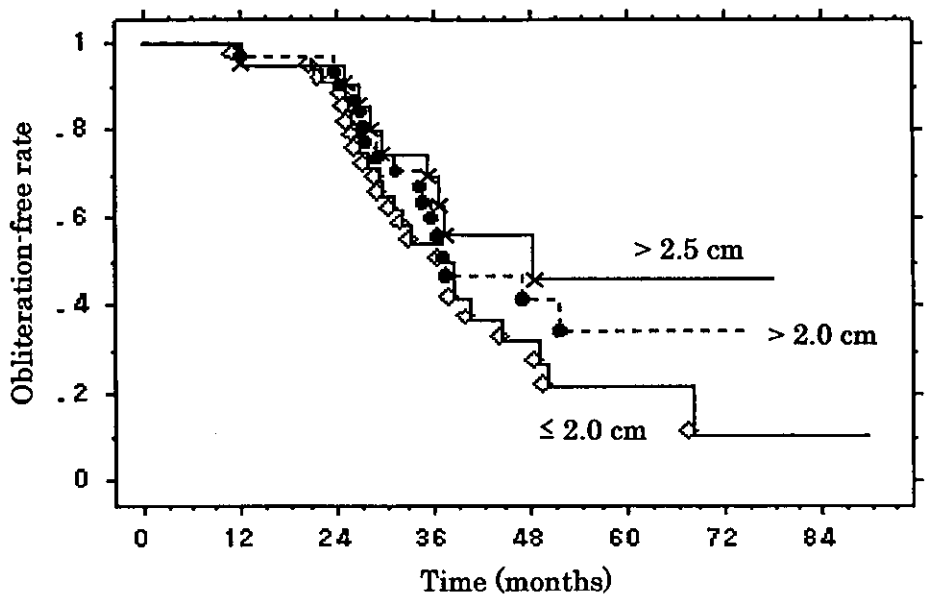


No. at Risk:

≤ 2.0 cm:	42	36	28	13	5	3	1
> 2.0 cm:	33	31	29	15	8	4	1
> 2.5 cm:	21	19	18	9	4	3	1

Fig. 2. Actuarial obliteration-free curves according to arteriovenous malformation (AVM) diameter.

Statistical analysis

For statistical analysis, we used a computer software statistical package (StatView for Windows, version 5, SAS Institute, Cary, NC). The actuarial rates of complete obliteration or T_2-weighted signal changes or postradiosurgical hemorrhage were calculated by the Kaplan-Meier method. The overall actuarial rate of obliteration was calculated using the total number of patients at risk for the denominator and the number of patients with angiographically demonstrated complete obliteration for the numerator. The log–rank test was used to compare the outcomes of the different groups. Univariate analysis of the clinical and angiographic AVM factors was performed using the log–rank test. The rates of post-STI hemorrhage were calculated from the time of STI using the Kaplan-Meier method, and patients were considered to be at risk of hemorrhage until the date of their last follow-up.

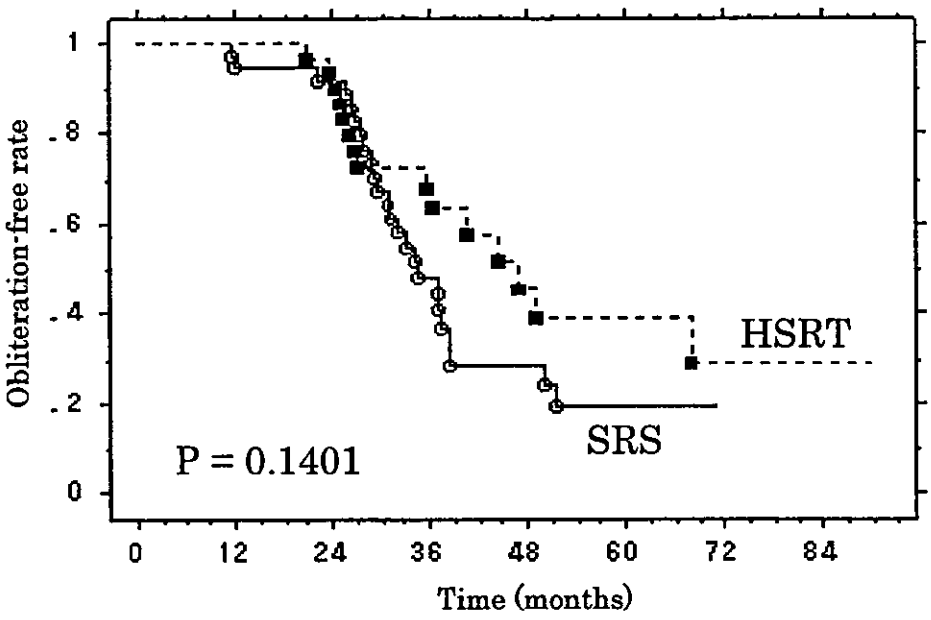
RESULTS

Follow-up

All 72 patients had clinical follow-up after STI (mean, 52 months; median, 48 months; range, 0–138 months). One patient did not appear for follow-up at all but was counted as a patient at risk of complete obliteration and was also used for the analysis of acute complications. One died of an unknown cause after angiographic confirmation of AVM obliteration and was counted as having angiographic obliteration. After angiographic confirmation of no obliteration, 1 patient died of bile duct adenocarcinoma and 1 patient died of treatment-related complications (details given below). These 2 patients were counted as angiographic failures in the analysis of obliteration. Four died before angiographic examination (rebleeding in 1, brain infarction in 1, and unknown causes in 2) and were counted as having been withdrawn before angiographic obliteration.

Obliteration

After STI, 57 of 75 AVMs were examined using angiography, and complete obliteration of the nidus was confirmed in 39 AVMs between 12 and 90 months (mean, 36 months; median, 32 months). Patients in whom the last angiographic study demonstrated partial obliteration or a residual presence of the AVM were considered to have treatment failure. The overall actuarial rate of obliteration was 43% (95% confidence interval [CI], 30–56%) at 3 years, 72% (95% CI, 58–86%) at 5 years, and 78% (95% CI, 63–93%) at 6 years. The actuarial obliteration rate for the 42 AVMs ≤2.0 cm in maximal diameter (66%) was 50% (95% CI, 32–68%) at 3 years and 79% (95% CI, 62–98%) at 5 years. For the 33 AVMs with a maximal diameter >2 cm (44%), the actuarial complete obliteration rate was 44% (95% CI, 26–62%) at 3 years and 66% (95% CI, 45–87%) at 5 years (p = 0.2674; Fig. 2). Similarly, the 3-year and 5-year complete obliteration rate was 39% (95% CI, 45–87%) and 57% (95% CI, 45–87%), respectively, for AVMs >2.5 cm. Figure 2 shows that the larger AVMs tended to become obliterated later. The 3-year and 5-year complete obliteration rate of AVMs in eloquent regions was 51% (95% CI, 32–70%) and 86% (95% CI, 70–100%), respectively.



No. at Risk:							
HSRT:	33	31	27	15	6	4	2
SRS:	42	35	30	13	6	2	0

Fig. 3. Actuarial obliteration-free curves according to treatment schedule.

The 3-year, 5-year, and 6-year actuarial complete obliteration rate was 32% (95% CI, 19–49%), 61% (95% CI, 39–83%), and 71% (95% CI, 47–95%), respectively, for patients treated with HSRT and followed angiographically for 21–90 months (mean, 37 months; median, 27 months) and was 52% (95% CI, 35–69%), 81% (95% CI, 66–96%), and 81% (95% CI, 66–96%), respectively, for patients treated with SRS and followed angiographically for 11–60 months (mean, 32 months; median, 31 months). The complete obliteration rates were not significantly different statistically between the HSRT and SRS groups (p = 0.1401; Fig. 3). The 3-year and 5-year complete obliteration rate was 26% (95% CI, 0–52%) and 53% (95% CI, 18–88%), respectively, for AVMs >2.5 cm treated with HSRT. The 3-year and 5-year complete obliteration rate of AVMs in eloquent regions treated with HSRT was 35% (95% CI, 12–58%) and 80% (95% CI, 56–100%), respectively.

Of the 16 AVMs with incomplete obliteration or residual AVM confirmed by angiography, 1 patient in the SRS group and 7 patients in the HSRT group were retreated with STI. For the second treatment, we used SRS with varying doses depending on the initial radiosurgical dose and the maximal tolerance dose of the brain. Of these 8 patients, 3 (1 in the SRS and 2 in the HSRT group) experienced obliteration. If we assume that the retreatment was not a failure, the obliteration rate at 3, 5, and 6 years was 43% (95% CI, 30–56%), 70% (95% CI, 57–83%), and 76% (95% CI, 63–99%), respectively.

Univariate analysis of the possible prognostic factors for obliteration showed that the variables of treatment method (SRS, HSRT), age, gender, history of hemorrhage, prior treatment (resection, embolization), and AVM characteristics (location, diameter, drainage vein, Spetzler-Martin grade) did not reach statistically significant levels (Table 2).

Complications

Of the 67 patients periodically examined using MRI, 39 (58%) exhibited a newly increased high signal surrounding their AVM site on T_2-weighted MRI. The 3-year actuarial rate for developing post-STI T_2-weighted signal changes was 64% (95% CI, 45–73%) for HSRT and 59% (95% CI, 42–76%) for SRS (Fig. 4). The cumulative actuarial rates for post-STI T_2-weighted signal changes were not significantly different statistically between the HSRT and SRS groups. Of the 72 patients, 9 (9.7%) experienced transient symptomatic adverse effects after STI, 7 of which were related to the T_2-weighted signal changes. All 9 patients recovered without a symptomatic deficit.

Of the 72 patients, 3 (4.2%) had permanent radiation-induced symptomatic adverse effects. One (1.4%) of the three permanent adverse effects was fatal. This patient had status epilepticus after surgery for a large AVM and had maintained a good performance status after STI for 47.6 months. However, the epilepsy appeared again after cyst formation due to the STI. She died of status epilepticus owing to the expansion of a radiation-related cyst 1 week before the planned surgery for the cyst. The other 2 patients had chronic neurologic deficits (double vision in one and slight paresis of the left leg in the other).

In 71 patients with MRI and/or CT follow-up, 5 (7.0%) were diagnosed with radiation necrosis. In the SRS group, 4 patients experienced radiation-related necrosis, 3 of which

Table 2. Various parameters for obliteration rates: univariate analysis

Variable	*n*	5-y Obliteration rate (95% CI)	*p*
Age (y)			
<20	9	56 ± 33	
≥20	66	73 ± 14	0.5698
Gender			
Male	43	75 ± 18	
Female	32	69 ± 20	0.73
History of hemorrhage			
Yes	37	91 ± 16	
No	38	67 ± 19	0.7712
Prior resection			
Yes	11	72 ± 30	
No	64	73 ± 15	0.8463
Prior embolization			
Yes	7	54 ± 44	
No	68	75 ± 14	0.0775
Treatment			
SRS	42	81 ± 15	
HSRT	33	61 ± 22	0.1401
Diameter (cm)			
≤2.0	42	79 ± 17	
>2.0	33	66 ± 21	0.2674
≤2.5	54	77 ± 15	
>2.5	21	57 ± 17	0.2324
Location			
Eloquent	34	86 ± 16	
Noneloquent	41	59 ± 20	0.1381
Drainage vein			
Deep	43	71 ± 17	
Superior	32	75 ± 22	0.8721
Spetzler-Martin grade			
I + II	44	72 ± 18	
III + IV + V	31	73 ± 27	0.963

Abbreviation: CI = confidence interval; other abbreviations as in Table 2.

were in patients with permanent radiation-induced symptomatic adverse effects. Radiation-related cyst formation was observed 2–3 years later in 3 patients with radiation necrosis after SRS. All 3 patients were to be treated in the HSRT group according to our decision tree but underwent SRS instead of HSRT (Table 3). In 33 patients who were treated with HSRT, 1 case of necrosis was observed that was symptomatically reversible.

Seven patients (18%) of the 39 with T_2-weighted signal changes and 4 patients (12%) of the 33 without T_2-weighted signal changes experienced radiation-induced symptomatic complications.

Hemorrhage

Post-STI hemorrhage was observed in 10 patients: 4 in the SRS group at a mean of 20 months (range, 1–21 months) and 6 in the HSRT group at a mean of 33 months (range 2–93). Of these 10 patients, 3 experienced neurologic deterioration owing to bleeding of the AVM after STI. One patient experienced hemiparesis after SRS. One experienced seizure and left homonymous hemianopsia after HSRT. One patient died just after AVM bleeding at 14 months after HSRT. The 5-year actuarial accumulative intracranial hemorrhage rate after STI was 15.2% (95% CI, 5.4–25.0%) for all patients combined, 22.3% (95% CI, 5.8–38.8%) for HSRT patients, and 7.8% (95% CI, 0–16.2%) for SRS patients. The annual intracranial hemorrhage rate was 5.6% during the first year and 5.5% during the second year for all patients combined. It was 9.2% and 3.1% for HSRT patients at 1 and 2 years after STI and 3.6% and 4.4% for SRS patients, respectively. No statistically significant difference was found between the HSRT and SRS groups in the postradiosurgical hemorrhage rate (p = 0.2442). The actuarial accumulative intracranial hemor-

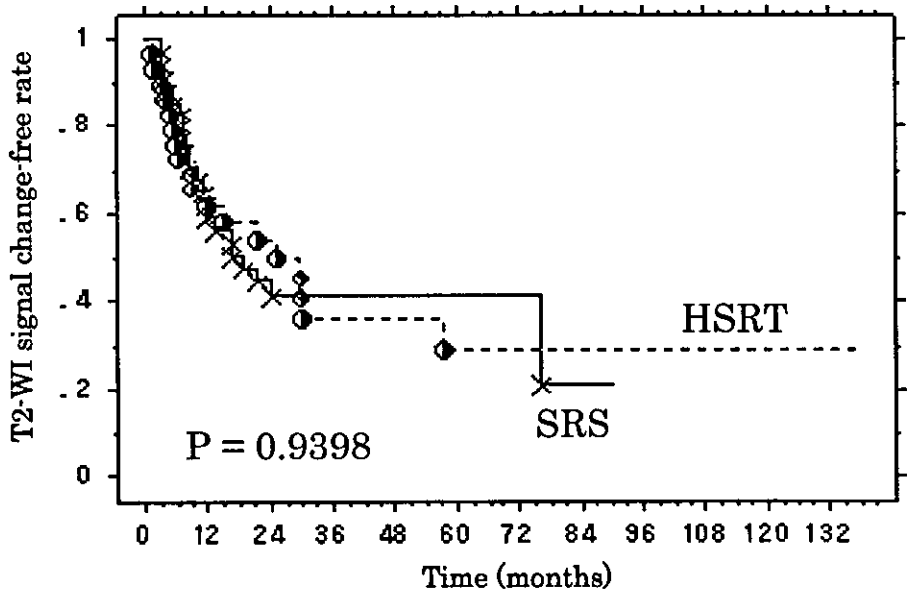


Fig. 4. T_2-weighted signal change curves according to treatment schedule.

Table 3. Results of treating with SRS instead of HSRT

Pt. No.	Age (y)/ Gender	KPS	Prior medical history	Prior treatments (*n*)	Location (Spetzler-Martin grade)	Maximal diameter (cm)	Reason for SRS	Dose (cGy)	Angiographic obliteration	Symptomatic complications and treatment
1	53/M	90	Headache (incident)	None	Right basal ganglia (III)	2.2	Disagreement	2500	Residual	Radiation necrosis, cyst formation, steroids, glycerol infusions, mild headache
2	16/F	90	Headache, nausea	None	Left frontal (I)	2.7	Child	2000	Complete	None
3	39/M	90	Headache, left limb numbness	None	Left thalamus (III)	0.9	Disagreement	2500	Complete	Radiation necrosis, cyst formation, steroids, glycerol infusions, hyperbaric oxygen therapy, tremor, seizure, persistent hemiparesis
4	19/F	60	Hemorrhage, coma	Surgery	Right frontal (II)	3.5	Physical instability	2250	Residual	Radiation necrosis, cyst formation, steroids, glycerol infusions, seizure, death from status epilepticus
5	30/M	80	None (incident)	None	Right thalamus (III)	2.3	Disagreement	2000	Residual	None
6	29/F	80	Hemorrhage	Embolization (2)	Left thalamus (III)	2.0	Disagreement	2500	Complete	None
7	29/F	90	Headache, right internal carotid cave aneurysm (unruptured)	None	Right frontal (motor area) (III)	2.0	Disagreement	2500	Complete	None
8	41/M	70	Hemorrhage, hemiparesis	Embolization (8)	Left corpus callosum, frontal (III)	3.4	Disagreement	1500	Residual	None
9	16/F	90	Hemorrhage, coma	Ventricular drainage	Left paraventricle (III)	2.0	Child	2250	Complete	None
10	55/M	90	None (incident), Budd-Chiari syndrome	None	Right internal caudate head (III)	3.5	Disagreement	2500	Complete	None
11	46/M	70	Hemorrhage, seizure, coma	Ventricular drainage	Left thalamus (III)	1.3	Disagreement	2000	—	None
12	17/F	90	Hemorrhage, seizure, coma	Ventricular drainage, VP shunt	Left basal ganglia (III)	1.0	Disagreement	2500	Complete	None
13	78/M	80	Multiple brain infarction, Parkinson disease, hypertension, viral hepatitis	None	Left basal ganglia (III)	0.5	Physical instability mental deficiency	2500	—	None

Abbreviations: SRS = stereotactic radiosurgery; HSRT = hypofractionated stereotactic radiotherapy; Pt. No. = patient number; M = male; F = female.

rhage rate at 5 years for AVMs ≤2.0 cm was 12.4% (95% CI, 0.6–23.2%) and for AVMs >2.0 cm was 17.7% (95% CI, 4–30.4%). The difference did not reach statistical significance.

Of the 13 patients who had been treated with SRS instead of HSRT, 7 (53%) had confirmed complete obliteration and 4 had partial obliteration or residual AVM by angiography (Table 3). Radiation necrosis and cyst formation was observed in 3 patients each (23%). Two patients experienced intracranial hemorrhage after treatment.

DISCUSSION

The primary subject of our study was to examine the appropriateness of our treatment policy compared with previous reports in which SRS alone was used. Particularly for AVMs >2.0–2.5 cm (44% > 2.0 cm and 29% > 2.5 cm in our series) and AVMs in eloquent areas (45% of our series), making a comparison with the previous report is quite important. However, we found that it was quite difficult to compare the results of STI for AVMs among different institutions.

The crude obliteration rates of AVMs after SRS vary significantly from 40% to 85% at 3 years and 33% to 93% at 5 years (9–24). If we adopt these crude obliteration rates using the number of patients who underwent angiography as the denominator, the crude complete obliteration rates for our treatment were 92% (12 of 13) at 3 years for 33 AVMs with a maximal diameter >2 cm. This crude obliteration rate was better than that observed in previous papers but obviously was dependent on the selection bias and was far from a determination of the actual outcome of treatment. Because recent improvements in MRI and magnetic resonance angiography have helped to preclude unnecessary confirmatory angiography for patients with patent AVMs, the numerator can be very close to the denominator without an improvement in the treatment method.

The number of reports using the Kaplan-Meier method for the analysis of the obliteration rate is increasing. Miyawaki *et al.* (23) have used the Kaplan-Meier method and reported a 33% 5-year actuarial rate of angiographic obliteration, assuming MRI/magnetic resonance angiography obliteration and retreatment to be failures, as we did. Touboul *et al.* (25) have reported 62.5% ± 7% as the 5-year actuarial obliteration rate for 100 AVM patients. Pan *et al.* (20) reported a 75% actuarial complete obliteration rate at 40 months. Our results showed a 72% (95% CI, 58–86%) overall actuarial obliteration rate. Considering that 44% of the patients had AVMs >2.0 cm in our series, the treatment outcome of our study is at least comparable with those of the previous studies. The decision tree in our treatment policy of STI, including HSRT, was not detrimental for cerebral AVMs.

The treatment method was not a prognostic factor in this analysis, even though larger AVMs were more frequent in HSRT. The diameter of AVM was not a statistically significant prognostic factor for angiographic obliteration in this series. This latter result was not seen in our preliminary study (17), in which size (≤2 cm or not) was a statistically significant favorable factor ($p = 0.05$). The finding that diameter was not a statistically significant factor may have been because the number of patients with occluded large AVMs increased in accordance with the longer follow-up period. Younger age was suggested to be a statistically significant factor in our previous study, but age also disappeared as a statistically significant factor in the present study. This result may also have been because the patients with AVMs >2.0 cm who experienced complete obliteration with HSRT were older, with a median age of 45 years (range, 18–74 years).

Late radiation-induced symptomatic injury occurred in 3–18% of the patients with AVMs in the previous reports (12, 15, 16, 22, 23, 27, 28). Symptomatic complications appeared in the patients with larger AVMs and those who received higher doses of SRS as predicted by the radiobiologic volume effect models of the central nervous system (29). Steinberg *et al.* reported that 50% (10 of 20) had major or minor complications with doses >18 Gy and volumes >13 cm^3 (24). Miyawaki *et al.* (23) reported that radiation necrosis occurred when minimal doses of 18 Gy and maximal doses of 34 Gy were administered to treatment volumes ≥14 cm^3 (mean, 27.8 cm^3). Flickinger *et al.* (26) found that eloquent location and volume irradiated to ≥12 Gy were significant risk factors for symptomatic radiation necrosis. However, in our series, symptomatic radiation injury was not more frequent in patients with larger AVMs or in patients with AVMs in eloquent regions. Radiation necrosis and cyst formation were observed in 4 of 42 in the SRS group and 1 of 33 in the HSRT group, the latter of which included larger AVMs. All three cyst formations were seen in patients who should have been treated by HSRT in our protocol but were treated with SRS instead. We decreased the SRS dose for these patients, in principle, but the dose reduction might have been too small. However, if we had used a lower dose, the obliteration rate in these patients might have been lower.

We have used the same hypofractionated schedule for 140 brain metastases with a mean diameter of 6.7 cm (range, 0.006–48.3 cm) in 75 patients. We found that the schedule was as safe as we have seen in the present study with a radiation necrosis rate of 2.7% (2 patients) (30). These brain metastasis results and the results of the present AVM study suggest that our hypofractionation schedule is safe and close to the maximal tolerance dose. The maximal tolerance dose is consistent with the prediction made by the radiobiologic model of Brenner *et al.* (4), assuming an α/β ratio of 2.0 (3).

The annual bleeding rate after STI was 5.5–5.6% in this series, within the range of the natural history of untreated AVMs, which runs from 2% to 17% annually (31–33). The number of AVMs that bled after STI was greater in the HSRT group (6 of 33) than in the SRS group (4 of 42) in this series. Also, the bleeding rate in the first year for HSRT was three times the rate of the SRS patients, although the

difference did not reach statistical significance. Stefani *et al.* (34), in prospective analyses of follow-up data from 390 patients with brain AVMs, found that large and deep-seated AVMs were the most important and significant factors associated with a greater risk of future hemorrhagic events. The greater bleeding rate in the first year in the HSRT group may have been related to the larger size of the AVMs. Steiner *et al.* (24) indicated that patients treated with radiosurgery may be at a decreased risk of hemorrhage once obliteration has effectively occurred. In our series, the actuarial obliteration rates for the HSRT group increased after 2 years. This might have been in relation to the decrease in the hemorrhage rate from 9.2% to 3.1% during the first 2 years of follow-up. The small number of patients prevented us from speculating more about the difference.

For large AVMs, staged SRS has been shown to be an effective approach (35). In this approach, SRS is repeated during an interval of 5–36 months. Because we have also experienced good obliteration rates after repeated treatment of patient AVMs, we agree that staged STI may be one of the treatment options for large AVMs. This does not preclude the potential importance of HSRT as the initial treatment for large AVMs. Each approach should be considered one of several options for treating this difficult disease.

CONCLUSION

Our treatment policy using SRS and HSRT was effective in producing an obliteration rate and complication rate compatible with those found in previous SRS studies. HSRT may have a wider therapeutic window in the treatment of AVMs ≥2.5 cm or AVMs in eloquent areas, because the selection bias in our treatment decision tree could favorably affect SRS but not HSRT. Some might conclude that the SRS dose in this series (minimal dose range, 12–20 Gy; mean, 19.3), was too high and that HSRT possibly has a lower obliteration rate than SRS. The current study does not answer the question of whether SRS using lower doses such as 15–18 Gy at the periphery of the AVM can achieve results similar to HSRT. We also cannot answer the question of whether HSRT has a role in decreasing late radiation necrosis for small AVMs and AVMs in noneloquent areas. Only a prospective randomized trial will answer these questions. An optimal hypofractionation schedule may be worth additional investigation, although the optimal dose distribution and rigid fixation continue to be the critical requirements for STI of AVMs in the central nervous system (36).

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Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 3, pp. 847–852, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.04.034

CLINICAL INVESTIGATION **Lymphoma**

PILOT STUDY OF MODIFIED VERSION OF CHOP PLUS RADIOTHERAPY FOR EARLY-STAGE AGGRESSIVE NON-HODGKIN'S LYMPHOMA OF THE HEAD AND NECK

TAKESHI NISHIOKA, M.D.,* KAZUHIKO TSUCHIYA, M.D.,* SEIKO NISHIOKA, M.D.,* TOSHIHIRO KITAHARA, M.D.,* KEIICHI OHMORI, D.D.S.,† AKIHIRO HOMMA, M.D.,‡ HIDEFUMI AOYMA, M.D.,* MASANOBU SHINDOH, D.D.S., PH.D.,§ AND HIROKI SHIRATO, M.D.*

Departments of *Radiology and ‡Otolaryngology, Hokkaido University School of Medicine; Departments of †Radiology and §Oral Pathology, Hokkaido University School of Dentistry, Sapporo, Japan

Purpose: To evaluate the safety and efficacy of a modified version of cyclophosphamide, doxorubicin, vincristine, prednisone (pirarubicin, cyclophosphamide, vincristine, and prednisone [THP-COP]) plus radiotherapy for early-stage aggressive non-Hodgkin's lymphoma of the head and neck.

Methods and Materials: Between December 1993 and December 1999, 41 patients with early-stage non-Hodgkin's lymphoma with intermediate-grade histologic features were enrolled in our study. The mean patient age was 51 years. Of the 41 patients, 27 had Stage I and 14 Stage II disease. The primary site was Waldeyer's ring, a neck node, or an extranodal site in 14, 11, and 16 patients, respectively. The immunophenotype was B cell in 29 and T cell in 12 patients. All patients were in the low-risk category according to the International Prognostic Index. Chemotherapy consisted of 40 mg/m^2 i.v. pirarubicin (THP-Adriamycin), 750 mg/m^2 i.v. cyclophosphamide, and 1.0 mg/m^2 i.v. vincristine, on Day 1 and 40 mg/m^2 p.o. prednisone on Days 1–5. The combination chemotherapy was given twice at a 14-day interval. Radiotherapy was given to involved areas at a fraction size of 2.0–2.5 Gy up to a total of 40 Gy within 4–5 weeks. The mean follow-up period was 63 months.

Results: The 5-year overall survival rate was 89%. The 5-year cause-specific survival and progression-free survival rate was 90% and 81%, respectively. The 5-year progression-free survival rate for patients with Waldeyer's ring primaries was 93%. Patients with tumor <5 cm in size had greater 5-year progression-free survival than those with tumor >5 cm in size (85% vs. 33%, $p < 0.05$, log–rank test). Grade 4 neutropenia was seen in 12% of patients; however, 93% of patients (38 of 41) received chemotherapy as scheduled with the support of granulocyte colony-stimulating factor.

Conclusion: Biweekly THP-COP plus radiotherapy is feasible and effective for Stage I-II low-risk non-Hodgkin's lymphoma.

Non-Hodgkin's lymphoma, Lymphoma, Radiotherapy, Head and neck, Biweekly.

INTRODUCTION

Radiotherapy (RT) plays an important role in the treatment of localized non-Hodgkin's lymphoma (NHL). Combined with chemotherapy, RT can cure a high percentage of patients with aggressive histologic features (1, 2). The results of a randomized study comparing three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus RT to chemotherapy alone for localized aggressive lymphomas were very impressive clinically (3). The administration of several cycles of chemotherapy followed by RT has become a standard treatment for early-stage aggressive lymphomas. Newer regimens, such as MACOP-B, m-BACOD, CytaBOM, and ProMACE (4–8), which were initially thought to be more effective, failed to show an advantage over CHOP. During the period of these "what-is-best-regimen" studies, several prognostic factors were clarified, and the International Prognostic Index (9–12) is now widely used to classify patients into different prognostic groups. It is of note that in some studies, head-and-neck NHL had a good prognosis (13, 14). RT alone can be effective for localized nonbulky aggressive NHL (1). In the early 1990s, before treatment was standardized, our concern was to develop a less toxic regimen for locally confined aggressive head-and-neck NHL. In 1993, we started using a weakened form of CHOP-based chemotherapy plus RT. Although our patients were not large in number, our study differed from others in that all patients were treated with the same regimen during a relatively short period. Previous reports on RT for head-and-neck NHL used collections of data during long periods (18–30 years) from patients treated

Reprint requests to: Takeshi Nishioka, M.D., Department of Radiology, Hokkaido University School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8648, Japan. Tel: (+81) 11-706-5977; Fax: (+81) 11-706-7876; E-mail: trout@radi.med.hokudai.ac.jp

Received Dec 29, 2003, and in revised form Apr 14, 2004. Accepted for publication Apr 16, 2004.

Table 1. Patient characteristics

Characteristic	
Patients (*n*)	41
Age (y)	
Range	17–75
Mean	51.3
<60 (*n*)	24
≥60 (*n*)	17
Stage (*n*)	
I	27
II	14
Pathologic finding (*n*)	
Diffuse large cell	30
Diffuse mixed	10
Diffuse small	1
Immuno phenotype (*n*)	
B cell	29
T cell	1
T/NK cell	1
Primary site (*n*)	
Waldeyer's ring	14
Nodal	11
Extranodal	16
LDH level	
Normal	41
High	0
B symptoms	
Yes	0
No	41

Abbreviations: NK = natural killer; LDH = lactate dehydrogenase.

with various regimens (13, 14, 16). This resulted in an estimated number of patients annually of 2.6–7.8. In this article, we present the efficacy and safety of our modified version of CHOP plus RT and discuss its clinical impact.

METHODS AND MATERIALS

Patient characteristics

This prospective study was conducted between December 1993 and December 1999 at the Hokkaido University Hospital. Forty-one patients with head-and-neck NHL were enrolled in the study. The inclusion criteria were as follows: age <75 years, clinical Stage I-II, intermediate-grade histologic features by Working Formulation Group criteria, Karnofsky performance status >60, and a primary site in the head and neck rather than the skin. Immunohistochemical staining was performed in all patients to determine the cell subtype (T cell or B cell). Clinical staging was done according to the Ann Arbor classification system. Our institutional review board approved this study, and all patients provided informed consent.

The clinical characteristics of the 41 patients are summarized in Table 1. The mean patient age was 51 years (range, 17–75 years); 26 patients were male and 15 female. Of the 41 patients, 27 had Stage I and 14 Stage II disease. The performance status was >80 in 39 patients and 70 in 2 patients. The immunophenotype was B cell in 29 and T cell in 12 patients. The primary site was Waldeyer's ring, a neck node, or an extranodal site in 14, 11, and 16 patients, respectively. Ten nasal lymphomas were included; all showed a T-cell phenotype. To determine the T cell/natural killer (NK) cell phenotype, immunostaining of CD3, CD43, CD45RO, and CD56 was performed. The histologic type was diffuse large cell in 30 patients, diffuse mixed cell in 11 patients, and diffuse small cell in 1 patient. All patients were in the low-risk group (i.e., 0–1 risk factor, according to the International Prognostic Index [9]). No patients had B symptoms. The pretreatment evaluation included physical examination, complete blood count, liver function tests, lactate dehydrogenase level, bone marrow biopsy, and radiologic examination. The mean follow-up period was 63 months (median 64).

Treatment

Treatment consisted of two courses of chemotherapy plus involved-field RT. Each course of chemotherapy included the following agents: pirarubicin 40 mg/m^2 i.v. on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, vincristine 1.0 mg/m^2 i.v. on Day 1, and prednisone 40 mg/m^2 p.o. on Days 1–5 (THP-COP). The chemotherapy regimen was repeated at an interval of 14 days; the second course was started on Day 15. Granulocyte colony-stimulating factor (G-CSF), 75 μg/m^2/d s.c., was given when the white blood cell (WBC) counts fell to <3000/mm^3. G-CSF was used until the WBC count rose to 8000/mm^3. The second course of chemotherapy was postponed if the WBC count was <3000/mm^3 on Day 15. RT was performed with a ^{60}Co unit or a 6-MV X-ray machine. A total dose of 40 Gy was given in 16–20 fractions, four fractions weekly, within 4–5 weeks. The RT treatment area varied according to the primary site and clinical stage. RT was confined to the primary site alone for extranodal Stage I lymphoma, the primary site and the whole neck for extranodal Stage II lymphoma, the whole neck alone for nodal Stage I-II disease, and the whole neck and Waldeyer's ring for Waldeyer's Stage I-II disease. RT was given after chemotherapy for B-cell lymphoma. For T-cell lymphoma, RT was given before chemotherapy. This treatment policy was based on our previous experience (15) of an unfavorable tumor response during chemotherapy for nasal T-cell/NK lymphoma. Each treatment (i.e., chemotherapy or RT) was started when the side effects of the preceding treatment had subsided.

Assessment of response and treatment-related toxicity

The tumor response was evaluated 2 weeks after completion of the entire treatment regimen. A complete response was defined as the disappearance of all target lesions. A partial response was defined as at least a 30% decrease in the sum of the longest diameters of the target regions. Stable disease was defined as a response that did not meet the criteria of a partial response. Finally, progressive disease was disease that had grown or increased despite treatment. The acute toxicity of chemotherapy was assessed according to the National Cancer Institute Common Toxicity Criteria

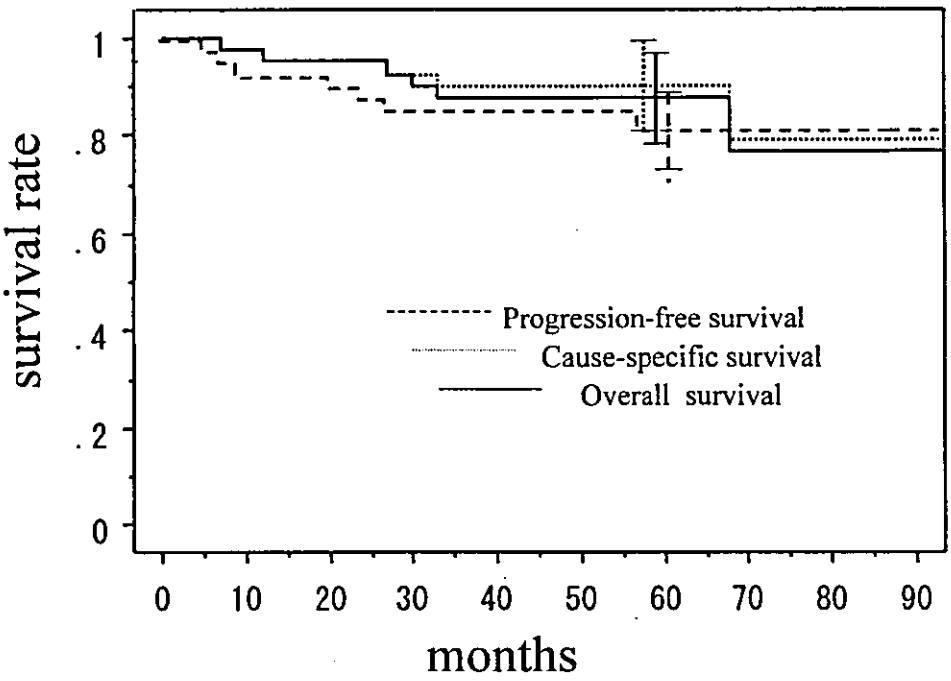

Fig. 1. Cause-specific, progression-free, and overall survival rates for all patients.

and that of RT according to the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria.

Statistical analysis

The Kaplan-Meier method was used to calculate the survival and progression-free survival rates, and the log-rank test was used to compare results between groups.

RESULTS

Initial response to treatment

Of the 41 patients, 37 were assessed for tumor response; 4 patients had had the tumor removed at biopsy. For those with B-cell lymphoma, a complete response was achieved in 83% after two courses of THP-COP and in 92% of patients after combined chemotherapy and RT. For patients with T-cell lymphoma, a complete response was achieved in all patients after RT. Overall (i.e., T- and B-cell lymphomas), a complete response was achieved after combined therapy in 94% of the 37 assessable patients.

Survival and pattern of recurrence

The overall survival rate at 5 years was 89%. The 5-year cause-specific survival and progression-free survival rate for all patients was 90% and 81%, respectively (Fig. 1). Seven patients experienced recurrence, and five died of the disease. The 5-year overall local control rate for all 41 patients was 93%. Six of the seven recurrences occurred within 27 months. The details of the recurrences are summarized in Table 2. The 5-year progression-free survival rate was 93%, 76%, and 70% for those with a Waldeyer's ring, extranodal, and nodal primary site. Additionally, the 5-year progression-free survival rate was 87% for those with B-cell lymphoma and 76% for those with T-cell lymphoma (difference not statistically significant). The 5-year progression-free survival rate by stage and age was 80% and

Table 2. Recurrence cases

Age (y)/ gender	Stage	Maximal tumor diameter (cm)	Primary site	Histologic type (immunophenotype)	Recurrence site (RT field)
62/F	I	2.7	Nasal cavity	Diffuse large (T)	Skin Nasal cavity (in-field)
54/M	I	5.8	Nasal cavity	Diffuse large (T)	Brain
50/F	I	2.5	Neck	Diffuse small (T)	Inguinal area
55/M	I	2.5	Neck	Diffuse large (B)	Inguinal area
68/M	II	2.6	Neck	Diffuse mixed (B)	Inguinal area
56/M	II	8.5	Tonsil	Diffuse large (B)	Inguinal area, paraaortic
65/M	I	4.4	Maxillary sinus	Diffuse large (B)	Ethmoid sinus (at field edge)

Abbreviations: RT = radiotherapy; F = female; M = male.

86% for those with Stage I and Stage II and 80% and 83% for those aged ≥60 years and <60, respectively. None of these differences were statistically significant. Patients with tumors <5 cm in the maximal dimension had a better 5-year progression-free survival rate than those with tumor >5 cm (85% vs. 33%, p <0.05, log–rank test). When dividing patients by a tumor cutoff of 3 cm, the statistically significant difference in the 5-year progression-free survival rate disappeared; nevertheless, larger tumors still showed a lower rate compared with smaller tumors (67% for tumors ≥3 cm vs. 87% for tumors <3 cm).

Toxicity and protocol compliance

After chemotherapy, Grade 4 neutropenia (WBC <1000/mm^3) occurred in 5 (12%) and hepatotoxicity in 8 (20%) of 41 patients. Grade 3 liver enzyme elevation (serum glutamic-oxaloacetic transaminase/serum glutamic-pyruvic transaminase between 5.1 and 10 times greater than normal) was seen in 2 (5%) of 41 patients and Grade 1-2 liver enzyme elevation in 6 (15%) of 41 patients. Of the 8 patients who developed hepatotoxicity, 2 were hepatitis B carriers. A brisk herpes zoster skin lesion developed in 1 patient.

The dose of chemotherapeutic agents for the second course of therapy was reduced by 25% in the 2 hepatitis B-positive patients because of hepatotoxicity, and the second course of chemotherapy was omitted entirely for the patient with an active herpes zoster lesion. Of the 41 patients, 32 (80%) received the second course of chemotherapy, as scheduled, on Day 15, and 8 (20%) needed a delay (1–5 days) before undergoing the second course. The total time of G-CSF use was 0–21 days (median, 10 days).

After RT, Grade 3 toxicity (confluent fibrinous mucositis/severe pain requiring narcotic analgesics) developed in 11 (27%) of 41 patients. Toxicity was more frequently seen in patients treated with 40 Gy in 16 fractions (32% or 7 of 22 patients) compared with those who received 40 Gy in 20 fractions (21% or 4/19 patients). Of the 41 patients, 38 (91%) received RT as scheduled, and 3 (9%) needed an interruption of 1–6 days because of mucositis.

The overall treatment time for chemotherapy combined with RT was 48–71 days (mean, 60 days; median, 62 days).

DISCUSSION

The results of this study demonstrate that biweekly THP-COP and local RT is feasible and effective for localized head-and-neck NHL. The 5-year survival and progression-free survival rates were similar to those reported in a large randomized study (3), which showed the superiority of three cycles of standard CHOP and RT compared with eight cycles of CHOP alone for localized Stage I-II aggressive lymphoma. The complete response rate in the present study, 94%, was also comparable to their result, 75% (3). If one looks at studies of the head and neck, our results are similar to, or even better than, those seen in other studies of Stage I-II aggressive lymphoma (13, 16).

The possible explanations for our favorable results are several. First, although treatment consisted of a weakened form of CHOP-based chemotherapy (i.e., pirarubicin rather than doxorubicin), the shortened interval of our chemotherapy may have increased the dose intensity of each drug within a certain period, in this case, 2 weeks. A few studies have determined the importance of dose intensity in achieving better tumor control. Tanosaki *et al.* (17) reported an improved complete remission rate by increasing the dose intensity of cyclophosphamide in their biweekly CHOP regimen. Donnelly *et al.* (18) reported that survival and relapse-free survival using the CHOP regimen were almost the same for young and elderly patient groups as long as the dose intensity was maintained. They suggested that age is not a prognostic factor. Rather, older patients tend to be slower in recovering from blood cell count perturbations, leading to longer intervals between treatments and resulting in lower dose intensity. With "prophylactic G-CSF" use, treatment delay was not required for most of the older patients and the dose intensity was kept to 90% of the standard CHOP regimen (18).

Second, most patients in the current study did not have adverse prognostic factors. In a large randomized study of Stage I-II aggressive lymphoma, Miller *et al.* (3) observed a poor overall survival rate of 48% for patients with more than two of the following adverse risk factors: age >60 years, Stage II, increased serum lactate dehydrogenase, and performance status of 2 or more. In the present study, no patients had more than two of these adverse factors. Bulky tumor has been reported to be a poor prognostic factor (16, 19, 20). In our study, 3 patients had tumors >5 cm in size, and this patient group had lower survival rates. Most of our patients had tumors <5 cm in size; this could also account for our favorable results. Another prognostic factor may be the primary site. Thirty-six percent of our patients had primaries in Waldeyer's ring. Good treatment results have been reported for this site compared with other sites in the head and neck (13, 14). One of the interesting findings in our study was the relatively good outcome for those with T-cell lymphoma. T-cell type tumors are generally thought to behave badly clinically; in particular, nasal T-cell type lymphomas are well known for their aggressiveness (15, 21–23). Although the results for those with T-cell lymphoma were, nevertheless, worse than for those with B-cell lymphoma, the 5-year progression-free survival rate of 75% for patients with T-cell lymphoma in our study was better than that seen in the literature (62% for Stage I-II nasal T-cell lymphoma in the study by Shikama *et al.* [23] and 59% for nasal T/NK cell lymphomas in the study by Kim *et al.* [21]). Only 1 patient had NK-cell lymphoma in our study, which may also explain our favorable results. NK cell lymphomas are classified as a distinct entity with a particularly aggressive clinical course (24). Hence, patients with this subtype may have been referred directly to a medical oncologist.

One of the drawbacks of our study was the use of the Working Formulation Group criteria for pathologic classi-

fication. We did, however, perform immunohistochemical staining to determine the B-cell/T-cell subtype in all cases. During the study period, pathologists at our institution were aware of the emergence of MALT lymphoma, which is now considered low grade; cases of this type were not included in our study. Consequently, we do not believe the results of our study are outdated.

Concerning the toxicity of biweekly THP-COP, Grade 3 hematologic toxicities occurred in only 9% of patients. This result was probably owing to the use of G-CSF. Timely use of G-CSF seems to be necessary to maintain the 2-week interval for biweekly CHOP administration (17). The other common toxicity was hepatic damage; Grade 3 hepatotoxicity occurred in 6% of patients. Although the incidence of liver toxicity was not great, this toxicity was the basis for dose modification of the second course of chemotherapy for 2 patients. Our results are consistent with those of several studies that have reported the susceptibility of hepatitis B carriers to cytotoxic agents (25–27). This underscores the importance of careful monitoring of hepatic function in such patients.

RT was tolerated in most of our patients. Grade 3 oropharyngeal mucositis was seen in 27% of patients, although less frequent in patients treated with 2 Gy/fraction compared with those treated with 2.5 Gy/fraction. No patients treated with 2 Gy/fraction developed recurrence. Our current practice is to give a total dose of 40 Gy in 20 fractions. Optimal dose-fractionation schedules, particularly when combined with chemotherapy, are still under investigation. Recently, Wilder *et al.* (28) reported an interesting dose–disease control relationship. They standardized the total doses of 294 patients by assuming an α/β of 10 with a fraction size of 1.8 Gy, and showed that the total dose required for tumor control after standard CHOP chemotherapy was 29.1–39.1 Gy for tumors <3.5 cm in diameter and 39.2–50.8 Gy for tumors 3.5–10 cm in diameter. A high local control rate (93% at 5 years) was achieved in our study, with total doses equivalent to 40.7–42.4 Gy by the conversion formula. The high local control rate in our study supports the observations of Wilder *et al.* (28). Regarding RT technique, only 2 patients developed an in-field or field-edge recurrence. With improvement of precise three-dimensional treatment planning, the incidence of this type of recurrence should decrease.

CONCLUSION

Using biweekly THP-COP and RT, high overall survival and progression-free survival rates were obtained in patients with Stage I-II aggressive lymphoma of the head and neck. Lymphomas arising from Waldeyer's ring had a particularly good prognosis. NHL comprises a variety of clinical and pathologic entities with different prognoses, most of which are still not completely understood. Recent studies using microarray assay (29, 30) reported that the prognosis may vary even within the same histologic type. In the future, treatment of NHL will be more selective using clinical and molecular prognostic information. Intensive regimens will be justified for patients with a large tumor or for those with poor prognosis (as determined by molecular markers) small tumors. For patients with a favorable prognosis, modified CHOP-like regimens, such as the one in this study, may be a viable alternative to the standard three-cycle CHOP plus RT regimen.

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ORIGINAL ARTICLE

Randomized Phase II Trial of Concomitant Chemoradiotherapy Using Weekly Carboplatin or Daily Low-Dose Cisplatin for Squamous Cell Carcinoma of the Head and Neck

Akihiro Homma, MD, PhD,[a] Hiroki Shirato, MD, PhD,[b] Yasushi Furuta, MD, PhD,[a] Takeshi Nishioka, MD, PhD,[b] Nobuhiko Oridate, MD, PhD,[a] Kazuhiko Tsuchiya, MD, PhD,[b] Tatsumi Nagahashi, MD,[a] Hidefumi Aoyama, MD, PhD,[b] Yukio Inuyama, MD, PhD,[a] Satoshi Fukuda, MD, PhD,[a] *Sapporo, Japan*

PURPOSE

This randomized, phase II study aimed to compare concomitant chemoradiotherapy using weekly carboplatin or daily low-dose cisplatin as a treatment for squamous cell carcinoma of the head and neck.

PATIENTS AND METHODS

One hundred nineteen patients with moderate- to advanced-stage disease were eligible for the study. Fifty-three patients had stage II disease, 28 had stage III, and the remaining 38 had stage IV disease. Primary tumor sites included the larynx (N = 63), oropharynx (N = 30), hypopharynx (N = 23), and oral cavity (N = 3). Each patient received either a weekly carboplatin dose (100 mg/m^2) in one arm or daily cisplatin (4 mg/m^2) in the other arm for the initial 4 weeks of radiotherapy. The radiotherapy dose of 65 Gy was given in 26 fractions over 45 days, dependent on a good tumor response at 40 Gy. Forty-nine (81.7%) of 60 patients treated with carboplatin and 41 (69.5%) of 59 patients treated with cisplatin received the full dose of radiotherapy. Surgical resection was optionally used for the remaining patients.

RESULTS

The median follow-up time was 63 months. The local control rate at 5 years was 56.2% for the carboplatin-treated arm and 35.5% for the cisplatin-treated arm, respectively. The 5-year overall survival rate did not significantly differ between treatments: 71.4% for carboplatin and 66.0% for cisplatin. Hematologic toxicity was more frequent in the carboplatin-treated arm. No difference was observed in surgical complications or in radiation-related adverse effects.

DISCUSSION

These findings suggest that weekly carboplatin treatment is preferable to daily low-dose cisplatin. This could be because the total dose of cisplatin was too low to be effective. *(Cancer J 2004;10:326–332)*

KEY WORDS

Carboplatin, chemoradiotherapy, cisplatin, head and neck carcinoma, randomized trial

Numerous types of platinum-based concomitant chemoradiotherapy have been reported to be effective for head and neck squamous cell carcinoma.[1-6] Our institution has investigated concomitant weekly carboplatin treatment and radiotherapy in phase I/II studies since 1990.[7,8] We found that this treatment achieved a higher local recurrence-free survival rate than treatment with radiotherapy alone in the historical control group.[8] However, several studies showed excellent results with chemoradiotherapy using daily low-dose cisplatin with a radiotherapy dose of up to 40 Gy.[9-12] In the mid-1990s, daily low-dose cisplatin was suggested to increase tumor control with less toxicity compared with weekly high-dose drug delivery.[13] We therefore began a randomized, phase II study to select an appropriate protocol to use against radiotherapy alone in future randomized trials. We compared our weekly carboplatin protocol[8] with a

From the [a]Department of Otolaryngology–Head & Neck Surgery and the [b]Department of Radiation Medicine, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan.

Received on September 6, 2004; accepted for publication September 9, 2004.

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Reprint requests: Akihiro Homma, MD, PhD, Department of Otolaryngology—Head & Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan. E-mail: ak-homma@med.hokudai.ac.jp.

daily low-dose cisplatin protocol established by Masaki et al[14] in Osaka, Japan, in 1993.[14]

PATIENTS AND METHODS

Eligibility criteria were as follows: histologically proven squamous cell carcinoma of the head and neck, excluding cancers of the T1N0M0[15] glottic region, nasopharynx, and paranasal sinus lesions. All patients were 75 years old or younger and had not received any previous treatment for the tumor. Patients were required to be free of other cancers as well as distant metastases. A World Health Organization performance status of 0–2 was required, in addition to the following: a white-cell count ≥ 4000 per mm^3, a platelet count of ≥ 100,000 per mm^3, a hemoglobin concentration of ≥ 9.5 g/dL, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels < 2 × the upper limits of the normal range, a total bilirubin concentration < 2.0 mg/dL, a serum creatinine concentration < 1.5 g/dL, a blood urea nitrogen concentration < 25 mg/dL, and a creatinine clearance > 60 mL/min. The size of the disease had to be measurable by computed tomography (CT), magnetic resonance imaging, and endoscopic examination. Informed consent was required before entry into the study. Patients who were pregnant or breast feeding were not eligible. Eligible patients were registered at the data center outside the hospital. The patients were classified according to the clinical stage and the primary site and were assigned to receive one of the two chemotherapeutic agents.

Chemotherapy was administered in both arms during the first 4 weeks of radiotherapy. Patients did not receive prophylactic hydration or antiemetics. In the carboplatin arm, a dose of 100 mg/m^2 of the body surface in 250 mL of 5% glucose was administered intravenously 1 hour before radiotherapy every 7 days for the first 4 weeks. Therefore, the total amount of carboplatin was 400 mg/m^2. In the cisplatin arm, a dose of 4 mg/m^2 of the body surface in 100 mL of physiologic salt solution was administered intravenously 1 hour before radiotherapy on every radiotherapy day during the first 4 weeks. Therefore, the total amount of cisplatin was 64 mg/m^2.

Dose modification was not permitted considering the low dosage of the chemotherapeutic agents. Modification of the schedule was regarded as minor when (1) carboplatin was administered three times or cisplatin nine to 15 times, or (2) radiotherapy was interrupted for 15 days or less. Modification was regarded as major when (1) carboplatin was administered two times or less or cisplatin eight times or less, or (2) radiotherapy was interrupted for more than 15 days.

All patients received external radiotherapy to the primary sites and regional lymphatic area using 4- or 6-mV photons from linear accelerators. Treatment planning was performed using a CT simulator and a three-dimensional dose-calculation computer throughout the study period. In cases of suspected lymph-node metastasis, the lower neck region and supraclavicular fossa were prophylactically irradiated using an anterior single port to a total of 40 Gy. After the initial dose, the response of the primary tumor was evaluated using endoscopic examination and/or CT or magnetic resonance imaging. A remarkable tumor response was defined as one leaving only a small residual tumor or no tumor after a greater than 50% decrease in gross maximum tumor area. Because of the difficulty in quantitative evaluation, we have not classified the tumor response in more detail.

Patients with a primary tumor that demonstrated a remarkable response at 40 Gy were advised to receive radical radiotherapy. Surgical resection was optionally used for the remaining patients, who had a poorer tumor response, provided that the tumor was resectable and the patients accepted the treatment. Nodal metastasis was treated with radiotherapy alone if the nodal response was deemed remarkable. Otherwise, the nodes were surgically removed if they were resectable, provided the patients accepted the treatment. The dose to the spinal cord was kept below 40 Gy in all instances. Electron beams were used to give a boost to the posterior cervical lymph nodes after 40 Gy.

The treatment schedule defined by the institute was used: a daily dose of 2.5 Gy four times a week. Hypopharyngeal cancers required a large field, including the upper parapharyngeal lymphatic region, and in these cases, 2.0 Gy was used as the daily dose. The total dose in the radical radiotherapy treatments was 65 Gy in 26 fractions over 45 days. For hypopharyngeal cancers, 66 Gy was administered in 33 fractions over 57 days. Salvage surgery was permitted for pathologically proven relapses or for residual tumors after 65–66 Gy of irradiation was administered, provided the patients accepted the treatment.

We used overall survival as the primary endpoint. The tumor response at 40 Gy, and therefore local recurrence-free survival, could be biased because of the difficulty in the endoscopic and imaging examination. However, the practice is justifiable for reducing surgical complications after full-dose radiotherapy in our community. The secondary endpoint was determined as the local control rate. Local control rate was calculated as patients who died without local failure and were classified as "locally controlled" at the last follow-up. Patients who underwent surgery for primary disease after 40 Gy and those with persistent or recurrent primary disease after 65 Gy were considered to have had local failures in the local control rate. The date of failure was determined as the time of the initial clinical diagnosis of local relapse. The Kaplan-Meier method and log-rank test were used to calculate the overall survival rate and the

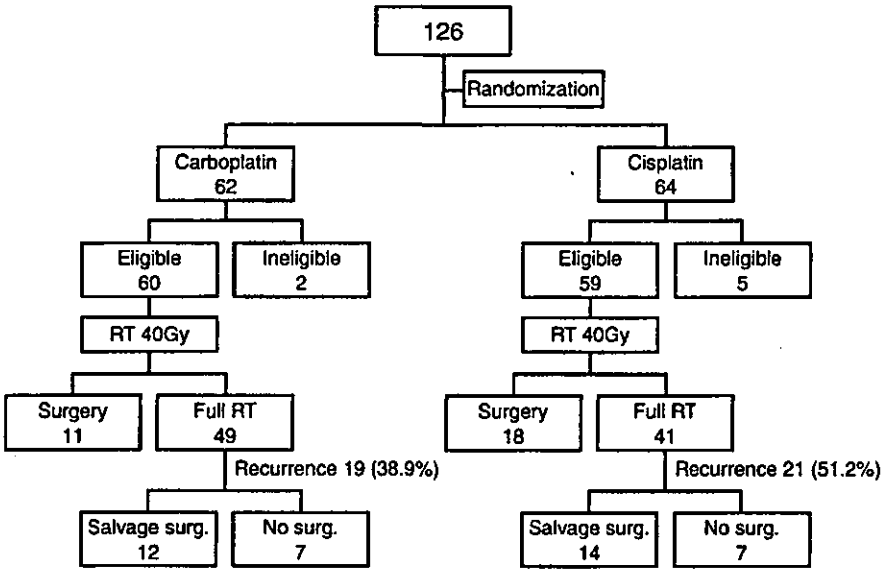

FIGURE 1 Actual number of patients and their treatments in a randomized phase II trial of concomitant chemoradiotherapy using weekly carboplatin or daily low-dose cisplatin for squamous cell carcinoma of the head and neck.

local control rate. Statistical calculations were performed using the Statview software package (version 5.0, Abacus Concepts, Inc., Berkeley, CA). Contingency table analyses based on Chi-square statistics were used to determine the statistical significance of associations between categorical variables. Fisher's exact probability test was used to compare acute adverse effects using NCI-CTC version 2.0 between the two arms. Late treatment-related toxicity was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scheme.[16]

RESULTS

From March 1995 to August 2000, 126 patients were enrolled in the study (Fig. 1). Of these, seven patients did not fulfill the inclusion criteria and were subsequently excluded, two patients had T1N0M0 glottic cancer, two patients had a synchronous primary cancer, and three patients had abnormal laboratory results. The baseline characteristics of the 119 remaining patients are summarized in Table 1. Sixty patients were eligible in the carboplatin group and 59 in the cisplatin group. The characteristics of the two treatment groups did not differ statistically from each other. The median and mean follow-up periods were 63 and 56 months, respectively, with a follow-up period ranging from 24 to 88 months.

Violation of the treatment occurred in one patient receiving carboplatin, who refused chemotherapy. Major modifications of the treatment schedule occurred in five patients who received treatment in the carboplatin arm and five in the cisplatin arm. Minor modifications of

TABLE 1 Characteristics of Patients in a Randomized Phase II Trial of Concomitant Chemoradiotherapy Using Weekly Carboplatin or Daily Low-Dose Cisplatin for Squamous Cell Carcinoma of the Head and Neck

Characteristics		Carboplatin	Cisplatin	Total
Sex	Male	59	54	113
	Female	1	5	6
Age	Median	62	61.5	
	Mean	61.0	61.7	
	Range	43–74	46–73	
Stage	II	28	25	53
	III	12	16	28
	IV	20	18	38
Site	Larynx	32	31	63
	Oropharynx	14	16	30
	Hypopharynx	13	10	23
	Oral cavity	1	2	3

the schedule were seen in six patients who received carboplatin and in six who received cisplatin. The reasons for the modifications are shown in Table 2.

The 5-year overall survival rate was 71.4% for carboplatin-treated patients and 66.0% for cisplatin-treated patients (Fig. 2). This difference was not statistically significant ($P = 0.217$). However, the local control rate at 5 years was statistically significant: 56.2% in carboplatin-treated patients and 35.5% for cisplatin-treated patients ($P = 0.034$; Fig. 3).

TABLE 2 **Compliance with Treatment in a Randomized Phase II Trial of Concomitant Chemoradiotherapy Using Weekly Carboplatin or Daily Low-Dose Cisplatin for Squamous Cell Carcinoma of the Head and Neck**

Compliance Level	Carboplatin	Cisplatin
Violation		
No chemotherapy given	1	
Refusal of chemotherapy	1	
Major modification	5	5
Chemotherapy stopped before completion (carboplatin : ≤ 2 times, cisplatin : ≤ 8 times)	2	3
Slight deterioration of renal function tests	2	2
Melena		1
Radiotherapy interruption > 15 days	2	1
Mucositis	2	
Severe nausea and a general fatigue		1
Chemotherapy stopped before completion (carboplatin : ≤ 2 times, cisplatin : ≤ 8 times) and radiotherapy interruption > 15 days	1	1
Hyponatremia	1	
Severe nausea and a general fatigue		1
Minor Modification	6	6
Chemotherapy stopped before completion (carboplatin: 3 times, cisplatin: 9–15 times)	4	4
Slight deterioration of renal function tests	2	2
An error	2	1
Mucositis		1
Radiotherapy interruption ≤ 15 days	2	2
Mucositis	2	2
Total	12	11

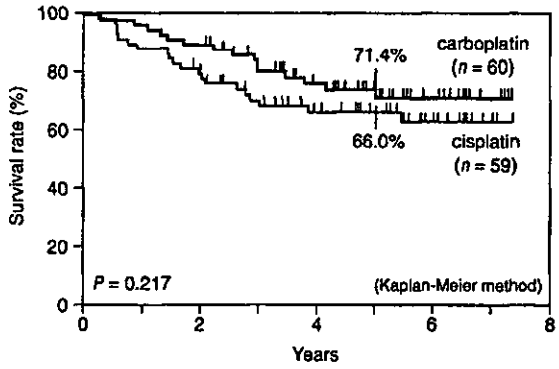

FIGURE 2 Overall survival of all patients in the randomized phase II trial of concomitant chemoradiotherapy using weekly carboplatin or daily low-dose cisplatin for squamous cell carcinoma of the head and neck.

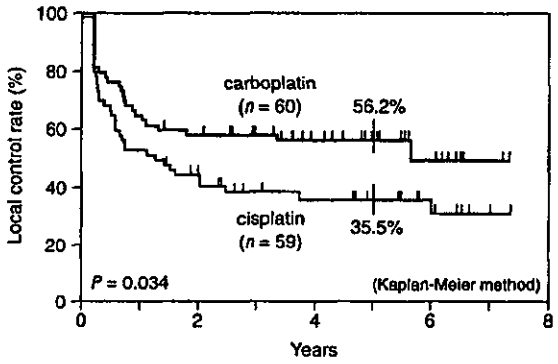

FIGURE 3 Local control in all patients in the randomized phase II trial of concomitant chemoradiotherapy using weekly carboplatin or daily low-dose cisplatin for squamous cell carcinoma of the head and neck.

Forty-nine (81.7%) of 60 patients receiving carboplatin and 41 (69.5%) of 59 patients receiving cisplatin also received the full dose of radiotherapy. Surgical resection was used at 40 Gy in 11 carboplatin-treated patients and in 18 cisplatin-treated patients ($P = 0.122$).

Recurrences at the primary site with or without lymph node relapse were observed in 15 (31%) of 49 carboplatin-treated patients who received the full dose of radiotherapy; the condition of eight (53%) of these patients was salvaged by surgery. Three patients had persistent neck disease without primary recurrence, and one of the three underwent successful salvage surgery. Nineteen (46%) of 41 cisplatin-treated patients who received the full dose of radiotherapy developed recurrences at the primary site with or without lymph node relapse; the condition of nine (47%) of these was salvaged by surgery. Two patients had persistent neck dis-

ease without primary recurrence, and one of these underwent successful salvage surgery. The difference in relapse rate after full-dose radiotherapy and the success rate of salvage surgery did not reach statistically significant levels.

There was no difference in the distant metastasis-free rate between the two methods of treatment. Three patients receiving carboplatin and four receiving cisplatin died of distant metastasis without locoregional recurrence. There was no difference in the rate of secondary primary cancers that developed in the follow-up period; this cancers developed in seven of the patients receiving each treatment (14 patients total).

The numbers of patients who experienced severe acute toxicities are shown in Table 3. Hematologic toxicity was more frequent after carboplatin treatment ($P = 0.0164$). Mucositis and nausea/vomiting were more frequent in the cisplatin group, but the difference was not statistically significant. One fatal adverse event was reported for each treatment. One patient who received carboplatin died of a cerebral infarction, which occurred 3 weeks after radiotherapy was completed. The patient was dehydrated after radiation mucositis, which caused a shortage of oral intake. One patient in the cisplatin group died of acute pneumonia during the treatment.

The rates of mucocutaneous fistula and free-flap necrosis were calculated to assess surgical complications. Forty-three patients who underwent a total laryngectomy with or without partial pharyngectomy were assessed. Of these, 25 underwent surgery after 40 Gy and 18 underwent surgery after full-dose radiotherapy. There was no difference in the incidence of mucocutaneous fistula between the two groups. The free-flap necrosis rate was calculated in 19 patients who underwent free-flap transfer for reconstruction. There was no difference in the complication rate between the two treatment methods (Table 4).

There were no apparent differences in late radiation-induced adverse reactions. Late radiation-induced adverse reactions of grade 3 or more were observed, one in a carboplatin-treated patient and two in cisplatin-treated patients. Bone necrosis developed in one carboplatin-treated patient with oropharyngeal cancer after a tooth extraction. Severe laryngeal edema developed in two patients treated with cisplatin.

TABLE 3 Acute Toxic Effects In a Randomized Phase II Trial of Concomitant Chemoradiotherapy Using Weekly Carboplatin or Daily Low-Dose Cisplatin for Squamous Cell Carcinoma of the Head and Neck

Grade 3–5 Toxicities	Carboplatin	Cisplatin	*P* Value*
Hematologic	8	1	0.0164
Mucositis	2	7	NS
Dermatitis	10	7	NS
Nausea and vomiting	0	2	NS
Serum ALP elevation	1	0	NS
Fatal	1	1	NS

Abbreviation: ALP, alkaline phosphatase.

DISCUSSION

Single-agent concomitant chemoradiotherapy was superior to radiotherapy alone in the long-term follow-up of a randomized trial for head and neck cancers.[17] This was supported by recent systematic reviews in which cisplatin-based chemoradiotherapy was suggested to be superior to radiotherapy alone.[13,18] The meta-analysis showed a small but significant survival benefit in favor of chemotherapy,[19] although the appropriate treatment agents and dose schedule had not yet been determined.

Our randomized, phase II study compared the two agents cisplatin and carboplatin, as well as daily and weekly administration schedules, respectively. Both of the treatment schedules tested in this trial are widely used in Japan, so it is misleading to discuss the superiority of daily schedules over weekly schedules, or carboplatin treatment over cisplatin. Instead, this study shows that the weekly carboplatin schedule is more appropriate than the low-dose daily cisplatin schedule as a candidate to be tested in a randomized phase III trial in comparison with radiation alone.

The daily cisplatin treatment schedule was based on the results of the regional phase I/II studies.[9,14] Other

TABLE 4 Surgical Complications In a Randomized Phase II Trial of Concomitant Chemoradiotherapy Using Weekly Carboplatin or Daily Low-Dose Cisplatin for Squamous Cell Carcinoma of the Head and Neck

Complication	No. at Risk	Carboplatin	Cisplatin	*P* Value*
Mucocutaneous fistula	43	3/17	7/26	NS
Surgery after 40 Gy	25	1/10	4/15	NS
Surgery after full dose	18	2/7	3/11	NS
Free flap necrosis	19	2/9	1/10	NS
Surgery after 40 Gy	16	0/6	1/10	NS
Surgery after full dose	3	2/3	0/0	NS

*Chi-square test.

dose-escalation work had shown that 6 mg/m² daily administration throughout radiotherapy is appropriate in phase I studies,[20,21] and recent prospective phase II and III trials have confirmed its feasibility and effectiveness.[10-12] The total dose of cisplatin in the present study is much lower than those used in other studies reported in the literature. In light of recent large trials, cisplatin-treated patients in our study might have received a suboptimal dose intensity: the outcome of concomitant chemoradiotherapy with daily cisplatin administration might have been improved further by the use of a daily dose of 6 mg/m² and a total dose of 200 mg or more.[13,18] The efficacy and toxicity of cisplatin treatment in our study are almost the same as that following radiotherapy alone.

Another limitation of our study was the decision to use surgical treatment at 40 Gy. It would have been preferable to administer a full dose of radiation to all patients in order to compare the two schedules, but we could not change our institutional policy at the time of the study. The risk of performing surgery after full-dose radiotherapy exceeds the prospect of a nonsurgical cure for patients demonstrating a poor response to 40 Gy. The apparent reduction in the number of patients who received surgery at 40 Gy after carboplatin treatment might have been owing to an earlier response of the tumor at 40 Gy. This speculation is supported by the similarity in overall survival between the two treatments, despite the difference in the local control rate. We cannot comment on this matter because of the limitation of our study design.

Although our schedule of 2.5 Gy administered four times a week was used for most of the patients, the rates of major surgical complications, mucocutaneous fistula, and free-flap necrosis, as well as the late radiation-induced adverse effects, were considered acceptable in both groups, even after the full dose of radiation. The local control rate in the low-dose cisplatin-treated group was too low to be recommended. The same rate after carboplatin treatment can be improved further if surgical treatment is not performed at 40 Gy. Because surgical complications did not increase, even after full-dose radiotherapy, we suggest that this, in association with the carboplatin schedule used in this trial, might be a reasonable treatment.

Gene expression has been investigated in patients with squamous cell carcinoma of the head and neck to predict the sensitivity of, and resistance to, chemoradiotherapy.[22,23] Molecular imaging techniques are also expected to improve the therapeutic ratio of chemoradiotherapy for head and neck cancers.[24] However, it remains impractical to select patients who would respond more favorably to a specific agent in chemoradiotherapy. Instead, prospective randomized trials should be used to find the optimal treatment.

In conclusion, the combination of weekly carboplatin administration and concomitant radiotherapy is considered to be a good candidate for comparison with radiation alone in future trials for the treatment of squamous cell carcinoma of the head and neck.

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