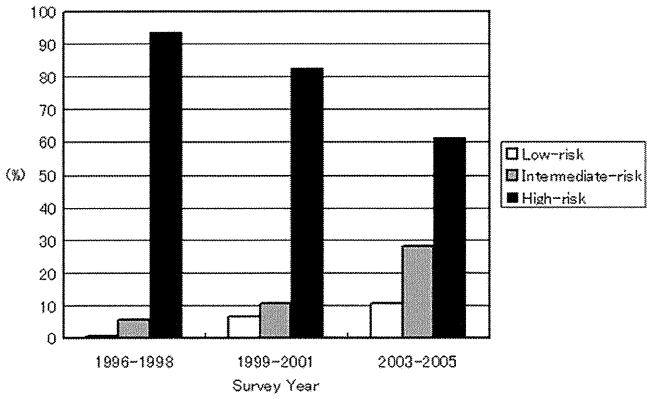

Fig. 1. Distribution of patients with prostate cancer according to risk group among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

total dosage revealed that 24.8% of patients received total radiation doses below 60 Gy in the 1996 to 1998 PCS, decreasing to only 2.0% from 2003 to 2005. Also, only 17.4% of patients received total doses of >70 Gy from 1996 to 1998, which increased dramatically to 52.0% from 2003 to 2005 (Fig. 3). Increased radiation doses were administered predominantly in academic institutions (Table 2).

The percentage of patients receiving hormone therapy from 2003 to 2005 (81.1%) was almost the same as that from 1996 to 1998 (86.3%) and that from 1999 to 2001 (89.7%). Hormonal therapy was used before, during, and after radiotherapy for a mean duration of 30.1 ± 29.8 months, 43.9 ± 36.7 months, and 40.6 ± 34.3 months, respectively (86.3% of patients in 1996-1998; 89.7% of patients in 1999-2001; and 81.1% in 2003-2005). The proportion of patients receiving hormone therapy was analyzed according to risk group. Most patients in the intermediate- and high-risk groups were treated with hormone therapy during 1996 to 1998, 1999 to 2001, and 2003 to 2005 survey periods (Fig. 4). In the low risk-group, approximately 50% to 70% of patients were treated with hormone therapy in the periods 1999 to 2001 and 2003 to 2005. We could not precisely analyze the incidence of low-risk patients treated with hormone therapy during the 1996 to 1998 period because only 1 patient, who was not treated with hormone therapy, was available for this analysis.

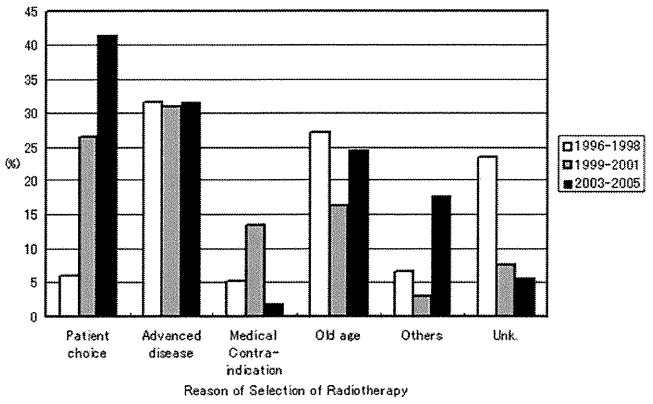

Fig. 2. Reasons of selection of EBRT for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

FTE radiation oncologists

For academic institutions, the mean numbers of full-time equivalent (FTE) radiation oncologists increased gradually over time (results of the surveys for 1996-1998, 1999-2001, and 2003-2005 were 2.13, 2.36, and 2.86, respectively). For nonacademic institutions, the mean numbers of FTE radiation oncologists also increased gradually over time (results for 1996-1998, 1999-2001, and 2003-2005 were 0.57, 0.62, and 0.75, respectively), but the numbers were extremely low compared with those in academic institutions.

Comparisons of changing trends in patient and treatment characteristics between Japan and the United States

Changing trends between Japan and the United States were analyzed with regard to patient and treatment characteristics by using the US PCS data reported by Zelefsky *et al.* (25). In Japan, the proportions of patients with stage T3 to T4 disease and PSA levels >20 ng/ml decreased gradually from 1996 to 1998 to 2003 to 2005, but the proportions of patients with T3 to T4 disease, a Gleason score of 8 to 10, and a PSA level of >20 ng/ml were over 30% among the three surveys (Fig. 5a). On the other hand, in the United States, the proportions of patients with T3 to T4 disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were almost the same, and the proportions of patients with T3 to T4 disease, a PSA of >20 ng/ml, and a Gleason score of 8 to 10 were approximately 20% or less during the survey period (Fig.5b).

Regarding treatment characteristics, in Japan, the proportions of patients receiving conformal radiotherapy and higher radiation doses (72 Gy or more) increased, as 84.9% of patients were treated with conformal therapy, and 16.9% of patients were treated with higher radiation doses in 2003 to 2005. On the other hand, use of hormone therapy was over 80% during the survey periods (Fig.6a). In the United States, the proportions of patients receiving hormone therapy and higher radiation doses (72 Gy or more) increased continuously over the survey periods, and the proportions of patients receiving hormone therapy and higher radiation doses were approximately 45% to 50% (Fig. 6b). Concerning conformal therapy in the United States, 80% of patients were treated with conformal radiotherapy in 1999, which was almost the same frequency as patients treated from 2003 to 2005 in Japan.

DISCUSSION

Results of the current study indicate that there were significant increases in the proportions of prostate cancer patients with stage T1 to T2 disease and lower initial PSA values in the 1996 to 2005 survey periods in Japan. Numbers of patients in the low-risk group increased gradually, while

Table 2. Treatment characteristics

Treatment	PCS survey 1996-1998 (n = 161)	1999-2001 (n = 283)	2003-2005 (n = 397)	Significance (p value)
Received radiotherapy				
Energy (≥10 MV) (%)				
Yes (no. patients/total) (%)	98/161 (60.9%)	208/279 (74.6%)	312/386 (80.8%)	<0.0001
Missing data	0	4	11	
Portal films or electric portal images used (%)				
Yes (no. patients/total) (%)		210/280 (75.4%)	388/397 (97.7%)	<0.0001
Missing data		3	0	
All fields treated each day (%)				
Yes (no. patients/total) (%)	44/65 (67.7%)	215/283 (76.0%)	363/397 (91.4%)	<0.0001
Missing data	96	0	0	
CT-based treatment planning (%)				
Yes (no. patients/total) (%)	130/161 (80.7%)	241/282 (85.5%)	361/397 (90.9%)	0.0006
Missing	0	1	0	
Received conformal radiotherapy (%)				
Yes (no. patients/total) (%)	79/161 (49.1%)	142/283 (50.2%)	337/397 (84.9%)	<0.0001
Received pelvic irradiation (%)				
Yes (no. patients/total) (%)	69/161 (42.9%)	102/283 (36.0%)	95/397 (23.9%)	<0.0001
Radiation dose (cGy)				
A+B (total)				
Median (range)	6,500 (2,200–7,400)	6,840 (1,400–8,200)	7,000 (800–8,410)	<0.0001
Mean ± SD	6,090.9 ± 990.5	6,602.9 ± 731.1	6,764.0 ± 621.9	<0.0001
A median (min-max)	6,500 (2,200–7,400)	6,600 (1,400–8,200)	7,000 (800–8,410)	<0.0001
Mean ± SD	6,250.9 ± 976.8	6,610.3 ± 766.5	6,855.8 ± 708.0	<0.0001
B median (min-max)	5,940 (3,400–7,000)	6,900 (3,000–8,000)	6,600 (3,000–7,640)	<0.0001
Mean ± SD	5,622.4 ± 885.6	6,592.6 ± 681.9	6,654.9 ± 480.5	<0.0001
Prescription dose levels (Gy) (no. patients/total) (%)				
<60	40/161 (24.8%)	17/282 (6.0%)	8/396 (2.0%)	<0.0001
60-65	36/161 (22.4%)	56/282 (19.9%)	57/396 (14.4%)	
65-70	57/161 (35.4%)	102/282 (36.2%)	125/396 (31.6%)	
≥70	28/161 (17.4%)	107/282 (37.9%)	206/396 (52.0%)	
Missing data	0	1	1	
Higher prescription dose levels (no. patients/total) (%)				
<72	159/161 (98.8%)	261/282 (92.6%)	329/396 (83.1%)	<0.0001
≥72	2/161 (1.2%)	21/282 (7.4%)	67/396 (16.9%)	
Missing data	0	1	1	
Received hormone therapy (%)				
Yes (no. patients/total) (%)	138/160 (86.3%)	253/282 (89.7%)	321/396 (81.1%)	0.0284
No (no. patients/total) (%)	21/160 (13.1%)	29/282 (10.3%)	73/396 (18.4%)	
Unknown	1/160 (0.6%)	0/282 (0.0%)	2/396 (0.5%)	
Missing data	1	1	1	
Received chemotherapy				
Yes (no. patients/total) (%)	20/159 (12.6%)	17/274 (6.2%)	5/394 (1.3%)	<0.0001
No (no. patients/total) (%)	137/159 (86.2%)	255/274 (93.1%)	387/394 (98.2%)	
Unknown	2/159 (1.3%)	2/274 (0.7%)	2/394 (0.5%)	
Missing data	2	9	3	

Abbreviation: SD = standard deviation.

numbers of patients in the high-risk group decreased gradually. These results suggest that the likelihood of early-stage prostate cancer patients being treated with radiotherapy is greater than ever before in Japan. In the United States, most of the prostate cancer patients have early-stage tumors, and radiotherapy has been recognized as the first-line therapy for prostate cancer (25–28). Because of the prevailing use of PSA screening and the increasing number of patients treated with radiotherapy in Japanese institutions (29), the opportunities for treating early-stage prostate cancer patients with radical EBRT should increase even more in the future.

In the current study, the data for a Gleason combined score were missing for 73.9% of the patients in the 1996 to 1998 PCS and 39.6% of the patients in the 1999 to 2001 PCS, while data for only 5.5% of the patients in 2003 to 2005 PCS were missing. These results suggest that previously in Japan, physicians did not realize the importance of the

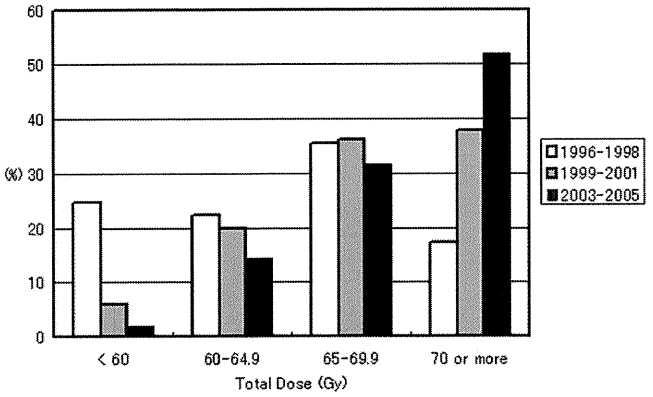

Fig. 3. Distributions of total radiation doses of external beam radiotherapy for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

Gleason combined score, but recently, they are becoming aware that the Gleason combined score is of critical importance in the evaluation and management of prostate cancer patients. Further studies are required to confirm whether physicians in Japan will routinely use the Gleason combined score in the management of prostate cancer patients in future.

The current study also revealed a remarkable change in the reason for choosing radiotherapy in Japan among the 1996 to 2005 survey periods. Only 5.9% of the patients were treated with radiotherapy by their own choice from 1996 to 1998, but 41.4% of patients chose radiotherapy from 2003 to 2005. EBRT did not become a popular treatment modality for prostate cancer in Japan until the end of the 1990s. A strong surgical tradition and an insufficient number of radiation oncology centers capable of delivering appropriate treatment prevented earlier dissemination of this type of therapy. However, in conjunction with significant improvements in the availability of new radiation treatment planning technologies and methodologies for treatment planning and delivery, Japanese patients are becoming increasingly aware of the effectiveness of radiotherapy for prostate cancer (30, 31). Therefore, the increasing percentage of patients choosing radiotherapy might reflect a growing acceptance of radical external EBRT as one of the main treatments for prostate cancer patients in Japan.

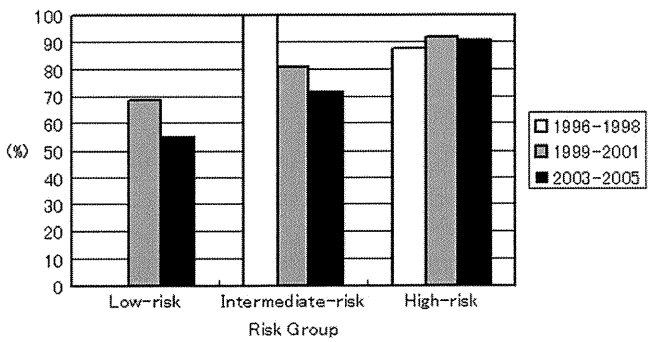

Fig. 4. Hormonal therapy distribution according to risk group for prostate cancer in Japan among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

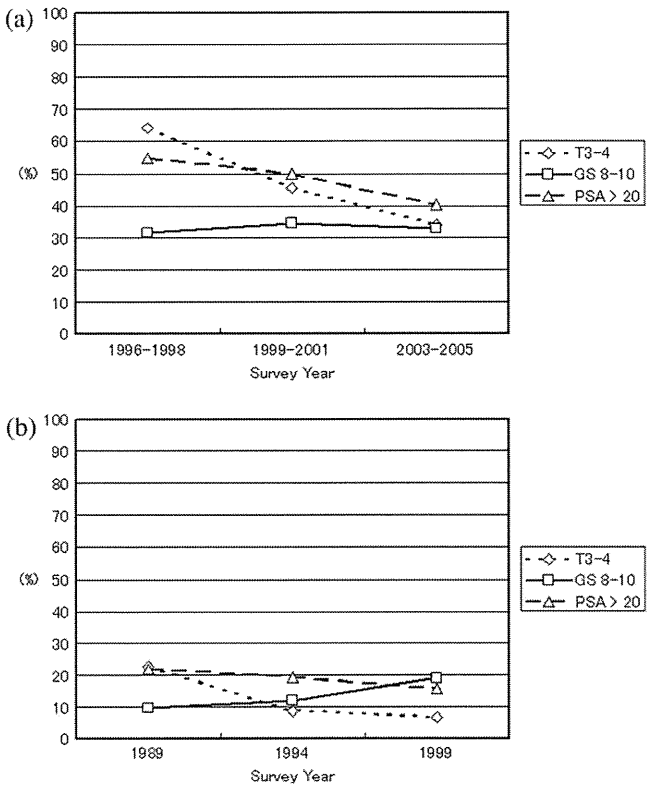

Fig. 5. (a) Changing trend in patient characteristics in Japan. (b) Changing trend in patient characteristic in the United States. (Data from ZelefskyMJ, Moughan J, Owen J, et al. Changing trends in national practice for external beam radiotherapy for clinically localized prostate cancer: 1999 patterns of care survey for prostate cancer. Int J Radiat Oncol Biol Phys 2004;59:1053-1061)

Moreover, the radiotherapy strategy appears to have changed among the 1996 to 1998, 1999 to 2001, and 2003 to 2005 survey periods. The frequency of CT-based treatment planning increased up to 90.9% in 2003 to 2005, and the usage of conformal therapy increased rapidly from 2003 to 2005 (84.9%). The median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing up to 70 Gy from 2003 to 2005. Also, the proportions of patients receiving total radiation doses below 60 Gy decreased, while the proportions of patients receiving total doses of >70 Gy increased rapidly during the survey period (Fig. 3). These results indicate that patients receiving lower radiation doses with obsolete treatment equipment was more common between 1996 and 1998, while higher doses with high-technology radiation equipment prevailed between 2003 and 2005. US PCS results indicate that many prostate cancer patients have been routinely treated with total doses of >70 Gy in the United States (25, 28). The use of increasing radiation doses in Japan might reflect the widespread dissemination of clinical trial results (32–35) and also a growing acceptance by radiation oncologists and urologists that radical EBRT is effective for treating prostate cancer (30, 31).

Results of the current study indicate that hormone therapy was commonly used in conjunction with radiotherapy during the survey period in Japan. Moreover, it was not only

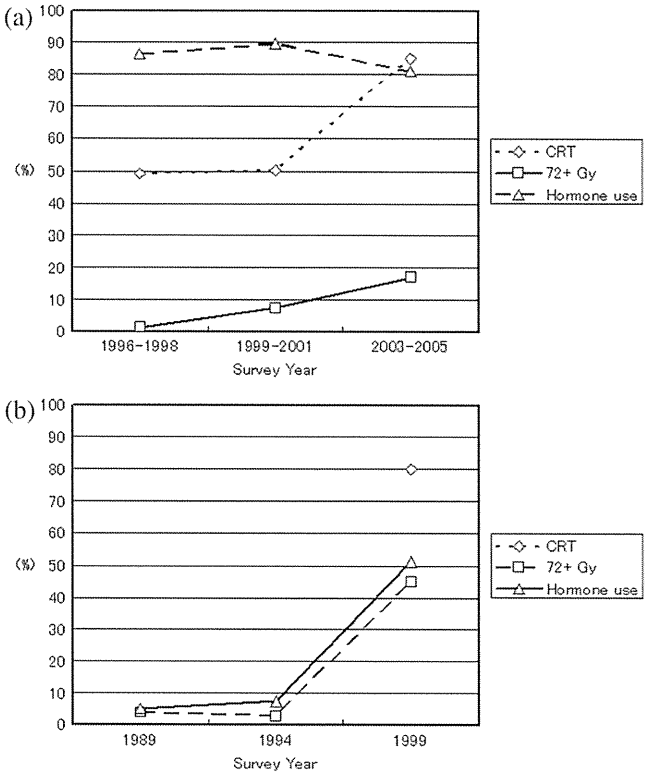

Fig. 6. (a) Changing trend in treatment characteristics in Japan. (b) Changing trend in patient characteristics in the United States. (*Data from* Schröder FH, Hugosson J, Roobol MJ, *et al.* Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-1328.)

patients in the intermediate- and high-risk groups but also patients in the low-risk group who were frequently treated with hormone therapy during 1999 to 2001 and 2003 to 2005 (Fig. 4). However, several studies from the United States have indicated that radical radiotherapy alone could control the disease in low-risk patients. Zietman *et al.* (34) indicated that a total dose of 70 Gy was sufficient to control the disease when the pretreatment PSA level was less than 10 ng/ml. Hanks *et al.* (35) found that prostate cancer patients with a pretreatment PSA level of <10 ng/ml did not benefit from a dose escalation above 70 Gy (35). Therefore, radical EBRT without hormone therapy has been the primary treatment for patients in the United States with low-risk diseases. The high rate of health insurance coverage for Japanese people may explain the frequent administration of hormone therapy in Japan (36). Another reason may be that at present, many Japanese radiation oncologists may consider the higher dose levels (>72 Gy) unnecessary for prostate cancer patients when combined with long-term hormone therapy. Therefore, radical EBRT without hormone therapy should also be the treatment of choice for low-risk patients in Japan.

In the current study, the mean numbers of FTE radiation oncologists increased gradually over time in both academic and nonacademic institutions. However, the median number of FTE radiation oncologists remained low, especially in nonacademic institutions. Publication data documenting a progressive increase in the number of prostate cancer patients treated with radiotherapy in every institution, demonstrating a need for both academic and nonacademic Japanese institutions to upgrade their radiation equipment and to recruit more radiation oncologists (29).

Changing trends between Japan and the United States were analyzed with regard to patient and treatment characteristics. In Japan, proportions of patients with T3 to T4 disease, a Gleason score of 8 to 10, and a PSA level of >20 ng/ml were all over 30%, but proportions of patients with T3 to T4 disease and a PSA level of >20 ng/ml decreased gradually during the survey period (Fig. 5a). In the United States, the proportions of patients with T3 to T4 stage disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were almost the same, and the proportions of patients with T3 to T4 stage disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were approximately 20% or less during the survey period (Fig.5b). These results indicate that although patients in Japan had more advanced disease than those in the United States, patient characteristics in Japan have been changing, becoming more similar to patients in the United States. Further studies are required to confirm this finding.

Concerning treatment characteristics: in Japan, proportions of patients receiving conformal radiotherapy and higher radiation doses have been increasing, and 84.9% of patients were treated with conformal therapy, and 16.9% of patients were treated with higher radiation doses in 2003 to 2005 (Fig. 6a). In the United States, conformal therapy was administered to 85% of patients in 1999, and higher radiation doses (72 Gy or more) have increased continuously from 1989 to 1999 (Fig. 6b). These results indicate that although radiotherapy characteristics were still developing in Japan compared to the United States, the proportions of modern radiotherapy have been increasing both in Japan and the United States during the survey period.

The percentage of patients receiving hormone therapy remained high during the periods from 1996 to 1998 to 2003 to 2005 in Japan. On the other hand, there was a rapid increase in the use of hormone therapy in the United States from 1994 to 1999. The significantly increased use of hormone 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 (32, 33). The randomized Radiation Therapy Oncology Group 8610 trial demonstrated an increase in disease-free survival at 2 years (76% vs. 62% survival) for locally advanced prostate cancer patients treated with neoadjuvant total androgen blockade plus radiation compared to those treated with radiation therapy alone (33). In Japan, hormone therapy was administered to approximately 90% of patients with high-risk disease, and these high rates of hormone therapy have continued for several years. Therefore, radiotherapy in conjunction with hormone therapy appears to be an accepted approach for the unfavorable risk group in Japan and in the United States.

CONCLUSIONS

By comparing the PCS results of 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys, we can delineate changes in the process of care for prostate cancer patients treated with radiotherapy in Japan. Study data indicate a trend toward increasing early-stage disease and increasing proportions of patients treated with higher radiation doses with advanced equipments, suggesting that radical EBRT is gaining acceptance as a first-line treatment for prostate cancer in Japan. Also, our results indicate that patterns of care for prostate cancer in Japan are becoming more similar to those in the United States. In the future, to optimize the delivery of radiotherapy, more advanced equipment and more FTE radiation oncologists are warranted. Also, repeat surveys and point-by-point comparisons of results from other countries, such as the United States, will demonstrate how EBRT for prostate cancer has been developed and optimized for patients in Japan.

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Regular Paper

Concurrent Chemoradiotherapy with S-1 as First-line Treatment for Patients with Oropharyngeal Cancer

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Concurrent chemoradiotherapy/S-1/Oropharyngeal cancer.

Purpose: S-1 is an oral fluoropyrimidine. The purpose of this study was to review the clinical outcomes of S-1 with concurrent radiotherapy for patients with oropharyngeal cancer. **Materials and Methods:** Between 2002 and 2007, 38 patients with oropharyngeal cancer treated concurrently with S-1 and definitive radiotherapy were reviewed. The clinical stage was Stage I in 4 patients, Stage II in 7, Stage III in 7, and Stage IV in 20. S-1 was administered orally twice daily for 4 consecutive weeks followed by a 2-week drug withdrawal. The initial dose of S-1 was 65 mg/m^2/day. All patients were treated using three-dimensional conformal radiotherapy with a median total dose of 65.1 Gy (range, 60.0–71.0 Gy). Clinical outcomes and major acute toxicities were analyzed based on medical records and clinical follow-up. **Results:** With a median follow-up time of 33 months, the 3-year estimates of local-regional control, distant metastases-free survival, disease-free survival, and overall survival for all patients were 75%, 80%, 65%, and 80%, respectively. The 3-year estimates of local-regional control according to stage were 100% for Stages I and II, 86% for Stage III, and 56% for Stage IV. The rate of ≥ Grade 3 acute mucositis was 32%, and the rate of ≥ Grade 3 hematological toxicities was 8%. No other severe toxicities were observed. **Conclusions:** Concurrent chemoradiotherapy with S-1 was found to be effective, especially for early disease. The treatment-related toxicities were acceptable, and the incidence of myelotoxicity was low. Further study must be carried out to compare with other chemotherapy regimens.

INTRODUCTION

The treatment of oropharyngeal cancer has traditionally been surgery alone, radiotherapy alone, or a combination of both. There is little evidence to suggest that either primary surgery or radiotherapy is superior in terms of disease control or survival. Radiotherapy is preferred at many institutions because of the presumed lower morbidity and better functional and cosmetic outcomes compared with surgical treatment.[1)] Recently, many randomized trials have shown that chemoradiotherapy (CRT) improves locoregional control and survival in treating locally advanced head and neck cancer.[2–7)] In the 2006 German meta-analysis of 32 trials, 5-fluorouracil (5-FU) as a single drug and cisplatin as a single drug or in combination with 5-FU was found to exhibit the largest benefit.[8)]

At our institution, patients with cancer of the oropharynx have been initially treated with concurrent CRT to preserve organ function as much as possible. At a radiation dose of 40–45 Gy, the primary disease is evaluated clinically and/or by imaging. If complete response is achieved at the primary site, CRT is continued with neck dissection planned for residual neck disease after completion of CRT. If persistent primary disease is obvious, surgery is performed. The chemotherapy regimen used in the CRT has generally utilized 5-fluorouracil (5-FU) as a single agent. CRT with 5-FU has been shown to provide better therapeutic results than radiotherapy alone.[9)] We have developed a combination therapy including 5-FU, vitamin A, and radiotherapy (FAR therapy) for head and neck cancer, and the effectiveness of the FAR

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therapy has been reported.[10–12)]

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is a novel oral fluoropyrimidine that combines tegafur, a metabolically activated prodrug of 5-fluorouracil (5-FU), with 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo).[13)] CDHP enhances the pharmacological actions of 5-FU by potently inhibiting its degradation, and Oxo reduces the incidence of gastrointestinal toxicities by suppressing the activation of 5-FU in the gastrointestinal tract. In a pharmacokinetic study of S-1, plasma 5-FU concentrations were shown to be almost equivalent to those obtained with continuous venous infusion of 5-FU.[14)] In the late phase II trials in patients with advanced or recurrent head and neck cancer in Japan,[15)] S-1 alone showed an overall response rate of 28.8% and a response rate at the primary lesion of 48.1%. In addition to the high response rates, the incidences of adverse effects were shown to be low. In the late Phase II clinical trials of S-1 alone in 449 patients, the incidences of ≥ Grade 3 adverse reactions were less than 10%, except for neutropenia (11.1%).[16)] These data led us to use S-1 concurrently with radiotherapy instead of 5-FU for patients with head and neck cancer.

The purpose of this study was to present the Kyushu University Hospital experience with concurrent CRT with S-1 in treating oropharyngeal cancer and to compare our findings with previous literature on this topic.

MATERIALS AND METHODS

Between 2002 and 2007, 45 patients with newly diagnosed oropharyngeal cancer without distant metastases were started on concurrent CRT with S-1 at the Kyushu University Hospital. After a radiation dose of 40–45 Gy, when an evaluation of the primary disease was performed, 7 of these 45 patients underwent surgery because of residual tumor at the primary site. Thirty-seven patients with complete response and one with unresectable residual tumor at the primary site continued CRT to a total dose of ≥ 60 Gy. These 38 patients who received definitive radiotherapy with S-1 were included in the present analysis.

The patient characteristics are shown in Table 1. Thirty-four (89%) of the patients were men, and the median age was 61 years (range, 37–82 years). Thirty-six patients (95%) had squamous cell histology. The primary sites were the lateral wall in 26 patients, the superior wall in 6, the posterior wall in 4, and the anterior wall in 2. Twenty-eight patients had a T1-2 primary and 10 patients had a T3-4 primary. Twenty-six patients (68%) were node positive. The stage distribution according to the International Union Against Cancer 2002 classification was as follows: 4 Stage I (10%), 7 Stage II (18%), 7 Stage III (18%), and 20 Stage IV (54%).

S-1 was administered orally twice daily for 3 or 4 consecutive weeks followed by a 2-week drug withdrawal from the beginning to the end of radiotherapy. The initial dose of S-1 was 65 mg/m^2 according to a phase I study of concurrent radiotherapy with S-1;[17)] patients with a body surface area (BSA) of more than 1.5 m^2 received 100 mg daily, those with a BSA of 1.25 m^2 or more but less than 1.5 m^2 received 80 mg daily, and those with a BSA of less than 1.25 m^2 received 50 mg daily. If patients had renal dysfunction, their initial daily dose was reduced from 100 mg to 80 mg or from

Table 1. Patients' characteristics

Characteristics	No. of patients
Gender	
Male	34
Female	4
Performance Status	
0	16
1	21
2	1
Histology	
Squamous cell carcinoma	36
Adenosquamous cell carcinoma	1
Mucoepidermoid carcinoma	1
Subsite	
Lateral wall	26
Superior wall	6
Posterior wall	4
Anterior wall	2
2002 UICC* T-stage	
T1	9
T2	19
T3	4
T4	6
2002 UICC* N-stage	
N0	12
N1	6
N2	19
N3	1
2002 UICC* Stage	
I	4
II	7
III	7
IV	20

*UICC = International Union Against Cancer.

80 mg to 50 mg according to the level of creatinine clearance. If patients developed toxicities, their daily dose was reduced or S-1 administration was discontinued on the physicians' recommendation. The initial dose of S-1 was 120 mg in one patient, 100 mg in 20 patients, 80 mg in 16 patients, and 60 mg in one patient.

All patients received external beam radiotherapy. Three-dimensional conformal radiotherapy was delivered through a linear accelerator with a 4 MV X-ray. Conventional fractionation was used with a daily dose of 1.8–2.0 Gy, 5 times per week. Initial radiation fields generally encompassed the primary tumor, the bilateral neck, and the supraclavicular fossae. Lateral two fields with or without a single anterior field were used. After the dose of 40–45 Gy, the primary lesion and the lymphadenopathy were boosted with reduced field to a total dose of 60–70 Gy.

The overall survival, local control rate, regional control rate, local-regional control rate, and rate of distant metastases were calculated using the Kaplan-Meier method. The survival and local-regional control rates were calculated from the first day of radiotherapy to the date of the event. The statistical significance of differences between the survival curves was assessed with the log-rank test. A p value less than 0.05 was considered to be significant. Acute and late toxicity was assessed using the Common Terminology Criteria for Adverse Events, version 3.0.

RESULTS

Treatment outcomes

All patients completed the scheduled radiotherapy course. The radiotherapy ranged from 60.0 to 71.0 Gy (median, 65.1 Gy). Thirty-four patients (89%) had a treatment break longer than 3 days to allow for evaluation of the primary disease at a dose of 40–45 Gy and/or due to acute mucositis. The median treatment time of radiotherapy was 9.1 weeks (range, 6.0–12.0 weeks). The administration of S-1 was discontinued in 2 patients, with one showing elevated serum creatine values and the other developing nausea. The dose of S-1 was reduced during treatment in 2 patients due to Grade 2 thrombocytopenia. Neck dissection was performed within 3 months of the completion of treatment in 10 of the 12 patients who had suspected persistent disease in the neck, as assessed clinically or by imaging. However, only one of these 10 patients had pathologically viable carcinoma cells.

The median follow-up time was 33 months (range, 3.4–78.3 months). Of the 38 patients, 17 patients with early disease (T1-2 and N0-1) had no locoregional recurrences. Of the remaining 21 patients with advanced disease (T1-2 and N2-3 or T3-4 and any N), 8 (33%) developed locoregional recurrences. The characteristics of these patients with local and regional failures are summarized in Table 2. There was one isolated local recurrence at the primary site at the 7-month follow-up. Three patients developed recurrences at the primary site and the neck at 4, 7, and 15 months after treatment. Four additional patients developed nodal recurrences. Two of the 8 patients with locoregional failure underwent surgery, and successful salvage was achieved. At the last contact, 5 of the 8 patients with locoregional failure had died of disease, 2 who had undergone surgery were alive without disease, and one patient who had received chemotherapy was alive with disease.

Distant metastases developed in one of the 17 patients with early disease, and in 5 of the 21 patients with advanced disease. Four of these 6 patients with distant failure had disease control above the clavicles. The site of distant metastases was the lung in 4 patients, the bone in one patient, and the mediastinal lymph node in one patient. At the last contact, 2 of the 4 patients with distant metastases and locoregional control had died of disease, one with mediastinal lymph node metastasis who had received chemoradiotherapy was alive without disease, and one who had received chemotherapy was alive with disease.

The 3-year rates of local-regional control by disease stage were as follows: Stage I, 100%; Stage II, 100%; Stage III, 86%; Stage IV, 56%; and overall, 75% (Fig. 1). The 3-year

Table 2. Characteristics of patients who developed local-regional recurrences

Patient	Primary site	Stage	Site of failures	Time to first failure (months)	Salvage therapy	Clinical status
1	Tonsil	T3N0	Local	7.2	None	Died of disease
2	Posterior wall	T2N2c	Local, regional	15.2	Surgery	Alive without disease
3	Base of tongue	T4bN2c	Local, regional, distant	3.8	Chemotherapy	Died of disease
4	Soft palate	T4bN2b	Local, regional, distant	7.1	Chemotherapy	Died of disease
5	Tonsil	T3N2b	Regional	31.3	Surgery	Alive without disease
6	Tonsil	T2N2b	Regional	25.2	Chemotherapy	Alive with disease
7	Base of tongue	T4aN2c	Regional	10.8	None	Died of disease
8	Tonsil	T2N2c	Regional, second primary	4.6	None	Died of disease

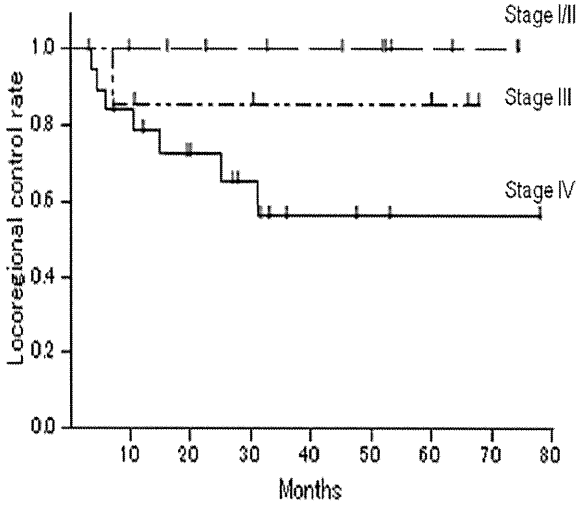

Fig. 1. Kaplan-Meier estimate of locoregional control probabilities by Stage.

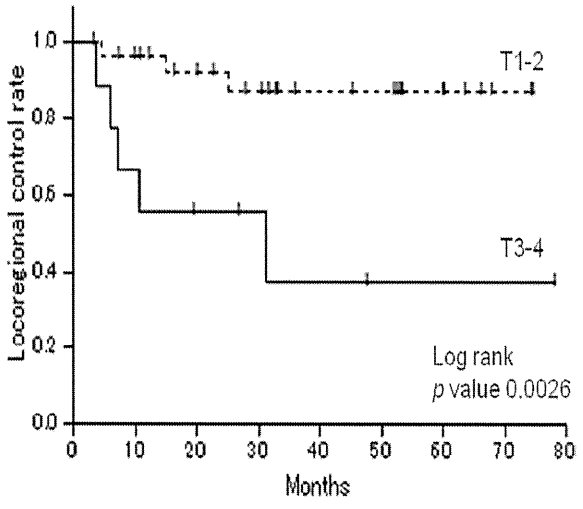

Fig. 2. Kaplan-Meier estimate of locoregional control probabilities by T-stage.

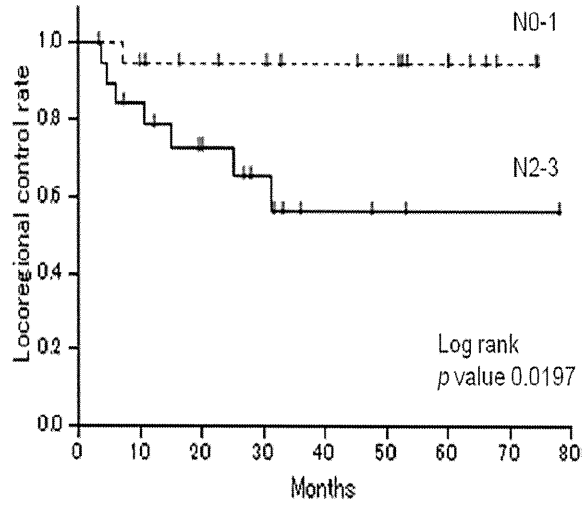

Fig. 3. Kaplan-Meier estimate of locoregional control probabilities by N-stage.

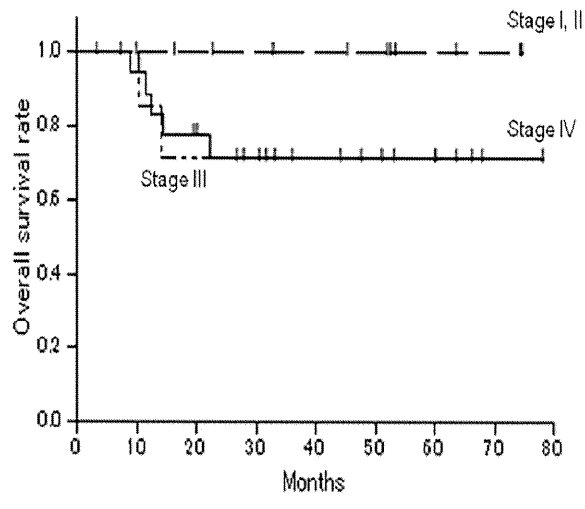

Fig. 4. Kaplan-Meier estimate of overall survival by Stage.

rates of ultimate local-regional control, including patients successfully treated with salvage therapy after a local-regional recurrence, were as follows: I, 100%; II, 100%; III, 86%; IV, 71%; and overall, 83%. T-stage (T1-2 vs. T3-4) and N-stage (N0-1 vs. N2-3) were significantly associated with local-regional control in the univariate analysis. The 3-year local-regional control rate for patients with T1-2 disease was 87% compared with 37% for patients with T3-4 disease (p = 0.0026) (Fig. 2). The 3-year local-regional control rate for patients with N0-1 disease was 94% compared with 56% for patients with N2-3 disease (p = 0.0197) (Fig. 3). Overall treatment time (< 9.0 weeks vs. ≥ 9.0 weeks, p = 0.2480) and total radiation dose (< 65.0 Gy vs. ≥ 65.0 Gy, p = 0.2152) were not associated with local-regional control. The 3-year rates of distant metastases by disease stage were as follows: Stage I, 0%; Stage II, 0%; Stage III, 13%; Stage IV, 29%; and overall, 18%. The 3-year overall survival rates by disease stage were as follows: Stage I, 100%; Stage II, 100%; Stage III, 71%; Stage IV, 71%; and overall, 79% (Fig. 4).

Acute and late toxicity

The acute toxicity of chemoradiotherapy by site and grade is detailed in Table 3. The incidence of acute mucositis higher than Grade 2 was 31%. Four of the 38 patients (11%) needed either a nasogastric feeding tube or total parenchymal nutrition during treatment. The rate of Grade 3 leukopenia was only 5.2%. No other severe acute toxicities were observed.

Late complications were scored according to the Radiation

Table 3. The incident of acute toxicity by site and grade

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	≥ Grade 3 (%)
Non hematological toxicities						
Skin	–	33	5	–	–	0
Mucosa	–	4	22	12	–	31.5
Nausea	36	–	2	–	–	0
Diarrhea	36	2	–	–	–	0
Hematological toxicities						
Leukopenia	9	13	14	2	–	5.2
Thrombocytopenia	26	8	4	–	–	0
Anemia	1	29	7	1	–	2.6

Therapy Oncology Group (RTOG) criteria. One patient developed Grade 2 osteoradionecrosis of the mandible. There were no late complications of ≥ Grade 3 except for xerostomia.

DISCUSSION

Radiotherapy and chemotherapy play an important role in treating oropharyngeal cancer. These two modalities may be given concurrently or sequentially. Previously reported randomized trials and meta-analyses have demonstrated that concomitant chemoradiotherapy significantly improves survival and locoregional control compared with radiotherapy alone in the treatment of advanced head and neck cancer. Radiotherapy with concurrent chemotherapy is considered to be the standard treatment for advanced oropharyngeal cancer when nonsurgical treatment is planned. Radiotherapy alone, however, is favored for the treatment of early-stage oropharyngeal cancer because treatment outcomes with radiotherapy alone are not compromised. The National Comprehensive Cancer Network guidelines (2008) recommend definitive radiotherapy or surgery for early oropharyngeal cancer (T1-2 and N0-1).

Platinum-based regimens are most widely used in the concurrent settings, although various chemotherapy regimens have been used. A systematic review published in 2000 by Browman *et al.* included stratification for the use of a platinum agent as well as for combination chemotherapy or no combination therapy.[3] Platinum-based regimens were the only ones resulting in a statistically significant difference when used either alone or in combination. In the MACH-NC meta-analysis, the effects of chemotherapy were significantly higher with platinum than with other agents when used as single-agent chemotherapy, although no significant difference was seen between platinum-based regimens and other regimens in multi-agent chemotherapy.[18] In the recent German meta-analysis, 5-FU as a single drug and cisplatin as a single drug or in combination with 5-FU exhibited the largest benefit.[8] However, these platinum-based regimens have substantial toxicities and are not suitable for all patients.

S-1 is an oral fluoropyrimidine developed to improve the tumor-selective cytotoxicity of 5-FU and reduces gastrointestinal toxicity through the addition of two modulators, CDHP and Oxo.[13] S-1 shows antitumor activity in head and neck cancer when used in monotherapy for advanced or recurrent disease, with an overall response rate of 28.8%.[15] In addition, the incidence of adverse reactions of Grade 2 or more is low (1.7–25.4%). S-1 also has a radiosensitizing effect, which has been shown in preclinical trials of a human oral cancer cell lines, human oral cancer xenografts, and human colon cancer xenografts.[20–22] Moreover, some clinical trials have recently shown the efficacy of S-1 and concurrent radiotherapy for head and neck cancer.[23–26]

In the present study, the 3-year overall survival and locoregional control were 100% for Stage I–II. The local-regional control rates achieved with radiotherapy alone for Stage I–II disease were 73–100% in previous studies.[27–30] One of these studies was an institutional review that included 176 patients with Stage I–II oropharyngeal cancer reported by Selek *et al.*[27] They reported that the T-stage classification was associated with local-regional control. The 5-year local-regional control rate for patients with T1-Tx disease was 90% compared with 77% for patients with T2 disease. In this study, the local-regional control rate for T2 disease was 100% as well as that for T1 disease in patients with Stage I–II. Concurrent CRT with S-1 for early-disease oropharyngeal cancer compared favorably with radiotherapy alone, especially for Stage II disease.

The 3-year overall survival rate for Stage III–IV disease was 71% and the local-regional control rate was 65% in this study. These rates are comparable to those observed in the GORTEC 94-02 study in which conventional fractionated radiation was given with concomitant chemotherapy using

three cycles of carboplatin and 5-FU.[31] In the GORTEC 94-01 study, the 3-year overall survival was 51% and the 3-year locoregional control rate was 66%. The rate of local failure in this study was lower than that achieved in the GORTEC study. Four patients (15% of the patients with Stage III–IV disease) developed local relapse in our study, whereas 33% experienced local recurrence in the GORTEC study. However, these relatively good outcomes achieved with CRT with S-1 in the present study could be because the 7 patients who received surgery after a dose of 40–45 Gy due to residual primary tumors were excluded for the analysis. In addition, some of the patients lacked a long follow-up time. Therefore, further study will be needed in order to confirm the effectiveness of concurrent CRT with S-1 for the oropharyngeal cancer.

In terms of compliance with concurrent CRT with S-1, all patients completed the planned radiotherapy. The rate of higher than Grade 2 mucositis was 31%, and no hematological toxicities and dermatitis of higher than Grade 2 were observed. No severe late complications except for xerostomia were seen. Concurrent use of S-1 with radiotherapy was considered to be tolerable. However, the duration of radiotherapy was prolonged, with a median treatment break of 13 days. There were two main reasons for this treatment break. One is that it was necessary to evaluate primary disease at a dose of 40–45 Gy to determine whether the radiotherapy should be continued, and the other was the presence of acute mucositis. Most of patients who Percutanenous endoscopic gastrostomy (PEG) has not been performed at our institution thus far. The prolongation of the overall treatment time in radiotherapy has been shown to be related to a decreased local control rate in the treatment of head and neck cancer.[32–35] In the German meta-analysis, smaller survival benefits were observed in studies with a prolonged overall treatment time in chemoradiotherapy.[8] Although the treatment outcomes in our study were comparable to those reported previously, as described above, efforts must be rigorous in giving nutrition support such as PEG, recommendations for oral and dental hygiene, and controlling pain during radiotherapy in order to prevent treatment-related interruptions.

In conclusion, we observed 100% 3-year locoregional control for Stage I–II disease and 65% control for Stage III–IV disease with concurrent chemoradiotherapy with S-1. This regimen was found to be effective, especially for early-stage oropharyngeal cancer. The rate of hematological toxicity was lower than that obtained with platinum-based regimens. The acute mucositis was a limiting factor. Further studies are needed to define the optimal schedules of radiotherapy with S-1 and to compare the outcomes of S-1 to platinum-based regimens. We have started a randomized trial of CDDP versus S-1 in chemoradiotherapy for head and neck cancer.

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Clinical Results of Definitive Chemoradiotherapy for Patients With Synchronous Head and Neck Squamous Cell Carcinoma and Esophageal Cancer

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Objectives: To assess the efficacy and toxicity of radical chemoradiotherapy for patients with synchronous head and neck squamous cell carcinoma (HNSCC) and esophageal cancer (EC).

Methods: Thirty-four patients with synchronous HNSCC and EC were treated mainly with radical chemoradiotherapy at the same time. Median external radiation dose for HNSCC and EC was 70 Gy (range, 60–70.5 Gy), except for 2 patients with tongue cancer, who underwent brachytherapy and 60 Gy (range, 45–70 Gy), respectively. Thirty-one patients were treated with concurrent chemoradiotherapy with cisplatin and/or 5-fluorouracil or TS-1 (oral anticancer agent that combines tegafur, a metabolically activated prodrug of 5-fluorouracil, with 5-chloro-2, 4-dihydoroxypyridine, and potassium oxonate).

Results: Thirty-three patients completed the intended treatment. The response rate was 94%, with 26 complete responses (76%) and 6 partial responses (18%). At a median follow-up of 17.3 months, 2-year rates of overall survival, cause-specific survival, and disease-free survival were 44%, 52%, and 33%, respectively. Initial failure patterns were local failure in 14 patients (63%), regional progression in 3 patients (13%), and distant metastasis in 6 patients (27%). The most common acute toxicity was myelosuppression, with 8 patients experiencing grade 3–4 toxicity. Three patients experienced grade 3 mucositis and pharyngitis. No patients experienced late morbidity of grade 3 or higher.

Conclusions: Definitive chemoradiotherapy for patients with synchronous HNSCC and EC is feasible with a low mortality rate and acceptable morbidity.

Key Words: radiotherapy, synchronous, head and neck squamous cell carcinoma, esophageal cancer

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Multiple squamous cell carcinomas often arise in the upper aerodigestive tract.[1–3] The association of multiple tumors in that area has been explained by the concept of field cancerization.[4,5] Neoplasms of the head and neck (HN) and the esophagus area are seen most frequently, although other combinations occur.[6–8] In patients with head and neck squamous cell carcinoma (HNSCC), routine endoscopy of the esophagus at diagnosis results in more frequent detection of second primary esophageal cancer (EC) at an early stage.[9,10] The management and clinical course of these patients with multiple squamous cell carcinomas are poorly documented. The poor prognosis of each carcinoma and their anatomic proximity complicate the therapeutic strategy and limit the treatment options for each location.[11] In the past, patients with synchronous HNSCC and EC were thought to be candidates for palliative treatment.[12] This was partly because surgical resection for synchronous HNSCC and EC was thought to be too definitive and inappropriate for these patients and to offer only a small chance of cure.[12] There have been very few studies focusing on definitive therapeutic strategies for such patients, and treatment options are controversial.[13,14] In contrast to several studies on surgical treatment[13,15] for patients with synchronous HNSCC and EC, the feasibility, efficacy, and toxicity of definitive chemoradiotherapy for the treatment of these patients has not been evaluated enough yet. Thus, we retrospectively analyzed clinical findings, particularly clinical outcomes including cause of death, for patients with synchronous HNSCC and EC who had been treated with definitive chemoradiotherapy.

MATERIALS AND METHODS

Patient Characteristics

A total of 34 patients underwent definitive radiotherapy for synchronous HNSCC and EC at the National Kyushu Cancer Center and Kyushu University Hospital from 1995 to 2007. The median age of these patients was 64 years (range, 49–85 years). The median Karnofsky Performance Status was 90 (range, 70–100). The primary sites of HNSCC were as follows: larynx, 3 (9%); mesopharynx, 9 (26%); hypopharynx, 19 (56%); oral floor, 1 (3%); and tongue, 2 (6%). All patients were evaluated according to the 1997 International Union Against Cancer tumor, node, metastasis classification. T and N stages of HNSCC and EC are listed in Table 1. Pretreatment diagnostic evaluations consisted of barium swallow, endoscopy with Lugol's iodine, cervical and abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) of HN area, and bone scintigraphy. Whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) scan was not routinely performed.

Treatment Planning

Radiotherapy for HNSCC and that for EC were performed simultaneously. Twenty patients were treated with a 2-dimensional (2D) technique, whereas 14 patients received three-dimensional conformal radiotherapy (3D-CRT). The initial radiotherapy fields included the HN and mediastinal region for 32 patients, and HN and mediastinal and upper abdominal region for 2 patients. For HN treatment, external radiotherapy was performed using a cobalt-60 or 4 to 6 MV photon beam. Thirty-two of the 34 patients received external beam radiation therapy (EBRT) alone and 2 patients received EBRT and brachytherapy. The target volume was defined by means of endoscopic evaluation, physical examination, CT, MRI, and/or PET. The radiotherapy tech-

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niques mainly used a standard 3-field arrangement, 2 lateral fields to treat the primary tumor and upper neck and 1 AP field to treat the lower neck. A single field or 2 lateral fields were also used depending on the case. The daily fractional EBRT dose was 1.5 to 2 Gy, administered 5 days per week, for all patients. Median total radiation dose for HNSCC was 70 Gy (range, 60–70.5 Gy), except for 2 patients with tongue cancer who were treated with brachytherapy after EBRT. In one of these 2 patients, permanent radioactive seeds, ^{198}Au grains, were used for the treatment of tongue cancer and 20 Gy was prescribed to the marginal line after EBRT of 19.8 Gy in 11 fractions. The other patient was treated with afterloaded high-dose-rate brachytherapy with plastic tubes and the prescribed dose was 50 Gy in 10 fractions per 5 days after EBRT of 30 Gy in 20 fractions. Five patients, who were evaluated as CR for primary sites and as PR for neck nodal involvement, were offered neck dissection followed by chemoradiotherapy.

TABLE 1. Sites and Stages of HNSCC and EC

HNSCC	
T stage	
T1	8
T2	12
T3	3
T4	11
N stage	
N0	14
N1	3
N2	14
N3	3
Location	
Larynx	3
Mesopharynx	9
Hypopharynx	19
Oral Floor	1
Tongue	2
EC	
T stage	
T1	24
T2	3
T3	4
T4	3
N stage	
N0	27
N1	7

Staging was defined according to UICC (1997).

For esophageal treatment, radiotherapy was performed using a cobalt-60 or 6 to 21 MV photon beam. Median dose for EC was 60 Gy (range, 45–70 Gy) with conventional fraction sizes (1.5–2 Gy). After the initial anterior/posterior field included the primary tumor and metastatic lymph nodes at 30 to 40 Gy, simulation was performed to reduce the RT field and exclude the spinal cord by using an oblique opposed field.

Chemotherapy was performed concurrently with radiotherapy in 31 patients (91%). The other 3 patients did not receive chemotherapy because of advanced age, renal dysfunction, or refusal. Chemotherapy consisted of 2 courses of cisplatin in 9 patients, 2 courses of 5-fluorouracil/cisplatin in 11 patients, or TS-1 (oral anticancer agent that combines tegafur, a metabolically activated prodrug of 5-fluorouracil, with 5-chloro-2, 4-dihydoroxypyridine, and potassium oxonate) for 4 weeks in 10 patients. In 1 patient, carboplatin was selected instead of cisplatin because creatinine clearance was <60 mL/min. The choice of chemotherapy regimen depended on the managing physician.

Criteria for Response and Toxicity

A complete response was defined as disappearance of the tumor mass on endoscopy, CT, MRI, and/or PET. A partial response was defined as more than 30% regression based on one-dimensional measurement by means of endoscopy, CT or MRI, and no response was defined as less than 30% regression or less than 20% progression.

Acute and late toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Analysis

Overall survival (OS), cause-specific survival (CSS), and disease-free survival (DFS) rates were calculated by using the

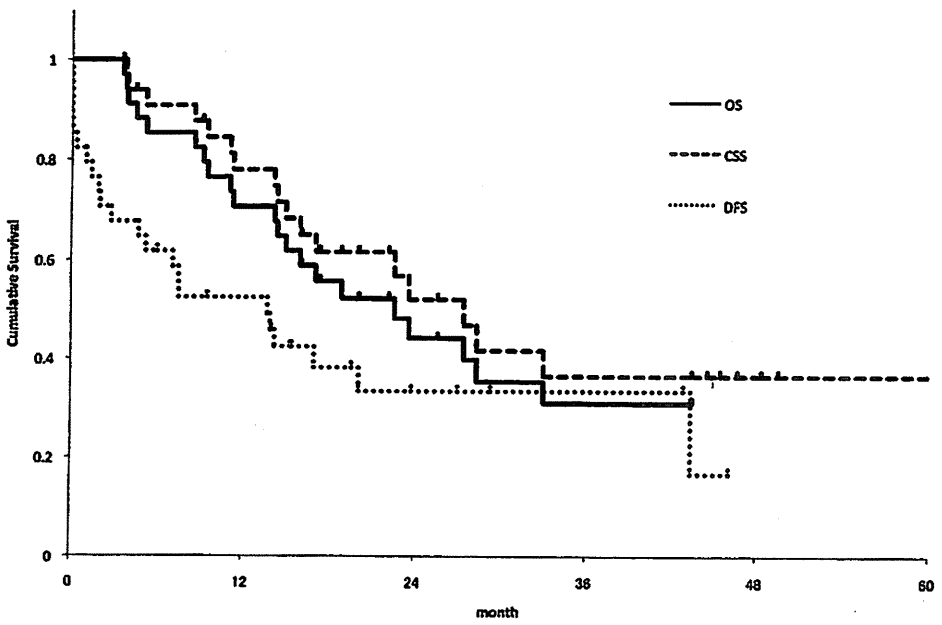

FIGURE 1. Overall survival, cause-specific survival and disease-free survival for all patients.

Kaplan-Meier method. When calculating CSS, patients who were alive at the last follow-up or had died of causes other than HNSCC or EC were censored. DFS was defined as the absence of disease in HNSCC and EC. All time points were calculated from the initiation of chemoradiotherapy. Statistical difference in survival was compared with log-rank tests. A P of less than 0.05 was regarded as statistically significant.

RESULTS

Of the 34 patients, 33 completed the intended treatment. The treatment was tolerated well in all but 1 patient, who could not complete chemoradiotherapy because of impaired Performance Status. Eighteen patients (53%) required a treatment break for 1 to 4 weeks. Treatment was discontinued for 2 to 4 weeks in 7 of those patients due to toxicity such as myelosuppression, mucositis, and/or pharyngitis. A period of 1 to 4 weeks was needed to determine whether to continue chemoradiation or switch to surgery in 11 patients.

All patients were evaluated for toxicity. The most common acute toxicity was myelosuppression, with 7 (21%) of the patients experiencing grade 3–4 toxicity. In addition, grade 3 mucositis and pharyngitis occurred in 3 patients and 1 patient, respectively. Seven patients required treatment breaks because of these toxicities.

No patient experienced late morbidity of grade 3 or higher. Three patients had feeding disorder due to esophagostenosis with grade 2, and 1 patient required thyroid hormone treatment because of hypothyroidism.

The median period of overall treatment was 67 days (range, 50–104 days) except for 1 patient in whom treatment was discontinued at 16 days. For the 34 patients with synchronous HNSCC and EC, the response rate was 94% with 26 complete responses (CR) (76%) and 6 partial responses (PR) (18%). Five patients, who were evaluated as CR for primary sites and as PR for neck nodal involvement, were offered neck dissection followed by chemoradiotherapy. Of those 5 patients, 2 had no evidence of pathologic residual carcinoma. At a median follow-up of 17.3 months (range, 4–65 months), 2-year rates of OS, CSS, and DFS were 44%, 52%, and 33%, respectively (Fig. 1).

At the last evaluation, 12 patients were still alive and 5 of them with locoregional recurrence underwent salvage surgery such as pharyngolaryngectomy or esophagectomy. Ten patients died of HNSCC, 5 died of EC, 3 died of other cancers, and 2 died of noncancer-related causes such as pneumonia or disseminated intravascular coagulation. For the remaining 2 patients, the exact cause of death could not be determined retrospectively.

Twenty-two patients experienced recurrence of HNSCC or EC. Fourteen patients had local progression as a component of initial failure (63%), and local progression occurred in the setting of distant failure in 1 patient. In 3 patients (13%), local progression was initially in the regional lymph nodes, all cases being HN lesions. Six patients (27%) had distant metastasis as a first site of failure (Table 2). Three patients with local recurrence had salvage surgery such as laryngectomy or esophagectomy and were still alive at the last evaluation.

Figure 2 shows the OS curves in our series according to the stage of EC. OS in patients with stage I–II EC was significantly better than in patients with stage III–IV EC (P = 0.0001). The 2-year rate of OS in the 27 patients with HNSCC and stage I–II EC was 56%. Survival of patients with stage I–II HNSCC tended to be better than that of patients with stage III–IV HNSCC. However, the survival difference was not statistically significant (P = 0.06) (Fig. 3). Among the 27 patients who had stage I–II EC, survival was significantly better in patients with stage I–II HNSCC comparing to those with stage III–IV HNSCC (P = 0.02) (Fig. 4). The 2-year rate of OS was 86% in the 8 patients with stage I–II HNSCC and stage I–II EC. No statistical significance in overall survival was observed in patient age and treatment duration.

TABLE 2. Patterns of Initial Disease Progression

Origin	HN	Esophageal	Both
Local	5	6	2
Regional	3		
Distant	4	1	
Local +distant	1		
Unknown			2

DISCUSSION

We showed the efficacy and feasibility of simultaneous definitive chemoradiotherapy for patients with HNSCC and EC. To the best of our knowledge, though many reports recommend surgical

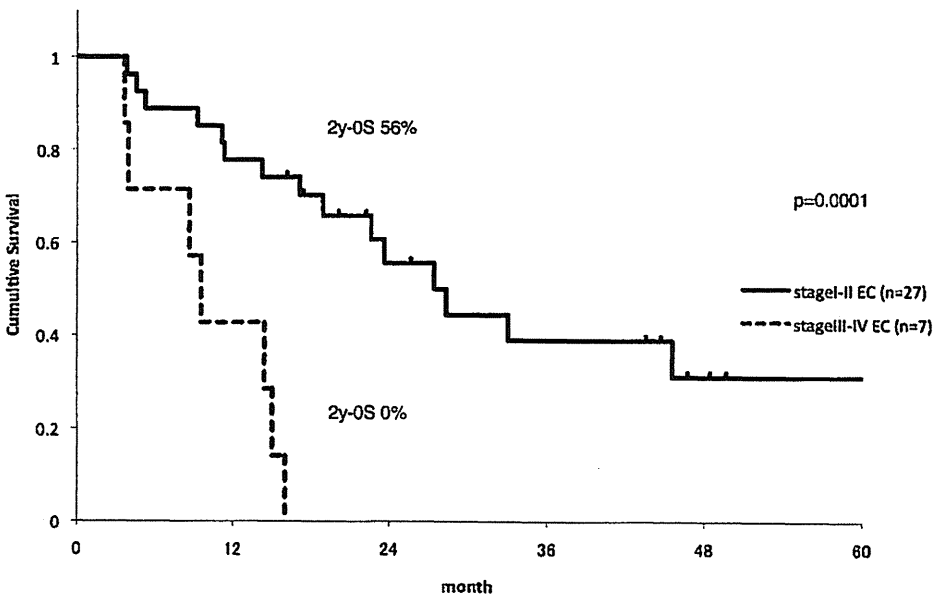

FIGURE 2. Overall survival according to stages of EC. The group of stage I–II EC (n = 27) includes HNSCC with stage I-II (n = 8) and stage III-IV (n = 19). The group of stage III–IV EC (n = 7) includes HNSCC with stage I-II (n = 3) and stage III-IV (n = 4).

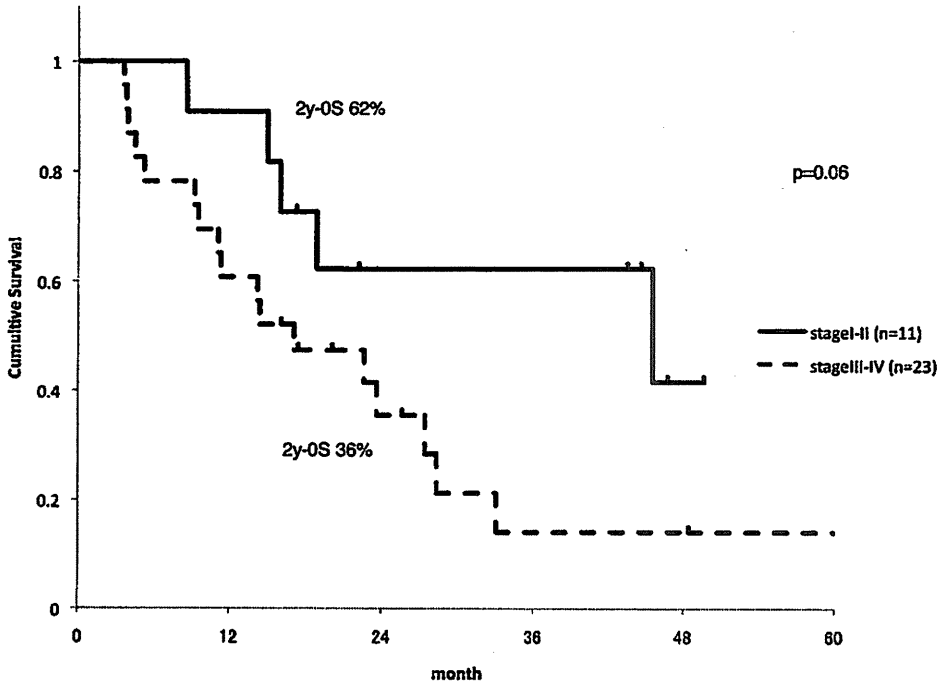

FIGURE 3. Overall survival according to stage of HNSCC.

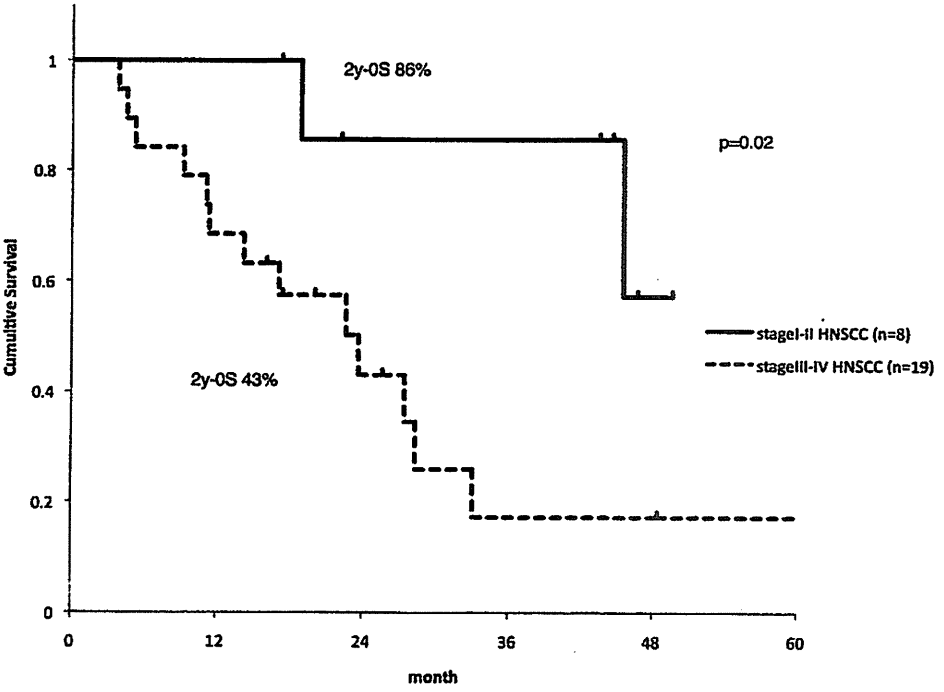

FIGURE 4. Overall survival according to stages of HNSCC with only stage I-II EC.

resection as a standard treatment policy,[16–19] there have been only a few previous studies in which the outcome of patients with HNSCC and EC mainly treated with radiotherapy was analyzed.

Guillot et al[20] retrospectively reviewed 22 patients with multiple synchronous squamous cell carcinomas of the upper aerodigestive tract who had been treated with neoadjuvant chemotherapy followed by radiotherapy or surgery. Twelve patients were free of disease after locoregional treatment and mean survival was 17 months. Nguyen et al[21] evaluated neoadjuvant chemotherapy and irradiation in 24 patients with synchronous squamous cell carcinoma of the upper aerodigestive tract. Sixteen patients (66%) had complete remission in both cervical and mediastinal sites. The median survival was 12 months and survival rate was 5% at 24 months. Welz et al[22] treated 24 patients with synchronous HNSCC and EC by a radiation based curative approach, and they reported that the median overall survival was 37 months.

In our series, 14 patients (64%) had a complete response and 5 of them were still alive at the time of evaluation. The median survival was 19 months and the 2-year survival rate was 44%. These results are comparable to results of previous studies.[20–22] The 2-year survival rate

in patients with EC of stage I–II was 56%. Thus, favorable prognosis can be expected by definitive chemoradiotherapy in patients with synchronous HNSCC and EC if the coexisting EC is early stage (stage I–II). Furthermore, survival of patients with stage I-II diseases for both HNSCC and EC was excellent (2-year OS = 86%). Chemoradiotherapy is considered to be an effective treatment option for synchronous early-stage HNSCC and EC.

Although acute toxicity of grade 3 or higher was observed in 7 patients (21%), 33 of the 34 patients completed the treatment and no patient experienced late severe toxicity of grade 3 or higher. Our results indicate that definitive chemoradiotherapy for synchronous HNSCC and EC is feasible and effective.

The impact synchronous double primary cancer on survival of cancer patients has not been clear. Robinson et al[23] reported that survival of HNSCC patients without second primary cancer (SPC) was better than that of HNSCC patients with second primary cancer. The presence of EC was found to have an adverse effect on the survival of patients with HNSCC.[24] With regard to the effect of SPC on the of patients with EC, Kagei et al reported that the survival outcome of EC was not different between patients with SPC and those without SPC.[25] Poon et al[8] also reported that survival rates of patients with EC did not significantly differ between patients with and those without SPC. These results suggest that the dismal prognosis of EC overshadows the moderate effect of SPC on survival. The difference in the impact of SPC on survival of patients with HNSCC and survival of patients with EC might be due to the presentation of most patients with EC at an advanced stage, and their prognosis was poor regardless of whether another primary cancer was present or not.[8] In fact, Kagei et al[25] showed that the overall survival rate of patients with early-stage EC was better for patients without synchronous SPC than for patients with synchronous SPC. For synchronous HNSCC and EC, treatment should be selected in consideration of the prognosis of the disease. The present study showed that the survival of patients with synchronous HNSCC and EC was significantly affected by the stage of EC (stage I–II vs. stage III–IV). The results of our study and previous studies suggest that the stage of EC is more important for predicting survival of patients with synchronous HNSCC and EC. We found that the stage of coexisting HNSCC also significantly influenced the survival of patients with early-stage EC.

Past studies showed that patients with HNSCC had higher rates of early-stage EC than did only EC patients, and a significant difference was found between the 2 groups in terms of tumor, node, metastasis stage groupings.[26,27] In our series, 27 patients (79%) with EC had stage I–II disease, and their survival rate was significantly better than that of patients in stage III-IV. This suggests that intense screening and surveillance resulted in high detection rates for cases of early-stage EC, which have a chance of cure with definitive treatment.

CONCLUSION

Definitive chemoradiotherapy in the presence of synchronous HNSCC and EC can be performed safely without increase in morbidity and mortality rates. Although there is no standard approach for this group of patients, definitive chemoradiotherapy is a good curatively intended treatment option if comorbid EC is in stage I–II.

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Japanese Structure Survey of Radiation Oncology in 2007 with Special Reference to Designated Cancer Care Hospitals

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Background and Purpose: The structure of radiation oncology in designated cancer care hospitals in Japan was investigated in terms of equipment, personnel, patient load, and geographic distribution. The effect of changes in the health care policy in Japan on radiotherapy structure was also examined.
Material and Methods: The Japanese Society of Therapeutic Radiology and Oncology surveyed the national structure of radiation oncology in 2007. The structures of 349 designated cancer care hospitals and 372 other radiotherapy facilities were compared.
Results: Respective findings for equipment and personnel at designated cancer care hospitals and other facilities included the following: linear accelerators/facility: 1.3 and 1.0; annual patients/linear accelerator: 296.5 and 175.0; and annual patient load/full-time equivalent radiation oncologist was 237.0 and 273.3, respectively. Geographically, the number of designated cancer care hospitals was associated with population size.
Conclusions: The structure of radiation oncology in Japan in terms of equipment, especially for designated cancer care hospitals, was as mature as that in European countries and the United States, even though the medical costs in relation to GDP in Japan are lower. There is still a shortage of manpower. The survey data proved to be important to fully understand the radiation oncology medical care system in Japan.

Key Words: Structure survey · Radiotherapy facility · Radiotherapy personnel · Radiotherapy equipment · Caseload · Medical care system

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Japanische Strukturerhebung zur Radioonkologie im Jahr 2007 unter besonderer Berücksichtigung von auf Krebsbehandlung spezialisierten Krankenhäusern

Hintergrund und Ziel: Es wurde die Struktur der Radioonkologie in auf Krebsbehandlung spezialisierten Krankenhäusern in Japan untersucht, und zwar im Hinblick auf Ausrüstung, Personal, Patientenaufkommen und geografische Verteilung. Ebenso

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wurden die Auswirkungen von Veränderungen in der japanischen Gesundheitsfürsorge-Politik auf die Strahlungstherapie-Struktur untersucht.

Material und Methodik: Die Japanische Gesellschaft für radiologische Therapie und Onkologie hat eine Erhebung zur nationalen Struktur der Strahlungsonkologie im Jahr 2007 durchgeführt. Dabei wurden die Strukturen von 349 auf Krebsbehandlung spezialisierten Krankenhäusern und 372 anderen Strahlentherapie-Einrichtungen verglichen.

Ergebnisse: Die jeweiligen Ergebnisse in Bezug auf die Ausrüstung und das Personal in den auf Krebsbehandlung spezialisierten Krankenhäusern und anderen Einrichtungen waren: Linearbeschleuniger pro Einrichtung: 1,3 bzw. 1,0; jährliche Patientenzahl pro Linearbeschleuniger: 296,5 bzw. 175,0. Das jährliche Patientenaufkommen pro Vollzeitäquivalent-Radioonkologe betrug 237,0 bzw. 273,3. In geografischer Hinsicht stand die Anzahl der auf Krebsbehandlung spezialisierten Krankenhäuser in Relation zur Bevölkerungszahl.

Schlussfolgerung: Die Struktur der Radioonkologie in Japan war, was die Ausrüstung und insbesondere die auf Krebsbehandlung spezialisierten Krankenhäuser betrifft, ebenso ausgereift wie oder ausgereifter als in europäischen Ländern und in den Vereinigten Staaten, obwohl die medizinischen Kosten im Verhältnis zum BIP in Japan geringer sind. Es besteht weiterhin ein Mangel an Arbeitskräften. Die Erhebungsdaten haben sich als bedeutsam für ein umfassendes Verständnis des Radioonkologie-Krankenpflegesystems in Japan erwiesen.

Schlüsselwörter: Strukturerhebung · Strahlentherapie-Einrichtung · Strahlentherapie-Personal · Strahlentherapie-Ausrüstung · Patientenaufkommen · Medizinisches Versorgungssystem

Introduction

In developed countries in Europe, such as France, Germany, Italy, and the UK, as well as in the United States, the rates of radiotherapy use for cancer treatment are as high as 50% or more because there are sufficient radiotherapy facilities and personnel, such as radiation oncologists (ROs), medical physicists (MPs), and radiotherapy technologists (RTTs) [1, 2, 5, 11]. On the other hand, the current utilization rate of radiotherapy for new cancer patients in Japan is only 26.1% [19] and surgery is still predominant. In Japan, the Cancer Control Act has been implemented since 2007 in response to patients' urgent petitions to the government [8]. This law strongly advocates the promotion of radiotherapy. At the same time, the Ministry of Health, Labor, and Welfare began the accreditation of "designated cancer care hospitals (DCCHs)" with the aim of correcting regional differences in the quality of cancer care and strengthening cooperation between regional cancer care hospitals [3, 9, 13]. The Japanese Society of Therapeutic Radiology and Oncology (JASTRO) has conducted national structure surveys of radiotherapy facilities in Japan every 2 years since 1990 [18, 19]. The structure of radiation oncology in Japan has improved in terms of equipment and its functions in response to the increasing number of cancer patients who require radiotherapy.

In this study, the recent structure of radiation oncology in Japan was analyzed with special reference to DCCHs in terms of equipment, personnel, patient load, and geographic distribution. The effect of changes in the cancer care policy by the Japanese government on radiotherapy structure was also investigated. Furthermore, the medical care situation in Japan was compared with European countries and the United States.

Materials and Methods

JASTRO carried out a national structure survey of radiation oncology in 2007 by administering a questionnaire in 2008 [19]. The questionnaire consisted of items related to the number of treatment machines and modality by type, the number of personnel by job category, the number of patients by type, and the site. A response was received from 721 of 765 (94.2%) radiotherapy facilities in Japan. There were 377 DCCHs facilities by the end of fiscal year 2009. The surveys were not returned by 16 facilities, and 13 facilities did not have departments of radiotherapy at the time of the survey. Thus, the structures of 349 DCCHs and 372 other radiotherapy facilities were analyzed. In this survey, full-time equivalent (FTE) (40 hours/week only for radiation oncology service) data were surveyed depending on clinical working hours for radiotherapy of each staff. SAS® 8.02 (SAS Institute Inc., Cary, NC, USA) [12] was used for the statistical analysis. The statistical significance was tested by means of the X^2 test, Student's t test, or analysis of variance (ANOVA).

The Japanese Blue Book Guidelines (JBBG) [6, 7] were used for comparison with the results of this study. These guidelines pertain to the structure of radiation oncology in Japan based on Patterns of Care Study (PCS) [15, 17] data.

Results

Current Situation of Radiation Oncology

Table 1 shows the current situation of radiation oncology in Japan. The numbers of new patients and total patients in all radiotherapy facilities in Japan were estimated at approximately 181,000 (170,229 × 765/721) and 218,000 (205,087 × 765/721), respectively. For DCCHs, the corresponding numbers were approximately 117,000 (112,101 × 364/349) and 141,000 (135,383 × 364/349). The number of patients in DCCHs, thus, accounted for approximately 65% of the number of patients, both new and total (117,000/181,000 and 141,000/218,000), in all radiotherapy facilities. The average numbers of new patients/facility were 321.2 for DCCHs and 156.3 for the other radiotherapy facilities, and for the average numbers of total