their regimen, whereas 67% completed their regimen in the standard CF group.

However, the advantages of daily low-dose CF compared with standard CF have not been confirmed because there has been a paucity of prospective comparative studies. Furthermore, a new regimen that is between standard CF and daily low-dose CF, called intermediate CF, has emerged. Ohtsu et al.[12] administered two courses of chemotherapy consisting of CDDP 40 mg/m^2 on days 1 and 8 and 5FU 400 mg/m^2 on days 1–5 and 8–12, with total irradiation of 60 Gy.

Therefore, in the present study, because the ideal chemotherapy regimen with radiotherapy for esophageal cancer has not been established, we compared the acute toxicities and completion rates of these regimens.

The rate of grade 3/4 esophagitis ranged from 12% to 18% in each arm, with no significant differences between treatment groups. Grade 4 esophagitis (esophageal perforation) was observed in one case. However, it was not considered to be treatment-related as it was a T4 case, and perforation occurred soon after treatment started. Thus, there do not appear to be any differences with respect to esophagitis.

Nausea was significantly more severe in arm C than in the other regimens, which suggests that it depends on the CDDP dose. Based on this result, daily low-dose CF is better than standard CF.

Although the differences were not significant, the rate of hematological toxicity was lower in arm A than in the other regimens. Two reasons may explain why arm A was associated with less hematological toxicity. First, daily low-dose administration may have caused less toxicity. The dosages of the chemotherapeutic agents used in arm A were slightly lower than in the other arms. Furthermore, there was no difference in hematological toxicity between arms B and C, which had almost the same total doses of CDDP and 5FU. Therefore, arm A appears to have milder toxicity than the other arms, which is supported by the higher completion rate for arm A than for the other regimens.

Because this trial was not randomized and the number of patients was small, the conclusions that can be reached are limited. However, each arm did show comparatively good survival. Despite the high rate of patients with clinical stage III or above (45%, 71%, and 43% in arms A, B, and C, respectively), 3-year survival rates of 40%, 31%, and 62% were seen in each arm, respectively (Fig. 2). A larger, randomized, controlled trial is needed; and it has already begun as a Japan Clinical Oncology Group (JCOG) trial. On the basis of our results, differences in toxicity and survival between arms of the study may be small.

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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).

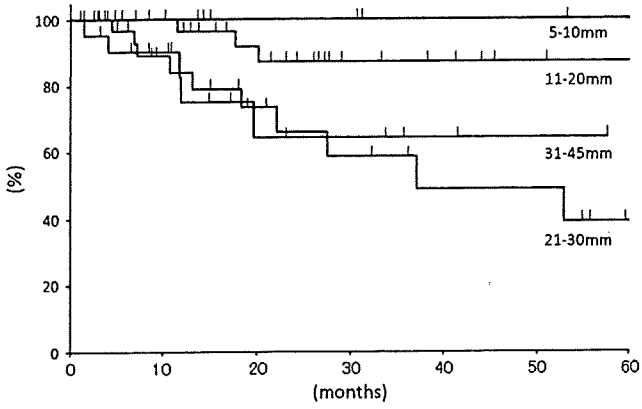

Fig. 1. Kaplan-Meier curve of overall survival rates for the patients with a tumor size (diameter) of 5 to 10 mm ($n = 11$), 11 to 20 mm ($n = 47$), 21 to 30 mm ($n = 35$), and 31 to 45 mm ($n = 22$).

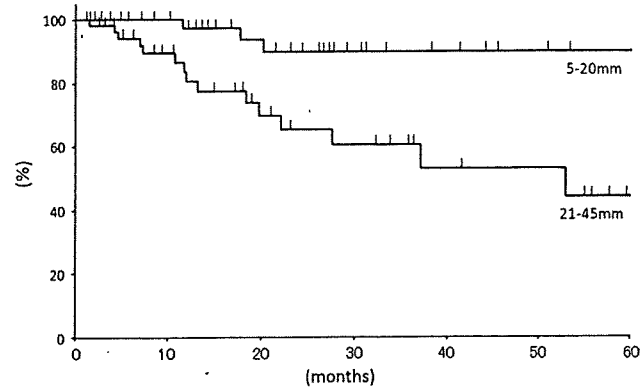

Fig. 2. Kaplan-Meier curve of overall survival rates for the patients with a tumor size (diameter) of 5 to 20 mm ($n = 58$) and 21 to 45 mm ($n = 57$). A statistically significant difference was found ($p < 0.0005$) between the two groups.

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

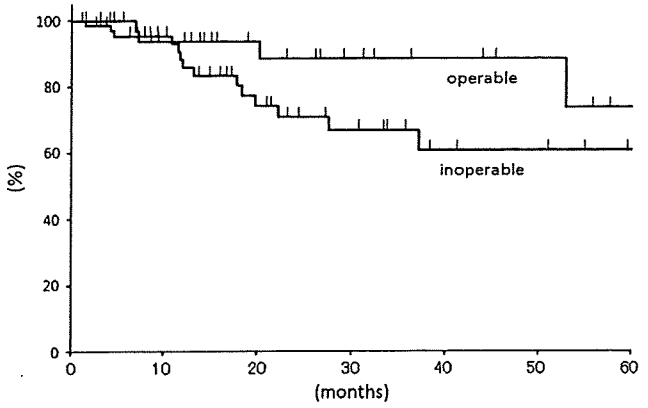

Fig. 3. Kaplan-Meier curve of overall survival rates for operable (n = 43) and inoperable (n = 72) patients. No statistically significant difference was found (p = 0.07) between two groups.

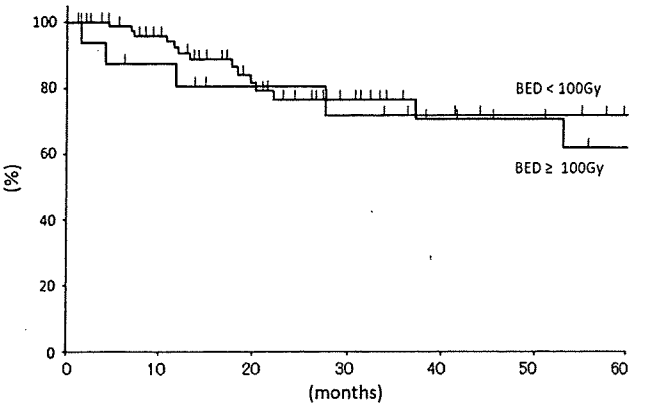

Fig. 4. Kaplan-Meier curve of overall survival rates for the patients with a biologic effective dose (BED) <100 (n = 17) and a BED ≥100 (n = 98). No statistically significant difference was found (p = 0.95) between the two groups.

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.

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

SURVEY OF STEREOTACTIC BODY RADIATION THERAPY IN JAPAN BY THE JAPAN 3-D CONFORMAL EXTERNAL BEAM RADIOTHERAPY GROUP

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Purpose: To recognize the current status of stereotactic body radiotherapy (SBRT) in Japan, using a nationwide survey conducted by the Japan 3-D Conformal External Beam Radiotherapy Group.

Methods and Materials: The questionnaire was sent by mail to 117 institutions. Ninety-four institutions (80%) responded by the end of November 2005. Fifty-three institutions indicated that they have already started SBRT, and 38 institutions had been reimbursed by insurance.

Results: A total of 1111 patients with histologically confirmed lung cancer were treated. Among these patients, 637 had T1N0M0 and 272 had T2N0M0 lung cancer. Metastatic lung cancer was found in 702 and histologically unconfirmed lung tumor in 291 patients. Primary liver cancer was found in 207 and metastatic liver cancer in 76 patients. The most frequent schedule used for primary lung cancer was 48Gy in 4 fractions at 22 institutions (52%), followed by 50Gy in 5 fractions at 11 institutions (26%) and 60Gy in 8 fractions at 4 institutions (10%). The tendency was the same for metastatic lung cancer. The average number of personnel involved in SBRT was 1.8 radiation oncologists, including 1.1 certified radiation oncologists, 2.8 technologists, 0.7 nurses, and 0.6 certified quality assurance personnel and 0.3 physicists. The most frequent amount of time for treatment planning was 61–120min, for quality assurance was 50–60min, and for treatment was 30min. There were 14 (0.6% of all cases) reported Grade 5 complications: 11 cases of radiation pneumonitis, 2 cases of hemoptysis, and 1 case of radiation esophagitis.

Conclusion: The current status of SBRT in Japan was surveyed.

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The following institutes in Japan participated in this survey: National Defense Medical College, Yamanashi University, Tohoku University, Keio University, Osaka Rosai Hospital, Hokkaido University, Yamagata Saiseikan Hospital, Hiroshima University, Tokyo Metropolitan Hiroo Hospital, Oita National Hospital, Asahikawa Municipal Hospital, Kitazato University, Tokyo University, Nara Medical College, Kagoshima Satunan Hospital, Kobe IBRI Hospital, Saitama Medical College, NTT East Sapporo Hospital, Gifu University, Hakodate Municipal Hospital, Ibaraki Prefectural Central Hospital, Obihiro Kosei Hospital, Mie University, Chiba Cancer Center, Showa University, Kyushu University, Hyogo Medical Center for Adults, Nagasaki Prefectural Shimabara Hospital, Sapporo Municipal Hospital, Fukui Red Cross Hospital, Kameda General Hospital, Yamaguchi University, Daiyukai General Hospital, Musashino Red Cross Hospital, Hokkaido Cancer Center, Sapporo Medical College, Nihon University, Handa Municipal Hospital, Tenri Hospital, Saitama Cancer Center, Tokyo Medical College Hachioji Center, Aichi Cancer Center, Hiroshima Red Cross Hospital, Kobe University, Kashiwabara General Hospital, Hitachi General Hospital, Hirosaki University, Iwate Tanzawa Hospital, Sendai Kosei Hospital, Furukawa Municipal Hospital, Takeda General Hospital, Tokyo Metropolitan Komagome Hospital, Nagaoka Red Cross Hospital, Fukui University, Hiroshima Prefectural Hospital, Tokushima University, Kagawa University, Kumamoto University, West Kobe Medical Center, Jyuntendo University Hospital, Osaka Medical College, Asahikawa Kohsei Hospital, Gunma University, Japan Defense Structure Central Hospital, St. Luke's International Hospital, Maebashi Red Cross Hospital, Sagamihara Kyodo Hospital, Toyama Municipal Hospital, Shizuoka Saiseikai Hospital, Shiga University, Rinku Central Medical Center, Kurume University, Niigata Cancer Center, Aichi Medical College, Asanokawa General Hospital, Ehime University, Osaka University, Osaka City University, Osaka Red Cross Hospital, Osaka Medical Center for Cancer, Okayama University, Nagoya Second Red Cross Hospital, Kanazawa University, Kawasaki Medical College, Nagoya City University, Nagoya University, The Cancer Institute Hospital, Gifu Prefectural Hospital, Yokohama Municipal Hospital, Kyushu Cardiovascular Center, Kinki University, Konan St. Hill Hospital, National Cancer Center Hospital, National Cancer Center Hospital East, National Kure Hospital, Saga University, Shikoku Cancer Center, Shizuoka Cancer Center, Yokohama Rosai Hospital, Shizuoka General Hospital, Jichi University, JA Hiroshima General Hospital, Yamagata University, St. Marianna University, Seirei Hamamatsu General Hospital, Teikyo University, Tokai University, Tokyo Medical University, Tokyo Women's Medical University, Toyohashi Municipal Hospital, Nagasaki University, Nagoya National Hospital, and Kyoto University.

Conflict of interest: none.

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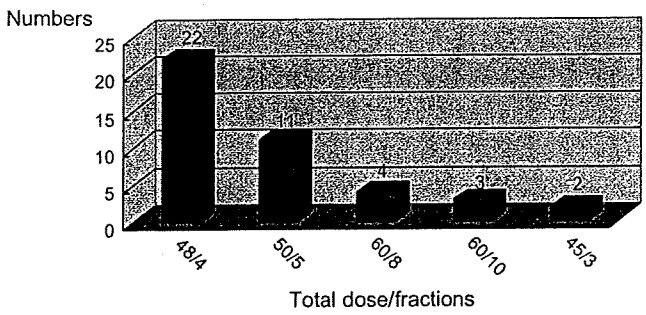

Fig. 1. Fractionation schedules of stereotactic body radiotherapy used in primary T1N0M0 lung cancer. The most common schedule was 48 Gy in 4 fractions.

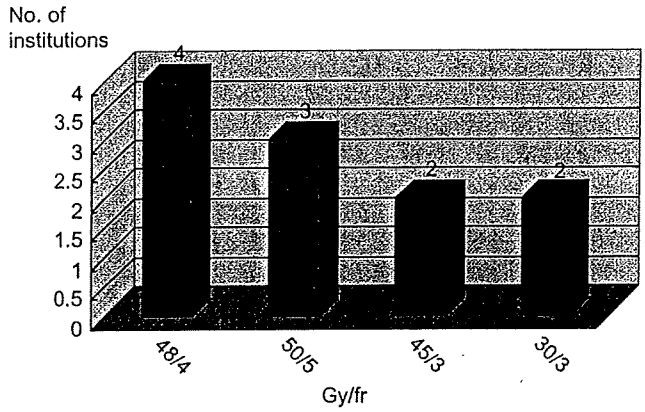

Fig. 3. Fractionation schedules of stereotactic body radiotherapy used in primary liver cancer. The most common schedule was 48 Gy in 4 fractions.

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.

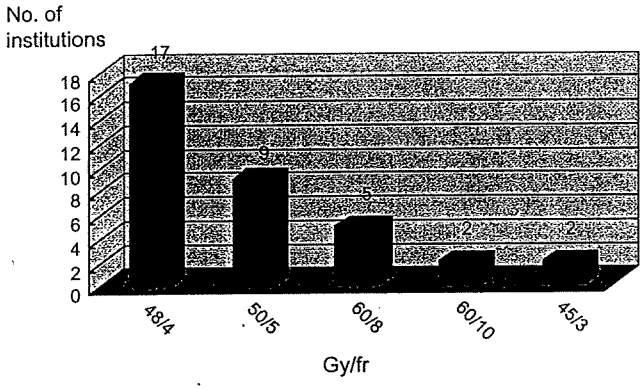

Fig. 2. Fractionation schedules of stereotactic body radiotherapy used in primary T2N0M0 lung cancer. The most common schedule was 48 Gy in 4 fractions.

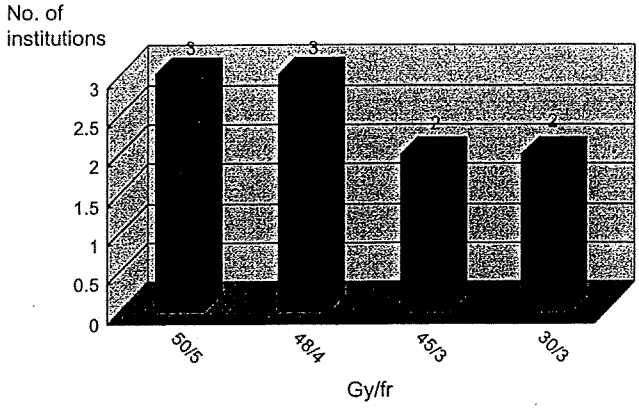

Fig. 4. Fractionation schedules of stereotactic body radiotherapy used in secondary liver cancer. The most common schedules were 50 Gy in 5 fractions and 48 Gy in 4 fractions.

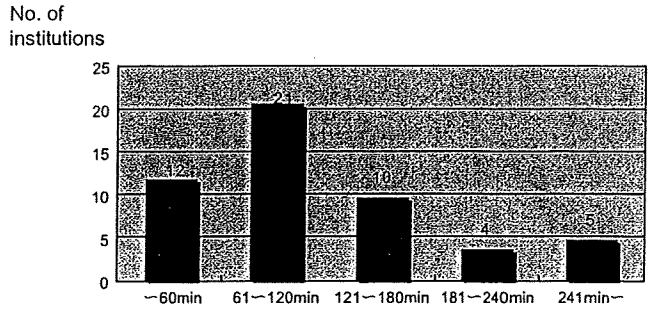

Fig. 5. Amount of time used for treatment planning (RTP) of stereotactic body radiotherapy. The most common time was 61–120 min.

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.

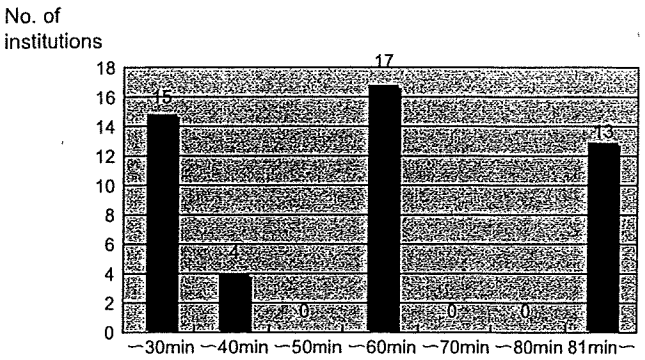

Fig. 6. Amount of time used for the single quality assurance (QA) of stereotactic body radiotherapy. The most common time was 50–60 min.

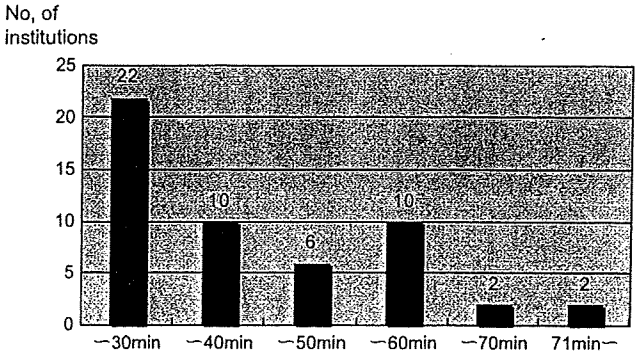

Fig. 7. Amount of time used for single daily treatment of stereotactic body radiotherapy. The most common time was <30 min.

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

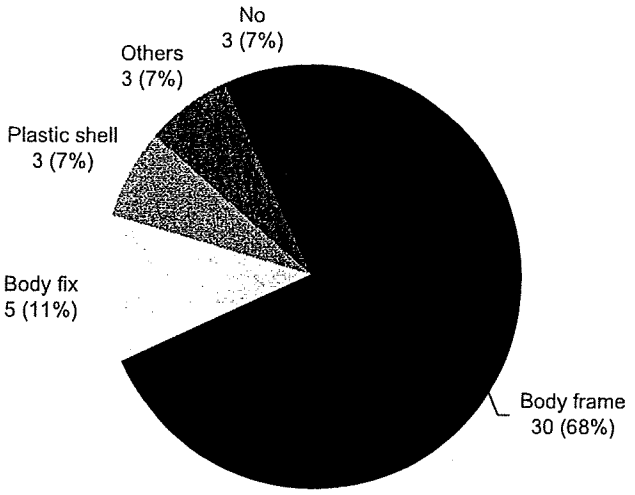

Fig. 8. Fixing apparatus used for stereotactic body radiotherapy. Body frame was most frequently used.

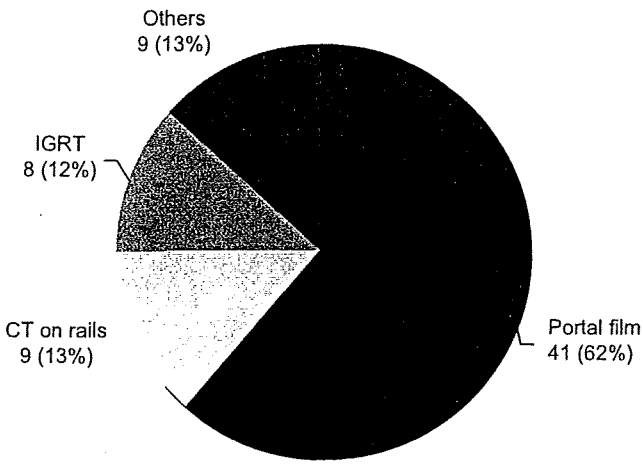

Fig. 9. Verification methods used for stereotactic body radiotherapy. Portal film was most frequently used. IGRT = image-guided radiotherapy; CT = computed tomography.

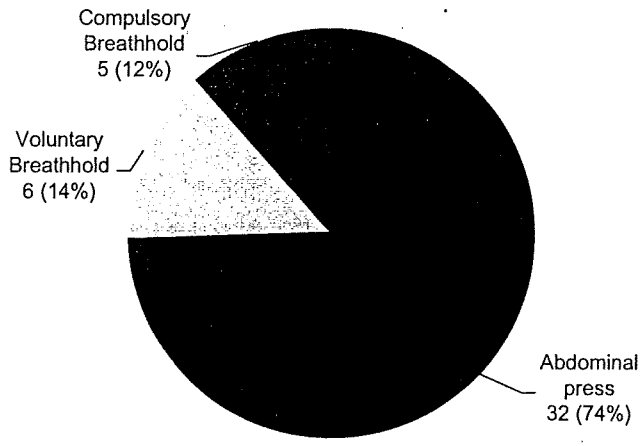

Fig. 10. Respiratory regulation method used for stereotactic body radiotherapy. Abdominal press was most frequently used.

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.

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CLINICAL INVESTIGATION

RECTAL DOSE AND SOURCE STRENGTH OF THE HIGH-DOSE-RATE IRIDIUM-192 BOTH AFFECT LATE RECTAL BLEEDING AFTER INTRACAVITARY RADIATION THERAPY FOR UTERINE CERVICAL CARCINOMA

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Purpose: The purpose of this study was to reconfirm our previous findings that the rectal dose and source strength both affect late rectal bleeding after high-dose-rate intracavitary brachytherapy (HDR-ICBT), by using a rectal dose calculated in accordance with the definitions of the International Commission on Radiation Units and Measurements Report 38 ($ICRU_{RP}$) or of dose–volume histogram (DVH) parameters by the Groupe Européen de Curietherapie of the European Society for Therapeutic Radiology and Oncology.

Methods and Materials: Sixty-two patients who underwent HDR-ICBT and were followed up for 1 year or more were studied. The rectal dose for ICBT was calculated by using the $ICRP_{RP}$ based on orthogonal radiographs or the DVH parameters based on computed tomography (CT). The total dose was calculated as the biologically equivalent dose expressed in 2-Gy fractions (EQD_2). The relationship between averaged source strength or the EQD_2 and late rectal bleeding was then analyzed.

Results: When patients were divided into four groups according to rectal EQD_2 (≥ or <median dose) and source strength (≥ or <2.4 $cGy.m^2.h^{-1}$), the group with both a high EQD_2 and a high source strength showed a significantly greater probability of rectal bleeding for $ICRU_{RP}$, D_{2cc}, and D_{1cc}. The patients with a median rectal dose above the threshold level did not show a greater frequency of rectal bleeding unless the source strength exceeded 2.4 $cGy.m^2.h^{-1}$.

Conclusions: Our results obtained with data based on $ICRU_{RP}$ and CT-based DVH parameters indicate that rectal dose and source strength both affect rectal bleeding after HDR-ICBT. © 2009 Elsevier Inc.

High-dose rate, Intracavitary brachytherapy, Late rectal complications, Source strength, ^{192}Ir.

INTRODUCTION

Brachytherapy is essential in radiotherapy for cervical carcinoma and is often combined with external beam radiation therapy (EBRT) for radical treatment. Several studies have suggested that control rates are significantly improved with EBRT and brachytherapy compared with EBRT alone (1, 2). High-dose-rate remote afterloading intracavitary brachytherapy (HDR-ICBT) is widely used throughout Asia and Europe, and its use is steadily increasing in the United States (3). A patterns-of-care study performed in Japan from 1999 to 2001 showed that approximately 90% of patients with cervical cancer who underwent ICBT were treated with HDR and that iridium-192 (^{192}Ir) was used as the ICBT source at almost half of the institutes enrolled in the study (4).

However, rectal complications are a major concern for patients with uterine cervical carcinoma who are treated with a combination of EBRT and ICBT. We previously reported that patients treated not only with a rectal biologically effective dose (BED) ≥100 Gy_3 but also with an average source strength of >2.4 $cGy.m^2.h^{-1}$ had a high incidence of rectal bleeding. To our knowledge, this was the first report to demonstrate the effect of source strength and rectal BED on rectal complications after HDR-ICBT in patients with uterine cervical carcinoma (5). However, we were unable to calculate the rectal dose by using the International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$) because we did not start using radiopaque gauze for vaginal packing until 2003. Instead, the rectal point

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dose for ICBT was calculated by inserting a lead wire into the rectal lumen.

Recently, the working group for gynecologic brachytherapy of the Groupe Européen de Curietherapie of the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) introduced guidelines for contouring the target volumes and organs at risk (OARs) for three-dimensional image-based treatment planning for cervical carcinoma. This group also proposed guidelines for analyzing the dose–volume histogram (DVH) parameters calculated from these volumes (6, 7). A minimum dose for the most irradiated tissue volume of 0.1cc ($D_{0.1cc}$), 1cc (D_{1cc}), and 2cc (D_{2cc}) for, respectively, the rectum, the sigmoid, and the bladder is recommended for routine recording.

Since 2003 we have been using radiopaque gauze for vaginal packing and have obtained computed tomography (CT) during the first session of the HDR-ICBT procedure. The purpose of this study was to reconfirm, by using the retrospectively calculated rectal dose in accordance with the definitions of $ICRU_{RP}$ or GEC-ESTRO DVH parameters obtained by CT, our findings that rectal dose and source strength both affect late rectal bleeding.

METHODS AND MATERIALS

Patient characteristics

A total of 87 patients with histologically proven carcinoma of the uterine cervix were treated at the Department of Radiation Oncology, Osaka University Hospital, Osaka, Japan between February 2003 and May 2007. Patients were staged according to the International Federation of Gynecology and Obstetrics criteria and clinically examined without general anesthesia by a gynecologic oncologist and a radiation oncologist using palpation, cystoscopy, and sigmoidoscopy. Abdominal CT and pelvic magnetic resonance imaging (MRI) were performed to help with appropriate staging. Complete blood counts and liver and renal function tests were also performed. Twenty-five patients were excluded from the study because 3 had received interstitial brachytherapy, 11 were lost to follow-up, 5 died or showed local recurrence within 1 year after radiotherapy, and 6 had for various reasons not undergone CT during the first session of HDR-ICBT. We analyzed the remaining 62 patients, who had been treated with ^{192}Ir HDR-ICBT using a tandem-ovoid or tandem-cylinder applicator and followed up for 1 year or more (median, 42 months; range, 12–62 months). The stage distribution of the patients was as follows: 10 with Stage I disease (16%), 27 with Stage II (44%), 21 with Stage III (34%), and 4 with Stage IV (6%). The median age of the study cohort was 69 years (range, 35–86 years).

Radiotherapy

Both EBRT and HDR-ICBT were performed as previously described (5), with some modifications. The treatment schedules for EBRT and HDR-ICBT are listed in Table 1. A set of Fletcher-type (Fletcher-Williamson Asian-Pacific) metal applicators (Nucletron International B.V., Veenendaal, The Netherlands) was mainly used for ICBT. For patients with vaginal infiltration or with a narrow vagina, a tandem with a vaginal cylinder was used. Anterior and posterior vaginal packing with radiopaque gauze was used to maximize the distance from the source to the bladder wall and the rectal wall. Calculation of the dose profiles was based on orthogonal radiographs taken during each individual application, and the $ICRU_{RP}$ dose was estimated from these films with a treatment planning system (Plato, Nucletron). A series of transverse CT images of the pelvis with the applicators inserted was also obtained in 2.5- or 5-mm steps during the first HDR-ICBT. Concurrent chemoradiotherapy was administered to 25 of the patients (40%). Nedaplatin, an analog of cisplatin developed in Japan, was administered 5 times weekly at 35 mg/m^2 with a concurrent EBRT and ICBT.

Table 1. Treatment schedule for uterine cervical carcinomas

Tumor stage	WP (Gy)	CS (Gy)	ICBT
T1a	0	0	7.2 Gy × 4
T1b	0	40	7.2 Gy × 4
T2	20	30	7.2 Gy × 4
T3	30	20	6.8 Gy × 4
T4	40	10	6.8 Gy × 3

Abbreviations: WP = whole-pelvic irradiation; CS = pelvic irradiation with midline block; ICBT = intracavitary brachytherapy.

Calculation of rectal dose

Cumulative DVH was analyzed according to the recommendations of the GEC-ESTRO Working Group (7). The rectum was contoured from the bottom of the ischial tuberosity to the sigmoid flexure by using the external wall contour. The minimal dose received by the 0.1-cc, 1-cc, and 2-cc volumes with the highest irradiation ($D_{0.1cc}$, D_{1cc}, and D_{2cc}, respectively) was determined. To determine the dose from the combined EBRT (whole pelvic irradiation dose, excluding the fractions with central shielding) and ICBT, the total dose (EBRT + ICRT) was calculated as the biologically equivalent dose in 2-Gy fractions (EQD_2) using the linear quadratic model for incomplete sublethal damage repair (8). The equation used to calculate the EQD_2 was as follows:

$$EQD_{2total} = EQD_{2EBRT} + EQD_{2ICBT} = Nd(d + \alpha/\beta)/(2 + \alpha/\beta) + N_B d_B(d_B + \alpha/\beta)/(2 + \alpha/\beta)$$

where N is the fraction number of EBRT (before central shielding), d is the fractional dose of EBRT, N_B is the fraction number of HDR-ICBT, and d_B is the fractional dose of HDR-ICBT. The values used for late effects on OARs (*i.e.* bladder, rectum, and sigmoid colon) were α/β =3 Gy. For the first HDR-ICRT session, EQD_2 for $ICRU_{RP}$ was estimated from the orthogonal radiographs, and EQD_2 for the respective DVH parameters was estimated from CT images with the applicators inserted. For subsequent HDR-ICRT sessions, only EQD_2 for $ICRU_{RP}$ was estimated each time, whereas the DVH parameters obtained in the first session were reused because no CT scan was performed.

Follow-up and evaluation of late rectal complications

The patients were followed up by gynecologic and radiation oncologists on an outpatient basis every month in the first year, every 2 months in the second year, every 3 months in the third year, every 4 months in the fourth year, every 6 months in the fifth year, and annually thereafter until 10 years after treatment. Each follow-up examination included collection of clinical history; a physical examination comprising abdominal, pelvic bimanual and speculum examinations; and a Pap smear from the vaginal vault or uterine cervix. The method for the grading of rectal complications has been described previously (5). Grade 1 toxicity refers to minor

Table 2. Mean value of $ICRU_{RP}$ or dose–volume parameters according to rectal bleeding

Variable	Mean dose ± SD ($Gy_{\alpha\ \beta\ 3}$) Overall	Bleeding (-)	Bleeding (+)	p*
$ICUR_{RP}$	69 ± 17	64 ± 17	83 ± 20	<0.001
D_{2cc}	72 ± 16	68 ± 15	85 ± 14	<0.001
D_{1cc}	82 ± 2	76 ± 15	98 ± 19	<0.001
$D_{0.1cc}$	117 ± 49	107 ± 47	145 ± 41	0.004

Abbreviation: $ICRU_{RP}$ = International Commission on Radiation Units and Measurements Report 38 rectal reference point; D_{2cc}, D_{1cc}, $D_{0.1cc}$ = minimum dose received by the 2-cm^3, 1-cm^3, and 0.1-cm^3 volumes with the highest irradiation, respectively.

* Student's *t* test.

symptoms requiring no treatment; Grade 2 to symptoms responding to simple outpatients management; Grade 3 to distressing symptoms requiring hospitalization for diagnosis, minor intervention, or transfusion; and Grade 4 to fistula formation or the need for major surgical intervention.

Source strength

Data for the ^{192}Ir source strength were collected on each day of the HDR-ICBT session, and the average source strength was calculated over three or four ICBT sessions.

Statistical analysis

The actuarial rate of rectal bleeding was estimated using the Kaplan-Meier method, and differences between factors were examined with the log-rank test. Student's *t*-test was used to compare the mean dose when the rectal bleeding occurred to the mean dose without using the dose–volume parameters (D_{2cc}, D_{1cc}, $D_{0.1cc}$) or $ICRU_{RP}$ data.

RESULTS

Of the 62 patients, 17 (27%) developed late rectal bleeding, including 13 (21%) with Grade 1 toxicity, 2 (3%) with Grade 2, 0 (0%) with Grade 3, and 2 (3%) with Grade 4. The median EQD_2 representing the sum of the EBRT and HDR-ICRT dose was 65 Gy (range, 22-118 Gy) for $ICRU_{RP}$, 71 Gy (range, 29–112 Gy) for D_{2cc}, 80 Gy (range, 32–150 Gy) for D_{1cc}, and 108 Gy (range, 39–285 Gy) for $D_{0.1cc}$. Differences in the mean EQD_2 dose for patients with or without rectal bleeding are shown in Table 2. Patients with rectal bleeding received a significantly greater nominal total dose for $ICRU_{RP}$ ($p < 0.001$), D_{2cc} ($p < 0.001$), D_{1cc} ($p < 0.001$), and $D_{0.1cc}$ ($p = 0.004$). The patients were divided into low-EQD_2 (<median dose) and high-EQD_2 (≥median dose) groups. The actuarial rectal bleeding rate for each group is shown in Fig. 1. The 2-year rectal bleeding rates for the low-EQD_2 and high-EQD_2 groups were, respectively, 12% and 47% for $ICRU_{RP}$, 15% and 44% for D_{2cc}, 12% and 47% for D_{1cc}, and 8% and 51% for $D_{0.1cc}$. The high-EQD_2 group had a significantly greater rectal bleeding risk for all parameters ($ICRU_{RP}$, D_{2cc}, D_{1cc}, and $D_{0.1cc}$).

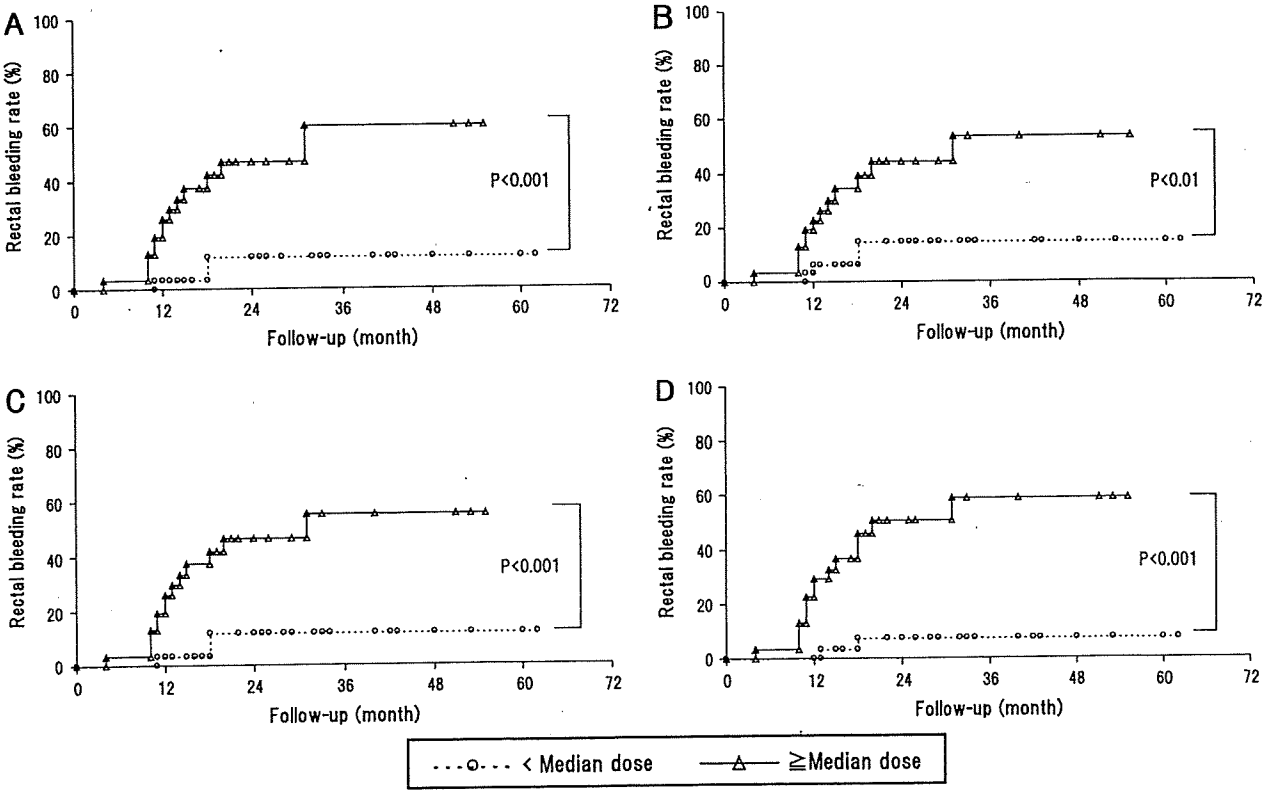

Fig. 1. Actuarial rectal bleeding rates for two groups based on the biologically equivalent dose in 2-Gy fractions (EQD_2) (<median dose vs. ≥median dose for each parameter). (A) International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$) (B) D_{2cc}. (C) D_{1cc}. (D) $D_{0.1cc}$.

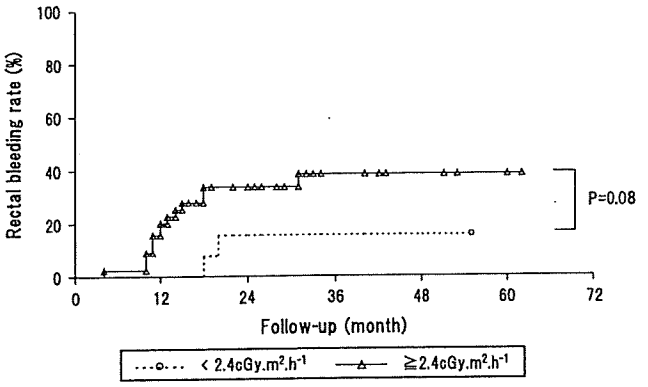

Fig. 2. Actuarial rectal bleeding rates for two groups based on ^{192}Ir source strength threshold values of 2.4 cGy.m^2.h^{-1}.

Patients were also divided into two groups based on the threshold source strength of 2.4 cGy.m^2.h^{-1} (the median source strength was 2.512 cGy.m^2.h^{-1} with a range of 1.904–4.631 cGy.m^2.h^{-1}). The group with the stronger source strength showed greater rectal bleeding, but the difference was not statistically significant (15% vs. 34% at 2 years; $p = 0.08$), as shown in Fig. 2.

Next, the patients were separated into four groups according to the median rectal EQD_2 and the threshold source strength of 2.4 cGy.m^2.h^{-1}; Group 1 (<median dose and <2.4 cGy.m^2.h^{-1}), Group 2 (<median dose and ≥2.4 cGy.m^2.h^{-1}), Group 3 (≥median dose and <2.4 cGy.m^2.h^{-1}), and Group 4 (≥median dose and ≥2.4 cGy.m^2.h^{-1}). The actuarial rectal bleeding rate for each group is shown in Fig. 3. There was a significant difference in rectal bleeding between Group 4 and Groups 1–3 for $ICRU_{RP}$, D_{2cc}, and D_{1cc}. For EQD_2 at $D_{0.1cc}$, there was a significant difference in rectal bleeding between Group 4 and Groups 1 and 2. Group 4 also had greater rectal bleeding than Group 3, but the difference was not statistically significant ($p = 0.1$). The relationship between the rectal dose and source strength for each patient is also shown in Fig. 4. Correlation coefficient analysis showed no significant relationship between rectal dose and source strength. Both patients with Grade 4 rectal bleeding were in Group 4. Clinical parameters of patients who did and did not develop late rectal bleeding were also compared (Table 3), but there was no significant difference between the two groups regarding age (<70 vs. ≥70 years old), stage (Stage I-II vs. Stage III-IV), or concurrent chemotherapy (No vs. Yes).

DISCUSSION

In a previous report, we demonstrated that patients with not only BED ≥100 Gy_3 but also an average source strength of >2.4 cGy.m^2.h^{-1} showed a correlation with a high incidence of rectal bleeding (5). To our knowledge, this was the first report to demonstrate the effect of source strength

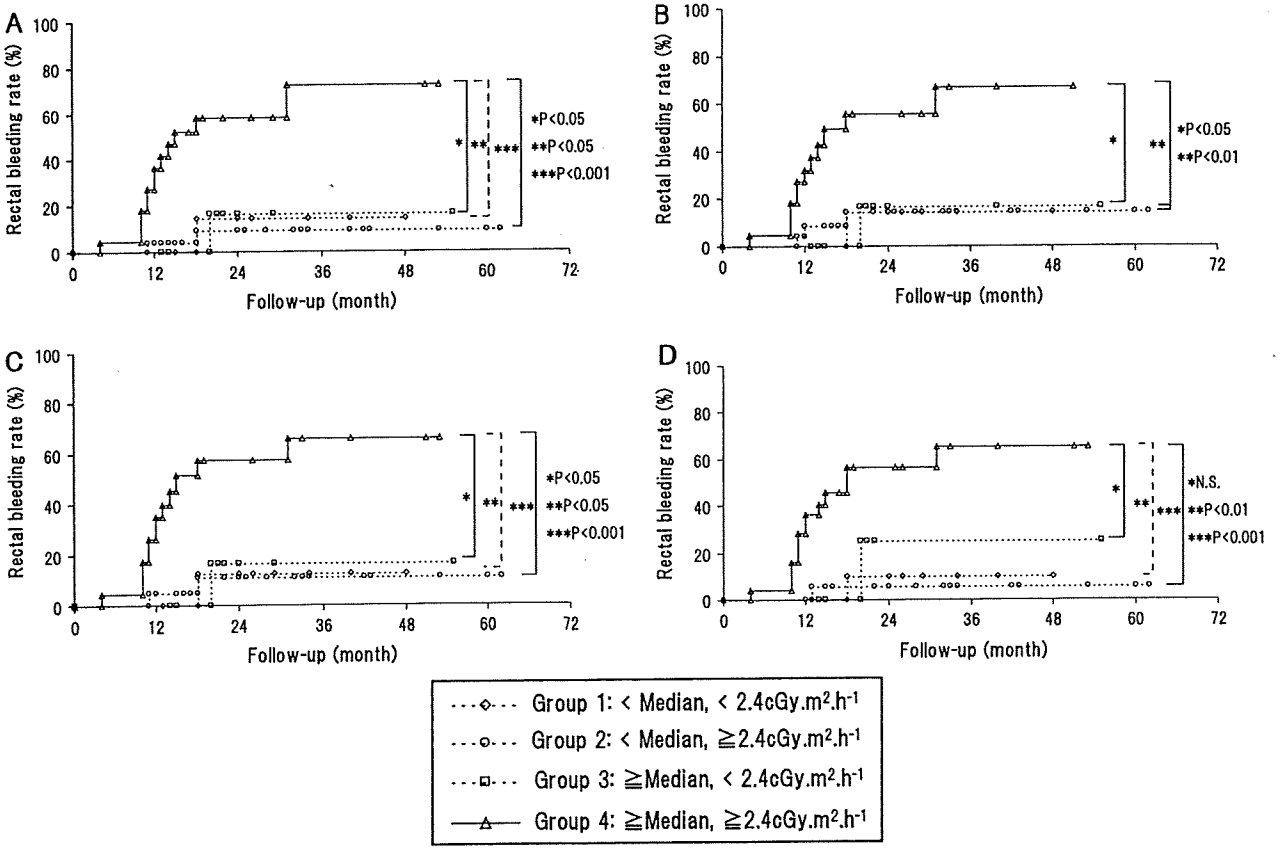

Fig. 3. Actuarial rectal bleeding rates for four groups based on the threshold values of the median dose and the source strength of 2.4 cGy.m^2.h^{-1}. (A) International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$). (B) D_{2cc}. (C) D_{1cc}. (D) $D_{0.1cc}$.

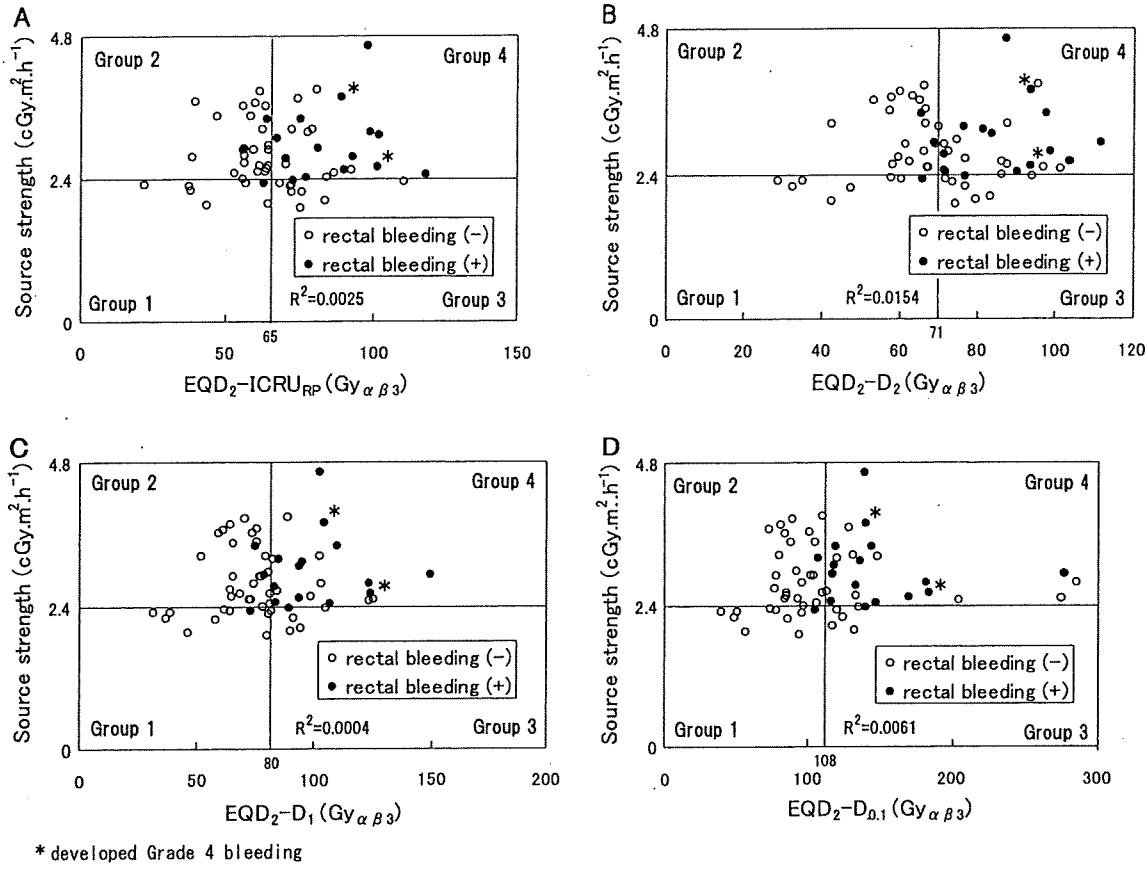

Fig. 4. Relationship of rectal dose and source strength for each patient. (A) International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$). (B) D_{2cc}. (C) D_{1cc}. (D) $D_{0.1cc}$.

and rectal BED on rectal complications after HDR-ICBT in patients with uterine cervical carcinoma. However, the previous study had a limitation in that we had defined the rectal dose as the dose to the lead wire inserted into the rectal lumen, which made it difficult to compare our result with those of other reports. We therefore decided this time to calculate the rectal dose by using the $ICRU_{RP}$ or GEC-ESTRO DVH parameters, which are considered to represent generally accepted dose points or parameters for communicating results among institutions. For the current study, the establishment of four groups of patients by using threshold levels for the rectal dose (≥ or <median dose) and source strength (≥ or <2.4 cGy.m^2.h^{-1}) showed that patients with values above the respective thresholds experienced a significantly greater frequency of rectal bleeding than did other patients. It should be noted that patients with a rectal median dose above the threshold did not show a greater frequency of rectal bleeding unless the source strength exceeded 2.4 cGy.m^2.h^{-1}. These results are in agreement with those reported by the previous study. These findings together suggest that rectal bleeding is affected not only by rectal dose but also by ^{192}Ir source strength during HDR-ICRT.

Table 3. Correlation of clinical factors with rectal bleeding

Factor	Patients, *n*	Rectal bleeding, *n* (%)		*p**
		No	Yes	
Age (y)				0.85
<70	32	24 (75)	8 (25)	
≥70	30	21 (70)	9 (30)	
Local stage				0.89
I–II	37	26 (70)	11 (30)	
III–IV	25	19 (76)	6 (24)	
CCRT				0.17
No	37	29 (78)	8 (22)	
Yes	25	16 (64)	9 (36)	

Abbreviation: CCRT = concurrent chemoradiotherapy.
* Log–rank test.

Figure 2 shows that the source strength is not the only prognostic factor for rectal bleeding (p = 0.08). For $D_{0.1cc}$ (which would correspond to the maximal dose as determined by X-ray–based planning), there was no significant difference in rectal bleeding between Group 4 (≥median dose and ≥2.4 cGy.m^2.h^{-1}) and Group 3 (≥median dose and <2.4 cGy.m^2.h^{-1}) (Fig. 3). These data indicate that the rectal dose is a more powerful prognostic factor for rectal bleeding than is the source strength.

In our previous study, the rectal dose was calculated as the BED by combining the EBRT and the HDR dose. In the current study, rectal dose is shown as the EQD_2 dose for reasons of simplicity and to allow for correlation with standard low-dose-rate (LDR) doses. The median EQD_2 values were 65 Gy

for $ICRU_{RP}$ and 71 Gy for D_{2cc}, which correspond to a BED Gy_3 of 107 Gy and 119 Gy, respectively. These values are a little higher than those of our earlier results using data obtained by inserting a lead wire into the rectal lumen (with a median BED of 101.5 Gy_3), because the lead wire in the lumen tends to separate from the rectal wall and thus to result in underestimation of the rectal wall dose as confirmed in the cohort of the present study (data not shown).

These days, conventional $ICRU_{RP}$ is not always considered to be the best predictor of rectal dose (9). However, there are a few reports of $ICRU_{RP}$ correlating well with D_{2cc} in a CT-based DVH analysis (10, 11). Additionally, GEC-ESTRO has recommended both $ICRU_{RP}$ and DVH parameters for recording and reporting because the correlation between dose–volume relations and dose–volume effect has scarcely been investigated (7). We therefore decided to analyze rectal dose by using both $ICRU_{RP}$ and CT-based DVH parameters. Many studies using $ICRU_{RP}$ (12, 13) or DVH parameters in HDR-ICBT have indicated that a higher rectal dose is significantly related with rectal bleeding. Noda *et al.* (14), using a CT-based rectal mucosal point dose, showed that a rectal BED ≥ 140 Gy_3 was associated with a significantly greater frequency of rectal complications, and Koom *et al.* (15) found that several DVH parameters obtained from three-dimensional CT-based treatment planning or $ICRU_{RP}$ are significantly associated with endoscopic scoring of mucosal changes in the rectum. However, these reports of CT-based DVH analysis results show only the relationship between rectal dose and rectal bleeding but do not deal with the power of the source.

The dose–rate effect has been analyzed in several LDR studies, which have shown that a higher dose–rate is associated with a higher incidence of late morbidity (16, 17). Therefore, we hypothesized that a higher dose–rate is also correlated with a higher incidence of rectal bleeding in ^{192}Ir HDR-ICBT. However, it is difficult to evaluate the dose–rate effect in ^{192}Ir HDR-ICBT compared with LDR-ICBT because the ^{192}Ir source has a short half-life (about 74 days) and attenuates rapidly during the treatment period (intra- or inter-fraction). In as much as the strength of the source is thought to affect the dose–rate, the ^{192}Ir source strength was measured on each day of the HDR-ICBT session, and the average source strength was calculated over three or four sessions as an indicator of the dose–rate.

The dose–rate effect at HDR is thought to be smaller than that at LDR because there is little impact of sublethal damage repair. However, the dose–rate effect at HDR is more complicated than at LDR because fractionation compensates for the relative lack of protection of late-responding normal tissues. An effect of dose–rate in HDR brachytherapy has been found in radiobiologic models (18, 19). Manning *et al.* (18) estimated the dose–rate effect using a single-plane template model, with examination of variability in dose–rate in brachytherapy performed with an HDR stepping source. Different late adverse effects were found between the relatively uniformly irradiated central zone of the template and the heterogeneously irradiated peripheral zone. The model also showed pronounced dependence on source strength, especially in cells of late-responding tissues with short repair times. In HDR treatment of cervical carcinoma using a stepping source, the instant dose–rate at each stepping point (dwell point) changes dramatically during the time course of irradiation. A peripheral location of the applicator, such as the rectal wall, may provide irradiation at an ultra-high dose–rate. Positioning of the source at the ovoid apex is likely to provide a higher dose–rate and a higher source strength, and it is likely to be associated with a late rectal effect.

One weakness of this study is that CT scans after insertion of an applicator were obtained only during the first HDR-ICRT session. However, the occurrence between sessions of substantial changes in the spatial relationship of the applicator relative to target structures and OARs have been demonstrated (20, 21), and these findings indicate the importance of individual treatment planning for each fraction. Examination of pelvic CT images for every ICBT session would allow precise calculation of dose parameters, but this approach would be time consuming and not cost effective in actual practice. The GEC-ESTRO group has provided recommendations for target delineation using MRI-contoured volumes (6, 7). MRI is superior to CT for imaging the normal anatomy of the female pelvis and for identifying the extent of cervical carcinoma, but we were unable to perform MRI scans during ICBT because of the lack of an MRI-specific applicator. Viswanathan *et al.* (22) reported that CT tumor contours can overestimate the tumor volume but that there were no significant differences between CT and MRI in terms of volumes or doses to the OARs. We therefore believe that CT-based contouring is adequate for DVH analysis of OARs.

In conclusion, this is the second report on evaluation of the effect of ^{192}Ir source strength on rectal bleeding in patients undergoing HDR-ICRT. Our results show that both rectal dose and source strength affect rectal bleeding after HDR-ICRT using $ICRU_{RP}$ and CT-based DVH parameters.

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Original Article

Postoperative Radiation Therapy After Complete Resection of Thymoma Has Little Impact on Survival

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BACKGROUND: Postoperative radiation therapy for thymoma is widely used, although the clinical benefits are controversial. Furthermore, to the authors' knowledge, the relation between postoperative radiation therapy and cell type classified by the World Health Organization (WHO) is not known. **METHODS:** The records of 324 patients (ages 17-83 years; mean, 51 years; 160 males and 164 females) who underwent complete resection of a thymoma between 1970 and 2005 were reviewed. Mediastinum postoperative radiation therapy was performed for 134 patients. Survival rates and patterns of recurrence were determined according to Masaoka stage and WHO cell type. **RESULTS:** The 10-year disease-specific survival rates for patients with and without postoperative radiation therapy were 92.8% and 94.4%, respectively ($P = .22$). Subset analyses after stratifying by Masaoka stage and WHO cell type demonstrated that the 10-year disease-specific survival rate for patients without postoperative radiation therapy with Masaoka stage I and II, as well as those with WHO cell types A, AB, or B1, was 100%, which was satisfactory. Furthermore, the rates for patients with Masaoka stage III/IV and those with WHO cell types B2/B3 with or without postoperative radiation therapy were not found to be significantly different. In 24 patients with disease recurrence, pleural dissemination was observed most often, followed by distant metastases; local disease recurrence without other recurrence occurred in 2. **CONCLUSIONS:** The authors concluded that surgical resection alone is sufficient for thymoma patients with Masaoka stage I and II, and those with WHO cell types A, AB, and B1. Furthermore, an optimal treatment strategy should be established for patients with Masaoka stage III/IV and WHO cell type B2/B3 thymomas. **Cancer 2009;115:5413–20. © 2009 American Cancer Society.**

KEY WORDS: thymoma, surgery, radiation therapy, complete resection, survival, Masaoka stage, World Health Organization histologic classification.

When classifying the advancement of thymomas, the Masaoka staging system[1,2] has been widely used because it is a good predictor of prognosis for those patients,[3] in addition to its clarity in assigning patients to an appropriate stage. Conversely, thymomas are also histologically classified based on a system proposed in 1999 and revised in 2004 by the World Health Organization (WHO).[4] In that classification, which is also

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