI, 64.8–85.4%], respectively. No significant difference was identified between Stage IA and IB subgroups.

In patterns of regional nodal recurrence, 8 patients (61.5%) showed nodal failure alone, 2 patients (15.4%) had nodal failure combined with local failure, and 3 patients (23.1%) showed nodal failure combined with distant metastases.

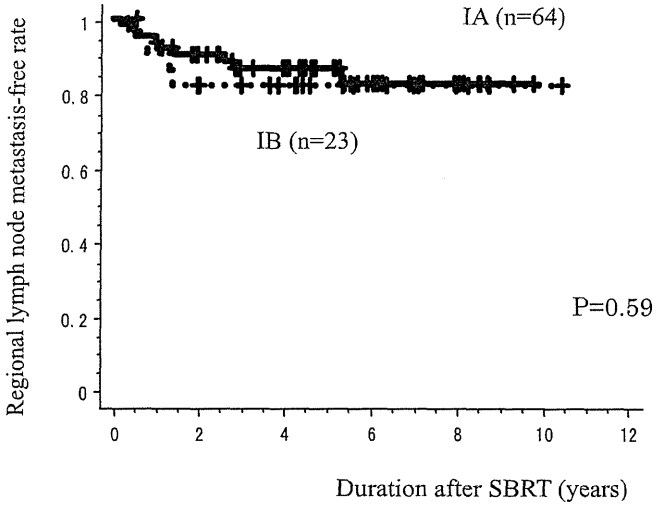

Fig. 2. Cumulative regional lymph node metastasis–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

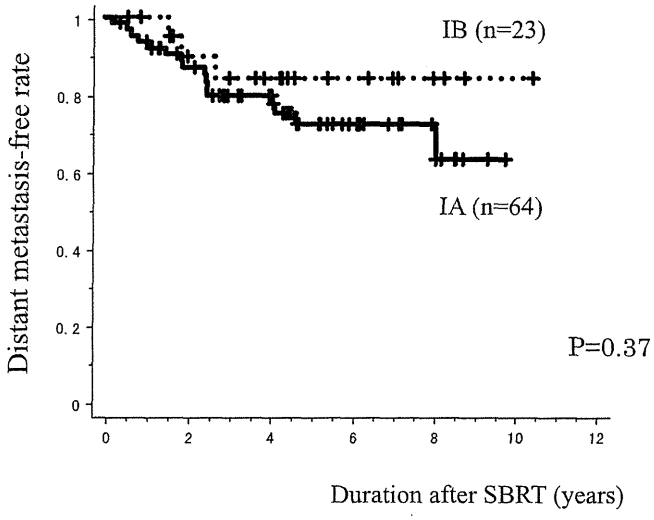

Fig. 3. Cumulative distant metastasis–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

Survival

Overall and cause-specific 5-year survival rates for total cases were 69.5% (95% CI, 58.8–80.1%) and 76.1% (95% CI, 65.9–86.3%), respectively. Overall and cause-specific survival curves according to stage are shown in Figs. 4 and 5, respectively. Five-year overall survival rate was 72.0% (95% CI, 59.6–84.4%) in Stage IA patients and 63.2% (95% CI, 42.7–83.6%) in Stage IB patients. A marginal but nonsignificant ($p = 0.14$) difference was found between overall survival rates of Stage IA and IB groups. In terms of histology, overall 5-year survival rate was 72.2% (95% CI, 59.2–85.2%) in the adenocarcinoma subgroup and 60.8% (95% CI, 38.4–83.2%) in the squamous cell carcinoma subgroup.

DISCUSSION

Exposing a tumor to a higher dose of radiation without increasing adverse effects can be achieved using stereotactic techniques. Stereotactic irradiation is an approach using

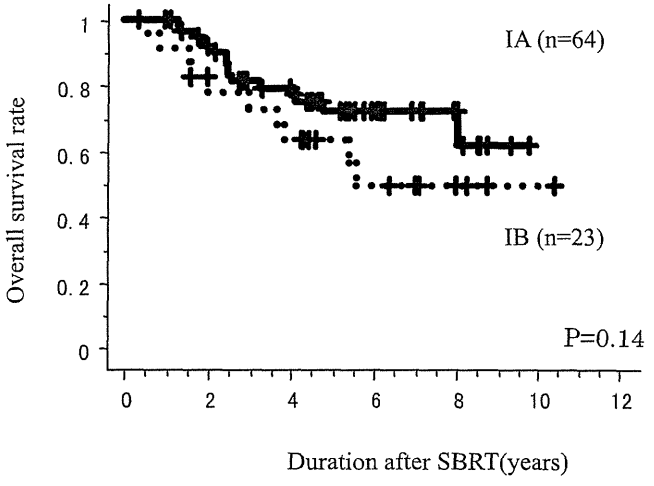

Fig. 4. Cumulative overall survival rate curves, according to stage. SBRT = stereotactic body radiotherapy.

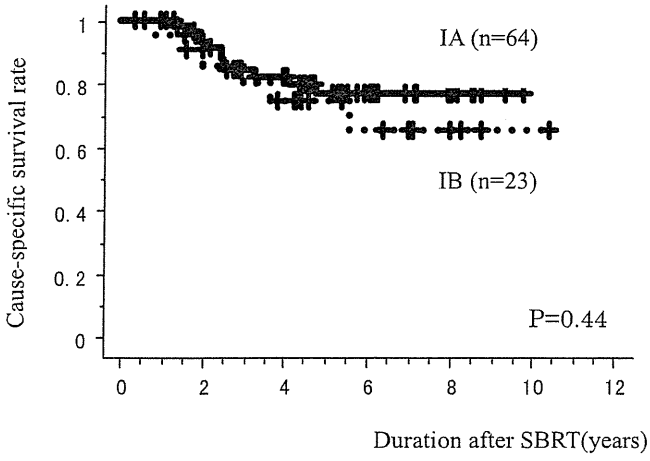

Fig. 5. Cumulative cause-specific survival rate curves, according to stage. SBRT = stereotactic body radiotherapy.

multiple noncoplanar convergent beams, precise localization with a stereotactic coordinate system, rigid immobilization, and single high-dose treatment, maximizing delivery to the tumor and minimizing the exposure of normal tissue. This approach can also substantially reduce overall treatment time from several weeks of conventional radiotherapy schedule to a few days, offering an important advantage to the patient. Stereotactic irradiation techniques are well established for the treatment of intracranial malignancies, but use in extracranial malignancies has been considered problematic because of the issues of fixation and internal motion. In 1994, Blomgren *et al.* (21) described a technique of SBRT using a custom-made body cast and stereotactic coordinates. In 1996, Uematsu *et al.* (22) reported a CT–linear accelerator unit sharing a common couch, enabling image-guided fractionated SBRT without rigid immobilization. Since verification of the effects and safety of SBRT for lung cancer (12), this treatment method has rapidly been adopted in many institutions (Table 2) (12–17, 23, 24). Although various fractionation schedules are undergoing evaluation around the world, a frequently used BED prescribed for tumors with SBRT for Stage I NSCLC in Japan has been set at a little over 100 Gy, as recommended in our previous study (18). However, concerning determination of the truly optimal dose of SBRT for Stage I NSCLC, many problems and controversies remain, such as dose-calculation algorithms (16), inhomogeneity corrections, essential dose for tumor control (24), and dose constraints for organs at risk (25, 26).

Although a number of articles on SBRT for Stage I NSCLC have been published, duration of follow-up in most cases has not been sufficiently long, and almost all treated patients were medically inoperable. The present study thus provides data on two important areas.

One was cumulative local recurrence and metastatic rates with a long duration of follow-up after SBRT. Rates of local control and metastases depend largely on the duration of follow-up and generally deteriorate as the duration of follow-up increases. Furthermore, recurrence rates have been reported in numerous articles, but most of them were crudely calculated rate. We have presented 5-year cumulative local control, regional lymph node recurrence–free and distant metastasis–free rates, calculated using Kaplan-Meier methods. The local progression–free rate in our results was unsatisfactory, particularly for the T2 tumor subgroup. The Japanese Clinical Oncology Group (JCOG) has thus started a multi-institutional dose-escalation study for Stage IB NSCLC patients (JCOG 0702).

Another meaningful result was the overall survival rate with a longer follow-up duration, allowing comparison between SBRT and surgery. Although the survival rate in this study was less than in our previous reports, we consider this information worth reporting, because median duration of follow-up was almost 5 years. Uematsu *et al.* (12) reported a 3-year overall survival rate of 86% in 29 medically operable patients with Stage I NSCLC, but the number of patients was small, and follow-up duration was relatively short. Because the number of medically operable patients treated with SBRT was very small in individual institutions, the present study collated the data of operable patients from multiple institutions. Whether the survival rate of SBRT was lower than that of surgery could not be clarified from our results. Representative 5-year overall survival rates of surgery for clinical

Table 2. Reports of SBRT for Stage I NSCLC

First author (reference)	*N*	Total dose (Gy)	Single dose (Gy)	BED (Gy)	Median follow-up (mo)	Local recurrence (%)	3-y overall survival (%)
Uematsu (12)	50	72	7.2	124	60	6*	6
Nagata (13)	42	48	12	106	52	3*	82
Onimaru (14)	28	48	12	106	27	36†	82 (Stage IA) 32 (Stage IB)
Onishi (15)	26	72	7.2	124	24	8*	75
Takeda (16)	63	50	10	100	31	5†	90 (Stage IA) 63 (Stage IB)
Koto (17)	31	45–60	7.5–15	105–113	32	29*	72
Hof (23)	10	19–26	19–26	55–94	15	40*	37
Fakiris (24)	47	60–66	20–22	180–211	50	12†	43

Abbreviations: SBRT = stereotactic body radiotherapy; NSCLC = non–small-cell lung cancer; BED = biologically effective dose ($\alpha/\beta = 10$).
* Crude data.
† Cumulative data calculated with Kaplan-Meier method.

Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

Clinical stage	United States (1)	Japanese National Cancer Center (2)	Japanese National Survey (3)	SBRT
IA	61	71	77	76
IB	40	44	60	64

Abbreviation: SBRT = stereotactic body radiotherapy.
Values are percentages.

Stage IA and IB NSCLC are listed in Table 3 (1–3), ranging approximately 60–75% for Stage IA and 40–60% for Stage IB. We cannot conclude that the survival rate for SBRT is equivalent to that for surgery, because the present data for SBRT are based on a retrospective study and small sample size. However, the background of patients treated by SBRT in this study seems likely to have included worse prognostic factors than those in patients treated surgically. Concerning the size and characteristics of tumors, good prognostic factors such as smaller tumor size (27) or lower-density mass (so-called ground-glass opacities) (28) might be more frequently included in patients treated with surgery, because the determination of histological malignancy before SBRT was difficult for such tumors. In addition, median age of patients treated by surgery was approximately 10 years younger in the surgical series (median, 60–65 years) than in the SBRT series (median, 75 years). We therefore believe that survival rates for SBRT in medically operable patients are potentially comparable to those for surgery.

Regarding treatment-related toxicity, the rate of severe (Grade ≥3) acute and short-term chronic complications after SBRT was very low and acceptable, despite the high age of those patients (median, 74 years) in our experience. In results for pulmonary lobectomy, Deslauriers *et al.* (29) reported much higher mortality and morbidity rates that increased with aging. In other reports, mortality rates for patients aged >70 years old after pulmonary lobectomy were 7.6% (30). Even though improvements of mortality and morbidity of surgery may have recently been achieved (31), in particular under a technique of video-assisted thoracoscopic lobectomy (32), we consider SBRT as a safer and less invasive treatment modality than surgery, at least for peripherally located lung tumor up to 5 years after treatment. However, reports of SBRT for centrally located lung tumor have shown a comparably high risk (25, 26), and long-term chronic toxicity remains unclear. A longer and larger follow-up of SBRT is needed.

We thus consider that SBRT may offer a useful option for initial radical treatment of at least peripheral Stage IA NSCLC, not only for medically inoperable patients but also for operable patients. However, regarding centrally located or large T2 tumors, surgery must still be recommended as the first choice of treatment until further data can be accumulated. Although we encountered only 1 case in the present study, pulmonary lobectomy and mediastinal lymph node resection were performed without difficulty for a locally recurring tumor after SBRT. Surgery might be an option as salvage therapy for locally recurrent cases after radical SBRT for Stage I NSCLC.

In Japan, the number of patients treated with SBRT has exploded, especially since SBRT for lung cancer has been covered by the national health insurance since 2004. A Phase II multi-institutional study of JCOG researching the efficacy and toxicity of SBRT for both medically operable and inoperable Stage IA NSCLC patients (JCOG 0403) started in 2004, and patient entry was completed in October 2008. A total of 90 medically inoperable and 65 operable patients have been enrolled. In the United States, a Phase II multi-institutional study of SBRT for only medically inoperable Stage I NSCLC patients (Radiation Therapy Oncology Group 0236) has been ongoing.

Even multi-institutional Phase II studies of SBRT for Stage I NSCLC may have inevitable selection bias compared with surgical series. A prospective randomized trial is essential to conclude whether outcomes of SBRT for medically operable patients are truly comparable to those of surgery. A protocol for randomized studies comparing SBRT with surgery for Stage I NSCLC has been initiated (33) but has not progressed. Such a randomized study is likely to prove very difficult to perform, because most patients may hope for more minimally invasive therapy, such as SBRT. Many more experiences for more patients with a longer follow-up duration are thus needed to confirm the safety and effects of SBRT as a radical treatment for operable Stage I NSCLC. If the experience of SBRT for medically operable Stage I NSCLC matures and produces no poor results in future, SBRT will have a marked impact on standard treatment procedures for lung cancer and provide good news for Stage I lung cancer patients, the prevalence of whom is likely to increase.

In conclusion, treatment results of SBRT reviewed from a Japanese multi-institutional database showed that SBRT is safe and promising as a radical treatment for operable Stage I NSCLC. The survival rate of SBRT is potentially comparable to that of surgery.

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Outcomes of Radiosurgery for Brainstem Arteriovenous Malformations

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BACKGROUND: Arteriovenous malformations (AVMs) in the brainstem yield a high risk of hemorrhage. Although stereotactic radiosurgery (SRS) is accepted, because of high surgical morbidity and mortality, outcomes are still unclear.

OBJECTIVE: We previously reported the early results of SRS for brainstem AVMs. Here, we obtained data from a longer follow-up for a larger number of patients and present precise outcomes based on the latest follow-up data.

METHODS: Forty-four patients with brainstem AVMs were treated by SRS. Outcomes such as the rates of obliteration, hemorrhage after treatment, and adverse effects were retrospectively analyzed.

RESULTS: The annual hemorrhage rate before SRS was 17.5%. The mean follow-up period after SRS was 71 months (range, 2-168 months). The actuarial obliteration rate confirmed by angiography was 52% at 5 years. Factors associated with higher obliteration rate were previous hemorrhage ($P = .048$) and higher margin dose ($P = .048$). For patients treated with a margin dose of $\geq$ 18 Gy, the obliteration rate was 71% at 5 years. Persistent worsening of neurological symptoms was observed in 5%. The annual hemorrhage rate after SRS was 2.4%. Four patients died of rebleeding, and disease-specific survival rate was 86% at 10 years after treatment.

CONCLUSION: Nidus obliteration must be achieved for brainstem AVMs because they possibly cause lethal hemorrhage even after SRS. Treatment with a high margin dose is desirable to obtain favorable outcomes for these lesions. Additional treatment should be considered for an incompletely obliterated nidus.

KEY WORDS: Arteriovenous malformation, Brainstem, Gamma knife, Stereotactic radiosurgery

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Arteriovenous malformations (AVMs)involving the brainstem yield a high risk ofhemorrhage and are often life-threatening.[1-4] Treatment modalities for these lesions include surgery, as reported in several series.[3-5] Stereotactic radiosurgery (SRS) is another option to treat brainstem AVMs to avoid risks of surgical removal. Although there are several reports of results of SRS for brainstem AVMs,[1,2,6,7] the precise outcomes are largely unknown because of the rarity of these lesions. We previously reported the results of SRS for 30 patients with brainstem AVMs and concluded that lower-dose treatment leads to treatment failure.[1] Thereafter, we have principally treated brainstem AVMs with enough margin $\geq$ 18 Gy on the basis of previous experience. To reevaluate the treatment outcomes of SRS for brainstem AVMs using the latest data available, we retrospectively analyzed outcomes of 44 patients with brainstem AVMs who underwent SRS at our institute.

ABBREVIATIONS: AVM, arteriovenous malformation; **SRS,** stereotactic radiosurgery

PATIENTS AND METHODS

Clinical Materials

Between July 1990 and October 2009, 44 patients with brainstem AVMs were treated by SRS at our institute with the Leksell Gamma Knife. The AVMs with a nidus that was partially or entirely located in the midbrain, pons, and medulla oblongata were defined as brainstem AVMs. The AVMs in the cisternal portion without involvement of brainstem parenchyma were excluded from this study. In all patients, diagnosis was confirmed with cerebral angiography in

combination with computed tomography (CT) or magnetic resonance imaging (MRI). Patients with an AVM nidus that had a largest diameter of < 3 cm were treated by SRS. One patient underwent evacuation of a hematoma in the cerebellum before SRS. One patient required ventricular drainage for acute hydrocephalus caused by intraventricular hemorrhage, and the other underwent ventriculoperitoneal shunt for obstructive hydrocephalus. Two patients were treated by endovascular approach before SRS. No patient underwent surgical removal of the nidus before SRS. The extent of the nidus was visually confirmed by at least 2 neurosurgeons on CT or MRI. The volume of this visually confirmed nidus was then calculated with computer software (Leksell GammaPlan, Elekta Instruments AB, Stockholm, Sweden) and was defined as AVM volume in this study. The modified radiosurgery-based grading system scores (AVM scores) proposed by Pollock and Flickinger[8] were also used to evaluate patient outcomes, calculated according to the following equation in brainstem AVMs: 0.1 × (AVM volume in cm^3) + 0.02 × (patient age in years) + 0.3 × 2.

The clinical characteristics are summarized in Table 1. Locations of AVMs were ventral midbrain, dorsal midbrain, pons, cerebellopontine angle, and medulla oblongata in 8, 8, 13, 8, and 6 patients, respectively. Forty-four patients were followed up for 2 to 168 months (mean, 71 months; median, 49 months) after SRS. Among them, 41 patients were followed up for > 1 year. Patient age at the time of SRS ranged from 5 to 68 years (mean, 40 years; median, 39 years). The mean largest diameter of the nidus was 16 mm (range, 7.5-27 mm). The mean nidus volume was 1.3 cm^3 (range, 0.1-3.9 cm^3). The mean radiosurgery-based AVM score was 1.52 (range, 0.75-2.13). Thirty-six patients (82%) experienced 46 hemorrhages before SRS. Between the time of diagnosis and SRS, excluding the first bleedings in patients who presented with hemorrhage, 10 hemorrhages were observed during 57 patient-years. By the person-years method, the annual hemorrhage rate after initial presentation until SRS was 17.5%. At the time of SRS, 31 patients (72%) showed neurological deficits caused by past hemorrhage. They presented with motor weakness in 10 (23%), sensory disturbance in 9 (20%), cerebellar ataxia in 11 (25%), and cranial nerve symptoms in 25 (57%). For SRS with the Gamma Knife, the maximal dose ranged from 20 to 50 Gy (mean, 37 Gy; median, 40 Gy) and margin dose ranged from 10 to 20 Gy (mean, 19 Gy; median, 20 Gy).

TABLE 1. Clinical Characteristics and Radiosurgical Dosimetry for Patients With Brainstem Arteriovenous Malformations

Characteristics	Value
No. of patients in analysis	44
M/F ratio	29/15
Age, y	
Range	5-68
Mean	40
Median	39
Clinical presentation, n (%)	
Hemorrhage	36 (82)
Headache	4 (9)
Incidental	2 (5)
Neurological deficit, n (%)	
No deficit	12 (27)
Motor deficit	10 (23)
Sensory disturbance	9 (20)
Cerebellar ataxia	11 (25)
Cranial nerve symptoms	25 (57)
Previous treatment, n (%)	
No previous treatment	39 (89)
Endovascular embolization	2 (5)
Hematoma evacuation	1 (2)
Ventricular drainage	1 (2)
Ventriculoperitoneal shunt	1 (2)
AVM score	
Range	0.75-2.13
Mean	1.52
Median	1.51
Radiosurgical dosimetry	
Maximum dose, Gy	
Range	20-50
Mean	37
Median	40
Margin dose, Gy	
Range	10-20
Mean	19
Median	20

Radiosurgical Treatment

After the Leksell stereotactic frame was fixed on the patient's head, the patient underwent stereotactic imaging to obtain precise information on the shape, volume, and 3-dimensional coordinates of the AVM nidus. Only biplanar stereotactic cerebral angiography was used for radiosurgical dose planning until February 1991. Thereafter, CT or MRI was used in combination with angiography. Treatment planning was jointly performed by neurosurgeons and radiation oncologists using commercially available software. The first-generation treatment planning software (KULA, Elekta Instruments AB), with which prescribed dose planning was manually superimposed on radiographic imaging films, was used until September 1998. Advanced planning software (Leksell GammaPlan, Elekta Instruments AB), which enabled us to display multiple radiographic images on the computer screen and simultaneously superimpose isodose lines on them, was used thereafter. In principle, the ideal dose applied to the margin of each AVM nidus was ≥ 18 Gy. However, 7 of 9 patients (78%) who underwent treatment until August 1991 were treated by margin doses < 17 Gy to avoid the risk of radiation injury.

Follow-up Evaluation and Statistical Analysis

After SRS, follow-up clinical examinations were performed at our hospital or by referring physicians. Serial cerebral angiography was performed every year until 1992. After 1993, the patients underwent CT or MRI with contrast enhancement every 6 months, and angiography was performed when obliteration of the AVM nidus was strongly suggested on those images.

Excellent outcome was defined as complete nidus obliteration without hemorrhage after treatment or adverse events.

Statistical analyses were performed with JMP 8 (SAS Institute Inc, Cary, North Carolina). The actuarial obliteration rate was calculated with the Kaplan-Meier method. The Cox proportional hazard model was used for univariate and multivariate analyses to evaluate factors potentially affecting nidus obliteration and adverse effects.

RESULTS

Obliteration Rate

Complete nidus obliteration was confirmed on angiography studies (Figure 1) in 20 patients (45%) within 6 to 75 months (median, 24 months) after SRS. The actuarial rates of AVM obliteration confirmed by angiography were 44% at 3 years and 52% at 5 years. In 2 cases, MRI demonstrated complete obliteration of the AVM nidus without angiographic confirmation. When these cases are counted as having complete obliteration of the nidus, the obliteration rates were 48% at 3 years and 57% at 5 years.

In other patients, no radiological change in nidus was confirmed in 4 patients by angiography and 1 patient by MRI. Reduction of nidus volume was confirmed in 5 patients by angiography (Figure 2) and 13 patients by MRI. One patient died of hemorrhage before a follow-up imaging study was performed. If complete obliteration was not obtained, all patients were conservatively observed without additional treatment.

Factors significantly associated with higher obliteration rate in the multivariate analysis were hemorrhagic onset (P = .048) and higher margin dose (P = .048; Table 2). For 37 patients who underwent treatment with a margin dose ≥ 18 Gy, the actuarial obliteration rate was 57 at 3 years and 71% at 5 years (Figure 3). Among 8 patients without prior hemorrhage, 6 patients were prescribed ≥ 18 Gy. On the other hand, 31 of 36 patients with a history of hemorrhage underwent treatment with a margin dose

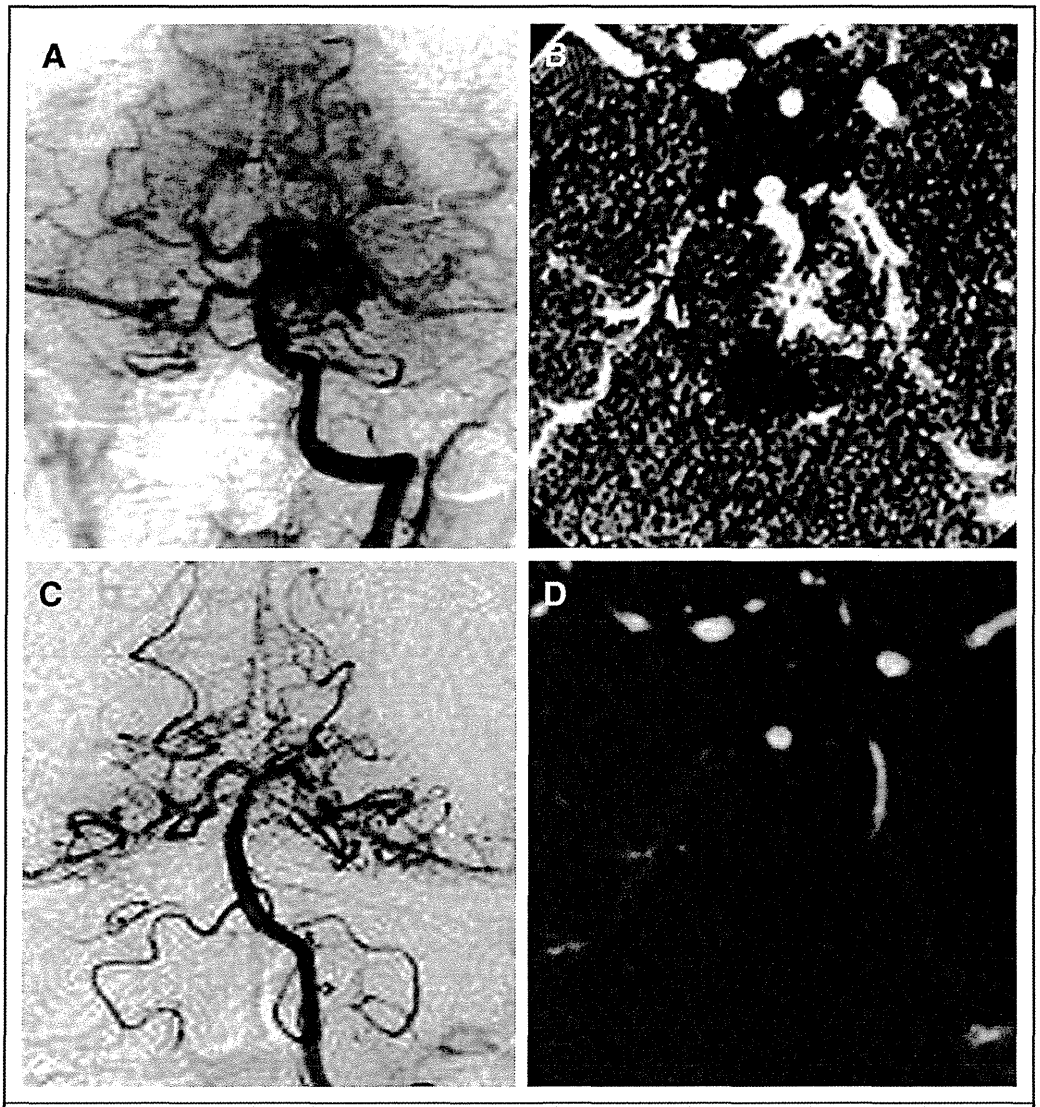

FIGURE 1. **A** *and* **B**, *pretreatment angiography* (**A**) *and MRI* (**B**) *of an arteriovenous malformation in the midbrain that presented with hemorrhage. A margin dose of 20 Gy was prescribed for the 2.9-cm³ nidus.* **C** *and* **D**, *complete nidus obliteration was confirmed 24 months after stereotactic radiosurgery by angiography* (**C**) *and MRI* (**D**).

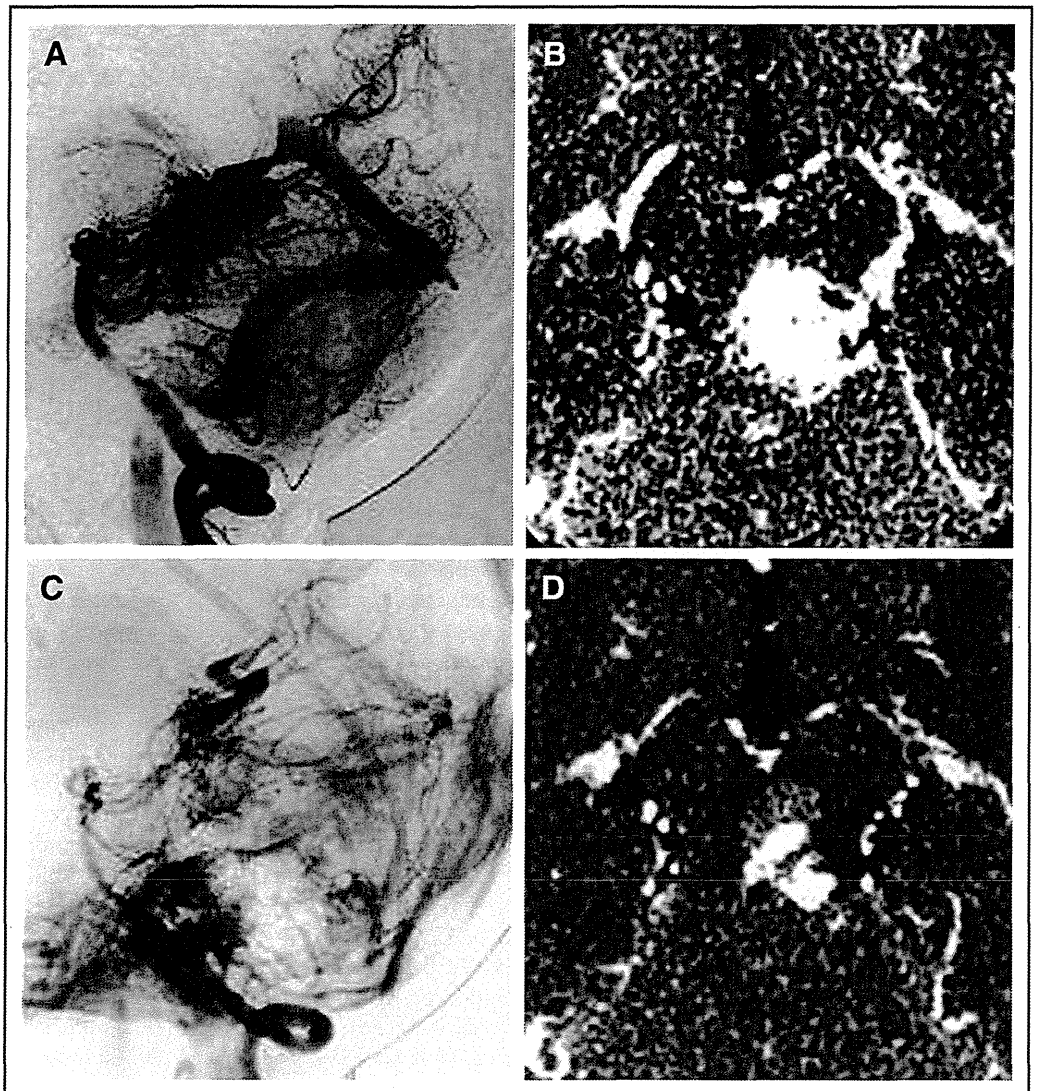

FIGURE 2. **A** *and* **B**, *pretreatment angiography* (**A**) *and MRI* (**B**) *of an arteriovenous malformation in the midbrain that presented with hydrocephalus. A margin dose of 17 Gy was prescribed for the 1.9-cm³ nidus.* **C** *and* **D**, *incomplete nidus obliteration was confirmed 48 months after stereotactic radiosurgery by angiography* (**C**) *and MRI* (**D**).

≥ 18 Gy. There was no significant correlation between history of hemorrhage and applied margin dose.

Complications and Hemorrhagic Events

Five patients (11%) developed T2-hyperintensity regions around an irradiated field confirmed by MRI 5 to 12 months (median, 7 months) after SRS. Neurological deterioration caused by radiation injury was observed in 2 patients (5%) 7 months after SRS. Of these 2 patients, 1 experienced transient ptosis, which lasted for 1 month, and the other presented permanent upward-gaze palsy.

Six patients experienced 6 hemorrhages 1 to 93 months (median, 15 months) after treatment during 253 patient-years. The annual hemorrhagic risk after SRS was 2.4%. All post-treatment hemorrhages occurred before angiographic confirmation of nidus obliteration. There was no bleeding after nidus obliteration in this cohort during 77 patient-years. The characteristics of the patients who suffered from hemorrhage after treatment are described in Table 3. Although age, volume, location of the nidus, AVM score, and number of hemorrhages before treatment were examined, there was no statistically significant factor associated with hemorrhage after treatment. Four

TABLE 2. Factors Associated With Angiographically Confirmed Obliteration of the Arteriovenous Malformation Nidus After Stereotactic Radiosurgery[a]

Factor	P		95% Confidence Interval	
	Univariate	Multivariate	Lower	Upper
Sex	.72	.83	0.413	3.312
Hemorrhage before treatment	.049[b]	.048[b]	1.013	104.870
AVM score	.99	.37	0.476	7.015
Use of advanced software in dose planning	.94	.88	0.247	2.860
Margin dose	.001[b]	.048[b]	1.169	4.032

[a]AVM, arteriovenous malformation.
[b]$P < .05$.

patients died of rebleeding 1 to 93 months (median, 27 months) after SRS. Therefore, the disease-specific survival rate at 3, 5, and 10 years was 95%, 92%, and 86%, respectively. Of the 4 patients who died of hemorrhage after treatment, 2 patients had lesions in the pons, 1 had a dorsal midbrain lesion, and the other had a lesion in the ventral midbrain. There was no correlation between nidus location and death. There was no significant factor associated with each radiation-induced neurological adverse effect and mortality caused by rebleeding in this cohort.

For 37 patients who underwent treatment with a margin dose ≥ 18 Gy, nidus obliteration without adverse events or hemorrhage after treatment (excellent outcome) was achieved in 20 (54%) (5 of 7, 2 of 6, 5 of 10, 4 of 8, and 4 of 6 in patients with ventral midbrain, dorsal midbrain, pons, cerebellopontine angle, and medulla oblongata AVMs, respectively; Figure 4).

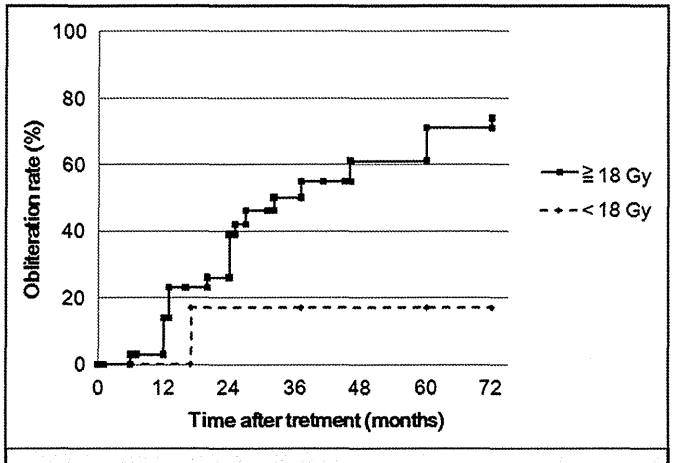

FIGURE 3. *Kaplan-Meier curve showing cumulative rate of complete nidus obliteration stratified by margin dose.*

There was no statistical difference between locations. Excellent outcome was achieved in 10 of 20 patients (50%) whose AVM score was < 1.5 and 10 of 24 patients (42%) whose AVM score was ≥ 1.5. There was no statistical difference between these 2 groups. Furthermore, excellent outcome was achieved in 1 of 6 patients (17%) who underwent treatment planned only by angiography and in 19 of 38 patients (50%) who underwent treatment planned by angiography plus CT or MRI, although it was not statistically different ($P = .20$).

DISCUSSION

Deep-seated AVMs possess higher hemorrhagic risk and are more likely to cause devastating hemorrhage.[9-12] The annual bleeding rate of untreated brainstem AVMs is reported to be 15.1%,[3] which is consistent with our results, and the annual rate of rebleeding is 17.8%.[13] Considering this high risk of hemorrhage associated with brainstem AVMs, earlier extirpation is desirable before repeated hemorrhages. For this purpose, microsurgical resection can be a preferable treatment option. However, surgery can be applicable for only limited cases, and morbidity and mortality associated with surgical removal are not negligible, ranging from 20% to 25% and from 0 to 20%, respectively.[3,4,14] Because the associated risks depend largely on the nidus location within the brainstem, safe removal is not feasible for AVMs located in the ventral midbrain, pons, and medulla oblongata.[3] On the other hand, as for SRS, we found that there was no significant difference in outcomes among each location within the brainstem, and the associated morbidity was less than that with surgical removal, which was reported to range from 5% to 12%.[1,2,6,7] Despite the result that annual bleeding rate was reduced from 17.5% to 2.4% after SRS, hemorrhage from incompletely obliterated nidus can be critical and remains an issue of major concern. The rate of complete obliteration was 52% at 5 years and was lower than that of AVMs in other locations. This lower obliteration rate is consistent with other reports of results of radiosurgery for deeply located AVMs involving brainstem AVMs, which were 43% to 66%.[2,6] As discussed in other reports,[6] the intention to reduce the treated volume to reduce the risk of complications might have led to insufficient coverage of the entire nidus and thus resulted in a lower obliteration rate. At present, it is important to deliver a sufficient margin dose for small AVMs, ideally > 18 Gy, to achieve complete nidus obliteration on SRS. Radiation tolerance limit of the brainstem is controversial despite precise analyses.[15] However, a higher margin dose may cause severe radiation adverse events. Because the evidence of SRS for brainstem AVM is limited, we should carefully apply higher doses, and cautious follow-up is mandatory. An AVM score > 2.25 was associated with poor outcomes in a previous report,[6] although no patients in our series had a score > 2.25. For brainstem AVMs, an AVM score of 2.25 corresponds to a 12.5-cm^3 nidus in a 20-year-old patient, a 8.5-cm^3 nidus in a 40-year-old patient, or a 4.5-cm^3 nidus in a 60-year-old patient. Therefore, an AVM with a score

TABLE 3. Characteristics of the Patients Who Suffered From Hemorrhage After Treatment[a]

Age, y	Location	Volume, cm^3	AVM Score	No. of Hemorrhages Before Treatment	Timing of Hemorrhage After Treatment, mo	Outcomes After Treatment
24	Dorsal midbrain	0.4	1.12	1	1	Alive
56	Dorsal midbrain	3.6	2.08	0	93	Dead
37	Pons	0.2	1.36	1	1	Dead
53	Pons	0.4	1.70	2	37	Dead
45	Ventral midbrain	0.5	1.55	2	16	Dead
64	Cerebellopontine angle	2.5	2.12	1	13	Alive

[a]AVM, arteriovenous malformation.

< 2.25 or a nidus volume that is smaller than approximately 10 cm^3 might be a good candidate for SRS. For larger lesions, multimodality treatment strategy combined with SRS, surgical removal, and endovascular treatment should be discussed.[3,5,16] Because there was no evidence regarding repeated treatment for brainstem AVMs, we conservatively observed the patients for whom complete obliteration could not be achieved. However, concerning the aggressive nature of brainstem AVMs even after SRS, additional treatment should be considered because the safety and efficacy of repeated radiosurgery or surgical removal for incompletely obliterated AVMs in other locations have been established.[17,18] Although obliteration rates changed from 57% to 71% between 3 and 5 years after treatment, it is not clear whether this result warrants observation even 3 years after treatment. Concerning aggressive hemorrhage from an incompletely obliterated nidus, retreatment or microsurgical resection might be considered for incompletely obliterated lesions at about 3 years after first SRS.[18] In our series, previous hemorrhage was associated with higher obliteration rate, consistent with previous reports.[19,20] Although the reasons for this association are not clear, the endothelial damage caused by the hemorrhage possibly promotes occlusion of the internal lumen and thrombosis of AVMs, as indicated in previous studies.[21-23]

Delayed complications such as hemorrhage from obliterated AVMs, chronic encapsulated expanding hematoma, and delayed cyst formation were not observed in our cohort, probably owing to the relatively small size and deep location, because it is known that larger AVMs at lobar locations are at higher risk for those adverse events.[24] However, these late complications occur even > 10 years after treatment, and evaluating the incidence now is premature. At present, those complications are reported as relatively rare phenomena,[24] but the cumulative risk might be much higher in young patients with long lives ahead of them. Therefore, continual follow-up is recommended even after AVM obliteration has been demonstrated on angiography. In this study, we presented the outcomes of SRS for brainstem AVMs on the basis of our maximum follow-up data, but SRS is a relatively new treatment modality, and our knowledge of its long-term risks is still limited. We need to observe patients carefully for longer periods.

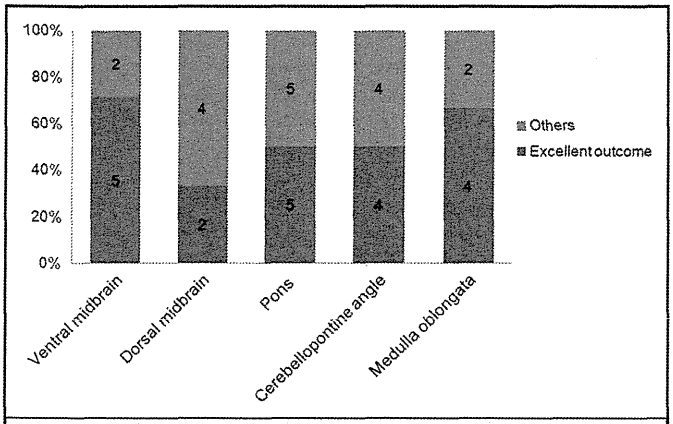

FIGURE 4. *The number and rate of patients for whom complete nidus obliteration without new deficit or rebleeding was achieved in each location.*

CONCLUSION

From the long-term follow-up data, we confirmed that a sufficient margin dose was necessary to effectively obliterate brainstem AVMs. Even with sufficient doses, radiation-related morbidity was relatively low, and SRS was considered to be acceptable as an alternative treatment for small brainstem AVMs. Because incompletely obliterated lesions could cause lethal hemorrhage, additional treatment, including reirradiation and surgical resection, should be considered when complete obliteration cannot be achieved by first SRS. Arteriovenous malformations, especially in the ventral midbrain, pons, and medulla oblongata, where total surgical removal is difficult, would be a good candidate for SRS. However, for large AVMs or lesions in the dorsal midbrain or cerebellopontine angle, surgical removal or a combination of SRS, surgery, and endovascular treatment might be appropriate. The incidence and the risk of delayed complications are still not clear, and we should continue to observe patients carefully, even after angiographic obliteration has been confirmed after SRS.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

Although stereotactic radiosurgery (SRS) is a useful treatment modality for brainstem arteriovenous malformation (AVMs), long-term outcomes of the disease after radiosurgery are unclear. The authors report single-institute results of long-term follow-up in 44 patients with brainstem AVMs treated by SRS. They described that the actuarial obliteration rate was 52% at 5 years and that for patients who were treated with margin dose of $\geq$ 18 Gy, obliteration rate was 71% at 5 years. The annual hemorrhage rate reduced steeply from 17.5% (before SRS) to 2.4% (after SRS) with low associated morbidity. There was no significant difference in outcomes regarding nidus location within the brainstem. They showed that SRS was acceptable as an alternative treatment for brainstem AVMs. This article provides us with a new long-term follow-up data regarding obliteration rate and clinical outcomes of brainstem AVMs followed after SRS.

In this report, 6 hemorrhages occurred after SRS. Among them, 2 patients bled within 1 month after the treatment. According to the statistical analysis, there was no significant correlation between hemorrhage after SRS and the following factors: patient age, volume, location of nidus, AVM score, and number of hemorrhages before treatment. However, other factors may influence posttreatment hemorrhage such as angiographic characteristics, including venous drainage and dose distribution of higher isodose in the nidus. Because hemorrhage from brainstem AVMs can result in high morbidity and mortality, further analysis is needed to evaluate the factors that may be associated with posttreatment hemorrhage.

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Koga et al have provided us with an interesting series of patients with brainstem arteriovenous malformations (AVMs) treated with radiosurgery. Few articles in the literature have focused on the management of this specific group of patients, who are often difficult to treat. The AVMs of the small group of patients reported here have demonstrated their aggressive nature with an annual rate of bleeding before radiosurgery of 17.5%. The 5-year actuarial obliteration rate (confirmed by angiography) is only 52% here, with 10% of the patients dying of rebleeding, and a disease-specific survival rate of only 86% at 10 years. The explanation of these quite disappointing results compared with our own data is, in our opinion, the low dose used in the treatment regimen. Because of the high risk of functional deficit related to any radiation injury of the brainstem, many centers are using a low-margin-dose policy in this group of patients. In our series[1] of 45 patients treated in Marseille, France, for brainstem AVMs with a mean margin dose of 23 Gy, the obliteration rate was 82%. The obliteration rate in those receiving $>$ 20 Gy at the margin was superior at 85%. In this series, 75% of the patients have bled before radiosurgery and 2 bled after. More important, only 2

patients remained neurologically worse, and 2 died of rebleeding (4,4%). In line with Koga et al, we think that our series demonstrates that much better results may be obtained with the use of a higher dose in the treatment regimen. Instead of a dramatic reduction in the marginal dose, safety must be ensured by a cautious analysis of the angioarchitecture on the stereotactic angiography and magnetic resonance imaging and confinement of the treatment volume to the nidus proper with the exclusion of arterial feeders, draining veins, and perinidal angiogenesis. Risk prediction models like the one reported by Flinkinger et al[2] are very useful, but they must not be misused. They must be applied with the following 2 major principles kept in mind: These models do not take into account the role of the degree and extent of restrictive definition of the target to the nidus proper, and the worst postradiosurgery complication is bleeding in the brainstem.

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Koga et al report the outcomes of Gamma Knife radiosurgery in a select group of patients with arteriovenous malformation (AVMs) in critical areas of the brainstem. Because of these locations, optimal doses for obliteration have to be tempered by the risk of adverse radiation effects in valuable real estate. They confirm that a minimal dose to the AVM margin of ≥ 18 Gy can enhance the obliteration rate. In this series, the rate by 5 years is as high as 57% of patients. We believe that the radiosurgical technology must provide excellent conformality of the 3-dimensional dose delivery and high selectivity of the dose, so that critical structures receive tolerable doses of radiation. Both volumetric magnetic resonance imaging and angiography must be used to target the AVM. Residual AVMs after a period of 3 to 5 years must have additional options considered because the hemorrhage rate continues to present major morbidity or mortality risks to the patient. Relatively few patients will benefit from endovascular techniques because total obliteration is almost never achieved and volumes are frequently the same after embolization, even if flow is reduced to a component of the AVM. Some patients may become eligible for surgery at centers with excellent microsurgical skills. Some patients will benefit from repeat radiosurgery. The risk-benefit analysis in brainstem AVM patients is quite complex.

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CLINICAL INVESTIGATION **Radiation Oncology Practice**

JAPANESE STRUCTURE SURVEY OF RADIATION ONCOLOGY IN 2007 BASED ON INSTITUTIONAL STRATIFICATION OF PATTERNS OF CARE STUDY

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Purpose: To evaluate the ongoing structure of radiation oncology in Japan in terms of equipment, personnel, patient load, and geographic distribution to identify and improve any deficiencies.

Methods and Materials: A questionnaire-based national structure survey was conducted from March to December 2008 by the Japanese Society of Therapeutic Radiology and Oncology (JASTRO). These data were analyzed in terms of the institutional stratification of the Patterns of Care Study.

Results: The total numbers of new cancer patients and total cancer patients (new and repeat) treated with radiation in 2007 were estimated at 181,000 and 218,000, respectively. There were 807 linear accelerator, 15 telecobalt, 46 Gamma Knife, 45 ^{60}Co remote-controlled after-loading, and 123 ^{192}Ir remote-controlled after-loading systems in actual use. The linear accelerator systems used dual-energy function in 539 units (66.8%), three-dimensional conformal radiation therapy in 555 (68.8%), and intensity-modulated radiation therapy in 235 (29.1%). There were 477 JASTRO-certified radiation oncologists, 826.3 full-time equivalent (FTE) radiation oncologists, 68.4 FTE medical physicists, and 1,634 FTE radiation therapists. The number of interstitial radiotherapy (RT) administrations for prostate, stereotactic body radiotherapy, and intensity-modulated radiation therapy increased significantly. Patterns of Care Study stratification can clearly identify the maturity of structures based on their academic nature and caseload. Geographically, the more JASTRO-certified physicians there were in a given area, the more RT tended to be used for cancer patients.

Conclusions: The Japanese structure has clearly improved during the past 17 years in terms of equipment and its use, although a shortage of personnel and variations in maturity disclosed by Patterns of Care Study stratification were still problematic in 2007. © **2010 Elsevier Inc.**

Structure survey, Radiotherapy facility, Radiotherapy personnel, Radiotherapy equipment, Caseload.

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INTRODUCTION

The medical care systems of the United States and Japan have very different backgrounds. In 1990 the Patterns of Care Study (PCS) conducted a survey of the structure of radiation oncology facilities in 1989 for the entire census of facilities in the United States (1). In 1991 the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) conducted the first national survey of the structure of radiotherapy (RT) facilities in Japan based on their status in 1990, with the results reported by Tsunemoto (2). The first comparison of these two national structure surveys to illustrate and identify similarities and differences in 1989–1990 was conducted by Teshima *et al.* (3) and reported in 1996. The resultant international exchange of information proved especially valuable for Japan, because we could improve our own structure of radiation oncology based on those data.

The Japanese structure has gradually improved in terms of a greater number of cancer patients who are treated with radiation as well as public awareness of the importance of RT. The Japanese Society of Therapeutic Radiology and Oncology has conducted national structure surveys every 2 years since 1990 (4), and in 2006 an anticancer law was enacted in Japan, which strongly advocates the promotion of RT and an increase in the number of radiation oncologists (ROs) and medical physicists. The Japanese Ministry of Education, Sciences, and Sports is supporting the education of these specialists at university medical hospitals. Findings of international comparisons and the consecutive structural data gathered and published by JASTRO have been useful for an understanding of our current position and future direction (4, 5). In this report the recent structure of radiation oncology in Japan is analyzed and compared with the data of 2005 (5).

METHODS AND MATERIALS

From March to December 2008, JASTRO conducted a questionnaire based on the national structure survey of radiation oncology in 2007. The questionnaire dealt with the number of treatment machines by type, number of personnel by category, and number of patients by type, site, and treatment modality. To measure variables over a longer period of time, data for the calendar year 2007 were also requested. The response rate was 721 of 765 active facilities (94.2%). The data from 573 institutions (79.5%) were registered in the International Directory of Radiotherapy Centres in Vienna, Austria, in October 2008.

The PCS was introduced in Japan in 1996 (6–15). The Japanese PCS used methods similar to those of the American version, which used structural stratification to analyze national averages for the data in each survey item by means of two-stage cluster sampling. We stratified RT facilities throughout the country into four categories for the regular structure surveys. This stratification was based on academic conditions and the annual number of patients treated with radiation at each institution, because academic institutions require and have access to more resources for education and training whereas the annual caseload also constitutes essential information related to structure. For the study reported here, the following institutional stratification was used: A1, university hospitals/cancer centers treating 440 patients or more per year; A2, university hospitals/cancer centers treating 439 patients or fewer per year; B1, other national/public hospitals treating 140 patients or more per year; and B2, other national hospital/public hospitals treating 139 patients or fewer per year.

We used SAS 8.02 (SAS Institute, Cary, NC) (16) for statistical analyses, and statistical significance was tested by means of chi-square test, Student *t* test, or analysis of variance.

RESULTS

Current situation of radiation oncology in Japan

Table 1 shows that the numbers of new patients and total patients (new plus repeat) undergoing radiation in 2007 were estimated at 181,000 and 218,000, respectively, showing a 7.3% increase over 2005 (5). According to the PCS stratification of institutions, 40.1% of the patients were treated at academic institutions (Categories A1 and A2), even though these academic institutions constituted only 18.6% of the 765 RT facilities nationwide.

Table 1. Patterns of Care Study stratification of radiotherapy facilities in Japan

Institution category	Description	Facilities (*n*)	New patients (*n*)	Average new patients/facility* (*n*)	Total patients (new + repeat) (*n*)	Comparison with data of 2005† (%)	Average total patients/facility* (*n*)	Comparison with data of 2005† (%)
A1	UH and CC (≥440 patients/y)	71	49,866	702.3	60,398	10.0	850.7	2.3
A2	UH and CC (<440 patients/y)	71	17,974	253.2	21,867	2.1	308.0	−3.6
B1	Other (≥140 patients/y)	288	78,154	271.4	94,188	6.1	327.0	6.8
B2	Other (<140 patients/y)	291	24,235	83.3	28,634	9.6	98.4	8.8
Total		721	170,229‡	236.1	205,087‡	7.3	284.4	5.9

Abbreviations: UH = university hospital; CC = cancer center hospital; Other = other national, city, or public hospital.

* $p < 0.0001$.

† Rate of increase compared with data of 2005. The calculating formula was as follows: $\frac{data\ of\ 2007\ (n) - data\ of\ 2005\ (n)}{data\ of\ 2005\ (n)} \times 100\ (\%)$.

‡ The number of radiotherapy institutions was 765 in 2007, and the number of new patients was estimated at approximately 181,000; the corresponding number of total patients (new plus repeat) was 218,000.

The cancer incidence in Japan in 2007 was estimated at 692,502 (17), with approximately 26.1% of all newly diagnosed patients treated with radiation. This number has increased steadily during the last 17 years and is expected to increase further (12). In 1990 the rate was estimated to be approximately 15% (3). The corresponding rates were 16%, 17%, 20%, 22%, 23.3% (4), 24.5% (5), and 26.1% in 1995, 1997, 1999, 2001, 2003, 2005, and 2007, respectively.

Facility and equipment patterns

Table 2 shows an overview of RT equipment and related functions. There were 807 linear accelerator (linac) systems, 15 telecobalt systems, 46 Gamma Knife systems, 45 ^{60}Co remote-controlled after-loading systems (RALSs), and 123 ^{192}Ir RALSs in actual use. The linac system used dual-energy function in 539 units (66.8%), three-dimensional (3D) conformal radiation therapy (CRT) in 555 (68.8%), and intensity-modulated radiation therapy (IMRT) in 235 (29.1%). The IMRT function was used more frequently in the equipment of academic institutions (A1, 61.6%; A2, 31.9%) than that of nonacademic institutions (B1, 26.4%; B2, 13.0%). However, 3D CRT functions were disseminated widely in both academic and nonacademic institutions, with more than 50% even in B2 institutions. Image-guided radiation therapy functions have been gradually spreading from A1 institutions (28.5%) to the other types of institutions (8.2% to 11.1%), although the rate of expansion has remained low. The annual numbers of patients per linac were 400 for A1 institutions, 238.6 for A2, 296.2 for B1, and 98.4 for B2. The number of institutions with telecobalt in actual use showed a major decrease to 15, and Gamma Knife was installed more frequently in B1 and B2 institutions. A significant replacement of ^{60}Co RALSs with ^{192}Ir RALSs was observed especially in academic institutions, whereas the number of new-type ^{60}Co RALSs in use did not increase. Six particle machines were registered in this survey, two with carbon beam and five with proton beam irradiation. One machine at Hyogo is delivering either carbon or proton. Although Heavy Ion Medical Accelerator in Chiba (HIMAC) at Chiba has two synchrotrons, it was registered as one machine in the 2007 survey. The total number of new cancer patients treated at these six institutions was estimated at 1,643 (0.9% of all new patients in Japan). Twenty-one advanced institutions were included in the A1 Category and treated more than 800 patients per year. They were equipped with linac with dual-energy function (77.6% of the institutions), 3D CRT function (91.4%), and IMRT function (65.5%), as well as with ^{192}Ir RALS (85.7%) and a computed tomography (CT) simulator (95.2%).

Table 3 shows an overview of RT planning and other equipment. X-ray simulators were installed in 60.9% of all institutions and CT simulators in 65.6%, with the latter exceeding the former for the first time in 2007. There was a significant difference in the rate of CT simulators installed by institutional stratification, from 93% in A1 institutions to 52.6% in B2 institutions. Very few institutions used magnetic resonance imaging for RT only, whereas computer use for RT recording was pervasive.

Staffing patterns and patient loads

Table 4 shows the staffing patterns and patient loads by institutional stratification. "Full time or part time" indicates the style of employment. Even full-time ROs must share the diagnosis in a week in smaller institutions like B2 institutions. We considered that these numbers were not sufficient for accurate evaluation of personnel. Therefore full-time equivalent (FTE) (40 hours/week only for radiation oncology service) data were surveyed depending on clinical working hours for RT of each person. For example, FTE of a person who has 4 days working is 0.8 and that of 1 day is 0.2. The FTE of an institution that has 3 persons with 0.8, 0.2, and 0.4 is calculated as 1.4 in total. This is a measure to represent actual personnel at each institution. The total number of FTE ROs in Japan was 826.3, whereas the average numbers were 4.3 for A1 institutions, 1.4 for A2, 1.0 for B1, and 0.5 for B2. The number in B1 institutions improved by 12.1% compared with 2005 (5). The overall patient load per FTE RO in Japan was 248.2, and the numbers for A1, A2, B1, and B2 institutions were 200.1, 218.2, 327.3, and 209.9, respectively, with the patient load for B1 institutions being by far the highest. The increase in the rate of FTE ROs was 6.7% over 2005 (5). In Japan 39% of the institutions providing RT have their own designated beds, where ROs must also take care of their inpatients. The percentage distribution of institutions by patient load per FTE RO is shown in Fig. 1, indicating that the largest number of facilities featured a patient/FTE staff level in the 101 to 150 range and the second largest number was in the 151 to 200 range. The blue areas of the bars show that 56% of the institutions (405 of 721) had fewer than 1 FTE RO. Compared with the data of 2005 (5), the patient load is shifting to a larger volume.

A similar trend was observed for RT technologists and their patient load by institutional stratification. The percentage distribution of institutions by patient load per radiation technologist is shown in Fig. 2. The largest number of facilities had a patient–per–RT technologist level in the 101 to 120 range, with the second largest number showing a range of 61 to 80 and the third largest showing a range of 121 to 140. There were 68.4 FTE medical physicists and 106.6 RT quality assurance (QA) staff. For this survey, personnel numbers were checked for duplicate reporting by individual identification on staffing data, and these data will be analyzed in detail in another report. Finally, there were 494.4 FTE nurses.

Distribution of primary sites, specific treatment, and palliative treatment

Table 5 shows the distribution of primary sites by institutional stratification. The most common disease site was breast, followed by lung/bronchus/mediastinum and genitourinary sites. In Japan the number of patients with prostate cancer undergoing RT was 16,225 in 2007, an increase of 22.7% over 2005 (5). By disease site, the rate of increase

Table 2. Equipment and its function and patient load per equipment type by Patterns of Care Study institutional stratification

Radiotherapy equipment and its function	A1 (n = 71)		A2 (n = 71)		B1 (n = 288)		B2 (n = 291)		Total (n = 721)		Comparison with data of 2005 (%)
	n	%	n	%	n	%	n	%	n	%	
Linear accelerator	151		91		296		269		807		5.5*
With dual-energy function	116	76.8†	64	70.3†	216	73.0†	143	53.2†	539	66.8†	1.7‡
With 3D CRT function (MLC width ≤1.0 cm)	136	90.1†	63	69.2†	214	72.3†	142	52.8†	555	68.8†	8.4‡
With IMRT function	93	61.6†	29	31.9†	78	26.4†	35	13.0†	235	29.1†	6.9‡
With IGRT function	43	28.5†	10	11.0†	33	11.1†	22	8.2†	108	13.4†	
With CT on rail	7	4.6†	6	6.6†	17	5.7†	17	6.3†	47	5.8†	
With treatment position verification system	42	27.8†	18	19.8†	36	12.2†	14	5.2†	110	13.6†	
Annual No. patients/linac	400.0§		238.6§		296.2*		98.4§		243.2§		3.7*
Particle	4		0		1		1		6		
Betatron	0		0		0		0		0		
Microtoron	4		2		4		3		13		
Telecobalt (actual use)	6 (4)		2 (0)		7 (2)		13 (9)		28 (15)		
Gamma Knife	3		2		31		10		46		
Other accelerator	1		1		2		5		9		
Other external irradiation device	1		2		2		1		6		
New-type ^{60}Co RALS (actual use)	3 (3)	4.2‖ (4.2)	1 (1)	1.4‖ (1.4)	10 (10)	3.5‖ (3.5)	2 (2)	0.7‖ (0.7)	16 (16)	2.2‖ (2.2)	
Old-type ^{60}Co RALS (actual use)	6 (5)	8.5‖ (7.0)	5 (2)	7.0‖ (2.8)	24 (20)	8.3‖ (6.9)	4 (2)	1.4‖ (0.7)	39 (29)	5.4‖ (4.0)	
^{192}Ir RALS (actual use)	56 (55)	78.9‖ (77.5)	31 (29)	43.7‖ (40.8)	35 (35)	12.2‖ (12.2)	5 (4)	1.7‖ (1.4)	127 (123)	17.6‖ (17.1)	
^{137}Cs RALS (actual use)	1 (1)		1 (1)		2 (1)		0 (0)		4 (3)		

Abbreviations: A1 = university hospitals/cancer centers treating 440 patients or more per year; A2 = university hospitals/cancer centers treating 439 patients or fewer per year; B1 = other national/public hospitals treating 140 patients or more per year; B2 = other national hospital/public hospitals treating 139 patients or fewer per year; 3D CRT = three-dimensional conformal radiotherapy; MLC = multileaf collimator; IMRT = intensity-modulated radiotherapy; IGRT = image-guided radiation therapy; CT = computed tomography; linac = linear accelerator; RALS = remote-controlled after-loading system.

* Rate of increase compared with data of 2005. The calculating formula was as follows: $\frac{data\ of\ 2007\ (n) - data\ of\ 2005\ (n)}{data\ of\ 2005\ (n)} \times 100\ (\%)$.

† Percentage calculated from number of systems by use of this function and the total number of linear accelerator systems.

‡ Comparison with data of 2005. The calculating formula was as follows: Data of 2007 (%) − Data of 2005 (%).

§ Number of patients over number of linear accelerators; institutions without linear accelerators excluded from calculation.

‖ Rate of institutions that have this equipment (Ratio of institutions that have two or more equipment).

Table 3. Radiotherapy planning and other equipments by Patterns of Care Study institutional stratification

RT planning and other equipment	A1 (n = 71)		A2 (n = 71)		B1 (n = 288)		B2 (n = 291)		Total (n = 721)		Comparison with data of 2005[†] (%)
	n	%*	n	%*	n	%*	n	%*	n	%*	
X-ray simulator	55	76.1	52	69.0	165	56.6	173	59.5	445	60.9	−8.8
CT simulator	74	93.0	58	77.5	210	69.1	155	52.6	497	65.6	10.3
RTP computer (≥2)	277 (60)	100 (84.5)	117 (26)	100 (36.6)	370 (57)	97.2 (19.8)	306 (25)	91.1 (8.6)	1070 (168)	95.3 (23.3)	2.2 (2.8)
MRI (≥2)	201 (60)	95.8 (84.5)	137 (54)	93.0 (76.1)	502 (185)	97.2 (64.2)	349 (71)	95.2 (24.4)	1189 (370)	95.8 (51.3)	1.1 (3.8)
For RT only	1	1.4	3	4.2	7	2.4	0	0	13	1.5	—
Computer use for RT recording	63	88.7	64	90.1	268	93.1	245	84.2	640	88.8	0.9

Abbreviations: A1 = university hospitals/cancer centers treating 440 patients or more per year; A2 = university hospitals/cancer centers treating 439 patients or fewer per year; B1 = other national/public hospitals treating 140 patients or more per year; B2 = other national hospital/public hospitals treating 139 patients or fewer per year; RT = radiotherapy; CT = computed tomography; RTP = radiotherapy planning; MRI = magnetic resonance imaging.

* Ratio of institutions that have equipment (Ratio of institutions that have two or more equipment).

† Comparison with data of 2005. The calculating formula was as follows: data of 2007 (%) − data of 2005 (%).

was the highest for prostate cancer, at 22.7%; the second highest was for breast cancer, at 20.1%; and the third highest was for lung cancer, at 14.9%. Stratification of institutions indicates that the rate of increase was notable for lung at A1, B1, and B2 and the corresponding rates for prostate cancer were high at A1, A2, and B1, from 24.7% to 26.2%. On the other hand, the corresponding rate for breast was the lowest (15.6%) at A1, whereas those at A2, B1, and B2 ranged from 20.7% to 22.5%.

Table 6 shows the distribution of usage of specific treatments and the number of patients treated with these modalities by PCS stratification of institutions. Use of interstitial irradiation, radioactive iodine therapy for prostate cancer, stereotactic body RT, and IMRT increased significantly by 19.0%, 52.4%, 50.2%, and 270.7%, respectively, over 2005 (5). On the other hand, the use of intraoperative RT decreased significantly by 35.1% and that of hyperthermia decreased by 41.5%. Institutional stratification shows that there was a dramatic increase of 623.6% in the use of IMRT in B1 (5). In 2007, 58 institutions (8%) actually used IMRT. This percentage was significantly lower than 235 linac systems with IMRT function (29.1%) as shown in Table 2.

Table 7 shows the number of patients with brain or bone metastasis treated with radiation according to the same institutional stratification. The B1 institutions treated more patients with brain metastasis (13.9% of all patients) than other types of institutions, whereas usage of radiation for bone metastasis ranged from 11.4% for A1 to 17.4% for B2. Overall, more patients with bone metastasis were treated with radiation at nonacademic than at academic institutions. Compared with the data of 2005 (5), the number of patients with brain metastasis increased by 38.6%.

Geographic patterns

Figure 3 shows the geographic distributions for 47 prefectures of the annual number of patients (new plus repeat) per 1,000 population arranged in order of increasing number of JASTRO-certified ROs per 1,000,000 population (18). There were significant differences in the use of RT, from 0.9 patients per 1,000 population (Saitama and Okinawa) to 2.1 (Miyagi). The average number of patients per 1,000 population per quarter ranged from 1.42 to 1.69 (p = 0.0996). The more JASTRO-certified physicians there were in a given area, the more RT tended to be used for cancer patients, although the correlation was of borderline significance. A similar trend was observed in 2005 (5). The utilization rate of RT in every prefecture increased in 2007 compared with 2005. However, the rate in 2007 was not related to a prefecture's population density, as we also observed in the data for 1990 (3).

DISCUSSION

In 1990 there were fewer facilities for radiation treatment and patients treated with radiation in Japan than in the