3 or higher leukopenia, neutropenia, thrombocytopenia and anemia occurred in 37, 22, 11 and 18 patients, respectively. Grade 3 or higher mucositis and dermatitis developed in 20 and 18 patients, respectively.

Late toxicities are listed in Table 6. Three Grade 3 osteomyelitis of the mandible occurred in this series. One patient died because of late toxicity due to lethal mucosal bleeding. The patient diagnosed as cT3N1M0 with histology of Type I received 80 Gy to the primary site including additional SRT boosts of 10 Gy due to an insufficient response at the planned 70 Gy. The patient developed active mucosal bleeding in the nasopharynx, and died five years later. We experienced no Grade 3 or higher late toxicity of brain necrosis, visual disturbance or swallowing disturbance.

DISCUSSION

A randomized control trial showed survival advantages of concurrent chemoradiotherapy over radiation alone, thus it is believed to be the standard treatment for locally advanced NPC. In the IGS, Stage III–IVB patients with NPC were randomized to CRT or RT, and the combined CRT group was treated with radiation and concurrent triweekly CDDP followed by three adjuvant cycles of FP [1]. The 3-year rate of OAS of the RT-only group was significantly lower than that of the CRT group (46% vs 76%; $P < 0.001$), and the same results were noted for the 3-year rate of PFS (24% vs 69%; $P < 0.001$). However, some problems with the results from the IGS were identified. Firstly, results of the RT arm in the IGS seem to be unacceptably bad because the reported 3-year rates of OAS for the same stages were over 70%. One of the reasons for this discrepancy is that the rate of WHO type I histology in the IGS series (24%) is larger than that of endemic regions, which is believed to have adversely impacted on clinical results. Secondly, the compliance of chemotherapy was insufficient in the IGS. The completion rates of planned chemotherapy of concurrent and adjuvant series were reported as 63% and 55%, respectively. In order to confirm this result, the IGS should be extrapolated in endemic regions [4]. In Hong Kong, the NPC-9901 trial on patients with T1-4N2-3M0 disease was designed to confirm the therapeutic ratio achieved by the IGS regimen. Regarding the compliance of chemotherapy, 65% of patients completed all six cycles, and 79% had five cycles. The CRT arm achieved significantly higher failure-free survival (72% vs 62% at 3 years, $P = 0.027$), mostly as a result of improvements in locoregional control. However, DMFS did not improve significantly (76% vs 73%, $P = 0.47$) and OAS was identical (78% vs 78%, $P = 0.97$). In other RCTs reported by Lin and Chen, the CRT arm significantly improved PFS and OAS [2, 3].

There is also evidence by meta-analysis dealing with eight randomized trials of 1753 patients regarding locally advanced NPC. In this analysis, the pooled hazard ratio of death for adding chemotherapy was 0.82 (95% confidence interval, 0.71–0.94; $P = 0.006$), corresponding to an absolute survival benefit of 6% at 5 years (56% vs 62%). A

Table 4. Compliance of chemotherapy

	n	median (range)
Total cycles given		
1	2	
2	7	
≥3	87	
Total dose given		
Cisplatin (mg/m^2)		300 (150–340)
Nedaplatin (mg/m^2)		375 (80–400)
5-fluorouracil (mg/m^2)		12 000 (3050–12 000)

Table 5. Acute, severe and life-threatening toxicities due to chemoradiotherapy

Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	unknown	≥ Gr 3
Leukopenia	4	12	43	32	5	0	4	37
Granulocytopenia	18	27	28	17	5	0	5	22
Anemia	6	33	39	14	4	0	4	18
Thrombocytopenia	28	37	10	8	3	0	4	11
Liver dysfunction	71	20	5	1	0	0	1	1
Renal dysfunction	71	28	0	0	0	0	1	0
Vomiting	33	14	50	3	0	0	0	3
Mucositis	0	13	67	19	1	0	0	20
Dermatitis	0	37	45	17	1	0	0	18
Salivary gland changes	1	13	86	0	0	0	0	0

Table 6. Late, severe and life-threatening toxicities due to chemoradiotherapy

Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	≥ Gr 3
Swallowing dysfunction	95	4	1	0	0	0	0
Visual dysfunction	99	0	1	0	0	0	0
Hearing impairment	81	5	14	0	0	0	0
Osteomyelitis	96	0	1	3	0	0	3
Brain necrosis	99	1	0	0	0	0	0
Bleeding	99	1	0	0	0	1	1

significant interaction was observed between the timing of chemotherapy and overall survival ($P = 0.005$), with the highest benefit resulting from concomitant chemotherapy [5]. However, increasing acute toxicities caused by administration of chemotherapy were also reported in this analysis. In the IGS, acute toxicities of ≥ Grade 3 were reported as 50% and 76% for RT and CRT arms, respectively. Similarly, in the NPC-9901 trial, toxicities of ≥ Grade 3 were observed as 53% and 84% for RT and CRT arms, respectively ($P < 0.01$). The 3-year actuarial rate of late toxicity was slightly higher in the CRT arm than in that of the RT arm, although it was not significant (28% vs 13%, $P = 0.24$).

In our institute, we adopted alternating CRT for NPC from 1987. In a previous report, 32 patients with NPC received alternating CRT, and the 5-year rates of OAS and PFS were 75% and 63%, respectively. A Phase II study of alternating chemoradiotherapy for patients with NPC was performed in four medical institutions including our institution from 1997 and reported promising results with high compliance (91%), of which the 2-year OAS and PFS rates were 94% and 83%, respectively [10]. In the present study with longer follow-up and a larger cohort, the 5-year rates of OAS and PFS were 78.1% and 68.3%, respectively. We think these data are comparable with previous series. In addition, we believe that acute and late complication rates were sufficiently low according to longer follow-up with 65.9 months.

We believe alternating chemoradiotherapy has several advantages in CRT for NPC. Because the radiation field has to be large, severe mucositis and dermatitis sometimes develops and leads to a treatment break. In addition, late complications, such as disturbances in swallowing or hearing sometimes become significant problems. Alternating chemoradiotherapy has the potential benefit in reducing acute toxicities. As for reported data of the NPC-9901 trial, acute mucositis and skin reactions over Grade 3 were observed in 62% and 20% patients in the CRT arm, respectively. In the present study, acute mucositis or dermatitis of ≥ Grade 3 developed in 20% and 18%, respectively. By alternating chemotherapy and radiotherapy, we could also use intensive multi-agent chemotherapy regimens such as FP or FN without increasing acute and late complications. Although our data is a retrospective analysis in a single institute, the 5-year rate of OAS in the present study (78.1%) was more promising than that of the IGS trial (67%). Regarding the compliance of chemotherapy, over 90% patients in the present study could receive three courses of chemotherapy and 70% of our cohort had completed planned full doses. As a result the total dose of chemotherapy in patients who received a reduced dose was still about 80% of the planned dose. Our data is thought to be more encouraging than that of the IGS, in which only 55% patients completed the planned chemotherapy. Failure patterns in CRT for NPC patients are thought to be both loco-regional, but also in distant sites. In the present study, DMFS at 5-years was 87.8%, which was higher than that of the reported series. The 3-year DMFS rate of the NPC-9901 study was reported as 76%. We believe that it was caused by the advantages of intensive chemotherapy in the present study. An unexpected RT break was needed in 14 patients (14%), of which only 2 patients needed RT breaks longer than one week.

The argument against alternating CRT is that planned RT interruptions may lead to sacrifices in treatment efficacy. In many studies, it is well known that prolongation of overall treatment time negatively influences clinical outcomes. *In vitro*, accelerated repopulation occurred 28 days after the start of RT; thus, prolongation of treatment time led to the development of radiation resistance. In the present study, OTT was not significantly related to clinical outcome. One of the reasons is that the high compliance of the present study would have helped avoid essential prolongation of OTT in our cohort.

In the present series, WHO type I histopathology was a significantly unfavorable factor of both OAS and PFS. The incidence of WHO type I histology in Western countries is very different from East Asian countries. In the IGS series conducted in North America, the rate of WHO type I histology was 22%, which was higher than the rates in studies

conducted in endemic regions. WHO type I histopathology, keratinizing squamous cell carcinoma, was reported to be much less related to EBV infection than non-keratinizing carcinoma. It was also reported to be less sensitive to RT [11]. However, there are not so many reports regarding clinical results. One of the reasons is that the proportion of type I histopathology is very low in endemic regions. In Japan, the proportion of type I histopathology is about 20%, which was similar to North America. Kawashima *et al.* reported a Japanese multi-institutional survey of 333 NPC patients, in which the proportion of type I histopathology was 19% [12]. In that series, type I histopathology proved to be a significantly worse prognostic factor of OAS and PFS on both UVA and MVA. In the present study, the population of type I histopathology was 8%; however, these eight patients had remarkably poor prognosis. Six of the eight patients developed treatment failure. In our series, WHO type I histopathology was a significantly worse factor of both OAS (3-year rates; 50.5% vs 89.3%; $P < 0.0001$) and LRPFS (3-year rates; 21.4% vs 84.5%, $P < 0.0001$). The majority of failure patterns of these patients were in loco-regional sites. In order to improve treatment outcomes of these patients, dose escalation without increasing adverse events is believed to be promising. In recent years, intensity-modulated radiation therapy (IMRT) is widely used for head and neck cancer because of its dose conformity ability for PTV, reducing doses to normal tissue. RTOG 0225, a multi-institutional Phase II trial was conducted to test the feasibility of IMRT with or without chemotherapy for NPC. A 90% LRPF rate was reported as well as an acceptably low incidence of Grade 3 adverse events without xerostomia of Grade 4 [13]. In our institution, we started IMRT for NPC patients using Helical Tomotherapy until June 2006, and we have reported our preliminary clinical results [14]. In the future, dose escalation for patients with type I histopathology using IMRT will be helpful for improving clinical results.

The 5-year rates of PFS and LRPFS of patients with T4 were significantly inferior to those with T1–3, even though there was no significant difference in the 5-year rates of DMFS between these two groups. Because of the proximity of tumors to critical structures such as the brain-stem, spinal cord, optic pathway and temporal lobes, the radiation fields and dose coverages for primary tumors are often compromised. Preliminary results of radiation dose escalation for patients with T3–T4 NPC show good local control (2-year rate of locoregional control; 95.7%) and survival (2-year rate of OAS; 92.1%) [15]. For these patients, dose escalation using IMRT is also promising improved clinical results.

The 5-year rates of OAS and DMFS of patients with N3 were significantly inferior to those with N0–2 in the present series. On the other hand, N3 showed no apparent correlation with worsening LRPF. From this result, patients with N3 are expected to have a higher incidence of distant metastasis. Thus, a more effective regimen of chemotherapy should be considered to overcome limitations. In fact, TAX 324, a randomized Phase III trial, has shown the distinct survival advantages of multi-agent intensive chemotherapy including docetaxel and FP over PF for locally advanced head and neck cancer [16].

We believe that the present results for alternating chemoradiotherapy are promising compared to previously reported series of concurrent chemoradiotherapy. However, several subgroups with some risk factors proved to have insufficient outcomes. In order to refine clinical results without increasing adverse events, there is room for modification especially in patients with high-risk factors. Dose escalation using IMRT for type I histopathology and/or T4 disease and more intensive modifications of chemotherapy for N3 disease should be considered in future.

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Journal of Radiation Research, 2012, 53, 906–915
doi: 10.1093/jrr/rrs052 Advance Access Publication 22 July 2012

Treatment outcomes of definitive chemoradiotherapy for patients with hypopharyngeal cancer

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(Received 6 March 2012; revised 28 May 2012; accepted 13 June 2012)

We analyzed the efficacy of definitive chemoradiotherapy (CRT) for patients with hypopharyngeal cancer (HPC). Subjects comprised 97 patients who were treated with definitive CRT from 1990 to 2006. Sixty-one patients (62.9%) with resectable disease who aimed to preserve the larynx received induction chemotherapy (ICT), whereas 36 patients (37.1%) with resectable disease who refused an operation or who had unresectable disease received primary alternating CRT or concurrent CRT (non-ICT). The median dose to the primary lesion was 66 Gy. The median follow-up time was 77 months. The 5-year rates of overall survival (OS), progression-free survival (PFS), local control (LC), and laryngeal preservation were 68.7%, 57.5%, 79.1%, and 70.3%, respectively. The T-stage was a significant prognostic factor in terms of OS, PFS and LC in both univariate and multivariate analyses. The 5-year rates of PFS were 45.4% for the ICT group and 81.9% for the non-ICT group. The difference between these groups was significant with univariate analysis ($P = 0.006$). Acute toxicity of Grade 3 to 4 was observed in 34 patients (35.1%). Grade 3 dysphagia occurred in 20 patients (20.6%). Twenty-nine (29.8%) of 44 patients with second primary cancer had esophageal cancer. Seventeen of 29 patients had manageable superficial esophageal cancer. The clinical efficacy of definitive CRT for HPC is thought to be promising in terms of not only 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.

Keywords: hypopharyngeal cancer; chemoradiotherapy; survival; laryngeal preservation; local control

INTRODUCTION

Hypopharyngeal cancer (HPC) is usually diagnosed at an advanced stage and treated using multidisciplinary modalities. Chemoradiotherapy (CRT) is currently considered the standard treatment for unresectable head and neck cancer. It is also thought to be a treatment option for patients with resectable locally advanced lesions. Therefore, the number of patients treated with CRT, especially for organ preservation, is increasing. Several types of chemotherapy regimens have been reported to have positive outcomes, and concurrent CRT (CCRT) has become a standard treatment for patients with the aim of preserving the larynx [1, 2]. However, CCRT is reported to be accompanied by markedly increased toxicity compared to radiation alone, and patients who receive CCRT followed by salvage surgery sometimes have serious and intractable complications [3].

Induction chemotherapy (ICT) is often used in clinical practice for patients with advanced HPC and plays a considerable role in organ preservation and reduction of distant metastases [4]. To reduce treatment toxicities and avoid the risk of salvage surgery, we used ICT for patients with resectable tumors with the aim of optimally selecting candidates for larynx preservation.

CCRT regimens with cisplatin (CDDP) and 5-fluorouracil (5-FU) have been used in patients with advanced head and neck cancer. However, severe acute mucositis has been reported with these regimens [2]. For patients treated with

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

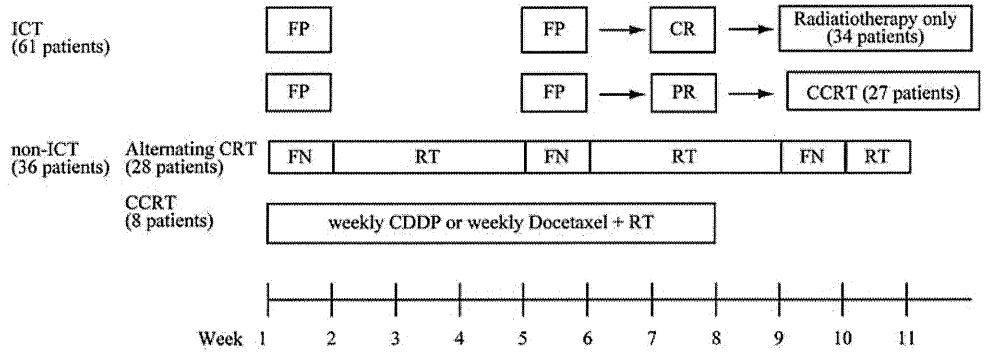

Fig. 1. Treatment scheme of the induction chemotherapy (ICT) group and the non-ICT group. ICT was used in 61 patients (63%). In the ICT protocol, two courses of 5-FU and CDDP (FP) were administered to 52 patients. Patients who achieved a complete response with ICT were treated with radiotherapy only, 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 ($P = 0.006$).

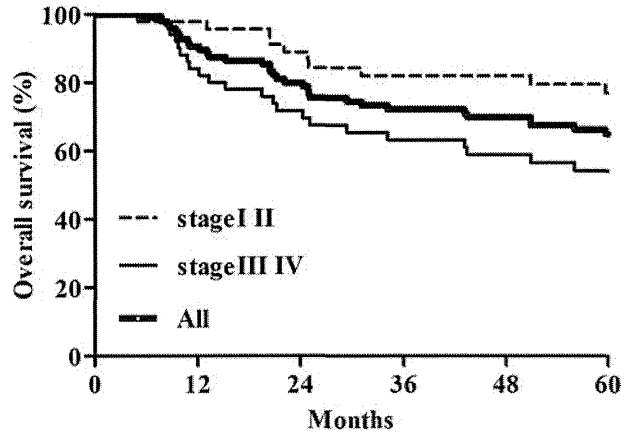

Fig. 2. Overall survival curves of all patients and groups divided by stage.

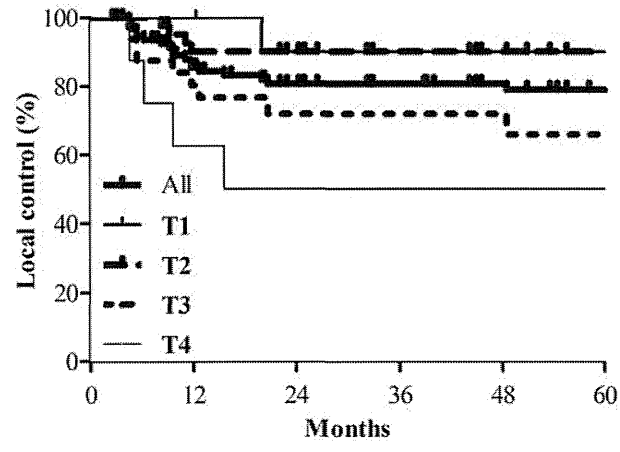

Fig. 3. Local control curves of all patients and groups divided by T-stage.

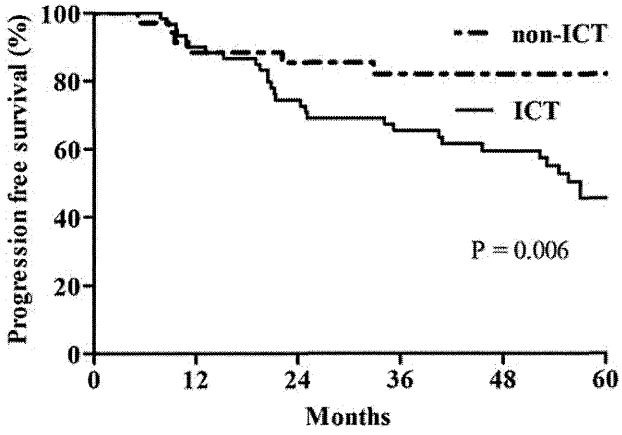

Fig. 4. Progression-free survival of groups using induction chemotherapy (ICT) and non-ICT. The difference between the two groups was statistically significant ($P = 0.006$).

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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Jpn J Radiol (2012) 30:349–353
DOI 10.1007/s11604-012-0052-0

CASE REPORT

A case of cervical multicentric Castleman disease treated with intensity-modulated radiation therapy using helical tomotherapy

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Received: 8 September 2011 / Accepted: 4 January 2012 / Published online: 19 January 2012

Abstract Castleman disease (CD) is a rare lymphoproliferative disorder. Two clinical entities are described: a unicentric form with disease confined to a single lymph node region and a multicentric form characterized by generalized lymphadenopathy and systemic symptoms. Although surgery is regarded as standard therapy for the unicentric form, no consensus has been reached concerning the standard treatment for multicentric CD. We report here a case of cervical multicentric CD treated with intensity-modulated radiation therapy (IMRT), using helical tomotherapy to minimize xerostomia in comparison with conventional radiotherapy. A 29-year-old woman complained of neck swelling. Computed tomography showed lymphadenopathy in both sides of the neck. The patient was diagnosed with the plasma cell subtype of CD on biopsy. After initial treatment with prednisone, IMRT was planned to avoid normal structures, for example the parotid gland. The cervical lymphadenopathy shrank gradually during IMRT with 44 Gy in 22 fractions. Four years and 3 months after IMRT, regrowth of cervical lymph nodes has not been detected. The parotid function improved dramatically on quantitative salivary scintigraphy between 3 and 12 months after IMRT. Radiotherapy could be an option for multicentric CD, and IMRT is an effective means of minimizing xerostomia in head and neck lesions.

Keywords Castleman disease · Multicentric · Plasma cell · Intensity modulated radiation therapy · Xerostoma

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Introduction

Castleman disease was first described in 1954 by Castleman et al. [1] and it is still poorly understood because of its rareness. This lymphoproliferative disorder has been histopathologically categorized into two main subtypes and one mixed variant as follows: a hyaline vascular subtype (HV), plasma cell subtype (PC), and mixed variant (MV) [2]. The HV subtype is the most common histological variant of Castleman disease, accounting for 90% of cases. The HV subtype is characterized by small, hyalinized follicles surrounded by circumferentially arranged layers of small lymphocytes interconnected by a prominent vascular stroma. The PC subtype appears as germinal centers with dense plasma cell infiltration in the less vascular interfollicular stroma. The MV subtype is pathologically a mixture of the two other subtypes. Two

clinical entities have also been described: a unicentric form with disease confined to a single lymph node region and a multicentric form characterized by generalized lymphadenopathy, and systemic symptoms such as fever, night sweats, weight loss, splenomegaly, anemia, and hypoalbuminemia [3]. This classification correlates with histopathological variants. The HV subtype is mostly unicentric and the PC and MV subtypes seem to be mostly multicentric [4]. Surgery is regarded as the standard therapy for the unicentric form, with several retrospective series reporting excellent response [5]. Radiotherapy (RT) has also been described as a definitive treatment for both unicentric and multicentric Castleman disease with variable response [5].

A reduction in the ability to produce saliva (i.e., xerostomia) is a common toxicity associated with RT of head-and-neck cancers [6]. In particular, reduced stimulated salivary flow, which is often permanent, negatively affects patient quality of life. Modern RT techniques, in particular intensity-modulated radiation therapy (IMRT), enable highly conformal dose distributions that can selectively spare critical organs at risk, for example the parotid salivary glands. Helical tomotherapy (HT) is a novel IMRT treatment modality. HT is a form of 3D conformal radiation therapy in which treatment beams are spatially and temporally modulated to maximize the dose delivered to the tumor while minimizing the dose delivered to normal structures [7]. In addition, detectors within the tomotherapy system provide megavoltage computed tomographic (MVCT) images of the patient, which can be obtained immediately before treatment for setup, registration, and repositioning. This paper describes a case history of multicentric Castleman disease at cervical sites treated with HT to minimize xerostomia.

Case report

A 29-year-old woman presented to the department of otorhinolaryngology with a complaint of neck swelling. She had no systemic symptoms, for example fever or anemia. Physical examination revealed multiple palpable tumors in the cervical lesions. Computed tomography (CT) of the neck showed a lymphadenopathy in the cervical lesions. CT of the neck to the pelvic site showed no abnormality other than hemangioma of the spleen. There were no laboratory abnormalities. An infection test including HIV turned out to be negative. An incisional biopsy of the cervical enlarged lymph node was performed to obtain material for histological examination. Histopathology from the specimen revealed germinal centers with dense plasma cell infiltration (Fig. 1a) and germinal centers penetrating vessels (Fig. 1b), as seen in the PC subtype of Castleman disease. Because the tumor was regarded as unresectable, prednisone was proposed at a dose of 20 mg/day to reduce the size of the tumor, to relieve the patient's discomfort due to cervical lymphadenopathy. Although the tumor decreased to some extent after a while, it became enlarged again on cessation of prednisone treatment. Because her symptom was only discomfort due to cervical lymphadenopathy, we believed local therapy such as RT might be effective, at least for a palliative purposes. IMRT with HT was planned to minimize xerostomia compared with conventional RT. Magnetic resonance imaging (MRI) of the neck before IMRT showed a lymphadenopathy in both sides of the neck (Fig. 2a, b). The enlarged cervical nodes were levels Ib, II, III, IV, and V. Gross tumor volume (GTV) was defined as a lymph node with a more than 10 mm short axis on MRI. Clinical target volume (CTV) included the GTV with an expansion of 10 mm.

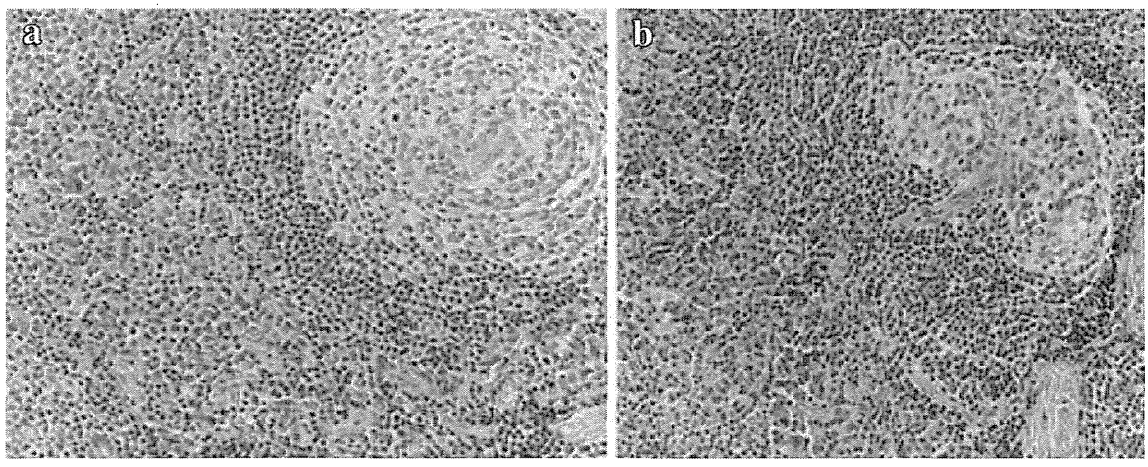

Fig. 1 Histopathology of the specimen revealed germinal centers with dense plasma cell infiltration (**a**) and germinal centers penetrating vessels (**b**) as seen in the plasma cell subtype of Castleman disease (H&E staining)

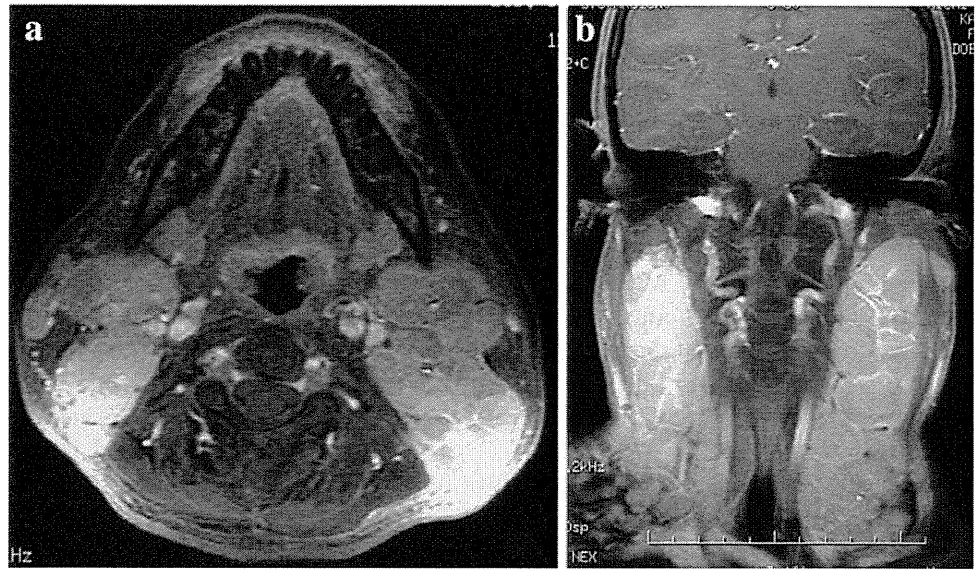

Fig. 2 Contrast-enhanced MRI of the neck. Lymphadenopathy in both sides of the neck on an axial section (**a**) and a coronal section (**b**)

Prophylactic nodal irradiation was not used. Planning target volume (PTV) was defined as CTV with 5-mm margins in all dimensions. Normal structures such as organs at risk (OAR) included the brainstem, spinal cord, brain, lens, eyeball, optic chiasma, optic nerve, inner ear, oral cavity, mandible, parotid gland, larynx, and lung. A planning dose at D95 (95% of the PTV receiving the prescribed dose) was prescribed to the PTV at 50 Gy in 25 fractions. Other radiotherapy-planning techniques and the dose constraints for OAR were similar to those in a report on nasopharyngeal cancer [8]. The patient received daily MVCT acquisitions for setup verification. Figure 3 shows a dose–volume histogram (DVH) and dose distributions of the patient. At the midcourse of radiation treatment, another kilovolt CT was taken to evaluate the change of dose distribution caused by shrinkage of tumor or body weight loss. A CT scan for evaluation for change of dose distribution was archived in the Tomoprovider and an adaptive dose distribution was made from these images using the initial planning beam data on the DQA system. The adaptive dose distribution was evaluated visually using the dose coverage of PTV and the change of dose distribution on the cord, stem, and parotid gland. Because the dose distribution of PTV and these OAR seemed acceptable, we did not change the RT plan. This patient experienced some acute toxicity including grade 3 mucositis, grade 2 dysgeusia, grade 2 xerostomia, and a grade 2 skin reaction on the National Cancer Institute's (NCI) Common Toxicity Criteria, version 3.0. The patient required temporary interruption of IMRT because of this acute toxicity. Finally, the total dose was reduced to 44 Gy in 22 fractions over 46 days. The cervical lymphadenopathy shrank gradually during IMRT on physical examination (Fig. 4a, b), and the patient's discomfort due to cervical lymphadenopathy was relieved. At present, 4 years and 3 months after IMRT, no signs of tumor regrowth have been detected (Fig. 4c).

Parotid function was evaluated by quantitative salivary scintigraphy and the xerostomia grade using NCI toxicity criteria, version 3.0. Parotid saliva excretion was measured by the maximum excretion ratio (MER) in the parotid region on salivary scintigraphy. The method of salivary scintigraphy was similar to that in a report on nasopharyngeal cancer [8]. The MERs of the right salivary gland were 61.7, 25.1, and 48.7%, and those of the left salivary gland were 45.3, 19.0, and 35.9% before initial treatment, 3, and 12 months after the completion of IMRT, respectively. The parotid function of both sides was improved dramatically between 3 and 12 months after IMRT. Xerostomia was also improved from grade 2 to grade 0 between 3 and 12 months after IMRT.

Discussion

We report a case of cervical multicentric Castleman disease treated with IMRT using HT. Cervical lymphadenopathy shrank gradually during IMRT. Four years and 3 months after IMRT, no signs of regrowth of cervical lymphadenopathy have been detected. A standard approach to clinical management has yet to be agreed for multicentric Castleman disease. Primary RT has been described in numerous case reports and small case series as one strategy for treatment of both the unicentric and multicentric forms of Castleman disease. Vries et al. [5] presented an overview of all studies that evaluated the use of primary RT in

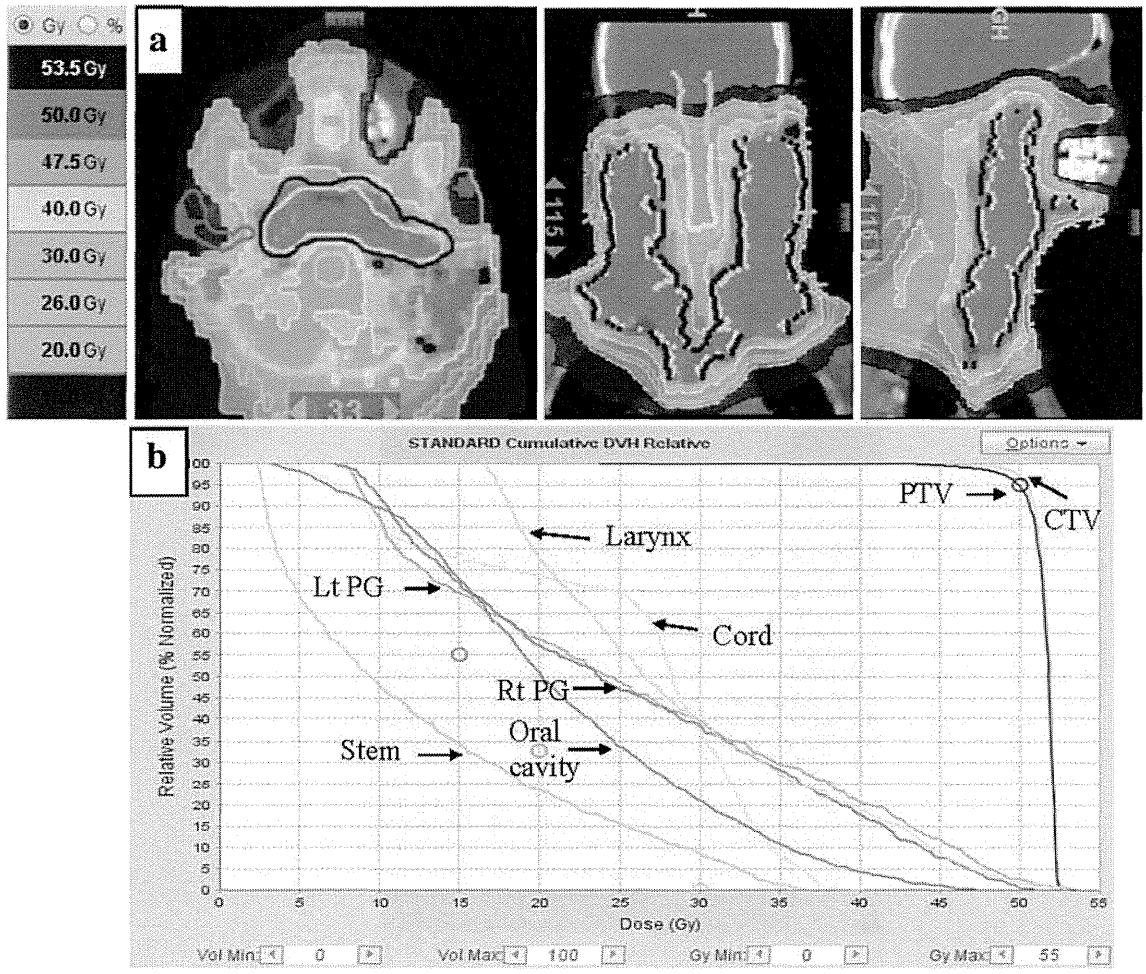

Fig. 3 Dose distribution for the patient with cervical multicentric Castleman disease. **a** Dose volume histogram (DVH) of typical normal structures as organ at risk (OAR) and target volume (**b**). *CTV* clinical target volume, *PTV* planning treatment volume, *PG* parotid gland, *IE* inner ear

Castleman disease, for both unicentric and multicentric disease, with doses ranging from 12 to 50 Gy. Responses to primary RT for treatment of both forms of Castleman disease ranged from no response to complete response. With regard to the dose of RT, no correlation could be observed between dose and response. Most patients were treated with a dose between 40 and 50 Gy; however, the dose of RT varied from 12 to 50 Gy in patients with a complete response. Other concerns about the RT method, for example an appropriate margin of GTV or the need for prophylactic irradiation, are issues for the future, because no study has evaluated correlation between RT methods and tumor control. Adaptive radiotherapy is an approach to correct for morphological changes in a patient's anatomy, for example tumor and normal tissue variations as a result of treatment [9]. We did not change the RT plan because the change of the dose distribution seemed acceptable.

As there is currently no consensus on treatment of multicentric Castleman disease, physicians tend to reject RT because of its toxicity, especially for head and neck lesions. In this case, the parotid function and xerostomia improved dramatically after IMRT. IMRT is an effective method to minimize xerostomia in head and neck lesions. There is also a little concern about radiation-induced second primary cancer or late complications, for example carotid artery stenosis in the long-term future. The clinical management of multicentric Castleman disease remains controversial, and we should recognize there are approaches other than RT, for example rituximab-based treatment or chemotherapy [10].

In conclusion, we report a case of cervical multicentric Castleman disease treated with IMRT using HT. To date, no signs of regrowth of cervical lymphadenopathy have been detected. The parotid function on quantitative salivary scintigraphy and xerostomia improved dramatically within

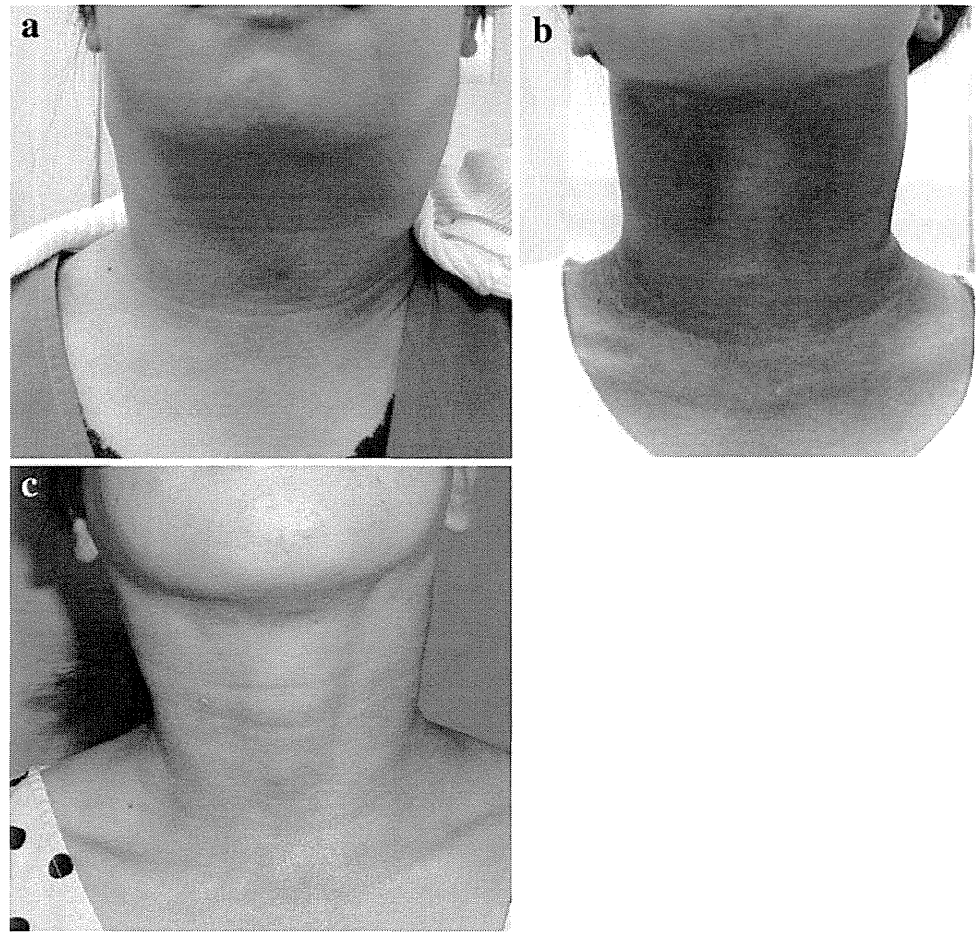

Fig. 4 Before IMRT. Lymphadenopathy in both sides of the neck. **a** At the time of completion of IMRT. Lymphadenopathy in both sides of the neck shrank. **b** Four years and 3 months after IMRT. No regrowth of lymphadenopathy was observed (**c**). *IMRT* intensity-modulated radiation therapy

12 months after completion of IMRT. RT could be an option for multicentric Castleman disease, and IMRT can reduce xerostomia compared with conventional RT in head and neck lesions.

Conflict of interest The authors declare no conflict of interest.

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Breast Cancer
DOI 10.1007/s12282-012-0412-8

ORIGINAL ARTICLE

Feasibility of intraoperative radiation therapy for early breast cancer in Japan: a single-center pilot study and literature review

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Received: 22 May 2012 / Accepted: 28 August 2012

Abstract
Background Intraoperative radiation therapy (IORT) is under evaluation in breast-conserving surgery because the feasibility of the IORT procedure including transportation of the patient under general anesthesia is not well established. Thus, this prospective single-center study aimed to test the feasibility of IORT at a single dose of 21 Gy in Japanese breast cancer patients.
Methods The primary endpoint was early toxicity; the secondary endpoint was late toxicity. Patients with histologically or cytologically proven primary early breast cancer were eligible. Inclusion criteria were as follows: (1) $T < 2.5$ cm; (2) desire for breast-conserving surgery; (3) age >50 years; (4) surgical margin >1 cm; (5) intraoperative pathologically free margins; and (6) sentinel node negative. Exclusion criteria were (1) contraindications to radiation therapy; (2) past radiation therapy for the same breast or chest; (3) extensive intraductal component; and (4) a tumor located in the axillary tail of the breast. All patients gave written informed consent. Partial resection was performed with at least a margin of 1 cm around the tumor. The patient was transported from the surgical suite to the radiation room. Radiation (Clinac® 21EX, Varian Medical Systems, Inc.) at 21 Gy was delivered directly to the mammary gland. Toxicity was evaluated with the Common Terminology Criteria for Adverse Events V4.0.
Results Five patients were enrolled in this pilot study and received 21 Gy. Follow-up ranged from 7.8 to 11.0 months (median 10.2). Intraoperative transportation to the radiation room during the surgical procedure under general anesthesia was performed safely in all patients. Treatment-related toxicities within 3 months were deep connective tissue fibrosis (grade 1, $n = 3$) and pain (grade 1, $n = 3$). There was no case of wound infection, wound dehiscence, or soft tissue necrosis. Overall, there was no severe adverse event.
Conclusions The procedure was tolerated very well in this first group of Japanese female patients treated with IORT, as was the case with European women. A longer follow-up is needed for the evaluation of any potential late side effects or recurrences. A phase II study is now being conducted for the next group of patients (UMIN000003578).

Keywords Breast cancer · Intraoperative radiotherapy · Early breast cancer

Abbreviations

ALND	Axillary lymph node dissection
APBI	Accelerated partial breast irradiation
ASTRO	American Society for Therapeutic Radiation Oncology
BCT	Breast-conserving therapy
DCIS	Ductal carcinoma in situ
EBRT	External beam radiation
EIC	Extensive intraductal component
ELIOT	Electron intraoperative therapy
ER	Estrogen receptor

This study was presented in part at the 7th International Society of Intraoperative Radiation Therapy, Baveno Italy, 2012.

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Published online: 25 September 2012