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Postoperative hyperfractionated IMRT with weekly cisplatin for head and neck cancer: phase IIa trial

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ABSTRACT

Postoperative chemoradiotherapy (POCRT) is the standard treatment for patients with head and neck squamous cell carcinoma (HNSCC) with high-risk features (positive microscopic margins and/or extranodal extensions). We hypothesized that dose escalation using hyperfractionation in intensity-modulated radiotherapy (HF-IMRT) improves POCRT outcomes; however, no prospective trial has assessed the feasibility of POCRT in HF. Therefore, we evaluated the feasibility of POCRT using HF-IMRT. HNSCC patients with positive microscopic margins and/or extranodal extension following surgery were included. HF-IMRT (73.6 Gy in 64 fractions twice daily) was administered along with cisplatin at 40 mg/m^2 once a week for seven cycles during radiotherapy. The primary endpoint was the proportion of patients who completed treatment, which included the planned radiotherapy and the administration of $\geq$200 mg/m^2 of cisplatin. Feasibility was defined as the proportion of patients who completed treatment >60% using a one-sided binomial test. Ten patients were registered between October 2021 and April 2023. One patient was excluded because of tumor recurrence before POCRT. The median follow-up time was 18.2 months, and the proportion of patients who completed treatment was 88.9%. The median total dose of cisplatin was 240 mg/m^2. The percentage of patients with grade 3 acute non-hematological adverse events was 77.8%. No patient experienced grade 4 or higher acute adverse events or grade 3 or higher late adverse events. POCRT using HF-IMRT is feasible for achieving adequate cisplatin doses and safe radiotherapy in patients with HNSCC.

Keywords: hyperfractionation; altered fractionation schedule; postoperative chemoradiotherapy; intensity-modulated radiotherapy; head and neck cancer

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide, with a total of 890 000 new cases and 450 000 deaths in 2018. The number of patients with HNSCC is expected to increase by 30%, resulting in 1 080 000 new cases annually by 2030 [1]. Oral cavity, p16-negative oropharyngeal, hypopharyngeal and laryngeal cancers are primarily associated with tobacco and alcohol consumption; however, p16-positive oropharyngeal cancer is associated with human papillomavirus infection and has a better prognosis than other forms of HNSCC [2]. Patients with HNSCC who undergo surgical resection with high-risk features (positive microscopic margins and/or extranodal extension) require postoperative chemoradiotherapy (POCRT: 66 Gy in 33 fractions once daily) combined with cisplatin treatment [3–5]. Despite multimodality treatment, many patients experience tumor recurrence. The estimated 2-year loco-regional control and progression-free

survival rate are 73 and 56%, respectively [6, 7]. In addition, the total dose of cisplatin administered during definitive chemoradiotherapy is associated with improved overall survival (OS) of patients with HNSCC [8]. In the postoperative setting, the relationship between cumulative cisplatin dose and OS is unclear; however, considering the evidence for the concurrent use of cisplatin in POCRT, improvements in POCRT outcomes without interference with adequate cisplatin administration are considered important.

The efficacy of dose escalation using standard fractionation (SF) and the conventional two/three-dimensional conformal radiotherapy technique of postoperative radiotherapy for HNSCC was not demonstrated in a previous randomized control trial [9]. However, the usefulness of hyperfractionated radiotherapy with concurrent chemotherapy in a definitive setting was addressed in a network meta-analysis [10]. Therefore, we aimed to improve POCRT using hyperfractionation (HF) and intensity-modulated radiotherapy (IMRT). HF is an altered fractionation (AF) schedule for radiotherapy involving the delivery of small-dose fractions twice daily without shortening the overall treatment time by more than 1 week. This allows higher total doses compared with SF [11, 12]. HF is the only AF schedule that has demonstrated a survival benefit compared with SF during radiotherapy alone without increasing late toxicities in patients with HNSCC [12, 13]. Previous meta-analyses have demonstrated a survival benefit when adding chemotherapy to HF for locally advanced HNSCC [14, 15]. Importantly, concurrent chemoradiotherapy using HF showed significantly better results compared with concurrent chemoradiotherapy using SF in terms of event-free survival (HR 0.80, 95% confidence interval (CI) 0.65–0.98) in a network meta-analysis [9]. In addition, IMRT may improve compliance with POCRT by reducing the incidence of adverse events expected with HF-related dose escalation because it allows for dose concentration toward target structures and reduces the dose to organs at risk (OAR), thereby reducing the incidence of adverse events in patients with HNSCC [16–18]. We hypothesized that dose escalation to 73.6 Gy using HF-IMRT for POCRT improves loco-regional control and survival without increasing late toxicities; however, to our knowledge, no prospective trial has assessed the safety and efficacy of POCRT using HF. In this study, we evaluated the feasibility of POCRT using HF-IMRT to achieve adequate cisplatin dosing and safe completion of radiotherapy.

MATERIALS AND METHODS

Study design and eligibility

We designed a single-arm multi-institutional phase IIa clinical trial and recruited patients from Kyoto University Hospital and Kobe City Medical Center General Hospital. The study was approved by the Kyoto University Certified Review Board (CRB5180002) and registered with the Japan Registry of Clinical Trials (jRCTs051210100). Written informed consent was obtained from all patients. The inclusion criteria were as follows: (i) histologically confirmed squamous cell carcinoma in the resected specimen; (ii) primary tumor located in the oral cavity, oropharynx, hypopharynx or larynx; (iii) positive microscopic margins and/or extranodal extension; (iv) within 60 days of surgery; (v) age 20–80 years; (vi) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; (vii) previously untreated with radiotherapy in the head and neck region; and (viii) preserved organ functions. The upper limit of 80 years old was set in consideration of the feasibility of chemotherapy. Patients with p16-positive oropharyngeal squamous cell carcinoma were excluded because of its better prognosis than other types of HNSCC [2].

Procedures

Before treatment, head-to-chest contrast-enhanced computed tomography was performed for radiotherapy planning. The patients were immobilized in a supine position using a head mask. The clinical target volume (CTV) for initial irradiation (CTV initial) included the tumor bed and the prophylactic lymph node areas [19, 20]. Patients who met all of the following criteria were omitted from receiving contralateral neck irradiation: (i) patients with oral cavity or oropharyngeal cancer without primary tumor extension to the contralateral region; and (ii) without contralateral lymph node metastasis. The positive microscopic margins and/or extranodal extension areas were expanded by 15–20 mm to the CTV for boost irradiation (CTV boost). Each CTV was expanded by 5 mm to establish the planning target volume (PTV) for the initial and boost irradiations (PTV initial and PTV boost), thereby compensating for any setup errors and organ movements. IMRT was mandatory with 4–10 MV photon beams. Radiotherapy was delivered at 73.6 Gy in 64 fractions twice daily using HF and a sequential technique (twice daily for 5 days per week with a daily interval time of at least 6 hours, 1.15 Gy per fraction). For PTV initial, 50.6 Gy was administered in 44 fractions twice daily, followed by 23 Gy in 20 fractions twice daily for PTV boost. The prescribed dose was normalized to 50% of the volume for each PTV. Because the standard prescribed dose for POCRT was 66 Gy in 33 fractions, we set the number of fractions to 60–66 based on the definition of HF (increasing the number of fractions without shortening the overall treatment time by more than one week) [11]. Furthermore, the number of fractions had to be set to 62 or more so that cisplatin could be administered seven times. We referred to the prescribed dose of HF with chemotherapy in a definitive setting used in previous clinical trials (77 Gy in 70 fractions twice daily [21], and 74.4 Gy in 62 fractions twice daily [22]) and the time-dose factor (TDF) for stroma at each prescribed dose was 103.3 and 104.6, respectively [23, 24]. Thus, the TDF for the dose prescription in our study was set to be 100–105. As a result, we set the dose prescription of 73.6 Gy in 64 fractions twice daily. (TDF = 101.1). According to the LQ model, the two Gy equivalent dose was 68.4 Gy (α/β ratio of 10) to evaluate tumor control and 61.1 Gy (α/β ratio of 3) to assess late toxicities, such as dysphasia and mucosal ulcer [25]. Because the LQ model does not take the time factor into consideration, we estimated the actual dose to be higher compared with these doses (68.4 and 61.1 Gy) despite taking into account the repair of sublethal injury [26]. Nevertheless, we considered these doses acceptable because the prescribed dose in our study was decided by referring to the prescribed dose in previous clinical trials. Because the risk of recurrence is high around the positive microscopic margins and/or extranodal extension areas and the dose escalation seemed meaningful in the high-risk area, especially in extranodal extension areas, the dose escalation was only performed for PTV boost [27, 28]. OARs were delineated based on the guidelines [29] and the dose constraints for the OARs are listed

in Supplementary Table 1. The margin of the planning organ at risk volume was defined as 3 mm. Cisplatin was administered at 40 mg/m^2 once a week for seven cycles during radiotherapy, whereas adjuvant chemotherapy was not allowed. The use of induction chemotherapy was permitted based on the physician's choice. The criteria for the suspension/discontinuation of radiotherapy or the reduction of the cisplatin dose are described in the supplementary file. Follow-up was scheduled weekly for 90 days after the initiation of radiotherapy. The patients were then followed regularly by head and neck surgeons and radiation oncologists to evaluate adverse events, including dysphagia, soft tissue necrosis and osteonecrosis. Signs of tumor recurrence were also assessed through routine physical and imaging tests, including computed tomography, magnetic resonance imaging or fluorodeoxyglucose-position emission tomography. The frequency of imaging tests was not defined in the protocol and the frequency was determined by the physician. Adverse events were graded using common terminology criteria for adverse events, version 5.0 [30].

Endpoints

The primary endpoint was the proportion of patients who completed treatment. The total dose of cisplatin during definitive radiotherapy significantly correlates with survival in patients with HNSCC, and a total dose ≥200 mg/m^2 is recommended [8, 31, 32]. In contrast, the threshold dose of cisplatin in POCRT is unclear. We defined treatment completion as a cumulative cisplatin dose ≥200 mg/m^2 and the finalization of scheduled radiotherapy within 66 days from the initiation of radiotherapy. The threshold dose of cisplatin was referred to as definitive chemoradiotherapy. We set the period of radiotherapy within 66 days to achieve the treatment package time (from surgery to completion of postoperative radiotherapy) within 100 days [33]. The secondary endpoints were as follows: (i) the proportion of patients with grade 3 or higher acute non-hematologic adverse events; (ii) laryngeal edema requiring emergency procedures (such as tracheostomy or tracheal intubation); and (iii) other serious acute and late adverse events. Acute adverse events were defined as those related to chemoradiotherapy occurring within 90 days of radiotherapy initiation, whereas late adverse events were defined as those related to chemoradiotherapy occurring over 90 days following the initiation of radiotherapy. Serious adverse events were defined as the presence of grade 4 non-hematologic adverse events, deaths during the treatment protocol or within 30 days of the last treatment protocol date, and treatment-related deaths. Nutritional intake was evaluated before and 90 days after radiotherapy initiation. The patients were assessed for survival, loco-regional recurrence (disease progression above the clavicle), and distant metastases with a data cutoff of 3 November 2024.

Statistical analysis

The sample size was calculated to be 10 patients with a predicted percentage of patients completing treatment of 80% and a threshold of 50% based on previous reports using a one-sided binomial test (one-sided alpha of 0.2 and a power of 80%). The 80% CI for the completion rate was calculated using the Clopper–Pearson method. We defined the treatment protocol as feasible once the proportion of patients with treatment completion exceeded 60% [3, 4, 34–39]. Patients who discontinued treatment following the initiation of radiotherapy were included in the analysis, whereas those who did not start the treatment protocol (for any reason) before radiotherapy were excluded. All statistical analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participant flow

Between October 2021 and April 2023, 11 patients met the eligibility criteria, and 10 were registered at Kyoto University Hospital. One patient refused to participate in our clinical trial. Because of the COVID-19 outbreak, only one patient met the eligibility criteria at Kobe City Medical Center General Hospital but refused to participate; therefore, no patients from this center were registered in the clinical trial. One patient was excluded from the analysis because of tumor recurrence before POCRT. Therefore, nine patients were included in the final analyses.

Patient characteristics

Patient characteristics and outcomes are listed in Tables 1 and 2, respectively. The median patient age was 65 years (range: 33–79 years), and 6 (66.7%) patients were male. Five (55.6%) and four (44.4%) patients had ECOG performance statuses of 0 and 1, respectively. The pathological stage was IVA in four (44.4%) patients and IVB in five (55.6%) patients based on the Union for International Cancer Control 8th edition. The primary tumor site was the oral cavity in eight (88.9%) patients and the oropharynx in one (11.1%) patient. Four (44.4%), two (22.2%) and three (33.3%) patients had positive microscopic margins, extranodal extension or both, respectively. Contralateral neck irradiation was omitted in two (22.2%) patients. Seven (77.8%) patients received induction chemotherapy before surgery: one cycle of fluorouracil/cisplatin (800/80 mg/m^2) in three patients, two cycles of fluorouracil/cisplatin (60/800 mg/m^2) in one patient, one cycle of fluorouracil/docetaxel/cisplatin (750/75/70 mg/m^2) in one patient, two cycles of oral fluoropyrimidine derivative S-1 (120 mg/body) in one patient, and one cycle of oral fluoropyrimidine derivative S-1 (100 mg/body) in one patient.

Outcomes

The median follow-up time was 18.2 months (range: 11.5–32.9 months). All patients completed radiotherapy, and eight of nine patients received cisplatin at a total dose of ≥200 mg/m^2. The proportion of patients who completed treatment was 88.9% (80% CI: 63.2–98.8%), and the lower limit of CI exceeded 60%. The median overall radiotherapy treatment duration was 45 days (range: 43–49 days). Three (33.3%) patients required radiotherapy suspension (median: 1 day, range: 1–3 days) because of lung infection ($n = 2$) and neutropenia ($n = 1$). The representative dose distributions are shown in Fig. 1. Dose-volume indices for PTV and OARs are listed in Table 3. The median total cisplatin dose was 240 mg/m^2 (range: 150–280 mg/m^2). One patient with a total cisplatin dose <200 mg/m^2 discontinued cisplatin during POCRT because of a cisplatin allergy.

Details of the acute adverse events are listed in Table 4. Seven of nine patients (77.8%) experienced grade 3 acute non-hematological adverse events [mucositis in four (44.4%); lung infection in three

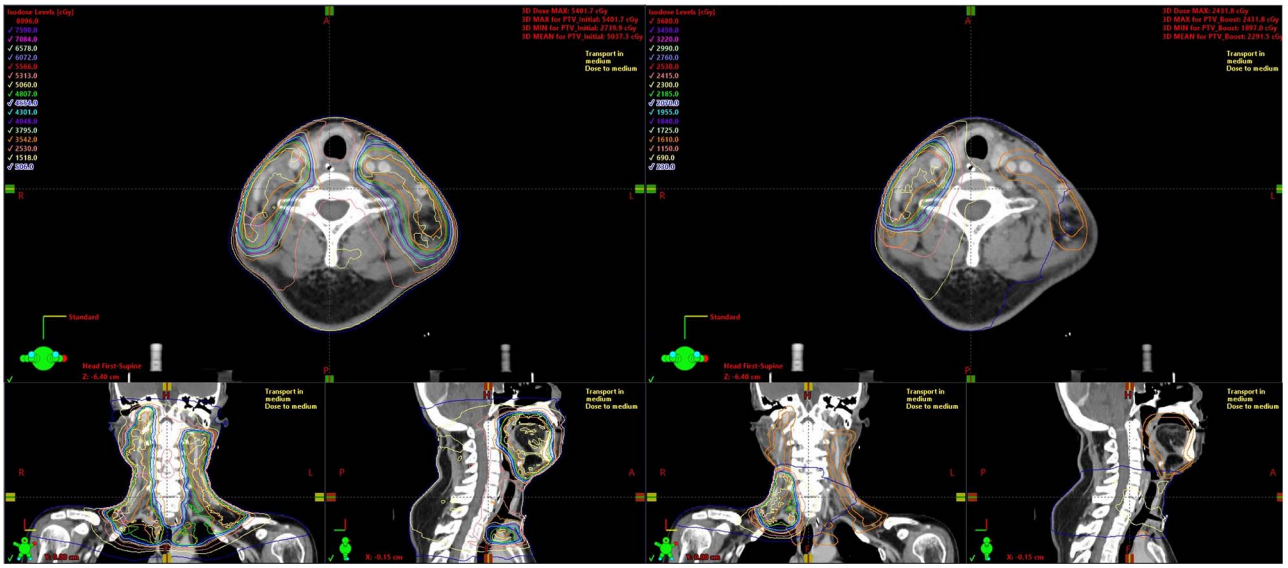

Fig. 1. Representative dose distributions for the initial plan (left side) and boost plan (right side).

Table 1. Patient characteristics

	n	%
Age (years), median [range]	65 [33–79]	
PS		
0	5	55.6%
1	4	44.4%
Histology		
Squamous cell carcinoma	9	100.0%
Origin		
Oral cavity	8	88.9%
Oropharynx	1	11.1%
Pathological stage (UICC 8th)		
IVA	4	44.4%
IVB	5	55.6%
Induction chemotherapy before surgery		
Yes	7	77.8%
No	2	22.2%
High-risk adverse feature		
Extranodal extension	2	22.2%
Positive microscopic margins	4	44.4%
Extranodal extension + positive microscopic margins	3	33.3%

PS, performance status; UICC 8th, Union for International Cancer Control 8th edition.

(33.3%); nausea in two (22.2%); and dysphagia in one (11.1%)]. The oral cavity was the primary site in all patients who experienced grade 3 mucositis. Six of nine patients (66.7%) experienced grade 3 acute hematologic adverse events [leukopenia in five (55.6%); neutropenia in four (44.4%); and anemia in one (11.1%)]. No patient experienced grade 4 or higher acute adverse events (including laryngeal edema requiring emergency procedures such as tracheostomy or tracheal intubation) or other severe adverse events. Five of nine patients (55.6%) experienced grade 2 late adverse events. Specifically, two patients [22.2%] experienced osteonecrosis in the PTV boost area. One of these patients had a history of wound dehiscence before radiotherapy, experienced recurrent wound dehiscence 23 days after radiotherapy initiation, and subsequently developed osteonecrosis 7 months after radiotherapy initiation. The other experienced osteonecrosis 13 months after radiotherapy initiation. Both patients recovered from osteonecrosis with medical management. The incidence rates of other grade 2 late adverse events were as follows: dysgeusia in two (22.2%), dry mouth in two (22.2%), mucositis in one (11.1%) and hypothyroidism in one (11.1%). No grade 3 or higher late adverse events were observed during this period. The primary nutritional intake methods at the time of registration were oral ($n = 7$) and nasogastric tube ($n = 2$) intake. At 90 days following the initiation of radiotherapy, the nutritional intake method was oral for all patients.

Five patients experienced a recurrence. One patient experienced both loco-regional (in the PTV boost area) and distant recurrences. Two had loco-regional recurrence alone (in the PTV initial area). Two had a distant recurrence alone. No patients experienced contralateral lymph node recurrences outside the irradiated fields, including two patients who did not receive prophylactic contralateral neck irradiation. One patient (#1 in Table 2) died of small bowel cancer without HNSCC recurrence. The other patient (#4 in Table 2) experienced an accidental asphyxiation. The patient had received a subtotal glossectomy and modified radical neck dissection. After surgery, the patient had difficulty eating, which improved following rehabilitation during POCRT. Ten months after the start of POCRT, the patient experienced a local recurrence, and swallowing deteriorated as a result of the recurrence. The patient received Boron Neutron Capture Therapy and chemotherapy, which resulted in a complete clinical response. However, the swallowing function did not recover after salvage therapy. The patient succumbed to asphyxiation while eating 8 months after the recurrence. Thus, we concluded that it was plausible that the

Table 2. Patient details and outcomes

ID	Age	PS	Sex	cTNM	pTNM	Surgery	Flap	Subsite	Adverse feature	CDDP dose	f/u	Clinical outcomes	Loco-regional control
1	70	1	M	cT4aN2cM0	pT4aN2cM0	Seg. man + bil. mRND	Fibula flap	Lower gum	Mi	200	12.7	DID	Yes
2	58	0	M	cT2N1M0	ypT2N2bM0	Res. buccal+ ips. mRND	No	Buccal mucosa	Mi	280	32.9	NED	Yes
3	68	0	F	cT4aN2bM0	ypT4aN1M0	Sub. glos + ips. mRND + con. SOHND	ALT flap	Tongue	Mi	240	21.2	DOD	No
4	50	0	F	cT4aN2cM0	ypT3N3bM0	Sub. Glos + bil. mRND	ALT flap	Tongue	E	280	18.2	DOD	No
5	79	1	M	cT3N2bM0	ypT4aN3bM0	Sub. glos + lat. Oro. + total laryng + bil. mRND	ALT flap	Base of tongue	Mi + E	150	11.7	DOD	Yes
6	65	1	M	cT4bN2bM0	ypT4bN3bM0	Sub. Glos + ips. mRND + con. SOHND	Cervical flap	Lower gum	Mi + E	200	23.2	AWD	No
7	33	0	F	rcT1N3bM0	pTisN3bM0	Par. Glos + bil. mRND	No	Tongue	E	240	19.5	NED	Yes
8	72	1	M	cT4aN1M0	ypT4aN3bM0	Sub. Glos + bil. mRND	ALT flap	Tongue	Mi + E	240	11.5	DOD	Yes
9	60	0	M	cT4aN2bM0	ypT2N2bM0	Seg. man + ips. mRND	Fibula flap	Lower gum	Mi	240	18.2	NED	Yes

PS, performance status; cTNM, clinical TNM stage according to UICC 8th; pTNM, pathological TNM stage according to UICC 8th; Flap, flap reconstruction; CDDP dose, total dose of cisplatin during postoperative chemoradiotherapy (mg/m^2); f/u, follow-up time (month); M, male; F, female; seg. man, segmental mandibulectomy; res. of buccal, resection of buccal mucosa; sub. Glos, subtotal glossectomy; par. Glos, partial glossectomy; lat. Oro, lateral oropharyngectomy; total laryng, total laryngectomy; ips., ipsilateral; con., contralateral; bil, bilateral; mRND, modified radical neck dissection; SOHND, supraomohyoid neck dissection; ALT, anterolateral thigh; Mi, positive microscopic margins; E, extranodal extension; NED, no evidence of disease; AWD, alive with disease; DOD, died of disease; DID, died from intercurrent disease.

asphyxiation resulted from the exacerbation of the tumor or salvage therapy, but it was unlikely related to the protocol treatment.

DISCUSSION

To our knowledge, this is the first prospective clinical trial evaluating the feasibility of POCRT using HF-IMRT for adequate cisplatin dosing and safe radiotherapy completion in patients with HNSCC. Treatment completion, defined as planned radiotherapy completion and treatment with $\geq$200 mg/m^2 of cisplatin, was achieved in 88.9% of the patients.

The RTOG0129 and GORTEC9902 trials evaluated the benefits of AF compared with SF in definitive chemoradiotherapy for HNSCC; however, both trials failed to show any advantage of AF in terms of outcome [38, 39]. In both trials, the AF arm received moderately accelerated HF, which shortened the duration of radiotherapy by >1 week with only slight changes in total irradiation dose [40]. Consequently, the AF arm received two concurrent cycles of chemotherapy, whereas the SF arm received three cycles. In the RTOG0129 trial, the proportion of patients administered $\geq$200 mg/m^2 of cisplatin was only 62.5% in the AF arm compared with 84.2% in the SF arm [39]. Thus, the efficacy of AF may have been offset by differences in chemotherapy intensity. In the network meta-analysis, there was no significant difference in event-free survival between accelerated HF with chemotherapy and SF with chemotherapy (HR 0.96, 95% CI: 0.85–1.07), which is in contrast to the results for HF with chemotherapy [10]. Thus, the use of AF in chemoradiotherapy for HNSCC remains controversial [41, 42].

We developed a novel POCRT regimen using HF-IMRT with weekly cisplatin administration, which did not decrease the intensity of chemotherapy. All patients completed radiotherapy, and 88.9% of the patients received $\geq$200 mg/m^2 of cisplatin, with a median total dose of 240 mg/m^2. The JCOG1008 trial compared weekly versus tri-weekly cisplatin administration in POCRT (66 Gy in 33 fractions once daily) for HNSCC and showed non-inferiority for the weekly approach. The median total dose of cisplatin administered in the weekly arm was 239 mg/m^2 and 86.8% of the patients completed the treatment. Although the definition of treatment completion in the JCOG1008 trial differed slightly from that in our study, treatment compliance in the JCOG1008 trial was similar to that of our study [34]. Therefore, our regimen of POCRT using HF-IMRT is clinically feasible.

In the JCOG1008 trial, the proportions of patients with grade 3 or higher acute mucositis and radiation dermatitis in the weekly group were 28% (34 in 122 patients) and 12% (14 in 122 patients), respectively. In our study, 44% of patients had grade 3 or higher acute mucositis and 0% had radiation-induced dermatitis. In the present study, the primary site was the oral cavity in eight out of nine patients, and seven of nine patients included the oral cavity in the PTV boost. In addition, the oral cavity was the primary site in all patients who experienced grade 3 mucositis. The high prevalence of the primary site in the oral cavity may account for the high incidence of mucositis. The escalating radiation dose may also increase the incidence of grade 3 or higher acute mucositis; however, no patient experienced grade 4 or higher adverse events. In addition, the median overall duration of radiotherapy treatment in our study was 45 days, which is similar to that reported in the JCOG1008 trial [i.e. 49 days (interquartile range, 46–50)]. Notably, our study did not require long-term treatment

Table 3. Dose volume indices for planning target volume and organs at risk

Structure	Index	Median	Minimum	Max
Body	Dmax	77.7 Gy	76.8 Gy	79.3 Gy
PTV initial	D50%	57.9 Gy	51.8 Gy	69.6 Gy
PTV boost	D50%	73.7 Gy	73.3 Gy	73.9 Gy
Spinal cord PRV	Dmax	36.6 Gy	27.1 Gy	41.9 Gy
Brainstem PRV	Dmax	29.2 Gy	19.9 Gy	36.6 Gy
Mandible	D2 cm^3	71.5 Gy	49.9 Gy	71.7 Gy
Parotid_ipsilateral	Dmean	25.3 Gy	12.8 Gy	38.1 Gy
Parotid_contralateral	Dmean	18.8 Gy	7.2 Gy	24.1 Gy
Larynx out of PTV	Dmean	39.0 Gy	20.9 Gy	47.3 Gy
Constrictor muscle out of PTV	Dmean	37.7 Gy	26.9 Gy	45.6 Gy
Cochlea_ipsilateral	Dmean	12.2 Gy	1.6 Gy	26.8 Gy
Cochlea_contralateral	Dmean	9.4 Gy	1.5 Gy	26.5 Gy
Brain	Dmax	38.7 Gy	10.7 Gy	49.2 Gy

PTV, planning target volume; PRV, planning organ at risk volume; Dmax, max dose to structure; D50%, minimal dose to most exposed 50% of structure; Dx cm^3, minimal dose to most exposed 2 cm^3 of structure; Dmean, mean dose to structure.

Table 4. Details of acute adverse events

Adverse events	Grade 2	Grade 3	Grade 4–5
Leukopenia	1 (11.1%)	5 (55.6%)	0 (0%)
Neutropenia	1 (11.1%)	4 (44.4%)	0 (0%)
Anemia	5 (55.6%)	1 (11.1%)	0 (0%)
Thrombopenia	3 (33.3%)	0 (0%)	0 (0%)
Mucositis	3 (33.3%)	4 (44.4%)	0 (0%)
Lung infection	0 (0%)	3 (33.3%)	0 (0%)
Nausea	0 (0%)	2 (22.2%)	0 (0%)
Dysphagia	0 (0%)	1 (11.1%)	0 (0%)
Radiation dermatitis	5 (55.6%)	0 (0%)	0 (0%)
Dry mouth	4 (44.4%)	0 (0%)	0 (0%)
Dysgeusia	3 (33.3%)	0 (0%)	0 (0%)
Hyponatremia	1 (11.1%)	0 (0%)	0 (0%)
Upper respiratory infection	1 (11.1%)	0 (0%)	0 (0%)

suspension [34]. Thus, the high proportion of mucositis in our study was considered acceptable.

Osteonecrosis is a serious late adverse event that occurs following radiotherapy for head and neck cancer. The incidence of osteonecrosis in the modern era is 4–8%, with a median time to development of 27 months. Patients with oropharyngeal or oral cancers, or those receiving a radiation dose to the mandible of 50 Gy or higher, are considered at risk for osteonecrosis [43, 44]. In our study, the proportion of patients with grade 2 osteonecrosis was 22.2%. The high proportion of patients may be related to the high proportion of patients with oral cancer in our study, which resulted in high median values for the irradiated dose in the mandible ($D2cm^3$ = 71.5 Gy). On the other hand, no patients experienced grade 3 or higher late adverse events, including osteonecrosis. The cumulative incidence of late adverse effects of at least grade 3 was reported to be approximately 40% [3]. Further follow-up is needed to confirm whether a low proportion of severe adverse effects will be maintained in patients who received HF-IMRT.

Generally, salvage surgery can be performed for loco-regional recurrence after definitive chemoradiotherapy; however, it is often challenging for in-field recurrence following postoperative radiotherapy [45, 46]. Although re-irradiation is an option for salvage therapy, a previous study showed a poor prognosis from re-irradiation, including grade 4 acute adverse events (17.7%), grade 5 acute adverse events (7.6%), grade 3 late adverse events (19.4%), grade 4 late adverse events (3.0%), and low 5-year OS (3.8%) [47]. Therefore, we considered that the improvement in local control is required more for the combination of surgery and POCRT compared with definitive chemoradiotherapy because of the difficulty of salvage therapy, particularly in patients with high-risk features and a poor prognosis [6, 7]. The dose escalation of POCRT may improve local control; however, the increase in adverse events is a concern. In addition, radiotherapy has both acute

and late effects on the skin and subcutaneous tissues that severely affect the healing of surgical wounds. The combination of surgery and postoperative radiotherapy was reported to worsen patient quality of life compared with definitive radiotherapy [48–50]. In the present study, only one patient (11.1%) experienced grade 2 wound dehiscence, and no patients experienced grade 3 or higher late adverse events during the short follow-up period. Our strategy of POCRT using HF-IMRT with the goal of reducing the severe late toxicities following POCRT should be confirmed through long-term follow-up.

Our study had several limitations. First, it was conducted at two hospitals; however, all enrolled patients were registered at the same hospital. Second, the study design was poor enough to prove our hypothesis in the present study. The sensitivity and power used to estimate the sample size were low, which indicates a small study sample size. In addition, we did not assume that POCRT could not be started after registration, and the number of patients included in the analysis was one less than we had expected; thus, the sample size should have been set higher. However, eight of the nine patients completed the treatment and the lower limit of the CI for the completion rate exceeded 60.0%. Thus, our study proved the feasibility of POCRT using HF-IMRT. Third, all registered patients except one had oral cancer. Therefore, it is unclear whether POCRT using HF-IMRT is feasible for patients with laryngeal and pharyngeal cancers. Finally, the median follow-up period was 18.2 months; thus, the evaluation of late adverse events and efficacy was insufficient. To overcome these limitations, we plan to conduct a phase IIb trial to evaluate the long-term safety and efficacy of POCRT using HF-IMRT for HNSCC, including laryngeal and pharyngeal cancers. Based on the feasibility of our protocol treatment, we will use the same regimen in the phase IIb trial. In conclusion, POCRT using HF-IMRT is feasible for achieving adequate cisplatin dosing and safe radiotherapy completion in patients with HNSCC.

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SUPPLEMENTARY DATA

Supplementary data is available at *Journal of Radiation Research* online.

CONFLICT OF INTEREST

The other authors have no Conflict of Interest.

DATA AVAILABILITY

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Our trial was approved by the Kyoto University Certified Review Board (CRB5180002). Written informed consent was obtained from all patients.

AUTHOR CONTRIBUTIONS

SH, AN, MK, MN, MY and TM designed the study. All authors participated in the data collection. SH and AN performed the statistical analyses. The first version of the manuscript was written by SH, and all authors contributed to subsequent versions of the manuscript. All the authors have read and approved the final version of the manuscript.

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