Table 1. Patient characteristics in two surveys

	JPCS-1 (95–97) (n = 258)	JPCS-2 (99–01) (n = 81)	P-value
Age (y)	53.6 ± 11.5	56.5 ± 10.7	0.482
Menstrual status			0.063
Pre-	86/258 (33.3)	19/81 (23.4%)	
Peri-	17/258 (6.6)	2/81 (2.5)	
Post-	106/258 (41.1)	46/81 (56.8)	
Unknown/missing	49/258 (19.0)	14/81 (17.3)	
Pathologically T stage			0.548
pTis	0/258 (0.0)	0/81 (0.0)	
pT0	1/258 (0.4)	0/81 (0.0)	
pT1	43/258 (16.7)	13/81 (16.1)	
pT2	116/258 (44.9)	33/81 (40.8)	
pT3	45/258 (17.4)	13/81 (16.0)	
pT4	27/258 (10.5)	15/81 (18.5)	
Unknown/missing	26/258 (10.1)	7/81 (8.6)	
Number of pathologically positive axillary lymph nodes			0.010
0	48/258 (18.6)	10/81 (12.3)	
1–3	51/258 (19.8)	19/81 (23.5)	
≥4	119/258 (46.1)	49/81 (60.5)	
Unknown/missing	40/258 (15.5)	3/81 (3.7)	
Final microscopic margin			<0.001
Positive	11/258 (4.3)	17/81 (21.0)	
Close (≤2 mm)	10/258 (3.9)	2/81 (2.5)	
Close (2–5 mm)	0/258 (0.0)	1/81 (1.2)	
Close (>5 mm)	0/258 (0.0)	0/81 (0.0)	
Negative	183/258 (70.9)	51/81 (63.0)	
Unknown/missing	54/258 (20.9)	10/81 (12.3)	
Estrogen receptor status			0.012
Not done	35/258 (13.6)	7/81 (8.6)	
Positive	61/258 (23.6)	28/81 (34.6)	
Negative	57/258 (22.1)	26/81 (32.1)	
Unknown/missing	105/258 (40.7)	20/81 (24.7)	
Progesterone receptor status			<0.001
Not done	39/258 (15.1)	7/81 (8.6)	
Positive	48/258 (18.6)	23/81 (28.4)	
Negative	50/258 (19.4)	29/81 (35.8)	
Unknown/missing	121/258 (46.9)	22/81 (27.2)	

JPCS, Japanese Patterns of Care Study.

analyses (17–20). For the last two decades, breast conservative therapy has become more frequently performed in Japan. The national survey conducted by the Japanese Breast Cancer Society indicated that ~40% of patients with breast cancer received breast conservative therapy in 2000, and that

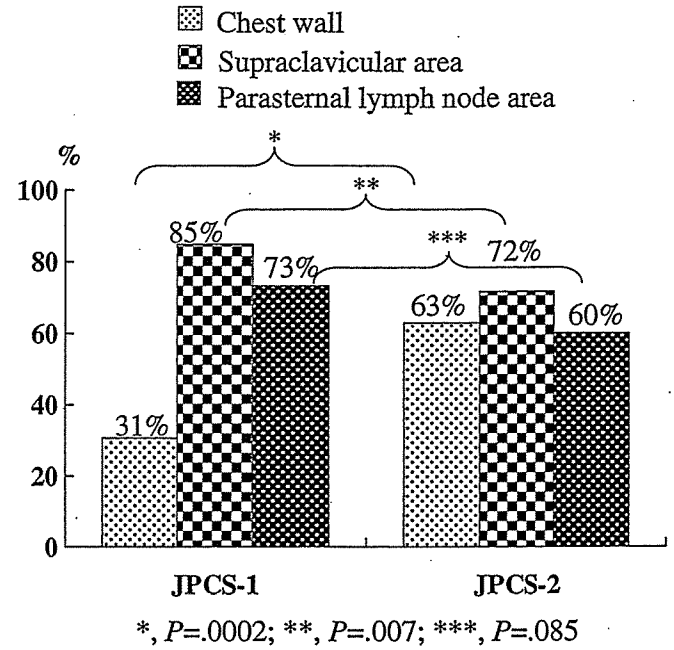

Figure 1. The radiotherapy target volume in patients who received PMRT. The majority of patients in the first survey received irradiation of the regional lymph node area alone. In the second survey, the radiotherapy target volume including the chest wall and regional lymph nodes was applied more frequently. JPCS, Japanese Patterns of Care Study

nowadays more than half of the patients receive such treatment (21). However, three prospective randomized trials indicated that PMRT improved the overall survival of pre-menopausal and post-menopausal patients with locally advanced breast cancer who had pathologically four or more axillary positive nodes, and that PMRT has been used widely in the United States and in the other Western countries (2–5). Fowble reviewed a large number of reports regarding chest wall recurrence after mastectomy, and reported that 8–36% of patients with four or more pathologically positive nodes underwent treatment with mastectomy and adjuvant systemic chemotherapy (2). However, in Japan PMRT has been used infrequently in patients with adverse risk factors, because many Japanese surgeons consider that chest wall recurrence is infrequent after mastectomy and systemic therapy alone (22). However, the evidence-based guidelines for clinical practice conducted by the Japanese Breast Cancer Society recommended that PMRT should be applied in patients with pathologically four or more axillary positive nodes. These clinical guidelines may have affected the increment in a number of patients receiving PMRT in Japan. The dissemination of high-quality evidence that does not result in the progress of practical techniques would expose patients to severe adverse effects. We should monitor clinical practice to evaluate whether appropriate radiotherapy for PMRT is being performed.

PMRT has been recommended for patients with four or more pathologically proven axillary positive nodes and/or advanced primary disease (8). The clinical benefit of PMRT for patients without adverse risk factors is controversial (23,24). Smith

Table 2. Radiotherapy technique in two surveys

	JPCS-1‡ (n = 258)	JPCS-2 (n = 81)	P-value
Total radiation dose (Gy) (median, range)	49 (10–60)	49 (18–60)	0.738
Fraction size (Gy) (median ± standard deviation)	2.0 ± 0.2	2.0 ± 0.1	0.490
Beam quality of chest wall irradiation*			<0.001
Photon (≤6 MV) (%)	59/79 (74.7)	26/51 (51.0)	
Photon (>6 MV) (%)	6/79 (7.6)	2/51 (3.9)	
Electron (%)	13/79 (16.5)	23/51 (45.1)	
Mixed beam (^{60}Co and X-ray 15 MV) (%)	1/79 (1.2)	0/51 (0.0)	
Wedge filter (yes)† (%)	11/66 (16.7)	11/28 (39.3)	0.001
Boost (yes) (%)	7/258 (2.7)	5/81 (6.2)	0.141

*Calculations were performed only for patients who received chest wall irradiation.
†Calculations were performed only for patients who received chest wall irradiation using photon beam.
‡JPCS, Japanese Patterns of Care Study.

et al. (23) reported that PMRT provided clinical benefits for patients with T1-2 disease and positive axillary nodes. However, some other investigators argued that the role of PMRT had not been defined for patients with T1-2 disease and positive axillary nodes (25). Hence further studies should be performed to establish the indications for PMRT. Our surveys showed that among patients with breast cancer who received postoperative radiotherapy, the proportion of PMRT decreased from 22.9% in JPCS-1 to 9.7% in JPCS-2. This observation does not imply a decrease in the absolute number of patients who received PMRT in Japan, but rather suggests an increment in the number of patients who received breast conservative therapy. The proportions of patients with adverse risk factors, including four or more pathologically proven axillary positive nodes and/or advanced T stage, increased from 57 to 72% between the two studies. The eligibility for PMRT may be influenced by the outcome of the prospective randomized trials in the late 1990s, and PMRT came to be avoided for patients with low risk factors (3–5).

A recent meta-analysis demonstrated that PMRT with an optimal radiation dose ranging from 40 to 60 Gy in 2 Gy fractions, and an appropriate target volume, including chest wall and regional lymph node area, was associated with a statistically significant 6.4% increase in absolute survival (7). However, an inappropriate PMRT technique with an inadequate or excessive dose of radiotherapy or an inappropriate target volume failed to show clinical benefit. Our two surveys demonstrated some problems in radiotherapy techniques for PMRT. In the first survey, the majority of patients received regional lymph node irradiation alone, which was known as the hockey-stick technique. In the second survey, the radiotherapy target volume more frequently included the chest wall and regional lymph nodes. Multiple radiation fields covering anatomically complex sites require a high-quality radiotherapy technique, including three-dimensional radiation planning and quality assurance to avoid severe toxicities. The dose distribution is essential to determine the administration of wedge filter and to evaluate the irradiated lung and heart volume. In the United States, dose distribution in the iso-center plane was calculated in ~95% of patients (11). However, in our survey the dose distribution in the iso-center plane was calculated only in 40% patients, and the multiple-plane dose distribution was calculated only in 15% patients. No improvement of quality assurance was found either in the academic or in the non-academic facilities. Although the immobilization cast is an important item to reproduce the irradiation field in daily treatment, it was used in less than half of the patients in our surveys.

The main limitation of our surveys was the eligibility criteria used. The aim of our surveys was to clarify the clinical procedures applied in patients with breast cancer who received postoperative radiotherapy. The eligibility criteria for our surveys were set up to collect data for patients who received postoperative radiotherapy, including breast conservative therapy and PMRT. The population of patients who received breast conservative therapy has been increasing, and the relative size of the population receiving PMRT has decreased. We could not collect data for patients with PMRT to determine the changes in the clinical procedure sufficiently. Our surveys excluded patients with multiple gross tumors and/or diffuse microcalcification on pretreatment mammography, but the survey for PMRT should include these patients to determine the nationwide status of PMRT. In future studies, we should consider the eligibility criteria to determine the changes in the clinical procedure of PMRT.

Donabedian emphasized three components of quality of care: structure, process and outcome (15). Good processes of care help to achieve good clinical outcome for the patients, while poor processes are associated with insufficient outcome. However, we did not evaluate the correlation between poor radiotherapy technique and clinical outcome, including survival and adverse effects, because of the short follow-up time and small sample size. A survey with small sample size cannot clarify the interactions between poor processes and insufficient clinical outcome. "No difference" in the survey with small sample size does not necessarily mean the "same." Even if the poor process is not significantly associated with poor clinical outcome, this hasty interpretation does not justify by any means that a poor radiotherapy technique is acceptable. In addition, repeated analyses of the correlation between each clinical parameter and the outcome may lead to misunderstanding of the observed phenomenon because of multiplicity. A process survey including large sample size may not be efficient and economical. In contrast, a process survey using a relatively small sample size is convenient and useful to compare the observed clinical practice with the optimal radiotherapy technique that is considered appropriate according to the textbooks or previously reported evidence. However, the definition of optimized sample size for a survey is controversial.

A recent meta-analysis demonstrated that use of an inappropriate radiotherapy technique that applied excessive radiation dose and/or inappropriate target volume was associated with an increment in non-breast cancer mortality (7). In Japan, the infrastructure of radiation oncology units has been insufficient to provide safe medical service in both academic and non-academic facilities (13). The radiation oncology staff, including radiation oncologists, technologists, dosimetrists and oncology nurses, should be enriched to provide good clinical practice for the patients. An efficient monitoring system using optimized surveys combining the structure survey and process survey should be established for good clinical practice.

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ORIGINAL ARTICLE: CLINICAL

Treatment of primary intraocular lymphoma with radiation therapy: A multi-institutional survey in Japan

KOICHI ISOBE[1,2], YASUO EJIMA[1,3], SUNAO TOKUMARU[1,4], NAOTO SHIKAMA[1,5], GEN SUZUKI[1,6], MITSUHIRO TAKEMOTO[1,7], EMIKO TSUCHIDA[1,8], MIWAKO NOMURA[1,9], YUTA SHIBAMOTO[1,10], & NAOFUMI HAYABUCHI[1,6]

[1]*Japanese Society for Therapeutic Radiology and Oncology Lymphoma Study Group, Japan,* [2]*Department of Radiology, Chiba University Hospital, Chiba, Japan,* [3]*Division of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan,* [4]*Department of Radiology, Saga Medical School, Saga, Japan,* [5]*Department of Radiology, Shinshu University, School of Medicine, Matsumoto, Japan,* [6]*Department of Radiology, Kurume University, Kurume, Japan,* [7]*Department of Radiology, Okayama University Hospital, Okayama, Japan,* [8]*Division of Radiation Oncology, Department of Molecular Genetics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan,* [9]*Department of Radiology, Mie University Hospital, Tsu, Japan, and* [10]*Department of Radiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*

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Abstract

This study evaluated the clinical features and treatment outcome of 15 patients with primary intraocular lymphoma. There were nine females, with a median age of 68 years. Thirteen patients presented with bilateral lesions and median time from the onset of symptoms to diagnosis was 12 months. All but one showed the B-cell phenotype. All patients received radiation therapy (RT) with a median of 41 Gy and 10 were administered chemotherapy as well. Three patients were treated with high-dose methotrexate and nine received prophylactic cranial irradiation (PCI) with a median of 30.6 Gy. Thirteen patients obtained a complete remission. The 2-year overall and disease free survival were 74% and 58%, respectively. Although only one patient experienced local recurrence, PCI did not prevent intracranial recurrence. One patient developed a grade 3 cognitive disturbance. It was concluded that ocular RT was effective to control primary lesions. However, some modifications are indispensable to improve outcomes.

Keywords: *Primary intraocular lymphoma, PIOL, radiation therapy, chemotherapy, PCNSL*

Introduction

Primary intraocular lymphoma (PIOL), formally known as ocular reticulum cell sarcoma, is an uncommon clinical manifestation of non-Hodgkin's lymphoma, which arises in the retina or the vitreous humor [1–7]. It usually develops in patients in the fifth and sixth decade of life as a chronic, relapsing and steroid-resistant uveitis and vitritis [3,8–10]. Patients often complain of blurred vision, a painless loss of vision and floaters. According to the previous reports, it took several years from the onset of symptoms to establish a diagnosis of PIOL in some studies [8,9,11–13]. Therefore, physicians should be clinically suspicious of PIOL when uveitis is resistant to treatment with steroids. Cytological or pathological studies of a vitreous biopsy are the most common procedure to confirm a diagnosis of PIOL. However, it is sometimes difficult to make a diagnosis of PIOL, because (1) the cellular content of vitreous samples may be sparse, (2) the number of reactive cells present in the specimen and (3) lymphoma cells are fragile [2–8,11]. In such cases, immunohistochemical studies, flow cytometry and polymerase chain reaction of the rearranged immunoglobulin gene are helpful [14].

Correspondence: Koichi Isobe, MD, Department of Radiology, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba 260-8677, Japan. Tel: +81-43-226-2100. Fax: +81-43-226-2101. E-mail: isobeko@ho.chiba-u.ac.jp

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Intraocular lymphoma may occur independently, prior or subsequent to a primary central nervous system lymphoma (PCNSL). Primary intraocular lymphoma develops intracranial involvement in 60–85% of patients during their course [2–8,11]. On the contrary, recent estimates suggest that 15–25% of patients with PCNSL have ocular disease [3,9]. This previously rare disease has become more frequent along with the increase in the incidence of PCNSL; however, the clinical features and optimal treatment for PIOL have to be clarified.

Until now, many case series and review articles have been published in the literature, but most of these reports contained both PIOL and PCNSL or ocular involvement of systemic lymphoma, which are distinct from PIOL [1–9,11–35]. Thus, we have compiled a multi-institutional retrospective analysis to clarify the clinical features and optimal management of PIOL.

Materials and methods

A survey of patients with PIOL was carried out in May 2005. Between January 1990 and February 2005, eight of 17 institutions of the Japanese Society for Therapeutic Radiology and Oncology Lymphoma Study Group responded on a questionnaire that there were eligible patients. Eligible patients had previously untreated, histologically or cytologically proven non-Hodgkin's lymphoma demonstrating intraocular involvement. Those who had CNS involvement or systemic disease were excluded from this study. Histopathological diagnosis was based upon REAL (revised European–American classification of lymphoid neoplasms) or WHO (World Health Organization) classification [36,37]. However, cytological examination hampered the confirmation of sub-type of lymphoma in some patients. Immunohistochemical study using antibodies against CD20, CD43, CD45RO and CD79a were performed.

In principle, the staging procedures included physical examination, complete blood cell count, liver and renal function tests, ophthalmological examinations with a slit lamp, gallium scintigraphy, computed tomography (CT) of the neck, chest, abdomen and pelvis and bone marrow aspiration or biopsy. An examination of cerebrospinal fluid was undertaken to rule out disseminations. Brain magnetic resonance imaging (MRI) and/or CT was mandatory to exclude ocular involvement of PCNSL.

Since this study was a retrospective multi-institutional survey, treatment strategies were dependent upon the discretions of the treating physician. However, all patients received radiation therapy (RT) using photon beams with two lateral opposed fields. Response to the treatment was determined by ophthalmological findings and imaging studies including brain CT and/or MRI and CT scan from neck to pelvis, according to the standard criteria proposed by Cheson et al. [38]. Overall survival (OAS) and disease-free survival (DFS) were calculated using the method of Kaplan and Meier [39]. The median follow-up was 19.2 months (range 6.9–73 months). Late sequelae were graded according to the National Cancer Institute common toxicity criteria version 2.0.

Results

Patient characteristics

A survey identified 15 patients with PIOL from eight institutions. The median age was 68 years (range 38–84 years) and the male-to-female ratio was 1:1.5. Detailed patient characteristics are shown in Table I. All but two patients presented with bilateral ocular lesions. No patients showed intracranial involvement or systemic diseases as it was an exclusion criteria in this study. Eleven patients had performance status 0–1 (based on the Eastern Cooperative Oncology Group). Median time from the onset of symptoms and diagnosis of PIOL was 12 months (range 5–24 months).

Six patients were diagnosed by histopathological examination and eight cytologically. Two patients required vitrectomy for diagnosis and four patients were diagnosed by vitreal biopsy. In the remaining patient, cytological examination was highly suggestive of lymphoma with monoclonal immunoglobulin heavy chain gene rearrangement. The pathological

Table I. Patient characteristics.

Case no	Age	Sex	Duration of symptom (Mo)	Laterality	Pathology
1	77	F	21	Bilateral	DLBCL
2	67	F	7	Bilateral	DLBCL
3	68	M	20	Bilateral	DLBCL
4	73	M	8	Right	B-NHL
5	56	F	12	Bilateral	DLBCL
6	73	F	12	Left	DLBCL
7	51	F	7	Bilateral	DLBCL
8	38	M	13	Bilateral	B-NHL
9	69	F	24	Bilateral	DLBCL
10	73	F	20	Bilateral	T-NHL
11	54	M	10	Bilateral	B-NHL
12	84	F	5	Bilateral	B-NHL
13	69	M	6	Bilateral	B-NHL
14	48	F	12	Bilateral	B-NHL
15	67	M	11	Bilateral	B-NHL

F; female, M; male, Mo; months, DLBCL; diffuse large B-cell lymphoma, B-NHL; B-cell non-Hodgkin's lymphoma, further unclassified, T-NHL; T-cell non-Hodgkin's lymphoma, further unclassified.

diagnosis was based upon an institutional pathology report without central review. Histopathological diagnosis was diffuse large B-cell lymphoma (DLBCL) in seven patients and B-cell non-Hodgkin's lymphoma (NHL), further unclassified, in seven. The remaining patient demonstrated T-cell receptor gene rearrangement and, as diagnosed as T-cell NHL, further unclassified. In laboratory tests, five patients demonstrated a LDH (lactate dehydrogenase) increment and the level of sIL-2R (soluble interleukin-2 receptor) was elevated in two of 12 patients.

Treatment and outcome

The treatment characteristics are shown in Table II. Eight patients received a combination of chemotherapy and RT, while five were treated solely by RT. The remaining two experienced disease progression to the central nervous system (CNS) during chemotherapy and received salvage RT thereafter. Of the 10 patients who received chemotherapy, only three were treated with high-dose methotrexate (MTX). Four patients received doxorubicin-containing chemotherapy and the remaining three received low-dose MTX. The chemotherapy regimen was dependent upon the discretions of the treating physician. All patients received RT using photon beams with two lateral opposed fields. The total dose of RT ranged from 30–46 Gy, with a median of 41 Gy. Nine patients, including two patients with unilateral disease at presentation, received prophylactic cranial irradiation (PCI), ranging in dose from 24–32 Gy, with a median of 30.6 Gy.

Table II. Treatment and outcome.

Case no	Treatment	Relapse	Outcome	Survival (Mo)
1	Chemo → RT	Brain	DOD	6.9
2	RT → Chemo	Brain	DOD	19.7
3	RT	Brain	DOD	41.3
4	Chemo → RT		NED	25.2
5	RT → Chemo		NED	19
6	RT		NED	27.6
7	Chemo	Brain	DOD	6.9
8	Chemo → RT	Right eye	AWD	73
9	Chemo → RT		NED	39
10	RT		NED	10.8
11	Chemo → RT		NED	27.9
12	RT		NED	18
13	RT	Testis	AWD	19.2
14	Chemo	Brain	AWD	11.4
15	Chemo → RT		NED	11.2

Chemo; chemotherapy, RT; radiation therapy, Mo; months, DOD; dead of disease, NED; no evidence of disease, AWD; alive with disease.

At the time of evaluation, 13 patients achieved complete remission (CR) or CR/unconfirmed (CRu), which resulted in an 87% CR rate (95% confidence interval [CI], 67–100%). Figure 1 shows survival curves in this series. The median OAS was 41 months. The 1- and 2-year OAS were 87% (95% CI, 70–100%) and 74% (95% CI, 47–100%), respectively. The corresponding figures with respect to DFS were 67% (95% CI, 43–91%) and 58% (95% CI, 33–84%), respectively, with a median of 34 months. There were seven patients who experienced recurrences or progression. The radiological studies demonstrated brain involvement in five patients and physical examination including ophthalmological study showed local recurrence and testicular involvement in one patient each. Two of nine patients who received PCI experienced CNS recurrence, while one in four who did not receive it developed brain involvement. ($P=0.50$, Fisher's exact test) Those who received high-dose MTX did not experience CNS recurrence. At the last contact, four patients had died of their disease.

Treatment sequelae

With regard to late adverse events, a 73 year old female developed a grade 3 cognitive disturbance 27 months after RT. She received 32 Gy of PCI without chemotherapy. She also developed turbidity of the vitreous body 2 years after RT. One patient developed Grade 2 cataract and another four assessable patients who survived more than 1 year experienced no late adverse events, including retinopathy, optic neuropathy, cataract or brain injury.

Discussion

Primary intraocular lymphoma is designated as an extra-nodal non-Hodgkin's lymphoma of the eye

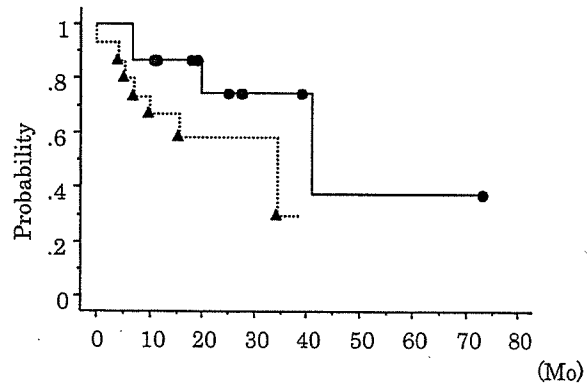

Figure 1. The curves for overall survival (solid line) and disease-free survival (dashed line).

without evidence of systemic or CNS disease. It was first described in 1951, and was originally named 'ocular reticulum cell sarcoma' [1]. Until now, many case series and review articles have been published in the literature, but most of these reports contained not only a small number of patients with PIOL, but also a large majority of PCNSL [1–28]. Thus, the findings from these reports were largely dependent upon PCNSL. Furthermore, some articles reported the ocular involvement of systemic lymphoma, which is distinct from PIOL [29–35]. These circumstances have obscured our understanding with regard to the clinical features and optimal management of PIOL. Thus, we summarize the patient characteristics in Table III. The median age of onset was 50s to 60s with some female preponderance. These findings are well in accordance with our current study.

Many researchers have concurred that the diagnostic difficulty and delay from presentation is one of the major problems in the management of PIOL [8,9,11–13]. The time from onset of ocular symptoms to diagnosis ranged from 1–48 months and many researchers argue that early diagnosis would lead to an improvement in outcome [8–10,12,13]. The diagnosis of PIOL was based upon cytological or histological examination of samples from the vitreous body, but these specimens are fragile and difficult to handle. Thus, in addition to routine cytological or histopathological examinations, some molecular studies, including polymerase chain reaction of the rearranged immunoglobulin gene, and flow cytometry would be helpful [14]. Although it was not diagnostic, Cassoux et al. [12] also recommended the measurement of the IL-10 to IL-6 ratio in the vitreous fluid. The utility of other markers such as LDH, sIL-2R and beta 2 microglobulin has not yet been evaluated.

Table III. Summary of literatures. Patient characteristics.

Ref	*n*	Age (median)	Male/ female	Time to diagnosis (median)
[1]	1	27	1/0	5
[9]	12	32–67 (58)	4/8	NR
[10]	6	46–74 (56)	4/2	1–48 (17)
[13]	4	61–70 (70)	3/1	NR
[15]	2	65–81	1/1	26–35 (30)
[16]	2	66–68	1/1	NR
[17]	1	56	1/0	48
[18]	1	37	0/1	6
[19]	1	37	0/1	8
[20]	5	62–72 (66)	1/4	NR
[21]	13	27–77 (66)	6/7	NR
[22]	1	62	1/0	NR
[23]	1	57	0/1	NR
[24]	4	46–61 (51)	2/2	NR
[25]	4	31–71 (50)	NR	NR
[27]	1	83	0/1	NR
[28]	8	NR	4/4	NR
Current	15	34–84 (68)	6/9	5–24 (12)

Ref; references, NR; not reported.

The most important issue that must be resolved has been the optimal treatment for PIOL. We summarize literatures concerning treatment, outcome and late sequelae in Table IV. Old series published in 1980s indicated that RT was first choice of treatment. Several reports discussed the optimal radiation doses and treatment portal. Some authors reported beneficial effect of RT with 35–45 Gy exclusively to the ocular lesions, given that CNS disease cannot be found [8,9]. On the other hand, other groups recommend PCI doses up to 45 Gy because the vast majority of patients eventually develop CNS diseases [15,18–22]. We observed only one local recurrence after RT with a median dose of 41 Gy in this series, which suggested that 40 Gy of RT is enough to eradicate PIOL. However, we were not able to demonstrate any decrease in CNS relapse after PCI with a median dose of 30.6 Gy. It is possible to hypothesize that higher doses are necessary to eliminate microscopic CNS disease. However, we have to be aware of the fact that higher dose RT might lead to detrimental late neurological deficits. In fact, an elderly woman developed a grade 3 cognitive disturbance after 32 Gy of PCI in this series. We did not experience CNS recurrence after high-dose MTX; thus, we advocate a strategy that combines high-dose MTX and PCI with doses of 30 Gy to control microscopic CNS disease.

In the place of RT, recent publications have recommended high-dose intravenous MTX following encouraging results in the treatment of PCNSL [3–7,12,23,25]. In fact, de Smet et al. [40] demonstrated that sustained cytotoxic MTX levels in the aqueous humor were achievable after 8.4 g/m^2 of systemic MTX administration. However, several groups have reported that ocular lesions were less responsive than those of CNS disease because vitreous MTX concentration was usually lower than that of the anterior chamber [5,25]. To overcome this problem, Fishburne et al. [41] used an intravitreal MTX injection. They reported that four patients with recurrent PIOL or PCNSL were successfully salvaged by intravitreal MTX injection without serious ocular toxic reactions. Intrathecal injection is another route for MTX administration; however, its efficacy remains to be confirmed [26].

Baumann et al. [35] treated a patient with ocular involvement from a primary breast lymphoma with high-dose cytosine arabinoside (Ara-C). They demonstrated that systemic administration of 3 g/m^2 of Ara-C also gained therapeutic levels in the anterior chamber and the vitreous humor similar to that of

Table IV. Summary of literatures. Treatment, outcome and late sequelae.

Ref	Treatment	CNS (%)	OAS (Mo)	Recommendations	Late Sequelae (%)
[1]	RT	NR	11	NR	NR
[9]	CS or RT	83	11–87	NR	NR
[11]	RT	0	24–109	NR	NR
[12]	Chemo or RT	48	NR	MTX	NR
[13]	RT + Chemo	75	14–103	Chemo	Cataract (50), Dry eye (40), Retinopathy (20), Keratopathy (20)
[15]	RT	50	9–39	RT (PCI)	Retinal atrophy (50)
[19]	RT + Chemo	0	48	Chemo + RT (PCI)	NR
[20]	Ara-C + RT	NR	6–42	Ara-C + RT (PCI)	NR
[21]	RT or Chemo	27	3–90	Ara-C + RT (PCI)	NR
[22]	Ara-C + RT	0	33	Ara-C + RT (PCI)	NR
[23]	MTX + Ara-C	0	NR	Chemo	Neurocognitive dysfunction (38)
[24]	Transplantation	0	46–84	Chemo	Cognitive dysfunction (32)
[25]	MTX	NR	8–85	MTX	No neurotoxicities
[27]	Oral Alkylator	0	8	NR	None
Current	RT + Chemo or RT	33	7–73	MTX + RT	Cognitive disturbance (10), Cataract (20)

Ref; references, CNS; central nervous system recurrence, OAS; overall survival, Mo; months, RT; radiation therapy, NR; not reported, CS: corticosteroid, Chemo; chemotherapy, MTX; methotrexate, Ara-C; cytosine arabinoside, PCI; prophylactic cranial irradiation.

high-dose MTX. Several groups have also demonstrated the efficacy of high-dose Ara-C, which suggested that it might be an alternative to high-dose MTX [20–22]. Jahnke et al. [27] showed that an oral alkylating cytostatic agent, trofosfamide, is effective with a favorable toxicity profile. They concluded that trofosfamide may offer an alternative treatment option for PIOL.

Radiation therapy rapidly improves patients' symptoms, but does cause late sequelae including cataracts, dry eye, optic neuropathy and retinopathy. Hoffman et al. [13] reported that 50% of patients developed cataracts. They also stated that 20% experienced retinopathy and 10% developed optic nerve atrophy. Other researchers have reported that half of the patients developed retinal atrophy after RT [15]. We also observed cataracts in 20% of patients. It has also been well known that detrimental neurocognitive dysfunction would develop after whole-brain irradiation. In fact, we observed a grade 3 cognitive disturbance in this series. In addition to whole-brain irradiation, chemotherapy, especially high-dose MTX, for elderly patients has also caused leukoencephalopathy. Two groups reported that about one-third of patients developed cognitive dysfunction after high-dose MTX or high-dose chemotherapy with stem cell support [23,24]. Thus, Valluri et al. [22] recommended that a combination of chemotherapy and lower dose RT may reduce radiation induced ocular morbidity.

In conclusion, the prognosis of intraocular lymphoma still remains poor, but it is impossible to establish optimal therapeutic strategies in a randomized trial due to its rarity. Systemic chemotherapy alone may not be sufficient to control PIOL and ocular RT appears still indispensable. The high incidence of CNS recurrence and the late sequelae such as cataracts, retinopathy and neurocognitive dysfunction were also problematic in the management of PIOL. From the literature review and our current experience, we recommend delivering 40 Gy of ocular RT, PCI with doses 30 Gy and high-dose MTX to control PIOL.

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CHOICE OF BEAM ENERGY AND DOSIMETRIC IMPLICATIONS FOR RADIATION TREATMENT IN A SUBPOPULATION OF WOMEN WITH LARGE BREASTS IN THE UNITED STATES AND JAPAN

INDRA J. DAS, PH.D., NAOTO SHIKAMA, M.D., CHEE-WAI CHENG, PH.D., and LAWRENCE J. SOLIN, M.D.

Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA; Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan; and Department of Radiology, Morristown Memorial Hospital, Morristown, NJ

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Abstract—Radiation complications are often related to the dose inhomogeneity (hot spot) in breast tissue treated with conservative therapy, especially for large patients. The effect of photon energy on radiation dose distribution is analyzed to provide guidelines for the selection of beam energy when tangential fields and limited slices are used to treat women with large breasts. Forty-eight patients with chest wall separation > 22 cm were selected for dosimetric analysis. We compared the maximum dose in the central axis (CAX) plane (2D) using 6-, 10-, and 18-MV photon beams in all patients and 3D data set for 16 patients. Correlation between hot spot dose (HSD), separation, breast cup size, breast volume, and body weight was derived with beam energy. Among the 48 patients in this study, HSD > 10% in the CAX plane was noted in 98%, 46%, and 4% of the population when 2D dosimetry was performed; however, with 3D study, it was in 50%, 19%, and 6% of the patients with 6-MV, 10-MV and 18-MV beams, respectively. The chest wall separation, body weight, and breast volume were correlated with the HSD in both the 2D and 3D plans. Patient's bra size was not correlated with the hot spot. The chest wall separation was found to be the most important parameter to correlate with hot spot in tangential breast treatment. Simple guidelines are provided for dose uniformity in breast with respect to chest wall separation, body weight, bra size, and breast volume with tangential field irradiations. © **2006 American Association of Medical Dosimetrists.**

Key Words: **Breast cancer, Radiation dose distribution, Hot spot, Beam energy.**

INTRODUCTION

Radiation dose distribution plays an important role in the outcome analysis of the radiation treatment. However, optimum dose distribution cannot be achieved in the majority of the patients who are treated with breast conservative therapy using three-dimensional (3D) planning with low-energy beams. Traditionally, low-energy beams have been used for breast treatment to provide adequate subcutaneous dose.[1] There is a growing trend of obesity in affluent countries, including the United States, which could impact the breast patient population treated with tangential fields. Often, treatment planning for breast cancer is performed on the central axis (CAX) slice only. However, with the availability of computed tomography (CT) simulation, more patients are being planned with 3D data sets, where hot spots in the entire breast tissue can be readily appreciated and an optimized plan can be used for the treatment. Unfortunately, the hot spot cannot be eliminated with simple wedge pair tangential technique for breast treatment. Various techniques such as field-within-a-field, multisegmented fields, and some form of intensity-modulated beams have been developed to reduce hot spots and to provide a uniform dose to the entire breast.[2–9] Intensity-modulated radiation therapy (IMRT) for breast cancer has also been employed. However, for most clinicians, IMRT for breast is still a debatable issue, due to the lack of suitable standardized optimization software and unavailability of long-term outcome data.

It is a known fact that dose uniformity in breast tissue decreases, especially for large breasts. An analysis of the frequency distributions of patients in the United States from patterns-of-care studies (PCS),[10] Japan, and our institutions (Fig. 1) shows fewer Japanese patients who have large breasts, which might impact the dosimetry of the tangential fields, compared to their United States counterparts. The chest wall separation in the Japanese patient population ranged from 14 to 27.5 cm, with a median value of 18.7 cm (Fig. 1). Among Japanese patients, 14% had large chest wall separation more than 22 cm. On the other hand, the chest wall separation in the United States patients' population ranged from 13 to 35 cm, with a median value of 21 cm.[10] A large subset of the patients (40%) treated in the United States is obese, with a chest wall separation in the range of 22–32 cm. The difference between the PCS and our patient population is significant, which could be attributed to the small pool size and the selection of patients in this study.

Reprint requests to: Indra J. Das, Ph.D., Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA 19104. E-mail: das@xrt.upenn.edu

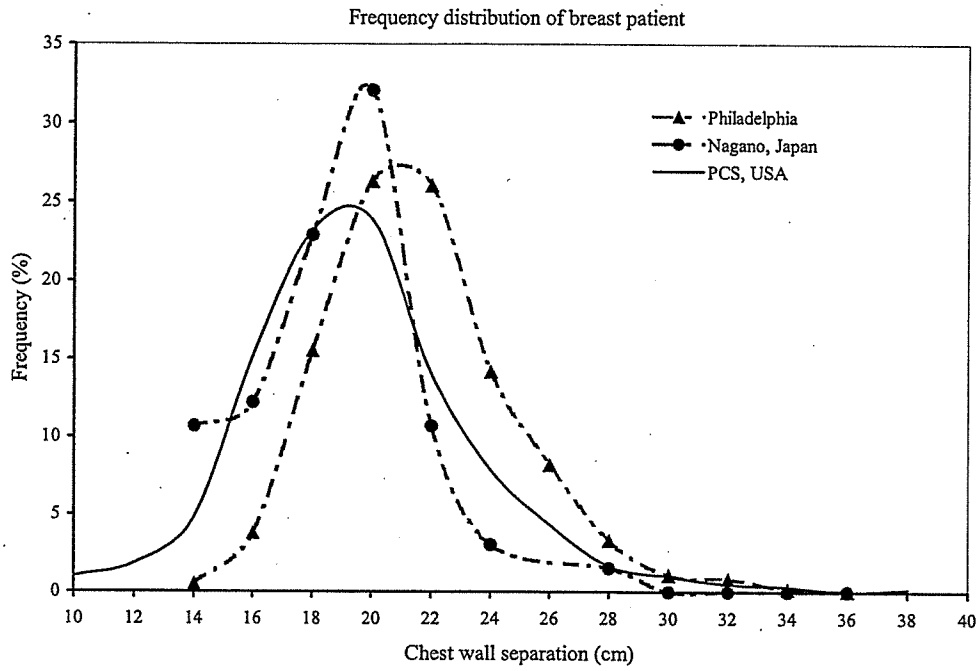

Fig. 1. Frequency distribution of the patient population in our institution, United States, and Japan.

Among the various risk factors associated with poor cosmetic result is breast size, which may indirectly be related to the dose uniformity.[11–20] Most radiation oncologists still favor low-energy photon beams for breast irradiation, although the rationale of such selection for large breasts is not clearly understood. While dose rate and dose uniformity seem to dictate the cosmetic outcome, it is not clear if the underlying issue is related to clinical or physical factors. Das *et al.*[21] reported that chest wall separation is the single most important parameter that is strongly correlated with dose inhomogeneity (hot spot) in tangential breast irradiation. Based on the hot spot criterion,[21] the patients with chest wall separation of more than 22 cm could benefit from treatment using high-energy photon beams degraded with a beam spoiler, to achieve good dose distribution in subcutaneous tissue and to reduce hot spots.[22]

In this study, we investigated the influence of high-energy photon beams on single slice (2D) and multi-slice 3D dose distribution of large-breasted (large chest wall separation) patients who are treated with conservative therapy. Selection of beam energy, in terms of hot spot and various physical parameters, is also presented.

METHODS AND MATERIALS

The chest wall separation was defined as the distance between the midline of the anterior chest wall and the point that was 2 cm below the palpable breast in the CAX plane.[21,23] We reviewed the breast patient population with respect to chest wall separation in Japan and the published data from PCS in the United States[10] for frequency distribution, as shown in Fig. 1. Forty-eight patients with chest wall separation greater than 22 cm in this study were selected from a Unites States population. We measured the chest wall separation in each patient manually or using the CT image in the CAX plane. This data is taken as a sample representation of the population of the breast treatment in Japan and the United States.

This study was performed retrospectively without compromising confidentiality of the patients and hence institutional review board approval was not deemed necessary. All patients were referred for whole breast radiation treatment after breast-conserving surgery. In 32 patients, calculation of dose distribution was performed using the CAX plane alone (2D), and in another 16 patients, calculation of dose distribution was performed using multi-slices (3D) using ROCS treatment planning system (San Diego, CA). Patients were immobilized using Alpha-Cradle and positioned supine with shoulders and elbows flexed and arm overhead. Using a CT simulator, patients were simulated on an inclined board. For 2D patient study, the simulation was performed on a conventional simulator. For 3D study, patients were aligned and positioned to fit through the CT aperture. The chest was carefully palpated to define the borders of the breast, which were marked with thin lead wires. Patients were scanned with 3-mm slice width and 3-mm step size for better digitally-reconstructed radiographs. Each study was transferred to the VoxelQ processor for virtual simulation. A clinical target volume (CTV) was defined on each slice to cover the breast tissue adequately, and the outer contour of CTV was placed on the breast surface. Calculation of breast volume was based on the contours of CTV. Lung volume was also delin-

eated on each slice. The medial border of the radiation field was at the midline of the anterior chest wall, and the lateral border was 2 cm beyond the palpable breast. The upper border was 2 cm beyond the cephalic extent of the palpable breast, and the lower border was 2 cm below the inframammary fold. Medial and lateral tangential fields were set up such that both covered the breast tissue adequately with 2–3 cm of lung tissue.

The posterior beam edge was made coplanar and nondivergent. The reference point of prescribed dose was defined to a point 1.5 cm above the posterior beam edge as described by Das *et al.*[21] Treatment planning was performed to give uniform dose distribution with proper wedge and beam weights for all patients. We compared the maximum dose in the CAX slice using 6-, 10-, and 18-MV photon beams in all 48 patients. ICRU-50[24] has defined hot spot dose (HSD) and maximum dose; however, clinically accepted hot spot[25] area is 2 cm^2, which is used in this study. We analyzed the correlation between hot spot in the CAX plane and such clinical factors as body weight and preoperative bra size, which were gathered from the patient's chart. For the 16 patients with 3D breast planning, we compared the maximum dose in the CAX plane with those in other calculation planes (off-axis +3 cm, +6 cm, +9 cm; cephalus, −3 cm, −6 cm, −9 cm; caudal) with inhomogeneity correction using 6-, 10-, and 18-MV photon beams. We also analyzed the correlation between the maximum dose in multi-slices with various parameters found in the chart such as body weight, preoperative bra size, and breast volume.

RESULTS

2D analysis

Figure 2 shows the hot spot data for a single slice study for 3 energies. Using a 6-MV photon beam, a maximum dose in the CAX plane of more than 10% of the prescribed dose was observed in 98% (47 of 48) of patients. With 10-MV photon beams, it was found in 46% (22 of 48) of patients. When using 18-MV photon beams, it was found only in 4% (2 of 48) of patients. Thus, chest wall separation was strongly correlated with maximum dose in the CAX plane, as shown also by Das *et al.*[21] The HSD was given a functional form with respect to chest wall separation (S).

$$HSD = \alpha S + \beta \quad (1)$$

The α and β are fitted parameters that are shown in Fig. 2 and are noted to be 1.56, 0.99, 0.62, and 78.5%, 84.7%, and 91.4% for the 6-, 10-, and 18-MV beams, respectively. This correlation can be used to predict the HSD in 2D planning. It is shown that ± 5% dose uniformity in breast tissue is hard to achieve with tangential field. The line at the 15% hot spot is drawn to show the choice of energy where such criterion cannot be met.

Body weight of the patient population ranged from 63 to 136 kg, and preoperative bra size ranged from 34B to 41DDD/46D. Body weight was slightly correlated with maximum dose in the CAX plane for all photon energies (Fig. 3). Similar to Eq. (1), HSD can be correlated with body weight with parameters as noted in Fig. 3

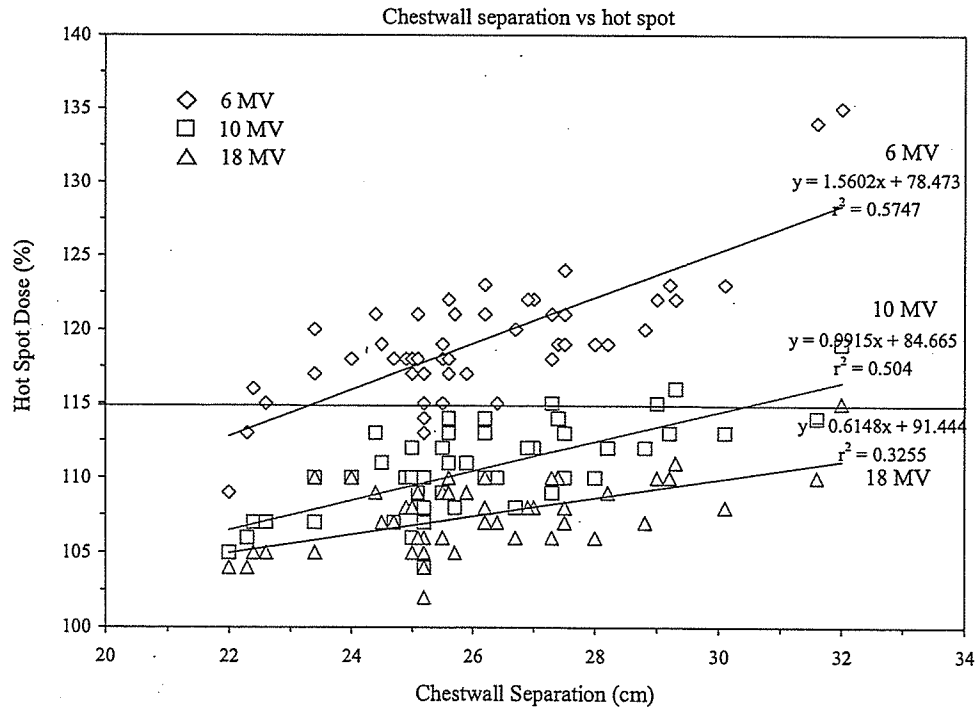

Fig. 2. The maximum HSD (%) at central axis slice vs. chest wall separation with various photon energies. Regression coefficients are also shown.

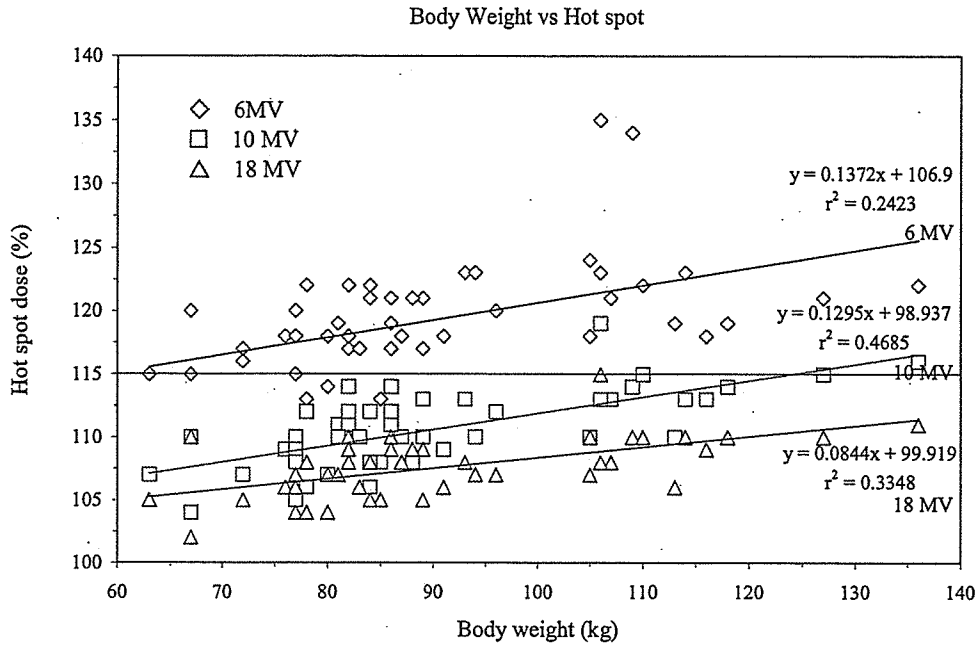

Fig. 3. The correlation between the maximum HSD (%) at central axis slice and body weight. Data with various photon energies and related regressions are shown.

for 6-, 10-, and 18-MV beams, with relatively poor regression coefficient r^2 0.24, 0.47, and 0.33, respectively. These fitted parameters shown in Figs. 2 and 3 are dependent on the accuracy of dose calculation, which varies significantly among various treatment planning systems, as noted by Cheng *et al.*[26] The present data and fitted parameters should be used with caution due to the variability of dose algorithm among the different planning systems. Preoperative bra cup size was not correlated with HSD at the CAX plane using 6-, 10-, or 18-MV photon beams, as shown in Fig. 4, with regression coefficients (r^2) of 0.05, 0.07, and 0.1, for the 6-,

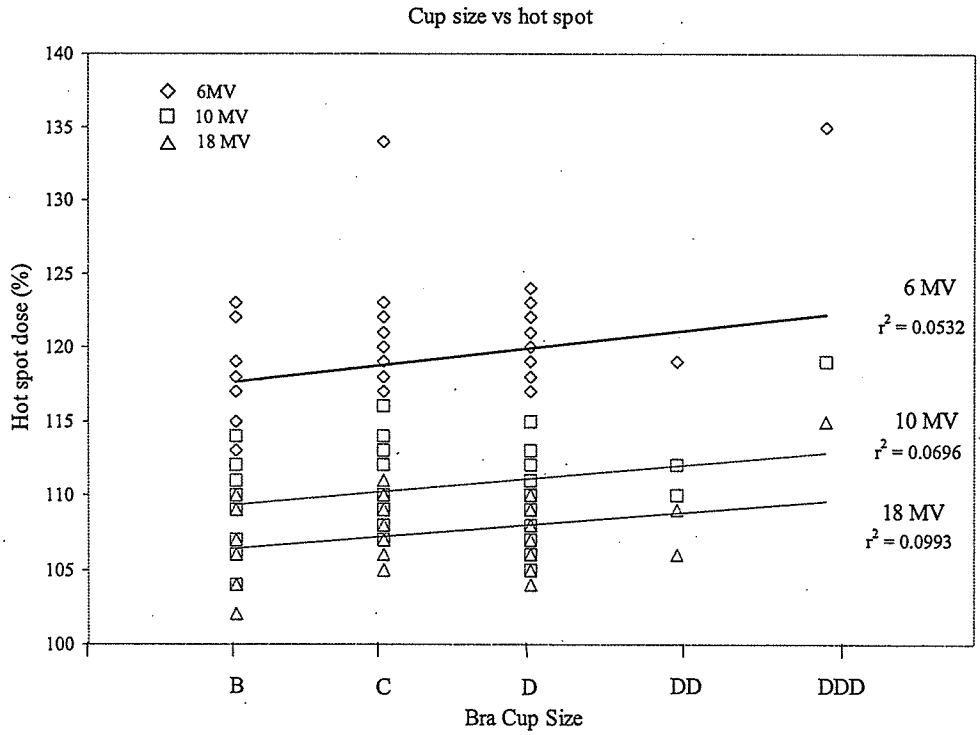

Fig. 4. The maximum HSD (%) at central axis slice plotted against breast cup size and photon energy.

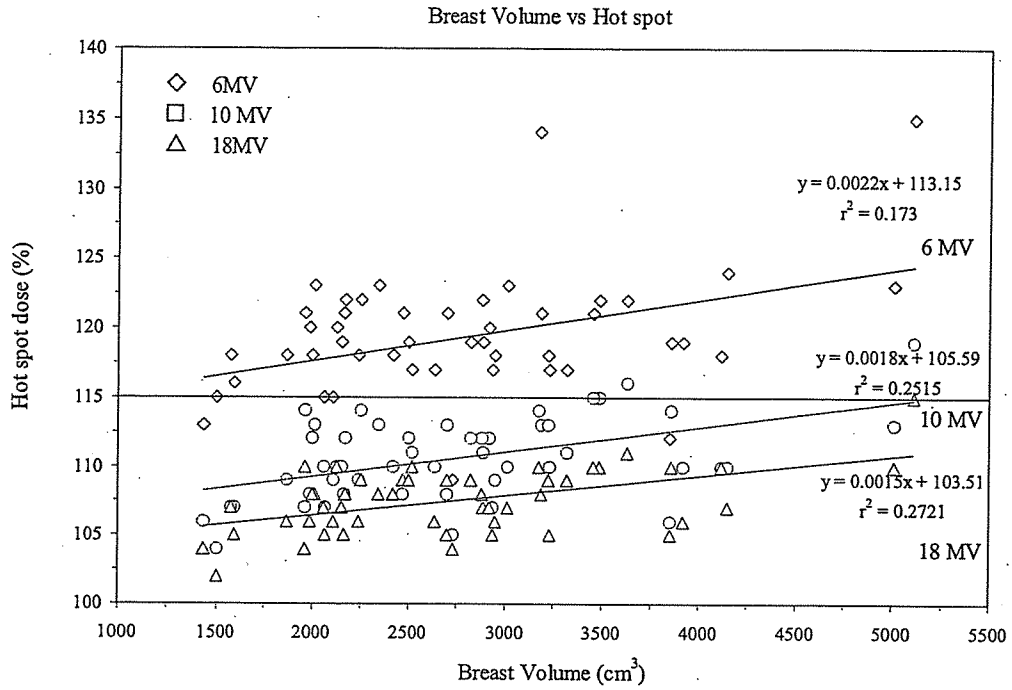

Fig. 5. The maximum HSD (%) vs. breast volume when 3D dose distribution is performed. Note that hot spot reduces with beam energy but increases linearly with breast volume.

10-, and 18-MV x-ray beams, respectively. It is obvious that bra size is a poor measure of the breast parameter and should not be used for quantitative dosimetry and outcome analysis. Although breast volume (breast size) is independent of the chest wall separation, a good correlation was observed in this study. The breast volume was also correlated with the HSD, as shown in Fig. 5, but with relatively weaker r^2.

3D analysis

Evaluation of dose distribution using 3D data set was accomplished in a limited set (16) of patients. The calculated breast volume ranged from 793 cm^3 to 3221 cm^3, and the median volume was 1423 cm^3 in the 3D study, as shown in Table 1. Even though a limited set of slices could provide a general dose distribution, as suggested by Cheng et al,[27] full CT data was used in this study to evaluate the global hot spot with proper inhomogeneity correction.

The correlation between the maximum HSD in 3D between chest wall, body weight, and breast volume was similar to the 2D results, except that the magnitude of the hot spots was higher. This is shown in Fig. 6 with respect to the chest wall separation. The error bar represents the

Table 1. Characteristics of patients for 3D dose calculation

Chest Wall Separation (cm)	Body Weight (kg)	Bra Cup Size	Breast Volume (cm^3)	Difference in HSD in 3D Breast to CAX (%)		
				6 MV	10 MV	18 MV
32.0	106	DDD	3050	6	4	3
24.0	105	DD	3221	3	3	2
24.4	89	DD	1706	10	7	7
27.5	107	D	1454	9	8	7
22.4	72	D	970	4	7	5
24.7	80	B	835	9	8	4
23.4	72	D	1511	10	9	7
22.6	63	D	1113	10	7	6
24.5	81	D	1450	7	6	7
22.0	77	D	1423	14	10	7
25.0	84	D	1685	10	8	7
23.4	67	D	793	9	8	5
24.9	87	D	1490	12	11	10
22.3	78	B	793	17	9	7
25.1	88	D	1174	11	12	8
25.5	91	D	1184	5	1	1

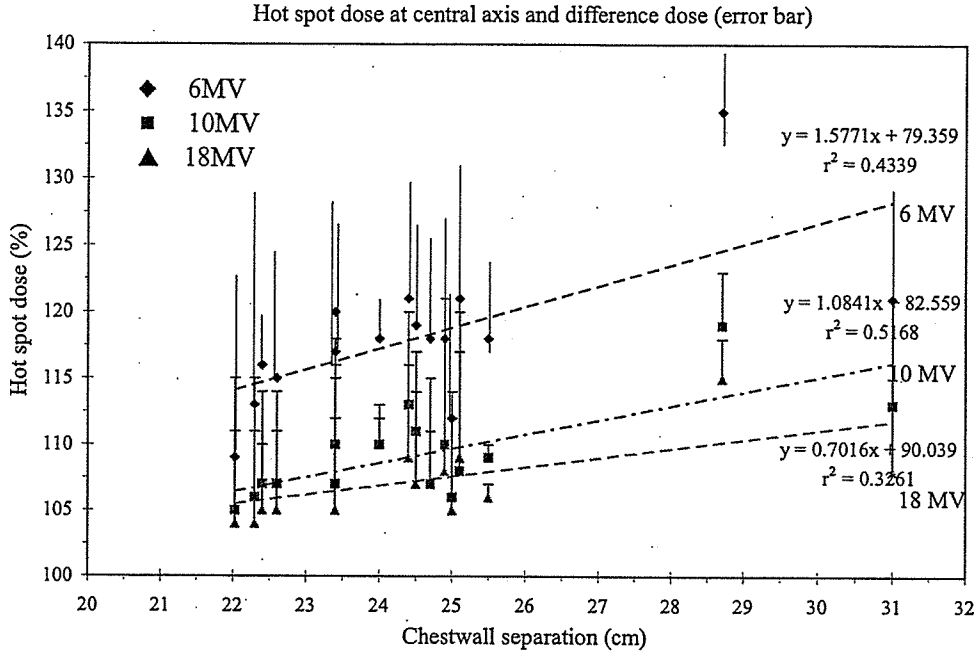

Fig. 6. Plot of HSD vs. chest wall separation when 3D (multi-slice) dose calculation is performed. The error bar indicates the differences in global hot spots to the central axis hot spot for various energies. The fitted parameters and regression coefficients are also noted.

difference in the global hot spot for 3D calculation. Using 6-MV photon beams, the maximum dose (> 10%) in multi-slice calculation was noted in 50% of the patients (Table 1). However, using 10- and 18-MV beams, HSD > 10% was found in only in 19% (3 patients) and 6%, (1 patient), respectively, when 3D multi-slice planning was used. The difference between the maximum dose in the multi-slice planning and that in the 2D planning calculation was not dependent on the chest wall separation, body weight, and preoperative bra cup size and breast volume as shown in Table 1. When 3D data was used, the dose inhomogeneity for 6-MV beam was much greater than that for the 10- and 18-MV photon beams, as noted in Fig. 6. Using 6-MV beams, the maximum dose was seen in the −9 cm or −6 cm plane cranial to the central in 81% (13 of 16) patients. However, with 10- and 18-MV beams, the HSD were seen in the −9-cm or −6-cm plane in 15 patients.

DISCUSSION

Dose uniformity in the target volume is greatly desired within ± 5%. However, with low-energy beams and wide separation of chest wall, often variation up to 15% is clinically tolerated in breast treatment. Dose inhomogeneity in breast tissue has been attributed to the lung correction, size of the breast, and beam energy.[18,21,28] Neal *et al.*[29] reported the positive correlation for breast dose inhomogeneity vs. bra cup size, breast area, and chest wall separation. Incidentally, when women with large breasts are planned and treated, high-energy beam is needed (Figs. 2–4). In our experience, bra cup size was not correlated with hot spots. On the other hand, body weight and breast volume had a weak correlation with dose inhomogeneity, given that we selected patients with large breasts who had chest wall separation of more than 22 cm in this study. The chest wall separation, which is easily acquired for treatment planning, was found to be the most important factor for estimation of dose uniformity in breast treatment.

At some institutions, patients with large breasts are treated with high-energy photon beams to achieve good dose distribution. However, high-energy photon beams reduce the subcutaneous dose because of the buildup phenomenon. Using 3D planning with varying photon energies, Solin *et al.*[30] demonstrated that the use of Cobalt-60 (^{60}Co) was associated with an increase in the magnitude and volume of hot spots, and high-energy photons, such as 10- and 15-MV, were associated with less acceptable target coverage at shallow depths. A Lucite beam spoiler or bolus can overcome the effects of skin sparing of high-energy photon beam.[22,31] Wertheim *et al.*[32] evaluated 1000 mastectomy specimens histologically, and reported that the incidence of skin involvement was uncommon in patients with early breast cancer. Also, Monson *et al.*[1] reported that machine energy less than 8 MV did not significantly affect treatment outcome, such as skin and breast recurrences, without bolus and beam spoiler. They reported skin failures represented less than 1% of failures in each energy, which included 4-, 6-, and 8-MV photon beams. In our institution, high-

energy photon beam with beam spoiler does not seem to lead to high frequency of local recurrence after breast conservative therapy.

Das *et al.*[21] reported that the HSD ranged between 115% and 125% depending on the treatment protocol and breast size, and only 57% of the patient population had hot spots of less than 10% on the central axis plane using 6-MV photon beam. Buchholz *et al.*[33] studied the dose inhomogeneity of off-axis planes for breast cancer, and suggested that in women with large breasts, a significant volume of breast tissue receives both a daily fractionated dose and a total dose of 10% or greater than the prescription dose. It was also noted that the greatest dose inhomogeneity occurred in the lower anatomical quadrants of the breast. Incidentally, our data showed that the greatest dose inhomogeneity was observed in the upper anatomical quadrants, where separation could be significant. The patients in our study were selectively chosen to have large breasts (S > 22 cm), which might have contributed to this difference. With the availability of 3D data sets from CT simulation, such issues are insignificant, because off-axis dose inhomogeneity should be considered in the planning of tumor bed with proper lung correction. Although this study does not provide clinical data for cosmesis or outcome, hot spots play an important role and should be avoided. The radiation outcome could also be dependent on the difference normalization points (dosimetry), fraction size, duration of treatment, the boost technique, surgical techniques, and chemotherapy.

Various studies[27,34] have analyzed the number of CT slices for breast planning; however, a 3D study provides a comprehensive data set to allow determination of global maximum and accurate inhomogeneity correction, as noted by Chin *et al.*[28] The role of 3D treatment planning for breast cancer has become important with the availability of CT data. A single slice (2D) approach for breast planning does not provide adequate knowledge of hot and cold spots, even though limited slices analysis has been suggested.[27] The data presented here could be used to estimate the expected HSD in a central axis slice with various parameters, which may lead to better decision making, either by changing the technique, as suggested by various groups, from supine to prone treatment,[35–38] or by increasing the beam energy. More refined treatment techniques such as the use of proton beams, IMRT, and segmented therapy with low energy have been proposed.[2,3,6–8,39–45] However, for most clinics, such options are not available, and the simple 2D technique is still prevalent.

CONCLUSIONS

A correlation between chest wall separation and HSD (dose heterogeneity) is presented for various photon energies in simple tangential breast treatment (Fig. 2). This correlation provides an easy estimate in selecting beam energy where high-energy photon beams may be useful to achieve good 2D and 3D dose distribution in patients with large breasts. For an acceptable hot spot of 15% in breast tissue, a chest wall separation > 22 cm may require energy higher than 6 MV and for chest wall separation > 28 cm, beam energy higher than 10 MV is needed (Figs. 2 and 3). For the Japanese population, our results show that low-energy beam could still be used for the majority of the patients. Body weight could be a surrogate for the breast size and chest wall separation, which is correlated with the hot spot and beam energy (Fig. 3). Bra size is not correlated with the hot spot and beam energy. A direct relationship is also provided when breast volume is available and maximum dose in breast with respect to beam energy is needed (Fig. 5). To appreciate the magnitude of the hot spot in the entire breast, single-slice approach should be avoided and a 3D dose distribution should be performed to appreciate the dose to the tumor bed and the degree of dose inhomogeneity.

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特集

PCSによるわが国の放射線治療の現状とEBM

1 乳癌PCS（PMRT例）

わが国における乳房切除後照射の問題点

鹿間直人*1　荒川和清*2　光森通英*3　山内智香子*3
武川英樹*4　手島昭樹*4　日本PCS作業部会

Patterns of Care Study: Role as a Monitor of Changing Practice Patterns in Post-Mastectomy Radiotherapy: Shikama N*1, Arakawa K*2, Mitsumori M*3, Yamauchi C*3, Takekawa H*4, Teshima T*4 and Japanese PCS Working Subgroup of Breast Cancer (*1Dept of Radiology, Shinshu Univ School of Med, *2Dept of Radiology, Ina General Hospital, *3Dept of Radiation Oncology and Image-applied Therapy, Graduate School of Med, Kyoto Univ, *4Dept of Medical Engineering, Oosaka Univ Faculty of Med)

The first survey (JPCS-1) was carried out in 1998～2000 and the second survey (JPCS-2) was carried out in 2001～2003. Patients with risk factors, including pathologically axillary positive nodes (≥4) and/or advanced primary disease (T3～4), accounted for 57% of the total number of patients who received PMRT in JPCS-1 and 72% of those in JPCS-2 (p=.039). Complex irradiation volumes including the chest wall and regional lymph nodes were applied in 18% of the patients in JPCS-1 and 44% of those in JPCS-2 (p<.0001). However, the dose distribution was calculated in only 42% of the patients in the two surveys (p=.467). The PCS survey is useful to monitor changing practice patterns of PMRT and to clarify the problems associated with radiotherapy.

Key words: Postmastectomy radiotherapy, Radiotherapy, Breast cancer, Patterns of care study
Jpn J Cancer Clin 51(13): 997～1002, 2005

はじめに

1990年代前半までは，局所進行期乳癌に関しては乳房切除後の術後放射線治療は局所再発の減少効果はあるものの生存率の向上には繋がらないとされてきた[1]．これまでの臨床試験では現在考えられているような適切な全身療法が行われていなかったことや，当時の放射線治療技術に問題があり心毒性を初めとする生命を脅かす遅発性有害事象を引き起こすことが後に判明した．しかし，1990年代後半に発表された三つのランダム化比較試験では乳房切除後の放射線治療は局所制御率を向上させるだけでなく，生存率をも向上させることが示された[2～5]．欧米では乳房切除後照射の適応や照射技術に関してコンセンサスが得られつつあり，2001年には米国がん治療学会（ASCO）は乳房切除後照射に関するガイドラインを報告し，広く一般臨床に浸透している[6,7]．一方，わが国でも2003年に厚生労働省科学研究費補助金医療技術評価総合研究事業を財政基盤として，「科学的根拠に基づく乳がん診療ガイドライン作成に関する研究」高嶋班（H14-医療-064）が組織されわが国初の本格的な診療ガイドラインが作成された．2005年には日本乳癌学会が，高嶋班

*1 信州大学医学部画像医学講座
*2 伊那中央病院放射線科
*3 京都大学大学院医学研究科放射線医学講座放射線腫瘍学・画像応用治療学
*4 大阪大学大学院医学系研究科医用物理工学講座

で作成した診療ガイドラインの改定を行い公表に至った（科学的根拠に基づく乳癌診療ガイドライン，日本乳癌学会編；金原出版）．

これまでにもわれわれはわが国の乳癌診療における放射線治療の現状把握と問題点を明らかにするため，Patterns of Care Study (PCS) の手法を用いてモニタリングを行い，放射線診療の構造や課程における問題点を明らかにするとともに警鐘を鳴らしてきた[8~10]．1990年代後半にデンマークとカナダから報告された信頼性の高いランダム化比較試験の前後に，われわれは2回の調査を行った．本稿では，わが国の診療が海外のエビデンスをどのように受け入れ変化しているのか，また1回目の訪問調査で明らかになった放射線治療の診療課程の問題点が改善されているのかを検討した．また，PCSの手法が乳房切除後照射の診療課程のモニタリングにどこまで有用であり，また今後さらに診療課程の改善を図るためにどのようなモニタリングを行うべきかを検討したので報告する．

1. 対象および方法

調査対象となる施設および症例を2段階クラスターサンプリング法にて選択し，1回目の調査は1995年から1997年までに放射線治療が行われた乳癌症例を，2回目の調査では1999年から2001年に放射線治療を受けた症例を対象とした[11]．調査方法の詳細はこれまでの報告の通りである[8]．調査対象は以下の条件を除外規準とした．1) 遠隔転移例，2) 両側乳癌，3) びまん性石灰化を呈する症例，4) 多発乳癌，5) 過去に胸部に放射線治療の既往のある症例，6) 男性，7) 同時重複癌を有する症例，8) 膠原病（リウマチを除く）を有する症例．1回目の調査では，全国556施設から79施設を抽出し，1,124症例のデータを収集し，また2回目の調査では641施設から76施設を抽出し，827症例のデータを集積した．施設層別の検討を行うため，大学病院およびがんセンターをA施設とし，それ以外の施設をB施設とした．

2. 結果

1回目の調査で集積した1,124例のうち，乳房温存療法症例が行われた症例が866例であり，乳房切除後照射例が258例（22.9%）であった．2回目の調査で収集した827例のうち，756例が乳房温存療法例であり，81例（9.7%）が乳房切除後照射例で（$p<0.00001$），2回目の調査では乳房切除後照射が行われた症例の割合が減少していた．乳房切除後照射の施行率が減少したという見方の他に，検診の普及などにより早期乳癌が多く発見され乳房温存療法が行われたために相対的に乳房切除術が施行された症例が減少したとの見方もでき，今回の結果からはわが国の乳房切除後照射の頻度を伺い知ることはできない．

現在の術後照射の適応と考えられている症例は，病理学的腋窩リンパ節転移4個以上を有する症例や，原発巣が進行期（T3，またはT4）の症例とされている．1回目の調査の148症例（57%）および，2回目の58症例（72%）がリスク因子を有する症例であり，2回目調査において術後照射が行われた症例のうち高リスク因子を有する症例の占める割合が増加していた（$p=0.039$）．

照射された部位に関しては，1回目の調査ではA施設およびB施設とも胸壁照射は一部の症例に行われたにすぎず，鎖骨上窩や傍胸骨リンパ節といった領域リンパ節への照射が中心であった．これに比べ，2回目の調査では両施設層とも領域リンパ節に加え，胸壁への照射が著明に増加した（図1）．先に述べた三つのランダム化比較試験では胸壁，鎖骨上窩リンパ節領域および傍胸骨リンパ節領域を含めており，ASCOの診療ガイドラインでは胸壁および鎖骨上窩リンパ節領域を照射野に含めることを推奨しており[2~4,6]，わが国における胸壁照射の急激な増加は海外のエビデンスの影響を受けていることが伺える．

1回目の調査で線量分布図が作成されていた症例は42%の症例であり，2回目の調査でも42%の症例であり経時的変化は見られなかった．これを施設層別に見ると，A施設の1回目の調査では46%の症例に，2回目の調査では52%の症例

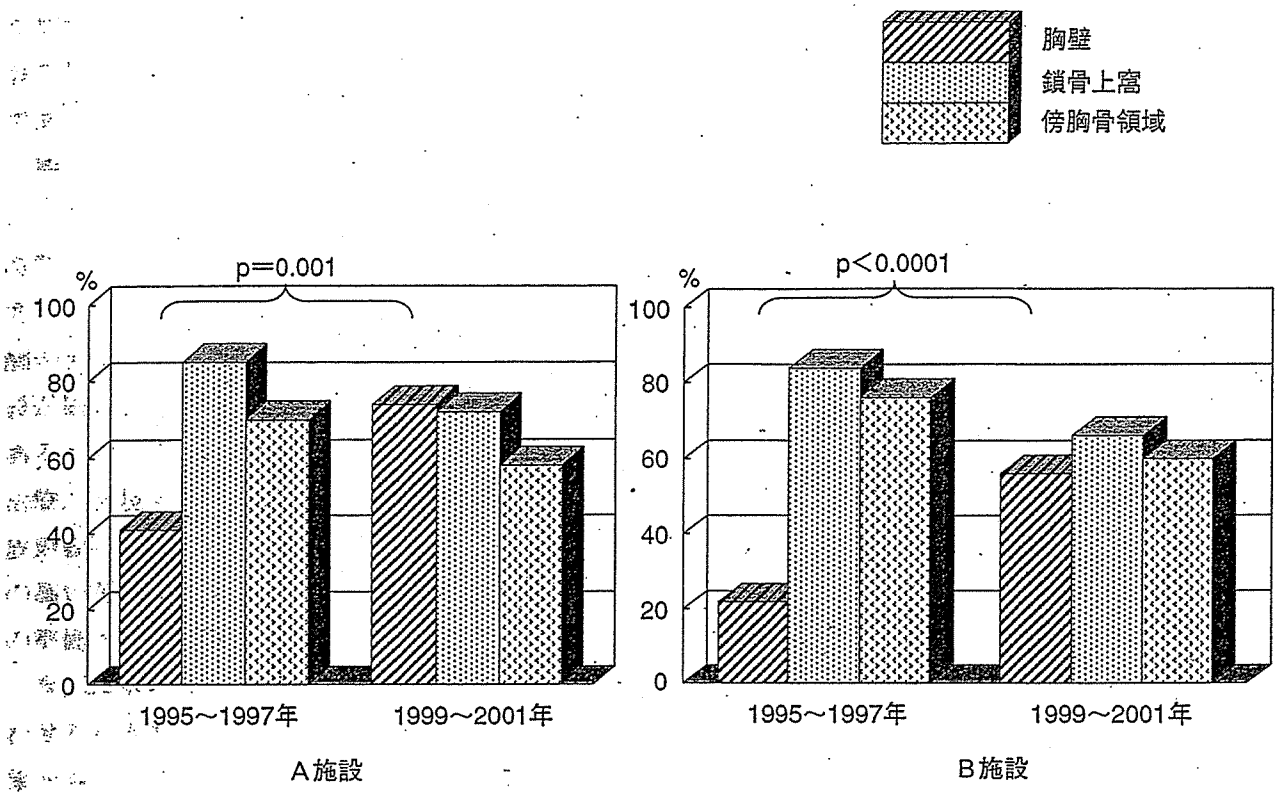

図1　施設層別の照射部位の変化
両施設層とも1999～2001年で明らかに胸壁照射の頻度が増えている．

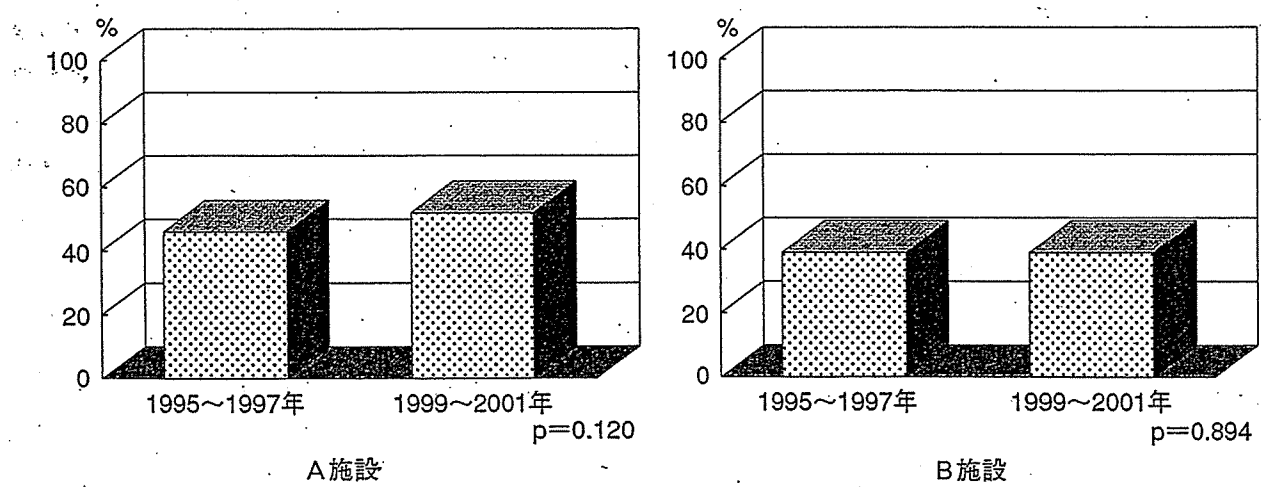

図2　施設層別の線量分布図作成状況の変化
両施設層とも線量分布図の作成は半数程度であり，経時的変化も見られない．

に線量分布図が作成されていた（p＝0.120）（図2）．また，B施設の1回目の調査では39％の症例に，2回目の調査では36％の症例に作成されていた（p＝0.894）．胸壁および領域リンパ節を同時に照射するためには精度の高い照射技術と注意深い線量評価が要求されているにもかかわらず，線量分布図を作成し評価することが十分に行われていない症例が半数以上であることを意味している．一方，毎回の照射を高い精度で再現するためには患者体位を保持する固定具の使用が望ましいとされるが，1回目の調査では14％の症例に使用されただけであったが，2回目の調査では35％の症例に使用されていた．A施設の固定具の使用状況は，21％から58％に改善したが（p＜0.0001），B施設の使用状況は9％から20％の改善にとどまった（p＝0.018）．固定具の使用状況