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CLINICAL INVESTIGATION

A MULTICENTER PHASE II STUDY OF LOCAL RADIATION THERAPY FOR STAGE IEA MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMAS: A PRELIMINARY REPORT FROM THE JAPAN RADIATION ONCOLOGY GROUP (JAROG)

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Purpose: **The aim of this study was to evaluate the efficacy and toxicity of moderate dose radiation therapy (RT) for mucosa-associated lymphoid tissue (MALT) lymphoma in a prospective multicenter phase II trial.**
Methods and Materials: **The subjects in this study were 37 patients with MALT lymphoma between April 2002 and November 2004. There were 16 male and 21 female patients, ranging in age from 24 to 82 years, with a median of 56 years. The primary tumor originated in the orbit in 24 patients, in the thyroid and salivary gland in 4 patients each, and 5 in the others. The median tumor dose was 30.6 Gy (range, 30.6–39.6 Gy), depending on the primary site and maximal tumor diameter. The median follow-up was 37.3 months.**
Results: **Complete remission (CR) or CR/unconfirmed was achieved in 34 patients (92%). The 3-year overall survival, progression-free survival, and local control probability were 100%, 91.9%, and 97.3%, respectively. Thirteen patients experienced Grade 1 acute toxicities including dermatitis, mucositis, and conjunctivitis. One patient developed Grade 2 taste loss. Regarding late toxicities, Grade 2 reactions including hypothyroidism, and radiation pneumonitis were observed in three patients, and Grade 3 cataract was seen in three patients.**
Conclusions: **This prospective phase II study demonstrated that moderate dose RT was highly effective in achieving local control with acceptable morbidity in 37 patients with MALT lymphoma.** © 2007 Elsevier Inc.

MALT lymphoma, Radiation therapy, Local control, Acute toxicity, Late adverse event.

INTRODUCTION

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) was first described in 1983 by Isaacson and Wright (1). After that, the revised European-American classification of lymphoid neoplasms (REAL) proposed it as a provisional entity (2), and the World Health Organization classification confirmed that it was a distinct disease entity (3). A recent nationwide study of malignant lymphoma among Japanese reported that it accounts for about 8.45% of all malignant lymphomas in Japan (4). Although it has been previously considered that only 5% to 10% of MALT lymphomas presented with Stage III or IV disease (5), several groups reported that 30% to 40% of MALT lymphomas were in advanced stages, and bone

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Conflict of interest: none.

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marrow involvement was found in 15% of patients (6–11). However, it has been well documented that MALT lymphomas demonstrate an indolent clinical course, regardless of the extent of the disease at presentation.

Because MALT lymphoma has been considered to be less responsive to standard chemotherapy than other aggressive lymphomas, radiation therapy (RT) or surgery has been used as the first line local treatment. Previous retrospective studies demonstrated excellent local control rates and progression-free survival (PFS) after RT (12–27). However, RT for orbital MALT lymphomas usually leads to late adverse events such as retinopathy, cataracts, or dry eye (12–21). In addition, with regard to the RT technique, the total dose and irradiated volume varies in the literature, with some reports containing other low-grade B-cell lymphomas such as small lymphocytic lymphoma or follicular lymphoma, which hampered investigators from establishing optimal radiotherapeutic parameters (12–15, 17–21). Furthermore, there have been no published prospective trials evaluating the appropriate dose and field of RT for MALT lymphoma, except for patients with localized gastric disease (26). Thus we conducted a multicenter phase II study to evaluate moderate dose (30.6–39.6 Gy) of RT, depending upon the primary site and tumor bulk. We present here our preliminary report with regard to the efficacy and toxicity of this regimen for localized MALT lymphoma.

METHODS AND MATERIALS

Eligibility criteria

Eligible patients had previously untreated, histologically proven MALT lymphoma with Stage IEA according to the Ann Arbor staging system. Patients with simultaneous or metachronous bilateral disease in the orbit, salivary gland, or breast were also eligible; however, those who demonstrated stomach or spleen involvement were excluded from this study. Patients had to be >19 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. The trial was conducted in accordance with the Declaration of Helsinki, with approval of the institutional review board at each institution. All patients provided written informed consent.

Staging and treatment

For staging of their disease, patients underwent a history and physical examination, complete blood counts, screening blood tests of hepatic and renal function, gallium scintigraphy, computed tomography (CT) of the head and neck, chest, abdomen and pelvis, esophagogastroduodenoscopy, and a bone marrow biopsy. All patients, who were treated by photons, received RT from a linear accelerator with an appropriate energy in accordance with the primary site. An appropriate energy electron field was applied to treat patients with conjunctival disease. The total dose of RT was dependent on the tumor location and its maximum diameter. Patients with orbital disease or those who had minimal residual disease after surgical removal received 30.6 Gy in 17 fractions. Tumors <6 cm received RT with 36 Gy in 20 fractions, and those with ≥6 cm of disease were treated 39.6 Gy in 22 fractions. The clinical target volume (CTV) was defined as an entire involved organ (orbit, thyroid, salivary gland, breast) or gross tumor volume (GTV) with at least 20 mm of margin. We did not intend to treat the adjacent first echelon lymph node region. A lens shield was placed unless the block compromised tumor coverage. Radiation doses were specified according to the report of ICRU 50.

Central pathology review and radiotherapy quality assurance

After the enrollment of the patients, unstained formalin-fixed paraffin sections of the diagnostic biopsy specimen were collected and sent to the central review board office. Hematoxylin-eosin-stained sections were histologically reviewed according to the World Health Organization classification by the central pathology review board for this study. For this purpose, immunohistochemical study using antibodies against CD3 (PS1, Novocastra, Newcastle upon Tyne, UK), CD5 (4C7, Novocastra, Newcastle upon Tyne, UK), CD10 (56C6, Novocastra), CD20 (L26, DakoCytomation, Glostrup, Denmark), BCL-2 (clone 124, DakoCytomation), and cyclin D1 (rabbit polyclonal antibody, MBL, Nagoya, Japan) were also performed. The diagnosis of the central pathology review board was regarded as the final one in cases where there was discrepancy between the diagnoses made by an institution and the board. All radiologic films or color photos that depicted extent of disease, radiation simulation films, port films, and RT charts were reviewed, and compliance with the protocol was judged in terms of field border placement, dose fractionation, and dose constraint to risk organs by the members of quality assurance (QA) subcommittee. The central pathologic review and radiotherapy QA were undertaken after planned registration was over. Neither pathologic review nor RT treatment plan review was performed before actual treatment.

Statistical methods

Primary end point of this study was progression-free survival (PFS). Previous retrospective series have shown that PFS was approximately 70% at 3 years after treatment (6). It was estimated that 35 eligible patients would have an 80% power of detecting an improvement in the expected 3-year PFS for this trial of 15% with a significance level of 0.05. To allow for exclusion after central histopathologic review, 40 patients were recruited for this study. The PFS was defined as the date from protocol registration to the date of reappearance of disease, progression of existing disease, or death from this MALT lymphoma, whichever was first. Other end points were overall survival (OS), local control probability (LC), response rate, and acute and late toxicities regarding RT. The OS, PFS, and LC were calculated using the method of Kaplan and Meier (28). Response was assessed using standard criteria (29). Acute toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Late effects were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

RESULTS

Patient characteristics

From April 2002 to November 2004, 40 patients were recruited from 12 institutions in Japan. Three patients were deemed ineligible after central pathologic review (low-grade B-cell non-Hodgkin's lymphoma, further unspecified in 2 patients, reactive lesion could not be excluded in 1 patient). Thus the remaining 37 patients were included in the present analysis. Detailed patient characteristics are shown in Table 1. There were 16 male and 21 female patients, ranging in age from 24 to 82 years, with a median of 56 years. The

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Age (years)	
Range	24–82
Mean ± SD	55 ± 14
Median	56
Sex	
Male	16 (43)
Female	21 (57)
Primary site	
Orbit	24 (65)
Conjunctival cases	17/24
Thyroid	4 (11)
Salivary gland	4 (11)
Waldeyer's ring	2 (5)
Prostate	1 (3)
Lung	1 (3)
Cecum	1 (3)

Abbreviation: SD = standard deviation.

primary tumor originated in the orbit including the conjunctiva in 24 patients, the thyroid in 4 patients, salivary gland in 4, Waldeyer's ring in 2, and prostate, lung, and cecum in 1 patient each. Two patients demonstrated bilateral conjunctival tumors at presentation. Two patients showed lactate dehydrogenase elevation. No patients had B symptoms because of the exclusion criteria in this study. Follow-up ranged from 19.6 to 52.9 months, with a median of 37.3 months.

Compliance, response, and survival

With regard to quality assurance of RT, 34 of 37 patients (92%) were judged per protocol, and the remaining 3 were acceptable deviations. Of the 3 acceptable deviations, 2 had insufficient margin placement around the CTV, and the remaining patient received protracted RT for personal reasons. Figure 1 provides an example of a digitally reconstructed radiograph (DRR) showing irradiation field and portal film for a patient with orbital MALT lymphoma. The median dose of RT was 30.6 Gy, and 27 patients received 30.6 Gy. Seven patients received 36 Gy, and the remaining 3 patients received 39.6 Gy. Four patients with conjunctival tumor received RT with lens shield. At the time of evaluation, 33 patients achieved complete remission (CR) or CR/unconfirmed (CRu), which resulted in an 89.2% CR rate (95% confidence interval [CI], 78.7–99.7%). The remaining four patients obtained partial remission (PR). Three patients experienced recurrence during the study period. Two recurrences occurred outside of the irradiation field, and the remaining one with a conjunctival tumor experienced local recurrence behind the lens block. Three-year PFS and LC were 91.9% (95% CI, 83.1–100%) and 97.3% (95% CI, 92.1–100%), respectively. As no patients died of any causes during the study period, 3-year OS was 100%. The disease control outcomes are summarized in Table 2.

Acute toxicities and late sequelae

A summary of the acute and late toxicities are shown in Table 3. Eighteen Grade 1 acute toxicities including dermatitis, mucositis, and conjunctivitis developed in 13 patients. One patient developed Grade 2 taste loss. With regard to late toxicities, Grade 1 reactions including pigmentation, hypothyroidism, and dry mouth were observed in 1 patient each. Three patients developed Grade 2 reactions including hypothyroidism, radiation pneumonitis. Three patients received surgery for cataract (Grade 3 reaction).

DISCUSSION

This is the first prospective study to evaluate the efficacy and toxicity of moderate dose RT for MALT lymphoma not originating in the stomach. We have demonstrated that the LC and PFS were 97.3%, and 91.9% at 3 years, respectively. Our findings demonstrated that RT was highly effective in achieving local control for localized MALT lymphoma. These favorable outcomes after RT are consistent with previous retrospective studies, which administered various doses of RT with a median of 25 to 40.5 Gy (12–21, 23–27). However, most of these studies delivered >40 Gy to some patients, and the fact that they included low-grade B-cell lymphomas other than MALT lymphomas obscured our understanding of the optimal dose of RT in the management of this lymphoma. Despite these limitations, many researchers concluded that 30 Gy of RT could achieve excellent local control. In our retrospective analysis for ocular adnexal MALT lymphoma, we did not find that higher than 30 Gy of RT produced any additional benefits compared with doses ≤30 Gy (30). These and our current findings strongly suggest that 30.6 Gy is appropriate for controlling ocular MALT lymphoma, and MALT lymphoma at other sites with minimal residual disease after surgery.

Although several groups treating solely MALT lymphoma mentioned that 25 to 30 Gy is enough to control the disease (23, 25), we could not determine whether lower doses would improve the therapeutic ratio, as no patients in this study received doses <30 Gy.

The next problem that should be resolved is the optimal target volume for MALT lymphoma. There are only a few studies that clearly demonstrate the target volume in the literature (14, 19–21, 23, 25–27). Moreover, as previously mentioned, these studies include low grade non-Hodgkin's lymphoma other than MALT lymphoma. For gastric MALT lymphomas, the entire stomach and perigastric nodes are considered to be the target volume (26, 27). Olivier *et al.* (20) also delivered RT to the affected parotid gland with or without the first-echelon node for parotid lymphoma. However, recurrences of MALT lymphoma usually occur at other mucosal sites, and the significance of RT to the echelon lymph nodes is unknown. On the one hand, Pfeffer *et al.* (31) showed that 4 of 12 patients with orbital lymphoma who received partial orbital irradiation experienced recurrence. In addition, we observed that 1 of 4 patients with conjunctival MALT lymphoma receiving RT with a lens shield developed local recurrence at 15 months after RT in this study. Thus it seems reasonable that the target volume for MALT lymphoma should include the entire affected organ.

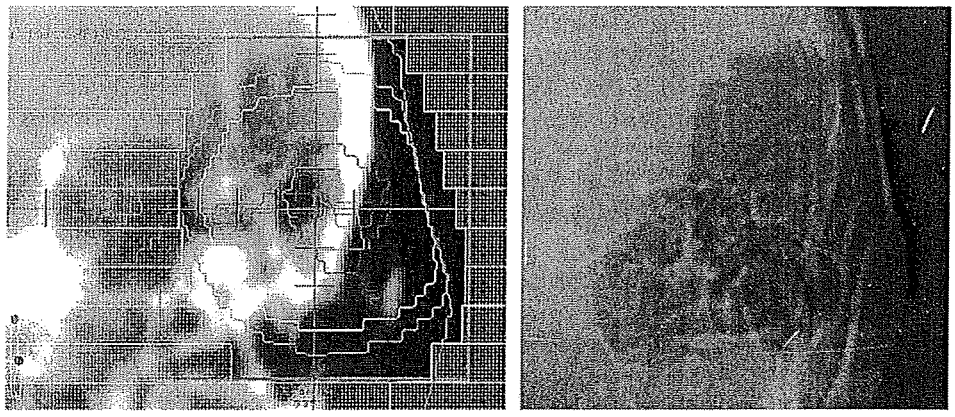

Fig. 1. Digitally reconstructed radiograph showing irradiation field (left) and portal film (right) for patient with orbital mucosa-associated lymphoid tissue (MALT) lymphoma.

It is well recognized that local RT is effective in controlling MALT lymphoma, on the one hand, and a pathologic link between some infectious agents, mainly bacteria and viruses, and MALT lymphoma has also been clearly established. It is also well known that gastric MALT lymphoma is closely associated with chronic gastritis caused by *Helicobacter pylori* (*H. pylori*) infection, and its eradiation achieved tumor regression in 70% to 80% of patients (32–34). Thus, it has been widely accepted that *H. pylori* eradiation is the first line treatment for *H. pylori*–positive gastric MALT lymphoma. Furthermore, small pilot studies demonstrated that high-grade MALT lymphoma or diffuse large B-cell lymphoma with areas of MALT lymphoma originating in the stomach also regressed after *H. pylori* eradication (35, 36). Recently, Ferreri *et al.* (37) demonstrated that *Chlamydia psittaci* (*C. psittaci*) DNA has been detected in 80% of ocular adnexal MALT lymphoma. They treated 9 patients with *C. psittaci* DNA-positive MALT lymphoma with antibiotic therapy, and found that 7 patients responded to the treatment with two CRs (38). Moreover, some cases of tumor regression after antimicrobial therapy have been reported in *Borrelia burgdorferi* associated cutaneous MALT lymphomas (39, 40). However, in the most extensively evaluated gastric MALT lymphomas associated with bacterial infection, several groups have reported that pathologic CR after *H. pylori* eradication did not guarantee molecular CR (41). Thus, whether antibiotic therapy could replace RT, surgery or chemotherapy as the first line treatment against localized MALT lymphoma should be evaluated in large, confirmatory clinical trials. Furthermore, three groups (42–44) have recently observed considerably lower prevalence of *C. psittaci* infection in patients with ocular adnexal lymphoma than that reported by Ferreri *et al.* (37).

Chemotherapy has also become another therapeutic option for MALT lymphoma. Several phase II studies demonstrated antitumor activity of the purine analogs fludarabine and cladribine (45, 46). Other groups have also shown that the anti-CD20 monoclonal antibody rituximab was effective for MALT lymphoma (47, 48). These findings also will be further elucidated in large scale clinical trials.

It usually takes a long time to develop late adverse events and recurrence after local RT. Late adverse events after local RT are described in the literature when treating orbital lymphoma. These included cataracts, dry eye, keratitis, and retinopathy (12–21, 25). Several groups reported that more than 34 or 35 Gy of RT increased the risk of late adverse events (15, 19). It should be emphasized that 30.6 Gy of RT caused Grade 3 cataract in three patients with a median follow-up of only 37.3 months. Some groups have reported that a lens shield can reduce late adverse events, especially cataract formation, without jeopardizing the local control rate (13, 14, 21, 25), but others did not (15–18). We recommend that physicians use caution when they apply a lens shield for conjunctival MALT lymphoma, because 1 of 4 patients with conjunctival tumor who were treated with a lens block in place experienced recurrence behind it.

Table 2. Summary of the treatment outcomes

Outcome	
Complete remission / Complete remission unconfirmed	33/37 (89.2%)
Partial remission	4/37 (10.8%)
Local control at 3 years	97.3%
Progression-free survival at 3 years	91.9%
Overall survival at 3 years	100%

Table 3. Summary of the acute and late toxicities

	No. of patients (%)			
	Grade 0	Grade 1	Grade 2	Grade 3
Acute toxicities				
Skin reaction	31 (84%)	6 (16%)	0	0
Conjunctivitis	31 (84%)	6 (16%)	0	0
Mucositis	31 (84%)	6 (16%)	0	0
Taste loss	36 (97%)	0	1 (3%)	0
Late toxicities				
Skin reaction	36 (97%)	1 (3%)	0	0
Dry mouth	36 (97%)	1 (3%)	0	0
Hypothyroidism	34 (92%)	1 (3%)	2 (5%)	0
Pneumonitis	36 (97%)	0	1 (3%)	0
Cataract	34 (92%)	0	0	3 (8%)

Although we observed three (8%) recurrences with a median follow up of 37.3 months, Wenzel *et al.* (22) reported that 43% of patients experienced recurrence after local treatment with a median of 11 months. Furthermore, Raderer *et al.* (49) recommended lifelong observation of all patients treated for MALT lymphoma because they documented late relapses with a median of 47 months. We have to extend follow-up prospectively to evaluate not only recurrence, but also the frequency and severity of late adverse events.

In conclusion, the preliminary results from this prospective phase II study confirm that RT was highly effective in achieving local control for localized MALT lymphoma, and 30.6 Gy was appropriate for controlling orbital MALT lymphoma and MALT lymphoma at other sites with minimal residual disease after extirpation without severe detrimental effects, which is consistent with many previous retrospective studies. However, we would acknowledge that our findings are best generalized to orbital MALT lymphoma, since two-thirds of the enrolled patients had disease at an orbital site. Furthermore, as we observed three Grade 3 cataract during this study period, we should emphasize that longer follow-up is indispensable to elucidate long-term local control probability and additional late effects from RT.

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Patterns of Care Study of Breast-conserving Therapy in Japan: Comparison of the Treatment Process between 1995–1997 and 1999–2001 Surveys

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Background: The Japan Patterns of Care Study (JPCS) conducted two national surveys to identify changes associated with the treatment process of care for patients undergoing breast-conserving therapy (BCT). Between the two national surveys, the Japanese Breast Cancer Society published its treatment guideline for BCT.
Method: The first survey collected data on 865 patients treated between 1995 and 1997 (JPCS-1), and the second on 746 patients treated between1999 and 2001 (JPCS-2) by extramural audits.
Results: There was a shift to an older age distribution in JPCS-2 compared with JPCS-1. In JPCS-2, the average patient age was 53.9 compared with 51.5 in JPCS-1 ($P < 0.001$). There was a reduction in the extent of breast surgery and the proportion of the patients who received quadrantectomy was 57.0% in JPCS-1 and 30.3% in JPCS-2 ($P < 0.001$). In JPCS-2, a cast or shell for immobilization was used at a significantly higher rate of 52.9% compared with 32.6% for JPCS-1 ($P < 0.001$). The rate of boost irradiation was increased in JPCS-2, especially for patients with a positive surgical margin; it was significantly increased to 83.5% in JPCS-2 compared with 53.9% in JPCS-1 ($P < 0.001$).
Conclusions: The second survey revealed a rapid change in the trend of the treatment of BCT in Japan and represented high compliance of the treatment guideline for BCT published by the Japanese Breast Cancer Society (JBCS) in 1999.

Key words: patterns of care study – breast cancer – breast conserving-therapy – radiation therapy

INTRODUCTION

Breast-conserving therapy (BCT) was incorporated into practice in the mid 1980s in Japan. Since then, the number of patients with breast cancer undergoing BCT has been rapidly increasing, and BCT is now the treatment of choice for early breast cancers in Japan. According to a national survey by the Japanese Breast Cancer Society (JBCS) in the year 2003 (1), 48.4% of patients received BCT. The Patterns of Care Study (USPCS) by the American College of Radiology has made significant contributions to improvements in care of patients with breast cancer in the United States (2,3). The Japan Patterns of Care Study Group (JPCS) started its national survey for breast cancer in 1998. The first survey (JPCS-1) collected data on 865 patients who underwent BCT between 1995 and 1997, and revealed considerable variation and some inappropriate implementation of the BCT treatment process in Japan at that time (4). On the other hand, the Japanese Breast Cancer Society published its treatment guideline for BCT in 1999. The purpose of this study is to compare the results of the two national surveys and to

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evaluate the impact of the JBCS guideline at the same time since the cases of JPCS-2 were treated after the publication of the guidelines.

MATERIALS AND METHODS

The JPCS conducted two national surveys. From September 1998 to December 1999, JPCS-1 collected the data on patients treated between1995 and 1997, and from July 2002 to June 2004, JPCS-2 collected data on patients treated between 1999 and 2001. The institutions and patients were selected by two-stage cluster sampling (5). For JPCS-1, 556 institutions nationwide were stratified into four classifications based on the Japanese facility master list in 1995, and for JPCS-2 640 institutions were stratified into four classifications in 2001. The JPCS-1 randomly selected 72 institutions and collected data on 865 BCT cases which were randomly sampled from lists of eligible patients that were supplied by the institutions. The JPCS-2 also selected 76 institutions and collected data on 746 cases. (Table 1).

Table 1. Difinition of facility categories and the number of patients registered in each category

	JPCS-1		JPCS-2	
	No. of facilities	No. of patients	No. of facilities	No. of patients
A facilities: university hospitals and cancer centers				
A1 facility				
JPCS-1: ≥300 patients per year	20	296	20	196
JPCS-2: ≥430 patients per year				
A2 facility				
JPCS-1: <300 patients per year	19	193	18	203
JPCS-2: <430 patients per year				
B facilities: commmunity-based hospitals				
B1 facility				
JPCS-1: ≥120 patients per year	18	256	20	210
JPCS-2: ≥130 patients per year				
B2 facility				
JPCS-1: <120 patients per year	15	121	18	137
JPCS-2: <130 patients per year				
Total	72	865	76	746

JPCS, Japan Patterns of Care Study Group.

The data was collected by extramural audits of institutions and the auditors were member physicians of the Japanese PCS Working Group. For JPCS-1, we used a data format that was developed on the basis on the USPCS data format and a computer file in FileMaker Pro® version 4.0 database (FileMaker Inc., Santa Clara, CA, USA). For JPCS-2, we developed a new data format on the Access® 2000 database (Microsoft) according to the revised best current management drafted by JPCS Working Subgroup of Breast Cancer. They consist of 316 and 362 items on the BCT process, respectively. The data was collected from all available resources at the location, not only from charts of the radiation oncology department. The eligibility criteria for these analyses were as follows: (1) female; (2) absence of gross multiple tumors; (3) absence of diffuse micro-calcification on pre-treatment mammography; (4) absence of distant metastases; (5) no bilateral lesions; (6) no prior or concurrent malignancies; (7) no prior history of the irradiation of the breast; and (8) no collagen vascular disease other than rheumatoid arthritis. The extent of surgery, prescription and technique of radiation therapy, and the regimen of systemic chemo-endocrine therapy were compared between the two surveys. In the tables below, 'unknown' indicates that the item in the format was filled with data labeled as 'unknown', whereas 'missing' means that the item in the format was left empty. We combined 'unknown' and 'missing' in the tables because their meanings were the same in most cases: no valid data was found in the given resources. 'Unknown/missing' data for categorical data were included in the ratio calculation, whereas the data for the continuous variables was excluded from the ratio calculation, as seen in a corresponding report from the USPCS (6). Paired and unpaired *t*-tests and chi-square tests were used for statistical analyses where appropriate. A P value of less than 0.05 was regarded as significant.

RESULTS

Patient Characteristics

The patient characteristics are shown in Table 2. Compared with JPCS-1, patients in JPCS-2 had an older age distribution. In JPCS-2, the average patient age was significantly increased from 51.5 in JPCS-1 to 53.9 ($P < 0.001$), and 60% of the patients were ≥ 50 years of age, compared with 47% in JPCS-1 ($P < 0.001$).

Evaluation and Staging

The evaluation and staging of the tumors are shown in Table 3. In JPCS-1, mammography was performed on 79.4% of the patients during their evaluation compared with 65.5% in JPCS-1, although the number of missing/unknown is large. In JPCS-1, the proportions of patients with tumors of <2 and 2–5 cm were 70.3 and 28.9%, respectively, although it was frequently unknown. In JPCS-2, 52.5% of the patients had tumors of <2 cm and 46.3% had 2–5 cm tumors.

Table 2. Patient characteristics

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Age	51.5 ± 11.2[a]	53.9 ± 11.6[a]
20–29	19 (2.2%)	12 (1.6%)
30–39	94 (10.9%)	51 (6.9%)
40–49	347 (40.1%)	236 (31.7%)
50–59	215 (24.8%)	221 (29.7%)
60–69	129 (14.9%)	154 (20.7%)
70+	62 (7.2%)	71 (9.5%)
Missing	9	1
Menstrual status		
Premenopausal	312 (36.1%)	265 (35.5%)
Perimenopusal	86 (9.9%)	33 (4.4%)
Postmenopousal	313 (36.2%)	372 (49.9%)
Unknown/Missing	154 (17.8%)	76 (10.2%)

[a]Mean ± SD.

Surgical Procedures

The results of the surgical procedures are shown in Table 4. There was a reduction in the extent of breast surgery, and the ratio of the patients who received quadrantectomy was 57.0% in JPCS-1 and 30.3% in JPCS-2 ($P < 0.001$).

Table 3. Evaluation and staging of the primary tumor

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Mammography performed		
Not performed	11 (1.3%)	10 (1.3%)
≤3 months before excision	539 (62.3%)	582 (78.0%)
After excision	8 (0.9%)	6 (0.8%)
Before and after initial excision	20 (2.3%)	4 (0.5%)
Unknown	287 (33.2%)	144 (19.3%)
Clinical size of the primary tumor	1.9 ± 0.9[a]	2.1 ± 1.8[a]
≤1.0 cm	140/713(19.6%)	49/667 (7.3%)
1.1–2.0 cm	361/713 (50.6%)	301/667 (45.1%)
2.1–3.0 cm	171/713 (24.0%)	232/667 (34.8%)
3.1–4.0 cm	28/713 (3.9%)	72/667 (10.8%)
4.1–5.0 cm	7/713 (1.0%)	5/667 (0.7%)
≥5.1 cm	6/713 (0.8%)	8/667(1.2%)
Missing	152	79
Clinical N stage (UICC 97)		
N0	741/831 (89.2%)	625/714 (87.5%)
N1	87/831 (10.5%)	85/714 (11.9%)
N2	3/831 (0.4%)	4/714 (0.6%)
Missing	34	32

[a]Mean ± SD.

Table 4. Surgery

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Extent of final breast surgery		
≤Tumorectomy[a]	47 (5.4%)	60 (8.0%)
Wide excision[b]	325 (37.5%)	460 (61.7%)
Quadrantectomy[c]	493 (57.0%)	226 (30.3%)
Missing	0	0
Axillary LN dissection		
Performed	816 (94.3%)	678 (90.9%)
Not performed	49 (5.7%)	68 (9.1%)
Extent of axillary dissection		
Level I	176/816 (21.6%)	175/678 (25.8%)
Level II	509/816 (62.4%)	319/678 (47.1%)
Level III	74/816 (9.1%)	151/678 (22.3%)
Unknown/missing	57/816 (7.0%)	33/678 (4.9%)
Sentinel lymph node biopsy performed		90/741 (12.1%)

LN, lymph node.
[a] Includes incisional biopsy, excisional biopsy, microdochectomy (single duct excision), and tumorectomy.
[b] Includes wide excision and partial mastectomy.
[c] Includes segmental resection and quadrantectomy.

Axillary LN dissection was performed on 94.3% of the patients in JPCS-1 and 90.9% in JPCS-2 ($P = 0.008$). On the other hand, 12.2% of the patients underwent sentinel lymph node biopsy (SLNB) in JPCS-2, although the data about SLNB was not collected in JPCS-1.

Histopathological Assessment

The results of the histopathological assessment are shown in Table 5. In JPCS-2, 79.6% of the pathology reports were shown on the charts and the rate was significantly higher than in the prior study ($P < 0.001$). The final microscopic margin was stated for 96.2% of the patients in JPCS-2 and for 88.8% in JPCS1 ($P < 0.001$). The surgical margin was defined as 'positive margin' in this study, when there were malignant cells at the surgical margin. The final microscopic margin was positive in 7.5 and 13.0% of the patients in JPCS-1 and JPCS-2, respectively. In JPCS-1, estrogen receptor evaluation was performed for 54.9% of the patients, and in JPCS-2 it increased to 78.0% ($P < 0.001$). In JPCS-1, 49.6% of the patients underwent progesterone receptor evaluation, and in JPCS-2 this increased to 75.0% ($P < 0.001$). In JPCS-1 and JPCS-2, axillary lymph node was pathologically positive in 21.9 and 26.0% of the patients, respectively ($P = 0.078$).

Systemic Therapy

Tamoxifen was given to 60.4% of the patients in JPCS-1 and 68.8% in JPCS-2 ($P < 0.001$). The administration of

Table 5. Results of histopathological assessment

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Pathology report on the chart		
Yes	564 (65.2%)	594 (79.6%)
No	260 (30.1%)	129 (17.3%)
Unknown/missing	41 (4.7%)	23 (3.1%)
Final microscopic margin		
Positive	65 (7.5%)	97 (13.0%)
Close (2 mm or less)	40 (4.6%)	39 (5.2%)
Negative	663 (76.7%)	582 (78.0%)
Unknown or not stated/missing	97 (11.2%)	28 (3.8%)
Estrogen receptor status		
Not performed	96 (11.1%)	27 (3.6%)
Positive	269 (31.1%)	373 (50%)
Negative	199 (23.0%)	201 (26.9%)
Insufficient tissue	7 (0.8%)	8 (1.1%)
Unknown/missing	294 (34.1%)	137 (18.4%)
Progesterone receptor status		
Not performed	114 (13.2%)	33 (4.4%)
Positive	252 (29.1%)	348(46.6%)
Negative	170 (19.7%)	203 (27.2%)
Insufficient tissue	7 (0.8%)	8 (1.1%)
Unknown/missing	322 (37.2%)	154 (20.6%)
Number of pathologically positive axillary lymph nodes		
0	569/729 (78.1%)	502/678 (74.0%)
1–3	126/729 (17.3%)	142/678 (21.0%)
≥4	34/729 (4.7%)	34/678 (5.0%)
Missing	136	68
Max	37	30

tamoxifen according to the hormone receptor is shown in Table 6. In JPCS-1 and JPCS-2, tamoxifen was administered to 72.5 and 85.3% of the receptor-positive patients, respectively ($P < 0.001$). Also, tamoxifen was given to 52.3% of the receptor-negative patients in JPCS-1, and 39.5% in JPCS-2 ($P = 0.03$). Chemotherapy, defined as all kinds of chemotherapy including single-agent oral administration of 5-FU or its derivatives, was administered to 38.7% of the patients in JPCS-1 and 35.0% in JPCS-2 ($P = 0.001$). The administration of chemotherapy according to pathological lymph nodes is shown in Table 7. For 64.4 and 73.9% of the patients who had pathologically positive lymph nodes, respectively, chemotherapy was administered in JPCS-1 and JPCS-2 ($P = 0.06$). In addition, the use of chemotherapy that incorporated at least one out of doxorubicin, cyclophosphamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, vinblastine, and vincristine increased

Table 6. Tamoxifen according to the hormone receptor

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Tamoxifen was given to:		
ER (+) or PgR (+)	234/323 (72.5%) Missing: 7/323 (2.2%)	365/439 (85.3%) Missing: 11/439 (2.5%)
ER (−) and PgR (−)	68/130 (52.3%) Missing: 6/130 (4.6%)	51/129 (39.5%) Missing: 5/129 (0.4%)
Receptor status unknown/ missing	220/412 (53.4%) Missing: 21/412 (5.1%)	97/178 (54.5%) Missing: 12/178 (6.7%)

ER, estrogen receptor; PgR, progesterone receptor.
[a]Mean ± SD.

significantly during the two survey periods, with 36.9% in JPCS-1 and 52.3% in JPCS-2 ($P = 0.02$).

Radiation Therapy

Table 8 presents details of the radiation planning. In JPCS-2, a cast or shell for immobilization was used on only 52.9% of the patients, although the rate was significantly higher than in JPCS-1 ($P < 0.001$). The clinical set-up of the radiation treatment was planned without the aid of computed tomography (CT) or X-ray simulation for 5.8% of JPCS-2 cases compared with 10.1% in JPCS-1 ($P = 0.002$). On the other hand, CT simulation was used for 26.7% of JPCS-2 cases compared with 22.2% of JPCS-1 cases ($P = 0.037$). Whole breast irradiation was performed on almost all cases in both surveys (Table 9). Additionally, 49.7% of JPCS-2 cases also had the regional nodes treated, compared with 53.7% in JPCS-1. Breast irradiation was given predominantly with photons of 6 MV (91.3%) in JPCS-2 compared with JPCS-1 (73.3%; $P < 0.001$). Photons of 10 MV without bolus, which is inappropriate for small breasts, was used on up to 4.4% of the patients in JPCS-1 and 2.0% in JPCS-2. Matching of the dorsal margin of tangential fields was not performed for 17.3% of JPCS 1 cases and 14.4% of JPCS-2 cases ($P = 0.069$). The median total dose to the whole breast was

Table 7. Chemotherapy for node-positive patients

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Chemotherapy[a] was given	103/160 (64.4%)	130/176 (73.9%)
Non-intensive[b]	54/103 (52.4%)	6/130 (4.7%)
Intensive[c]	38/103 (36.9%)	68/130 (52.3%)
Unknown/missing	11/103 (10.7%)	56/130 (43.1%)

[a]Includes all kinds of chemotherapy.
[b]Includes single-agent, oral administration of 5-FU or its derivative.
[c]Includes chemotherapy that incorporated at least one of the following: doxorubicin, cyclophosphamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, vinblastine, and vincristine.

Table 8. Radiotherapy planning

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Cast or shell was used		
Yes	282 (32.6%)	395 (52.9%)
No	578 (66.8%)	342 (45.8%)
Unknown/N/A/missing	5 (0.6%)	9 (1.2%)
Simulation		
Clinical set-up only	87 (10.1%)	43 (5.8%)
X-ray simulation without diagnostic CT	257 (29.7%)	233 (31.2%)
X-ray simulation with diagnostic CT	327 (37.8%)	270 (36.2%)
CT simulation	192 (22.2%)	199 (26.7%)
Missing	2 (0.2%)	1 (0.1%)

CT, computed tomography.

50 Gy in JPCS-1 and JPCS-2. Boost irradiation was administered to 16.9% of JPCS-1 patients and 27.4% of JPCS-2 patients ($P < 0.001$) (Table 10). In particular, for the patients with a positive surgical margin, the rate of boost irradiation was significantly increased to 83.5% in JPCS-2 compared with 53.9% in JPCS-1 ($P < 0.001$). The median boost dose was 10 Gy in both surveys.

DISCUSSION

The Patterns of Care Study was originally developed in the United States and assesses the evaluation and treatment patterns of malignancies. The Japan Patterns of Care Study Group started its national survey in 1998 and carried out two national surveys. This report documents the evaluation process and management of BCT in Japan.

BCT for breast cancer was introduced in Japan in the late 1980s, although it was started in the early 1970s in North America and Europe. At that time, it tended toward attaching great importance to surgery and the extent of breast surgery was large, although the feasibility of BCT had been recognized in the Western countries. Moreover, breast-conserving surgery (BCS) without radiation was commonly performed in Japan. In the 1990s, BCS spread rapidly and in 2003 the rate exceeded that of mastectomy in Japan. It was demonstrated that breast radiation significantly reduces ipsilateral breast recurrence in several important reports, and this treatment has been spreading in Japan. As a result, the rate of BCT without radiation has been decreasing and was 22.2% in 2003, although it might not be high enough (1). In PCS, the data from only patients who underwent radiation was collected but we could catch the general current of the process in BCT.

As regards patient characteristics, in JPCS-2 there was an older age distribution compared with JPCS-1. The shift could be a reflection of greater acceptance of conservative

Table 9. Technical details of whole breast radiotherapy

	JPCS-1 ($n = 865$)	JPCS-2 ($n = 746$)
Breast irradiation		
Performed	857/865 (99.1%)	745/746 (99.9%)
Not performed	8/865 (0.9%)	1/746 (0.1%)
Missing	0/865 (0%)	0/746 (0%)
Beam type for breast irradiation		
Orthovoltage	0/857 (0%)	16/745 (2.1%)
^{60}Co	124/857 (14.5%)	19/745 (2.6%)
Photons <4 MV	5/857 (0.6%)	11/745 (1.5%)
Photons ≥4 MV, <6 MV	406/857 (47.4%)	401/745 (53.8%)
Photons ≥6 MV, <8 MV	217/857 (25.3%)	268/745 (36.0%)
Photons ≥8 MV, <10 MV, with bolus	0/857 (0.0%)	0/745 (0.0%)
Photons ≥8 MV, <10 MV, without bolus	1/857 (0.1%)	1/745 (0.1%)
Photons ≥10 MV, with bolus	39/857 (4.6%)	4/745 (0.5%)
Photons ≥10 MV, without bolus	38/857 (4.4%)	15/745 (2.0%)
Photons ≥10 MV, bolus unknown	2/857 (0.2%)	0/745 (0.0%)
Electrons	23/857 (2.7%)	9/745 (1.2%)
Mixed	1/857 (0.1%)	1/745 (0.1%)
Missing	1/857 (0.1%)	1/745 (0.1%)
Matching of the dorsal margin of tangential fields		
None	144/833 (17.3%)	104/720 (14.4%)
Half beam used	181/833 (21.7%)	142/720 (19.7%)
Tilting	476/833 (57.1%)	458/720 (63.6%)
Others	0/833 (0%)	12/720 (1.7%)
N/A/unknown/missing	32/833 (3.8%)	5/720 (0.7%)
Use of beam modifiers on tangent breast fields		
Wedge on both fields	385/833 (46.2%)	429/720 (59.6%)
Wedge on lateral fields only	2/833 (0.2%)	21/720 (2.9%)
Compensators on both fields	1/833 (0.1%)	1/720 (0.1%)
No beam modifiers	392/833 (47.1%)	248/720 (34.4%)
Unknown/missing	53/833 (6.4%)	20/720 (2.8%)
Total dose for breast	4882.31 ± 327.41	4930.855 ± 214.17
<4400 cGy	12/851 (1.4%)	16/731 (2.2%)
4400–4599 cGy	79/851 (9.3%)	37/731 (5.1%)
4600–4799 cGy	91/851 (10.7%)	44/731 (6.0%)
4800–4999 cGy	29/851 (3.4%)	25/731 (3.4%)
5000–5199 cGy	629/851 (73.9%)	594/731 (81.3%)
≥5200 cGy	11/851 (1.3%)	15/731 (2.1%)
Missing	6	14
Max	6000	6000
Number of tangents treated/day		
Both	632/833 (75.9%)	614/720 (85.3%)
One only	157/833 (18.9%)	84/720 (11.7%)
Unknown/N/A/missing	44/833 (5.3%)	22/720 (3.1%)

Table 10. Technical details of primary site boost

	JPCS-1 ($n = 857$)	JPCS-2 ($n = 745$)
Boost was given to:		
Margin positive	35/65 (53.9%) Missing: 2/65 (3.1%)	81/97 (83.5%) Missing: 0/97 (0%)
Margin close (2 mm or less)	18/39 (46.2%) Missing: 0/39 (0%)	25/39 (64.1%) Missing: 0/39 (0%)
Margin negative	78/657 (11.9%) Missing: 42/657 (6.4%)	90/581 (15.5%) Missing: 0/581 (0%)
Margin unknown/missing	14/96 (14.6%) Missing: 10/96 (10.4%)	8/28 (28.6%) Missing: 0/28 (0%)
Boost dose	972.87 ± 172.3	1033.27 ± 242.0
<400 cGy	0/129 (0.0%)	1/199 (0.5%)
400–599 cGy	6/129 (4.7%)	5/199 (2.5%)
600–799 cGy	5/129 (3.9%)	9/199 (4.5%)
800–999 cGy	7/129 (5.4%)	31/199 (15.6%)
1000–1199 cGy	102/129 (79.1%)	113/199 (56.8%)
1200–1399 cGy	4/129 (3.1%)	5/199 (2.5%)
1400–1599 cGy	5/129 (3.9%)	25/199 (12.6%)
1600–1799 cGy	0/129 (0.0%)	10/199 (5.0%)
1800–1999 cGy	0/129 (0.0%)	0/199 (0%)
Missing	16	5
Max	1400	1600
Electron energy for boost		
<6	0/127 (0%)	11/189 (5.8%)
6–8 MeV	29/127 (22.8%)	86/189 (45.5%)
9–11 MeV	69/127 (54.3%)	71/189 (37.6%)
12–14 MeV	15/127 (11.8%)	16/189 (8.5%)
≥15MeV	7/127 (5.5%)	3/189 (1.6%)
Unknown/missing	7/127 (5.5%)	2/189 (1.1%)
Max	18 MeV	15 MeV

surgery and irradiation for older women as well as younger women. As regards evaluation, the rate of mentioning menstrual status rather than change of the status should be noted. Menstrual status is one of the most important factors in making the decision to use systemic therapy, but the data was unknown or missing in 17.8% of JPCS-1 patients. The rate was significantly decreased to 10.2% in JPCS-2, although it is still high.

The extent of surgical resection was significantly diminished and the rate of positive or close surgical margin was increased correlatively. This might be a result of reliance on breast irradiation. The rate of axillary dissection decreased in the second survey compared with the previous survey, which is consistent with the use of sentinel node biopsy (SNB). In 1996, sentinel lymph node (SLN) biopsy was introduced in Japan and has rapidly spread in Japan as in Western countries. It was reported that 21.5% of breast cancer patients in Japan underwent SLN biopsy in 2003 (7). However, in this study 61.8% of patients who underwent SNB also underwent axillary dissection.

The timing of the second survey was probably during the validation process for SNB by institutional surgeons. The use of SNB without axillary dissection will increase because current studies (8) have suggested that axillary dissection is not necessary for patients with negative sentinel nodes. Over the last few decades, there has been a major shift towards less invasive local treatment of breast cancer and BCT has largely replaced mastectomy as the surgical treatment of choice for early-stage breast cancer. In this trend, SLN biopsy will be accepted as an effective method of assessing axillary nodal status and avoiding unnecessary axillary dissection in patients with node-negative breast cancer. We therefore need to continue monitoring SNB.

The administration of tamoxifen was previously independent of the hormone receptor status, but was individualized according to the receptor status in the second survey. The trend was more significant in A facilities than in B facilities. Chemotherapy was given to more patients in the present study than in the previous one. However, the oral administration of 5-FU or its derivatives, which has been commonly used in Japan, was still carried out for 43.1% of the patients, and chemotherapy such as CMF or regimens including anthrathycline was uncommon. In Japan, medical oncology has not been established as a profession, and surgeons decide regimens under the present conditions. However, surgeons have been adopting the guidelines for Western countries to decide the chemotherapy regimens. Therefore, the rate of standard regimens will probably increase in the near future.

CT-based planning of irradiation to the conserved breast has been common compared with that in the United States (3). CT scans were used to generate isodose curves in 60.0% of JPCS-1 and 62.9% of JPCS-2 cases, and the rate was much higher than in the United States (22.9%). CT-based planning enables the decision to be made of individualized beam arrangements to adjust for variation in body habitus. Thereby, it can improve dose homogeneity throughout the target volume and generates dose–volume histograms of critical organs.

On the other hand, planning without the aid of CT or X-ray simulation was not unusual in JPCS-1. The present survey showed an increase in the use of CT-based or X-ray simulation. Regarding parameters for treatment planning such as a fixation system, matching of the dorsal margin of tangential fields or beam modifiers, suboptimal radiation therapy was performed on some patients in JPCS-1. Although it has been improved to some degree, there is space for improvement in some aspects of JPCS-2.

As expected, most patients in JPCS-2 underwent whole breast irradiation. The use of boost irradiation was

significantly increased in the present study, especially for patients with a positive surgical margin. The guidelines for BCT published by the JBCS recommend that boost irradiation to the tumor bed should be performed for patients with a positive or close surgical margin. Following these guidelines might result in an increase in the use of boost irradiation. Boost irradiation tends to be common even for patients with a negative surgical margin in Western countries, since usefulness of boost irradiation has been shown in two randomized trials (9,10). In the United States PCS, 88.7% of patients who underwent BCT received boost irradiation whether margin status was positive or not. However, it has not been accepted yet in Japan and this may have be a result of differences in the policies of margin assessment.

The current study revealed high levels of compliance with guidelines; however much more improvement is required in some points of radiation therapy. For example, a cast or shell for immobilization was used in only 52.9% of the patients in JPCS-2, although the rate was significantly higher than in JPCS-1. Regarding simulation, the clinical set-up of the radiation treatment was planned without the aid of CT or X-ray simulation for 5.8% of JPCS-2 cases, although the rate was decreased compared with JPCS-1.

In conclusion, the second survey revealed a rapid change in the trend of BCT treatment process in Japan. Although it also showed high compliance with the guidelines, there is room for improvement in the treatment process of BCT.

Conflict of interest statement
None declared.

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Results of the 1999–2001 Japanese Patterns of Care Study for Patients Receiving Definitive Radiation Therapy without Surgery for Esophageal Cancer

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Background: The third Japanese Patterns of Care Study (JPCS) was conducted for esophageal cancer patients receiving radiotherapy (RT). The aim of this study is to analyse the data of the non-surgery group.
Methods: Of the 621 patients receiving RT from 1999 to 2001, 385 non-surgical patients were analysed.
Results: Median age was 71 years and 85% were male. Karnofsky performance status (KPS) was ≥80 in 71% and better in T1 cases than in T2–4 cases. Ninety-nine per cent had squamous cell carcinoma and 56% had the main lesion in the middle thoracic esophagus. Twenty-one per cent had T1 disease, 12% T2, 38% T3 and 29% T4. Endoscopic ultrasound was used in 29% and mainly in T1 cases. Endoscopic mucosal resection was performed in 40% of mucosal cancer. Utilization of chemotherapy had remarkably increased compared with the 1995–1997 JPCS (61% versus 35%), however was significantly less in T1 cases than in T2–4 cases. The most frequently used agents for concurrent use were 5-fluorouracil and cisplatin. The median total dose of external beam RT (ERT) was 60 Gy and did not differ between T1 and T2–4 cases and also in comparison with the 1995–1997 JPCS. Brachytherapy was used in 10% and mainly in T1 cases.
Conclusions: Utilization of chemotherapy had remarkably increased. However the common treatment for T1 cases was RT alone. The standard dose of ERT was 60 Gy in spite of the increase in chemotherapy administration. Moreover, this survey showed significant differences in many parameters of treatment process between T1 and T2–4 cases.

Key words: Patterns of Care Study – esophageal cancer – radiotherapy – depth of tumor invasion

INTRODUCTION

To improve the quality of radiotherapy (RT), the Patterns of Care Study (PCS) was introduced to Japan from the USA, courtesy of the American College of Radiology in 1996. So far, three Japanese PCS (JPCS) surveys for esophageal cancer patients receiving RT have been performed. The first survey was conducted from 1996 to 1998 collecting data of patients treated from 1992 to 1994. In this 1992–1994 JPCS, the feasibility of JPCS was confirmed and the author concluded that institutional stratification including equipment and personnel had significantly affected the patterns of care for esophageal cancer (1). The second survey was carried out from 1998 to 2001, collecting data of patients treated from 1995 to 1997. The report of this survey emphasized that there had been several problems that needed resolving immediately, such as the use of inappropriate lower photon beam energy and the excess dose applied to the spinal cord (2,3). Moreover, the utilization rate of chemo-radiotherapy (CRT) in this survey was about 40%, and CRT was not

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established as the standard therapy for cancer of the esophagus during this time period. However, according to the results of the 1996–1999 PCS for esophageal cancer patients in the United States (USPCS) (4), 89% of patients received chemotherapy in addition to RT. The author concluded that this study confirmed the use of concurrent CRT as part of the standard practice for esophageal cancer. In addition, the significant rise in the use of endoscopic ultrasound (EUS) compared to the 1992–1994 USPCS was identified in this report. It was stated that this had been caused by the revision of the American Joint Committee on Cancer (AJCC) staging system from the old 1983 version to the current 1997 version in which T-classification relies on the depth of tumor invasion.

The objectives of this study were to evaluate the 1999–2001 JPCS data for esophageal cancer patients receiving RT without surgery and also to investigate the differences in treatment process according to the depth of tumor invasion.

METHODS

On the basis of the Japanese facility master list of 1999 (5), all radiation therapy facilities, composed of more than 700 institutions, were classified as follows: A1, academic institutions (cancer centers and university hospitals) treating $\geq$430 patients a year; A2, <430 patients; B1, other non-academic institutions treating $\geq$130 patients a year; and B2, <130 patients. A stratified two-stage cluster sampling was used to select facilities and patients for review (Fig. 1). In the first stage of sampling, facilities were randomly selected for investigation. In the second stage, random sampling of patients was performed from all eligible patients of each facility. Radiation oncologists of the JPCS Working Group, who visited each selected facility and reviewed the records of the selected patients, collected data from 2002 to 2004. For this survey, 76 facilities were selected (20 from A1, 18 from A2, 20 from B1 and 18 from B2). The number of selected facilities corresponds to a little over 10% of all RT facilities in Japan. The inclusion criteria were thoracic and abdominal esophageal cancer treated with RT from 1999 to 2001, squamous cell, adenosquamous cell or adenocarcinoma histology and Karnofsky performance status (KPS) of 60 or more. Patients with distant organ metastasis or other active malignancies within 5 years prior to treatment were excluded. Cervical esophageal cancer patients were excluded because the treatment strategy and the various parameters of RT differ from thoracic and abdominal cancer patients. The clinical data of 621 esophageal cancer patients receiving RT with or without surgery were accumulated. Of these, 385 patients (62%) who received RT without surgery were analysed (106 patients from A1, 88 from A2, 142 from B1 and 49 from B2).

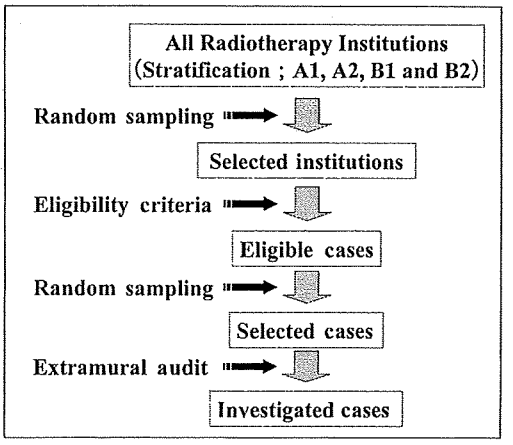

Figure 1. The method of random sampling. Patients were randomly selected by means of two-stage cluster sampling consisting of sampling of institutions from the four institutional strata in the first stage and sampling of patients from these institutions in the second stage. A1, academic institutions (cancer centers and university hospitals) treating $\geq$ 430 patients a year; A2, <430 patients; B1, other non-academic institutions treating $\geq$ 130 patients a year; and B2, <130 patients.

Statistical analyses were performed using the statistical analysis system (SAS) at the JPCS statistical center (6). Statistical significance was tested using the χ^2 test and Student's *t*-test.

RESULTS

Patient and Tumor Characteristics

Patient and tumor characteristics are listed in Table 1. The median age was 71 years and 85% of patients were male. Seventy-one per cent had KPS of 80 or more. Fifty-six per cent of patients had the main lesion in the middle thoracic esophagus and 99% had squamous cell carcinoma histology. According to the 1997 International Union Against Cancer (UICC) staging system, 79 patients (21%) had T1 disease, 51 patients (13%) T2 disease, 143 patients (37%) T3 disease and 112 patients (29%) T4 disease. Among the 79 patients with T1 disease, 15 (4%) had mucosal cancer and 64 (17%) had submucosal cancer. Sixteen patients were clinical stage I, 29% were stage II, 43% were stage III and 12% were stage IVa-b. The patient characteristics according to the depth of tumor invasion were shown in Table 2. The KPS of patients with T1 disease was better than patients with T2–4 disease ($P = 0.0001$).

Pretreatment Evaluation

Procedures of pretreatment evaluation are shown in Table 3. Ninety-four per cent of patients had an esophagram, and 96% underwent endoscopy. Computed tomography (CT) scans of the chest and abdomen were obtained in 97 and 90%, respectively. There was no significant difference in the use of these procedures according to the depth of tumor invasion. EUS was used in 29%. The utilization rates of EUS for T1, T2, T3 and T4 cases were 53, 29, 21 and 21%, respectively, and T1 cases underwent

Table 1. Patient and tumor characteristics

Characteristics	No. of patients	(%)
Total no.	385	
Age (yr)		
Range	46–94	
Median	71	
Sex		
Male	328	(85)
Female	57	(15)
KPS		
60–70	94	(29)
80	137	(41)
90–100	98	(30)
Missing	56	
Tumor main location		
Upper thoracic	76	(20)
Middle thoracic	216	(56)
Lower thoracic/abdominal	92	(24)
Missing	1	
Histology		
Squamous cell	376	(99)
Adenocarcinoma	1	(0)
Adenosquamous	2	(1)
Missing	6	
T-classification		
T1 all	79	(21)
Mucosal	15	(4)
Submucosal	64	(17)
T2	51	(13)
T3	143	(37)
T4	112	(29)
Missing	0	
Clinical stage		
I	57	(16)
II	101	(29)
III	150	(43)
IVa–b	41	(12)
Missing	36	

KPS, Karnofsky performance status.

it more frequently than T2–4 cases ($P = 0.0001$). Magnetic resonance imaging (MRI) was used on 15% of patients. The performance rates for T1, T2, T3 and T4 cases were 3, 13, 12 and 26%, respectively, and this procedure was performed significantly less in T1 cases than in T2–4 cases ($P = 0.0051$).

Treatment

Treatment characteristics are shown in Table 4. Ninety-three per cent of patients were hospitalized for treatment. There was no significant difference in the ratio of hospitalization between T1 and T2–4 cases. Planned treatment was accomplished in 83% of patients. The accomplishment rates for T1, T2, T3 and T4 cases were 94, 78, 82 and 77%, respectively, and the rate for T1 cases was higher than T2–4 cases ($P = 0.0441$). Endoscopic mucosal resection (EMR) was performed in 15% of T1 cases before RT, and the performance rates for mucosal and submucosal cancer were 40 and 9%, respectively.

Treatment Strategy

Of all patients, 61% received CRT and 39% received RT alone. The utilization rates of CRT for T1, T2, T3 and T4 cases were 28, 74, 58 and 79%, respectively, and there was a significant difference in the use of CRT between T1 and T2–4 cases ($P = 0.0001$). Among patients with T1 disease, 20% with mucosal cancer and 30% with submucosal cancer received CRT.

Radiotherapy

All patients included in this study received external beam RT (ERT). The median total dose of ERT was 60 Gy and the median fraction dose was 2 Gy. There was no difference in the median total dose and the median fraction dose of ERT between T1 and T2–4 cases. Regarding irradiation fields ($\geq$40 Gy), 66% of patients received whole mediastinal irradiation. Nodal irradiation fields ($\geq$40 Gy) according to the tumor main location were shown in Table 5. Patients with upper thoracic tumors were irradiated supraclavicular region in 53%, whole mediastinal region in 70% and upper abdominal region in 3%. Patients with middle thoracic tumors were irradiated supraclavicular region in 13%, whole mediastinal region in 69% and upper abdominal region in 16%. Patients with lower thoracic tumors were irradiated supraclavicular region in 8%, whole mediastinal region in 49% and upper abdominal region in 35%. Brachytherapy (BT) was used in 10% of patients as a means of boosting the primary tumor site. Seventy-four per cent of patients who received BT were treated by high-dose-rate source and 26% by low-dose-rate source. The performance rates of BT for T1, T2, T3 and T4 cases were 20, 14, 6 and 5%, respectively, and a significant difference in its use was found between T1 and T2–4 cases ($P = 0.0018$). Among patients with T1 disease, 27% with mucosal cancer and 18% with submucosal cancer received BT.

Chemotherapy

Chemotherapy was administered in 61% of patients, as mentioned above. Of these, 73% received chemotherapy

Table 2. Patient characteristics according to depth of tumor invasion

Characteristics	T1			T2	T3	T4	Total	T1 vs. T2–4 *P* value
	m	sm	all					
Age (yr)								
Range	54–88	53–87	53–88	46–88	48–94	47–90	46–94	0.551
Median	71	72	71	73	73	66	71	
Sex (%)								
Male	73	84	82	88	85	87	85	0.772
Female	27	16	18	12	15	13	15	
KPS (%)								
60–70	18	9	11	17	35	38	28	0.0001
80	9	44	38	52	45	35	42	
90–100	73	47	51	30	20	27	30	

m, mucosal cancer; sm, submucosal cancer.

concurrently with RT, 15% before RT and 12% after RT. The most frequently used individual agents for concurrent CRT cases were 5-fluorouracil (5-FU) (97%) and cisplatin (82%). The patients who were administered the combination of cisplatin and 5-FU concomitantly were 80% of concurrent CRT cases. When the combination of cisplatin and 5-FU was used for concurrent CRT, the administration schedules were daily administration in 64%, tri-weekly/monthly administration in 19%, weekly administration in 14% and others in 4%. There was no use of paclitaxel or docetaxel in this study.

Comparison with the 1995–1997 JPCS

Comparison of work up and process for non-surgical patients between the 1995–1997 JPCS survey and this survey is shown in Table 6. Work up to including age, gender, KPS and histology was almost the same. The administration rate of chemotherapy had remarkably increased (35% versus 61%) and the performance rate of BT had decreased (17% versus 10%). Regarding ERT, the median total dose and fraction dose of ERT did not change and the ratio of whole mediastinal nodal irradiation had increased (47% versus 66%).

Table 3. The frequency of use of pretreatment diagnostic procedures (%)

Procedures	T1			T2	T3	T4	Total	T1 vs. T2–4 *P* value
	m	sm	all					
Esophagram	73	90	87	94	95	96	94	0.0637
Endoscopy	100	100	100	98	96	93	96	0.1521
Endoscopic ultrasound	60	52	53	29	21	21	29	0.0001
CT scan, chest	93	93	93	98	99	98	97	0.1079
CT scan, abdomen	83	88	87	88	90	92	90	0.4374
MRI	0	4	3	13	12	26	15	0.0051

CT, computed tomography; MRI, magnetic resonance imaging.

DISCUSSION

In this survey, we evaluated the 1999–2001 JPCS data of esophageal cancer patients receiving RT without surgery and revealed significant differences in patterns of care according to the depth of tumor invasion. Among patient characteristics, a KPS of T1 cases was better than T2–4 cases in this survey. This possibly suggests that a ratio that definitive RT/CRT was chosen for operable T1 cases increased. It is thought to be attributable that the RT/CRT has been recognized as a curable treatment for T1 tumors.

In the report of the 1996–1999 USPCS for esophageal cancer, the significant rise in the use of EUS compared to the 1992–1994 USPCS was identified (4). The performance rate of EUS in this JPCS survey was higher than in the 1996–1999 USPCS (29% versus 18%). Furthermore, more than half of T1 cases had EUS and the performance rate was significantly higher in T1 cases than in T2–4 cases. In Japan, there is an original staging system created by the Japanese Society for Esophageal Diseases (7). The particularity of the Japanese staging system is that T1 disease is subclassified into mucosal cancer as T1a and submucosal cancer as T1b. The incidences of lymph node metastasis in mucosal cancer and submucosal cancer were reported as 0–5% and 41.4–53.3%, respectively (8–11), and the survival rate for submucosal cancer is significantly worse than for mucosal cancer (12–14). From this point of view, the

Table 4. Treatment characteristics (%)

Variables	T1			T2	T3	T4	Total	T1 vs T2–4 *P* value
	m	sm	all					
Hospitalization for treatment	93	87	89	88	94	96	93	0.0637
Complete planned treatment	93	94	94	78	82	77	83	0.0441
EMR before RT	40	9	15	2	1	0	4	0.0001
Treatment strategy								
CRT	20	30	28	74	58	79	61	0.0001
RT	80	70	72	26	42	21	39	
RT details								
ERT Dose (Gy)								
Total dose – median	60	60	60	60	60	61	60	–
Total dose – range	41.4–70	30–70	30–70	18–70	12–75	4–75.6	4–75.6	
Total dose – mean	57.7 ± 9.2	59.8 ± 8.4	59.4 ± 8.5	58.4 ± 11.2	59.6 ± 10.9	57.2 ± 14.3	58.7 ± 11.7	
Fraction dose – median	2.0	2.0	2.0	2.0	2.0	2.0	2.0	–
Fraction dose – range	1.8–2.0	1.2–2.4	1.2–2.4	1.0–2.2	0.9–3.0	0.9–2.0	0.9–3.0	
Fraction dose – mean	1.93 ± 0.10	1.97 ± 0.14	1.97 ± 0.13	1.92 ± 0.20	1.91 ± 0.27	1.86 ± 0.25	1.92 ± 0.23	
ERT Field (≥40 Gy)								
Whole mediastinum	54	59	58	76	64	70	66	0.1115
BT	27	18	20	14	6	5	10	0.0018
CTx								
Sequence of CTx								
Concurrent	–	–	85	76	69	71	73	
Pre-RT	–	–	4	9	20	15	15	
Post-RT	–	–	11	13	11	14	12	
Unknown	–	–	0	2	0	0	0	
Agent for concurrent CTx								
5-fluorouracil	–	–	96	91	100	98	97	
Cisplatin	–	–	65	80	88	82	82	
Nedaplatin	–	–	9	9	6	8	7	
Carboplatin	–	–	2	6	2	1	3	
Others	–	–	2	4	2	4	3	

EMR, endoscopic mucosal resection; RT, radiotherapy; CRT, chemo-radiotherapy; ERT, external beam radiotherapy; BT, brachytherapy; CTx, chemotherapy.

diagnosis of mucosal cancer or submucosal cancer is regarded as very important. The accuracy of EUS for the diagnosis of the depth of tumor invasion for esophageal cancer has been reported to be more than 80% (15, 16). The reason why the performance rate of EUS was high in T1 cases was that EUS was thought to be the most useful procedure for the diagnosis of mucosal cancer and submucosal cancer. As a new diagnostic procedure for esophageal cancer,

Table 5. Nodal irradiation fields according to the tumor location (%)

Tumor main location	ERT field (≥ 40 Gy)		
	Supraclavicular	Whole mediastinum	Upper abdomen
Upper thoracic	53	70	3
Middle thoracic	13	69	16
Lower thoracic/abdominal	8	49	35

positron emission tomography (PET) has recently been noted. The usefulness of PET for pretreatment staging, especially for detecting lymph node metastases, has been reported (17–20). Although PET was not investigated in this survey, this procedure should be examined in a future study in order to increase its future use.

EMR is effective and the least invasive treatment method for small mucosal cancer. Its local control rate is very high and is equivalent to esophagectomy (21–23). Because of the low rate of lymph node metastasis, additional treatment is not necessary for mucosal cancer after complete resection by EMR. However, in cases with positive margin or deeper invasion identified pathologically, additional treatment should be considered. In this survey, 40% of patients with mucosal cancer and 9% with submucosal cancer received EMR before radiotherapy. Recently, positive outcomes of RT and CRT following EMR have been reported (24,25). Considering the high performance rate of EMR before RT for mucosal cancer in this survey, this combination of treatments should be examined in detail in future.

Compared with the 1995–1997 JPCS, the performance ratio of CRT has remarkably increased. There are potentially several reasons such as the facts that several reports evaluating the efficacy of CRT have been published (26–29) and that the percentage of patients who were eligible for chemotherapy has increased. In spite of the increase in the use of chemotherapy, the most common treatment regimen for T1 cases was still RT alone during this time period. Recently, positive results of CRT for T1 cases have been reported (30,31) which means we need to investigate the transition of CRT for T1 cases in the next study.

Table 6. Comparison of process for non-surgical esophageal cancer patients between the 1995–1997 JPCS and the 1999–2001 JPCS

	1995–1997	1999–2001
Work up		
Age (median, years)	70	71
Male/Female (%)	85/15	85/15
KPS ≥80 (%)	72	71
Squamous cell carcinoma (%)	100	99
Treatment		
ERT – total dose (median, Gy)	60	60
– fraction dose (median, Gy)	2.0	2.0
Whole mediastinal irradiation (≥40 Gy, %)	47	66
Use of BT (%)	17	10
Administration of CTx (%)	35	61
Concurrent administration of CTx (%)	72	73

JPCS, Japanese Patterns of Care Study.

Regarding ERT, the median fraction dose and the median total dose were 2 and 60 Gy, respectively, and they were not different between T1 and T2–4 cases. This result suggests that the strength of RT was not weakened for T1 cases in the treatment of esophageal cancer. Furthermore, compared with the 1995–1997 JPCS, the median total dose did not change in spite of the remarkable increase in chemotherapy administration. This suggests that not a small number of the patients receiving CRT were treated by ERT with a dose of ≥60 Gy. According to the data of the 1996–1999 USPCS, the median total dose of ERT was 50.4 Gy (4). Additionally, the result of the phase III trial of CRT with high dose (64.8 Gy) versus standard dose (50.4 Gy) for esophageal cancer was published in 2002 (32). In this report it is concluded that the higher radiation dose did not increase survival or local/regional control and the standard radiation dose for patients treated with concurrent CRT was 50.4 Gy. The patients in our study were treated in 1999–2001, so we need to compare with the result of the next PCS in order to evaluate the change of irradiation dose after this report. However, when we look at the clinical situation, the result of this trial seems not to be accepted at this moment in Japan.

With the comparison of the ratio of whole mediastinal irradiation between this survey and the 1995–1997 JPCS, irradiation fields became wider. However, from the results of the analysis of irradiation fields according to the tumor main location, it is suggested that the three-field (supraclavicular, whole mediastinal and upper abdominal region) nodal irradiation was rarely used and the localized fields were used at a constant rate. Cardiopulmonary toxicities after CRT have become a topic of interest since the paper by Ishikura et al. (33). These toxicities may be attributable to the usage of chemotherapy and extremely large field such as the so-called 'super-long-T field'. As it is anticipated that long-term survivors after CRT for esophageal cancer will increase hereafter, investigations of late toxicities including cardiovascular toxicities, the optimum ERT dose and the optimum ERT fields need to be carried out.

The performance ratio of BT was 10% and patients with T1 disease had BT significantly more frequently than those with T2–4 disease. This result suggested that in Japan BT was often used to boost irradiation following ERT for T1 disease rather than for advanced cancer. Compared with the 1995–1997 JPCS, the performance ratio of BT has decreased (17% versus 10%). As a result of the introduction of CRT and use of the 3D-treatment technique, it is thought that there may be a change of direction in the use of BT for esophageal cancer in the future.

Regarding the sequence of chemotherapy administration, concurrent use with RT was the most common for any depth of tumor invasion. Cisplatin and 5-fluorouracil were the most frequently used agents in concurrent CRT. Evidence of the effectiveness of the combination of cisplatin and 5-fluorouracil has been shown for cancer of the esophagus (26–29), and it is thought that this has affected the choice of agents. However, as for the dosage method, daily low-dose administration was used most commonly without enough evidence. The evaluation of this method is entrusted to the future. Although the use of taxane has remarkably increased recently in the USA (4), this agent was not used at all during the time period in this survey. However, as docetaxel was covered by health insurance for esophageal cancer from 2004 in Japan, it is predicted that its use will increase in future.

CONCLUSIONS

We evaluated the 1999–2001 JPCS data for non-surgical esophageal cancer patients. The performance rate of CRT had remarkably increased compared with the 1995–1997 JPCS survey. However the common treatment for T1 cases was still RT alone. The standard dose of ERT was 60 Gy in spite of the remarkable increase in chemotherapy administration. Moreover, this survey showed significant differences in many parameters of work up and treatment process between T1 and T2–4 cases.

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Conflict of interest statement

None declared.

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