表4　国立がんセンターにおけるセンチネルリンパ節生検の成績

	非センチネルリンパ節の転移	
センチネルリンパ節の転移	陽性	陰性
陽性	16	14
陰性	3	48

False negative rate, 9.1%; overall accuracy, 96.3%; negative predictive value, 94.1%; positive predictive value, 100%

け実施した．術前化学療法後に原発巣がPR以上の効果を示し，かつ，治療後腋窩リンパ節転移が陰性であった88例をセンチネルリンパ節生検の対象とした．これらの平均腫瘍径は4.9cm（2.5cm～12.0cm）で，T4が6例，治療前に明らかにリンパ節転移を認めた42例も対象となっている（表3）．センチネルリンパ節生検は，色素－RI法を用いたものが80例で，色素法単独が8例となっている．結果として，センチネルリンパ節が同定できた症例は80例で，同定率は92%となる．これらの症例のセンチネルリンパ節とノンセンチネルリンパ節の転移の有無をまとめたものを表4に示す．センチネルリンパ節に転移を認めず，ノンセンチネルリンパ節に転移を認めたものは3例で偽陰性率は9%であり，全体として96%の症例においてセンチネルリンパ節が腋窩リンパ節全体の状況を正確に反映していることが証明された．臨床的諸因子とセンチネルリンパ節の同定率との関連を検討したが，治療前のリンパ節転移の有無，臨床的治療効果，病理組織学的治療効果は関連せず，唯一，T4d（炎症性乳癌）症例のみがセンチネルリンパ節の同定を困難にしていることが明らかとなった．一方，センチネルリンパ節が同定できた症例中，偽陰性になった症例は3例のみであったため，術前化学療法も含めてこれらに影響を与える因子は明らかではなかった．

まとめ

当院での術前化学療法後センチネルリンパ節生検の結果から，炎症性乳癌以外の術前化学療法が著効した症例において，センチネルリンパ節生検は十分に安全に実施できると結論づけられた．同定率は92%，偽陰性率は9%で，早期乳癌における成績と遜色のないものとなった．海外における最近の報告や多施設からの報告は，当院の結果を支持するものである．一方，2005年度にJournal of Clinical Oncology（JCO）に発表されたAmerican Society of Clinical Oncology（ASCO）のガイドラインでは，Preoperative systemic therapy後のセンチネルリンパ節生検に関して，①技術的には安全に実施することはできる，②Preoperative systemic therapy後のn0の意義が明らかでない，③これらの症例では，正確な腋窩リンパ節の転移状況の把握が治療方針を決める際に重要であること，④エビデンスが十分でない，ことより推奨されていない．正確な腋窩リンパ節の情報を得るという目的からするとセンチネルリンパ節生検をPreoperative systemic therapyの前に施行し，Preoperative systemic therapy後に実施する場合でもN0症例に限られるべきだと強調している[18]．

当院での成績から，強力で安定した化学療法の後，色素－RI法を用い熟練した手技のもとにセンチネルリンパ節生検は，安全に実施できることが確認された．術前化学療法が著効した乳癌症例では，腋窩リンパ節陽性率が25%程度になることから術前化学療法後にセンチネルリンパ節生検を実施することに意義があるものと考える．ただし，本対象が進行癌であるということを十分に認識し，腫瘍内科医，病理医，放射線診断医との連携のもとに，慎重に適応を決めて本手技を修練，実施することが望まれる．

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CLINICAL INVESTIGATION **Lung**

CHANGES IN PATTERNS OF CARE FOR LIMITED-STAGE SMALL-CELL LUNG CANCER: RESULTS OF THE 99-01 PATTERNS OF CARE STUDY—A NATIONWIDE SURVEY IN JAPAN

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Background: This study was undertaken to analyze the practice process of thoracic radiotherapy (TRT) and evaluate changes in patterns of care for patients with limited-stage small-cell lung cancer (LS-SCLC) in Japan.
Methods and Materials: The Patterns of Care Study (PCS) conducted the second nationwide survey of care process for patients with LS-SCLC treated by using TRT between 1999 and 2001.
Results: The PCS collected data for 139 patients with LS-SCLC (man-woman ratio, 5:1; median age, 69 years; age > 70 years, 43%; Karnofsky Performance Status > 70, 73%; and Stage III, 88%). Median total dose was 50 Gy. Twice-daily TRT was used in 44% of patients. Median field size was 12 × 14 cm. The most commonly used photon energy was 10 MV (77%), whereas obsolete techniques using ^{60}Co or X-ray energy less than 6 MV comprised 12%. Three-dimensional conformal therapy was used with 12% of patients. Computed tomography simulation was performed in 40% of cases. Only 12 patients (8.6%) received prophylactic cranial irradiation (PCI). Concurrent chemotherapy and TRT (CCRT) was used for 94 patients (68%). Only 6 patients (4.4%) entered clinical trials. Compared with the previous PCS 95-97, significant increases in the use of CCRT (34–68%; $p < 0.0001$), twice-daily TRT (15–44%; $p < 0.0001$), and PCI (1.7–8.6%; $p = 0.0045$) were observed, although the absolute number of patients receiving PCI was still extremely low.
Conclusions: Evidence-based CCRT and twice-daily TRT has penetrated into clinical practice. However, PCI is not yet widely accepted in Japan. © 2008 Elsevier Inc.

Patterns of Care Study, Small-cell lung cancer, Thoracic radiation therapy, Nationwide survey, Practice process.

INTRODUCTION

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice processes for selected malignancies during a specific period (1). In addition to documenting practice processes, the PCS is important in developing and spreading national guidelines for cancer treatment. In Sept 1998, the Japanese PCS conducted the first nationwide survey for patients with lung cancer treated using thoracic radiotherapy (TRT) between 1995 and 1997 (PCS 95-97). The main findings from the PCS 95-97 are summarized as follows. First, the use of TRT for patients with limited-stage small-cell lung cancer (LS-SCLC) in Japan is predominantly influenced by institutional characteristics, rather than age group. Second, patient age significantly influenced the use of chemotherapeutic modality, such as etoposide and cisplatin for patients with LS-SCLC (2, 3).

Because results of several key clinical studies of patients with LS-SCLC were reported between 1997 and 1999, it seems meaningful to evaluate whether practice processes in Japan were changed accordingly. The second PCS for lung cancer investigated patient characteristics, workup studies, the process of TRT, and use of chemotherapy in patients with LS-SCLC treated by using TRT between 1999 and

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2001. The objectives of the present study are as follows. First, compile processes in TRT for patients with LS-SCLC treated between 1999 and 2001, and second, compare patient characteristics and treatment modalities between the PCS 95-97 and PCS 99-01 in Japan.

METHODS AND MATERIALS

Between July 2002 and August 2004, the PCS conducted a second national survey of radiation therapy for patients with lung cancer in Japan. The Japanese PCS developed an original data format for patients with lung cancer. The PCS performed an extramural audit survey for 73 (38 academic and 35 nonacademic institutions) of 556 institutions by using stratified two-stage cluster sampling and collected data for 768 eligible patients with lung cancer. Data collection consisted of two steps of random sampling. Before random sampling, all institutions were classified into one of four groups. Criteria for stratification were described elsewhere (2, 4). Briefly, the PCS stratified Japanese institutions as follows: A1, such academic institutions as university hospitals or national/regional cancer center hospitals treating 430 or more patients per year; A2, academic institutions treating fewer than 430 patients; B1, nonacademic institutions treating 130 or more patients per year; and B2, those treating fewer than 130 patients per year. Cutoff values for numbers of patients treated per year between A1 and A2 institutions and B1 and B2 institutions were increased from those used in the previous PCS because of the increase in number of patients treated using radiation therapy in Japan (4).

Eligible patients included those with 1997 International Union Against Cancer Stages I–III lung cancer treated by using TRT between 1999 and 2001, with Karnofsky Performance Status (KPS) greater than 50 before the start of treatment and no evidence of other malignancies within 5 years. The International Union Against Cancer staging system was used because the PCS comprehensively surveyed patients with non-SCLC and those with SCLC. As mentioned, Stages I–III SCLC do not precisely match the definition of LS-SCLC by Mountain (5). However, no definition of this term has been universally accepted. The PCS survey of TRT charts showed that for patients with SCLC, the tumor could be encompassed within the TRT field. Thus, in the present study, all patients were regarded as having LS-SCLC.

The aims of this study are to provide patterns of practice concerning: (*1*) patient background; (*2*) workup studies; (*3*) TRT, including photon energies, total dose, spinal cord dose, field arrangements, prescription point, and use of prophylactic cranial irradiation (PCI); and (*4*) chemotherapy, including agents, number of chemotherapy cycles, sequence of chemotherapy, and TRT. Patient background included demographics and medical status, such as KPS, comorbidities, stage, and whether treated on an outpatient basis. In addition, practice patterns of the PCS 99-01 were compared with those of the PCS 95-97.

To validate the quality of collected data, the PCS used the Internet mailing list among all the surveyors. *In situ* real-time check and adjustment of the data input were available between each surveyor and the PCS committee. In tables, "missing" indicates that the item in the data format was left empty, whereas "unknown" means that the item in the format was completed with data unknown. We combined missing and unknown in tables because their meanings were the same in most cases; no valid data were obtained in the given resources. Cases with unknown values were included when both percentage and significance values were calculated. Statistical significance was tested by using chi-square test. A $p < 0.05$ was considered statistically significant. Overall survival, assessed from the first day of radiation therapy, was estimated by using the Kaplan-Meier product-limit method, and differences were evaluated using log-rank test.

RESULTS

Patient backgrounds

There were 141 patients with SCLC, which constituted 18% of all patients with lung cancer surveyed. Of those, 2 patients underwent initial surgical resection and adjuvant postoperative irradiation. Thus, in the present study, the PCS analyzed the remaining 139 patients who did not undergo surgery (Table 1).

There were 116 men and 23 women with an age range of 36–85 years (median, 69 years). Patients older than 70 years constituted 43% of the patient population. For that elderly patient pool, the institutional breakdown was as follows: 31% in A1, 39% in A2, 50% in B1, and 50% in B2 ($p = 0.037$). For comorbidities, the most frequent adverse medical conditions were cardiovascular disease (34%) and diabetes (14%). Seventy-three percent had KPS of 80% or greater. Comparison of four institutional groups failed to show differences in terms of patient background other than patient age and KPS. Patients with KPS of 80 or greater comprised 89% of A1, 55% of A2, 74% of B1, and 65% of B2 strata ($p = 0.0071$). A majority of patients (88%) had Stage III disease. There were no significant differences in distributions of T and N classifications or clinical stages between institutional groups. Only 5% of all patients were treated on an outpatient basis.

Workup studies

Workup studies are listed in Table 2. Pretreatment workup included chest computed tomography (CT) in 96%, bronchoscopy in 93%, brain CT or magnetic resonance imaging in 86%, and bone scan in 79% of surveyed patients. Chest/abdominal CT and bone scan were used for a majority of patients, whereas positron emission tomography (PET) was used for an extremely small number of patients. Comparison of four institutional groups failed to show differences in terms of workup studies.

Practice process of TRT

Thoracic radiotherapy methods are listed in Table 3. Median total dose of TRT was 50 Gy, and median field size was 12 × 14 cm. Median dose to the spinal cord was 42 Gy. A CT simulator was used for planning in 40% of patients. Three-dimensional conformal therapy was used in 12%. The planning target volume included the ipsilateral hilus in 96%, ipsilateral mediastinum in 96%, contralateral mediastinum in 84%, contralateral hilus in 17%, ipsilateral supraclavicular region in 25%, and contralateral supraclavicular region in 15%. Field reduction during the course of TRT was done for 61%. Twice-daily radiotherapy was used for 44%. Photon energy generally was 10 MV (77%), whereas obsolete techniques using ^{60}Co or X-ray energy less than 6 MV were used for 12%. Only 12 patients (8.6%) received PCI. Median dose of PCI was 25 Gy. Only 6 patients (4.4%) entered clinical trials.

Table 1. Patient and tumor characteristics

Characteristics	Stratification of institutions					p-value
	A1	A2	B1	B2	Total	
No. of patients	36	23	54	26	139	
Age (y)						0.037
Range	44–85	36–81	40–81	54–85	36–85	
Median	69	68	71	71	69	
>70 (%)	31	39	50	50	43	
Sex						0.780
Men	30	18	47	21	116	
Women	6	5	7	5	23	
Karnofsky performance status						0.013
≥80 (%)	89	55	74	65	73	
Clinical stage/UICC 1997						0.475
I	0	1	2	2	5	
IIA, IIB	3	3	4	1	11	
IIIA	10	6	19	10	45	
IIIB	23	13	28	13	77	
Unknown/missing	0	0	1	0	1	
T classification						0.569
T1–2	14	11	25	14	64	
T3–4	22	12	28	12	74	
Unknown/missing	0	0	1	0	1	
N classification						0.551
N0–1	7	4	9	6	26	
N2–3	29	19	44	20	112	
Unknown/missing	0	0	1	0	1	

Abbreviation: UICC = International Union Against Cancer.

Institutional stratification influenced several radiotherapeutic parameters (Table 4). Photon energy of 6 MV or greater was used for 97% of patients in A1, 96% in A2, 87% in B1, and 69% in B2 institutions ($p = 0.0006$). The ^{60}Co machines were not used in any A1 to B1 institutions. Twice-daily radiotherapy was used for 57 of 113 patients in A1 to B1 institutions, but only 4 of 26 patients in B2 institutions were treated in that manner ($p = 0.0012$). The PCI was used for 7 of 36 patients (19%) in A1 institutions, but only 5 patients (4.9%) in the remaining institutions ($p = 0.0073$). Use of a CT simulator was more frequent in A1 (52%) and A2 (65%) compared with B1 (34%) and B2 (17%) institutions ($p = 0.011$).

One hundred twenty-nine patients (93%) received systemic chemotherapy. Of those, platinum-based chemotherapy constituted 98%. Concurrent chemotherapy and TRT (CCRT) was used for 68% (73% of patients who received systemic chemotherapy). Median number of chemotherapy cycles was four. Median times from the first day of systemic chemotherapy to the first date and last date of TRT were 3 and 44 days, respectively. Proportions of patients who received chemotherapy were 97% in A1, 96% in A2, 91% in B1, and 89% in B2 institutions ($p = 0.49$).

Comparison between two PCS studies

Patient backgrounds and practice patterns in PCS 99-01 were compared with those in PCS 95-97. Differences between the two studies are listed in Table 5. Based on two-stage cluster sampling, the ratios of academic to nonacademic institutions were almost equal in the two surveys. Although median age in PCS 99-01 was slightly older than that in PCS 95-97, patients' backgrounds were similar in the studies. Use of obsolete treatment equipment (photon energy < 6 MV and ^{60}Co) decreased from 20% in PCS 95-97 to 12% in PCS 99-01 ($p = 0.06$). The greatest differences were seen in the use of twice-daily TRT and CCRT. Twice-daily TRT increased from 15% in PCS 95-97 to 44% in PCS 99-01 ($p < 0.0001$). Use of CCRT in PCS 99-01 was twice as high as in PCS 95-97 (68% vs. 34%; $p < 0.0001$). Although a significant increase in the use of PCI was observed (1.7–8.6%; p = 0.0045), the rate was still extremely low in Japanese practice.

Table 2. Percentage of patients examined by using each diagnostic technique in the course of staging

Chest CT	96%
Chest MRI	7%
Bronchoscope	93%
Bone scan	79%
Abdominal CT	88%
Positron emission tomography	2%
Brain CT or MRI	86%

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging.

Table 3. Process of thoracic radiation therapy for patients with limited-stage small-cell lung cancer

Median total dose (Gy)	50
Median spinal cord dose (Gy)	42
Use of CT simulator (%)	40
Three-dimensional conformal therapy (%)	12
Beam energy (%)	
^{60}Co	1.4
<6 MV	10.8
≥6 MV	88
Median field size (cm)	12 × 14
Field reduction during treatment (%)	61
IRB-approved protocol treatment (%)	4.4
Twice-daily radiotherapy (%)	44
Prophylactic cranial irradiation (%)	8.6
Area included in planning target volume (%)	
Ipsilateral hilus	96
Ipsilateral mediastinum	96
Contralateral mediastinum	84
Contralateral hilus	17
Ipsilateral supraclavicula	25
Contralateral supraclavicula	15
Systemic chemotherapy (%)	93
Concurrent chemotherapy and thoracic radiotherapy (%)	68

Abbreviations: CT = computed tomography; IRB = institutional review board.

Comparison of preliminary outcomes between studies

There are known limitations in survival analyses in this type of retrospective survey study. Still, preliminary outcome data in the two studies could be compared. Overall survival rates of the entire patient pool in each study are shown in Fig. 1. Two-year survival rates in PCS 95-97 and PCS 99-01 were 34% and 45%, with a median follow-up of only 11 months in both studies, respectively. Median survival times of the patient pools in PCS 95-97 and PCS 99-01 were 14 and 17 months, respectively. These differences did not reach a statistically significant level.

Table 4. Process of thoracic radiation therapy influenced by institutional stratification

	Stratification of institutions					
Characteristics	A1	A2	B1	B2	Total	*p*-value
Photon energy						0.0006
^{60}Co	0	0	0	2	2	
<6 MV	1	1	7	6	15	
≥6 MV	35	22	47	18	122	
Twice-daily fractionation used						0.0012
Yes	18	11	28	4	61	
No	18	12	26	22	78	
Treatment planning						0.011
Use of CT simulator (%)	52	65	34	17	40	
Prophylactic cranial irradiation used						0.0002*
Yes	7	2	3	0	12	
No	29	17	48	24	118	
Unknown/missing	0	4	3	2	9	

Abbreviation: CT = computed tomography.
* A1 vs. A2–B2; $p = 0.0073$.

Table 5. Comparison of treatment modalities between two studies

Background and treatment process	PCS 95-97 ($n = 174$)	PCS 99-01 ($n = 139$)
SCLC/all lung cancer (%)	16	18
Median age (y)	65	69
KPS > 70 (%)	70	73
Stage III (%)	87	88
Median total dose (Gy)	50	50
Photon energy <6 MV or ^{60}Co (%)	20	12
Use of CT-simulator (%)	NA	40
Twice-daily thoracic radiotherapy (%)*	15	44
Chemotherapy used (%)	92	93
Concurrent chemoradiation (%)†	34	68
Prophylactic cranial irradiation (%)‡	1.9	8.6
Survival at 2-years (%)	34	45

Abbreviations: PCS = Patterns of Care Study; SCLC = small-cell lung cancer; KPS = Karnofsky Performance Status; CT = computed tomography; NA = not available.
* $p < 0.0001$ by chi-square test.
† $p < 0.0001$ by chi-square test.
‡ $p = 0.0045$ by chi-square test.

DISCUSSION

Results of the present PCS reflect national treatment trends for TRT for patients with LS-SCLC in Japan between 1999 and 2001. Through this second nationwide audit survey and data analysis, PCS established the general patterns of care for patients with LS-SCLC in Japan. Results also show the influence of the structure of radiation oncology on the process of TRT and how state-of-the-art cancer care supported by clinical trial results has penetrated into the national practice process during the study period.

During the study period, TRT for LS-SCLC constituted less than one fifth of all radiation therapy for patients with lung cancer. This result was similar to data from the United States (6). Use of such staging studies as chest CT, bone scan, and PET scan for patients with SCLC was in line with guidelines (7) and very similar to the report from the United States (6). A PET scan in clinical use was still scarce. Only a small fraction of patients participated in clinical trials similar to those observed in the United States. In Japan, twice-daily TRT was used more frequently and PCI was used less frequently compared with the United States. However, it should be noted that subjects of the PCS in the United States were treated between 1998 and 1999, preceding the results of key studies that supported the use of twice-daily radiation therapy and PCI.

The study shows that more suitable photon energies were used in TRT at academic institutions. Thirty-one percent of patients in B2 institutions were treated with a linear accelerator with less than 6 MV or a ^{60}Co machine that did not meet the standard of care for equipment to treat patients with lung

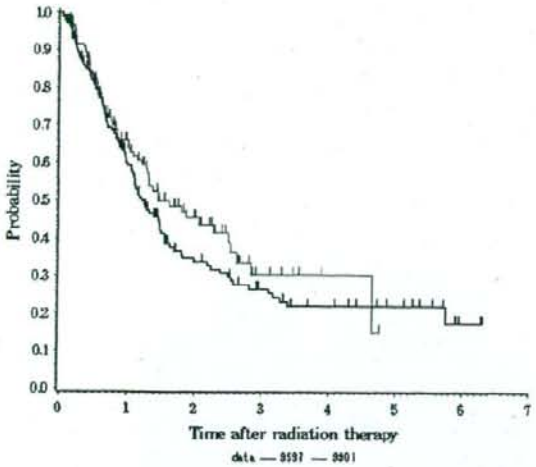

Fig. 1. Kaplan-Meier estimate of overall survival of patients with Stages I–III small-cell lung cancer surveyed in the 1995–1997 (dark line) and 1999–2001 (bright line) Patterns of Care Studies in Japan.

cancer, although this rate decreased from PCS 95-97 (>40% in B2) and was somewhat favorable compared with postoperative radiation therapy for patients with lung cancer in the same period (8). The availability of CT simulators was greater than 50% in academic institutions, but only one third in B1 and even lower in B2 institutions. In modern radiation therapy, CT-based treatment planning is essential for TRT to achieve optimal target coverage while reducing the dose to normal tissue. Twice-daily TRT was used more frequently for patients in A1 to B1 institutions than patients in B2 institutions. The PCI was used for 19% of patients in A1 institutions, but only 4.9% of patients in the remaining institutions. Although the general quality of radiation oncology improved from PCS 95-97, results of the present study show that institutional stratification still influences the structure and process of radiotherapy, such as availability of CT simulators, the flexibility of external beam energy selection, and use of evidence-based cancer care in Japan.

During the past 20 years, survival prolongation in patients with LS-SCLC was attained mainly by clinical trials that studied some aspect of radiation therapy, such as integration of TRT (9, 10), optimization of timing and fractionation of TRT (11), and introduction of PCI (12). The TRT is an essential component of the standard management of patients with LS-SCLC. Two meta-analyses showing the advantage of the addition of TRT to systemic chemotherapy, published in 1992 (9, 10), preceded our first national survey (PCS 95-97). In PCS 99-01, although 43% of all surveyed patients were older than 70 years and 23% of all patients had KPS of 70% or less, 93% of all patients received chemotherapy. This percentage is very similar to that in PCS 95-97 (2, 3).

When interpreting our data, it is important to note that they are limited to patients who received TRT as part of their overall treatment regimen. However, these two surveys showed that use of systemic chemotherapy was reasonably high in Japanese practice. Based on several studies published during the past 10 years, CCRT up front has emerged as a standard of care generating the highest survival rates (11, 13, 14). A landmark study supporting twice-daily TRT was published in 1999 after the previous PCS 95-97 (11). In that study, Turrisi *et al.* (11) showed a significant benefit in 5-year survival rate with the use of twice-daily TRT (45 Gy in 1.5 Gy fractions twice daily) concurrent with chemotherapy compared with once-daily TRT (45 Gy in 1.8 Gy fractions every day). Use of CCRT in PCS 99-01 (68%) was twice as high as in PCS 95-97 (34%). Similarly, there was a notable increase in the use of twice-daily TRT after PCS 95-97. In the present study, 44% of patients received twice-daily TRT, nearly three times as high as in PCS 95-97. Although it is still unclear whether twice-daily TRT to 45 Gy in 3 weeks is superior to a higher total dose of 60–70 Gy delivered by using more standard fractionation, it seems that diffusion of twice-daily TRT to Japanese practitioners was rapid. It seems likely that the marked increase in use of twice-daily TRT with concurrent chemotherapy in Japan contributed to the widespread use (95%) of inpatient treatment in PCS 99-01. In general, once-daily treatment is better accepted for outpatient care, whereas twice-daily scheduling is convenient for the care of inpatients, but at greater cost. Marked increases in the use of CCRT and twice-daily TRT indicates greater acceptance of these treatment modalities by radiation oncologists across Japan.

However, PCI has yet to be systematically adopted in Japanese practice. Despite the 1999 publication of another landmark trial that showed the survival advantage of PCI for complete responders (12), only 8.6% of all patients received this intervention. At the time of PCS 95-97, the role of PCI had not been established and it was used for only 1.9% of all patients (2). Before the present survey, it was expected that the percentage of patients who received PCI would be greater on the basis of the meta-analysis. Although a slight increase in use of PCI was observed, the rate was still extremely low in Japan. Information about the number of complete responders was outside the audit. However, a complete response rate of at least 50% is expected for study subjects (15). Whether this is caused by the small number of radiation oncologists in Japan or the small number of patients who received radiation therapy for cancer treatment is unknown. We reported previously that the number of full-time radiation oncologists is low, especially in nonacademic institutions in Japan (2). According to cancer statistics in Japan, radiation therapy was used for only 11.3% of all patients with cancer in 1999 compared with medical (27.5%) and surgical treatment (69.9%) (16). It is not clear why evidence-based PCI has not yet been widely accepted in Japan as opposed to the rapid diffusion of CCRT and twice-daily TRT in clinical practice. It appears that physicians in Japan hesitate to use PCI, and their patients are reluctant to receive PCI even if it is beneficial. Results of the ongoing third national survey in Japan will be particularly interesting in this regard.

Nonsignificant survival improvement in patient outcome was observed between PCS 95-97 and PCS 99-01. The current PCS has limitations in terms of outcome analysis because of a short follow-up period, significant variations in follow-up information according to institutional stratification (4, 17), and difficulties in outcome survey. One of the ultimate goals of the PCS is to determine how structure and processes of radiation therapy affect patient outcomes, including local control, survival, and quality of life. However, since 2006, personal information is strictly protected by law and outcome surveys are difficult to perform in Japan, even for patients with cancer. Cancer is not yet a reportable disease in Japan. Currently, limitations in data accumulation concerning patient outcomes in this type of survey encouraged us to develop new health care data collection systems and linkages among systems that make systematic recording and analysis of structure/process and outcome data part of routine quality monitoring (Japanese National Cancer Database, funded by the Ministry of Health, Labor, and Welfare Japan).

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Questionnaire Survey of Treatment Choice for Breast Cancer Patients with Brain Metastasis in Japan: Results of a Nationwide Survey by the Task Force of the Japanese Breast Cancer Society

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Objective: A nationwide survey was performed to investigate the current patterns of care for brain metastasis (BM) from breast cancer in Japan.
Method: A total of 351 survey questionnaires were sent to community or academic breast oncologists who were members of the Japanese Breast Cancer Society as of December 2005. The questionnaire consists of 40 multiple choice questions in eight categories.
Results: Of 240 institutions sent survey questionnaires, 161 (67.1%) answered; 60% of institutions answered with '<5' patients with BM every year; almost half (83 of 161) screened for BM in asymptomatic patients; surgical resection was rarely performed, as ~75% of institutions (118 of 160 institutions) answered 'none or one case of surgery per year'; 27% (41 of 154) preferred stereotactic radiosurgery (SRS) over whole-brain radiotherapy (WBRT) as the initial treatment in all cases, although ~70% (100 of 154) of them answered 'depend on cases'. The preference for SRS over WBRT mainly depends on the impressions of breast oncologists about both safety (late normal tissue damage and dementia in WBRT) and efficacy (better local control by SRS). Eighty-one percent (117 of 144) of institutions did not limit the number of SRS sessions as far as technically applicable.
Conclusion: SRS is widely used as the first choice for BM from breast cancer in Japan. Considerable numbers of Japanese breast oncologists prefer SRS over WBRT as the initial treatment for BM. A randomized trial comparing SRS and WBRT is warranted.

Key words: breast cancer – brain metastasis – stereotactic radiosurgery – whole-brain radiotherapy

INTRODUCTION

Brain metastasis (BM) is one of the most devastating complications of cancer and is usually associated with poor prognosis. The incidence of BM is high among patients with breast cancer, 10–20% in general (1). The incidence of BM in patients with HER2/neu over-expression is considered to be especially high, around 25–40% (2–5).

Whole-brain radiotherapy (WBRT) is the standard treatment for most patients with BM. For patients with a single BM, surgery followed by WBRT is superior to WBRT alone (6,7), although some studies does not support this (8). For patients with limited number (usually one to three) of BM, there is a controversy as discussed later (9). For patients with multiple (usually four or more) BM, WBRT is standard treatment.

Stereotactic radiosurgery (SRS) was developed in 1950s (10) and is now widely used as an alternative to surgery, WBRT and sometimes both. WBRT followed by SRS boost

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has also been studied (11,12) and is considered a standard treatment for patients with a single metastasis. Radiation-induced necrosis, especially after WBRT, is a rare but irreversible complication (13), which leads to the frequent use of SRS for the treatment of BM.

Withholding WBRT, SRS alone as upfront therapy is thought to be an alternative to BM (14–17). One prospective study compared SRS alone with SRS plus WBRT (18), which did not show a statistically significant difference in terms of overall survival. A relatively small sample size, decreased local control rate and lack of difference in neurological adverse events made it difficult to conclude that SRS alone was not inferior to SRS plus WBRT (19). Although this evidence confirms WBRT as standard treatment, SRS alone is widely used in daily practice.

BM in breast cancer is unique, compared with BM in other primaries, for certain reasons. The first is the high incidence of BM in breast cancer, especially in patients with the Her2/neu subtype, which has already been mentioned. The second is, BM in breast cancer is more radiosensitive than that in other primary such as non-small cell lung cancer or renal cell carcinoma. This may lead to better local control of BM by WBRT only. The third is the better prognosis after diagnosis of BM, especially in patients with Her2/neu positive subtype (20). This may lead to increased concern about radiation necrosis and failure of local control. For these reasons, BM in breast cancer is unique in terms of risk-benefit balance. A prospective trial, ideally exclusive to breast cancer, is needed for optimal usage of SRS.

As preparation for a future prospective trial, the task force of the Japanese Breast Cancer Society made a questionnaire survey of treatment choices for breast cancer patients with BM.

PATIENTS AND METHODS

A total of 351 survey questionnaires were sent to community or academic breast oncologists who were board members of the Japanese Breast Cancer Society, in December 2005. For most institutions, one breast oncologist was selected from each institution. For some large institutions, two or more oncologists were selected, because they have multiple hospitals or divisions that may have different treatment strategies. To avoid duplicated answers from the same treatment team, we attached the statement asking to unite one answer from one hospital or divisions. The questionnaire consists of 40 multiple choice questions in about eight categories, such as characteristics of hospitals, screening for BM, operation, radiation, re-irradiation, chemotherapy, SRS and cost.

RESULTS

Of 240 institutions to which we sent survey questionnaires, 161 (67.1%) answered. More than 90% of answers were obtained from surgical oncologists; the remainders were radiation and medical oncologists, reflecting the current situation that most patients with breast cancer are treated by surgeons in Japan. The background characteristics of each institution are summarized in Table 1. Both small and large institutions were included in this survey. In many institutions, BM was a rare complication (60% of institutions answered '<5' patients with BM every year), but some institutions treat many BM patients (>20 patients per year). In 75% (125 of 155) of institutions, the treatment decision is made by a neurosurgeon and/or radiation oncologist.

More than half the institutions (83 of 161) screened for BM, although no evidence exists to support a screening strategy (Table 2). Timing of screening for BM differed, although more than half of the institutions with a screening strategy screen at disease progression. Some institutions screened before starting trastuzumab.

Table 1. Characteristics of each institution

Characteristics	Category	Number	%
Number of new patients/year	1–50	34	21
	51–100	57	35
	101–150	30	19
	151–200	15	9
	201 over	25	15
Number of new BM/year	<5	95	60
	6–10	47	29
	11–20	13	8
	21 over	5	3
Radiation oncologist in your hospital?	Yes	121	75
	No	40	25
Stuff neurosurgeon in your hospital?	Yes	131	82
	No	29	18
Treatment decision mainly made by	Neurosurgeon	71	46
	Breast oncologist	40	25
	Radiation oncologist	32	21
	Conference	12	8

BM, brain metastasis.

Table 2. Screening

Question	Answer	Number	%
Screening for BM	Yes	83	52
	No	78	48
If yes, when?	At systemic progression	48	58
	Routinely	18	21
	Before Trastuzumab	9	11
	Other conditions	8	10

Surgical resection was less frequently used as local therapy for BM because ~75% of the institutions (118 of 160) answered 'none or one case who received surgical resection per year' (Table 3). The infrequent choice of surgical resection might be a result of the rigid indications for surgery. More than 60% of institutions answered that no evidence of systemic disease except for BM, or controlled systemic disease by systemic therapy was crucial for surgical resection. WBRT, not SRS, was dominantly used for postoperative radiotherapy.

The indication for WBRT is summarized in Table 4. Different from surgical resection, it was not dependent on prognosis (87% of institutions answered that they considered radiotherapy regardless of the prognosis, for symptom relief). Even in patients with a poor performance status, WBRT can be used. More than 30% of institutions (52 of 161) answered that they would consider WBRT for patients with ECOG PS 4, if clinically needed. Eighty-one percent of institutions (124 of 154 institutions) interrupted chemotherapy during WBRT, although some institutions did not.

Table 5 summarizes the questions about re-irradiation for patients who had progressed to BM after WBRT. More than 80% of institutions answered that they did not repeat radiotherapy except for SRS. Interval as an indication for re-irradiation is controversial. Sixteen institutions needed an interval before re-irradiation, whereas another 14 institutions did not. Regarding the risk of re-irradiation, most surgeons estimated that the risk was greater than a few percent, but did not present their estimate to patients numerically.

Table 6 summarizes the questions about SRS and cost. Only 7% (13 of 154) of institutions gave WBRT as their first choice, although ~70% (100 of 154) answered 'depend on cases'. The indication for SRS according to the metastatic site, size and the number of BMs largely influenced the treatment decision. Concerning the indication for SRS, 98% (98 of 100) of institutions limited SRS for only small (<3 cm) lesions. Seventy-one percent (76 of 108) of institutions choose SRS only for patients with a limited number (<5 lesions) of BMs. However, 81% (117 of 144) of institutions did not limit the number of sessions as long as neurosurgeons technically permitted SRS. There was no consensus concerning prognosis and PS as indications for SRS. SRS was preferred to WBRT for both safety (less dementia) and efficacy (better BM control) reasons. The cost of SRS was not precisely estimated by the majority of surgeons.

Table 3. Operation

Question	Category	Number	%
BM surgery cases/year	0–1	118	74
	2–5	37	23
	6–9	3	2
	10 or more	2	1
Indication for surgery	NED other than BM	55	32
	Stable systemic disease	53	31
	Prognosis more than 6 months	15	9
	Regardless of prognosis, if symptoms treatable only by surgery	48	28
Post-surgery radiation	WBRT	102	69
	SRS	45	31

NED, no evidence of disease; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery.

Table 4. Radiation

Question	Category	Number	%
Indication for RT	Prognosis	22	14
	Symptom improvement	136	84
	Upon request	3	2
PS	Only 0–2	53	33
	Only 0–3	56	35
	Regardless of PS, if communicable	39	24
	Regardless of communication, upon situation	13	8

RT, radiotherapy; PS, performance status.

Table 5. Repeat radiation

Question	Category	Number	%
Re-RT after WBRT?	Never	41	26
	Only SRS	94	58
	SRS or Local Rt	21	13
	If indicated, WBRT	5	3
For indication of repeat radiation (local RT or WBRT), does interval from first WBRT matter?	Yes (some interval needed)	16	53
	No	14	47
If you repeat radiation (SRS, local RT, WBRT), how do you tell patients about the risk of necrosis?	Will not tell	9	8
	Will tell, but not numerically	66	60
	<1%	0	0
	'a few percentage'	19	17
	'ten and a few %'	12	10
	'20–40%'	5	5

DISCUSSION

This survey revealed that SRS is widely used as the first choice for BM treatment for patients with breast cancer in Japan. Many Japanese breast oncologists prefer SRS to WBRT as radiation therapy against BM. There are

Table 6. Stereotactic radiosurgery

Question	Category	Number	%
First choice of RT for BM	SRS	41	27
	WBRT	13	8
	Depends on cases	100	65
If you answer 'depends on cases', depends on what?	Maximum size	70	
	Number of BM	100	
	Location of BM	45	
	Control of systemic disease	18	
	PS	28	
	Financial status and others	8	
Maximum size for SRS	<2 cm	30	27
	<2.5 cm	12	11
	<3 cm	66	60
	<4 cm	2	2
Maximum number of BM for SRS	Only single	3	3
	2–4	73	68
	5–10	18	16
	No limitation in number	14	16
How control of systemic disease influences choice of RT for BM?	If good control, SRS	12	43
	If poor control, SRS	16	57
How prognosis influences choice of RT for BM?	SRS for poor prog.	7	21
	SRS for better	11	32
	Any prog. If PS is good	16	47
How many times will you repeat SRS	Only once	6	4
	Twice	15	10
	Three times	6	4
	No limitation in number	117	82
What is the main reason you avoid WBRT?	Hair loss	8	10
	Dementia	29	35
	Long treatment	16	19
	Worse BM control	30	36
Experience of neurological disturbance after WBRT	Yes	39	27
	No	107	73
Do you know the cost of WBRT exactly?	Yes	25	14
	No	120	86
Do you know the cost of SRS exactly?	Yes	27	19
	No	116	81

discrepancies between NCCN guideline recommendations and the practice in Japan. For example, for a limited number of BM, 30% of Japanese breast oncologists use SRS as adjuvant treatment although NCCN guidelines recommend WBRT as adjuvant treatment after surgery. For multiple BM, 30% of Japanese breast oncologists use SRS for patients with more than five BM, although NCCN guidelines recommend WBRT. For both a limited number of, and multiple, BM 60% of Japanese breast oncologists use SRS, although NCCN guidelines recommend WBRT for patients with systemic disease refractory to aggressive treatment. What causes these discrepancies, a preference for SRS and reluctance to use WBRT? Our survey revealed that Japanese breast oncologists believe that SRS is a safer and more effective treatment than WBRT, as shown in Table 6. Interestingly, one of the major concerns about WBRT was dementia, although 70% had not actually experienced it. Nonetheless, they did not limit the number of sessions for SRS. It seems that they believe that SRS is much safer than WBRT. Lack of recognition of the precise cost of SRS also enhances this preference for SRS, because the current national insurance system covers 70–90% of the total costs of SRS, which costs 500 000 yen per session.

The present study suggests issues for future trials. First, as shown in Table 1, the treatment decision for BM is shared by neurosurgeons and radiation oncologists, so their collaboration is essential. Another suggestion is the consideration of screening. More than half of the institutions had screened for BM although there is no supporting evidence. This should be taken into account when designing a clinical trial because screening may detect BM earlier in its clinical course, influencing the treatment choice (fewer lesions may lead to more SRS) and the survival of BM patients as a result of lead-time bias. Preference for SRS and its reasons are also important. A future trial on SRS should answer two questions: first, is limitless repetition of SRS safer than WBRT in terms of the long-term adverse effects of radiotherapy? and second, is SRS superior to WBRT in terms of local control? To answer these two questions, we need a prospective trial comparing WBRT with SRS for patients with breast cancer having limited number, and small size, of BM. This kind of randomized study would need too large a sample size to be conducted in Japan only, so international collaboration would be needed.

One limitation of the present study is that a questionnaire from one oncologist at an institution does not demonstrate the pattern of practice at the institution perfectly, because there could be many biases such as recall bias, response bias and so on. Although the background of institutions shown in Table 1 seems to show that this survey describes the current pattern of practice in Japan well, actual data from each institution are more helpful. We have therefore planned a historical cohort study to reduce these biases.

In conclusion, the present study showed that SRS alone is widely used as BM treatment for patients with breast cancer in Japan. To address the issues of both safety and efficacy, a future prospective trial studying the optimal usage of screening, SRS and WBRT is warranted.

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Conflict of interest statement

None declared.

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REVIEW

Radical external beam radiotherapy for prostate cancer in Japan: differences in the patterns of care among Japan, Germany, and the United States

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Abstract Optimal management of radiotherapy for prostate cancer patients has become a major concern for physicians in Japan. We reviewed published reports identifying the differences in the patterns of care for prostate cancer patients treated with radical external beam radiotherapy in Japan, Germany, and the United States. The reports indicate that Japanese patients have more advanced primary disease than patients in Germany or the United States. These patient characteristics for Japan and the United States have been almost unchanged for several years. Regarding radiotherapy, conformal radiotherapy was less frequently administered to patients in Japan than patients in Germany or the United States, and the total radiation dose was higher in Germany and the United States than in Japan. Concerning changes in trends in the patterns of radiotherapy, the percentage of patients treated with higher dose levels in the United States has rapidly increased, whereas the percentage of patients receiving these dose levels in Japan has remained extremely low. On the other hand, hormonal therapy has been used more frequently in Japan than in Germany or the United States. These findings indicate that patient characteristics and patterns of care for prostate cancer in Japan are considerably different from those in Germany or the United States.

Key words Patterns of Care Study · Prostate cancer · Type of institution · Radiation therapy · Hormone therapy

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I ntroduction

In Japan, the number of deaths due to prostate cancer has been steeply increasing, especially among elderly patients. The proportion of prostate cancer deaths among total cancer deaths also increased from 0.9% in 1960 to 4.2% in 2000.[1] Since entering the prostate-specific antigen (PSA) era, clinicians are detecting

disease at an earlier stage, and the rates of successful treatment for early-stage patients are at historical highs. Moreover, radiotherapy has become much more common because of significant advances in treatment planning technology and methodology. Therefore, the optimal management of radiotherapy for prostate cancer patients has become a major concern in Japan. However, we have not been able to evaluate national practice processes properly owing to the limited information available.

The Patterns of Care Study (PCS) national survey is a retrospective study designed to establish national practice processes for selected malignancies over a specific time period.[2–4] In addition to documenting the practice process, the PCS is important for developing and disseminating national guidelines for cancer treatment that help promote a high-quality process of care in the country. To improve the quality of radiation oncology, PCS methodology was introduced to Japan from the United States.[5,6] The Japanese PCS Working Group of Prostate Cancer started a nationwide survey for patients who underwent radiotherapy between 1996 and 1998.[7,8] Subsequently, a second PCS of Japanese patients treated between 1999 and 2001 was conducted, and we have previously reported the results of the first and the second PCS regarding radical external beam radiotherapy for prostate cancer patients.[9–13]

In the current study, we reviewed the published reports of the Japanese 1999–2001 PCS study,[11] the German 1998–2000 PCS study,[14] and the 1999 United States PCS study,[15] focusing on differences in the patterns of care between Japan, Germany, and the United States during approximately the same time periods. In addition, we reviewed the changes in trends in the patterns of radiotherapy for prostate cancer patients in Japan and the United States by comparing their most recent PCS results.[10] Although the PCS results of Germany were derived from only a few institutions, we believe these results should at least roughly represent the German national averages in the patterns of care for prostate cancer.

Comparison of patient characteristics among Japan, Germany, and the United States

Ogawa et al. previously indicated that during the period of 1999–2001, most prostate cancer patients in Japan treated with radical external beam radiotherapy had advanced disease, with more than 80% of patients having intermediate or unfavorable risk diseases[11] (Table 1). In contrast, Zelefsky et al. showed that in the United States many prostate cancer patients had early-stage disease during 1999.[15] A comparison of patients in Japan with those in the United States found that the Japanese patients had more advanced disease than their U.S. counterparts.[12] The current study compared patients in Japan with those in Germany, as reported by Vordermark et al.,[14] and found that Japanese patients once again had more advanced disease than their German counterparts. Compared with their German and U.S. counterparts, Japanese patients had higher pretreatment PSA levels, more advanced T stage, and a higher proportion of Gleason scores of 8–10. The median PSA level in Japan was 20.0 ng/ml versus 11.3 ng/ml in Germany and <10 ng/ml in the United States. The median Gleason combined score and the percentage of Gleason combined scores of 8–10 were 7 and 34.5% in Japan, respectively, whereas the median Gleason combined score was 6 in Germany and the percentage of Gleason combined score of 8–10 was 18.8% in the Unites States. The percentage of T3-4 tumors was 45.6% in Japan versus 32.0% and 6.8% in Germany and in the United States, respectively. Moreover, comparing risk groups between Japan and the United States, the proportion of Japanese patients in the unfavorable risk group was 50.4% versus 24.0% in the United States. These results indicate that higher proportions of patients with advanced disease were treated with radical external beam radiotherapy in Japan than in Germany or the United States. Whether these differences among patients in Japan, Germany, and the United States resulted from differences in access to medical care or from biological differences between the tumors themselves remains unknown. Further investigation of potential differences in disease characteristics between individuals in these countries would be informative.

Changing trend in patient characteristics for Japan and the United States

Ogawa et al. compared the changes in patient characteristics for Japan and the United States, comparing their most recent PCS (1999–2001 Japan PCS and 1999 U.S. PCS) with their previous PCS (1996–1998 Japan PCS and 1994 U.S. PCS). They found that the patient characteristics in for both countries had remained almost unchanged between the study periods[12] (Table 2). Although the incidence of the patients with T3-4 diseases significantly decreased at 1999–2001, Japanese patients treated with radical radiotherapy continued to exhibit advanced disease (PSA >20 ng/ml and Gleason combined scores of 8–10). On the other hand, the proportion of U.S. patients with advanced disease remained low from 1994 to 1999. These results thus demonstrate persistence of the trend for Japanese patients to have more advanced

Table 1. Patient and treatment characteristics: comparison of PCS results among Japan, Germany, and the United States

Parameter	Japan/1999–2001[a]	Germany/1998–2000[b]	United States/1999[c]
No. of institutions	76	6	58
No. of patients investigated	283	148	392
Patient characteristics			
Age (years)			
Median	72	—	71
Mean	71.8	69	70.8
Pretreatment PSA level (ng/ml)			
Median	20.0	11.3	<10[d]
Mean	90.0	32.1	—
<10	28.7%	—	60.5%
≥10 but <20	21.3%	—	23.0%
≥20	50.0%	—	15.5%
Unknown	—	—	1.0%
Gleason combined score			
Median	7	9	≤6[e]
Mean	6.5	5.8	—
2–6	45.0%	—	54.3%
7	20.5%	—	25.8%
8–10	34.5%	—	18.8%
Unknown	—	—	1.1%
T stage			
TX-T0	0%	0%	7.8%
T1	8.1%	33.0%	43.9%
T2	40.1%	26.0%	33.7%
T3–4	45.6%	32.0%	6.8%
Unknown	2.6%	9.0%	7.8%
N stage			
N0	83.10%	87.0%	—
N1	6.40%	13.0%	—
Nx	9.40%	—	—
Risk group (%)			
Favorable	14.5%[g]	—	38.3%[f]
Intermediate	35.1%[g]	—	37.7%[f]
Unfavorable	50.4%[g]	—	24.0%[f]
Radiotherapy			
Energy (> 10 MV) (%)			
Yes	74.3%	—	73.0%
CT-based treatment planning			
Yes	85.5%	—	95.0%
Conformal therapy			
Yes	43.0%	100%	80.0%
Radiation dose (Gy)			
Median	68.4	—	—
Mean	66.0	69.1	—
Higher dose levels (≥ 72 Gy)			
Yes	7.5%	—	43.0%
Administration of pelvic irradiation			
Yes	33.0%	28.5%	23.2%
Hormonal therapy			
Yes	89.7%	70.5%	51.3%

PCS, patterns of care study; PSA, prostate-specific antigen; CT, computed tomography

[a] Ogawa et al.[11]

[b] Vordermark et al.[14]

[c] Zelefsky et al.[15]

[d] Because 60.5% of patients had PSA values <10 ng/ml, the median should be <10 ng/ml

[e] Because 54.3% of patients had Gleason combined score of 2–6, the median should be ≤6

[f] Favorable, zero adverse features; intermediate, one adverse features; unfavorable, two or more adverse features. Adverse features: PSA >10 ng/ml; Gleason combined score >6; T stage ≥3

[g] Favorable, zero adverse features; intermediate, one adverse features; unfavorable, two or more adverse features. Adverse features: PSA >10 ng/ml; poor differentiation; T stage ≥3

Table 2. Changes in trends in patient and treatment characteristics for Japan and the United States

Parameter	Japan			U.S.		
	1996–1998[a]	1999–2001[b]	Trends	1994[c]	1999[d]	Trends
Patient characteristics						
T stage >3	64%	46%	↓	9%	7%	→
PSA ≥20 ng/ml	55%	50%	→	12%	19%	→
GS ≥8	31%	35%	→	19%	15%	→
Treatment characteristics						
High dose (≥ 72 Gy)	2%	8%	→	3%	45%	↑
CT-based RT planning	81%	86%	→	71%	96%	↑
Hormone therapy usage	86%	90%	→	8%	51%	↑

GS, Glascow Score; RT, radiotherapy
[a]Ogawa et al.[10]
[b]Ogawa et al.[11]
[c]Zietman et al.[24]
[d]Zelefsky et al.[15]

Table 3. Radiation dose and hormone therapy usage distribution in Japan and the United States

Parameter	Japan (%)		United States (%)
	1996–1998[a]	1999–2001[b]	1999[c]
Radiation dose (Gy)			
<68	76.3	47.5	16.0
68 to <72	22.5	45.0	39.0
72 to <76	1.3	7.5	32.0
76–80	0	0	13.0
Hormone therapy usage			
Favorable	76.5	72.0	31.0
Intermediate	85.4	91.8	54.0
Unfavorable	87.1	91.1	79.0

[a]Data reanalyzed from the 1996–1998 Japan PCS results
[b]Ogawa et al.[13]
[c]Zelefsky et al.[15]

disease than their U.S. counterparts during approximately the period of 1990s.

Comparison of patterns of treatment among Japan, Germany and the United States

A previous comparison study by Ogawa et al. identified considerable differences in the patterns of care for prostate cancer between Japan and the United States[12] (Table 1). The current study also identified many differences in the patterns of radiotherapy not only between Japan and the United States but also between Japan and Germany. With regard to equipment, conformal radiotherapy was administered to only 43% of the patients in Japan versus 80% of patients in the United States and 100% in Germany. With regard to radiation doses, the mean total radiation dose for Germany was 69.1 Gy versus 66.0 Gy in Japan. Radiation doses employed in the United States were significantly higher than those used in Japan (Table 3), with almost half (45%) of the U.S. patients receiving prescribed dose levels of ≥72 Gy. The administration of higher radiation doses in Germany and the United States probably reflects the penetration into clinical practice of various reports published during the 1990s indicating that higher radiation doses were associated with a statistically significant improvement in outcome.[16,17] On the other hand, only a small number of patients in Japan (7.5%) received the higher doses (≥72 Gy) during 1999–2001. One reason for this difference may be the lower incidence of conformal radiotherapy in Japan. As mentioned above, conformal radiotherapy was administered to 85% and 100% of patients in the United States and Germany, respectively, but to only 43% of patients in Japan. Previous PCS results indicated that treatment processes in Japanese institutions were closely related to structural immaturity in terms of equipment.[4,9,11] Therefore, to provide high-quality radiotherapy in Japan,

facilities need appropriate treatment planning capability. Modern radiotherapy requires computed tomography (CT)-based treatment planning and conformal radiotherapy to improve the target dose distribution while concomitantly reducing the dose to normal tissues.[18] Another reason for the radiation dose difference may be the high incidence of hormonal therapy in Japan. At present, it is possible that many Japanese radiation oncologists consider the higher dose levels (≥72 Gy) unnecessary for prostate cancer patients when combined with long-term hormonal therapy.

With regard to hormonal therapy, differing patterns of care in hormonal therapy were found among Japan, Germany, and the United States. Most of the patients in Japan (89.7%) received hormonal therapy in conjunction with radiotherapy, whereas this combined therapy was administered less frequently in Germany (70.5%) and the United States (51.3%). Regarding the frequency of hormonal therapy for the various risk groups, the administration of hormonal therapy to favorable-risk patients was different in Japan than in the United States (Table 3). Most of the patients (72.0%) in the favorable-risk group in Japan during 1999–2001 were treated with hormonal therapy, whereas only 31% of favorable-risk patients received hormonal therapy in the United States. Several studies from the United States have indicated that radical radiotherapy alone could control prostate cancer in patients with a favorable-risk status. Zietman indicated that a total dose of 70 Gy was sufficient to control the disease when the pretreatment PSA level was <10 ng/ml.[19] Hanks et al. found that prostate cancer patients with a pretreatment PSA level of <10 ng/ml did not benefit from a dose above 70 Gy.[20] Therefore, radical external beam radiotherapy without hormonal therapy has been the primary treatment for patients in the United States with favorable-risk disease. On the other hand, 72% of the patients in the favorable-risk group in Japan were treated with long-term hormonal therapy. The high rate of health insurance coverage for Japanese people may explain the frequent administration of hormonal therapy in Japan.[21] However, because hormonal therapy has been found to be unnecessary for favorable-risk patients in the United States,[19,20] radical external beam radiotherapy without hormonal therapy may also be the treatment of choice for favorable-risk patients in Japan.

Changing trends in the patterns of treatment between Japan and the United States

Ogawa et al. compared the changes in trends in the patterns of care, and these changes were found to be quite different between Japan and the United States[12] (Table 2). Concerning radiotherapy, the United States has seen a rapid increase in CT-based treatment planning and in the percentage of patients treated with a higher dose levels (≥72 Gy) compared to the 1994 PCS results, with almost half (44.5%) of patients being treated with these higher doses in 1999 compared with 3% in 1994. In contrast, the percentage of patients receiving higher dose levels in Japan has remained below 10%, not only for 1996–1998 but also for 1999–2001. These changing trends in higher prescribed radiation doses and CT-based radiotherapy planning in the United States between 1994 and 1999 demonstrate a drastic change in these parameters over that 5-year period, whereas only minor changes, except the significant decrease of patients treated with <68 Gy (Table 3), occurred in Japan between 1996–1998 and 1999–2001.

Concerning hormone therapy, the percentage of patients receiving hormonal therapy remained high in Japan for the periods 1996–1998 and 1999–2001, whereas the use of hormonal therapy in the United States showed a rapid increase from 1994 to 1999. The significantly increased use of hormonal therapy for high-risk patients in the United States reflects the penetration and growing acceptance of clinical trial results that have demonstrated the efficacy of these treatment approaches.[22] The randomized trial RTOG 8610 demonstrated an increase in disease-free survival for locally advanced prostate cancer patients treated with neoadjuvant total androgen blockade plus radiotherapy compared with radiotherapy alone.[23] PCS results in the United States indicate a rapid increase in the use of hormonal therapy from 1994 to 1999, whereas PCS results in Japan indicate that the use of hormonal therapy in patients with unfavorable-risk disease has remained high (>90%) (Table 3). Therefore, radiotherapy in conjunction with hormonal therapy appears to be an accepted approach for the unfavorable-risk group in both Japan and the United States.

Conclusions

Comparisons of Japanese, German, and U.S. PCS results revealed several differences in the patterns of care among these countries. Higher proportions of patients treated with radical external beam radiotherapy in Japan had advanced disease compared with those in Germany and the United States. A specific comparison between Japan and the United States shows that this trend has continued over the past several years. Patterns of care for prostate cancer in Japan significantly differ from those in Germany and the United States, especially with respect to radiation dose and the use of hormonal therapy.

Moreover, changes in trends in the patterns of care also show differences between Japan and the United States. These results suggest that in Germany and the United States, radiotherapy for prostate cancer has become widely applied as an established treatment, whereas its use in Japan was still immature and developing during the period when this national survey was conducted.

We now are analyzing 2003–2005 Japan PCS data. Repeat surveys and point-by-point comparisons with results from other countries, such as Germany and the United States, should demonstrate how external beam radiotherapy for prostate cancer is being developed and optimized for patients in Japan.

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SPECIAL FEATURE: REVIEW ARTICLE

New trends in radiation therapy as a component of breast conserving therapy

Current status of accelerated partial breast irradiation

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Abstract Accelerated partial breast irradiation (APBI) is a radiotherapy method used in breast-conserving therapy. In APBI, the tumor bed is topically irradiated over a short period after breast-conserving surgery. The fundamental concept underlying APBI is that more than 70% of ipsilateral breast tumor recurrence occurs in the neighborhood of the original tumor, and that hypofractionated radiotherapy can be applied safely when the irradiated volume is small enough. It is expected to reduce the time and cost required for conventional whole breast irradiation while maintaining equivalent local control. Several techniques including multicatheter interstitial brachytherapy, intracavitary brachytherapy, intraoperative radiation therapy, and 3D conformal external beam radiation therapy have been proposed, and each of them has its own advantages and drawbacks. Although APBI is increasingly used in the United States and Europe, and the short-term results are promising, its equivalence with whole breast radiation therapy is not fully established. In addition, because the average breast size in Japan is considerably smaller than in the West world, the application of APBI to Japanese patients is technically more challenging. At this point, APBI is still an investigational treatment in Japan, and the optimal method of radiation delivery as well as its long-term efficacy and safety should be clarified in clinical trials.

Keywords Breast cancer · Breast conserving therapy · Radiation therapy · Accelerated partial breast irradiation

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Abbreviations

APBI	Accelerated partial breast irradiation
BCT	Breast-conserving therapy
IBTR	Ipsilateral breast tumor recurrence
WBRT	Whole breast radiation therapy
BCS	Breast-conserving surgery
TR/MM	True recurrence/marginal miss
EF	Elsewhere failure
EIC	Extensive intraductal component
IORT	Intraoperative radiation therapy
EBRT	External beam radiation therapy
LDR	Low dose rate
HDR	High dose rate

Introduction

Several studies have reported that the survival rate after breast-conserving therapy (BCT) ia similar to that following mastectomy. Thus BCT has been established as a standard treatment for early breast cancer [1–6]. Concerning the role of radiotherapy in BCT, a meta-analysis of seven randomized controlled studies in which lumpectomy alone was compared with the combination of lumpectomy and radiotherapy showed that radiotherapy significantly reduced the incidence of ipsilateral breast tumor recurrence (IBTR) [6–13]. In the NIH consensus statement announced in 1990, the importance of radiotherapy in BCT was emphasized; whole breast radiation therapy (WBRT) at a total dose of 45–50 Gy, a dose of 1.8–2.0 Gy per fraction, and, if necessary, boost irradiation of the tumor bed were recommended.

The reported long-term IBTR rates after breast-conserving surgery (BCS) without radiation are between 10