Table 2. Treatment characteristics

Hormonal therapy	
Yes	563 (82.9%)
No	116 (17.1%)
Content	
MAB	370 (65.7%)
LHRH analog	120 (21.3%)
Antiandrogen	34 (6.1%)
Orchiectomy	19 (3.4%)
Estrogen	8 (1.4%)
Unknown	12 (2.1%)
Period	
RT only	116 (17.1%)
NHT + RT	317 (46.7%)
NHT + RT + AHT	203 (29.9%)
RT + AHT	36 (5.3%)
Unknown	7 (1.0%)
Radiation therapy	
Dose distribution	
< 64.9 Gy	101 (15.0%)
65.0–69.9 Gy	178 (26.2%)
70.0–71.9 Gy	268 (39.4%)
72.0–74.9 Gy	66 (9.7%)
75.0–78.0 Gy	66 (9.7%)
Field arrangement for the prostate	
4 field	221 (32.9%)
> 4 field	9 (1.3%)
Dynamic conformal	421 (62.7%)
IMRT	16 (2.4%)
Unknown	5 (0.7%)
Conformal therapy	
Standard	130 (19.2%)
Conformal/IMRT	546 (80.4%)
Unknown	3 (0.4%)
Pelvic irradiation	
Yes	144 (21.2%)
No	535 (78.8%)

MAB, maximum androgen blockade; LHRH, luteinizing hormone-releasing hormone; RT, radiation therapy; NHT, neoadjuvant hormonal therapy, AHT, adjuvant hormonal therapy; IMRT, intensity-modulated radiotherapy.

biochemical relapse-free survival. PSA (relative risk, 1.002; 95% CI, 1.001–1.003; $P = 0.0041$), GS (relative risk, 1.166; 95% CI, 1.046–1.302; $P = 0.0055$), T classification (relative risk, 2.897; 95% CI, 1.999–4.230; $P = 0.0000$), pelvic irradiation (relative risk, 2.042; 95% CI, 1.328–3.273; $P = 0.0008$), and androgen abletion (relative risk, 0.321; 95% CI, 0.240–0.427; $P = 0.0000$) were identified as significant prognostic factors.

Table 3. Distribution of failures

	Low ($n = 89$)	Intemediate ($n = 140$)	High ($n = 450$)
PSA failure	10	28	122
Clinical failure	0	3	26
Local	0	1	3
Regional	0	0	4
Regional + Distant	0	0	3
Distant	0	2	15
Unknown	0	0	1
Death			
Prostate cancer	0	0	7
Others	5	9	17
Unknown	1	0	1

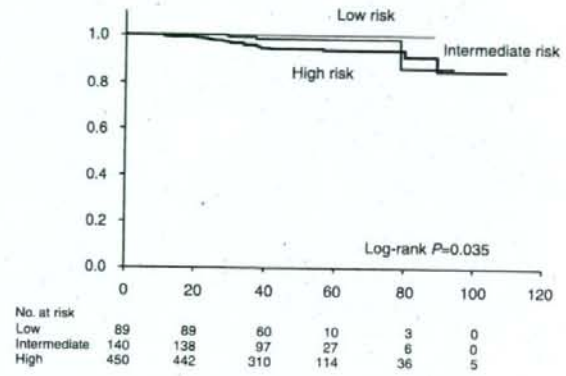

Figure 1. Clinical progression-free survival rates as a function of risk group.

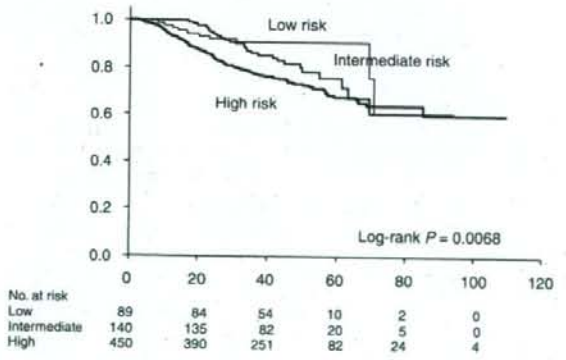

Figure 2. Biochemical relapse-free survival rates as a function of risk group.

Table 5 shows late morbidity after irradiation. Only 1.1% of patients experienced late morbidity of Grade 3. There were no cases of Grade 4 toxicity.

Table 4. Multivariate analysis of prognostic factors for biochemical relapse-free survival

Prognostic factor	Multivariate	
	Relative risk (95% confidence interval)	*P* value
Age (continuous variable)	0.987 (0.964–1.012)	0.3050
PSA (continuous variable)	1.002 (1.001–1.003)	0.0041
Gleason score (continuous variable)	1.166 (1.046–1.302)	0.0055
T stage (T1–T2 vs. T3–T4)	2.897 (1.999–4.230)	0.0000
Total dose (continuous variable)	0.962 (0.919–1.008)	0.1051
Pelvis irradiation (yes vs. no)	2.042 (1.328–3.273)	0.0008
Hormonal therapy (no vs. 1–23.9 m, ≥24 m)	0.321 (0.240–0.427)	0.0000
Year of radiotherapy (continuous variable)	1.050 (–1.203)	0.4668

Table 5. Late gastrointestinal and genitourinary morbidity

	Grade			
	1	2	3	4
Gastrointestinal				
Rectal bleeding	99	42	7	0
Others	3	0	0	0
Genitourinary				
Urininary incontinence	14	6	0	0
Stricture/stenosis	3	5	0	0
Urinary urgency	4	3	0	0
Bleeding	1	4	1	0
Others	8	2	0	0
Total	132 (19.4%)	62 (9.1%)	8 (1.1%)	0

DISCUSSION

The present study revealed the practical patterns of EBRT for prostate cancer in Japan. The majority of patients with prostate cancer who received radical radiotherapy had high-risk disease. The median radiation doses employed were 70 Gy, and EBRT was commonly combined with hormonal therapy. Radiotherapy seemed to be effective with little risk of normal tissue complications, although limited by its retrospective nature.

Radical prostatectomy (RP) has been established as one of the standard management options for prostate cancer. However, very few outcome studies have been reported on RP in Japan and Asian countries. Yokomizo et al. (12) have recently reported the treatment results of 1192 patients with clinical T1-2N0M0 prostate cancer, who had a RP from 1993 to 2002 without hormonal therapy at 37 institutions in Japan and whose PSA level after RP decreased to undetectable levels. With a median follow-up of 45.6 months, seven patients (0.6%) died from prostate cancer-related causes and 302 patients (25.3%) had a PSA recurrence. Although the characteristics of patients were totally different from those in our study, EBRT seems to be similarly effective.

A limitation of this study was the use of the ASTRO definition of biochemical failure in most patients. The new definition 'nadir of PSA + 2 ng/ml' is considered as the current standard definition for biochemical failure after radiotherapy with or without hormonal therapy (13). When this study was planned, the ASTRO definition of biochemical failure was still being used, although the adequacy of the ASTRO definition has come into question. We should keep in mind that the old ASTRO definition will result in worse short-term and better long-term results, and should be applied basically in patients treated with radiotherapy alone (13). In addition, another limitation of this study was the use of institutional GSs. It should be noted that central review of pathological specimens is essential to ensure the quality of analysis.

The radiation doses employed in Japanese institutions used to be lower than those typically used in the USA (5–7). However, the median dose to the prostate was 70 Gy in this study, and 58.9% of the patients were irradiated with doses ≥70 Gy. Several studies have revealed the radiation dose dependency on progression-free survival as well as biochemical relapse-free survival. However, radiation dose was not a significant prognostic factor in this study. It should be carefully evaluated whether higher doses improve survival, in the situation that the majority of the patients received hormone therapy.

Long-term hormonal therapy in combination with EBRT has been shown to be effective in high-risk patients (14). In the present study, adjuvant hormonal therapy was used in 34.8% of patients, and the median duration of hormonal therapy after radiotherapy was 38 months. However, the median follow-up was only 46 months. Although hormonal therapy and its duration was a prognostic factor in the multivariate analysis, assessment of the effects of long-term hormonal therapy is warranted in future studies.

The survey results demonstrated that more than 80% of patients were treated with a conformal technique, and treatments were delivered frequently using rotational conformal techniques. Because conformal radiotherapy using rotation techniques was developed by Takahashi (15), this technique has been particularly popular in Japan. In constrast, IMRT was performed in only 2.4% of patients. However, IMRT is gradually becoming widespread in Japan (16), and it may become one of the preferred treatment options for prostate cancer in Japan in the near future.

There is a great controversy regarding the effectiveness of elective pelvic radiotherapy in patients with high-risk prostate cancer. The analysis of a recent randomized trial has demonstrated that pelvic irradiation is associated with an improvement in the progression-free survival when neoadjuvant hormonal therapy is used in conjunction with EBRT (17). In the present study, pelvic irradiation was a prognostic

factor for biochemical relapse-free survival. However, more studies are needed to determine the best treatment for patients with high-risk prostate cancer.

To our knowledge, this study constitutes the largest series of prostate cancer patients treated with EBRT in Japan. EBRT is feasible for Japanese patients and produces favorable survival results. Although patients with T3–T4 tumor, high GSs, or high level of PSA had a poorer prognosis, the results of EBRT in Japan are generally promising. We believe it worthwhile to show the treatment results of EBRT for prostate cancer not only in Japan, but also in other Asian countries, because the number of patients with prostate cancer treated with radiotherapy in Asian countries will increase rapidly in the near future.

Funding

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Appendix

Participating Institutions: Akita University, Chiba University, Dokkyo Medical University Koshigaya Hospital, Gunma Prefectural Cancer Center, Gunma University, Hamamatsu University School of Medicine, Hyogo Cancer Center, Kitasato University, Kochi University, Kyorin University, Kyoto University, Kyushu Medical Center, Kyushu University, Mie University, Nara Medical University, National Cancer Center Hospital East, Niigata University, Nishi-Kobe Medical Center, Okayama University, Rinku General medical center, Saitama Medical Center, Shiga University, Shimane University, Shinshu University, Tenri Hospital, Toho University, Tokai University, Tokushima University, Tokyo Medical Center, Tokyo Metropolitan Fuchu Hospital, Tokyo Metropolitan Komagome Hospital, Tukuba University, University of Occupational and Environmental Health, Yamanashi University.

Conflict of interest statement

None declared.

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Patterns of Pretreatment Diagnostic Assessment and Staging for Patients with Cervical Cancer (1999–2001): Patterns of Care Study in Japan*

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Objective: To evaluate the patterns of pretreatment diagnostic assessment in uterine cervical cancer patients treated with definitive radiotherapy in Japan.
Methods: The Japanese Patterns of Care Study working group conducted a second extramural audit survey of 68 institutions and collected specific information on 631 patients with cervical cancer. All patients were treated with radiotherapy in 1999–2001. Of these, 324 patients treated without surgery were the subjects of this study.
Results: International Federation of Gynecology and Obstetrics-prescribed diagnostic procedures were performed at moderate rates in our study cohort. The performance rates of chest X-ray, intravenous urography, cystoscopy, and proctoscopy were 74, 54, 53, and 33%, respectively. Cross sectional imaging studies were frequently performed. Pelvic CT, abdominal CT, and pelvic MRI were performed in 88, 80, and 76%, respectively. Lymphangiography (1%) and surgical evaluation (1%) were rarely done. Only one patient underwent PET scans in this survey period.
Conclusions: This study demonstrated the patterns of pretreatment diagnostic assessment in cervical cancer patients treated with definitive radiotherapy in Japan.

Key words: cervix neoplasm – radiotherapy – patterns of care – FIGO

INTRODUCTION

The pretreatment assessment of cancer extension is extremely important for prognosis estimation and treatment planning. Additionally, a well-defined initial assessment enables the comparison of cancer treatment results among institutions or different treatment methods. The International Federation of Gynecology and Obstetrics (FIGO) provides a global staging system for gynecologic cancers (1). Most clinicians use this staging system in the treatment of uterine cervical cancer. The system describes the rules for stage classification in detail, and the permitted diagnostic procedures are clearly stated. However, some of the procedures included, such as intravenous urography, and skeletal X-rays, could be considered outdated. Although tumor diameter and pelvic nodal status are not accounted for in the FIGO staging system, they are estimated to be the important prognostic factors for cervical cancer (2). In several studies, tumor diameter as assessed by MRI was a significant prognostic indicator for patients with cervical cancer (3–5). Evaluation of pelvic or para-aortic lymph node status with optional imaging studies, such as CT, MRI, and lymphangiograpy, may also be useful for predicting prognosis (6).

Several studies describe the patterns of pretreatment work-up of cervical cancer in the USA (7–9); however, there are few studies from Japan. The objective of this study

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*Presented, in part, at the 91st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA).

Table 3. Pretreatment diagnostic procedures performed according to the FIGO stage

Procedure	Stage				Missing/unknown
	I	II	III	IVA	
Intravenous urography	17/43 (40%)	53/102 (52%)	74/122 (61%)	26/35 (70%)	6/22
Cystoscopy	18/43 (42%)	58/102 (57%)	64/122 (52%)	25/35 (71%)	6/22
Proctoscopy	12/43 (28%)	32/102 (31%)	43/122 (35%)	17/35 (49%)	4/22
Pelvic CT	40/43 (93%)	89/102 (87%)	112/122 (92%)	34/35 (97%)	11/22
Abdominal CT	35/43 (81%)	83/102 (81%)	103/122 (84%)	29/35 (83%)	8/22
Pelvic MRI	31/43 (72%)	84/102 (82%)	88/122 (72%)	27/35 (77%)	16/22

the treating physicians or were performed anew by the visiting surveyors at the time of the analysis. Despite this limitation, we were able to roughly approximate the tumor diameter and the lymph node status in each stage. In the next JPCS presently being conducted, the format has been revised to clarify the aforementioned points. Our data will aid in comparing outcome between Japan and other countries. Abdominal CT has diagnostic value in detecting extrapelvic metastases (i.e. liver and para-aortic node) and the presence of hydronephrosis or a non-functioning kidney. Despite the potential usefulness of CT and MRI, these cross-sectional imaging studies are listed as optional examinations in the FIGO system (1). FIGO also acknowledges the usefulness of these exams. However, FIGO does not accept them for staging purposes, primarily because these instruments are not generally available in developing countries. The FIGO system clearly states that findings from these exams should not be the basis for staging (1). Improper application of these exams could lead to staging migration (2). However, we believe that these cross-sectional imaging studies should be applied universally not to determine FIGO stage but to assess important prognostic factors, namely tumor diameter and nodal status.

Several randomized clinical trials (RCTs) performed in the USA demonstrated the therapeutic value of concurrent chemoradiotherapy (http://www.cancer.gov/newscenter/cervicalcancer). Most of these trials required extensive evaluation of para-aortic lymph nodes by surgical exploration or LAG. This limits the translatability of the recommendations from these trials to the Japanese clinical practice. LAG and surgical staging were rarely performed for patients in our survey. Although Eifel reported that lymph nodal status was assessed by LAG in 13.6%, and surgical evaluation in 12.2% in the US PCS (1996–99), other studies revealed that, the performance of LAG has been decreasing recently (7–9). A similar problem exists in the evaluation of tumor diameter. In the US RCTs, tumor diameter was determined by physical examination. However, tumor size assessment by physical examination is highly subjective. Thus an objective method such as CT or MRI is preferable particularly when patients are being stratified in a clinical trial. This would facilitate the translation of evidence to clinical practice.

PET was rarely performed during the study period in Japan despite being shown to be useful in the late 1990s (16). Its application is expected to increase in the future, because the Japanese health insurance plan has covered it since 2004.

In summary, the JPCS describes the general patterns of pretreatment diagnostic assessment in cervical cancer patients treated with definitive radiotherapy during 1999–2001 in Japan. Patterns of pretreatment work-up should be continuously monitored in order to avoid staging migration, to properly treat individual patients, and to fairly compare treatment methods.

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Conflict of interest statement

None declared.

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CLINICAL INVESTIGATION **Cervix**

PROSPECTIVE STUDY OF ALTERNATING CHEMORADIOTHERAPY CONSISTING OF EXTENDED-FIELD DYNAMIC CONFORMATIONAL RADIOTHERAPY AND SYSTEMIC CHEMOTHERAPY USING 5-FU AND NEDAPLATIN FOR PATIENTS IN HIGH-RISK GROUP WITH CERVICAL CARCINOMA

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Purpose: To assess the efficacy of alternating chemoradiotherapy combined with extended-field conformal radiotherapy for patients with high-risk cervical cancer.

Methods and Materials: Patients with previously untreated cervical cancer, with Stage III/IVA disease, or Stage IB/II with high-risk factor (primary tumor diameter ≥50 mm or positive lymph node) were entered into this study. Three cycles of chemotherapy with 3,500 mg/m^2 of 5-fluorouracil (5-FU) and nedaplatin (NDP) were accompanied with pelvic irradiation of 45.6–51.3 Gy in 24–27 fractions over 6 weeks. Prophylactic (36 Gy/20 fractions) or definitive (45–56 Gy) irradiation for para-aortic region was followed by pelvic irradiation.

Results: Between 1998 and 2004, 40 patients were recruited for this protocol study. Eighteen patients from Phase I setting were registered. Twenty-two patients were treated with NDP of 140 mg/m^2 (the recommended dose) in the Phase II segment. Twenty-five patients had T3 disease, and 25 patients had nodal disease including para-aortic involvement ($n = 5$). Overall/progression-free survival rates at 5 years were 78.8 and 66.5%, respectively. The median follow-up time was 61.8 months (25.5–106.7). Hematologic and gastrointestinal Grade 3 or more toxicities were relatively high rate (27.5–45%); however, they were well manageable. Two for bladder toxicity of Grade 3 were noted. Comparing the data from historical control group evaluated by magnetic resonance imaging, alternating chemoradiotherapy revealed a significant favorable factor for survival and disease recurrence in multivariate analysis ($p < 0.05$).

Conclusion: Acquired results from our unique protocol for cervical cancer with high-risk factor were thought to be promising, considering that the majority of our cohort consisted of high-risk population. © 2009 Elsevier Inc.

Extended field, Alternating chemoradiotherapy, Nedaplatin, Cervical cancer, Conformational radiotherapy.

INTRODUCTION

Standard treatment for patients with advanced-staged cervical carcinoma is now believed to be concurrent chemoradiotherapy. Chemoradiotherapy improves overall survival (OAS) and progression-free survival (PFS), whether or not platinum was used. Absolute benefit was reported as 10% advantage of OAS and 13% of PFS (1). Chemoradiation showed a significant benefit for local recurrence and a suggestion of a benefit for distant recurrence, although this trend was more markedly noted among patients with Stage I-II disease compared with those of Stage III -IVA (2–5). Contents of chemotherapy regimen was varied much, although weekly administration of cisplatin was now widely used because Gynecologic Oncology Group (GOG) 120 could not showed an apparent advantage of addition of 5-fluorouracil (5-FU) compared with single use of cisplatin (2, 6).

Nedaplatin (NDP) is an active agent for cervical carcinoma (7), shown to have treatment effects equivalent to those of the widely used cisplatin but with less renal and gastrointestinal toxicity (8). Its dose-limiting toxicities (DLT) are thrombocytopenia and myelosuppression, and its recommended dose (RD) in Japan is 100 mg/m^2. However, we have reported the possibility of dose escalation of NDP when used in combination with 5-FU before the administration of NDP. In our previous report, the RD of NDP was 150 mg/m^2 (9). Theoretically, the antitumor effect of concurrent administration is

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identical, but the increasing acute toxicity is an important problem. Thus the intensity of both radiotherapy and chemotherapy would be compromised in this setting. Alternating chemoradiotherapy (ALCRT) is a method for resolving this problem; avoiding the concurrent usage of these two modalities may reduce the acute toxicity, allowing the full dose of chemotherapy to be maintained. We have also reported excellent outcomes of ALCRT in nasopharyngeal cancer (10). As with nasopharyngeal cancer, patients with cervical cancer with advanced stage had hazard of metastatic disease progression, so intensity of chemotherapy is thought to be an important issue for patient management.

To investigate the efficacy and feasibility of ALCRT for high-risk cervical carcinoma, we performed a Phase I/II study at our institution.

METHODS AND MATERIALS

Eligibility criteria

Previously untreated patients with histologically diagnosed as squamous cell carcinoma of uterine cervix were entered into this study. Eligible patient was defined as having a high risk factor (Stage I-II; tumor size ≥50 mm or positive pelvic node OR all Stage III-IV disease); good performance status (PS), adequate organ function; age 20–75; and informed consent. Importance of prognostic indicator of magnetic resonance imaging (MRI) has been reported multi-institutional study (11, 12), and we take account for patient selection for this protocol. Patients with lymph node metastasis limited to para-aortic region who were diagnosed by imaging are also included this study.

Before enrollment, each patient underwent complete physical, laboratory, and stage assessments. The laboratory examinations consisted of complete blood count, serum chemistry, 24-h creatinine clearance, and electrocardiography. The staging workup included chest radiography, computed tomography (CT) of the whole abdomen, and pelvic MRI. Lymph nodes measuring 10 mm or more along the long axis on CT or MRI scan was defined as metastatic nodes. Patients were required to have a white blood cell count ≥3,000/μL, platelet count ≥100,000/μL, hemoglobin level ≥10.0 g/dL, normal hepatic (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level <2.5 times the upper normal limit) and renal function (24-h creatinine clearance level ≥60 mL/min), and normal electrocardiogram. Written informed consent was obtained from all patients. The protocol was approved by the institutional review board.

Response and toxicity evaluations

To evaluate responses and toxicity, all patients underwent complete blood count and serum chemistry analysis one to two times per week. The response evaluation was judged 2 months later from last day of whole treatment. Response evaluation was done with physical examination with smear cytology, pelvic MRI scan, and whole-abdominal CT scan.

Magnetic resonance imaging was repeated every 3–4 months for the first 2 years and twice per year thereafter. A CT scan of the whole abdomen was repeated every 6 months. Toxicity was assessed and graded using the National Cancer Institute Common Toxicity Criteria, version 3.0. The grading of late urinary and gastrointestinal toxicities due to radiotherapy was in accordance with the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer toxicity criteria (13). The DLT were defined as Grade 4 hematologic toxicities or any nonhematologic Grade 3 or higher toxicities, except diarrhea, nausea, and vomiting. The chemotherapy dose and schedule modifications for toxicity are shown in Table 1.

Phase I component

The primary end point of the Phase I part of the study was to determine the maximum tolerated dose (MTD) and the RD of NDP for the Phase II segment, when combined with 120-h infusion of 3,500 mg/m^2 5-FU and definitive radiotherapy on an alternating schedule, for patients with cervical cancer with high-risk factors.

Dose escalation scheme

The starting dose of NDP was 100 mg/m^2, as suggested by a previous study (9). Additional increases of 20 mg/m^2 up to the MTD were permitted. According to our previous report, the dose of NDP did not exceed 150 mg/m^2 (9). At least 3 patients were treated at each dose level. The end point to close the study was a DLT if observed in 2 of 3 patients or in 3 of 6 patients at the same dose levels.

Table 1. Chemotherapy and radiotherapy dose and schedule modifications for toxicity

Toxicity	Modifications
Chemotherapy	
Grade 4 leukopenia, granulocytopenia	25% reduction of both nedaplatin and 5-FU
Grade ≥3 thrombocytopenia	25% reduction of both nedaplatin
Grade 2 renal dysfunction	
Grade ≥3 diarrehea	25% reduction of 5-FU
Grade 2 liver dysfunction	
Grade ≥3 liver or renal reaction	Withheld additional chemotherapy
Nonhematologic Grade >3: toxicity, except for nausea/vomiting	Chemotherapy postponed until recovery
Radiotheraphy	
Grade 4 leukopenia, granulocytopenia	Postponed until recovery to Grade 2
Grade 4 thrombocytopenia	Postponed until recovery to Grade 2
Grade 3 leukopenia, granulocytopenia, and infection or Grade 2 fever	Postponed until recovery of infection and fever
Schedule modification	
Chemotherapy was started with a white blood cell count ≥2, 500 μ^{-1}, platelet count ≥100, 000 μ^{-1}, hemoglobin level ≥8.0 g dl^{-1}, total bilirubin ≤2.0 mg/dL serum creatinine ≤1.2 mg/dL, and esophagitis Grade ≤3. If these data did not fulfill the criteria, radiotherapy was continued until these data recovered . As soon as these data improved, the next cycle of chemotherapy should be started, resting radiotherapy between courses of chemotherapy.	

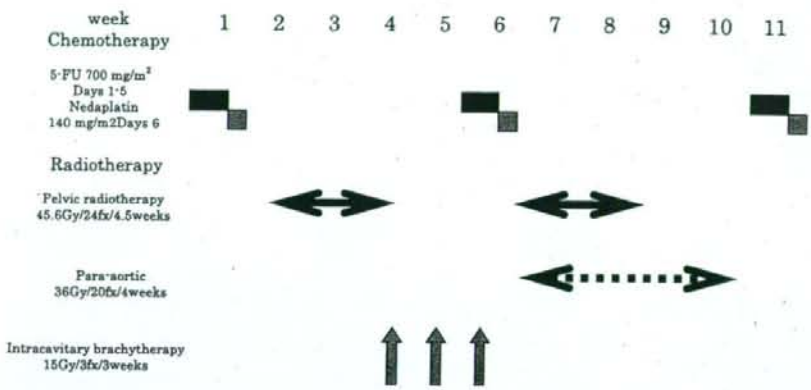

Fig. 1. Treatment scheme of the Phase I/II study of alternating chemoradiotherapy with nedaplatin and 5-FU in patients with advanced cervical carcinoma.

The previous doses before the MTD were considered the RD for the Phase II study.

Phase II component

The primary end point of the Phase II segment of the study was PFS of alternating chemoradiotherapy at the RD. The secondary end points were the OAS and the feasibility of this protocol. The same patient eligibility requirements, treatment schedules, dose and schedule modifications, and response and toxicity criteria as in the Phase I part of the study applied.

Treatment schedule and modifications

Chemotherapy. The treatment scheme is shown in Fig. 1. Prophylactic antiemetics therapy, using a 5-hydroxytryptamine type III receptor blocker and dexamethasone was given to all patients. The details of the administration of chemotherapy have been reported (9, 14). The dose of NDP was elevated to find MTD. MTD was decided to dose limiting toxicities as to Grade 4 of hematologic toxicities and Grade 3 of nonhematologic toxicities excluding diarrhea and nausea/vomiting. After deciding RD, patients were treated with RD of NDP.

Radiotherapy. Radiation therapy using a megavoltage photon beam (6–10 MV) by linear accelerator (CLINAC; Varian Medical Systems) was started 1–2 days after the end of systemic chemotherapy. The gross tumor volume (GTV) was defined as the total volume of the primary tumor evaluated by MRI scan (GTV primary) and the involved lymph nodes (GTV node) assessed by either MRI or abdominopelvic CT scan. A patient with lower vaginal involvement was arranged the adequate inferior margin of radiation field for tumor extent using iodine powder or metallic ring at planning setup. The clinical target volume (CTV) for involved lymph node (CTV node) was defined as the GTV node with 1cm margin in every direction. CTV pelvis was defined as entire uterus and regional pelvic lymph node according to the guidelines of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer consensus. CTV pan was defined as para-aortic lymph node region located up to upper border of the 12th thoracic spine. In general, CTV pan was included both inferior vena cava and abdominal aorta with 1-cm margin for every direction. The planning treatment volume (PTV) for involved lymph node (PTV node) was defined as the CTV node with a 0.5–1 cm margin. The PTV pelvis and PTV pan was defined as the CTV plus a 0.5–1 cm margin in all directions. Radiotherapy was given with daily 1.9 Gy fractions to 45.6 Gy in 24 fractions for PTV pelvis by biaxial dynamic conformal radiation therapy (11, 12, 15). If patients had a positive pelvic lymph node, they received 51.3 Gy of 27 fractions to PTV pelvis followed by an additional boost dose for PTV node up to a total dose of 57.3 Gy. Patients with positive pelvic lymph node or diagnosed as Stage III or more stage received a prophylactic para-aortic lymph node irradiation of 36 Gy with 20 fractions was planned by dynamic conformal radiotherapy (15). Patients with positive lymph node on para-aortic region receive an additional boost to PTV node up to 54 Gy. Radiotherapy was interrupted during the administration of the second and third cycles of chemotherapy. Intracavitary brachytherapy (ICBT) was accompanied with external beam radiotherapy (EBRT). Both EBRT for PTV primary and ICBT should not be treated in same day. During treatment course, MRI of the pelvis was taken to evaluate response. If primary tumor was thought to shrink to a sufficiently small volume within the high-dose volume of ICBT, brachytherapy was started. All EBRT was planned by radiation treatment planning system FOCUS or XiO (CMS Inc.). Before March 2002, the source of intracavitary brachytherapy was radium, and then was replaced with iridium. High-dose-rate ICBT was delivered using microselectron. The radiation therapy dose and schedule modifications for toxicity are shown in Table 1.

Statistical considerations

The survival time was defined as the period from the start of treatment to death or the last follow-up evaluation, and the PFS was defined as the period from the start of treatment to progression of disease or death, for any reason. The statistical differences between the two groups were assessed with the chi-square test. The OAS and PFS curves were calculated using the Kaplan-Meier method (16). The log–rank test (17) was used to compare survival curves. Cox-proportional hazards model (18) was used for a multivariate analysis.

RESULTS

Characteristics of patients

Between September 1998 and December 2004, 40 patients at the Aichi Cancer Center Hospital, Japan, were enrolled in this Phase I/II study. The patient characteristics of each group are shown in Table 2.

In the Phase I segment, 18 women were enrolled. In the Phase II segment, 22 women were enrolled using RD of NDP.

Phase I study

Dose escalation and toxicity. The principal toxicities observed in the Phase I study are summarized in Table 3. At the first dose level (100 mg/m^2), none of the 3 patients had DLT. At the second dose level (120 mg/m^2), 1 case of Grade 4 thrombocytopenia developed among the 6 patients. This dose level was considered safe, and the dose was increased to the next level. At the third dose level (140 mg/m^2), one case each of Grade 3 liver dysfunction and diarrhea developed among 6 patients. In next dose level (150 mg/m^2), two cases of neutropenia in 3 patients developed, then the MTD was determined to be 150 mg/m^2 and an RD of 140 mg/m^2 was used in the Phase II part.

Completion of therapy. As shown in Table 2, 23 of 40 patients were able to receive three cycles of chemotherapy. Four patients reduced their doses of NDP during the second cycle of chemotherapy. Twenty-three (58%) patients received the third cycle of systemic chemotherapy, but the NDP dose had to be reduced in 4 of these patients. Two patients received only a single cycle of chemotherapy because of toxicities. The 5-FU dose was not reduced in any patients in the Phase II part of the study. Delay or inability to administer the third cycle of chemotherapy was chiefly from hematologic toxicities.

Table 2. Patient characteristics and treatment contents

Factors	Number
Age (y)	54 (34–74)
Performance status	
0	4
1	36
T stage	
1b	
2a	2
2b	10
3a	3
3b	22
N stage	
0	15
I	25
FIGO stage	
I	3
II	11
III	21
IV	5
Maximum tumor size (mm)	61 (35–100)
Radiation theraphy	
EBRT	
Pelvic region (Gy)	53.6 (41.8–64.6)
Paraaortic region	36 (14.4–54)
OTT(days)	51 (34–78)
ICBT	
Source	
Radium	24
Iridium	16
A point dose	23.1 (7.5–27.6)
Fraction	2 (1–4)
Chemotherapy	
Dose of NDP (mg/m^2)	
100–120	9
140	28
150	3
Cycle of chemotherapy	
1	2
2	15
3	23

Table 3. Results of Phase I component

NDP (mg/m^2)	100	120	140	150	Total
Leukopenia	0/3	0/6	0/6	2/3	2/18
Anemia	0/3	0/6	0/6	0/3	0/18
Thrombocytopenia	0/3	1/6	0/6	0/3	1/18
Liver	0/3	0/6	1/6	0/3	1/18
Renal	0/3	0/6	0/6	0/3	0/18
Diarrhea	0/3	0/6	1/6	0/3	1/18
Emesis	0/3	0/6	0/6	0/3	0/18
Vomiting	0/3	0/6	0/6	0/3	0/18
Fever	0/3	0/6	0/6	0/3	0/18
Stomatitis	0/3	0/6	0/6	0/3	0/18
Total	0/3	1/6	2/6	2/3	5/18

A median dose of 53.6 Gy (range, 41.8–64.6 Gy) was administered to pelvic lesion by EBRT. All patients received ICBT using low-dose-rate or high-dose-rate ICBT. The median dose of sum of point A dose of ICBT was 23.1 Gy ranged from 7.5 to 27.6 Gy. All patients could be treated with planned pelvic radiotherapy including ICBT. The median dose of para-aortic region was 36 Gy (range, 14.4–54 Gy). Para-aortic irradiation stopped in 2 patients at 14.4 Gy and 18 Gy because of acute gastrointestinal toxicity. Five patients received an additional radiotherapy to involved para-aortic lymph node with a dose of 46–54 Gy using cone down technique.

Treatment outcomes

Response and survival. The following 22 patients were treated with dose level of RD. Between 1998 and 2004, 65 patients were treated with this protocol, and 40 patients of 65 were evaluated for treatment efficiency. The reasons for exclusion of 25 patients were patient's age, previous treatment before chemoradiotherapy, and refusal of chemotherapy. Thus we evaluated these 40 patients including Phase I study regarding to treatment outcome and feasibility. At the median follow-up of 61.8 months (range, 8.6–106.7 months), 10 patients had died of the disease, 3 were alive with the disease, and 27 were alive without disease.

The OAS and PFS rates at 5 years were 78.8% (95%CI, 65.6–92.1%) and 66.5% (95%CI, 51.4–81.6%), respectively.

Four patients had residual tumor or disease progression at the primary site, and 5 patients had relapses at the pelvic region with or without local failures. Eight patients had distant metastasis during the follow-up period. The OAS and PFS rates were not significantly different between patients received three cycles of chemotherapy and those with one or two cycles ($p > 0.05$).

Table 4. Adverse event of acute adverse event in alternating chemoradiotheraphy with all 40 patients

	1	2	3	4	% of toxicities Grade 3
Leukopenia	4	10	25	1	65
Neutropenia	4	14	14	5	47.5
Anemia	4	21	7	7	35
Thrombocytopenia	12	8	10	8	45
Liver	13	10	3	0	7.5
Renal	10	1	0	0	0
Diarrhea	14	15	9	2	27.5
Emesis	4	19	17	0	42.5
Vomiting	15	25	0	0	0
Fever	0	13	1	0	2.5

Toxicity

The toxicities observed in 40 patients during treatment and follow-up are shown in Table 4. The most common toxicity was leukopenia. Grade 3 or higher leukopenia and granulocytopenia occurred in 26 and 19 patients, respectively. Grade 3 or higher thrombocytopenia and anemia occurred in 18 and 14 patients, respectively. Grade 3 or higher diarrhea occurred in 11 patients. Significant increase of neutropenia and diarrhea was noted in patients with three cycles of chemotherapy compared to those of one or two cycles ($p < 0.05$). There was no treatment-related death. We experienced two cases of Grade 3 of urinary bladder and six Grade 2 of the rectum regarding to late adverse event. No patients developed with Grade 3 or higher of late rectal toxicity. Late toxicity of the rectum and bladder showed no significant difference between patients with three cycles of chemotherapy and those with one to two cycles.

Comparison of historical control group

Between 1986 and 1998, we treated 43 patients with radiotherapy alone who were thought to be eligible for this protocol criteria using staging workup including MRI. During this period, systemic chemotherapy is not generally planned in our institutes; the majority of patients visited during this period were recruited in this cohort. In addition, MRI study was routinely performed to evaluate tumor volumetry in this period. This group (*historical control group*) was compared with the ALCRT group. Patient's characteristics of both groups were summarized in Table 5. Age and radiation dose of the historical control group proved to be significantly higher compared with those of ALCRT ($p < 0.05$). Stage distribution and tumor size did not show a significant difference between the two groups, although tumor size of ALCRT group had a slightly larger than that of the historical control group. ALCRT group showed a tendency for larger ratio of patients with positive lymph node compared with that of the historical control group ($p = 0.07$).

OAS and PFS showed a significant improvement in ALCRT group by univariate analysis. The 5-year OAS rate of ALCRT group is 78.8% (95%CI, 65.6–92.1%) and that of the historical control group is 48.8% (95%CI, 33.9–63.8%; $p = 0.02$, Fig. 2). The 5-year PFS rate of ALCRT group is 66.5% (95%CI, 51.4–81.6%) and that of historical control group is 37.2% (95%CI, 22.8–51.7%; $p = 0.006$, Fig. 3).

Table 5. Patient characteristics of both protocol group and historical control group

Factor	Protocol group	Historical control
Age (median: y)	54*	67
Size (median: mm)	61	55
Pelvic radiation (mean: Gy)	53.6**	59.2
Stage III-IV (%)	65	69.8
Lymph node–positive (%)	62.5***	42.9

* $p < 0.0001$.
** $p = 0.017$.
*** $p = 0.07$.

In multivariate analysis, ALCRT also showed a significant reduction both death and disease progression (Table 6). Hazard ratio of the ALCRT group was 0.639 (95%CI, 0.41–0.96; $p = 0.03$) in OAS and 0.534 (95%CI, 0.35–0.81; $p = 0.002$) in PFS. Late adverse event according to bladder and rectum showed no significant increase in ALCRT group compared with those of historical control group ($p < 0.05$).

DISCUSSION

To the best of our knowledge, this is the first report of successful outcome of chemoradiotherapy using extended-field radiotherapy. The OAS and PFS rates at 5 years were 78.8% (95%CI, 65.6–92.1%) and 66.5% (95%CI, 51.4–81.6%), respectively. Our results of OAS and PFS are thought to be quite comparable to the reported data of concurrent chemoradiotherapy (5, 6, 19) (Table 7). Our protocol has shown acceptable treatment compliance without increasing late toxicities with relatively long follow-up (median, 61.8 months). In addition, our cohort has a higher proportion of both advanced clinical stage and lymph node involvement including para-aortic region compared with reported data (1, 5, 6, 19).

We believe dynamic conformal radiotherapy have a benefit to reduce toxicities especially for chemoradiotherapy setting

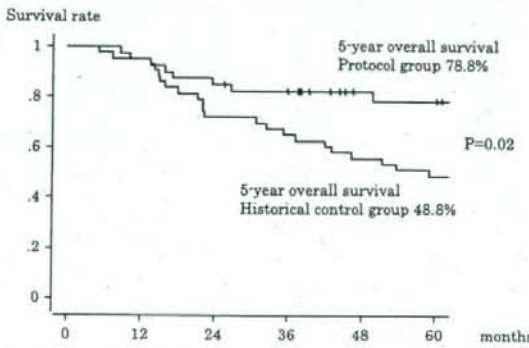

Fig. 2. Overall survival curves of groups of protocol treatment and historical control.

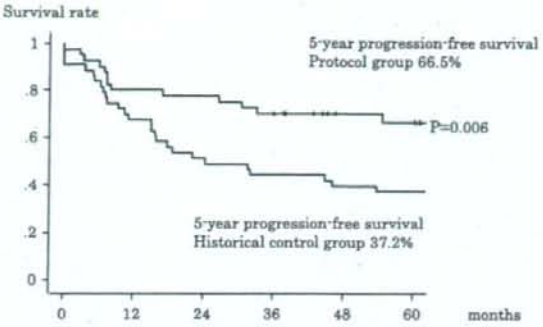

Fig. 3. Progression-free survival curves of groups of protocol treatment and historical control.

with large treatment volume such as extended-field radiotherapy (15, 20, 21). In many reports, researchers used a contiguous field technique for extended field treatment (22–26). This method had an advantage in a short treatment period and an accurate treatment volume. Sequential method such as ours is thought to have a deficit in longer treatment time and would have a potentially loss of disease control. Although patient number was small ($n = 5$), all patients with positive para-aortic disease are well controlled in our protocol. Thus we believe no apparent clinical disadvantage as to sequential radiotherapy for pelvic and para-aortic irradiation. There is another problem of sequential method as to field matching. Both pelvic and para-aortic field should be arranged carefully, because a gap between two fields had a potential risk of underdose or overdose. In this report, we did not experience both regional failure on gap area and late toxicity from excessive dose by overlapping. We also have reported acceptable outcome using sequential EBRT for para-aortic region in definitive and postoperative intent (15, 27). In these reports, para-aortic field was treated with four-field technique (27) or dynamic conformal radiotherapy (15) in sequential setting. In fact, many reports have failed to improve clinical results by simultaneous extended-field chemoradiotherapy (22–24). RTOG 0116 recruited patients with cervical carcinoma and high common iliac or para-aortic metastasis (22). Patients received extended contiguous field radiotherapy up to 54–59.4 Gy with concurrent administration of 40 mg/m^2 of weekly cisplatin. A total of 26 patients were entered, and

Table 6. Mulivariate analysis of several prognostic factor regarding to overall and progression-free survival

	Overall survival		Progression-free survival	
Factor (reference group)	Hazard ratio	p-value	Hazard ratio	p-value
Age (<62 y)	0.922	0.664	0.927	0.684
Stage (I–II)	1.10	0.600	1.073	0.673
Size (<60 mm)	1.10	0.597	1.409	0.049
Lymph node (no)	1.12	0.597	0.857	0.336
Modality (CRT)	0.639	0.031	0.534	0.0024

Table 7. Comparison clinical results of chemoradiotherapy with or without extended-field radiation

Author	Number	5-year survival	Toxicity (Grade 3 or more)
Varia	95	39 (3 y)	37.7
Grigsby	30	29 (4 y)	80
Maltefano	13	69	0
podczaski	33	31	6
Small	26	60 (18 months)	40
Present	40	78	5
chemoradiotherapy without extended field radiotherapy			
GOG85*	177	NS	4
GOG120			
Weekly CDDP	192	70	2.7
CDDP+5FU*	191	70	0.9
RTOG9001	193	73	13

Abbreviations: GOG = Gynecologic Oncology Group; CDDP = cisplatin; NS = not stated; * = same chemotherapy regimen; RTOG = radiation therapy oncology group.

developed 40% of late Grade 3/4 toxicity, including 8 patients requiring surgical intervention. Estimated OAS at 18 months was 60%. The majority of failure of these studies was based on low compliance from acute or late severe gastrointestinal toxicity. These reports also could not acquire comparable clinical results with standard chemoradiotherapy (22, 24). We reported promising clinical efficacy without increasing toxicity, so we believe sequential para-aortic irradiation should be taken into consideration in practice.

As for method of chemotherapy, cisplatin is now widely accepted as standard care for chemoradiotherapy for cervical cancer (2, 4, 6, 19). The GOG 120 study compared with definitive radiotherapy and hydroxyl-urea and concurrent chemoradiotherapy with cisplatin (6). In the GOG 120 study, two chemoradiotherapy arms were applied—such as weekly cisplatin and combination of 5FU and cisplatin (same arm of GOG 85). In recent report, there was no apparent benefit of addition of 5FU within both two arms, although dose of cisplatin varied much (100 mg/m^2 for the combined arm vs. 240 mg/m^2 for the weekly arm). In the RTOG 9001 study, 5-FU and cisplatin were used with concurrently in chemoradiotherapy arm. The sum of cisplatin of RTOG 9001 study was 225 mg/m^2. RTOG 9001 reported a subset analysis for Stage IB-II versus III-IV, statistical significance only for Stage IB-II subset was noted, leading some to suggest that chemoradiotherapy was not effective in more advanced disease stage (28). The update of RTOG 9001 demonstrated that, because the early stage of disease accrued to the protocol, a strong trend only was noted in the patients with more advanced disease (Stage III-IV) (5). Among three studies (GOG 85, GOG 120, RTOG 9001), the ratio of Stage III-IV disease ranged from 30% to 53.8%, and that of positive lymph node was 12.5–24%. In our cohort, the ratio of both advanced stage disease (III-IV: 65%) and positive lymph node was larger ratio (62.5%) compared with those reported study (4, 6, 19).

One of the reasons of our successful result regardless worse prognostic population of our ALCRT experience was sufficient dose intensity of systemic chemotherapy.

This method had an advantage of intensive drug administration because of minimizing acute toxicities, especially for mucosa and intestine; therefore, patients having potentially distant microscopic disease are thought to be better candidates for ALCRT. In previous report, major failure site of patient with Stage III disease in our institute was distant metastasis (12, 20), then we believe our treatment protocols are promising, especially for advanced disease and extended lymph node involvement with potentially hazards of para-aortic region. Using the ALCRT method, we could achieve high-dose administration (1.4 times higher than domestic standard dose of NDP) of a multidrug agent with successful compliance without increasing toxicity.

Finally, we have used NDP, the derivatives of cisplatin developed in Japan. This antitumor agent had a promising activity for cervical cancer (7, 8) and less toxicities of renal and gastrointestinal (29). We believe one of the reasons of our successful result of ALCRT was lower toxicity of NDP compared with cisplatin. In fact, our cohort showed no significant increase gastrointestinal toxicity and could archive a acceptable compliance of protocol compared with reported data using cisplatin (22). Again we should emphasize our reported effective outcomes of ALCRT with NDP for other malignancies (14, 30).

Our protocol seemed to have a promising advantage for patients with advanced disease or positive lymph node patients. However, this study has a definite limitation because of the retrospective comparison to historical matched control group. The several biases regarding patient selection and treatment content should be considered. In addition, our historical control group received radiotherapy alone, which was not present standard care.

But we believe that an acquired result of ALCRT was quite comparable, slightly better (78% vs. 70–73% in 5-year survival; Table 7) than those of standard chemoradiotherapy without para-aortic irradiation. Compared with their reported data, we should emphasize that our cohort had worse prognostic factors. To evaluate clinical efficacy of ALCRT, especially for more advanced disease or positive lymph node, properly randomized controlled trial comparing ALCRT with NDP with concurrent chemoradiotherapy using cisplatin should be tested in the future.

CONCLUSION

Using both dynamic conformational technique and ALCRT setting, extended-field radiation therapy could be successfully combined with intense multiagent chemotherapy. ALCRT is thought to significantly reduce both recurrence and mortality of patients with advanced cervical carcinoma, chiefly with Stage III or positive lymph nodes. We believed that our promising data of the Phase II study warranted advancing to Phase III study comparing ALCRT with NDP to standard concurrent chemoradiotherapy using cisplatin.

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Primary central nervous system lymphoma in Japan: Changes in clinical features, treatment, and prognosis during 1985–2004

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We have conducted nationwide surveys of primary central nervous system lymphoma (PCNSL) treated since 1985. In the present study, we newly collected data between 2000 and 2004 and investigated changes in clinical features and outcome over time. A total of 739 patients with histologically proven PCNSL undergoing radiotherapy were analyzed. Seventeen institutions were surveyed, and data on 131 patients were collected. These data were compared with updated data that were previously obtained for 466 patients treated during 1985–1994 and 142 patients treated during 1995–1999. Recent trends toward decrease in male/female ratio, increase in aged patients, and increase in patients with multiple lesions were seen. Regarding treatment, decrease in attempts at surgical tumor removal and increases in use of systemic chemotherapy and methotrexate (MTX)–containing regimens were observed. The median survival time was 18, 29, and 24 months for patients seen during 1985–1994, 1995–1999, and 2000–2004, respectively, and the respective 5-year survival rates were 15%, 30%, and 30%. In groups seen during 1995–1999 and during 2000–2004, patients who received systemic or MTX-containing chemotherapy had better prognosis than those who did not. Multivariate analysis of all patients seen during 1985–2004 suggested the usefulness of MTX-containing chemotherapy as well as the importance of age, lactate dehydrogenase level, and tumor multiplicity as prognostic factors. Thus, this study revealed several notable changes in clinical features of PCNSL patients. The prognosis improved during the last 10 years. Advantage of radiation plus chemotherapy, especially MTX-containing chemotherapy, over radiation alone was suggested. *Neuro-Oncology 10, 560–568, 2008 (Posted to Neuro-Oncology [serial online], Doc. D07-00151, June 17, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-028)*

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Primary central nervous system lymphoma (PCNSL) is becoming one of the most important tumors in neuro-oncology. It was rare previously but has increased during the last two decades.[1] With the increase in incidence, clinical features, diagnostic procedures, and physicians' recognition and treatment policy for the disease seemed to have changed considerably. With widespread recognition of the disease and improvement

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of diagnostic modalities, the disease may be diagnosed more readily than before. Treatment policy appears to have also changed considerably with respect to the role of surgical resection and the use of chemotherapy and radiotherapy.[2,3] Unfortunately, however, randomized studies on treatment have been scarce, and uncertainties still remain regarding the efficacy of chemotherapy, appropriate chemotherapy regimens, and appropriate use of radiation therapy.[2–5] Many studies using high-dose methotrexate (MTX)–containing chemotherapy have reported favorable treatment outcome,[6–17] whereas other studies have not necessarily supported the results.[1,18–20] Also, high toxicity of an MTX-containing regimen has been reported.[21]

In view of the relative rarity but importance of the disease, we have conducted nationwide studies on it. The purposes of the studies were to analyze clinical features and treatment characteristics and evaluate patient outcomes. The first study was conducted for the patients seen between 1985 and 1994 by Hayabuchi et al.[22] The next studies were conducted for those seen between 1995 and 1999 by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) Lymphoma Study Group (JLSG) and the Chubu Radiation Oncology Group (CROG) separately.[23,24] Recently, we collected new data on 131 patients seen between 2000 and 2004. In this study, we analyzed all these patients from the previous and recent surveys. Follow-up data were updated as far as possible also for the patients reported in the previous studies.

Materials and Methods

Subjects of all of the surveys were patients with histologically proven PCNSL who received radiation therapy. Patients who were suspected of having secondary CNS lymphoma were excluded at each institution. Those who did not complete planned radiotherapy were included. Clinical characteristics, treatment, and prognosis of each patient shown in the Results section were asked using a detailed questionnaire. Data on 466 patients had been collected from 62 institutions for patients seen between 1985 and 1994. For the period 1995–1999, a total of 142 patients were collected from 25 institutions with the two surveys conducted by JLSG and CROG; the results were published separately,[23,24] but in the present study, the data from the two surveys were combined. Recently, data on 131 patients seen between 2000 and 2004 were collected from 17 institutions belonging to JLSG or CROG. Submission of the data was approved at each institution. Thus, a total of 739 patients with histologically proven PCNSL were the subject of this study. Results for HIV titer were negative in all patients who had had the examination, and no other patients were considered to have AIDS-related PCNSL. For the most recent survey, 76% of the institutions had also been surveyed for the period 1995–1999, and 68% of the institutions surveyed for the period 1995–1999 had been included in the survey for the period 1985–1994.

Extent of surgical resection had not been asked in the survey for 1985–1994, but it was done in the subsequent surveys. Other items were common to all surveys, but because of the nature of the survey, a number of the items were unanswered by the investigators. Various chemotherapy regimens had been used, but for convenience of analysis, they were categorized as high-dose (>1 g/m^2) MTX-containing regimens or other regimens. Details of other chemotherapy regimens used during 1985–1999 were described previously;[22–24] 58% of non-MTX-containing regimens were cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) or similar regimens.[25] In the most recent period (2000–2004), 68% of non-MTX-containing regimens were CHOP or CHOP-based regimens and 18% were a dexamethasone-etoposide-ifosfamide-carboplatin (DeVIC) regimen. The remaining 14% were miscellaneous ones.

Differences in patient, tumor, and treatment characteristics between groups were examined by Fisher's exact test or *t*-test. Survival rates were calculated from the date of starting radiotherapy using the Kaplan-Meier method, and differences in pairs of survival curves were examined by the log-rank test. Multivariate analysis of prognostic factors was carried out using the Cox proportional hazards model. In doing multivariate analysis, patients were divided into two groups, and all the parameters were entered as dichotomous variables. All statistical analyses were carried out using computer programs, StatView Version 5 (SAS Institute Inc., Cary, NC, USA) and HALWIN (Gendaisuugakusha, Kyoto, Japan).

Results

Table 1 shows patient and tumor characteristics in the three groups treated during the three periods. Several remarkable changes were noted. There were more female patients in the period 2000–2004 than in the preceding period; the male/female ratio was near unity in the most recent series. Also, the median patient age was higher in the period 2000–2004 than in the preceding period. The proportion of patients with multiple tumors increased to 55% in the most recent series, whereas it was 38% and 40% in the previous series. Other patient and tumor characteristics did not differ significantly between the two pairs of groups.

Table 2 shows changes in treatment. Radiotherapy characteristics were similar in all three groups. Nearly 90% or more of the patients were treated with whole-brain irradiation with or without focal boost, and the mean total and whole-brain doses were 47–49 Gy and 36–38 Gy, respectively. Whole-spinal irradiation was employed in less than 10% of the patients throughout the three periods. However, there were steady increases in the proportion of patients undergoing systemic chemotherapy. Particularly, MTX-containing regimens have been increasingly used (in 72% of patients undergoing chemotherapy in the most recent period).

Figure 1 shows overall survival curves for the three groups. Patients treated between 1995 and 1999 and

Table 1. Patient and tumor characteristics

Characteristic		Period (Year) 1985–1994	1995–1999	2000–2004	p^*
Gender	Male (%)	276/466 (59)	96/142 (68)	67/131 (51)	0.077 0.0066
Age (years)	Median (range)	60 (5–86)	59 (15–93)	65 (30–90)	0.49 0.017
Performance status	3, 4 (%)	209/438 (48)	55/138 (40)	37/128 (29)	0.12 0.071
Lactate dehydrogenase	High (%)	103/267 (39)	42/113 (37)	32/121 (26)	0.82 0.092
B symptom	Yes (%)	33/418 (7.9)	13/127 (10)	6/122 (4.9)	0.47 0.15
Phenotype	T cell (%)	20/234 (8.5)	6/115 (5.2)	2/120 (1.7)	0.29 0.16
Tumor number	Multiple (%)	175/460 (38)	56/140 (40)	72/131 (55)	0.69 0.015
Tumor size (cm) at diagnosis	Mean ± SD	3.8 ± 1.4	3.8 ± 1.6	3.8 ± 1.2	0.71 0.96
CSF dissemination	Yes (%)	56/422 (13)	23/122 (19)	20/126 (16)	0.14 0.62

Abbreviation: CSF, cerebrospinal fluid.

*First and second p values are for comparison between 1985–1994 and 1995–1999 data and between 1995–1999 and 2000–2004 data, respectively. B symptom: fever (>38°C for 3 consecutive days), weight loss (>10% in 6 months), and/or drenching night sweats.

Table 2. Treatment characteristics

Characteristic		Period (Year) 1985–1994	1995–1999	2000–2004	p^*
Surgery	Biopsy (%)	—	71/142 (50)	83/131 (63)	—
Radiotherapy course	Not completed	25/466 (5.4)	6/142 (4.2)	5/131 (3.8)	0.028 0.67
Brain radiation field	Partial brain (%)	37/466 (7.9)	12/142 (8.5)	15/131 (11)	1.0 0.86
Spinal radiation	Yes (%)	37/445 (8.3)	8/142 (5.6)	4/131 (3.1)	0.42 0.37
Total dose (Gy)	Mean ± SD	48.4 ± 11.2	48.7 ± 10.8	47.0 ± 9.0	0.38 0.78
Whole-brain dose (Gy)	Mean ± SD	35.6 ± 13.7	37.5 ± 8.0	36.4 ± 6.0	0.20 0.082
I.v. chemotherapy	Yes (%)	212/420 (50)	87/142 (61)	99/131 (76)	0.43 0.032
MTX-containing regimen	Yes (%)	47/212 (22)	27/87 (31)	71/99 (72)	0.013 0.14
I.t. chemotherapy	Yes (%)	42/415 (10)	16/142 (11)	8/131 (6.1)	<0.0001 0.75
					0.14

Abbreviations: i.v., intravenous; MTX, methotrexate; i.t., intrathecal.

*First and second p values are for comparison between 1985–1994 and 1995–1999 data and between 1995–1999 and 2000–2004 data, respectively.

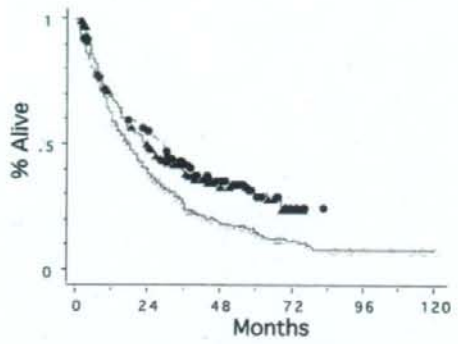

Fig. 1. Survival curves for patients with primary CNS lymphoma seen in 1985–1994 (○, $n = 466$), in 1995–1999 (●, $n = 142$), and in 2000–2004 (▲, $n = 131$). The second and third groups had significantly better survival rates than the first group ($p = 0.0004$ and 0.0033, respectively).

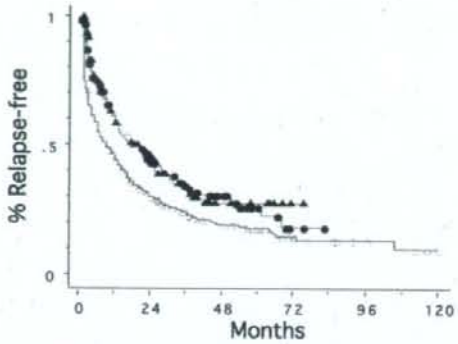

Fig. 2. Relapse-free survival curves for patients with primary CNS lymphoma seen in 1985–1994 (○, $n = 408$), in 1995–1999 (●, $n = 137$), and in 2000–2004 (▲, n = 127). The second and third groups had significantly better relapse-free survival rates than the first group ($p = 0.0020$ and 0.0010, respectively).

those treated between 2000 and 2004 had significantly better survival rates than those seen between 1985 and 1994 ($p = 0.0004$ and 0.0033, respectively); median survival time increased from 18 months to 29 and 24 months, respectively. The 5-year survival was 15%, 30%, and 30% for the periods 1985–1994, 1995–1999, and 2000–2004, respectively. Figure 2 shows relapse-free survival curves for the patients with known data on recurrence in the three periods. Relapse-free survival of the patients was also better in the more recent two periods than in the period 1985–1994 ($p = 0.0020$ and 0.0010, respectively). The median time to recurrence was 9, 18, and 20 months, and the 5-year relapse-free survival was 18%, 26%, and 28% for the periods 1985–1994, 1995–1999, and 2000–2004, respectively.

Table 3 summarizes survival data in the three groups according to patient- and tumor-related potential prognostic factors. In all the study periods, patients with age <60 years, WHO performance status (PS) of 0–2, or normal lactate dehydrogenase (LDH) level had significantly higher survival rates. Patients without B symptom or with a single tumor had better prognoses than those with B symptom or with multiple tumors, respectively, in the groups treated between 1985 and 1994 and between

Table 3. Survival data according to patient or tumor-related potential prognostic factors

		1985–1994				1995–1999				2000–2004			
Prognostic Factor		*n*	MST (Months)	5-YSR (%)	*p*	*n*	MST (Months)	5-YSR (%)	*p*	*n*	MST (Months)	5-YSR (%)	*p*
Gender	Male	276	17	17	0.92	96	30	31	0.23	67	17	29	0.40
	Female	190	20	13		46	23	27		64	26.5	32	
Age	<60	216	22	27	<0.0001	75	39	40	0.0011	44	68	53	0.0001
	≥60	250	14	5.2		67	16	17		87	17	18	
Performance status	0–2	229	24	20	<0.0001	83	37	32	0.0024	91	26.5	40	0.0010
	3, 4	209	12	10		55	12	27		37	13	5.8	
B symptom	Yes	33	10	0	0.030	13	13	15	0.0093	6	19	21	0.72
	No	385	18	17		116	35	34		116	25	36	
Lactate dehydrogenase	Normal	164	22	26	0.0007	71	38	36	0.016	89	35	37	0.0024
	High	103	14	5.7		42	16	25		32	13	15	
Tumor number	Single	285	22	18	0.0012	84	39	36	0.026	59	24	38	0.72
	Multiple	175	12	11		56	23	21		72	22	24	
Tumor size (cm)*	≤4 cm	204	19	14	0.84	69	29	29	0.38	61	26.5	31	0.21
	>4 cm	189	17	19		63	37	34		69	18.5	31	
CSF dissemination	Yes	56	10	14	0.039	23	50	33	0.50	20	32	37	0.74
	No	366	19	16		99	29	32		106	24.5	31	

Abbreviations: MST, median survival time; 5-YSR, 5-year survival rate; CSF, cerebrospinal fluid.

*Maximum tumor diameter at diagnosis.

Table 4. Survival data according to treatment-related factors

Prognostic Factor		1985–1994				1995–1999				2000–2004			
		n	MST (Months)	5-YSR (%)	*p*	*n*	MST (Months)	5-YSR (%)	*p*	*n*	MST (Months)	5-YSR (%)	*p*
Surgical resection	Extensive	—	—	—	—	32	28	32	0.99	21	23	27	0.45
	Nonextensive	—	—	—		104	29	29		105	24	29	
Radiation field	Whole brain	405	19	15	0.72	126	29	29	0.72	111	22	26	0.17
	Partial brain	34	16	17		10	35	38		15	37	47	
Spinal radiation	Yes	36	24	19	0.16	8	—	50*	0.76	3	—	67	0.23
	No	384	18	15		128	29	29		123	23	27	
Total dose (Gy)	<50	134	18	17	0.97	35	30	34	0.79	45	26	35	0.71
	≥50	305	8	16		101	29	29		81	23	27	
Whole-brain dose (Gy)	<40	156	18	18	0.43	54	30	32	0.68	54	36	36	0.048
	≥40	283	18	14		82	29	27		72	18.5	22	
I.v. chemotherapy	Yes	202	20	16	0.30	85	39	39	<0.0001	95	26.5	39	0.0006
	No	192	16	17		51	14	14		31	14.5	7.5	
MTX-containing chemotherapy	Yes	46	20	19	0.49	25	NR	54	0.0039	67	29	47	0.0016
	No	348	18	16		111	25	24		59	16.5	12	
I.t. chemotherapy	Yes	39	16	20	0.78	15	—	58	0.13	7	24	43	0.52
	No	350	19	16		114	27	26		119	23	27	

Abbreviations: MST, median survival time; 5-YSR, 5-year survival rate; i.v., intravenous; MTX, methotrexate; NR, not reached; i.t., intrathecal.

*4-year survival rate.

1995 and 1999, but the trends were not seen in the most recent series.

To analyze the influence of treatment-related factors on outcome, patients who did not complete radiotherapy (receiving less than 30 Gy) and died soon were excluded. Table 4 shows survival data according to the treatment-related factors; no factors were found to be associated with improved prognosis throughout all three periods. In groups treated during 1995–1999 and during 2000–2004, patients receiving systemic chemotherapy had better survival rates than those treated with radiation alone, and those who received MTX-containing chemotherapy had better prognosis than those who did not. However, these phenomena were not observed in patients treated during the preceding decade. In the most recent series, patients receiving whole-brain doses less than 40 Gy (including those treated with partial-brain fields alone) did better than those receiving higher doses. No other treatment-related factors were found to be associated with prognosis in univariate analysis. Figure 3 shows survival curves for patients receiving or not receiving chemotherapy during the three periods. In the two more recent periods, patients receiving chemotherapy had better survival rates than those receiving radiation alone ($p < 0.0001$ and $= 0.0006$, respectively). Figure 4 shows survival curves according to the chemotherapy regimen (with or without high-dose MTX). Although there were no differences by the use of MTX, there was a trend toward improved survival in patients undergoing high-dose MTX-containing chemotherapy during the period 1995–1999 ($p = 0.060$).

To further analyze the effect of chemotherapy, patients seen during 1995–1999 and 2000–2004 were combined and those with ages >70 years and PS 3 or 4 were excluded in addition to those receiving radiation doses of less than 30 Gy, because these patients are often not indicated for intensive systemic chemotherapy. Figure 5 shows survival curves for patients with or without chemotherapy and according to the chemotherapy regimens. In this selected group of patients, those receiving systemic chemotherapy had markedly better survival rates than those receiving radiation alone ($p = 0.0004$), and those receiving MTX-containing chemotherapy had better survival than those receiving other regimens of chemotherapy ($p = 0.049$). However, in patients seen during 1995–2004 with ages >70 years and/or PS 3 or 4 who received radiation doses of 30 Gy or higher, those receiving systemic chemotherapy had better survival rates than those receiving radiation alone (median survival: 19.5 vs. 8.5 months; 5-year survival: 24% vs. 4.9%; $p = 0.010$), whereas those receiving MTX-containing chemotherapy and those receiving other regimens had similar prognosis (median survival: 22 vs. 16.5 months; 5-year survival: 32% vs. 20%; $p = 0.57$).

Multivariate analyses were carried out for potential prognostic factors that were significant in univariate analyses (Table 5). Analyses were carried out for patients seen during 1995–1999 and 2000–2004 and for all the patients combined. Multivariate analysis for patients during 1985–1994 was carried out previously.[22] In the patient group seen between 1995 and 1999, lower age, better PS, absence of B symptom, and single tumor num-

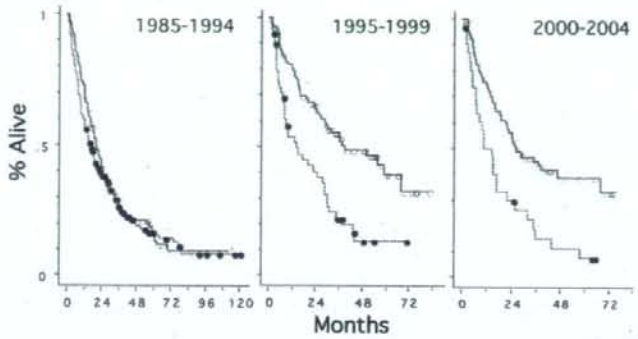

Fig. 3. Survival curves for patients with or without systemic chemotherapy. ○: chemotherapy (+) (n = 202, 85, and 95 for the three periods, respectively); ●: chemotherapy (–) (n = 192, 51, and 31 for the three periods, respectively). The difference was significant in the second and third groups (p = <0.0001 and 0.0006, respectively).

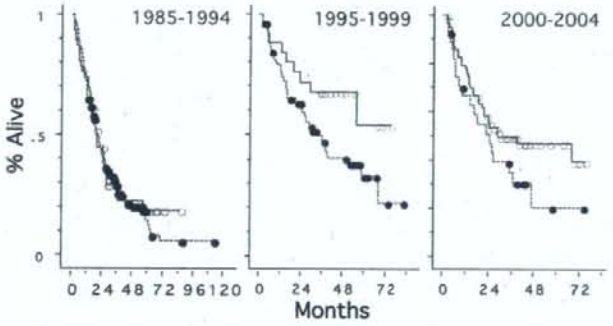

Fig. 4. Survival curves according to chemotherapy regimens. ○: high-dose methotrexate-containing regimens (n = 46, 25, and 67 for the three periods, respectively); ●: other regimens (n = 156, 60, and 28 for the three periods, respectively). The p values were 0.66, 0.060, and 0.13, respectively, for the three periods.

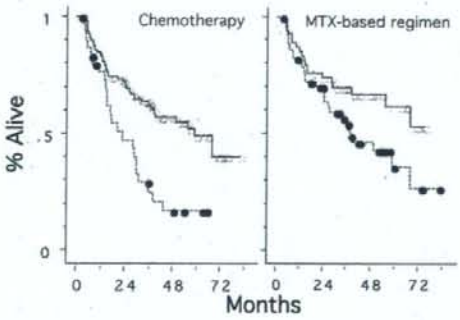

Fig. 5. Survival curves for patients with or without chemotherapy and according to chemotherapy regimens in patients seen between 1995 and 2004 with WHO performance status of 0–2 and ages <70 years receiving radiation doses of 30 Gy or higher. Left panel, ○: chemotherapy (+) (n = 108); ●: chemotherapy (–) (n = 31); p = 0.0004. Right panel, ○: high-dose methotrexate-containing regimens (n = 56); ●: other regimens (n = 52); p = 0.049.