definitive radiotherapy, we have used alternating CRT to reduce acute mucositis during treatment by avoiding concomitant administration of 5-FU without sacrificing the intensity of the chemotherapy.

To evaluate its clinical efficacy, we retrospectively reviewed the clinical results of HPC patients treated with definitive CRT at Aichi Cancer Center Hospital with relatively long follow-up.

MATERIALS AND METHODS

Patient and tumor characteristics

Ninety-seven patients with non-metastatic squamous cell HPC were treated with definitive CRT at Aichi Cancer Center Hospital between 1990 and 2006. The characteristics of the 97 patients are summarized in Table 1. The enrollment criteria were as follows: previously untreated and histologically confirmed squamous cell cancer without distant metastasis. Patients who received radiotherapy alone were excluded from this study. The treatment content of this cohort was as follows: patients with resectable disease and an aim to preserve the larynx received ICT followed by CCRT. Patients who did not want an operation or patients with unresectable disease received alternating CRT or CCRT. Tumors were staged according to the American Joint Committee on Cancer Staging, 5th version [5].

The pre-treatment evaluation consisted of a physical examination, laryngoscopy, biopsy of the primary site, chest radiography, computed tomography (CT) of the cervix and chest, and magnetic resonance imaging (MRI) of the primary site and neck disease. 18-fluorodeoxyglucose-positron emission tomography (18F-FDG PET) or PET/CT was also used after 2001.

Total parenteral nutrition or nasogastric (NG) tube feeding was performed on 39 patients (40%) due to inadequate oral

Table 1. Patient characteristics and treatment contents

Characteristics		All	ICT	non-ICT
Sex	Male	92	59	33
	Female	5	2	3
Age (years)	Median	65	64	66
	Range	36–86	36–80	43–86
Subsite	Postcricoid region	16	7	9
	Pyriform sinus	72	51	21
	Posterior wall	9	3	6
T	1	11	8	3
	2	43	20	23
	3	35	26	9
	4	8	7	1
N	0	33	16	17
	1	16	8	8
	2a	7	6	1
	2b	17	13	4
	2c	17	11	6
	3	7	7	0
Stage	I	5	2	3
	II	19	6	13
	III	22	13	9
	IVA	43	33	10
	IVB	8	7	1
Radiotherapydose (Gy)	Median	66.6	66.6	66.6
	Range	30.6–76.9	30.6–76.9	36–76
IMRT		6	6	0

intake during treatment. In this study a planned gastrostomy was not intended during treatment.

A planned neck dissection was performed in 21 patients (21.6%) who had highly advanced nodal disease (N2b, N2c, or N3) or residual neck disease after CRT. After 2001 the indication of a planned neck dissection was decided by 18F-FDG PET or PET/CT taken within three months after completion of CRT.

Radiotherapy

Ninety-one patients were treated with 3D conformal radiotherapy, and six patients were treated with intensity-modulated radiotherapy (IMRT) using helical tomotherapy. Six patients who were treated with IMRT received ICT. External beam radiotherapy was administered five times a week at a dose of 1.8–2.0 Gy in once-daily fractions using 6-MV photon beams. Treatment planning was made by an X-ray simulator or radiation planning system for 3D conformal radiotherapy.

Patients having conventional radiotherapy were initially treated with opposed lateral fields to the primary and upper neck areas matched to the anterior fields for the lower neck and supraclavicular regions up to 36–40 Gy. The primary lesion and involved neck nodes were further boosted to 66–70 Gy with oblique parallel opposed fields or a dynamic conformal method in order to spare the spinal cord. The gross tumor volume (GTV) was defined as the total volume of the primary lesion and the involved lymph nodes. The GTV was determined by a laryngoscopy, CT, MRI and 18F-FDG PET scan. A positive lymph node was defined as >10 mm in the short axis on CT/MRI or positive 18F-FDG PET findings. The clinical target volume (CTV) was defined as the GTV plus a 10-mm margin to cover microscopic disease. The planning target volume (PTV) was defined as the CTV plus 5-mm margins in every direction. The CTV prophylactic was designed to include the lymph nodes at Levels II–V, the retropharyngeal node and the subclavicular lymph node. The PTV prophylactic was defined as the CTV prophylactic plus 5-mm margins. The initial field included the PTV prophylactic.

Patients receiving IMRT were defined the same as patients receiving conventional radiotherapy. All patients treated with IMRT underwent treatment planning using simultaneous integrated boost methods. A planned delivery dose at D95 was calculated at the PTV/PTV prophylactic for 70 Gy/54 Gy in 35 fractions. Among the patients in this cohort, the median dose to the primary site was 66 Gy (range 30.6–76.9 Gy) and that for the involved lymph node was 63 Gy (range 30–78 Gy).

Chemotherapy

Patients were allocated to receive the ICT or non-ICT protocol (Fig. 1). Patients with resectable disease who aimed to preserve the larynx received ICT, and those who acquired a sufficient response were added to the radiotherapy or CRT protocols. Patients with resectable disease who refused an operation or who had unresectable disease underwent the non-ICT protocol. Of 97 patients, 80 (82%) underwent multi-agent chemotherapy consisting of CDDP and 5-FU (FP) or nedaplatin and 5-FU (FN). Chemotherapy consisted of continuous infusion of 5-FU at a dose of 600 mg/m^2/24 h for five days (Days 1–5). CDDP was given at a dose of 80 mg/m^2/24 h for two days (Days 6 and 7), or nedaplatin was given at a dose of 130 mg/m^2/6 h for one day (Day 6). ICT was used in 61 patients (63%). In the ICT protocol, two courses of FP were administered to 52 patients. Patients who achieved a complete response (CR) with ICT were treated with radiotherapy only, whereas patients who achieved a partial response (PR) received CCRT, which consisted of weekly or triweekly

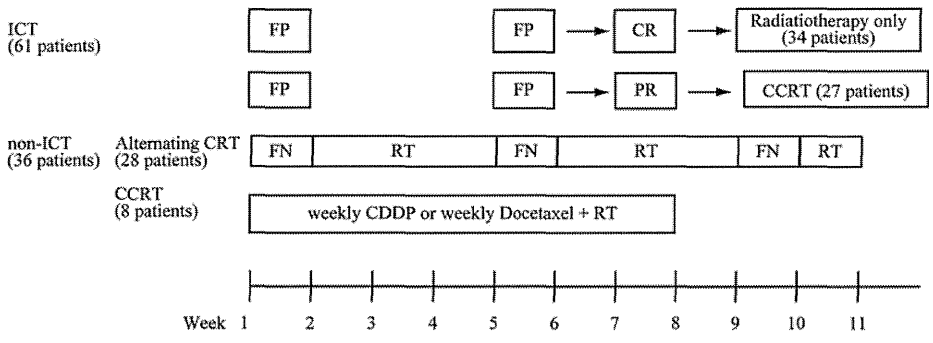

Fig. 1. Treatment scheme of the induction chemotherapy (ICT) group and the non-ICT group. ICT was used in 61 patients (63%). In the ICT protocol, two courses of 5-FU and CDDP (FP) were administered to 52 patients. Patients who achieved a complete response with ICT were treated with radiotherapy only, whereas patients who acquired a partial response received concurrent chemoradiotherapy (CCRT). Non-ICT was used in 36 patients (37%), 28 of whom were administered alternating chemoradiotherapy (CRT) consisting of three cycles of 5-FU and nedaplatin (FN) or 5-FU and CDDP (FP). Another eight patients received CCRT consisting of weekly CDDP or weekly docetaxel.

CDDP. Non-ICT was used in 36 patients (37%), 28 of whom were administered alternating CRT consisting of three cycles of FN or FP. Another eight patients received CCRT consisting of weekly CDDP or weekly docetaxel.

Follow-up

Patients were followed up monthly during the first six months and then every 3–6 months thereafter. Follow-up examinations included a physical examination, laryngoscopy, and a CT or MRI of the neck. 18F-FDG PET or PET/CT was also performed at least annually during follow-ups after 2001. An upper gastrointestinal endoscopy was performed once a year to detect double cancer after the end of CRT. Acute and late toxicity were scored according to the Common Terminology Criteria of Adverse Events, version 3.0 [6].

Statistical analysis

The survival period was calculated from the start of treatment to the date of death or the last follow-up. Progression-free survival (PFS) was defined as the time until an event of disease progression or death of any cause. Local control (LC) was defined as the time until an event of local disease progression or a residual tumor. Laryngeal preservation time was defined as the time until laryngectomy for any reason, except for partial excision. The rates of overall survival (OS), PFS, LC and laryngeal preservation were calculated using the Kaplan-Meier method. The difference between the two groups was tested with the log-rank test. Multivariate analyses were performed using Cox's proportion hazards model. A probability value of <0.05 was defined as significant.

RESULTS

Treatment outcomes

Ninety-four patients (96.9%) completed their scheduled CRT. The median duration of the overall time of ICT-plus-CRT or radiotherapy only was 104 days, and that of alternating CRT was 63 days. At the primary site, 88 patients (90.7%) achieved a CR, 7 (7.2%) had a PR, one (1.0%) had a mild response (MR), and one (1.0%) had progressive disease (PD) after completion of radiotherapy. As for neck disease, 75 patients (79.8%) achieved CR, 17 (17.5%) had PR, one (1.0%) had MR, one (1.0%) had no change, and two (2.0%) had PD. The median follow-up time of this cohort was 77.7 months (range 31.1–175 months). At the last follow-up, 58 (59.8%) of the 97 patients were alive, and 39 (40.2%) had died, of whom 25 (25.7%) patients died from HPC, five patients died from double cancer (two from esophageal cancer, one from lung cancer, one from stomach cancer and one from colon cancer), and nine patients died from other causes (pneumonia in four patients, aspiration asphyxia in one patient and unknown in four patients). Thirty-nine patients (41.2%) were alive without disease and 19 (19.6%) were alive with recurrent disease. The 5-year rates of OS, PFS, LC and laryngeal preservation rates for all patients were 68.7%, 57.5%, 79.1% and 70.3%, respectively. Figure 2 shows the OS curve for all patients and groups. The 5-year rate of OS of groups divided by Stage was 76.9% for Stage I–II and 51.5% for Stage III–IV. The 5-year rate of PFS was 72.3% for Stage I–II and 41.1% for Stage III–IV. The 5-year laryngeal preservation rates of both groups by stage were 85.4% for Stage I–II and 73.2% for Stage III–IV. The LC rate of groups divided by T-stage was 90.0% for T1, 90.1% for T2, 58.5% for T3, and 50.0% for T4 (Fig. 3). In the subgroup analysis, PFS rates at five years were 45.4% in the ICT group and 81.9% in the non-ICT group (Fig. 4); the difference in the PFS rate between these groups was statistically significant ($P = 0.006$).

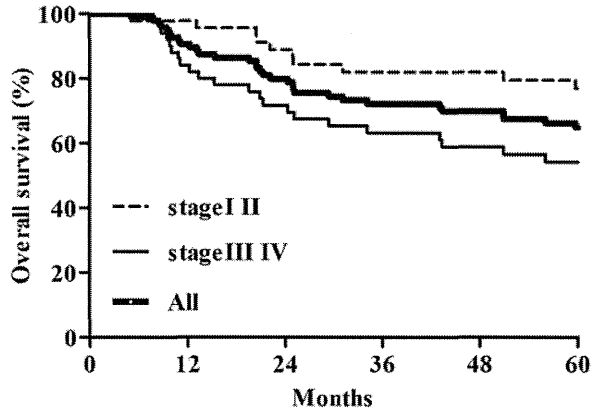

Fig. 2. Overall survival curves of all patients and groups divided by stage.

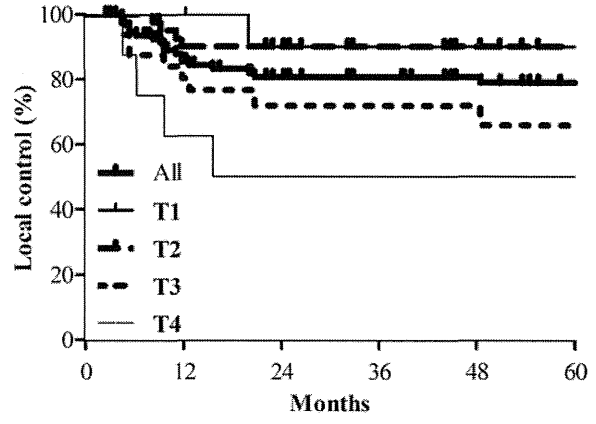

Fig. 3. Local control curves of all patients and groups divided by T-stage.

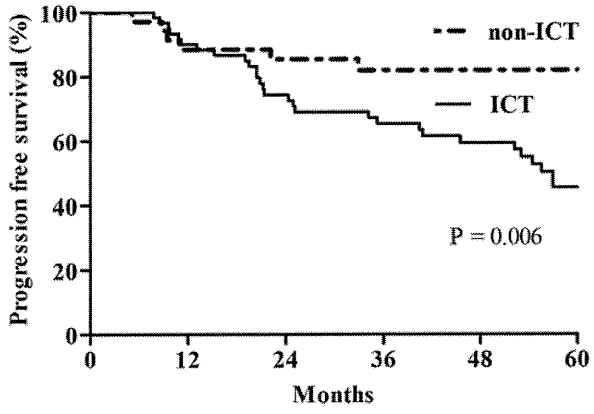

Fig. 4. Progression-free survival of groups using induction chemotherapy (ICT) and non-ICT. The difference between the two groups was statistically significant ($P = 0.006$).

Table 2. Second primary cancer

Site	Number
Esophagus	29
Stomach	11
Lung	5
Oropharynx	4
Colon	4
Larynx	2
Oral cavity	2
Prostate	2
Breast	1
Liver	1
Malignant lymphoma	1

Patterns of treatment failure

At the last follow-up in March 2012, 43 of 97 patients (44.3%) had developed treatment failure: 19 (19.6%) had developed local failure, 23 (23.7%) had developed lymph node failure, and 17 (17.5%) had developed distant failure. Of the 17 patients with distant failure, 11 patients had lung metastasis, four patients had bone metastasis and two patients had skin metastasis. Of the entire group of patients analyzed, 14 (14.4%) had recurrence at two or more sites. Of the 21 patients who received planned surgery, 11 patients (52.3%) developed recurrence. Nine (81.8%) of these patients developed recurrence at regional and/or distant sites.

Second primary cancer

Second primary cancer developed in 44 (45.3%) of the 97 patients (Table 2). The most common site was the esophagus (29 patients), followed by the stomach (11 patients), oropharynx (4 patients) and lung (5 patients). Both synchronous and metachronous double cancers were observed.

Among the 29 patients with esophageal cancer, eight patients were diagnosed before treatment with HPC and 21 patients were diagnosed simultaneously or after treatment for HPC. Of the 21 patients, 18 patients were manageable with curative intent. Seventeen of these patients had superficial esophageal cancer. Regarding the treatment of these 18 patients, six patients were treated with CRT and 12 patients underwent an endoscopic mucosal resection (EMR).

Univariate and multivariate analysis

Table 3 shows the results of the univariate analysis, and Table 4 shows the results of the multivariate analysis for OS, PFS and LC. On univariate analysis, the clinical stage (I–III vs IV), T-stage (T1–2 vs T3–4) and N-stage (N0–1 vs N2) were significant prognostic factors for OS (Table 3). The clinical stage, T-stage, N-stage, total duration of therapy, second primary cancer (yes vs no) and ICT (yes vs no) were significant prognostic factors for PFS. An advanced T-stage was the only significantly unfavorable factor for LC. Using multivariate analysis, only an advanced T-stage remained significant regarding prognostic factors of OS, PFS and LC. Although ICT was a significantly unfavorable factor for PFS in univariate analysis, it was not significant in multivariate analysis.

Treatment toxicities

Acute toxicities of Grade 3 to 4 were observed in 34 patients (35%) (Table 5). The most common hematologic toxicity of Grade 3 to 4 was thrombocytopenia (14.4%). Only one patient demonstrated skin reactions of Grade 3. Grade 3 dysphagia caused by acute mucositis occurred in 20 patients (20.6%).

Regarding late adverse events, pharyngeal edema of Grade 4 occurred in two patients and hypothyroidism of Grade 2 occurred in three patients. No treatment-related death was observed. Among the 20 patients who had Grade 3 dysphagia caused by acute mucositis, three patients remained permanently gastrostomy-dependent due to dysphagia. For these three patients, a gastrostomy was performed after completion of the initial treatment (range 9–14 months). One of these patients was still alive without recurrent disease at the last follow-up, and the other two patients had died due to double cancer.

DISCUSSION

We have reported the clinical results of definitive CRT for HPC at our institution. Table 6 shows the results of the treatment outcomes of HPC reported in past studies. Some

Table 3. Univariate analyses for correlation of prognostic factors according to overall survival, progression-free survival and local control

Factor		n	5-Year OS	P value	HR (95% CI)	5-Year PFS	*P* value	HR (95% CI)	5-Year LC	*P* value	HR (95% CI)
Age (years)	<65	47	68.1	0.149	1.000 (Referent)	60.1	0.613	1.000 (Referent)	83.8	0.120	1.000 (Referent)
	≧65	50	60.7		1.629 (0.760–3.492)	54.9		1.382 (0.883–1.913)	67.0		1.999 (0.837–4.775)
Subsite	PS	72	65.9	0.506	1.000 (Referent)	59.2	0.184	1.000 (Referent)	83.0	0.231	1.000 (Referent)
	Others	25	61.8		0.957 (0.386–2.375)	48.9		1.525 (0.828–2.843)	67.1		2.460 (0.874–6.929)
Stage	I–III	46	76.9	0.007*	1.000 (Referent)	72.3	0.004*	1.000 (Referent)	84.5	0.071	1.000 (Referent)
	IV	51	54.1		2.133 (0.996–4.565)	41.1		2.190 (1.198–4.006)	68.6		2.394 (1.010–5.674)
T	T1–2	54	76.3	0.003*	1.000 (Referent)	65.2	0.017*	1.000 (Referent)	88.1	0.001*	1.000 (Referent)
	T3–4	43	50.4		2.539 (1.161–5.554)	47.1		2.303 (1.221–4.341)	63.1		4.563 (1.870–5.140)
N	N0–1	49	75.7	0.005*	1.000 (Referent)	71.9	0.003*	1.000 (Referent)	84.1	0.074	1.000 (Referent)
	N2	48	54.0		2.876 (1.394–5.934)	42.9		2.463 (1.347–4.505)	68.7		2.252 (0.951–5.325)
RT dose (Gy)	<66.6	43	67.6	0.531	1.000 (Referent)	55.2	0.885	1.041 (0.561–1.934)	82.0	0.392	1.000 (Referent)
	≧66.6	54	62.9		1.394 (0.608–2.797)	61.0		1.000 (Referent)	74.3		1.563 (0.659–3.706)
Total duration of therapy (days)	<85	47	69.4	0.368	1.000 (Referent)	76.8	0.001*	1.000 (Referent)	85.9	0.118	1.000 (Referent)
	≧85	50	60.7		1.388 (0.650–2.936)	40.5		2.228 (1.22–4.071)	68.5		2.067 (0.873–4.895)
Second primary cancer	No	53	56.3	0.204	1.506 (0.800–2.835)	45.6	0.037*	0.558 (0.304–1.023)	73.3	0.368	1.499 (0.620–3.618)
	Yes	44	74.2		1.000 (Referent)	71.8		1.000 (Referent)	85.3		1.000 (Referent)
ICT	No	36	69.7	0.359	1.000 (Referent)	81.9	0.006*	1.000 (Referent)	87.6	0.118	1.000 (Referent)
	Yes	61	62.1		1.371 (0.634–2.963)	45.4		2.397 (1.285–4.473)	71.4		2.235 (0.923–5.416)

HR = hazard ratio, CI = confidence interval, RT = radiotherapy, PS = pyriform fossa, ICT = induction chemotherapy, OS = overall survival, PFS = progression-free survival, LC = local control.
*significant.

Table 4. Multivariate analyses for correlation of prognostic factors according to overall survival, progression-free survival and local control

	OS		PFS		LC	
Factor	**HR (95% C.I.)**	***P* value**	**HR (95% C.I.)**	***P* value**	**HR (95% C.I.)**	***P* value**
Stage	0.836 (0.088–6.128)	0.736	0.586 (0.074–4.620)	0.586	0.958 (0.109–8.467)	0.969
T	3.137 (1.580–6.225)	0.001*	1.822 (1.976–3.402)	0.044*	4.419 (1.562–12.503)	0.005*
N	2.491 (0.316–19.634)	0.386	2.854 (0.376–21.666)	0.310	1.934 (0.242–15.428)	0.534
Total duration of therapy (days)	NA	NA	1.538 (0.502–4.717)	0.451	NA	NA
Second primary cancer	NA	NA	0.618 (0.321–1.190)	0.151	NA	NA
ICT	NA	NA	1.631 (0.486–5.684)	0.442	2.573 (0.741–8.932)	0.137

ICT = induction chemotherapy, OS = overall survival, PFS = progression-free survival, LC = local control, HR = hazard ratio, C.I. = confidence interval, NA = not available
*significant

Table 5. Incidence of moderate to severe toxicity

	Number of patients by toxicity grade	
Factor	**Grade 3**	**Grade 4**
Acute toxicity		
Neutropenia	6	6
Thrombocytopenia	8	4
Anemia	6	0
Mucositis	20	0
Liver function	1	0
Renal function	0	0
Late toxicity		
Pharyngeal dysphagia	3	0
Laryngeal stenosis	0	2
Osteonecrosis of jaw	0	0

studies have also reported the efficacy of ICT for HPC [4, 7]. ICT was usually performed for resectable advanced disease because definitive radiotherapy was selected based on assessment of the tumor response after chemotherapy, and serious complications caused by salvage surgery could be avoided [3]. However, in various clinical studies, the LC and OS rates of the ICT groups were not superior to those of the CCRT groups [1]. Our study was a retrospective analysis using limited cases, and a selection bias could have affected the results. In our study as well, the results of the ICT group were slightly inferior to those of the non-ICT groups; the 5-year OS rates, 5-year PFS rates and 5-year LC rates of the ICT group vs non-ICT groups were 62.1% vs 69.7%, 45.4% vs 81.9% and 71.4% vs 87.6%, respectively.

Some studies have reported outcomes including other sites of head and neck cancer [1, 8, 9], including a postoperative series and a radiotherapy alone series [4, 10–12]. However, few reports regarding definitive CRT for HPC have been published [13, 14]. Lefebvre *et al.* [4] reported the results of a randomized Phase III study comparing an ICT arm with immediate surgery, with or without a postoperative radiotherapy arm, for patients with Stage II–IV HPC. One hundred and ninety-four patients were enrolled in this trial, and the 3/5-year OS rates were 57/30% for the ICT group and 43/35% for the postoperative radiotherapy arm, with 3/5-year disease-free survival (DFS) rates of 43/25% and 32/27%, respectively [4]. Tai *et al.* [14] published the treatment outcomes of ICT followed by CCRT in 42 patients with Stage III–IV HPC at a single institution. The 3-year OS, DFS and LC rates were 35.3%, 33.1% and 54.8%, respectively, with a median follow-up time of 42.9 months [14]. Our reported series included 73 patients with Stage III–IV disease (75%) with relatively longer follow-up, and the acquired results seem to be favorable compared to past studies. With multivariate analysis, the T-stage was the only significant prognostic factor for OS, PFS and LC. We believe our practical results are quite meaningful because of sufficient organ preservation and disease control.

Historically, dysphagia has been reported as significant late toxicity after CRT for patients with HPC. Fukuda *et al.* [9] reported that in low-dose weekly docetaxel-based

Table 6. Results of the treatment outcome for hypopharyngeal cancer

Authors, year	Primary	No. of patients	Treatment	No. of stage III–IV (%)	Chemotherapy	OS (%) (years)	PFS or DFS (%) (years)
Vandenbrouck (1987) [12]	HPC	152	RT alone	130 (85.5)	none	65 (3)	25 (3)
						40 (5)	NA
Lefebvre (1996) [4]	HPC	100	ICT + RT	93 (93)	CDDP + 5-FU	57 (3)	43 (3)
						30 (5)	25 (5)
Altundag (2004) [7]	HPC/LC	5/40	ICT + RT or ICT + CCRT	45 (100)	CDDP + 5-FU	78 (1)	50 (2)
Tai (2008) [14]	HPC	42	CCRT or ICT + CCRT	42 (100)	CDDP + 5-FU + MTX	35 (3)	33 (3)
Lambert (2009) [8]	HPC/LC	27/55	CCRT	82 (100)	CDDP + 5-FU	63 (3)	73 (3)
Fukada (2009) [9]	HPC	34	CCRT or ICT + CCRT	34 (100)	Docetaxel + CDDP + 5-FU	56 (3)	32 (3)
Present	HPC	97	CCRT or	73 (75)	CDDP + 5-FU (or NDP)	76 (3)	60 (3)
			ICT + CCRT (or RT alone)			68 (5)	57 (5)

HPC = hypopharyngeal cancer, LC = laryngeal cancer, RT = radiotherapy, ICT = induction chemotherapy, CCRT = concurrent chemoradiotherapy, CDDP = cisplatin, 5-FU = 5-fluorouracil, MTX = methotrexate, NDP = nedaplatin, OS = overall survival, PFS = progression-free survival, DFS = disease-free survival, LC = local control, NA = not assessed.

chemoradiotherapy for locally advanced oropharyngeal cancer or HPC patients, Grade 3 dysphagia occurred as late toxicity in two patients (3%), and percutaneous endoscopy gastrostomy (PEG) was required in one patient with Grade 3 dysphagia. Lambert *et al.* [8] reported that in concurrent platinum-based chemoradiotherapy for advanced laryngeal cancer and HPC patients, five patients (6%) were still dependent on PEG for adequate intake for a mean duration of 43 months after radiotherapy. In the present study, three patients (3%) were gastrostomy-dependent at the last follow-up because of Grade 3 dysphagia as late toxicity. However, this incidence was relatively low compared to the reported series. Mekhail *et al.* [15] reported that 91 out of 158 patients treated with definitive CRT or RT required feeding tube placement at some time during treatment, and the predictor of a need for feeding tube placement was a hypopharyngeal primary site, female gender, a T4 primary tumor, or treatment with CRT. Furthermore, they reported that PEG patients had more dysphagia than NG tube patients at three months (59% vs 30%, respectively; $P = 0.015$) and at six months (30% vs 8%, respectively; $P = 0.029$), and the median tube duration was 28 weeks for PEG patients compared with eight weeks for NG patients ($P < 0.001$). They suggested that PEG placement for longer periods of time was associated with protracted disuse of the muscle of deglutition, which may result in an increased incidence of pharyngeal stenosis after radiotherapy and may be associated with more persistent dysphagia. In the present study, four patients (4%) had an NG tube inserted some time during treatment for HPC, and none had a PEG tube inserted. In addition, 58 patients (60%) did not require a feeding tube and were able to continue oral intake during treatment. We suggest that these circumstances may be one reason for our lower rate of dysphagia. Among our 97 patients, only 27 patients (27%) underwent CCRT. Most patients underwent ICT or alternating CRT. Alternating CRT has the advantage of reducing toxicity due to reduced concurrent use of cytotoxic agents [16]. Therefore, mucosal toxicity may have been decreased in our series. With increasing treatment intensity, which includes docetaxel plus cisplatin and 5-FU-based sequential therapy, caution should be taken for severe late toxicity. It is necessary to provide attentive care to patients during and after treatment.

HPC patients are well known to have synchronous and metachronous malignancies, especially esophageal cancer. Kohmura *et al.* [17] reported that 18% of HPC patients investigated had esophageal cancer, which followed HPC in fewer than three years in all metachronous cases. Moreover, they reported that most hypopharyngeal cancers were at an advanced stage, but all of the esophageal cancers were at an early stage and were superficial. Morimoto *et al.* [18] reported that 41% of HPC patients investigated had esophageal cancer, and the 5-year OS rates with esophageal cancer were 83% in Stage 0, 47% in Stage I and 0% in Stage IIA–IVB. In this study, 29% of patients investigated had esophageal cancer and 52% of them were metachronous. Furthermore, all of the esophageal cancers following treatment for HPC were at an early stage, were superficial, and could be treated with EMR. We perform annual periodic endoscopic examinations of the upper aerodigestive tract for patients after treatment for HPC. Early detection of esophageal cancer enables successful minimally invasive treatment such as EMR or endoscopic submucosal dissection. To improve the clinical efficacy of HPC, early detection of metachronous malignancies is essential. Therefore, we believe that it is necessary to perform periodic endoscopic examination of HPC patients after treatment.

Recently, narrow band imaging has attracted attention as a screening examination for the head and neck region [19]. Late toxicity after CRT decreases the quality of life for HPC patients who are often first diagnosed at an advanced stage. Therefore, early detection and treatment of HPC in high-risk groups, such as heavy smokers and heavy alcohol consumers, with minimally-invasive screening examinations are expected to refine the clinical outcome of HPC patients.

In conclusion, the clinical efficacy of definitive CRT for HPC is thought to be promising not only for organ preservation but also disease control. Second primary cancer may have a clinical impact on the outcome for HPC patients, and special care should be taken when screening at follow-up.

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The usefulness of an independent patient-specific treatment planning verification method using a benchmark plan in high-dose-rate intracavitary brachytherapy for carcinoma of the uterine cervix

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To develop an easy independent patient-specific quality assurance (QA) method using a benchmark plan for high-dose-rate intracavitary brachytherapy for cervix cancer, we conducted benchmark treatment planning with various sizes and combinations of tandem-ovoid and tandem-cylinder applications with 'ideal' geometry outside the patient. Two-dimensional-based treatment planning was conducted based on the Manchester method. We predicted the total dwell time of individual treatment plans from the air kerma strength, total dwell time and prescription dose of the benchmark plan. In addition, we recorded the height (dh), width (dw) and thickness (dt) covered with 100% isodose line. These parameters were compared with 169 and 29 clinical cases for tandem-ovoid or tandem-cylinder cases, respectively. With regard to tandem-ovoid cases, differences in total dwell time, dh, dt and dw between benchmark and individual plans were on average $-0.2\% \pm 3.8\%$, -1.0 mm ± 2.6 mm, 0.8 mm ± 1.3 mm and -0.1 mm ± 1.5 mm, respectively. With regard to tandem-cylinder cases, differences in total dwell time, dh_{front} (the distance from tandem tip to tandem ring), dt and dw between benchmark and individual plans were on average $-1.5\% \pm 3.1\%$, -1.5 mm ± 4.9 mm, 0.1 mm ± 1.0 mm and 0.2 mm ± 0.8 mm, respectively. Of two cases, more than 13% differences in total dwell time were observed between benchmark plans and the clinical cases, which turned out to be due to the use of the wrong source position setting. These results suggest that our method is easy and useful for independent verification of patient-specific treatment planning QA.

Keywords: independent verification; treatment planning; Manchester method; benchmark plan; high-dose-rate intracavitary brachytherapy; uterine cervix

INTRODUCTION

Brachytherapy is an essential component of radiotherapy for the carcinoma of uterine cervix and is often combined with external beam radiation therapy (EBRT) for radical treatment. Several studies have suggested that control rates are significantly improved with EBRT and brachytherapy [1, 2]. High-dose-rate (HDR) remote afterloading intracavitary brachytherapy is widely used throughout Asia and Europe [3], and is becoming steadily more common in the USA [4].

The importance of independent verification of dosimetry prior to HDR brachytherapy treatment delivery has been recognized worldwide, and is specified in the guidelines of international regulatory agencies [5]. The Nuclear Regulation Commission (NRC) considers a 20% difference between the prescribed total dose and delivered dose to be a reportable medical event [5]. Thomadsen *et al.* identified 44 medical events in HDR brachytherapy between 1980 and 2001 in data from the NRC and International Atomic Energy Agency [6]. In fact, patients are often required to

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wait during treatment planning with an applicator inserted by a radiation oncologist, during which time errors and miscommunications can easily occur. This situation clearly indicates that patient-specific quality assurance (QA), including independent verification of treatment planning and confirmation of applicator geometry, should be done quickly and easily.

Many studies have reported independent verification methods for HDR brachytherapy treatment planning [7–16]. More recent reports have focused on the development of in-house software based on the AAPM TG 43 [17] formulism to calculate the dose at arbitrary points [13–15]. Although such software might be useful for the commissioning of treatment planning systems, human errors in individual treatment planning in clinical practice will not be identified due to the use of the same coordinate system, digitized applicator paths and dose point coordinates as those in the treatment planning system.

Although image-guided intracavitary brachytherapy has been enthusiastically investigated [18], treatment planning based on the Manchester method using two projection radiographs is still used [3]. One of the goals in intracavitary brachytherapy for carcinoma of the uterine cervix is to achieve the same level of consistency as the Manchester method. We have established the Osaka University Protocol based on the Manchester method with some modifications [19]. The goal of our institution is to achieve consistency with our protocol-based benchmark plans.

Here, we propose a very quick, simple and easy patient-specific independent verification method for Manchester method-based treatment planning using benchmark plans to detect human errors and evaluate the quality of the applicator geometry in the patient.

MATERIALS AND METHODS

Creation of benchmark plans

In this study, Fletcher-type (Fletcher-Williamson Asian-Pacific) tandem-ovoid and tandem-cylinder metal applicators (Nucletron International B.V., Veendaal, the Netherlands) were used. Various sizes and combinations of these applicators were constructed by one radiation oncologist with the 'ideal' applicator geometry outside the patient (Fig. 1a and b) and then reviewed by a medical physicist. We constructed eight kinds of tandem-ovoid and six kinds of benchmark plans (Table 1).

Figure 1c shows the 'ideal' geometry of a tandem-ovoid applicator used in our institution. Namely, a flange on the tandem tube is used at the origin, which is the cervical os

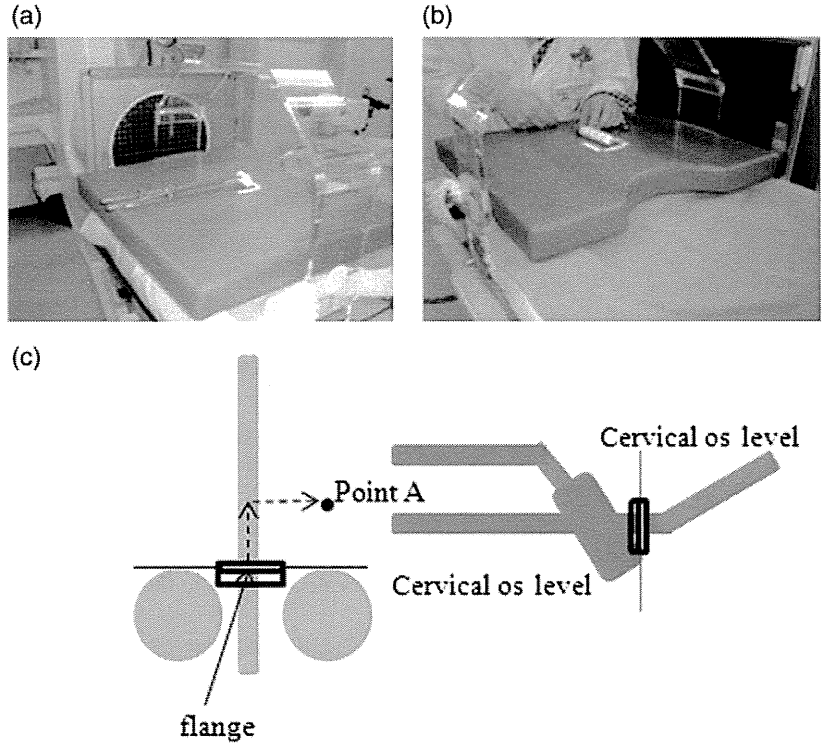

Fig. 1. Creation of benchmark plans. (**a**) Scheme for the construction of tandem-ovoid; (**b**) tandem-cylinder applications; (**c**) typical dose distribution with the tandem-ovoid application.

Table 1. Applicator settings used in benchmark plans

Tandem-ovoid			Tandem-cylinder		
Tandem length (cm)	Ovoid size		Cylinder diameter (cm)		
4	S	SS	2	2.5	3
5	S	SS	N/A	N/A	N/A
6	S	SS	2	2.5	3
7	S	SS	NA	NA	NA

The ovoid diameter of S size is 2.0 cm. The size of SS ovoid is half-cut-size of S ovoid. NA, not applicable.

and the tip of the ovoid is aligned with the origin (a flange on the tandem). Using these ideal applicator settings, treatment planning was performed with PLATO (Nucletron International B.V). Source dwell time was manually optimized based on the Manchester method as demonstrated by Tod and Meredith with minor modification [19–21]. Air kerma strength and total dwell time were then recorded. All benchmark plans were constructed by a medical physicist and reviewed by another medical physicist.

Prediction of total dwell time for individual patient treatments

Dose was calculated with the following formula introduced in AAPM TG43-U1 [22].

$$D(r,\theta) = S_K \times \Lambda \times \frac{G_L(r,\theta)}{G_L(r_0,\theta_0)} \times g_L(r) \times F(r,\theta) \times \text{dwell time} = S_k \times \text{dwell time} \times A$$

where S_K, Λ, G_L, g_L and F represent air kerma strength, dose rate constant, geometric function, radial dose function and anisotropy function, respectively. Here, we defined A as the product of Λ, G_L, $g_L(r)$ and $F(r, \theta)$.

The dose at the reference point in the benchmark plan is therefore calculated by the following:

$$D(r,\theta)_b = A_b \times S_{K\_b} \times \text{dwell time}_b \quad (1)$$

Similarly, the dose at point A in the individual plan is calculated by the following:

$$D(r,\theta)_t = A_b \times S_{K\_t} \times \text{dwell time}_t \quad (2)$$

If the 'ideal' tandem-ovoid geometry is achieved in the patient without any planning errors or misuse of the applicator, A_b is nearly equal to A_t. Dwell time in the individual plan can therefore be predicted by the following formula from (1) and (2):

$$\text{Dwell time}_t = \frac{D(r,\theta)_t \times S_{K\_b} \times \text{dwell time}_b}{D(r,\theta)_b \times S_{K\_t}} \quad (3)$$

where $D(r, \theta)_t$ and $D(r, \theta)_b$ represent the prescription dose of each treatment and the benchmark plan, respectively.

Comparison of dose shape with that of the benchmark plans

ICRU report 38 [23] recommends reporting the reference volume as well as total reference air kerma strength and absorbed dose at reference points. The reference volume is the volume encompassed by the reference isodose surface, which is represented by the major dimensions of the following:

(i) Height (dh), which is the maximum dimension along the tandem source measured on an 'oblique' sagittal plane;
(ii) Thickness (dt), which is the maximum dimension perpendicular to the tandem sources measured on a transverse plane;
(iii) Width (dw), which is the maximum dimension perpendicular to the tandem sources measured on a transverse plane.

In addition to the above parameters, we defined the dimensions of dh_{front} and dh_{ext}, which represent the distance from th 100% isodose line of the tip side of the tandem to the origin and that from the 100% isodose line of the connector side of the tandem to the origin, respectively (Fig. 2c).

Figure 2 shows the definitions of these parameters. For the tandem-cylinder, we recorded the additional parameters of dh_{front} and dh_{ext}, which represent the maximum dimension of the 100% isodose line of the tip side of the tandem to the tandem flange, and that of the connector side of the tandem to the tandem flange (Fig. 2c). These values were measured for individual treatment plans and compared with those of the benchmark plans.

Analysis of clinical cases

We retrospectively analyzed 168 and 29 clinical cases from 2009 through 2010 with a tandem-ovoid and tandem-cylinder, respectively. The difference in total dwell time between a benchmark plan and an individual treatment plan was calculated using the following formula:

$$\text{Relativedifference}(\%) = \frac{T_{individual} - T_{benchmark}}{T_{benchmark}} \times 100$$

where $T_{benchmark}$ and $T_{individual}$ represent the total dwell time of the benchmark and individual plans, respectively. Differences in dose distribution shapes, including dh or dh_{front}, and dh_{ext}, dt, and dw between the benchmark and

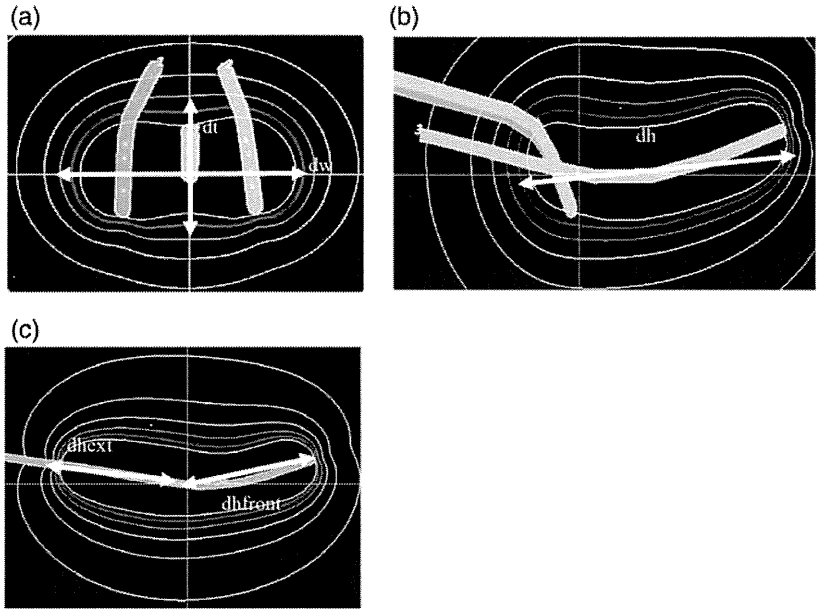

Fig. 2. Definitions of dh, dhfront, dhext, dt and dw used in this study based on ICRU report 38 [23]. These parameters were defined in the plane of the cervical os. (**a**) Transverse plane of tandem-ovoid case; (**b**) sagittal plane of tandem-ovoid case; (**c**) sagittal plane of tandem-cylinder case. Red line shows the isodose line of 100% of the prescription dose.

individual plans were calculated using the following formula:

$$\text{Relativedifference} = \text{shape}_{\text{benchmark}} - \text{shape}_{\text{individual}}$$

Where $\text{shape}_{\text{benchmark}}$ and $\text{shape}_{\text{individual}}$ represent the dose distribution shapes of the benchmark and individual treatment plans, respectively.

Correlations between the differences in total dwell time and those in dh, dt or dw among the benchmark and individual treatment plans were evaluated by Spearman's rank correlation coefficient using Dr. SPSS II software (IMB, New York, USA).

Tolerance levels for total dwell time, dh or dh_{front}, and dh_{ext}, dt, and dw were calculated by the following formula, which was first proposed by Venselaar *et al.* [24]

Tolerance level = mean deviation ± 1.96 SD

RESULTS

Tandem-ovoid cases

Prediction of total dwell time for individual treatment plans

Figure 3 shows a histogram of differences in total dwell time between benchmark and individual treatment plans.

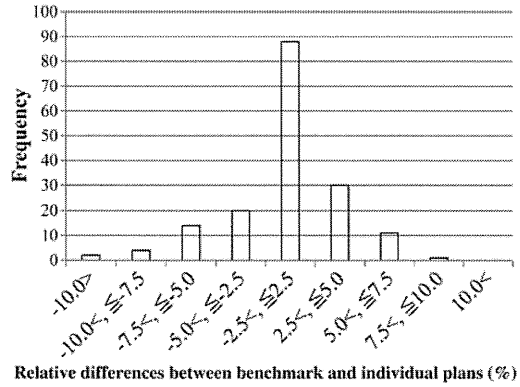

Fig. 3. Histogram of % differences in total dwell time between the benchmark and individual treatment plans.

Differences averaged –0.2% ± 3.8% (range, –13.3–9.6%), and exceeded 5% in 23 of 169 clinical cases.

Comparison of the dose distribution shapes of individual treatment plans with those of the benchmark plans

Figure 4 shows a histogram of differences in dose distribution shapes between the benchmark and individual treatment plans in tandem-ovoid applications. The differences in

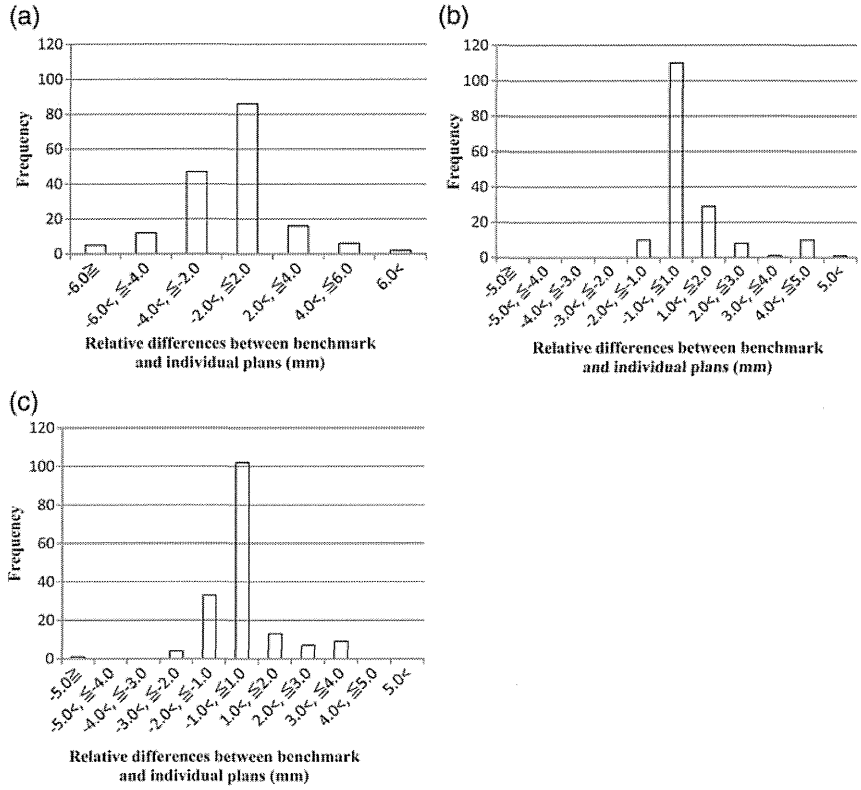

Fig. 4. Histogram of differences in (**a**) dh, (**b**) dt and (**c**) dw between the benchmark and individual treatment plans in mm.

dh, dt and dw between the benchmark and individual plans averaged −1.0 mm ± 2.6 mm (range, −8.6 mm to +6.5 mm), 0.8 mm ± 1.3 mm (range, −1.4 mm to +5.2 mm) and −0.1 mm ± 1.5 mm (range, −5.1 mm to +4.0 mm), respectively.

Regarding dh, 9 of 169 cases showed a difference between the benchmark and individual plans of greater than 5 mm. For dt and dw, in contrast, only one case showed a difference of more than 5 mm.

Subset analysis of cases with large deviations between the benchmark and individual treatment plans

We verified that all tandem-ovoid treatment plans were appropriately created without any planning errors, including wrong source position, wrong decay correction of source strength and inappropriate optimization or use of an unplanned size or combination of applicators. However, 24 of 169 cases had a >5% difference in total dwell time. To explain these differences, we investigated the correlation between differences in total dwell times and dh, dt and dw between the benchmark and individual plans. Figure 5a shows the relationship of differences in total dwell time (vertical axis) with those in dh (horizontal axis). Spearman's rank correlation coefficient ($r_s = 0.836$, $P < 0.01$) showed a strong relationship between the discrepancy in total dwell time and those in dh. In contrast, no correlations were found between the discrepancy in total dwell time and those in dt ($r_s = 0.371$, $P = 0.075$) or dw ($r_s = 0.290$, $P = 0.149$) (Fig. 5b and c).

Tandem-cylinder cases

Figure 6a shows differences in total dwell time between the benchmark and individual treatment plans. Differences averaged −1.5% ± 3.1% (range, −13.0% to +0.4%), with 2 of 29 cases exceeding 11%.

Figure 6b shows the differences in dh_{front}, dh_{ext}, dt and dw between the benchmark and individual treatment plans. Differences averaged −1.5 mm ± 4.9 mm (range, −19.0 mm to +4.0 mm), +1.8 mm ± 5.2 mm (range, −2.2 mm to +20.8 mm), +0.1 mm ± 1.0 mm (range, −1.3 mm to +4.3 mm) and +0.2 mm ± 0.8 mm (range, −0.4 mm to +3.9 mm), respectively. The differences in 2 of 29 cases, which also exceeded an 11% difference in total dwell time, exceeded −19 mm and +20 mm for dh_{front} and dh_{ext}, respectively. These cases were found to have been treated

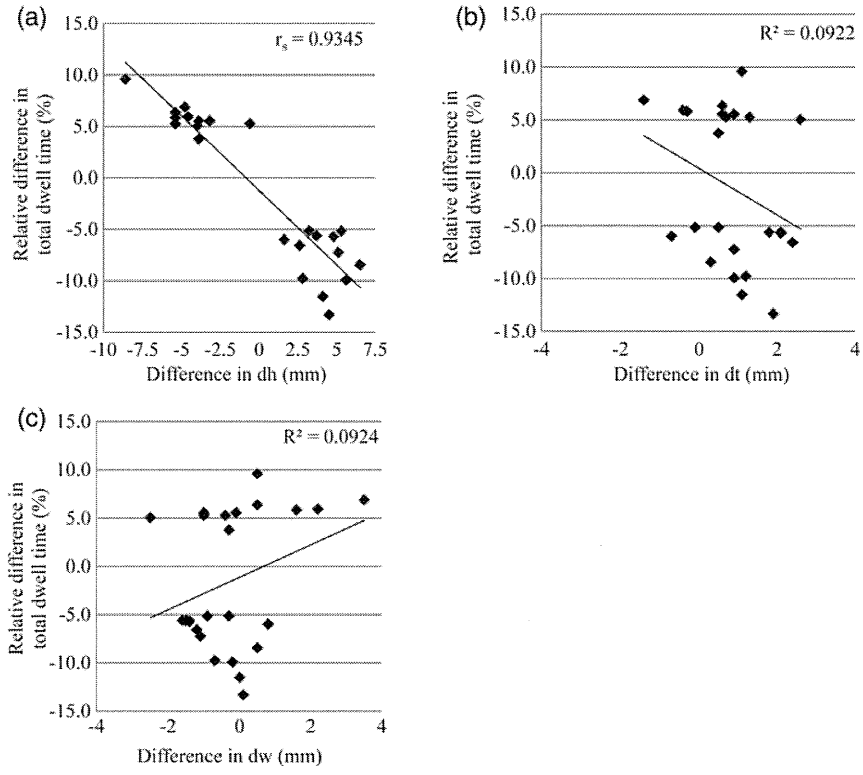

Fig. 5. Correlations between the differences in total dwell time and in (**a**) dh, (**b**) dt and (**c**) dw. Vertical axis shows the % differences in total dwell time between the benchmark and individual treatment plans, and the horizontal axis shows the differences in dh, dt or dw in mm between the benchmark and individual treatment plans.

with an unplanned tandem length, resulting in an incorrect setting for the source dwell positions in treatment planning.

Determination of tolerance limit

For tandem-ovoid cases, the tolerance level of total dwell time, dh, dt, and dw were –7.5% to +7.2, –6.0 mm to +4.1 mm, –1.8 mm to +3.4 mm and –3.0 mm to +2.8 mm, respectively (Fig. 7a).

For tandem-cylinder cases, two cases were excluded from the determination of tolerance limits because they were human error-related. Tolerance limits for total dwell time, dh_{front}, dh_{ext}, dt, and dw were –2.5% to +1.1%, –2.6 mm to +2.3 mm, –2.2 mm to +3.0 mm, –0.9 mm to +0.6 mm and –0.4 mm to +0.4 mm, respectively (Fig. 7b).

DISCUSSION

We used benchmark plans to establish a highly simple, easy, and fast independent treatment planning verification method for high-dose-rate intracavitary brachytherapy for carcinoma of the uterine cervix that requires no special skills such as developing TG43-based in-house software. Despite its great simplicity, analysis of a large number of clinical cases showed that our method was able to detect human error-related planning mistakes, and to evaluate the quality and consistency of applicator geometry.

The Manchester method, which was first suggested by Tod and Meredith in 1938, has been the most broadly used for the treatment of carcinomas of the uterine cervix, with some modifications from the original [20, 21]. They demonstrated an 'ideal' system in which loading patterns of milligrams of radium were determined based on the size of the tandem and ovoids to achieve as constant a dose rate at point A as possible, no matter what combination of applicators was used, and to ensure a suitable ratio between the intra-uterine and vaginal contribution [21]. This rule has been applied to high-dose-rate brachytherapy with an Ir-192 stepping source by modulating the weight of dwell times. In our institution, manual optimization in treatment planning is also based on the Manchester method with some modifications [19]. In addition, the applicator is set such that its geometry is consistent with the 'ideal' geometry specified in the benchmark plan. If there were any planning errors and inappropriate applicator setting, total

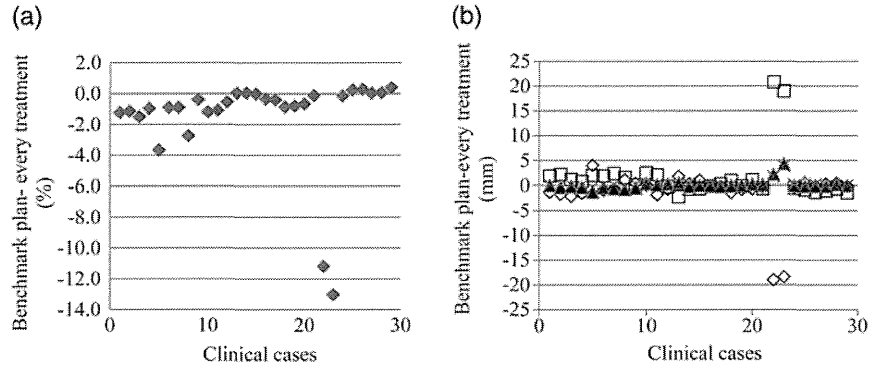

Fig. 6. Differences in (**a**) total dwell time, and (**b**) dh_{front}, dh_{ext}, dt and dw between the benchmark plans and clinical cases in tandem-cylinder settings. White squares, dh_{ext}; white diamonds, dh_{front}; black triangles, dt; and crosses, dw.

dwell time and dose distribution shapes, including dh, dt and dw, in individual treatment plans should agree with those of the benchmark plan. From these points, we established a method for the independent verification of patient-specific treatment planning QA by comparing benchmark plans with individual treatment plans.

Several other independent verification methods for individual treatment planning have been reported. Kumar *et al.* developed an in-house application that calculates the dose at arbitral points [13]. Lachaine *et al.* also developed an in-house application that achieves very fast calculation of point dose [14]. Such kind of applications are likely to be useful in the commissioning of treatment planning systems and partly also in individual treatment planning QA in terms of parameters such as source strength, treatment date and source table, which users input by themselves. However, because these applications use the same Cartesian coordinate system, digitized applicator paths and dose point coordinates as those in the treatment planning system, they are unable to detect human errors associated with the treatment planning process, such as setting of prescription point (Point A) with the wrong coordinate, the incorrect digitization of applicators, incorrect dose points or applicator points, improper magnification of simulation films, or use of an unplanned size or combination of applicators.

Several groups have previously proposed a method of checking total dwell time as a fraction of treatment length and dose prescription, or dose area index for planar implants and single catheter interstitial brachytherapy [8–11]. Recently, for example, Das *et al.* reported that total dwell time can be predicted from the reference volume covered with the prescribed dose (V100) in both single catheter and multiple catheter interstitial implants by the retrospective analysis of V100 from many clinical cases [12]. All these reports were focused on interstitial implants rather than intracavitary brachytherapy, however, and little information on intracavitary brachytherapy for carcinoma of the uterine cervix is available. In 1992, Thomadsen *et al.* demonstrated a method that assures the consistency of dwell times and dose distribution with previous treatment fractions and

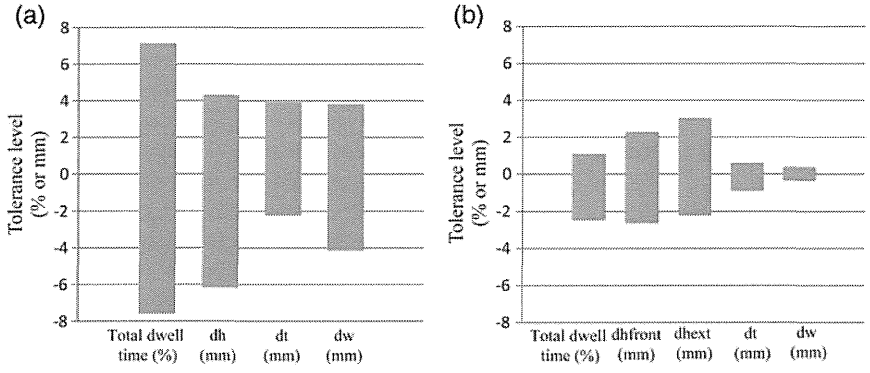

Fig. 7. Tolerance levels of (**a**) tandem-ovoid and (**b**) tandem-cylinder.

previous patients [7]. Although our method is basically similar to their concepts, we created benchmark plans in which the 'ideal' geometry of the tandem-ovoid or tandem-cylinder can be achieved because these applications are constructed outside the patient's body. Therefore the geometry of the applicator can be evaluated in every treatment by comparison with that of the 'ideal' geometry in the benchmark plan.

Although many independent verification methods have been reported, as described above, our present study is one of only a few to evaluate the usefulness of the method in a large number of clinical cases of intracavitary brachytherapy. In tandem-cylinder cases, two cases were found to have >11% differences in total dwell time between the benchmark and individual treatment plans, and >18 mm differences in dh_{front} and dh_{ext}. Review of these two cases showed that these differences were due to the unplanned use of tandem length, which resulted in the use of incorrect settings for the source dwell positions in treatment planning. The results clearly demonstrate that our method can easily identify such kinds of human error.

Regarding tandem-ovoid cases, a thorough review revealed no human-related planning errors. We next examined the reason why 24 cases of tandem-ovoid cases had >5% differences in total dwell time between the benchmark and individual plans. We found that these differences strongly correlated with differences in dh (Fig. 6), indicating that when the ovoid position shifts cranially compared with the benchmark plan, total dwell time decreases because the distance between the sources in the ovoids and point A becomes shorter. Conversely, if the ovoid position shifts caudally to the tandem flange compared with the benchmark plan, total dwell time increases, because the distance between sources in the ovoids and point A becomes larger. These facts indicate that our method is useful in not only finding human errors and software bugs but also in evaluating the quality of the applicator insertion technique. In other words, the evaluation of both the differences in total dwell time and dh could provide a good indicator for the quality of the applicator's geometry.

We set tolerance limits for differences in total dwell time and dose shape between the benchmark and individual treatment plans. Ezell *et al.* reported that they set action levels for per-patient intensity modulated radiation therapy verification using confidence limits [25], as first proposed by Venselaar *et al.* [24]. If the confidence limit is established with sufficient points to provide good statistics, then the value of 1.96σ suggests that variations in excesses of the limit would occur about 5% of the time. We determined the tolerance limits by using confidence limits for total dwell time, dt, dh (dh_{front}, and dh_{ext} for tandem-cylinder cases) and dw. To calculate tolerance limits, we excluded the two cases with >18% differences in tandem-cylinder cases to eliminate the effect of human error-related planning mistakes. These tolerance limits might be one indicator in the evaluation of individual treatment plans (i.e. rechecking of treatment planning, use of appropriate size of applicators, inappropriate applicator geometry, etc.).

One limitation of our study warrants mention, namely that our method is useful only for Manchester-based intracavitary brachytherapy. For carcinoma of the uterus, however, most treatment centers in the world have followed a traditional concept based on the Manchester loading patterns [3, 26]. Moreover, local control rates are significantly improved with EBRT and brachytherapy based on the Manchester method [1]. Our method therefore appears useful despite this limitation.

In conclusion, we established a highly simple, easy and quick independent verification method using benchmark plans for intracavitary brachytherapy based on the 2D-based Manchester method. Despite the great simplicity, our method can evaluate the quality of the applicator insertion technique, as well as identify human errors in treatment planning.

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Japanese structure survey of radiation oncology in 2009 based on institutional stratification of the Patterns of Care Study

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The ongoing structure of radiation oncology in Japan in terms of equipment, personnel, patient load and geographic distribution was evaluated in order to radiation identify and improve any deficiencies. A questionnaire-based national structure survey was conducted from March 2010 to January 2011 by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO). These data were analyzed in terms of the institutional stratification of the Patterns of Care Study (PCS). The total numbers of new cancer patients and total of cancer patients (new and repeat) treated with radiation in 2009 were estimated at 201,000 and 240,000, respectively. The type and numbers of systems in actual use consisted of Linac (816), telecobalt (9), Gamma Knife (46), ^{60}Co remote afterloading system (RALS) (29) and ^{192}Ir RALS systems (130). The Linac systems used dual energy function for 586 (71.8%), 3DCRT for 663 (81.3%) and IMRT for 337 units (41.3%). There were 529 JASTRO-certified radiation oncologists (ROs), 939.4 full-time equivalent (FTE) ROs, 113.1 FTE medical physicists and 1836 FTE radiation therapists. The frequency of interstitial radiation therapy use for prostate and of intensity-modulated radiotherapy increased significantly. PCS stratification can clearly identify the maturity of structures based on their academic nature and caseload. Geographically, the more JASTRO-certified physicians there were in a given area, the more radiation therapy tended to be used for cancer patients. In conclusion, the Japanese structure has clearly improved during the past 19 years in terms of equipment and its use, although a shortage of manpower and variations in maturity disclosed by PCS stratification remained problematic in 2009.

Keywords: Structure survey; radiotherapy facility; radiotherapy personnel; radiotherapy equipment; caseload

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INTRODUCTION

The medical care systems of the USA and Japan have very different backgrounds. In 1990, the Patterns of Care Study (PCS) conducted a survey of the structure of radiation oncology facilities in 1989 for the entire census of facilities in the USA [1]. In 1991, the Japanese Society for Therapeutic Radiation Oncology (JASTRO) conducted the first national survey of the structure of radiation therapy facilities in Japan based on their status in 1990, and the results were reported by Tsunemoto *et al.* [2]. The first comparison of these two national structure surveys to illustrate and identify similarities and differences in 1989–90 was conducted by the author and reported in 1996 [3]. The resultant international exchange of information proved especially valuable for Japan, where the structure of radiation oncology could be improved on the basis of those data.

The Japanese structure has gradually changed since a greater number of cancer patients are treated with radiation and public awareness of the importance of radiotherapy (RT) has grown. JASTRO has conducted national structure surveys every two years since 1990 [2] and every year since 2011. Furthermore, in 2006 the Cancer Control Act was approved in Japan, which strongly advocates the promotion of RT and an increase in the number of radiation oncologists (ROs) and medical physicists. The Japanese Ministry of Education, Sciences and Sports is supporting the education of these specialists at university medical hospitals. The findings of international comparisons and the consecutive structural data gathered and published by JASTRO have been useful for an understanding of our current position and future direction [4–7]. In this report, the recent structure of radiation oncology in Japan is analyzed and compared with the data of 2007 [6].

MATERIALS AND METHODS

From March 2010 to January 2011, JASTRO conducted a questionnaire based on the national structure survey of radiation oncology in 2009. The questionnaire dealt with the number of treatment systems by type, number of personnel by category and number of patients by type, site and treatment modality. To measure variables over a longer period of time, data for the calendar year 2009 were also requested. The response rate was 700 out of 770 (90.6%) of active facilities. The data from 241 institutions (31.3%) were also registered in the International Directory of Radiotherapy Centres (DIRAC) in Vienna, Austria in 2011.

The PCS was introduced in Japan in 1996 [8–17]. The Japanese PCS employed methods similar to those of the American version, which used structural stratification to analyze national averages for the data for each survey item by means of two-stage cluster sampling. For the regular structure survey, RT facilities throughout the country were stratified into four categories. This stratification was based on academic conditions and the annual number of patients treated with radiation at each institution, because academic institutions require and have access to more resources for education and training, while the annual caseload also constitutes essential information related to structure. For the study reported here, the following institutional stratification was used. A1: university hospitals/cancer centers treating 462 patients or more per year; A2: the same type of institutions treating 461 patients or fewer per year; B1: other national/public hospitals treating 158 patients or more per year; and B2: other national hospital/public hospitals treating 157 patients or fewer per year.

SAS 8.02 (SAS Institute Inc., Cary, NC, USA) [18] was used for statistical analyses and statistical significance was tested by means of the chi-squared test, Student's *t*-test or analysis of variance (ANOVA).

RESULTS

Current situation of radiation oncology in Japan

Table 1 shows that the numbers of new patients and total patients (new plus repeat) undergoing radiation in 2009 were estimated at 201 000 and 240 000, respectively, showing a 11.0% increase over 2007 [6], with 40% of the patients being treated at academic institutions (categories A1 and A2), even though these academic institutions constituted only 20% of the 700 radiotherapy facilities nationwide.

Cancer incidence in Japan in 2009 was estimated at 724 426 cases [19] with approximately 27.6% of all newly diagnosed patients treated with radiation. This number and corresponding rate have increased steadily over the last 19 years and is expected to increase further [14]. In 1990, the rate was estimated to be approximately 15% [3], and it was 16% in 1995, 17% in 1997, 20% in 1999, 22% in 2001, 23.3% in 2003 [4], 24.5% in 2005 [5], 26.1% in 2007 [6] and 27.6% in 2009.

Facility and equipment distribution patterns

Table 2 shows an overview of RT equipment and related functions. There were 816 Linac, 46 Gamma Knife, 29 ^{60}Co remote afterloading system (RALS), 130 ^{192}Ir and 1 ^{137}Cs RALS systems in actual use, as well as 9 of the 15 telecobalt systems installed. The Linac systems used dual energy function for 586 (71.8%), 3D conformal radiation therapy (3DCRT) for 663 (81.3%) and intensity-modulated radiation therapy (IMRT) for 337 units (41.3%). The IMRT function was employed more frequently for the equipment of academic institutions (A1: 73.4% and A2: 49.5%) than that of non-academic institutions (B1: 42.3% and B2: 18.1%). However, 3DCRT functions were disseminated widely in both academic and non-academic institutions, with 69% even in B2 institutions. The use of image-guided radiation