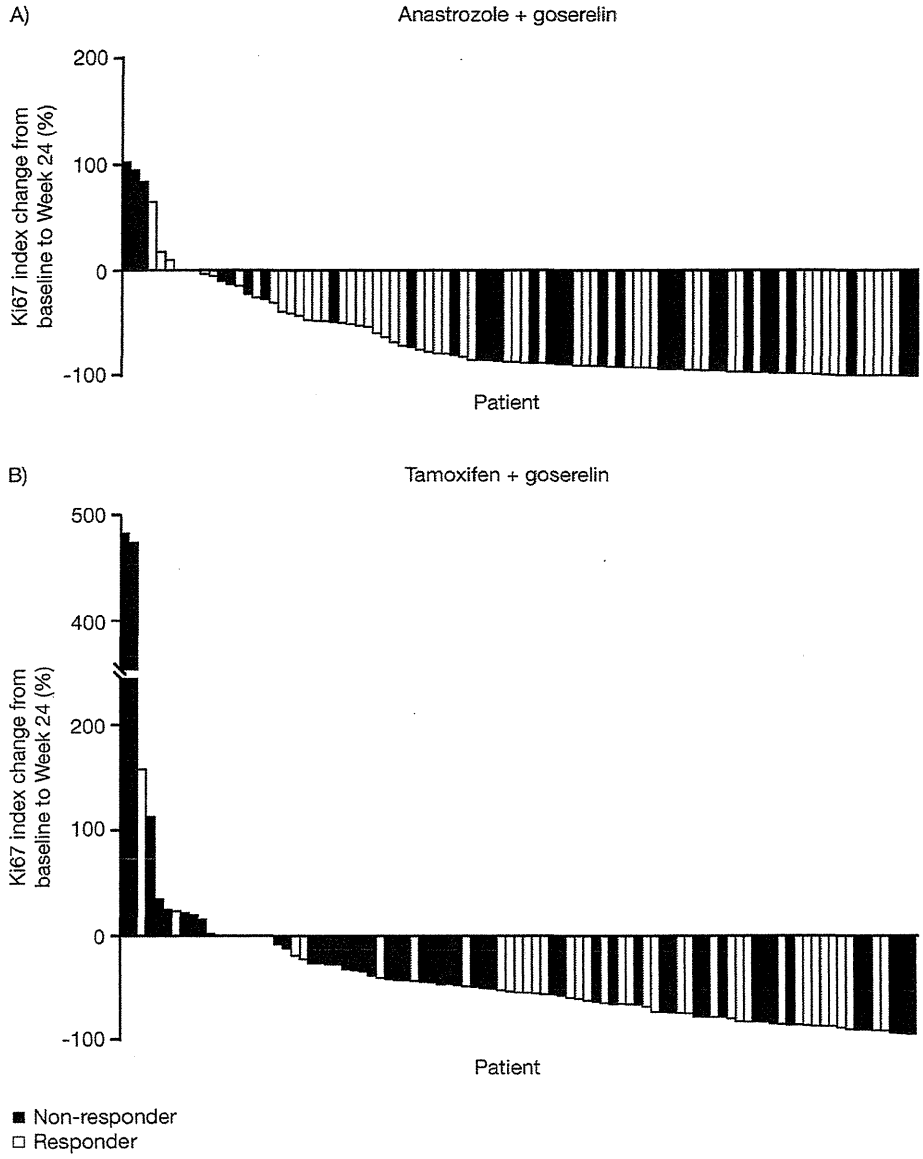

Figure 3. This is a waterfall plot of reductions in nuclear antigen Ki-67 levels in (A) the anastrozole plus goserelin treatment group and (B) the tamoxifen plus goserelin treatment group. Magnetic resonance imaging or computed tomography was used to measure responses. Responders were defined as those patients who had a complete or partial response during the 24-week treatment period.

the parallel adjuvant trial by the Austrian Breast and Colorectal Cancer Study Group (ABCSG) did not reflect outcomes related to the Ki-67 changes we observed: Results from the ABCSG-12 study indicated that there was no difference in disease-free survival between patients who received anastrozole versus tamoxifen (hazard ratio, 1.08; 95% CI, 0.81-1.44; $P = .591$).[26] The reason for this difference is not clear, although there were differences in the baseline characteristics of patients in each study: the STAGE study assessed a more hormone-dependent phenotype of tumor (ER-positive/HER2-negative in the STAGE study vs ER-positive/HER2-negative and ER-positive/HER2-positive in the ABCSG-12 trial), and the proportion of women with a body mass index >25 kg/m^2 was lower in the STAGE study (17% vs 33%). The ABCSG-12 group did not assess Ki-67 levels. It is also interesting to note that, as recently pointed out by Goncalves et al,[27] in our study, serum estradiol suppression

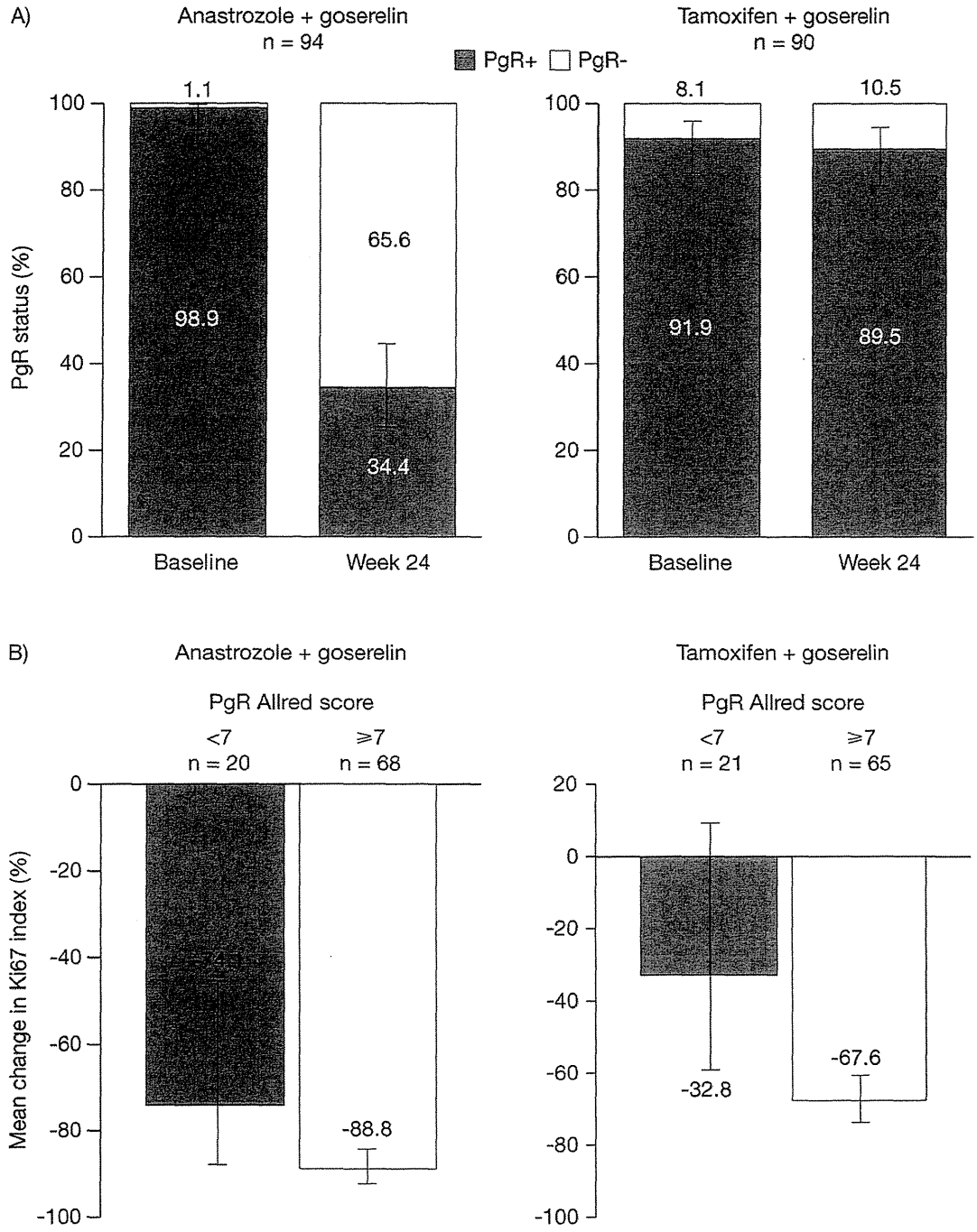

Figure 4. (A) Progesterone receptor status is illustrated at baseline and at 24 weeks. (B) Changes in the Ki-67 index and the baseline PgR Allred score are illustrated. PgR-positive (PgR+) indicates an Allred score >3; PgR-negative (PgR−), an Allred score <2.

appeared to decrease at week 24 compared with week 4, although the suppression was not statistically significant. This suggests the possibility of a gradual tachyphylaxis of the estrogen-suppressing effects of combined goserelin and anastrozole treatment, which potentially may explain the difference in outcomes between the ABCSG-12 and STAGE studies. However, further investigations would be required to confirm this.

TABLE 2. Preoperative Endocrine Prognostic Index Score

Treatment Group	No. of Patients	PEPI Score: No. of Patients (%)		
		0	1-3	≥4
Anastrozole plus goserelin	84	28 (33.3)	38 (45.2)	18 (21.4)
Tamoxifen plus goserelin	79	9 (11.4)	41 (51.9)	29 (36.7)
P for anastrozole vs tamoxifen		—	—	.002

Abbreviation: PEPI, Preoperative Endocrine Prognostic Index.
[a]*P* values were determined using the chi-square test.

In the current study, the best overall tumor response was superior with anastrozole compared with tamoxifen, irrespective of the baseline Ki-67 index. Within the anastrozole treatment group, we observed that the best overall tumor response was significantly better in patients who had a baseline Ki-67 index ≥20% versus patients who had a baseline Ki-67 index <20%. However, in the anastrozole group, we observed a numerically lower histopathologic response in patients who had a baseline Ki-67 index ≥20% compared with those who had a baseline Ki-67 index <20%. It was reported previously that baseline Ki-67 expression was not associated with outcome after neoadjuvant endocrine treatment (including anastrozole, letrozole, and tamoxifen) in ER-positive, postmenopausal women who had breast cancer.[19,25]

There was no apparent relation between a reduction in the Ki-67 index for responders and nonresponders in either treatment group. Although there tended to be more nonresponders among patients in the tamoxifen group who had less of a reduction in the Ki-67 index, the Spearman rank-correlation between the percentage change in the Ki-67 index and the best percentage change in greatest tumor dimension for the tamoxifen group was a modest 0.314. This observation is essentially consistent with what was reported previously by Dowsett et al, who conducted a similar analysis of postmenopausal patients who received neoadjuvant tamoxifen, anastrozole, and the tamoxifen/anastrozole combination.[28] This variation in the Ki-67 index change between responders and nonresponders indicates that the mechanism of estrogen-dependent growth is heterogeneous among breast tumors. Tumor growth is determined by a balance between cell proliferation and apoptosis. Stimulation of cell proliferation by estrogen may be dominantly implicated in tumor growth in some tumors, whereas inhibition of apoptosis by estrogen may be dominantly implicated in other tumors. Thus, a responder does not necessarily have a greater reduction in the Ki-67 index compared with a nonresponder if apoptosis is induced more strongly in the former than the latter after treatment.

In the neoadjuvant setting, endocrine therapy has demonstrated greater (or equivalent) efficacy in postmenopausal women with a lower Ki-67 index.[29,30] In contrast, in our study, both anastrozole and tamoxifen produced greater response rates in premenopausal women with a higher Ki-67 index. It is therefore possible that the main pathways of proliferative stimulation (and the effectiveness of endocrine treatments) may differ between premenopausal and postmenopausal women with ER-positive breast cancer, according to their level of Ki-67 expression. In general, high Ki-67 expression is traditionally is believed to offer a poor prognosis and is predictive of response to chemotherapy regimens.[31] However, our results suggest that endocrine therapy has at least comparable effectiveness for premenopausal patients with ER-positive breast cancer who have a high Ki-67 index.

No correlation could be determined between a change in the Ki-67 index and baseline ER status in either treatment group. However, the number of patients who were identified as PgR-positive decreased at week 24 in the anastrozole treatment group, an effect that was not observed in the patients who received tamoxifen plus goserelin. PgR expression also was reduced under neoadjuvant AI treatment for breast cancer in the ABCSG 17 study, although it remains to be determined whether the down-regulation of PgR may be used as a marker of clinical efficacy.[32] In our study, the reason why the positive rate of PgR was reduced in the anastrozole plus goserelin arm compared with the tamoxifen plus goserelin arm is most likely because of the estrogenic action of tamoxifen, which would induce PgR expression.

Although there may be a potential correlation between a reduction in Ki-67 and the baseline PgR Allred score in patients who receive anastrozole plus goserelin versus tamoxifen plus goserelin, further analyses will be required to determine whether a Ki-67 reduction in patients with high baseline PgR expression translates into a clinical benefit.

After treatment with anastrozole, a lower proportion of patients had a PEPI score ≥4 (indicating a high risk of

recurrence) compared with the tamoxifen treatment group. The PEPI model has been validated previously and has indicated significant differences in recurrence-free survival in the adjuvant setting between 3 PEPI risk groups (PEPI risk scores of 0, 1-3, and ≥4), with a PEPI score of 0 indicating a very low risk of relapse.[25] Data from the adjuvant treatment setting will provide added knowledge for the individualization of future adjuvant treatments after neoadjuvant therapy for breast cancer.

Currently, very little is known about the prognostic effect of Ki-67 in premenopausal women. However, in 1 recent study, the prognostic significance of Ki-67 was investigated in women with ER-positive breast cancer who had received short-term presurgical tamoxifen, and Decensi and colleagues reported that the Ki-67 response was a good predictor of recurrence-free survival and overall survival.[33]

To our knowledge, this is the first randomized study to investigate the potential of Ki-67 as a clinical biomarker for AI efficacy in premenopausal women with ER-positive breast cancer. It has been demonstrated that a reduction in Ki-67 expression as a result of neoadjuvant AI treatment can be a potentially useful marker of improved surgical outcomes in postmenopausal women with ER-positive breast cancer, and such a reduction has been identified as predictive of favorable outcomes in the adjuvant treatment period.[34] A reduction in Ki-67 expression during neoadjuvant treatment reportedly was greater with anastrozole versus tamoxifen in postmenopausal women who had ER-positive breast cancer,[18] and a parallel result also was observed in the corresponding adjuvant trial, in which recurrence-free survival also was greater for those who received anastrozole.[8] Yet another similar result was observed for letrozole, in which a greater Ki-67 reduction was observed compared with tamoxifen in the neoadjuvant setting.[35] Greater clinical effectiveness also was observed for letrozole in the neoadjuvant setting, both in terms of the objective response rate and the rate of breast-conserving surgery.[36]

In conclusion, tumor response was greater with anastrozole compared with tamoxifen, regardless of the baseline Ki-67 index, in premenopausal women who received goserelin as neoadjuvant therapy for ER-positive, early stage breast cancer. The current results indicate that endocrine therapy may offer a more tolerable treatment option than cytotoxic chemotherapy as neoadjuvant treatment for these patients, and further studies of the anastrozole plus goserelin treatment combination in this setting are warranted.

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CONFLICT OF INTEREST DISCLOSURES

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Diffusion pattern of low dose rate brachytherapy for prostate cancer in Japan

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Permanent implant brachytherapy for prostate cancer using iodine-125 seeds was adopted in Japan in 2003. Here, we report on the diffusion pattern of this treatment in Japan since 2003. We examined the annual numbers of prostate cancer patients per hospital in Japan, who were treated with iodine-125 seed implant brachytherapy with or without external beam radiation therapy between 2003 and 2011. The hospitals were excluded from the count if brachytherapy was begun in a hospital within the given year, and thus was only available for part of the year. In 2004, 269 patients were treated by brachytherapy at only two hospitals. However, the numbers increased rapidly. A total of 1412 patients were treated at 23 hospitals in 2005, 2783 patients were treated at 83 hospitals in 2008, and 3793 patients were treated at 109 hospitals in 2011. The mean/median numbers of patients treated per hospital were 61.4/42 in 2005, 33.5/25 in 2008, and 35.0/24 in 2011. The number of hospitals where 24 or fewer patients were treated in a year increased. On the other hand, the number of hospitals with a volume of >48 patients per year was stable. Because a relationship between provider volume and outcomes following oncological procedures was shown, a careful evaluation of the effectiveness of permanent implant brachytherapy for prostate cancer is needed. (*Cancer Sci*, doi: 10.1111/cas.12168, 2013)

When a medical technology, the usefulness of which has been established, is adopted in a country, how does the technology diffuse into medical practice? The speed and degrees of the diffusion depend upon many factors: consumer demand, promotional efforts of technology manufacturers, medical education, health insurance and payment systems, and governmental regulatory policies.[1]

Permanent implant brachytherapy for prostate cancer using iodine-125 (I-125) seeds was adopted in Japan in 2003.[2] The advantages of brachytherapy had been well recognized,[3] and the expectation for treatment was very high among Japanese urologists and radiation oncologists. In addition, the Cancer Control Act was approved in June 2006. Based on this law, the Basic Plan to Promote Cancer Control Programs was approved. One of its basic concepts is the equalization of cancer medical services including radiation therapy. This basic plan has stimulated the installation of new radiation therapy equipment at core hospitals.

In this study, we report on the diffusion pattern of permanent implant brachytherapy for prostate cancer in Japan since 2003, focusing in particular on the changes in the annual numbers of patients treated by brachytherapy per hospital since 2003.

Materials and Methods

We examined the annual numbers of prostate cancer patients per hospital in Japan, who were treated with I-125 seed implant brachytherapy with or without external beam radiation therapy. The use of palladium-103 (Pd-103) seeds, which is common in the United States, is not permitted in Japan. To elucidate the actual number of patients treated in a year, the hospitals were excluded from the count if brachytherapy was begun in a hospital within the given year, and thus was only available for part of the year. Because brachytherapy using I-125 seeds was adopted in Japan in 2003, the annual numbers of patients treated with brachytherapy between 2004 and 2011 were examined. These data were estimated from the database by Japanese Prostate Permanent Seed Implantation Study Group.[4] In Japan, I-125 seeds are supplied from two radiation source supply companies to medical institutions via the Japan Radioisotope Association (JRIA). Their database was also used to confirm the estimation.

Results

The total estimated number of patients treated with brachytherapy at hospitals where more than 1 year had passed since brachytherapy was first made available is shown in Table 1. In 2004, 269 patients were treated by brachytherapy only in two hospitals. However, the numbers increased rapidly. A total of 1412 patients were treated at 23 hospitals in 2005, 2783 patients were treated at 83 hospitals in 2008, and 3793 patients were treated at 109 hospitals in 2011.

Figure 1 shows the number of patients treated per hospital in 2005, 2008, and 2011. The mean/median number of patients treated per hospital was 61.4/42 in 2005, 33.5/25 in 2008, and 35.0/24 in 2011. Almost half of the patients in Japan were treated at the top six hospitals in 2005, at the top 18 hospitals in 2008, and at the top 22 hospitals in 2011. The number of hospitals in which 24 or fewer patients were treated in a year (i.e., two patients per month) was four in 2005, 40 in 2008, and 60 in 2011.

Figure 2 shows the distribution of the annual number of patients treated with brachytherapy per hospital from 2004 to 2011. The percentage of hospitals is also shown according to the number of patients per year in Table 1. The number of hospitals where 24 or fewer patients were treated in a year increased rapidly, in particular after 2006. On the other hand, the number of hospitals with a volume of >48 patients per year was stable.

Discussion

Although the advantages of brachytherapy were well recognized among Japanese urologists and radiation oncologists, low dose rate brachytherapy for prostate cancer using I-125 or Pd-103 seeds had not been allowed in Japan, because of the

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Table 1. Total number of hospitals/patients and the breakdown of hospitals according to the number of patients per year, among hospitals where more than 1 year has passed since brachytherapy was first made available

	2004	2005	2006	2007	2008	2009	2010	2011
Total number of hospitals	2	23	38	60	83	94	102	109
Estimated total number of patients	269	1412	1795	2516	2783	3112	3442	3793
Percentage of hospitals								
>96 patients/year	50.0	17.4	7.9	5.0	4.8	7.4	6.9	6.4
48–96 patients/year	50.0	30.4	28.9	23.3	10.8	10.6	11.8	11.9
24–48 patients/year	0.0	34.8	36.8	35.0	36.1	31.9	24.5	26.6
12–24 patients/year	0.0	17.4	10.5	18.3	32.5	28.7	35.3	33.9
≤12 patients/year	0.0	0.0	15.8	18.3	15.7	21.3	21.6	21.1

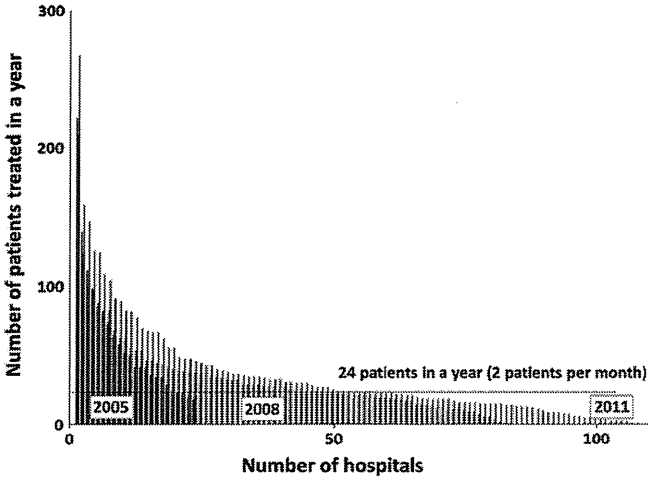

Fig. 1. The annual number of patients treated with brachytherapy per hospital in hospitals where more than 1 year had passed since brachytherapy was first made available, in 2005, 2008, and 2011.

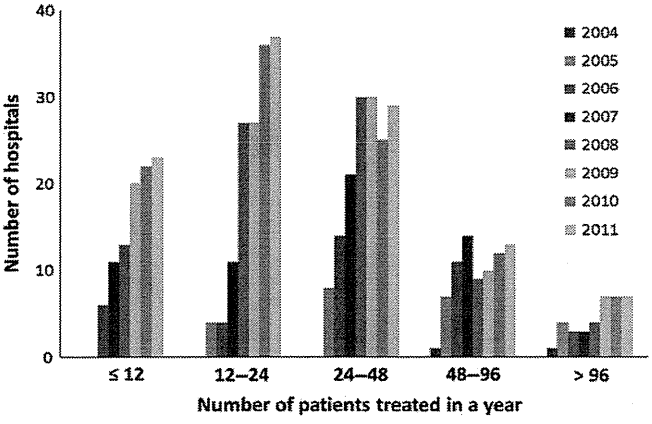

Fig. 2. Distribution of the annual number of patients treated with brachytherapy per hospital from 2004 to 2011.

strict Japanese laws on radiation safety.[2] However, after long discussions between members of the Japanese Society for Therapeutic Radiology and Oncology (JASTRO), the Japanese Urological Association (JUA), the Ministry of Health, Labor, and Welfare, and the Ministry of Education and Science, permanent implant brachytherapy for prostate cancer using I-125 seeds was approved in July 2003.[2] Even after permanent implant brachytherapy was permitted in Japan, only a limited number of institutions started the treatment, in part because of the very low price fixed by the Japanese health insurance system.[2] However, after a higher price for brachytherapy was approved by the Japanese health insurance system in April 2006, many institutes started providing the treatment, as shown in Figures 1 and 2. In particular, the number of hospitals with a low volume of patients increased.

Oncological procedures may have better outcomes if performed by high-volume providers. Killeen *et al.*[5] revealed that high-volume providers have significantly better outcomes for complex cancer surgery, in particular for pancreatectomy, esphagectomy, gastrectomy and rectal resection. In Japan, influences of hospital procedure volume on cancer survival have been under intense investigation using The Osaka Cancer Registry's data.[6–10] As for localized prostate cancer, Jeldres *et al.*[11] examined the effect of annual and cumulative provider volume on the rate of use of secondary therapies using a cohort of 3907 patients treated with definitive external-beam radiation therapy. They demonstrated lower rates of secondary therapy for providers with an annual provider volume >10 cases and for those with a cumulative provider volume >200 cases. Taussky *et al.*[12] showed that seed migration in prostate brachytherapy depended on experience and technique. Chen *et al.*[13] concluded that patients treated with brachytherapy by higher-volume physicians were at lower risk for recurrence and prostate cancer death. Interestingly, they showed that there was no significant association between hospital volume and recurrence, prostate cancer death or all deaths.

Japanese urologists and radiation oncologists have made a great effort to maintain the safety and quality of permanent implant brachytherapy for prostate cancer. JASTRO, JUA, and the Japan Radiological Society (JRS) have published guidelines for brachytherapy (in Japanese).[2,14] These guidelines require physicians involved in this treatment to attend an education course held by JRIA. The guidelines also strongly recommend that each institution administering this treatment should have a urologist certified by the JUA and a radiation oncologist certified by JASTRO and/or JRS in full-time employment.[2] In addition, training workshops have been held at regular intervals to maintain or improve the technical level of permanent implant brachytherapy for prostate cancer. It is not still clear whether the provider volume is associated with outcomes following brachytherapy for prostate cancer in Japan.

The diffusion of a new medical technique depends upon many factors including consumer demand and health insurance and payment systems.[1] In Japan, although health care is under the management of an obligatory insurance system, it is within the framework of a capitalist economy.[15] Given this situation, a new "Basic Plan to Promote Cancer Control Programs" was

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approved in 2012. In addition to the further promotion of radiation therapy and the training of doctors/staff members specializing in this area, the plan recommends the centralization of high-precision radiation therapy including intensity-modulated radiation therapy (IMRT) in each medical region.

There are several new options for patients with clinically localized prostate cancer including robotic surgery, brachytherapy, and IMRT. The majority of the published papers have shown similar treatment results in large-scale institutions. However, after the diffusion of a new medical technique, evaluation of the quality remains an important issue. Therefore, a nationwide multi-institutional cohort survey for prostate brachytherapy focusing on the effect of provider volume on treatment efficacy and safety is needed.

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Disclosure Statement

The authors have no conflict of interest.

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ORIGINAL ARTICLE

Primary CNS lymphoma treated with radiotherapy in Japan: a survey of patients treated in 2005–2009 and a comparison with those treated in 1985–2004

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Abstract
Background The aim of our study was to analyze changes over time in the characteristics, treatment, and outcome of patients with primary central nervous system lymphoma (PCNSL).
Methods Data on 315 patients with histologically proven PCNSL undergoing radiotherapy between 2005 and 2009 were collected from 20 Japanese institutions using a questionnaire. These data were then compared with data on 273 patients treated during the period 1995–2004 and those on 466 patients treated during the period 1985–1994.
Results In terms of patient and tumor characteristics, we found a significant increase in mean patient age in the 2005–2009 period compared to the 1985–2004 period (63 vs. 58–59 years, respectively) and in the percentage of patients with better performance status (PS) during the 2005–2009 period compared with the 1995–2004 period (World Health Organization PS 0–2: 73 vs. 65 %, respectively). Regarding treatment, relative to the 1995–2004 period, significant changes in the 2005–2009 period were (1) decreased rate of attempting tumor resection (23 vs. 44 %); (2) increased use of chemotherapy (78 vs. 68 %), and (3) increased use of methotrexate (MTX)-containing regimens (84 vs. 53 %). The 5-year overall survival rates were 15.3, 30.1, and 36.5 % for patients seen during the 1985–1994, 1995–2004, and 2005–2009 periods,

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respectively, but relapse-free survival did not improve between the 1995–2004 and 2005–2009 periods (26.7 vs. 25.7 % at 5 years, respectively). Patients receiving MTX-containing chemotherapy had 5-year survival rates of 19, 50, and 44 % during these three periods, respectively.
Conclusions Although patient backgrounds differed among the study periods, recent trends were a high patient age, better PS, avoidance of extensive tumor resection, more frequent use of chemotherapy, and improved survival. The recent improvement in survival may be due to improvements in second-line treatment and supportive care.

Keywords Lymphoma · Primary CNS lymphoma · Radiotherapy · Chemotherapy · Soluble interleukin-2 receptor

Introduction

Primary central nervous system lymphoma (PCNSL) is increasing in incidence and is currently one of the most important primary brain tumors. As a consequence, the clinical features of the disease as well as diagnostic procedures, recognition guidelines, and treatment policies have changed considerably. With the widespread recognition of the disease and improvement in diagnostic modalities, patient status, tumor characteristics, and treatment policy appear to be changing gradually [1–7]. Unfortunately, however, randomized studies on the treatment of PCNSL have been scarce, and uncertainties still remain regarding appropriate management [1–7].

In view of the relative rarity of PCNSL coupled with its increasing incidence and importance, we have been conducting nationwide surveys aimed at analyzing changes in the clinical features of the disease, treatment characteristics, and outcomes of the patients. The first study was conducted by Hayabuchi et al. [8] on patients seen between 1985 and 1994. The following two studies were conducted independently by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) Lymphoma Study Group (JLSG) and the Chubu Radiation Oncology Group (CROG) [9, 10] and included patients seen between 1995 and 1999. The fourth study was conducted by the JLSG and CROG and included those patients seen between 2000 and 2004 [11]. Data on a total of 739 patients were collected from the four previous studies. Given the time span of >5 years since the 2000–2004 survey, the Japan Radiation Oncology Study Group (JROSG) collected data on patients seen between 2005 and 2009. In the study reported here, we analyzed all of the patients in the previous and most recent surveys. Follow-up information was updated whenever possible for patients reported in the earlier studies.

Materials and methods

The study design was approved by the institutional review board (IRB) of Nagoya City University (Approval Number 506). Submission of the data was approved by the IRBs at each participating institution. Subjects of all of the surveys were patients with histologically proven PCNSL who had received radiation therapy. Patients who were suspected of having secondary CNS lymphoma were excluded from enrolling in the survey by each institution. Those patients who did not complete the planned radiotherapy were included. The clinical characteristics of the patients, their treatment, and the prognosis, shown in the Results, were obtained using a detailed questionnaire.

For our survey, we collected data on 315 patients from 20 Japanese medical institutions who started radiation therapy between 2005 and 2009. In the previous surveys, data on 466 patients from 62 institutions seen between 1985 and 1994 were collected [8], and for the period of 1995–1999, a total of 142 patients from 25 Japanese medical institutions were surveyed within the framework of the surveys conducted by JLSG and CROG, respectively

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[9, 10]. For the period of 2000–2004, 131 patients from 17 institutions were surveyed by the JLSG and CROG. The results of these previous surveys were published separately [8–11]. Since the number of patients included in the 1995–1999 and 2000–2004 surveys is relatively small compared to the preceding and current surveys, patient data for these two time periods were combined for this analysis ($n = 273$ for the period of 1995–2004). Thus, we compared data on 466, 273, and 315 patients receiving treatment for PCNSL in the periods 1985–1994, 1995–2004, and 2005–2009, respectively.

A total of 1,054 patients with histologically proven PCNSL therefore constituted the study population (subjects). Human immunodeficiency virus titer was negative in all patients who had received the test, and none of the other patients were considered to have acquired immunodeficiency syndrome-related PCNSL. Of the 20 institutions that participated in the most recent survey, eight (40 %) had also participated in the 2000–2004 survey; 76 % of the institutions which participated in the 2000–2004 survey had also participated in the 1995–1999 survey, and 68 % of the institutions participating in the 1995–1999 survey had also been included in the1985–1994 survey.

The extent of surgical resection had not been ascertained in the 1985–1994 survey, but it had been determined in the subsequent surveys. All other items were common to all surveys. Only one new item was added to the most recent survey: the soluble interleukin-2 receptor (sIL-2R) level before treatment. The performance status (PS) was scored using the World Health Organization (WHO) criteria, and the pre-surgery PS was used for this analysis. A number of items for which data were unclear in the previous surveys were included in the newest survey, and updated information was obtained. As is expected in such a survey, a number of items were unanswered by the investigators. Various chemotherapy regimens had been used, but for the convenience of analysis, these were categorized as either a high-dose ($\geq$1 g/m^2) methotrexate (MTX)-containing regimen, or others; about two-thirds of non-MTX-containing regimens were vincristine–cyclophosphamide–doxorubicin–prednisolone or similar regimens [12].

Differences in patient, tumor, and treatment characteristics between groups were examined using the Fisher's exact test. Survival rates were calculated from the date of the patient starting radiotherapy using the Kaplan–Meier method, and differences in pairs of survival curves were examined with the log-rank test. All statistical analyses were carried out using StatView ver. 5 (SAS institute, Cary, NC) and HALWIN (Gendaisuugakusha, Kyoto, Japan). The median length of follow-up for living patients was 33, 40.5, and 35 months for the 1985–1994, 1995–2004, and 2005–2009 periods, respectively.

Results

Table 1 shows patient and tumor characteristics in the three patient groups treated during the three survey periods. Several marked changes were noted. The mean patient age and proportion of patients with PS 0–2 have increased over time. The proportion of patients with multiple tumors was 52 % in the most recent series, while it was 38 and 47 % in the previous series. Other patient and tumor characteristics did not differ significantly between the pairs of groups, except that the proportion of T cell PCNSL was relatively higher in patients surveyed in the 1985–1994 study.

Table 2 shows the changes in treatment that occurred over time. As a surgical procedure, biopsy alone was performed in 77 % of the patients in the most recent series, whereas it had been performed in 56 % of the patients during 1995–2004. Over 90 % of the patients were treated with whole-brain irradiation with or without a focal boost throughout all study periods. The use of spinal irradiation decreased from 4.6 % during the 1995–2004 period to 1.6 % during the 2005–2009 survey. Mean total doses did not differ significantly among the three periods survey. Whole-brain doses were lower in 1995–2004 and 2005–2009 than in 1985–1994. In contrast, there were steady increases in the proportion of patients undergoing systemic chemotherapy over time. In particular, MTX-containing regimens steadily increased (in 84 % of patients undergoing chemotherapy in the most recent period).

Figure 1 shows the overall survival curves for the three groups. Patients treated between 1995 and 2004 and those treated between 2005 and 2009 showed significantly better survival rates than those treated between 1985 and 1994 (both $P < 0.0001$); the median survival time increased from 18 to 26 to 35 months, respectively. The 5-year survival was 15.3, 30.1 and 36.5 % for the 1985–1994, 1995–2004, and 2005–2009 periods, respectively. The P value between 1995–2004 and 2005–2009 was 0.062. Figure 2 shows the relapse-free survival curves for the patients with known data on recurrence in these three periods. Relapse-free survival of the patients was also better in the two more recent periods than in the period of 1985–1994 (both $P < 0.0001$). The median time to recurrence was 9, 20, and 21 months, and the 5-year relapse-free survival was 17.8, 26.7, and 25.7 % for 1985–1994, 1995–2004, and 2005–2009, respectively. There was no difference between the two most recent periods ($P = 0.62$).

Table 3 summarizes the survival data on the three groups according to patient- and tumor-related potential prognostic factors. In all study periods, patients aged <65 years and those with WHO PS of 0–2 had significantly higher survival rates. In one or two of the three series, patients without B symptoms, those with a normal lactate dehydrogenase (LDH) level, those with a single

Table 1 Patient and tumor characteristics

Characteristic	Survey period (years)			P^a
	1985–1994 (n = 466)	1995–2004 (n = 273)	2005–2009 (n = 315)	
Gender				
Male	276 (59)	163 (60)	191 (61)	0.90
				0.82
Age (years)				
Mean ± SD	58 ± 13	59 ± 11	62 ± 11	0.016
Median (range)	60 (5–86)	61 (15–93)	63 (17–85)	0.024
Performance status (PS)				
0–2	229/438 (52)	174/266 (65)	226/309 (73)	0.0006
				0.012
Lactate dehydrogenase				
High	103/267 (39)	74/234 (32)	99/305 (32)	0.11
				0.84
B symptoms[b]				
Yes	33/418 (7.9)	19/249 (7.6)	30/299 (10)	0.90
				0.33
Phenotype				
T cell	20/234 (8.5)	8/235 (3.4)	8/302 (2.6)	0.020
				0.61
Tumor number				
Multiple	175/460 (38)	128/271 (47)	163/315 (52)	0.015
				0.28
Tumor size at diagnosis (cm)				
Mean ± SD	3.8 ± 1.4	3.8 ± 1.4	2.7 ± 1.9	1.0
				0.30
CSF dissemination				
Yes	56/422 (13)	43/248 (17)	29/308 (9.4)	0.15
				0.83

Data are presented as the number of patients with the percentage given in parenthesis, unless indicated otherwise

CSF cerebrospinal fluid

[a] First and second P values are for comparison between the 1985–1994 and 1995–2004 surveys, and between the 1995–2004 and 2005–2009 surveys, respectively

[b] B symptoms: fever (>38 °C for 3 consecutive days), weight loss (>10 % in 6 months), and/or drenching night sweats

tumor, and those without CSF dissemination on diagnostic imaging had better prognoses, but the tumor size was not associated with the prognosis. Figure 3 shows survival curves according to the LDH and sIL-2R levels in the most recent series. Patients with an elevated sIL-2R level tended to have a poorer prognosis ($P = 0.054$). Regarding the association between LDH and sIL-2R levels, 51 % of patients with a high LDH level also had a high sIL-2R level, while the remaining 49 % had a normal sIL-2R level.

To analyze the influence of treatment-related factors on the outcome, patients who did not complete radiotherapy (receiving <30 Gy) and those who died soon after completing radiotherapy were excluded from the analysis. Table 4 shows survival data according to the treatment-related factors; no factors were found to be associated with an improved prognosis throughout all three periods. In the groups treated during 1995–2004 and 2005–2009, patients receiving systemic chemotherapy had better survival rates than those treated with radiation alone, and those who received MTX-containing chemotherapy had or tended to have a better prognosis than those who received other regimens. However, these phenomena were not observed in patients treated during the preceding decade. No radiotherapy-related factors were found to be associated with the prognosis, except that five patients receiving spinal irradiation had a poorer prognosis in the 2005–2009 series. Figure 4 shows the survival curves for patients treated with high-dose MTX-containing chemotherapy and radiation during the three survey periods; the patients seen during 1995–2004 and those seen during 2005–2009 had significantly better survival rates than those treated during 1985–1994 ($P = 0.0030$ and 0.0002, respectively), but there was no difference between the two most recent periods ($P = 0.95$).

Discussion

Given the increasing importance of PCNSL tumor in neuro-oncology, medical organizations in Japan consider it

Table 2 Treatment characteristics

Characteristic	Period (year)			P^a
	1985–1994 (n = 466)	1995–2004 (n = 273)	2005–2009 (n = 315)	
Surgery				
Biopsy	–	154/273 (56)	241/315 (77)	–
				0.000
Radiotherapy course				
Not completed	25/466 (5.4)	11/273 (4.0)	5/315 (1.6)	0.42
				0.070
Brain radiation field				
Partial brain	37/466 (7.9)	27/273 (9.9)	21/315 (6.7)	0.36
				0.16
Spinal radiation				
Yes	37/445 (8.3)	12/261 (4.6)	5/315 (1.6)	0.061
				0.034
Total dose (Gy)				
Mean ± SD	48.4 ± 11.2	47.9 ± 10.0	46.9 ± 8.6	0.61
				0.35
Whole-brain dose (Gy)				
Mean ± SD	35.6 ± 13.7	33.3 ± 13.0	33.9 ± 8.1	0.02
				0.57
Iv chemotherapy				
Yes	212/420 (50)	186/273 (68)	245/315 (78)	0.000
				0.008
MTX-containing regimen				
Yes	47/212 (22)	98/186 (53)	206/245 (84)	0.000
				0.000
It chemotherapy				
Yes	42/415 (10)	24/273 (8.8)	32/306 (11)	0.56
				0.50

Data are presented as the number of patients with the percentage given in parenthesis, unless indicated otherwise

Iv intravenous, *MTX* methotrexate, *It* intrathecal

[a] First and second *P* values are for comparison between the 1985–1994 and 1995–1999 surveys, and between the 1995–2004 and 2005–2009 surveys, respectively

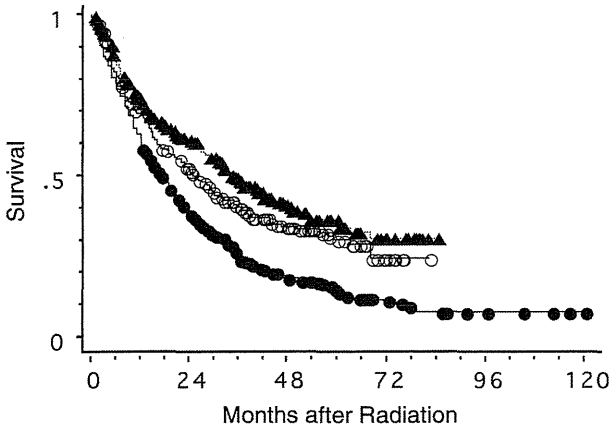

Fig. 1 Survival curves for patients with primary central nervous system lymphoma (PCNSL) seen in 1985–1994 (*filled circle*, n = 466), 1995–2004 (*open circle*, n = 273), and 2005–2009 (*filled diamond*, n = 315). Patients surveyed in 1995–2004 and 2005–2009 showed significantly better survival rates than those surveyed in 1985–1994 ($P < 0.0001$), but there was no difference between the 1995–2004 and 2005–2009 groups ($P = 0.062$)

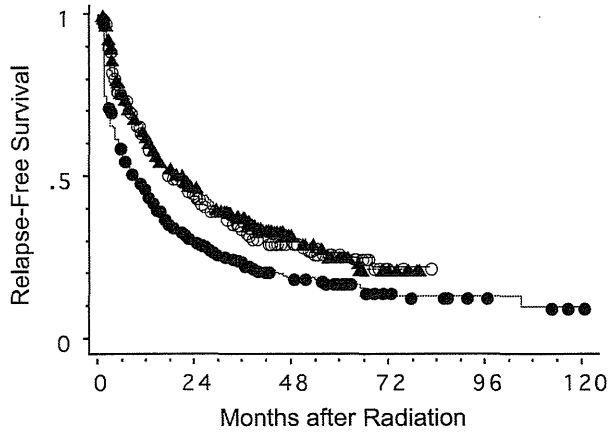

Fig. 2 Relapse-free survival curves for patients with PCNSL seen in 1985–1994 (*filled circle*, n = 408), 1995–2004 (*open circle*, n = 264), and 2005–2009 (*filled diamond*, n = 315). The patients surveyed in 1995–2004 and 2005–2009 showed significantly better relapse-free survival rates than those surveyed in 1985–1994 ($P < 0.0001$), but there was no difference between the 1995–2004 and 2005–2009 groups ($P = 0.62$)

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

Prognostic factor	1985–1994				1995–2004				2005–2009			
	n	MST	5-YSR (%)	*P*	*n*	MST	5-YSR (%)	*P*	*n*	MST	5-YSR (%)	*P*
Gender												
Male	276	17	17	0.92	163	26	30	0.76	191	37	38	0.31
Female	190	20	13		110	25	30		124	31	36	
Age (years)												
<65	294	20	21	0.0001	158	36	40	<0.0001	153	42	47	0.0009
≥65	172	14	5.4		115	17	15		162	29	23	
Performance status (PS)												
0–2	229	24	20	<0.0001	149	37	37	<0.0001	226	48.5	44	0.0001
3, 4	209	12	10		74	13	14		83	11.5	14	
B symptoms												
Yes	33	10	0	0.030	19	15	15	0.028	30	31	30	0.26
No	385	18	17		232	29	35		269	36	39	
Lactate dehydrogenase												
Normal	164	22	26	0.0007	160	35	37	0.0001	206	40	42	0.050
High	103	14	5.7		74	16	21		99	29	28	
Tumor number												
Single	285	22	18	0.0012	143	29	37	0.065	152	40	43	0.096
Multiple	175	12	11		128	23	23		163	31	31	
Tumor size (cm)[a]												
≤3.5	196	19	15	0.60	125	28	28	0.93	160	37	42	0.45
>3.5	197	17	18		137	26	34		131	33.5	29	
CSF dissemination												
Yes	56	10	14	0.039	43	43.5	36	0.45	29	15	26	0.022
No	366	19	16		205	26	32		279	37	39	

MST Median survival time in months, *5-YSR* 5-year survival rate

[a] Maximum tumor diameter at diagnosis

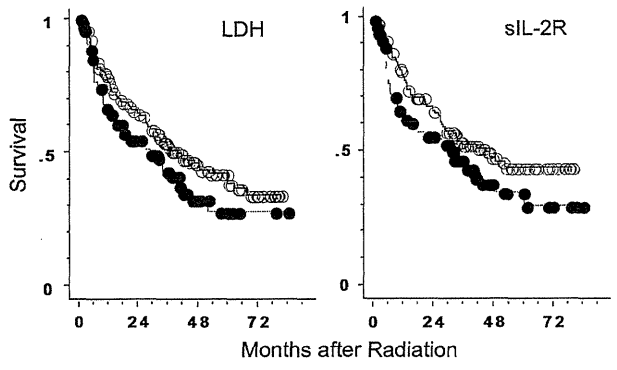

Fig. 3 Survival curves for patients treated between 2005 and 2009 according to the serum lactate dehydrogenase (*LDH*) and soluble interleukin-2 receptor (*sIL-2R*) levels. *Open circle* Normal level ($n = 206$ for LDH and 135 for sIL-2R), *filled circle* elevated level ($n = 99$ for LDH and 95 for sIL-2R). The *P* value was 0.050 for LDH and 0.054 for sIL-2R

meaningful to survey data on PCNSL every 5 years. To date, these surveys have been conducted by radiation oncology groups (JASTRO-JLSG, CROG, and JROSG) and, therefore, patients undergoing radiotherapy have been the subjects of these surveys. Consequently, data on patients treated with chemotherapy alone are unavailable, which is a limitation of our study. Although treatment with chemotherapy alone seems to be increasing in use in Western countries [13–15], such a treatment strategy was not popular in Japan before 2010—and was in fact exceptional. Therefore, we are confident that these survey data represent the status of PCNSL treatment up to and including 2009 in Japan. More recently, the strategy of primary chemotherapy with deferred radiotherapy appears to be gaining acceptance in Japan also, so these data might serve as a control for the evaluation of different treatment modalities in the future. Another limitation of our study is the long study period; patient backgrounds may considerably differ among the study periods, and comparison among patients in the different eras may be inappropriate for some items.

Various changes have been noted with regard to patient and tumor characteristics. The recent increase in aged patients may be related to the fact that subjects of these

Table 4 Survival data according to treatment-related factors

Prognostic factor	1985–1994				1995–2004				2005–2009			
	n	MST	5-YSR (%)	*P*	*n*	MST	5-YSR (%)	*P*	*n*	MST	5-YSR (%)	*P*
Surgical resection												
Extensive	–	–	–	–	53	24.5	30	0.66	40	40.5	12	0.63
Non-extensive	–	–	–		209	26	29		270	34	38	
Radiation field												
Whole brain	405	19	15	0.72	236	24.5	28	0.21	289	36	37	0.67
Partial brain	34	16	17		26	35	43		21	32	28	
Spinal radiation												
Yes	36	24	19	0.16	11	NR	55	0.30	5	5	–	0.0091
No	384	18	15		251	26	28		302	36	37	
Total dose (Gy)												
<50	134	18	17	0.97	80	28.5	34	0.98	141	42	41	0.38
≥50	305	8	16		182	25	28		169	32.5	31	
Whole-brain dose (Gy)												
<40	156	18	18	0.43	109	32	34	0.91	216	35.5	40	0.43
≥40	283	18	14		153	23	25		94	32	28	
Iv chemotherapy												
Yes	202	20	16	0.30	180	36	39	<0.0001	242	42	41	<0.0001
No	192	16	17		82	14	10		68	12.5	13	
Iv chemotherapy regimen												
MTX	46	20	19	0.66	92	55.5	50	0.061	203	45	44	0.0031
Other	156	21	15		88	29	30		39	27	23	
It chemotherapy												
Yes	39	16	20	0.78	22	NR	53	0.10	32	NR	59	0.097
No	350	19	16		232	24.5	26		269	34	34	

NR Not reached

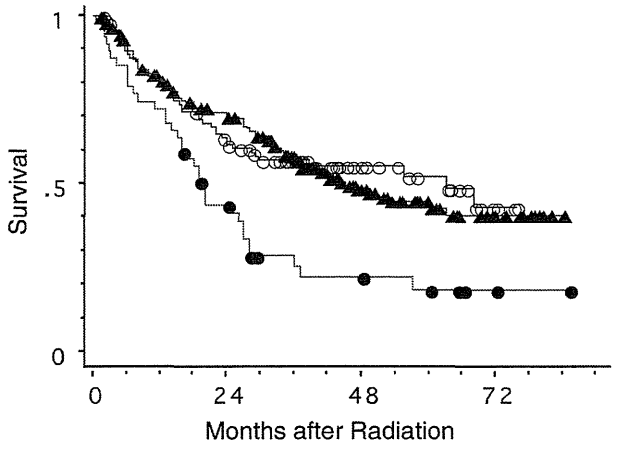

Fig. 4 Survival curves for patients treated with high-dose methotrexate-containing chemotherapy plus radiation in 1985–1994 (*filled circle*, $n = 46$), 1995–2004 (*open circle*, $n = 92$), and 2005–2009 (*filled diamond*, $n = 203$). The P value was 0.0030 for 1985–1994 vs. 1995–2004, 0.0002 for 1985–1994 vs. 2005–2009, and 0.95 for 1995–2004 vs. 2005–2009

surveys are histologically proven PCNSL patients. One possible explanation is the increasing acceptance in recent years of biopsy—even in aged patients—to confirm the diagnosis. The incidence of multiple tumors appears to be increasing, being 52 % in the most recent period compared to 38 and 47 % in the two earlier surveys, respectively; most previous reports suggest an incidence of between 30 and 40 % [16–19]. The improvement in imaging modalities and techniques, including the more frequent use of magnetic resonance imaging, may have contributed to the improved detection of small tumors. The proportion of T-cell lymphoma was high (8.5 %) in the 1985–1994 period, possibly reflecting the difficulty in determining the phenotype of lymphoma in that era.

In terms of treatment, attempts at tumor resection have decreased because it is now clear that surgical resection does not contribute to an improved prognosis [2, 11]. The results of our survey also supports this conclusion. However, Weller et al. [20] recently stated that resection of PCNSL might play a beneficial role provided that surgery is safely conducted. We noted no major changes in

radiotherapy between the different surveys. Shibamoto et al. [21] suggested the possible use of partial-brain radiation for solitary lesions, but such a policy has yet to spread nationwide. Reducing total as well as whole-brain radiation doses using chemotherapy has not become popular in Japan. The increased use of systemic chemotherapy and, in particular, MTX-based regimens appear to be a worldwide trend, as was also shown in our study.

The prognosis of PCNSL patients has improved recently. Improvement in supportive care may at least in part have contributed to these changes. The 5-year survival was 30.1 and 36.5 % in 1995–2004 and 2005–2009, respectively. However, relapse-free survival rates did not differ between these two periods, suggesting that although second-line treatment at recurrence has prolonged survival, the cure rate has not yet improved. This trend was also true for patients treated with high-dose MTX and radiation; no improvement was seen for the most recent period, suggesting that, in terms of cure, more than half of PCNSLs are resistant to currently available treatment. New treatments are therefore urgently needed.

Many prognostic factors of PCNSL, such as age, PS, and tumor multiplicity, have been reported [8, 11, 17, 19, 22], and the results of the univariate analyses we conducted in our study agree with previously published data. Consequently, we did not present the multivariate analysis data. In the most recent survey, we paid attention to sIL-2R as a prognostic marker and observed that patients with a high sIL-2R level tended to have a poorer prognosis. The prognostic value of sIL-2R has been reported for extracranial lymphoma [23, 24], but, to our knowledge, its role in PCNSL has not been reported. The serum sIL-2R level reflects the total amount of activated T lymphocytes and is correlated with disease activity [25]. It can also be elevated in cancers other than lymphoma, collagen disease, and infection [25, 26]. Since sIL-2R and LDH levels do not necessarily correlate with each other, sIL-2R may be another useful prognostic marker for PCNSL.

Very recently, a few Japanese groups have started to treat PCNSL patients with chemotherapy alone, following the trend set in Western countries. A randomized European study of chemotherapy alone versus chemotherapy + radiation indicated that chemotherapy alone was associated with a decreased progression-free survival, although overall survival was similar, partly due to the use of radiotherapy as a second-line treatment [27]. Since most studies are conducted in phase II settings, the data presented in our study may serve as a basis for studying the treatment and prognosis of PCNSL patients in Japan.

In conclusion, the results of our study reveal that recent trends in PCNSL are increased patient age, better PS, tumor multiplicity, avoidance of extensive tumor resection, more frequent use of high-dose MTX-containing chemotherapy, and improved survival, with no improvement in relapse-free survival. Newer strategies are therefore necessary to further improve the prognosis of PCNSL patients, and the present data may serve as a basis for designing new studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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Kasuya et al. Radiation Oncology 2013, 8:139
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RADIATION ONCOLOGY

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Distribution patterns of metastatic pelvic lymph nodes assessed by CT/MRI in patients with uterine cervical cancer

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Abstract

Background: To investigate the three-dimensional (3D) distribution patterns of clinically metastatic (positive) lymph nodes on pretreatment computed tomography (CT)/magnetic resonance imaging (MRI) images of patients with locally advanced cervical cancer.

Methods: We enrolled 114 patients with uterine cervical cancer with positive nodes by CT/MRI (≥10 mm in the shortest diameter). Pretreatment CT/MRI data were collected at 6 institutions. The FIGO stage was IB1 in 2 patients (2%), IB2 in 6 (5%), IIA in 3 (3%), IIB in 49 (43%), IIIB in 50 (44%), and IVA in 4 (4%) patients. The median cervical tumor diameter assessed by T2-weighted MRI was 55 mm (range, 10–87 mm). The anatomical distribution of the positive nodes was evaluated on CT/MRI images by two radiation oncologists and one diagnostic radiologist.

Results: In these patients, 273 enlarged nodes were assessed as positive. The incidence of positive nodes was 104/114 (91%) for the obturator region, 31/114 (27%) for the external iliac region, 16/114 (14%) for the internal iliac region, 22/114 (19%) for the common iliac region, and 6/114 (5%) for the presacral region. The external iliac region was subdivided into four sub-regions: lateral, intermediate, medial, and caudal. The obturator region was subdivided into two sub-regions: cranial and caudal. The majority of patients had positive nodes in the cranial obturator and/or the medial external iliac region (111/114). In contrast, few had positive nodes in the lateral external iliac, caudal external iliac, caudal obturator, internal iliac and presacral regions. All cases with positive nodes in those low-risk regions also had positive nodes in other pelvic nodal regions concomitantly. The incidence of positive nodes in the low-risk regions/sub-regions was significantly related to FIGO stage ($p=0.017$) and number of positive nodes ($p<0.001$).

Conclusions: We demonstrated the 3D distribution patterns of clinical metastatic pelvic lymph nodes on pretreatment CT/MRI images of patients with locally advanced cervical cancer. These findings might contribute to future individualization of the clinical target volume of the pelvic nodes in patients with cervical cancer.

Keywords: Radiotherapy, Lymph node, Clinical target volume, Uterine cervical cancer

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Background

Radiotherapy plays very important roles in the treatment of uterine cervical cancer. Definitive radiotherapy for cervical cancer consists of external beam radiotherapy and intracavitary brachytherapy. Recently, external beam radiotherapy techniques have advanced considerably, as have those for intracavitary brachytherapy. Treatment planning for uterine cervical cancer has transitioned from a two-dimensional (2D) approach based on bony landmarks to a three-dimensional (3D) technique based on computed tomography (CT)/magnetic resonance imaging (MRI). Intensity-modulated radiotherapy (IMRT) has been proven to have a significant dosimetric advantage and less toxicity compared with conventional 2D/3D treatment planning for various malignancies, including gynecologic cancers [1]. It is essential to define the proper clinical target volume (CTV) for appropriate delivery of IMRT. Guidelines that provide a standard definition of CTV nodes are now published by the Radiation Therapy Oncology Group (RTOG) [2], UK investigators [3] and the Japan Clinical Oncology Group (JCOG) [4]. However, these guidelines were developed mainly from information on the normal anatomical pelvic lymph node distribution. The actual distribution of clinically metastatic (positive) nodes in the pelvis has not been studied in definitive radiotherapy series. If areas with a low risk of node metastases could be deleted from the CTV, toxicity could be reduced without sacrificing regional control.

The purpose of this study was to investigate the 3D distribution patterns of clinically metastatic nodes assessed by CT/MRI in patients with uterine cervical cancer.

Methods

We enrolled 114 patients with uterine cervical cancer who were diagnosed as having clinically metastatic (positive) pelvic nodes by CT/MRI (≥10 mm in the shortest diameter) and treated by definitive radiotherapy/chemoradiotherapy at 6 institutions between January 2001 and December 2007. This study conformed to the ethical principles contained in the Declaration of Helsinki [5], and was approved by the institutional review board of the principal investigator (T.T.). Lymph nodes greater than or equal to 10 mm in the shortest diameter, as assessed by CT/MRI, were defined as positive in this study. Patient characteristics are summarized in Table 1. Digitized CT/MRI images burned to CD-ROMs were collected from each institution. The images were reviewed by two radiation oncologists (G.K., T.T.) and one diagnostic radiologist (A.Y.).

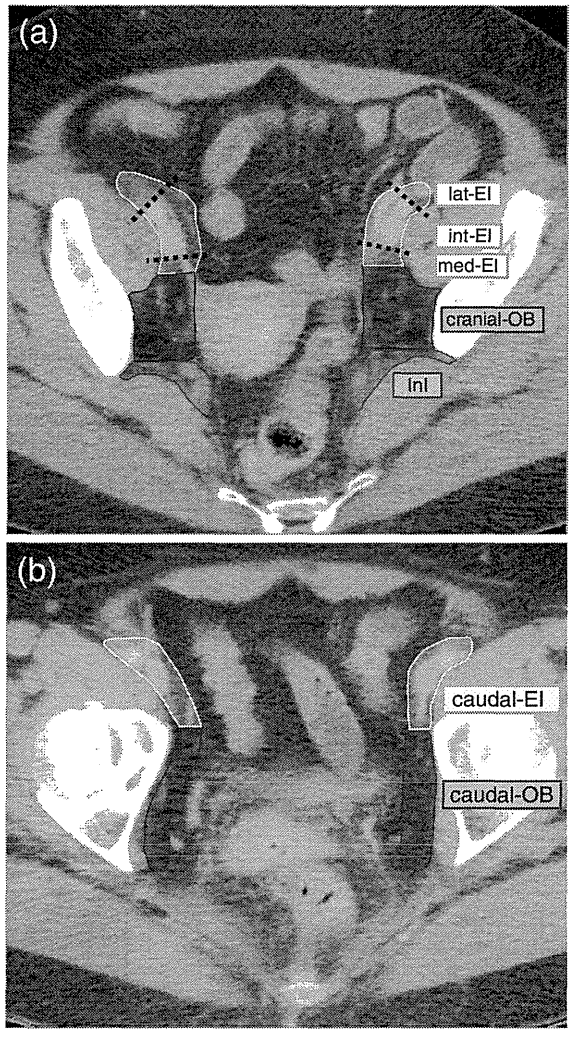
Pelvic lymph node area was divided into five anatomical regions: the obturator region, the external iliac region, the internal iliac region, the common iliac region, and the presacral region. The external iliac was further divided into four sub-regions: the medial external iliac, the intermediate external iliac, the lateral external iliac, and the caudal external iliac. The subcategories of medial external iliac, intermediate external iliac, and lateral external iliac refer to the definitions proposed by Taylor et al. [6] and Lengelé et al. [7]: medial external iliac=the dorsal area of attachment and along the external iliac vein, intermediate external iliac=the anterior area between the external iliac artery and vein, and lateral external iliac=the lateral area of the external iliac artery. These three sub-regions are all located cranial to the aspect of the femoral head. On the other hand, the caudal external iliac is located caudal to the aspect of the femoral head. The obturator was also divided into two sub-regions, with the border of the aspect of the femoral head as the external iliac: cranial obturator and caudal obturator. An atlas of these sub-regions (except for common iliac region) is presented in Figure 1 (a)-(b).

First, the number of positive nodes in each region and in the sub-regions was counted. Next, the distribution

Table 1 Patient characteristics (n=114)

Characteristic	(n)
FIGO stage	
IB1	2
IB2	6
IIA	3
IIB	49
IIIB	50
IVA	4
Age	
median 52	range 26-88
Histology	
SCC	109
Adeno	5
Tumor size*	
<20 mm	0
21-40 mm	18
41-60 mm	58
61 mm<	38
Number of metastatic LN in the pelvis	
1	32
2	36
3	23
4	14
≥5	9

*assessed by MRI.
FIGO=Federation Internationale de Gynecologie et de Obstetrique.
SCC=Squamous cell carcinoma.
LN=Lymph node.



OB=obturatorregion, EI = external iliac region, lat-EI = lateral external iliac region, int-EI = intermediate external iliac region, med-EI = medial external iliac region, InI= internal iliac region, PS = presacralregion

Figure 1 Atlas of the CTV nodes: regions and sub-regions. Middle-level of pelvis' for (**a**), and 'low-level of pelvis' for (**b**).

patterns of the positive nodes were analyzed in each area.

Statistical analyses were performed with the chi-square test. A probability level of 0.05 was chosen for statistical significance.

Results

There were 273 positive nodes as assessed by CT/MRI. The median number of positive nodes per patient was 2 (range, 1–7). Figure 2 shows the incidence of positive nodes in each nodal region. The area that most frequently contained positive nodes was the obturator region. In contrast, positive nodes were rarely observed in the presacral region. Table 2 shows the anatomical distribution of positive nodes in the pelvis. A solitary positive node was observed only in the obturator and the external iliac regions. In contrast, no solitary positive node was observed in the internal iliac, common iliac, and presacral regions. Within the obturator and external iliac regions, positive nodes were rarely observed in the caudal and lateral external iliac sub-regions. Ninety-seven percent of the patients (111/114) had one or more positive nodes in the cranial obturator and/or the medial external iliac regions. A solitary positive node was observed only in the cranial obturator, and medial/intermediate external iliac regions. For other regions or sub-regions, patients with positive nodes also had positive nodes concomitantly in other pelvic nodal