を安全に行うためには放射線治療計画装置が必須であり，また放射線治療器の安全な使用には機器の精度管理が欠かせない．がん診療拠点病院の指定の関係から放射線治療部門の整備を進める施設も多いと思われるが，機器の整備や人材配置にはかなりの資金的負担が病院に生じる．また，放射線治療専門の医師の不足は危機的状況であるが，医師のみならず放射線治療専任の技師の育成や放射線物理士の育成に関しても解決しなければならない課題が多く，早期に人材育成のためのシステム作りを構築し，がん診療レベル向上を図らねばならない．

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ORIGINAL ARTICLE

Comparison of cisplatin and 5-fluorouracil chemotherapy protocols combined with concurrent radiotherapy for esophageal cancer

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Abstract
Purpose. The optimal chemotherapeutic protocol for the treatment of esophageal cancer has not yet been established. This study was performed to identify the differences in toxicity and completion rates of various chemotherapy protocols with that goal in mind.
Materials and methods. A total of 61 patients with esophageal cancer were enrolled in this study between June 2002 and January 2004. The total radiotherapy dose was 64 Gy. Three chemotherapy protocols were used. Arm A comprised daily low-dose cisplatin (CDDP) and 5-fluorouracil (5FU) (CF protocol) (3 mg/m^2 and 180 mg/m^2, respectively). Arm B was intermediate between arm A and C (CDDP 7 mg/m^2 and 5FU 250 mg/m^2 on days 1–5, 8–12, 29–33, and 36–40). Arm C comprised two courses of standard CF (CDDP 70 mg/m^2 on day 1 and 5FU 600 mg/m^2/24 h on days 1–4).
Results. Although there were no significant differences in hematological toxicity between the protocols, leukocytopenia was slightly milder in arm A. Nausea was significantly more severe in arm C. The completion rate was higher in arm A. The 3-year survival rates were 40%, 31%, and 62%, respectively.
Conclusion. The daily low-dose CF protocol showed a trend of mild toxicity regarding leukocytopenia. However, we could not find statistical difference between arms. It also showed a better completion rate than the other two arms.

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Key words Esophageal cancer · Chemoradiation therapy · Cisplatin · 5-Fluorouracil

Introduction

Concurrent chemoradiation therapy has been widely used for esophageal cancer. Cooper et al.[1] reported a 5-year survival rate of 26% in the group undergoing 50 Gy radiotherapy with chemotherapy consisting of cisplatin (CDDP) 75 mg/m^2 and 5-fluorouracil (5FU) 1000 mg/m^2. Today, this type of regimen, involving intermittent administration of CDDP and 5FU (standard CF protocol), is widely given; and it has been confirmed that it is better than radiotherapy alone.[2–4] Standard CF with radiotherapy is an effective form of treatment, although it is associated with relatively frequent, severe, acute toxicity.

On the other hand, daily administration of low-dose CDDP and 5FU (daily low-dose CF) with radiotherapy has been reported to result in less toxicity than standard CF.[5–11] Sasamoto et al.,[8] in a prospective study, showed less hematological toxicity in the daily low-dose group than in the standard CF group.

Furthermore, a new type of regimen, which would be classified as "intermediate CF" (between standard CF and daily low-dose CF) has emerged. Ohtsu et al.[12] reported 3-year survival of 23% with two courses of CDDP (40 mg/m^2 on days 1 and 8) and 5FU (400 mg/m^2/24 h on days 1–5 and 8–12).

However, to the best of our knowledge, there have been no prospective studies comparing the clinical outcomes of low-dose CF with standard CF. Thus, we tried to compare these three representative chemotherapy regimens (standard CF, daily low-dose CF, intermediate CF).

The purpose of this study was to evaluate the acute toxicities and completion rates of these three regimens using data obtained from our routine clinical work. Each participating institution used one of these three regimens as standard chemoradiation therapy for esophageal cancer. This study was supported by the Japanese Radiation Oncology Study Group (JROSG).

Materials and methods

Study design

This study was reviewed and approved by the review board of each participating institution, and all patients gave their written informed consent prior to enrolment in the study. The study was designed to evaluate differences in the acute toxicities and completion rates among the three chemotherapy protocols that were used as standard chemoradiation therapy in the daily clinical practice of each institution.

Chemotherapy arms

Three representative chemotherapy protocols were selected (standard CF, daily low-dose CF, intermediate CF). Each institution performed one of the chemotherapy regimens, which was then given concurrently with thoracic radiotherapy (64 Gy in 32 fractions).

These chemotherapy protocols, daily low-dose CF, intermediate CF, and standard CF, were named arm A, arm B, and arm C, respectively. The study schema is shown in Fig. 1.

Arm A involved daily low-dose CF (CDDP 3 mg/m^2/30 min and 5FU 180 mg/m^2/24 h) given on each day of radiotherapy. This regimen was based mainly on the report from Hsu et al.[5] in which study there was a 56% incidence of grade 3 leukocytopenia. Based on that study and other reports, we reduced the doses of the chemotherapeutic agents to less than those used in these previous studies to increase the completion rate.

Arm B consisted of CDDP 7 mg/m^2 and 5FU 250 mg/m^2/24 h on days 1–5, 8–12, and 29–33. This regimen was based on data from the study by Ohtsu et al.[12] As our total irradiation dose was higher than theirs and we did

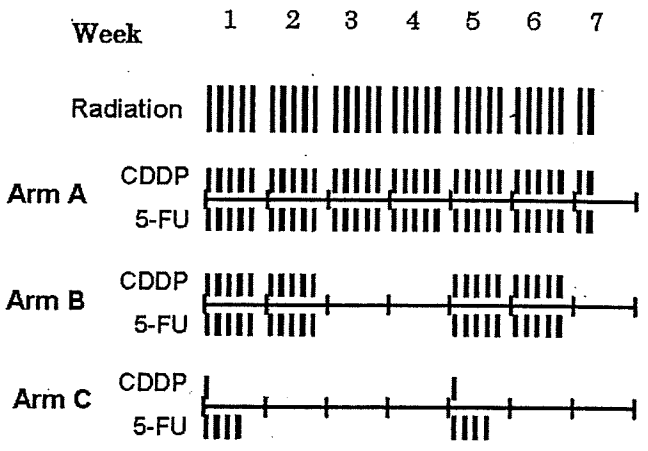

Fig. 1. Schema of the chemoradiation protocols. Radiation comprised 2.0 Gy/day, 5 days a week. Arm A [daily low-dose CDDP/5FU (CF) protocol]: CDDP (cisplatin) 3 mg/m^2/30 min + 5-fluorouracil (5FU) 180 mg/m^2/24 h on each day of radiotherapy. The total doses of CDDP and 5-FU were 96 and 5760 mg/m^2, respectively. Arm B (intermediate CF protocol): CDDP 7 mg/m^2 + 5FU 250 mg/m^2/24 h on days 1–5, 8–12, 29–33, and 36–40. Total doses of CDDP and 5FU were 140 and 5000 mg/m^2, respectively. Arm C (standard CF protocol): CDDP 70 mg/m^2 on days 1 and 29 + 5FU 600 mg/m^2/24 h on days 1–4 and 29–32. Total doses of CDDP and 5-FU were 140 and 4800 mg/m^2, respectively

not interpose radiotherapy, the dose of the chemotherapy was modified from their original regimen.

Arm C involved two courses of chemotherapy (CDDP 70 mg/m^2 on day 1 with 5FU 600 mg/m^2/24 h on days 1–4). This arm represents the standard CF protocol. The doses of CDDP and 5FU were slightly decreased for two reasons: Severe adverse effects occurred in 48% of patients in the Radiation Therapy Oncology Group (RTOG) 85–01 trial[1]; and the radiation dose in the present study was higher than that in the RTOG 85–01 trial.[1]

Thirteen JROSG member institutions were entered into the present study. Five were entered in arm A, five in arm B, and three in arm C.

Eligibility

Eligibility criteria included the following: (1) International Union against Cancer (UICC) TNM clinical stage I–IVA; (2) age between 20 and 80 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; (3) adequate organ function—white blood cell (WBC) count >3000/mm^3, hemoglobin >8 g/dl, platelets >100 000/mm^3, total bilirubin <1.5 mg/dl, creatinine <1.0 g/dl, creatinine clearance >60 ml/min, no severe electrocardiogram changes (e.g., acute ischemic changes, poorly controlled arrhythmias); and (4) written informed consent to participate in the study. Exclusion criteria included esophageal perforation before treatment; history of another active cancer; or severe complications, such as poorly controlled heart disease, liver cirrhosis, diabetes, or infectious disease.

Overall, 61 patients (56 men, 5 women) with previously untreated esophageal squamous cell carcinoma were enrolled between June 2002 and January 2004. The details of the patients' characteristics are shown in Table 1. Two patients were excluded from the study before treatment began at their or their family's request. Two other cases that deviated from the eligibility criteria and another that deviated from the treatment protocol (excess radiation dose) were also excluded from the analysis.

Radiotherapy

We adopted 64 Gy of total irradiation dose based on the study by Minsky et al. (INT0122[13] and INT0123[14]). They compared 64.8 Gy and 50.0 Gy with chemotherapy and found no survival benefit with 64.8 Gy; however, they concluded that the dose escalation did not increase acute toxicities.

Two opposing anteroposterior fields with 6- to 20-MV photons, including the primary esophageal tumor, metastatic lymph nodes, and prophylactic lymph nodes, were irradiated with an initial dose of 40 Gy. The patients were treated 5 days per week with daily fractions of 2 Gy. The fields were extended approximately 4 cm longitudinally beyond the primary tumor margins with reference to radiotherapy planning computed tomography (CT) and endoscopic findings. The prophylactic area included bilateral supraclavicular fossa for patients with cervical and upper thoracic esophageal cancer and the root of the celiac artery for those with abdominal esophageal cancer.

After the initial radiotherapy dose of 40 Gy, a boost irradiation dose of 24 Gy to the macroscopic lesion was performed using the two opposing oblique fields to avoid the spinal cord.

Dose modifications

The chemotherapy dose was reduced by 50% if the WBC count was <2000/mm^3, the platelet count was <50 000/mm^3, the blood urea nitrogen (BUN) was >25 mg/dl, or the serum creatinine was >1.3 mg/dl. Fever >38°C was not considered tumor fever.

Table 1. Patients' characteristics

Characteristic	Arm A	Arm B	Arm C
Total no. of patients	20	27	14
Male/female	19/1	24/3	13/1
Age (years), median and range	69 (55–78)	68 (57–79)	58 (51–71)
Stage			
I	4 (20%)	2 (7%)	5 (36%)
IIA	4 (20%)	2 (7%)	0 (0%)
IIB	3 (15%)	4 (15%)	3 (21%)
III	7 (35%)	13 (48%)	5 (36%)
IV	2 (10%)	6 (23%)	1 (7%)

Statistics: age, $P = 0.079$; clinical stage, $P = 0.058$ (Kruskal-Wallis test)

Chemotherapy was canceled if the WBC count was <1000/mm^3, the platelet count was <30 000/mm^3, the BUN was >30 mg/dl, or the creatinine was >1.5 mg/dl.

Statistical analysis

The RTOG acute radiation morbidity criteria were used for evaluation of acute toxicities. Differences in toxicities and completion rates between arms were analyzed using the Kruskal-Wallis test.

Results

The incidence of acute toxicity in each arm is shown in Table 2. The differences in the incidence rates of grade 3/4 esophagitis between arms were not significant. Grade 4 esophagitis (esophageal perforation) was observed in one patient in arm A.

The incidence of Grade 3/4 leukocytopenia was slightly less in arm A than in the other arms, although the differences were not statistically significant (P = 0.051). The rate of grade 3/4 thrombocytopenia was lowest in arm A, although the differences between arms were not significant. Platelet transfusion was required in only one patient (arm B). There were no significant differences in the rate of anemia between arms.

Table 2. Adverse events

Adverse event	Arm A	Arm B	Arm C
Esophagitis	3 (18%)	3 (12%)	2 (14%)
Leukocytopenia	3 (18%)	7 (29%)	4 (29%)
Thrombocytopenia	0 (0%)	2 (8%)	1 (7%)
Erythrocytopenia	1 (6%)	2 (8%)	1 (7%)
Nausea	4 (24%)	4 (17%)	11 (79%)

All adverse events were grade 3/4 except for nausea, which was grade 2/3 [Radiation Therapy Oncology Group (RTOG) acute radiation morbidity criteria]

Nausea was significantly more severe in arm C (P < 0.01). There were no significant differences with regard to liver or renal function between arms, and there were no patients with grade 3/4 dysfunction among those included in the analysis.

One patient in arm C died of pneumonia during treatment. In this case, autopsy demonstrated that the cancer had disappeared. None of the other cases showed clinically significant respiratory symptoms (grade 2 or above).

Compliance

The completion rates of the patients in each arm were 100%, 74%, and 86%, respectively (P = 0.027). Of the 27 patients in arm B, 5 (19%) did not complete chemotherapy; two of these cases were due to myelosuppression, and the remaining three were due to renal dysfunction. Of the 14 patients in arm C, 2 (14%) did not complete therapy: one due to renal dysfunction and the other due to severe pneumonia. Overall, tolerability appeared to be better in arm A than in the other arms.

Survival

Although the observation period was relatively short and the number in each arm was small, a survival analysis was performed. The median observation period for all survivors was 45 months (range 7–70 months). The median survival time (MST) of all patients was 23 months, and the 3-year overall survival rate was 42%. The 3-year survival rates of arms A, B, and C were 40%, 31%, and 62%, respectively (Fig. 2). The 3-year disease-free survival rate of all patients was 29%, and those for each arm were 40%, 22%, and 27%, respectively. However, it was not possible to compare the survival rates among the arms because the patients' backgrounds differed.

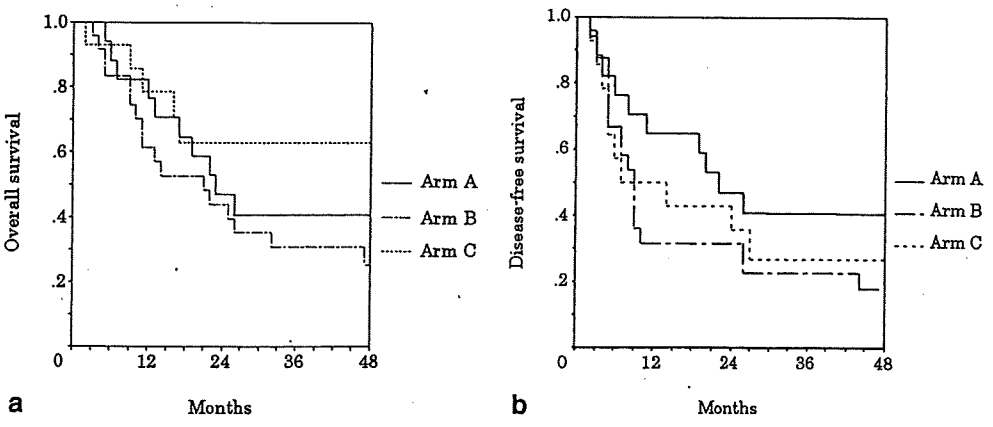

Fig. 2. **a** Overall patient survival (Kaplan-Meier). The 3-year survival rates for arms A, B, and C were 40%, 31%, and 62%, respectively. **b** The 3-year disease-free survival rates for arms A, B, and C were 40%, 22%, and 27%, respectively

There was one patient (arm B) with sudden cardiac arrest within 3 months after treatment. This patient had a past history of old myocardial infarction. The cause of death was unclear because no autopsy was performed; however, no obvious causal link between this episode and the protocol treatment was evident.

Discussion

Randomized controlled studies comparing chemoradiation therapy with radiotherapy alone for esophageal cancer have been reported since the 1990s.[1–4] Cooper et al.[1] reported in the RTOG 85–01 trial that the 5-year survival rate was 26% in the chemoradiation group undergoing 50-Gy radiotherapy with concurrent CDDP 75 mg/m^2 and 5FU 1000 mg/m^2/24 h chemotherapy. It has been confirmed that this regimen (standard CF) is better than radiotherapy alone, and it has been widely used. However, the regimen is associated with relatively high acute toxicity, which limits its use in elderly patients and in patients whose general condition is poor.

On the other hand, daily low-dose CF has been used for esophageal cancer with the expectation that it would have less acute toxicity. Hsu et al.[5] reported a 3-year survival rate of 24% in patients given chemoradiation therapy with daily CDDP and 5FU doses of 6 mg and 225 mg, respectively. They noted that 72% of patients could complete their planned chemoradiation therapy without interruption.

Recently, a daily low-dose CF protocol has been widely adopted in a number of institutions in Japan, and there have been many reports of its use [6–11] (Table 3). Furthermore, outcomes following daily low-dose CF may equal those following standard CF. Ito et al.[7] reported a 2-year survival of 24%, and they also noted that 85% of patients were able to complete their planned therapy. Sai et al.[9] reported that the median survival time was 15 months in the daily low-dose CF group and 14 months in the standard CF group. They also found that 79% of the daily low-dose CF group could complete

Table 3. Previous reports for chemoradiation therapy for esophageal cancer

Study	Year	Regimen (radiotherapy/CDDP/5FU)	MST (months)	Survival
Daily low-dose CF group				
Hsu[5]	1999	50–60 Gy CDDP 6 mg/m^2 5FU 225 mg/m^2	8	3-year: 24%
Itoh[7]	1999	60 (40.0–80.2) Gy + CDDP 3–6 mg/m^2 + 5FU 200 mg/m^2	10–11(?)	2-year: 24%
Sasamoto[8]	2007	60–70 Gy+ + CDDP 3–6 mg/m^2 + 5FU 250–300 mg/m^2	19	2-year: 40% 3-year: 32% 5-year: 20%
Sai[9]	2004	60 Gy + CDDP 5 mg/m^2 + 5FU 200 mg/m^2	15	2-year: 50%
Intermediate CF group				
Ohtsu[12]	1999	60 Gy + CDDP 40 mg/m^2 + 5FU 400 mg/m^2	9	3-year: 23%
Standard CF group				
Cooper[1] (RTOG 85-01)	1992	50 Gy + CDDP 75 mg/m^2 + 5FU 1000 mg/m^2*4	14.1	5-year: 26%
Hironaka[15]	2003	60 Gy + CDDP 80 mg/m^2 + 5FU 800 mg/m^2	33	3-year: 49% 5-year: 46%
Minsky[14] (INT0123)	2002	64.8 Gy + CDDP 75 mg/m^2 + 5FU 1000 mg/m^2	13	2-year: 31%
Sai[9]	2004	60 Gy + CDDP 70 mg/m^2 + 5FU 200 mg/m^2	14	2-year: 39%
Minsky[13] (INT0122)	1999	64.8 Gy CDDP 75 mg/m^2 5FU 1000 mg/m^2	20	3-year: 30% 5-year: 20%

MST, median survival time; CF, CDDP + 5FU protocol; CDDP, cisplatin; 5FU, 5-fluorouracil

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).

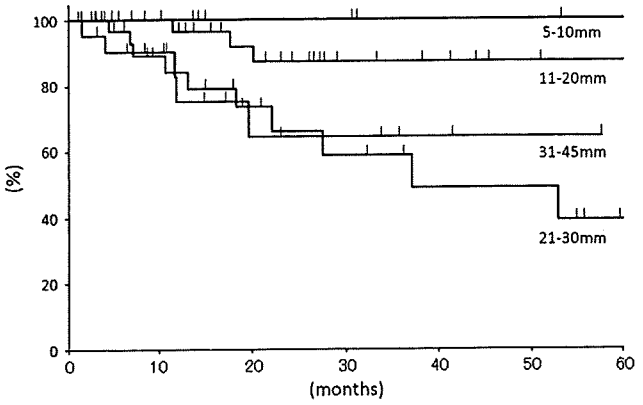

Fig. 1. Kaplan-Meier curve of overall survival rates for the patients with a tumor size (diameter) of 5 to 10 mm ($n = 11$), 11 to 20 mm ($n = 47$), 21 to 30 mm ($n = 35$), and 31 to 45 mm ($n = 22$).

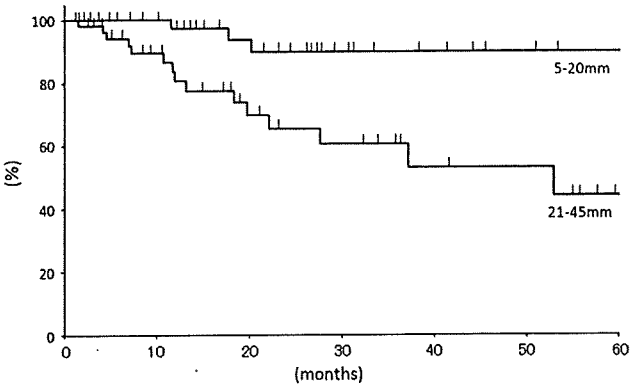

Fig. 2. Kaplan-Meier curve of overall survival rates for the patients with a tumor size (diameter) of 5 to 20 mm ($n = 58$) and 21 to 45 mm ($n = 57$). A statistically significant difference was found ($p < 0.0005$) between the two groups.

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

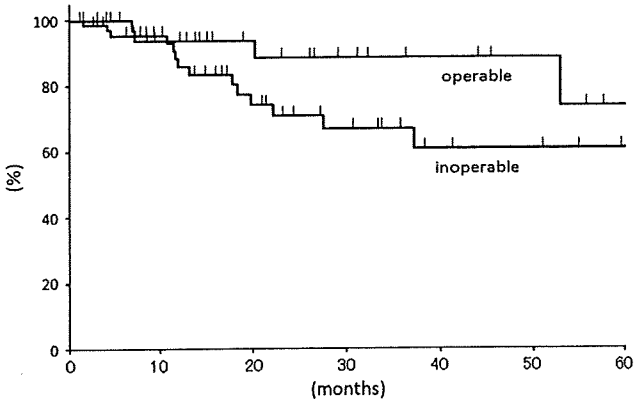

Fig. 3. Kaplan-Meier curve of overall survival rates for operable (n = 43) and inoperable (n = 72) patients. No statistically significant difference was found (p = 0.07) between two groups.

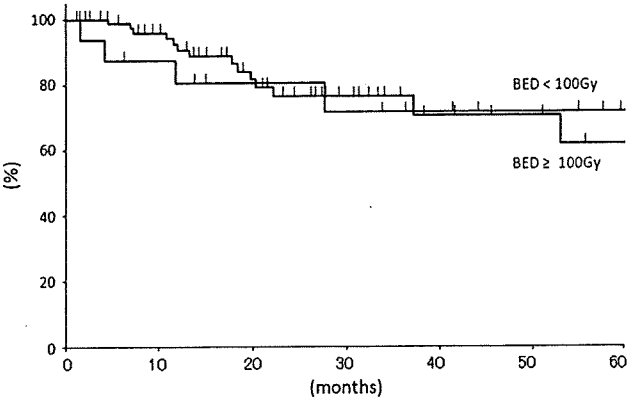

Fig. 4. Kaplan-Meier curve of overall survival rates for the patients with a biologic effective dose (BED) <100 (n = 17) and a BED ≥100 (n = 98). No statistically significant difference was found (p = 0.95) between the two groups.

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. © 2009 Elsevier Inc.

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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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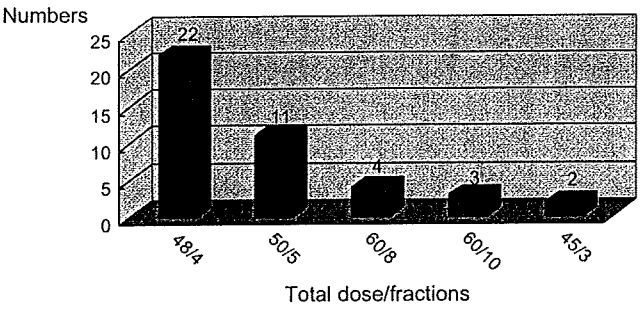

Fig. 1. Fractionation schedules of stereotactic body radiotherapy used in primary T1N0M0 lung cancer. The most common schedule was 48 Gy in 4 fractions.

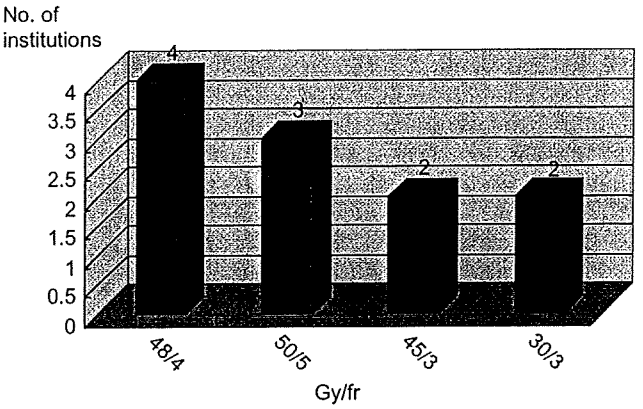

Fig. 3. Fractionation schedules of stereotactic body radiotherapy used in primary liver cancer. The most common schedule was 48 Gy in 4 fractions.

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.

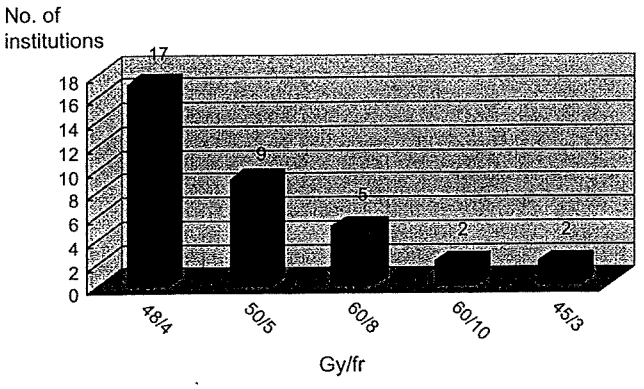

Fig. 2. Fractionation schedules of stereotactic body radiotherapy used in primary T2N0M0 lung cancer. The most common schedule was 48 Gy in 4 fractions.

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.

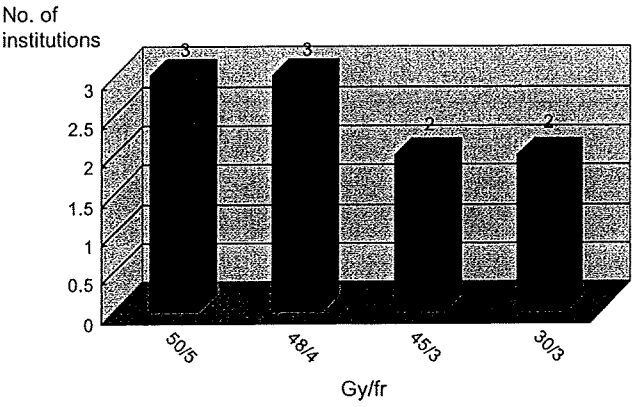

Fig. 4. Fractionation schedules of stereotactic body radiotherapy used in secondary liver cancer. The most common schedules were 50 Gy in 5 fractions and 48 Gy in 4 fractions.

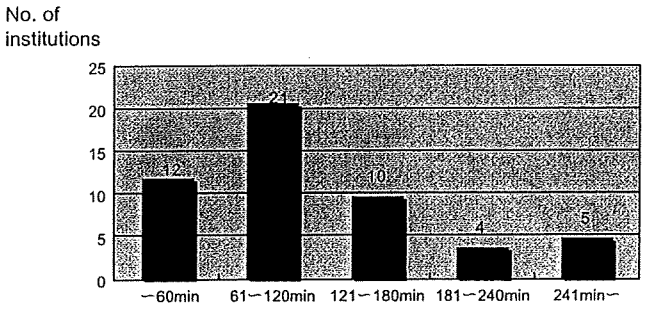

Fig. 5. Amount of time used for treatment planning (RTP) of stereotactic body radiotherapy. The most common time was 61–120 min.

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.

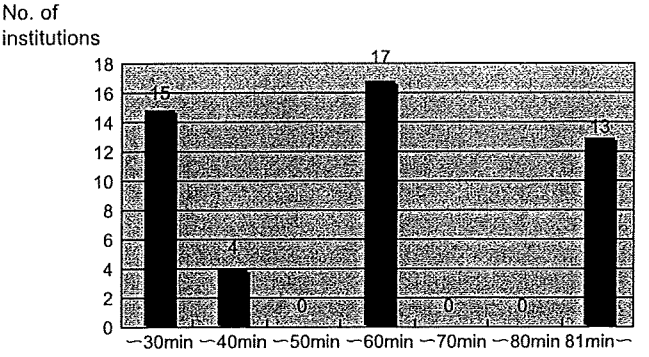

Fig. 6. Amount of time used for the single quality assurance (QA) of stereotactic body radiotherapy. The most common time was 50–60 min.

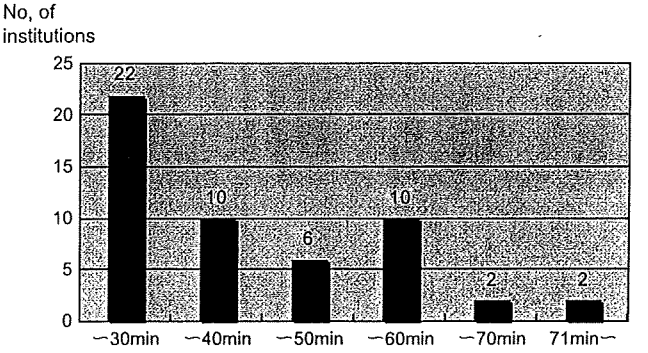

Fig. 7. Amount of time used for single daily treatment of stereotactic body radiotherapy. The most common time was <30 min.

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

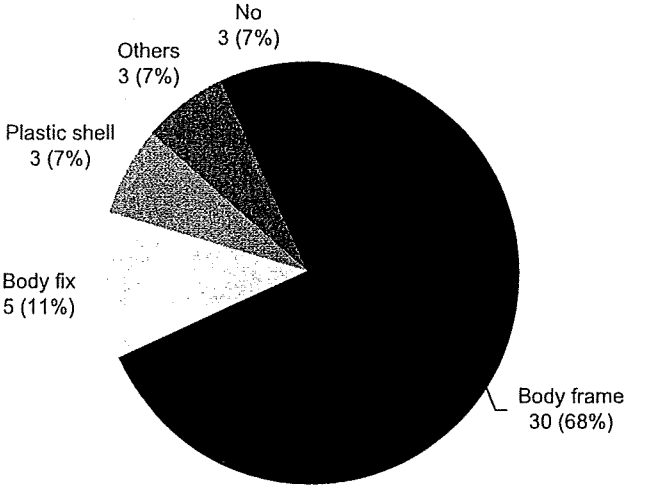

Fig. 8. Fixing apparatus used for stereotactic body radiotherapy. Body frame was most frequently used.

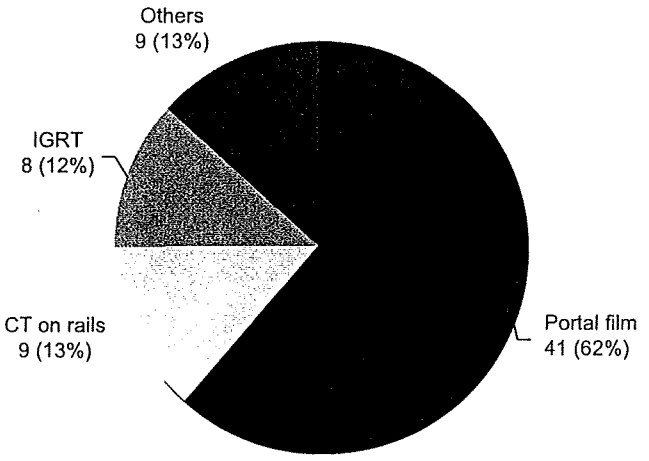

Fig. 9. Verification methods used for stereotactic body radiotherapy. Portal film was most frequently used. IGRT = image-guided radiotherapy; CT = computed tomography.

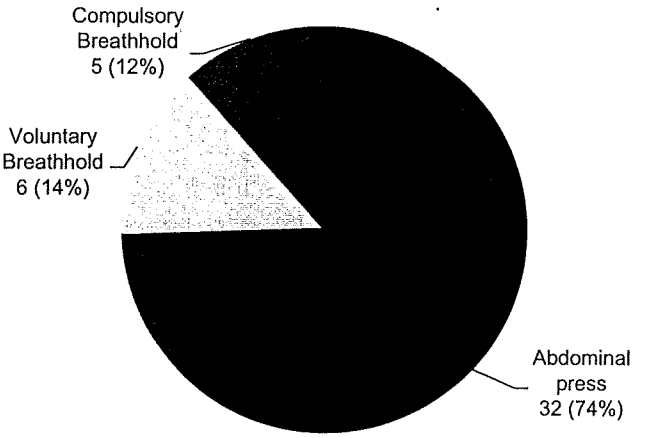

Fig. 10. Respiratory regulation method used for stereotactic body radiotherapy. Abdominal press was most frequently used.

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