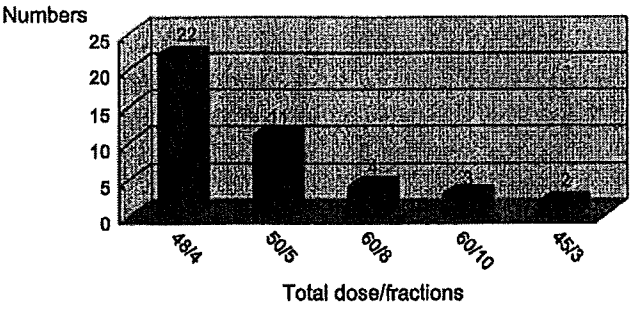

Fig. 1. Fractionation schedules of stereotactic body radiotherapy used in primary T1N0M0 lung cancer. The most common schedule was 48 Gy in 4 fractions.

Fig. 3. Fractionation schedules of stereotactic body radiotherapy used in primary liver cancer. The most common schedule was 48 Gy in 4 fractions.

SBRT, Survey, Stereotactic radiotherapy, Lung cancer, Liver cancer.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a new technique to treat early lung or liver cancer. This technique uses a hypofractionation schedule and was introduced in the late 1990s (1–5). Recently, many articles have been published from Japan, the European Union, and the United States describing promising clinical results, especially for early-stage lung cancer (6–31). However, a few complications, including death, have also been reported. Because reimbursement for this treatment was approved by the Japanese governmental health insurance in 2004, a rapid increase has been seen in the number of institutions providing SBRT. Therefore, to appraise the present status of SBRT in Japan, a nationwide survey was conducted by the Japan 3-D Conformal External Beam Radiotherapy Group.

METHODS AND MATERIALS

To review the current status of SBRT in Japan, this study was conducted to evaluate the number of institutions, number of patients, quality assurance (QA), technique, and complications of SBRT.

This questionnaire was mailed to 117 institutions. Ninety-four institutions (80%) responded by the end of November 2005. Fifty-three institutions indicated having already started SBRT, and 38 institutions had already received reimbursement from the government.

RESULTS

A total of 1111 patients with histologically confirmed lung cancer were treated. Stagewise among these patients, 637 had T1N0M0, 272 had T2N0M0, and 202 had T3–4N0M0 lung cancer. Metastatic lung cancer was found in 702 patients and histologically unconfirmed but radiologically diagnosed lung tumor in 291. Primary liver cancer was found in 207 patients and metastatic liver cancer in 76.

The most frequent schedules used for primary lung cancer were 48 Gy in 4 fractions at 22 institutions (52%), followed by 50 Gy in 5 fractions at 11 institutions (26%) and 60 Gy in 8 fractions at 4 institutions (10%), as shown in Fig. 1. The schedule tended to be the same for metastatic lung cancer, as shown in Fig. 2.

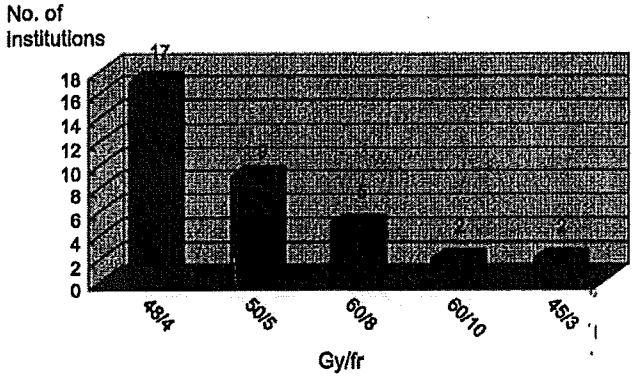

Fig. 2. Fractionation schedules of stereotactic body radiotherapy used in primary T2N0M0 lung cancer. The most common schedule was 48 Gy in 4 fractions.

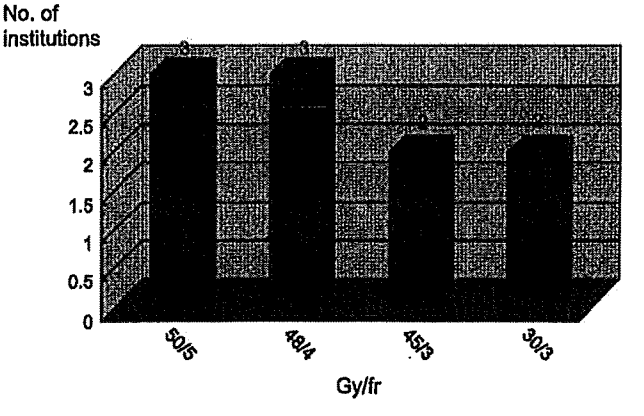

Fig. 4. Fractionation schedules of stereotactic body radiotherapy used in secondary liver cancer. The most common schedules were 50 Gy in 5 fractions and 48 Gy in 4 fractions.

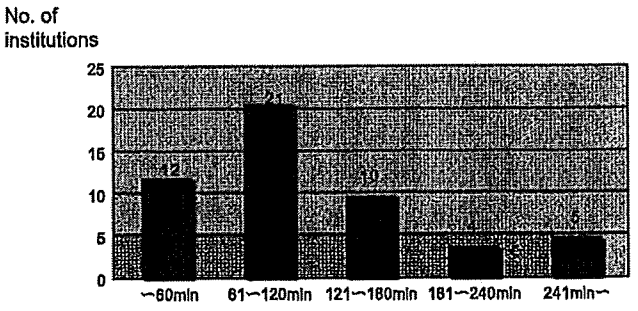

Fig. 5. Amount of time used for treatment planning (RTP) of stereotactic body radiotherapy. The most common time was 61–120 min.

The most frequent schedules used for primary liver cancer were 48 Gy in 4 fractions at four institutions, followed by 50 Gy in 5 fractions at three institutions and 45 Gy or 30 Gy in 3 fractions at two institutions, as shown in Fig. 3. The schedule tended to be the same for metastatic liver cancer, as shown in Fig. 4.

The average number of personnel involved in SBRT was 1.8 radiation oncologists, which included 1.1 certified radiation oncologists, 2.8 technologists, 0.7 nurses, and 0.6 certified QA personnel and 0.3 physicists.

The most frequent time consumed for treatment planning was 61–120 min, as shown in Fig. 5. For QA it was 50–60 min, as shown in Fig. 6, and for single daily treatment it was <30 min, as shown in Fig. 7.

The most frequently used fixing apparatus was a body frame at 30 institutions (68%), followed body fix system, plastic shell, and others, as shown in Fig. 8.

The most frequent verification method before each treatment was portal film at 41 institutions (62%), followed by 9 institutions (13%) with CT on rails and 8 (12%) with an image-guided radiotherapy system, as shown in Fig. 9.

The most common respiratory state was free breathing at 40 institutions (77%), followed by breath-holding at 7 (13%) and respiratory-gated irradiation at 5 (10%). Thirty-two institutions (74%) used abdominal compression, followed by 6 (14%) using voluntary breath holding and 5 (12%) using compulsory holding, as shown in Fig. 10.

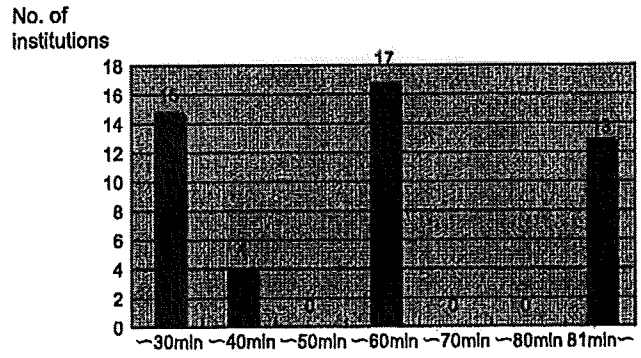

Fig. 6. Amount of time used for the single quality assurance (QA) of stereotactic body radiotherapy. The most common time was 50–60 min.

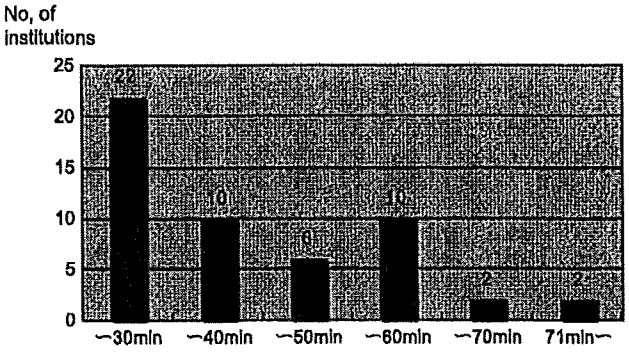

Fig. 7. Amount of time used for single daily treatment of stereotactic body radiotherapy. The most common time was <30 min.

Eighteen institutions (34%) used Focus-Xio (CMS, St. Louis, MO), followed by Eclipse (Varian Medical Systems, Palo Alto, CA) in 15 (28%), the Pinacle system (Philips, Milpitas, CA) in 11 (20%), and the RPS-700 system (Mitsubishi, Tokyo, Japan) in 5 (9%). Forty-three institutions (79%) used fixed noncoplanar beams, nine used dynamic arc therapy, and three used both rotational and dynamic therapy. Forty-eight institutions (94%) used lung heterogenous corrections.

There were 14 (0.6% of all cases) reported cases of Grade 5 complications: 11 cases of radiation pneumonitis, 2 cases of hemoptysis, and 1 case of radiation esophagitis.

DISCUSSION

In Japan, SBRT has been approved as a new method for the treatment of early lung cancer and oligometastatic lung tumors, early liver cancer, oligometastatic liver tumors, and spinal arteriovenous malformation.

However, to limit abuse of this high-technology treatment, the government set up several requirements for radiotherapy institutes to obtain reimbursement. The first requirement is to have a minimum of one full-time experienced radiation oncologist, one radiation physicist, and one experienced technician. The second requirement is for the apparatus for

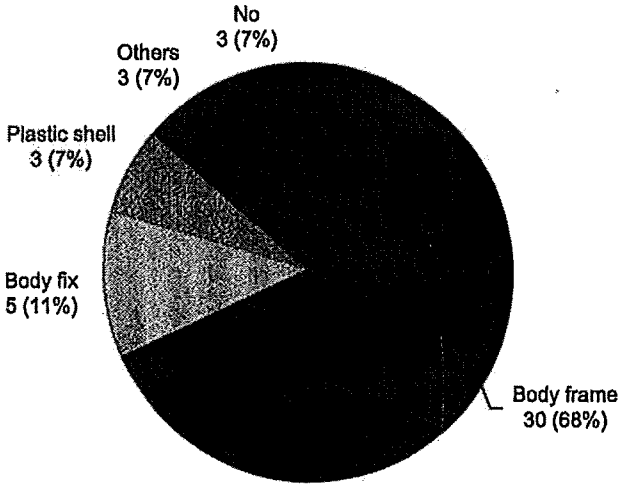

Fig. 8. Fixing apparatus used for stereotactic body radiotherapy. Body frame was most frequently used.

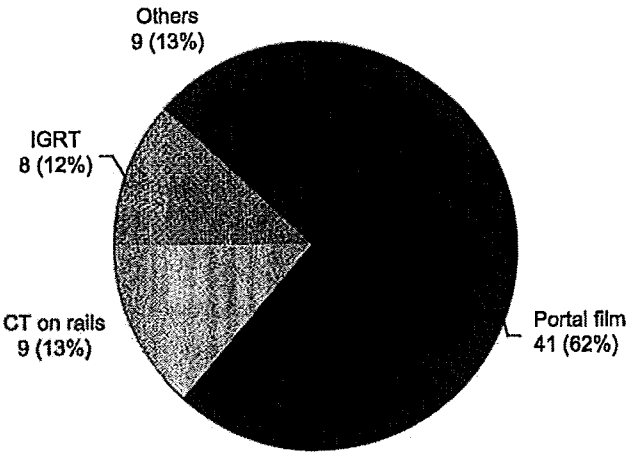

Fig. 9. Verification methods used for stereotactic body radiotherapy. Portal film was most frequently used. IGRT = image-guided radiotherapy; CT = computed tomography.

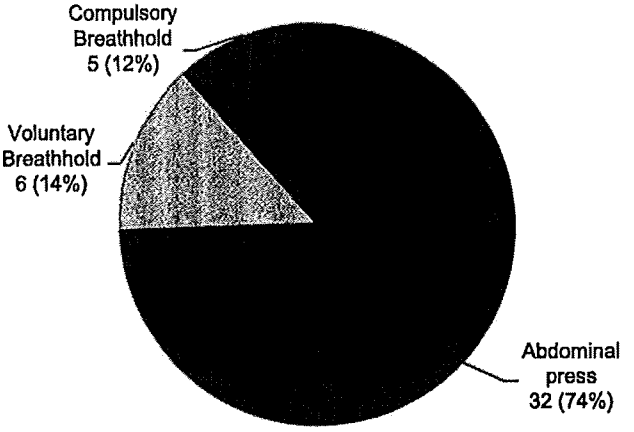

Fig. 10. Respiratory regulation method used for stereotactic body radiotherapy. Abdominal press was most frequently used.

SBRT to include a CT simulator, a three-dimensional radiation treatment-planning system, a microdosimeter, and a water phantom. The third requirement is to perform SBRT under institutional QA guidelines and to limit the setup error of the isocenter to within 5 mm.

In 2005, of the more than 700 radiation oncologic departments, 53 institutions had started SBRT.

The most frequent indication for SBRT was primary lung cancer, followed by secondary lung cancer, primary liver cancer, secondary liver cancer, and spinal arteriovenous malformation. One of the most important points of this survey was to recognize serious complications of SBRT. In total, 11 serious pulmonary Grade 5 complications, 2 bronchial bleedings, and an esophageal ulceration were encountered. Our retrospective analysis revealed that most of these pulmonary Grade 5 patients also had interstitial pneumonitis, although 2 had no underlying pulmonary disease. These 2 patients are suspected to have had underlying interstitial pulmonary disease without manifestation in chest X-rays. Inasmuch as SBRT is known to be basically harmless, rare Grade 5 complications should be carefully studied.

This survey will continue to be performed to recognize current trends and results.

REFERENCES

1. Lax I, Blomgren H, Näslund I, *et al.* Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* 1994;33:677–683.
2. Blomgren H, Lax I, Näslund I, *et al.* Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. *Acta Oncol* 1995;34:861–870.
3. Lax I, Blomgren H, Larson D, *et al.* Extracranial stereotactic radiosurgery of localized targets. *J Radiosurgery* 1998;1: 135–148.
4. Blomgren H, Lax I, Göranson H, *et al.* Radiosurgery for tumors in the body: Clinical experience using a new method. *J Radiosurgery* 1998;1:63–74.
5. Uematsu M, Shioda A, Tahara K, *et al.* Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients. *Cancer* 1998;82:1062–1070.
6. Wulf J, Haedinger U, Oppitz U, *et al.* Stereotactic radiotherapy of targets in the lung and liver. *Strahlenther Onkol* 2001;177: 645–655.
7. Herfarth KK, Debus J, Lohr F, *et al.* Stereotactic single dose radiation therapy of liver tumors: Results of a phase I/II trial. *J Clin Oncol* 2001;19:164–170.
8. Uematsu M, Shioda M, Suda A, *et al.* Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: A 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666–670.
9. Nagata Y, Negoro Y, Aoki T, *et al.* Clinical outcomes of 3D conformal hypofractionated single high dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2002;52:1041–1046.
10. Timmerman R, Papiez L, McGarry R, *et al.* Extracranial stereotactic radioablation: Results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003;124: 1946–1955.
11. Onimaru R, Shirato H, Shimizu S, *et al.* Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. *Int J Radiat Oncol Biol Phys* 2003;56:126–135.
12. Lee S, Choi E, Park H, *et al.* Stereotactic body frame based fractionated radiosurgery on consecutive days for primary or metastatic tumors in the lung. *Lung Cancer* 2003;40:309–315.
13. Wulf J, Haedinger U, Oppitz U, *et al.* Stereotactic radiotherapy of primary lung cancer and pulmonary metastases: A non-invasive treatment approach in medically inoperable patients. *Int J Radiat Oncol Biol Phys* 2004;60:186–196.
14. Onishi H, Araki T, Shirato H, *et al.* Stereotactic hypofractionated high-dose irradiation for stage I non-small cell lung carcinoma. *Cancer* 2004;101:1623–1631.
15. Nagata Y, Takayama K, Matsuo Y, *et al.* Clinical outcomes of a phase I/II of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427–1431.
16. Wulf J, Baier K, Mueller G, *et al.* Dose-response in stereotactic irradiation of lung tumors. *Radiother Oncol* 2005;77:83–87.
17. Zimmermann F, Geinitz H, Schill S, *et al.* Stereotactic hypofractionated radiation therapy for stage I non-small cell lung cancer. *Lung Cancer* 2005;48:107–114.
18. McGarry R, Papiez L, Williams M, *et al.* Stereotactic body radiation therapy for early stage non-small cell lung cancer:

Phase I study. *Int J Radiat Oncol Biol Phys* 2005;63: 1010–1015.
19. Schefter T, Kavanagh B, Timmerman R, *et al.* A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. *Int J Radiat Oncol Biol Phys* 2005;62:1371–1378.
20. Takayama K, Nagata Y, Negoro Y, *et al.* Treatment planning of stereotactic radiotherapy for lung cancer. *Int J Radiat Oncol Biol Phys* 2005;61:1565–1571.
21. Baumann P, Nyman J, Lax I, *et al.* Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. *Acta Oncol* 2006;45:787–795.
22. Fritz P, Kraus HJ, Muhlnickel W. Stereotactic single-dose irradiation of stage I non-small cell lung cancer and lung metastases. *Radiat Oncol* 2006;1:30.
23. Nyman J, Johansson KA, Hulten U. Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer—mature results for medically inoperable patients. *Lung Cancer* 2006;51:97–103.
24. Xia T, Li H, Sun Q, *et al.* Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable stage I/II non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;66:117–125.
25. Hara R, Itami J, Kondo T, *et al.* Clinical outcomes of single-fraction radiation therapy for lung tumors. *Cancer* 2006;1006: 1347–1352.
26. Kavanagh BD, McGarry R, Timmerman RD. Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases. *Semin Radiat Oncol* 2006;16:77–84.
27. Timmerman R, McGarry R, Yiannoutsos C, *et al.* Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833–4839.
28. Wulf J, Guckenberger M, Haedinger U, *et al.* Stereotactic radiotherapy of primary liver cancer and hepatic metastases. *Acta Oncol* 2006;45:838–847.
29. Kavanagh B, Schefter T, Cardenes H, *et al.* Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. *Acta Oncol* 2006;45:848–855.
30. Dawson L, Eccles C, Craig T. Individualized image guided iso-NTCP based liver cancer SBRT. *Acta Oncol* 2006;45: 856–864.
31. Timmerman R, McGarry R, Yiannoutsos C, *et al.* Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833–4839.

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CLINICAL INVESTIGATION **Lung**

CLINICAL OUTCOMES OF STEREOTACTIC BODY RADIOTHERAPY FOR SMALL LUNG LESIONS CLINICALLY DIAGNOSED AS PRIMARY LUNG CANCER ON RADIOLOGIC EXAMINATION

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Purpose: Image-guided biopsy occasionally fails to diagnose small lung lesions, which are highly suggestive of primary lung cancer. The aim of the present study was to evaluate the outcome of stereotactic body radiotherapy (SBRT) for small lung lesions that were clinically diagnosed as primary lung cancer without pathologic confirmation.
Methods and Materials: A total of 115 patients were treated with SBRT in 12 institutions. Tumor size ranged from 5 to 45 mm in diameter, with a median of 20 mm.
Results: The 3-year and 5-year overall survival rates for patients with a tumor size ≤20 mm in diameter ($n = 58$) were both 89.8%, compared with 60.7% and 53.1% for patients with tumors >20 mm ($n = 57$) ($p < 0.0005$), respectively. Local progression occurred in 2 patients (3.4%) with a tumor size ≤20 mm and in 3 patients (5.3%) with tumors >20 mm. Among the patients with a tumor size ≤20 mm, Grade 2 pulmonary complications were observed in 2 (3.4%), but no Grade 3 to 5 toxicity was observed. In patients with a tumor size >20 mm, Grades 2, 3, and 5 toxicity were observed in 5 patients (8.8%), 3 patients (5.3%), and 1 patient (1.8%), respectively.
Conclusion: In patients with a tumor ≤20 mm in diameter, SBRT was reasonably safe in this retrospective study. The clinical implications of the high local control rate depend on the accuracy of clinical/radiologic diagnosis for small lung lesions and are to be carefully evaluated in a prospective study. © 2009 Elsevier Inc.

Lung cancer, Stereotactic radiotherapy, Stereotactic body radiotherapy.

INTRODUCTION

Pathologic diagnosis is essential for the treatment of primary lung cancer. However, image-guided biopsy occasionally fails to diagnose small lung lesions, which are highly suggestive of primary lung cancer. When patients refuse re-biopsy or surgical resection, watchful waiting is usually indicated. There are other groups of patients in whom a pathologic diagnosis is very difficult to make, such as those with medical reasons for not being able to undergo biopsy and those with a history of surgical resection of non–small-cell lung cancer (NSCLC) and a small peripheral lung lesion on follow-up computed tomography (CT). The patients in the latter group often have difficulty undergoing a second surgical resection because of lowered respiratory function resulting from the previous surgery. Patients with cancer who are under watchful waiting are at risk for invasive growth of the primary tumor, lymphatic spread, and distant metastasis. Patients who choose to receive elective surgical resection of the small lung lesions to quantify the pathologic diagnosis may experience serious respiratory dysfunction. A proportion of the patients who do not have malignant tumors are inevitably overtreated and experience surgical complications.

Stereotactic body radiotherapy (SBRT) has been one of the treatments for Stage I NSCLC in medically inoperable patients. Recently, high local control and survival rates of SBRT were

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reported in several studies (1–7). Onishi *et al.* summarized the results of a Japanese series retrospectively and reported that a pulmonary complication rate of above Grade 2 arose in only 5.4% of patients (1). For the patients who received a dose compatible with the biologic effective dose (BED) of 100 Gy or more, the local control rate was 91.6%. For the patients who were judged to have been operable but who were treated with SBRT, the 5-year overall survival rate was 70.8%, which is equivalent to that achieved in the previously mentioned surgery series (1).

A serious question among radiation oncologists is whether it is ethically justifiable not to give SBRT to those patients who have peripheral lung lesions highly suggestive of lung cancer but who failed to have lung cancer diagnosed pathologically. If SBRT is as safe as image-guided re-biopsy and as effective as surgical resection, it may be ethical to give SBRT to these patients. However, we cannot answer this question, because the risk and benefit have not been compared between elective surgical resection, watchful waiting, and SBRT for small peripheral lung lesions without pathologic confirmation.

We have found in a national survey of SBRT that a small number of patients with the clinical diagnosis of NSCLC are actually treated with SBRT without pathologic confirmation in each institution. The aim of the present study was to evaluate the outcome of SBRT for peripheral small lung lesions that were clinically diagnosed as primary lung cancer without pathologic confirmation in 12 institutions during the past 10 years in Japan.

METHODS AND MATERIALS

Eligibility criteria

Twelve institutions were selected from the member institutions of the Japan Clinical Oncology Group trial, JCOG0403, for which the quality of clinical record and dosimetry accuracy of SBRT had already been evaluated by audit (8). This is a multi-institutional retrospective study using the same eligibility criteria, which were that (a) surgery was contraindicated or refused, (b) the tumor diameter was <50 mm, (c) tumors were highly suggestive of primary lung cancer and diagnosed as Stage I lung cancer clinically but the patients did not have a pathologic diagnosis, and (d) the performance status was 0 to 2 according to World Health Organization guidelines.

Patients

A total of 115 patients who were highly suspected of having lung cancer but who lacked pathologic confirmation of the disease were diagnosed with Stage I lung cancer clinically and treated with SBRT in 12 institutions during the last 10 years in Japan. The patient characteristics are given in Table 1. There were 93 cases of T1N0M0 and 22 cases of T2N0M0 disease. The number of medically operable and inoperable patients was 43 and 72, respectively. Tumor size was recorded at the maximum diameter on the CT scan taken at the start of radiotherapy. The median tumor size was 20 mm (range, 5–45 mm). The median follow-up period was 14 months (range, 1–142 months). There were 11 patients whose follow-up period was <4 months at the time of this analysis.

Diagnosis was based on CT findings and enlargement of the lesion on sequential examination with or without fluorodeoxyglucose (FDG)–positron emission tomography (PET) findings. The tumors were diagnosed as highly suggestive of primary lung cancer by diagnostic radiologists when there was definitive enlargement of the lesion on sequential CT examination and/or positive findings on FDG-PET without any metastatic lesion in the diagnostic evaluation. Several findings such as the configuration of the lung lesion were also used in the diagnosis. Of 72 patients who were examined with FDG-PET, 67 patients had positive findings on FDG-PET. Other clinical history and findings as well as laboratory findings were also used for diagnosis as much as possible to prevent inclusion of patients with metastatic lung tumors or inflammatory or granulomatous lesions in the study population.

Table 1. Characteristics of patients (115 patients)

Characteristic	Value
Age (y)	
Median	77
Range	50–92
Gender (*n*)	
Male	87
Female	28
Tumor size (mm)	
Median	20
Range	5–45
T stage (*n*)	
T1	93
T2	22
Medical condition (*n*)	
Operable	43
Inoperable	72

The reasons for the lack of pathologic confirmation were as follows: (a) bronchoscope- or CT-guided biopsy failed in 59 patients, and these patients refused re-biopsy or surgical resection; (b) 21 patients were not indicated for a biopsy procedure or surgery because of medical complications; (c) 14 patients refused a biopsy procedure as well as surgery even at the initial examination; (d) a biopsy was not indicated in 14 patients because their history of NSCLC was strongly suggestive of the new development of a second primary NSCLC, likely inoperable, and they refused surgery; and (e) a biopsy was not indicated in 7 patients because there was little possibility to confirm the pathology because of the tumor's small size, and these patients refused surgery.

Radiotherapy

All patients underwent irradiation using stereotactic techniques. Three-dimensional treatment planning was performed using non-coplanar static ports or dynamic arcs. Various techniques using breathing control or gating methods and immobilization devices such as a vacuum cushion with or without a stereotactic body frame were used to reduce respiratory internal margins. Appropriate margins were adopted for the clinical target volume and the planning target volume.

A total dose of 30 to 70 Gy at the isocenter was administered in two to 10 fractions. Using a linear-quadratic model, we defined the BED as $nd(1+d/\alpha/\beta)$, with Gray units, where n was the fractionation number, d was the daily dose, and the α/β ratio was assumed to be 10 for tumors. The BED was not corrected with values for tumor doubling time or treatment term. The median BED at the isocenter in this study was 106 Gy (range, 56–141 Gy).

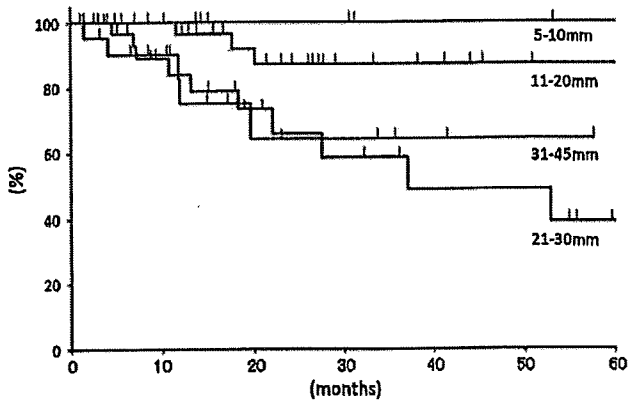

Fig. 1. Kaplan-Meier curve of overall survival rates for the patients with a tumor size (diameter) of 5 to 10 mm ($n = 11$), 11 to 20 mm ($n = 47$), 21 to 30 mm ($n = 35$), and 31 to 45 mm ($n = 22$).

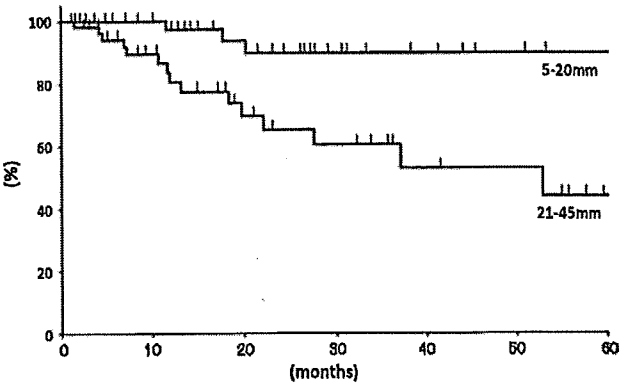

Fig. 2. Kaplan-Meier curve of overall survival rates for the patients with a tumor size (diameter) of 5 to 20 mm ($n = 58$) and 21 to 45 mm ($n = 57$). A statistically significant difference was found ($p < 0.0005$) between the two groups.

Ethical considerations

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

Statistical analysis

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

RESULTS

Survival

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

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

Local tumor response and distant metastases

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

Toxicities

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

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

DISCUSSION

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

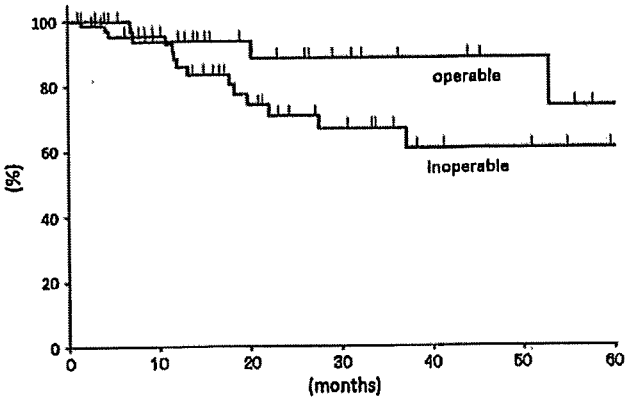

Fig. 3. Kaplan-Meier curve of overall survival rates for operable (n = 43) and inoperable (n = 72) patients. No statistically significant difference was found (p = 0.07) between two groups.

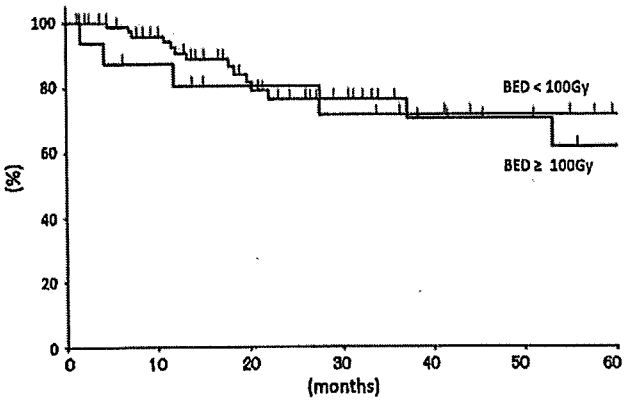

Fig. 4. Kaplan-Meier curve of overall survival rates for the patients with a biologic effective dose (BED) <100 (n = 17) and a BED ≥100 (n = 98). No statistically significant difference was found (p = 0.95) between the two groups.

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

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

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

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

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

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

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

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

CONCLUSION

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

REFERENCES

1. Onishi H, Shirato H, Nagata Y, *et al.* Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94–S100.
2. Uematsu M, Shioda A, Suda A, *et al.* Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: A 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666–670.
3. Nagata Y, Takayama K, Matsuo Y, *et al.* Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427–1431.
4. Koto M, Takai Y, Ogawa Y, *et al.* A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. *Radiother Oncol* 2007;85:429–434.
5. Nyman J, Johansson KA, Hulten U. Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer—mature results for medically inoperable patients. *Lung Cancer* 2006;51:97–103.
6. Onimaru R, Fujino M, Yamazaki K, *et al.* Steep dose-response relationship for stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;70:374–381.
7. McGarry RC, Papiez L, Williams M, *et al.* Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: Phase I study. *Int J Radiat Oncol Biol Phys* 2005;63: 1010–1015.
8. Nishio T, Kunieda E, Shirato H, *et al.* Dosimetric verification in participating institutions in a stereotactic body radiotherapy trial for stage I non-small cell lung cancer: Japan clinical oncology group trial (JCOG0403). *Phys Med Biol* 2006;51:5409–5417.
9. Shaffer K. Role of radiology for imaging and biopsy of solitary pulmonary nodules. *Chest* 1999;116:519S–522S.
10. Libby DM, Henschke CI, Yankelevitz DF. The solitary pulmonary nodule: Update 1995. *Am J Med* 1995;99:491–496.
11. O'Reilly PE, Brueckner J, Silverman JF. Value of ancillary studies in fine needle aspiration cytology of the lung. *Acta Cytol* 1994;38:144–150.
12. Mack MJ, Hazelrigg SR, Landreneau RJ, *et al.* Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule. *Ann Thorac Surg* 1993;56:825–830; discussion 830–822.
13. Gould MK, Maclean CC, Kuschner WG, *et al.* Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: A meta-analysis. *J Am Med Assoc* 2001;285: 914–924.
14. Jeong SY, Lee KS, Shin KM, *et al.* Efficacy of PET/CT in the characterization of solid or partly solid solitary pulmonary nodules. *Lung Cancer* 2008;61:186–194.
15. Nomori H, Watanabe K, Ohtsuka T, *et al.* Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. *Lung Cancer* 2004;45:19–27.
16. Lamy P, Grenier J, Kramar A, *et al.* Pro-gastrin-releasing peptide, neuron specific enolase and chromogranin A as serum markers of small cell lung cancer. *Lung Cancer* 2000;29:197–203.
17. Solaini L, Prusciano F, Bagioni P, *et al.* Video-assisted thoracic surgery (VATS) of the lung: Analysis of intraoperative and postoperative complications over 15 years and review of the literature. *Surg Endosc* 2008;22:298–310.
18. Okada M, Koike T, Higashiyama M, *et al.* Radical sublobar resection for small-sized non-small cell lung cancer: A multicenter study. *J Thorac Cardiovasc Surg* 2006;132:769–775.

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5TH JUCTS AND THE 5TH S. TAKAHASHI MEMORIAL INTERNATIONAL JOINT SYMPOSIUM

EFFECT OF AUDIO COACHING ON CORRELATION OF ABDOMINAL DISPLACEMENT WITH LUNG TUMOR MOTION

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Purpose: To assess the effect of audio coaching on the time-dependent behavior of the correlation between abdominal motion and lung tumor motion and the corresponding lung tumor position mismatches.

Methods and Materials: Six patients who had a lung tumor with a motion range >8 mm were enrolled in the present study. Breathing-synchronized fluoroscopy was performed initially without audio coaching, followed by fluoroscopy with recorded audio coaching for multiple days. Two different measurements, anteroposterior abdominal displacement using the real-time positioning management system and superoinferior (SI) lung tumor motion by X-ray fluoroscopy, were performed simultaneously. Their sequential images were recorded using one display system. The lung tumor position was automatically detected with a template matching technique. The relationship between the abdominal and lung tumor motion was analyzed with and without audio coaching.

Results: The mean SI tumor displacement was 10.4 mm without audio coaching and increased to 23.0 mm with audio coaching ($p < .01$). The correlation coefficients ranged from 0.89 to 0.97 with free breathing. Applying audio coaching, the correlation coefficients improved significantly (range, 0.93–0.99; $p < .01$), and the SI lung tumor position mismatches became larger in 75% of all sessions.

Conclusion: Audio coaching served to increase the degree of correlation and make it more reproducible. In addition, the phase shifts between tumor motion and abdominal displacement were improved; however, all patients breathed more deeply, and the SI lung tumor position mismatches became slightly larger with audio coaching than without audio coaching. © 2009 Elsevier Inc.

Lung cancer, tumor motion, respiratory gated radiotherapy, audio coaching, correlation.

INTRODUCTION

During conventional radiotherapy (RT) planning for tumor movement with respiration, an internal margin is added around the clinical target volume to ensure complete coverage of the clinical target volume as it moves because of respiration within a treatment session (1). Therefore, it follows that a large amount of the surrounding normal tissue will be irradiated, increasing the amount of healthy tissue irradiated and limiting the maximal dose that can be prescribed to the tumor itself. An abdominal plate, called "diaphragm control (DC)," has been reported to be suitable for lung tumors to regulate respiratory motion (2). Although DC has been applied for patients during stereotactic body RT (SBRT) when the lung tumor motion was >8 mm at our institution, it was found that DC sometimes had little effect and was unusable because of poor respiratory function.

As techniques to explicitly account for respiratory-induced tumor movement, breath-hold (3–5), respiratory gated RT (6–10), and four-dimensional (11, 12) techniques are effective in reducing internal margin, resulting in a lower dose to the normal tissue and thus a lower risk of complications. Among these techniques, respiratory gated RT has been successfully applied to thorax and abdomen lesions in some institutions (6–10). During respiratory gated RT, the treatment device is periodically turned on and off, in phase or amplitude with the patient's breathing pattern, to restrict

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the range of tumor positions during dose delivery. Two types of gating methods have been categorized: internal and external gated RT. Internal gated RT accurately delivers a dose by monitoring the tumor position in real time using implanted fiducial markers (8). External gated RT requires the acquisition of a respiration surrogate signal to represent the tumor position (6, 7, 9, 10). Although external gated RT is less invasive for patients, the accuracy of the correlation depends on the stability of the tumor-surrogate phase or amplitude relationships during the treatment course.

In our institution, we are scheduled to perform external gated RT for patients who need DC during SBRT for lung cancer or advanced-stage lung cancer; however, we have been concerned about the correlation between the abdominal displacement and lung tumor motion in the superoinferior (SI) direction. Although Ahn *et al.* (13) and Hoisak *et al.* (14) reported a generally strong correlation without implanted fiducial markers, no guarantee exists that similar results have been obtained at our institution. Some researchers have also reported that the phase of organ motion does not necessarily match that of the surrogate motion (13–19). Phase shifts must be addressed to maintain the accuracy of the gating window. Ionascu *et al.* (17) used a real-time RT system and quantitatively estimated the time-dependent behavior of the correlation between abdominal displacement and implanted fiducial marker motion, and their corresponding amplitude mismatches. They suggested that it is necessary to increase the treatment margins to ensure the phase shifts.

The preliminary study for gated RT began under an institutional review board-approved protocol in May 2007. We developed an in-house method to investigate the tumor–abdominal motion relationship without implanted fiducial markers and showed a high correlation between these motions for 11 patients with lung cancer during free breathing (19). In addition, we have been planning to incorporate audio coaching to improve the efficiency of external gated RT for patients with an irregular breathing pattern (20, 21). Although Kini *et al.* (20) concluded that audio coaching improved the stability of respiration frequency, the effect of audio coaching on phase shifts and their corresponding lung tumor position mismatches have not yet been examined.

The purpose of the present study was to assess the effect of audio coaching on the correlations of abdominal displacement with lung tumor motion in the SI direction and the SI lung tumor position mismatches between abdominal displacement as a surrogate for the lung tumor position and the measured lung tumor position.

METHODS AND MATERIALS

Patients

Of the patients who underwent SBRT in four fractions for lung tumors between May 2007 and December 2007, 6 patients, who met following criteria, were enrolled in the present study: the lung tumor was clearly identified by X-ray fluoroscopy (Acuity, Varian Medical Systems, Palo Alto, CA) and the average peak-to-trough SI extent of the lung tumor displacement was >8 mm with X-ray fluoroscopy, as verified by several radiation oncologists. Of the 6 patients, 4 were men and 2 were women (median age, 78 years; range, 62–81). The lung tumors were located in the right middle lobe ($n = 1$), right lower lobe ($n = 3$), left upper lobe ($n = 1$), and left lower lobe ($n = 1$). The patient characteristics are listed in Table 1.

Data acquisition

A marker block with two infrared reflecting dots was placed on the anterior abdominal surface of the patient. The anteroposterior (AP) abdominal skin surface displacement was measured using the real-time positioning management system (Varian Medical Systems). The SI lung tumor motion was simultaneously acquired using X-ray fluoroscopy from the anterior of the patients. The X-ray fluoroscopy video signal was recorded at a frame rate of 30 Hz. The screen of the computer monitoring the abdominal displacement was displayed in parallel on the X-ray fluoroscopy console monitor using the remote desktop feature (maximal data transfer rate, 1 Gb/s) in Windows XP Professional so that the lung tumor motion and abdominal displacement were displayed on the same screen (Fig. 1). From the results of the preliminary verification, the phase error due to the signal delay of the local area network connection was sufficiently small (19).

All patients underwent an X-ray fluoroscopic examination of 60 s in duration with free breathing. They were then asked to breathe following simple audio coaching, such as "breathe in, breathe out," at a suitable tempo for each patient. They were trained for 5 min with the audio coaching to ensure they were comfortable with the breathing tempo and to make any adjustments necessary. After the breathing exercise, an X-ray fluoroscopic examination was performed again with audio coaching for 60 s. The X-ray fluoroscopy console monitor on which the abdominal displacement was simultaneously displayed was recorded on a digital video disk for each measurement. The measurements were performed at SBRT planning (Session 1), the second treatment session (Session 2), and at the end of treatment (Session 3). The interval between Sessions 1 and 3 was 10 days, and the duration of SBRT was within 1 week.

Tracking procedure and analysis

Custom software was developed by a medical physicist (M.N.) to automatically identify the lung tumor position to be detected on fluoroscopic images. The feasibility of our method for identifying the lung tumor position has been previously proved (19).

First, the software reads the recorded fluoroscopic images and runs the following procedure. A reflective marker position was detected using binary image processing and the mean AP abdominal displacement was then calculated. After measuring the reflective marker position, a rectangular region of interest (ROI) was set in the image that sufficiently contained the extent of lung tumor motion throughout the whole breathing cycle. A median filter with a 3×3 filter kernel was used to reduce the noise within the ROI. Image histograms within the ROI were equalized to enhance the contrast between the lung tumor and the background; thereafter, a template matching technique was applied to automatically detect the lung tumor. We have found that a basic single-template approach for lung tumor tracking does not work well for lung tumor tracking on X-ray fluoroscopic images because of the following tumor motion characteristics: the projected lung tumor shape and appearance vary more or less as a function of the breathing phase; and the X-ray fluoroscopic image intensities change with chest expansion and contraction. To reduce the false detection of the lung tumor position, three templates of the lung tumor for the exhale (end-ex), inhale

Table 1. Patient characteristics

Pt. No.	Age (y)	Gender	PS	Tumor location	Tumor size (mm)
1	78	Male	0	RLL	23
2	77	Male	1	RLL	20
3	62	Female	0	LLL	18
4	81	Male	0	LUL	29
5	77	Female	0	RLL	15
6	78	Male	0	RML	27

Abbreviations: Pt. No. = patient number; PS = performance status; RLL = right lower lobe; LLL = left lower lobe; LUL = left upper lobe; RML = right middle lobe.

(end-in), and middle (mid) respiratory phase were used. The method of difference measures ($D_k, k \in [end\text{-}in, end\text{-}ex, mid]$), based on the square of the difference between the templates and the background image, was defined as follows:

$$D_{end-in}(x,y) = \sum_{i=0}^{M-1}\sum_{j=0}^{N-1}\{f(x+i,y+j) - g_{end-in}(i,j)\}^2 \quad (1)$$

$$D_{end-ex}(x,y) = \sum_{i=0}^{M-1}\sum_{j=0}^{N-1}\{f(x+i,y+j) - g_{end-ex}(i,j)\}^2 \quad (2)$$

$$D_{mid}(x,y) = \sum_{i=0}^{M-1}\sum_{j=0}^{N-1}\{f(x+i,y+j) - g_{mid}(i,j)\}^2 \quad (3)$$

where N and M represent the length and width of the template, and $f(x, y)$ and $g_k(x, y)$, ($k \in [end\text{-}in, end\text{-}ex, mid]$) is the pixel intensity at location (x, y) of the ROI and templates, respectively. The region of minimal difference can be determined as the location of the lung tumor (x^*, y^*), as follows:

$$(x*, y*) = \arg\min_{(x,y)\in ROI}(D_{end-in}(x,y), D_{end-ex}(x,y), D_{mid}(x,y)) \quad (4)$$

The average displacement of lung tumor motion was measured according to the maximal peak-to-trough SI extent of the tumor displacement. To evaluate the tumor–abdominal phase relationship, the cross-correlation of the time-synchronized tumor–abdominal motion and its phase shifts was calculated. The SI lung tumor position mismatches between the predicted and measured lung tumor position were computed according to the method of Ionascu *et al.* (17). The mean value and 99% confidence interval of the SI lung tumor position mismatches were also calculated. The one-sided Wilcoxon test was performed for the statistical analyses. Values of $p < .01$ were regarded as significant.

RESULTS

Figure 2a,b illustrates the SI tumor displacement and AP abdominal displacement during the full respiratory cycle with and without audio coaching, respectively. The error bars represent the standard deviation (SD). The mean ± SD of tumor displacement was 10.4 ± 3.0 mm (range, 8.2–18.9) for patients during free breathing (FB). Audio coaching increased the displacement to a mean ± SD of 23.0 ± 11.6 mm (range, 10.1–46.2). The mean ± SD of abdominal displacement was 6.5 ± 2.2 mm for FB. These values increased to 17.3 ± 6.1 mm with audio coaching. A significant difference was observed between these groups in both displacements ($p < .01$).

Table 2 lists the correlation coefficients of tumor motion with abdominal displacement for each patient with and without audio coaching. The mean ± SD of the correlation coefficients was 0.95 ± 0.02 (range, 0.89–0.97) for FB. The maximal phase shift was 0.13 s for FB. The mean ± SD of the correlation coefficients was 0.97 ± 0.02 (range, 0.93–0.99) for audio coaching. The mean correlation coefficient between these groups was also significant ($p < .01$). Figure 3a,b shows a diagram of the lung tumor displacement vs. time and a scatterplot of the lung tumor displacement vs. abdominal displacement for Patient 5 in Session 3, respectively. Of all the patients, the greatest improvement in the correlation coefficient was observed for Patient 5. Using audio coaching, the average SI tumor displacement increased from 9.4 to 18.5 mm (Fig. 3a), and the observed phase shift between the tumor motion and abdominal displacement was reduced (Fig. 3b).

The SI lung tumor position mismatches for FB and audio coaching are summarized in Table 3. These mismatches persisted and varied daily. Although the SI lung tumor position mismatches became larger in 75% of all sessions with audio coaching compared with FB, no significant difference was observed between these groups ($p = .01$). The SI lung tumor position mismatches were within an average of 1.70 mm for FB and 2.09 mm for audio coaching.

DISCUSSION

Treatment planning and dose delivery of external gated RT requires intra- and interfraction reproducibility of the tumor–surrogate relationship (13, 14, 19) and stability of the intra- and interfraction target position (22) during the treatment course. In the present study, we evaluated the effect of audio

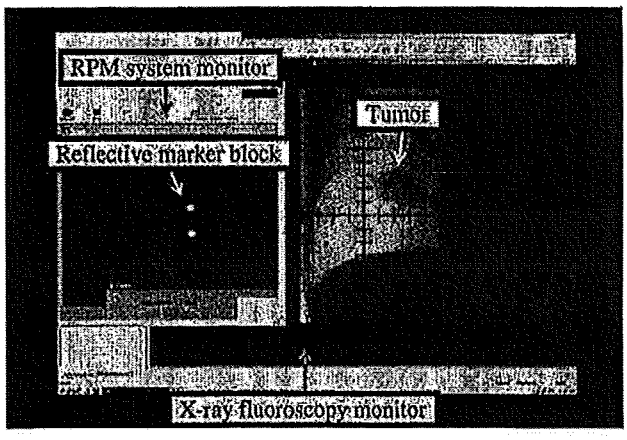

Fig. 1. Parallel display of real-time positioning management system monitor showing abdominal motion using reflective marker block and chest fluoroscopic image, which can project tumor shape from anterior of patient.

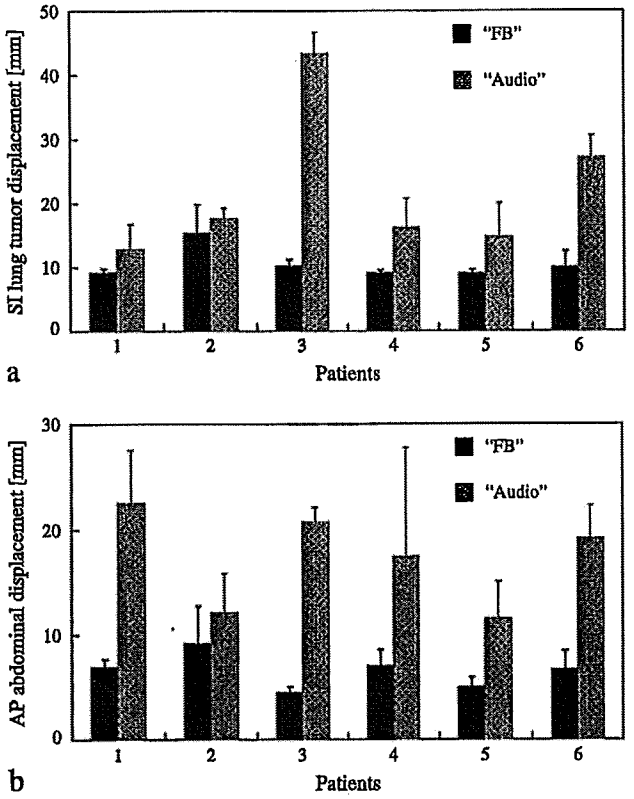

Fig. 2. (a) Superoinferior tumor displacement and (b) anteroposterior abdominal displacement averaged for consecutive respiratory cycles with and without audio coaching. Error bars show standard deviation.

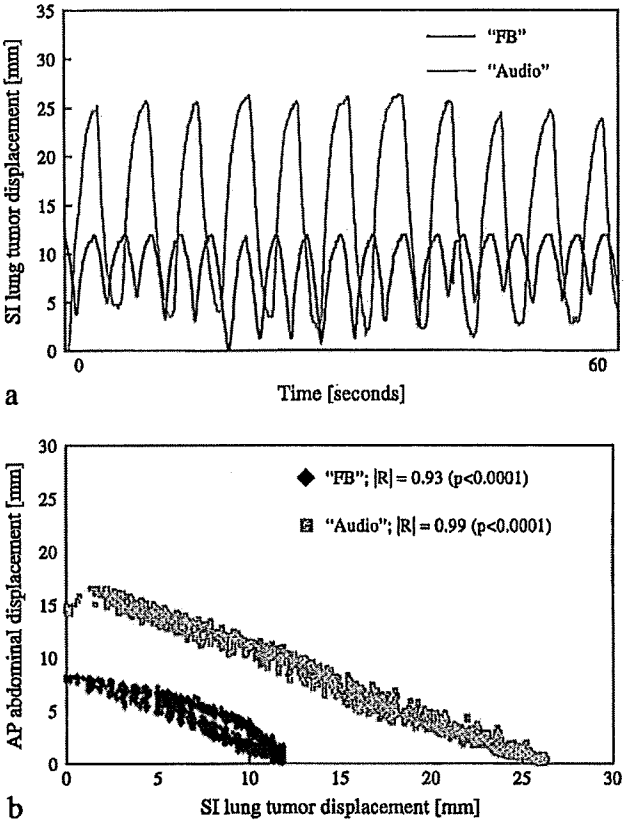

Fig. 3. (a) Time course of superoinferior lung tumor position and (b) scatterplot showing relationship with abdominal position for Patient 5 in Session 3, with and without audio coaching.

coaching on the correlation of abdominal displacement with lung tumor motion and SI lung tumor position mismatches using a template matching technique. Audio coaching generally led to an increase in the abdominal and lung tumor displacements in the AP and SI direction, respectively. Although a significant difference was shown in the tumor–abdominal correlation between the audio coaching and FB, the SI lung tumor position mismatches became slightly larger with audio coaching than without audio coaching.

A strong correlation between the external surrogate signals and internal tumor motion is required to perform external gated RT securely. Ahn *et al.* (13) used skin markers as the external surrogate signal and verified the relationship between the movement of the skin and the target organ. They showed a strong correlation (mean ± SD, 0.77 ± 0.12) between the skin and tumor movement, especially for sites in the lower lung. Hoisak *et al.* (14) assessed the correlation of abdominal displacement with the tumor motion as seen on X-ray fluoroscopy for multiple days, and reported a correlation range of 0.39–0.98. Because of the smaller phase shifts in our study than in their study, high correlation coefficients were obtained with FB. A possible cause of the phase shifts included the breathing type. Two main types of breathing exist: chest breathing and abdominal breathing. We estimated that the tumor and abdominal skin surface might move concurrently in abdominal breathing, which would result in reducing the phase shifts between the lung tumor and abdominal skin surface. In contrast, a slight time lag would occur between the abdominal skin surface and the lung tumor motion in chest breathing. If chest breathing is directed to abdominal breathing, external gated RT using an abdominal motion signal would then be performed more accurately because of the better tumor–abdominal correlation. In addition, patients tended to breathe consciously during audio coaching; thus, chest breathing might switch to abdominal breathing (23). The diaphragm is an important muscle and controls abdominal and lung tumor movement during respiration. Using audio coaching, the relaxation/contraction of the diaphragm might be stimulated. Thus, it is possible that

Table 2. Tumor–abdominal motion correlation coefficients throughout measurement sessions

	Free breathing			Audio coaching		
Pt. No.	Session 1	Session 2	Session 3	Session 1	Session 2	Session 3
1	0.97	0.97	0.97	NA	0.98	0.99
2	0.96	0.96	0.95	0.96	0.98	0.98
3	0.97	0.96	0.94	0.99	0.98	0.99
4	0.93	0.95	0.94	0.94	0.93	0.94
5	0.89	0.96	0.93	NA	0.99	0.99
6	0.93	0.97	0.97	0.95	0.96	0.97

Abbreviations: Pt. No. = patient number; NA = not available (patient did not participate in measurement session).

Table 3. Mean SI lung tumor position mismatches with and without audio coaching

	Free breathing (mm)			Audio coaching (mm)		
Pt. No.	Session 1	Session 2	Session 3	Session 1	Session 2	Session 3
1	0.49 (0.47–0.52)	0.71 (0.68–0.73)	0.61 (0.59–0.64)	NA	0.52 (0.49–0.54)	0.71 (0.67–0.75)
2	1.70 (1.63–1.77)	0.88 (0.85–0.92)	1.00 (0.95–1.06)	1.66 (1.58–1.74)	1.12 (1.08–1.17)	0.53 (0.50–0.55)
3	1.21 (1.15–1.26)	1.26 (1.18–1.33)	0.61 (0.58–0.64)	1.60 (1.51–1.69)	1.70 (1.60–1.79)	1.18 (1.13–1.24)
4	0.44 (0.42–0.46)	0.73 (0.70–0.76)	0.67 (0.64–0.70)	1.49 (1.40–1.57)	1.82 (1.74–1.89)	0.93 (0.89–0.97)
5	0.84 (0.80–0.88)	0.53 (0.50–0.55)	0.86 (0.86–0.90)	NA	0.57 (0.54–0.60)	0.69 (0.65–0.72)
6	0.77 (0.73–0.81)	0.45 (0.42–0.48)	0.69 (0.66–0.71)	1.30 (1.24–1.37)	1.72 (1.61–1.82)	2.09 (1.98–2.20)

Abbreviations: SI = superoinferior; other abbreviations as in Table 2.
Data in parentheses are 99% confidence intervals.

stimulation might have resulted in amplification of the lung tumor and abdominal displacement in the present study.

Although audio coaching significantly improved the tumor–abdominal motion correlation ($p < .01$), the total tumor movement as measured during the full respiratory cycle became larger, comparable with the results of Haasbeek *et al.* (24). Audio coaching not only stimulated tumor movement (Fig. 2a), but often resulted in a slight increase in the differences between the predicted and measured lung tumor position in the SI direction (Table 3). For example, the mismatch was an average of ≥1 mm for 62.5% of audio coaching compared with 22.2% of FB. Seppenwoolde *et al.* (25) used implanted fiducial markers and reported that the lung tumor moved with a degree of deviation from the mean trajectory position. Because the tumor largely moves during the respiration cycle, the deviation would be more pronounced. This would result in an increase in the SI lung tumor position mismatches. In contrast, audio coaching reduced the SI lung tumor position mismatches in 25% of the sessions. Thus, it was difficult to identify which factor, phase shift or tumor displacement, predominantly affected the SI lung tumor position mismatches in the present study. Additional margins or expansion of the gating window would be needed to compensate for these uncertainties in clinical practice.

An additional issue in external gated RT with audio coaching alone is an increase in the SI lung tumor position mismatches resulting from the larger motion range of the lung tumor. Haasbeek *et al.* (24) also concluded that differences in lung tumor position >5 mm between FB and audio coaching were detected in ≤56% of lung tumors with a motion range >10 mm (24). On the basis of our results, and theirs, it is more important to manage respiratory motion when applying audio coaching alone to external gated RT. As one of the methods to reduce SI lung tumor position mismatches, audiovisual biofeedback is expected to be suitable (26). The advantage of audiovisual biofeedback compared with audio coaching is that patients can maintain an arbitrary depth of respiration. Thus, it should result in a decrease in the mismatches between the predicted and measured lung tumor position.

CONCLUSION

Audio coaching served to increase the degree of correlation and made it more reproducible. In addition, the phase shifts between the tumor motion and abdominal displacement improved. All patients breathed more deeply, and the SI lung tumor position mismatches became slightly larger with audio coaching than without audio coaching.

REFERENCES

1. International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy: Report No. 62 (supplement to ICRU report No. 50. Bethesda: ICRU; 1999.
2. Negoro Y, Nagata Y, Aoki T, *et al.* The effectiveness of an immobilization device in conformal radiotherapy for lung tumor: Reduction of respiratory tumor movement and evaluation of the daily setup accuracy. *Int J Radiat Oncol Biol Phys* 2001; 50:889–898.
3. Hanley J, Debois MM, Mah D, *et al.* Deep inspiration breath-hold technique for lung tumors: The potential value of target immobilization reduced lung density in dose escalation. *Int J Radiat Oncol Biol Phys* 1999;45:603–611.
4. Rosenzweig KE, Hanley J, Mah D, *et al.* The deep inspiration breath-hold technique in the treatment of inoperable non small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2000;48: 81–87.
5. Mah D, Hanley J, Rosenzweig KE, *et al.* Technical aspects of the deep inspiration breath-hold technique in the treatment of thoracic cancer. *Int J Radiat Oncol Biol Phys* 2000;48: 1175–1185.
6. Ramsey CR, Cordrey IL, Oliver AL. A comparison of beam characteristics for gated and nongated clinical x-ray beams. *Med Phys* 1999;26:2086–2091.
7. Paoli J, Rosenzweig KE, Yorke E, *et al.* Comparison of different respiratory levels in the treatment of lung cancer: Implications for gated treatment. *Int J Radiat Oncol Biol Phys* 1999;45: 386–387.
8. Shirato H, Shimizu S, Kunieda T, *et al.* Physical aspects of a real-time tracking system for gated radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;48:1187–1195.
9. Ford EC, Mageras GS, Yorke E, *et al.* Evaluation of respiratory movement during gated radiotherapy using film and electronic portal imaging. *Int J Radiat Oncol Biol Phys* 2002;52:522–531.
10. Berson AM, Emery R, Rodriguez L, *et al.* Clinical experience using respiratory gated radiation therapy: Comparison of free-breathing and breath-hold techniques. *Int J Radiat Oncol Biol Phys* 2004;60:419–426.

11. Keall PJ, Kini V, Vedam SS, *et al.* Motion adaptive X-ray therapy: A feasibility study. *Phys Med Biol* 2001;46:1–10.
12. Keall PJ, Joshi S, Vedam SS, *et al.* Four-dimensional radiotherapy planning for DMLC-based respiratory motion tracking. *Med Phys* 2005;32:942–951.
13. Ahn S, Yi B, Suh Y, *et al.* A feasibility study on the prediction of tumour location in the lung from skin motion. *Br J Radiol* 2004;77:588–596.
14. Hoisak JD, Sixel KE, Tirona R, *et al.* Correlation of lung tumor motion with external surrogate indicators of respiration. *Int J Radiat Oncol Biol Phys* 2004;60:1298–1306.
15. Vedam SS, Keall PJ, Kini V, *et al.* Determining parameters for respiratory gated radiotherapy. *Med Phys* 2001;28:2139–2146.
16. Ozhasoglu C, Murphy MJ. Issues in respiratory motion compensation during external-beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;52:1389–1399.
17. Ionascu D, Jiang SB, Nishioka S, *et al.* Internal-external correlation investigations of respiratory induced motion of lung tumors. *Med Phys* 2007;34:3893–3903.
18. Mageras GS, Yorke ED, Rosenzweig A, *et al.* Fluoroscopic evaluation of diaphragmatic motion reduction with a respiratory gated radiotherapy system. *J Appl Clin Med Phys* 2001;2: 191–200.
19. Nakamura M, Narita Y, Matsuo Y, *et al.* Correlative analysis of abdominal motion with lung tumor motion for non-invasive respiratory gated radiotherapy. *J Jpn Soc Ther Radiol Oncol* 2008;20:119–125.
20. Kini VR, Vedam SS, Keall PJ, *et al.* Patient training in respiratory-gated radiotherapy. *Med Dosim* 2003;28:7–11.
21. Kubo HD, Wang L. Introduction of audio gating to further reduce organ motion in breathing synchronized radiotherapy. *Med Phys* 2002;29:345–350.
22. Juhler NT, Korreman SS, Pedersen AN, *et al.* Intra- and interfraction breathing variations during curative radiotherapy for lung cancer. *Radiother Oncol* 2007;84:40–48.
23. Neicu T, Berbeco R, Wolfgang J, *et al.* Synchronized moving aperture radiation therapy (SMART): Improvement of breathing pattern reproducibility using respiratory coaching. *Phys Med Biol* 2006;51:617–636.
24. Haasbeek CJA, Spoelstra FOB, Lagerwaard FJ, *et al.* Impact of audio-coaching on the position of lung tumors. *Int J Radiat Oncol Biol Phys* 2008;71:1118–1123.
25. Seppenwoolde Y, Shirato H, Kitamura K, *et al.* Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;53:822–834.
26. George R, Chung TD, Vedam SS, *et al.* Audio-visual biofeedback for respiratory-gated radiotherapy: Impact of audio coaching and audio-visual biofeedback on respiratory-gated radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;65:924–933.

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INTRA-ARTERIAL INFUSION CHEMOTHERAPY USING CISPLATIN WITH RADIOTHERAPY FOR STAGE III SQUAMOUS CELL CARCINOMA OF THE CERVIX

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Purpose: To examine the effectiveness of concomitant intra-arterial infusion chemotherapy (IAIC) using cisplatin (CDDP) with radiotherapy for Stage III squamous cell carcinoma of the cervix.

Materials and Methods: We analyzed 29 cases of Stage III squamous cell carcinoma of the uterine cervix treated with radiotherapy and IAIC of CDDP from 1991 to 2006. External-beam therapy was given to the whole pelvis using four opposing parallel fields with an 18-MV linear accelerator unit. A central shield was used after 30–40 Gy with external whole-pelvic irradiation, and the total dose was 50 Gy. High-dose-rate brachytherapy was given with ^{192}Ir microSelectron. The dose at Point A was 6 Gy per fraction, 2 fractions per week, and the total number of fractions was either 3 or 4. Two or three courses of IAIC were given concomitantly with CDDP 120 mg or carboplatin 300 mg.

Results: We confirmed excellent medicine distribution directly by using computed tomographic angiography. The 5-year overall survival rate for Stage III patients was 62%, the cause-specific survival rate was 70%, and the local relapse-free survival rate was 89%. Local recurrence, distant metastasis, and occurrences of both were 7%, 38%, and 3%, respectively. The incidence of severe acute hematologic adverse reactions (Grade ≥3) was 27% for all patients; however, all recovered without interruption of radiotherapy. Severe nonhematologic effects (Grade ≥3) were 3%, including nausea and ileus. Only 1 patient's radiotherapy was interrupted for a period of 1 week because of ileus. Severe late complication rates (Grade ≥3) for the bladder, rectum, and intestine were 3%, 3%, and 10%, respectively.

Conclusion: A combination of IAIC and systemic chemotherapy should be considered to improve the prognosis of patients with Stage III squamous cell carcinoma of the cervix. © 2009 Elsevier Inc.

Cervical carcinoma, Intra-arterial infusion chemotherapy, Radiotherapy, High-dose-rate brachytherapy.

INTRODUCTION

Radical radiotherapy (RT) for patients with uterine cervical cancer is well established, and equally good treatment results have been obtained compared with early-stage surgical treatment. However, the prognosis for patients with advanced uterine cervical cancer is still poor. To improve the prognosis for patients with advanced cervical cancer, further effort is required. Since 1999 many investigators have started paying attention to platinum-based concurrent chemoradiotherapy (CCRT) (1–11), since the National Cancer Institute announced its recommendation of CCRT for cervical cancer, based on the treatment results of five randomized trials (12–16). However, there are some differences between the West and Japan in treatment policy: in the West, patient age for CCRT is approximately in the 40s (median), younger than Japanese patients, who are approximately in their 60s. In addition, patients with early-stage (IB–IIB) cancer receive CCRT in Europe and America, whereas they receive surgery in Japan. The abovementioned studies (1–16) exhibit evidence of the effectiveness of CCRT in patients with early-stage (IB–IIB) cervical cancer, whereas no obvious evidence of survival benefit has been shown for patients with locally advanced cervical cancer.

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Intra-arterial infusion chemotherapy (IAIC) is considered useful for improvement of local control and survival, and many investigators have an interest in the use of neoadjuvant chemotherapy before radical surgery or RT and in the use of concurrent chemoradiotherapy (17–38). Many investigations have shown encouraging results for local control, but many reports have shown no definite effect on survival. There have been few reports on IAIC combined with concurrent RT. Moreover, there have been few reports concerning the evaluation of drug distribution.

We investigated the effect of concurrent IAIC with radical RT for advanced (Stage III) squamous cell carcinoma of the cervix. We have previously reported our experience with locally advanced (Stage II or higher) cervical cancer treated with this strategy (36). In this study we confirmed whether the anticancer drug had satisfactorily entered the tumor. Drug distribution was evaluated with computed tomographic angiography (angio-CT), and the drug was shown to be evenly distributed throughout the tumor.

We limited the cases to Stage III squamous cell carcinoma only, added patients treated between 1999 and 2006, and analyzed the long-term outcome for patients treated with concurrent IAIC and RT.

METHODS AND MATERIALS

Patients

Twenty-nine patients with Stage III squamous cell carcinoma of the cervix who were treated by RT and IAIC using cisplatin (CDDP) with curative intent at Hiroshima University from 1991 to 2006 were evaluated. The tumor was staged according to International Federation of Gynecology and Obstetrics criteria, and all patients were confirmed as Stage III. Two patents had Stage IIIA disease, and 27 patients had Stage IIIB disease. We excluded patients with obvious para-aortic lymph node (PAN) metastasis by CT at initial diagnosis. Patients were initially evaluated and staged by physical and pelvic examination by gynecologists and radiation oncologists, without general anesthesia.

Patient characteristics are shown in Table 1. Mean patient age was 56 years (range, 26–72 years). Stage III tumors were classified into three sizes: small (tumor slightly extending to the pelvic wall), medium (tumor massively extending to one pelvic wall), and large (tumor extending to both pelvic walls) (39). The number of patients with a small tumor was 1, with medium was 16, and with large was 12. There were 9 patients with keratinizing type, 19 with non–keratinizing type, and 1 with a further different type. Pelvic lymph node swelling was diagnosed by CT, and a clinically positive node was defined as a lymph node with a minimum diameter of >1 cm on CT. There were 7 patients with mild coexisting illness (*e.g.*, hypertension, diabetes mellitus). Previous abdominal surgery had been carried out in 9 patients.

Treatment policies

Our treatment policies are listed in Table 2. To decrease patient discomfort at application, our rate of whole-pelvic external irradiation was higher; however, our rate of intracavitary irradiation was lower than that of the Japanese general rules for clinical and pathologic management of uterine cervical cancer (39). We used IAIC for locally advanced cervical cancer.

Table 1. Patient characteristics

Patients	29
Age (y), mean (range)	56 (26–72)
Stage III tumor size*	
Small	1
Medium	16
Large	12
Histology	
Keratinizing	9
Nonkeratinizing	19
Other	1
Lymphadenopathy	
Yes	7
No	22
Coexisting illness (*e.g.*, diabetes mellitus, hypertension)	
Yes	7
No	22
Previous abdominal surgery (*e.g.*, appendectomy)	
Yes	9
No	20

Values are number except where noted.

* Small tumor (S): tumor slightly extending to the pelvic wall; medium tumor (M): tumor massively extending to one pelvic wall; large tumor (L): tumor extending to both pelvic walls.

Radiotherapy

External-beam RT (EBRT) was given to the whole pelvis using the parallel-opposed (anteroposterior–posteroanterior) technique or the four-field box technique with an 18-MV linear accelerator unit. The daily fraction size was 1.8–2 Gy, with 5 fractions weekly. The superior border of the anteroposterior–posteroanterior fields was the superior edge of L5, the inferior border was the obturator foramen, and fields extended laterally to 1.5–2 cm outside of the true pelvis. The anterior border of the lateral fields was over the anterior edge of the pubic symphysis, and the posterior border was the anterior surface of the sacrum. A central shield was used after 30–40 Gy (mean, 36.4 Gy) with external whole-pelvic irradiation, and the total dose was 50 Gy (mean, 50 Gy). High-dose-rate intracavitary brachytherapy was given with ^{192}Ir micro-Selectron for 27 patients. The dose at Point A was 6 Gy per fraction, 1 or 2 fractions per week, and the number of fractions was 3 or 4. Mean total dose of high-dose-rate intracavitary brachytherapy was 20.4 Gy (range, 12–30 Gy). For 2 patients, low-dose-rate intracavitary brachytherapy was

Table 2. Radiotherapy treatment policies

Stage	External irradiation (Gy): Whole pelvis	Central shield	Intracavitary irradiation (Point A [Gy])/fractions
I	0–30	45–50	18–30/3–5
II			
Small	0–30	45–50	18–30/3–5
Large	24–36	14–26	18–24/3–4
III			
Small–medium*	30–36	14–16	18/3
Large*	34–40	10–14	12–24/2–4
IVA*	36–50	0–14	12–24/2–4

Stage III tumor sizes as defined in Table 1 footnote.

* With chemotherapy (including intra-arterial infusion) where possible.

used. Total treatment time was 6 to 7 weeks. We performed EBRT in the morning and brachytherapy in the afternoon on the day of brachytherapy.

Intra-arterial infusion chemotherapy

Concurrent intra-arterial infusion chemotherapy was performed using CDDP or carboplatin (CBDCA). In the case of poor renal function due to aging, hydronephrosis, or for any other reason, we used CBDCA instead of CDDP. We performed catheterization according to Seldinger's technique. As a general rule, at first infusion the drug was administered through the bilateral uterine arteries to be distributed to the primary tumor. For the second infusion, the bilateral internal iliac artery was used, to perfuse pelvic lymph nodes (Fig. 1). The dose of CDDP was 100–120 mg/body (mg/patient), and in the case of CBDCA the dose was 300 mg/body (mg/patient). At first, the proportion of CDDP dose to the bilateral arteries was determined according to the proportion of tumor stain on the angiographic findings. Since 2001 we have used angio-CT (interventional procedures with CT) and obtained CTPA (CT during pelvic arteriography) to confirm the distribution of the enhanced area for the tumor. We determined the proportion of CDDP dose to the bilateral arteries on the basis of the findings of the pelvic examination, CT/MRI, and CTPA; homogeneous distribution for the tumor was obtained (Fig. 2). The theoretical bases and technical details of our IAIC have been described previously (36).

Regarding the timing of IAIC and RT, the RT theoretically should be done immediately after administration of CDDP (CBDCA) if the effect of CDDP (CBDCA) for radiation sensitization is expected. However, because clinically the patient has to maintain bed rest after IAIC overnight for hemostasis, it is impossible to administer RT immediately after IAIC. Until April 2000 we stopped RT for 1 day at the time of IAIC. In our institution, brachytherapy or IAIC was only performed in the afternoon. Therefore, CDDP (CDBCA) administration and brachytherapy were not performed on the same day. However, after May 2000, to avoid prolongation of treatment time, EBRT was performed in the morning and IAIC in the afternoon.

The number of patients treated with CDDP was 22 and with CBDCA was 7. The length of injection time was 5–10 min. To perform IAIC concomitantly during 6 to 7 weeks of RT, we performed the first IAIC at the start of RT, and 3 or 4 weeks later a second IAIC was performed. Two or three cycles of IAIC were performed every 3 to 4 weeks. Most patients (27 [93%]) received two cycles of IAIC; 1 patient refused the second IAIC; and another patient had a very large tumor (diameter approximately 8 cm), and response was insufficient (partial response) after two cycles of IAIC, so a third cycle of IAIC was carried out. We use 31 cycles of injections for internal iliac arteries, 20 for uterine arteries, 6 for the two together, and 1 for ovarian artery.

Follow-up

After completion of RT, patients were followed monthly for the first year, every 2 months during the second year, every 3 or 4 months in the third to fifth year, and twice yearly thereafter. At the time of each consultation the patient was evaluated by pelvic examination. To evaluate disease status and recurrence, patients underwent a CT scan of the chest, abdomen, and pelvis every 6 months. Suspected persistent or recurrent disease was confirmed by biopsy wherever possible. Treatment failures were classified as pelvic recurrences or distant metastasis. Late radiation complications were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (40). The median duration of follow-up was 60 months (range, 11–156 months). Information concerning disease status, late complications, and cause of death was available for 97% (follow-up rate) of the patients either from institutional records, through telephone contact directly with the patient or her relatives, or through communication with the referring physicians. One patient could not be observed 1 year after treatment. The patient developed vaginal recurrence 5 months after treatment and received brachytherapy using a vaginal cylinder.

Statistical analysis

Survival was measured from the date of initiation of therapy to the date of death or the most recent follow-up using the Kaplan-Meier

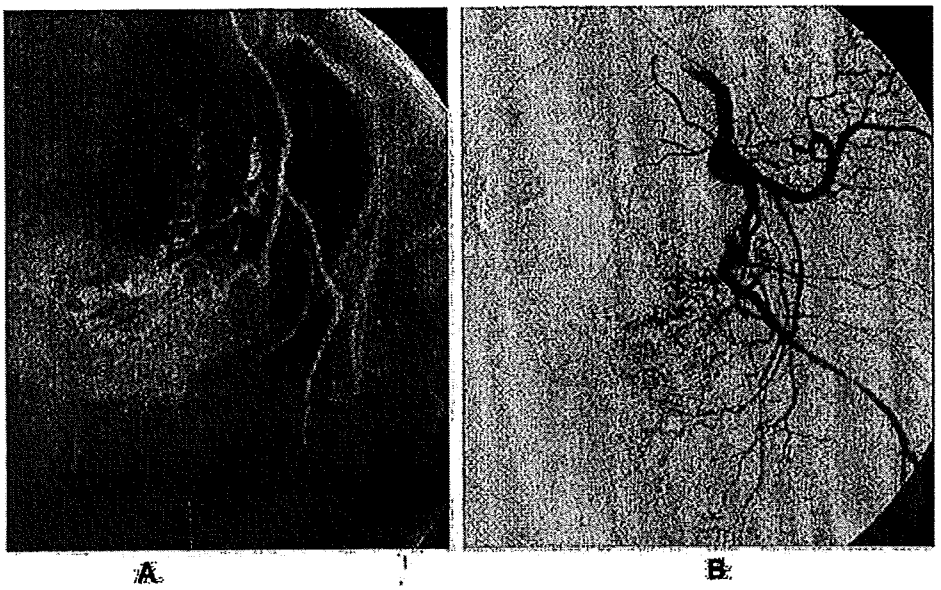

Fig. 1. Intra-arterial infusion chemotherapy (IAIC). (A) A super-selective left uterine arteriography before the first IAIC. At first infusion, cisplatin was administered through bilateral uterine arteries to be distributed to the primary tumor. (B) A selective left internal iliac arteriography before the second IAIC. At second infusion, bilateral internal iliac artery was used to perfuse pelvic lymph nodes and the primary tumor.

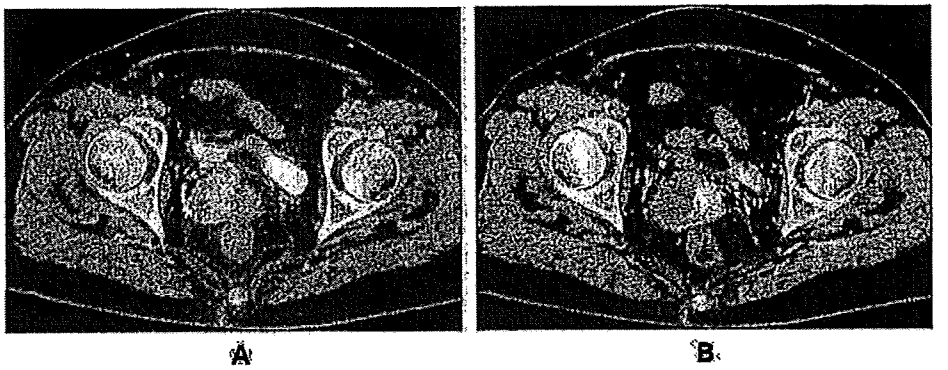

Fig. 2. Computed tomography during pelvic arteriography. Bilateral uterine arteriography before the first infusion. (A) Infusion from right uterine artery. (B) Infusion from left uterine artery. In the case in which the tumor is enhanced by the area, the proportion of cisplatin dose would be 4 to 1 for right to left. The dose of cisplatin was determined according to findings of pelvic examination CT/MRI, and CTPA. The enhanced area on the right is larger than on the left.

method, with significance compared by the Wilcoxon test. Overall survival was used to assess the death rate due to cervical cancer. The time to disease recurrence in the pelvis was measured from the date of initiation of therapy to the date of first disease recurrence or progression in the primary cervical tumor or vagina. Because of the long follow-up period, some deaths were not related to cervical carcinoma. Therefore, we also estimated cause-specific survival on the basis of available information on the cause of death. For calculation of cause-specific survival, deaths owing to cervical cancer, deaths resulting directly from treatment-related complications, and death occurring from unknown causes less than 5 years after treatment were scored as events.

RESULTS

Technical successful rate

The technical successful rate of this study was 100%. All of the catheterizations to the objective blood vessels were successful. However, at the time of the second IAIC, arteries had sometimes narrowed because of RT and IAIC. As a result it was occasionally impossible to catheterize to the objective blood vessel. We did not consider this to be a technical failure. There were no technical complications of the IAIC (*e.g.*, hematoma, catheter-related thrombosis) during catheterization in this study.

Local–regional control rate

Figure 3 shows the local–regional control rate after the start of treatment. The 5-year local control rate was 89%.

Overall survival, cause-specific survival, and risk factors

Five-year rates of overall survival and cause-specific survival were 62% and 70%, respectively (Fig. 4). The 5-year survival rate for the small–medium tumor group (n = 17; small 1, medium 16) and the large tumor group (n = 12) was 74% and 46%, respectively (p = 0.083), which tended to be better in the small–medium tumor group (Fig. 5). The 5-year survival rate was 65% in the negative lymph node metastasis group and 51% in the positive lymph node metastasis group, which tended to be better in the negative lymph node metastasis group, but the difference was not significant (p = 0.4856). There were no apparent differences for the results regarding number of IAIC cycles.

Cause of death and patterns of recurrence

Status at the time of last follow-up for all patients is as follows. Of the 12 patients who died before July 2008, 8 died of cervical cancer, 1 of radiation complications, 1 of second primary cancer (lung cancer), 1 of intercurrent disease (mediastinal inflammation), and 1 of an unknown cause. Sixteen patients are alive, and 1 patient has been lost to follow-up.

Patterns of recurrence are listed in Table 3. The methods of diagnosing recurrence were pelvic examination, biopsy, and imaging. Two local recurrences, including one local uncontrolled case, were diagnosed by biopsy of the cervix and vagina. The other patient, who had both local and distant metastasis, was diagnosed by CT imaging for local recurrence; however, metastasis of the pancreatic head was diagnosed by biopsy using endoscopic retrograde cholangiopancreatography. Diagnosis of the distant metastasis was obtained by CT.

Rates of initial local recurrence, distant metastasis, and both were 7% (2 of 29), 38% (11 of 29), and 3% (1 of 29), respectively. One patient did not show local control. The

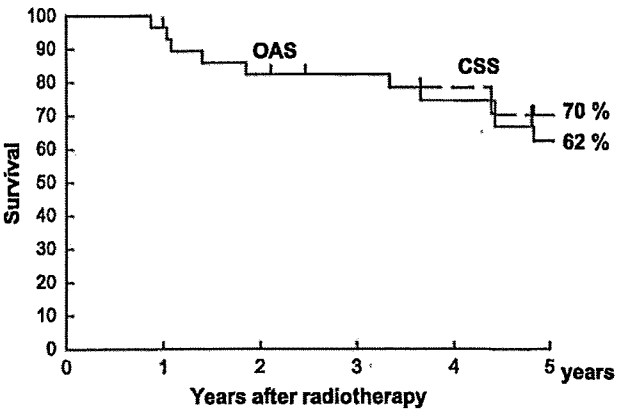

Fig. 3. Overall survival (solid line) and cause-specific survival (dashed line).

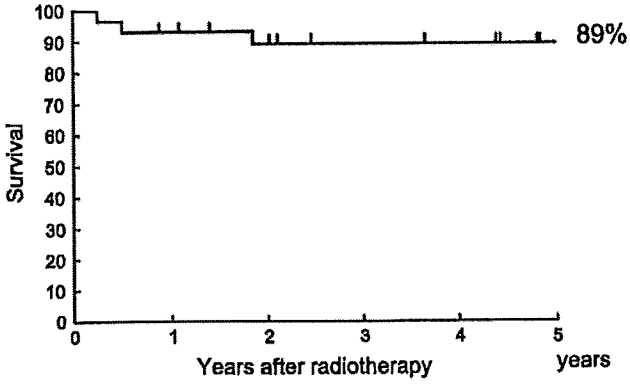

Fig. 4. Local relapse-free survival.

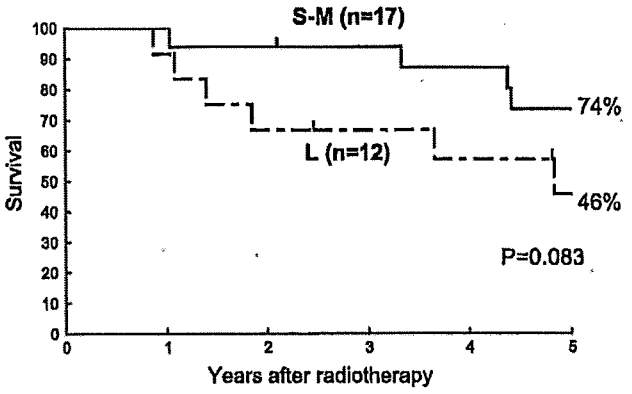

Fig. 5. Overall survival by tumor size. Solid line represents overall survival rates of 17 patients with small- and medium-sized tumor; dashed line represents that of 12 patients with large tumors.

patient had a medium-sized tumor and died of progressive local disease (cervix) without distant metastasis. Of the 28 patients who showed local control, only 2 developed local recurrences: 1 patient had vaginal recurrence, and the other had both local and distant metastasis. Sites (patient number) of distant metastases were PAN (8 patients), multiple lymph nodes (PAN, media stinal and virchow's lymph nodes) and lung (1), multiple liver, lung, and PAN (1), and lung and bone (1). Sites of both local recurrence and distant metastasis were peritoneal carcinoma, including the cervix and pancreatic head. The most frequent site of distant metastasis was PAN (28% [8 of 29]). In these 8 patients, all, apart from 1 patient who refused RT at 32 Gy, received radical RT (50–60 Gy) with or without chemotherapy. Of these 7 patients, 1 had a second relapse in the radiation field, and the remaining 6 patients were controlled. However, of these 6 patients, 3 had another lymph nodes metastasis.

Treatment sequelae

Acute toxicities according to CTCAE version 3.0 are listed in Table 4. These were transient and rendered nonlethal. Rates of Grade 3 hematologic effects were 7% for anemia, 24% for leukocytopenia, and 0 for thrombocytopenia, but no interruption of RT was needed. Rates of severe nonhematologic effects (Grade ≥3) were 3% for nausea and ileus. Only 1 patient who developed ileus during RT had RT interrupted for 1 week.

Another complication that was observed with this combined-modality treatment was CDDP sensorimotor neuropathy of the bilateral lower limbs. The neuropathy was mild sensory and motor deficit, and it slowly self-resolved within several years. No clinically significant renal toxicity was noted.

Late complications are listed in Table 5. Of 29 patients, 5 (17%) developed Grade 3 complications. Grade 3 enteritis was observed in 3 patients: 2 patients had paralytic ileus, and 1 patient had perforation of the small intestine and partial resection of the small intestine. One patient had a Grade 3 late complication of bladder tamponade. A Grade 3 small bowel complication was observed in 1 patient, who suffered from radiation enteritis with perforation of the ileum 3 months after RT and received surgical correction. Grade 5 proctitis was observed in 1 patient (3%). The patient was 68 years old and had chronic hepatitis. She had refractory rectal bleeding and fell into a shock state and died 4 years and 3 months after RT. There was no evidence of recurrence at that time.

DISCUSSION

Because the treatment policy of RT for cervical cancer is different between the West and Japan, we compared treatment results within Japan. In Japan, treatment results of high-dose-rate brachytherapy (mainly RT alone) for Stage III disease were as follows. Five-year overall survival for patients with Stage III disease was reported by many investigators as 47–56%, with mean of 51.2% (41–46). On the other hand, 5-year overall survival rates for low-dose-rate brachytherapy were 45–60%, with mean of 48.6% (41, 42, 45–47). In this study the overall survival rate was 62%. Compared with the above-mentioned results, our results are reasonably good.

Since 1999 many investigators have started paying attention to CCRT (1–11), since the National Cancer Institute announced its recommendation of CCRT for cervical cancer, based on the treatment results of five randomized trials (12–16). However, there are some differences between the West and Japan in treatment policy: in the West, patient age for CCRT is approximately in the 40s (median), younger than Japanese patients, who are approximately in their 60s. Additionally, patients with early-stage (IB–IIB) cancer receive CCRT in Europe and America, whereas in Japan they receive surgery. The treatment schedule for radical RT in Europe and America is different from that in Japan in terms of overall treatment time, central shield, and dose rate of brachytherapy. Therefore, the regimen of CCRT in Europe and America does not apply to Japanese patients.

In Japan, a comparison of treatment results between RT alone and CCRT has been reported from retrospective research by the Japan Radiation Oncology Study Group (48). There are no significant differences in overall survival between the two groups by stage (Ib–II and III–IV), though there is a bias that age is low, performance score is excellent, tumor diameter is large, and many pelvic lymph node