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Pain control in head and neck radiotherapy

Multicenter phase II study of an opioid-based pain control program for head and neck cancer patients receiving chemoradiotherapy

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ABSTRACT

Background: The aim of this multi-center phase II study was to clarify the clinical benefit of an opioid-based pain control program for head and neck cancer patients during chemoradiotherapy.

Patients and methods: Head and neck cancer patients who were to receive definitive or postoperative chemoradiotherapy were enrolled. The opioid-based pain control program consisted of a three-step ladder, with basic regimens of:

Step 1: acetaminophen at 500–1000 mg three times a day.
Step 2: fast-acting morphine at 5 mg three times a day before meals for a single day.
Step 3: long-acting morphine administered around-the-clock, with a starting dosage of 20 mg/day and no upper limit set in principle.

Patients and methods: The primary endpoint of this study was compliance with radiotherapy.

Results: A total of 101 patients from 10 institutions were registered between February 2008 and May 2009 and included in the analysis. The major combination chemotherapy regimen was cisplatin alone (76%). The rate of completion of radiotherapy was 99% and the rate of unplanned breaks in radiotherapy was 13% (13/101, 90% confidence interval: 9.9–16.5%). Median maximum quantity of morphine used per day was 35 mg (range 0–150 mg).

Conclusions: Use of a systematic pain control program may improve compliance with CRT.

Several recent randomized phase III studies have confirmed the value of radiotherapy and concurrent high-dose single-agent cisplatin in almost all stages of locally advanced head and neck cancer [1–5], and platinum-based chemotherapy and concurrent radiotherapy regimens with or without induction chemotherapy are widely used in clinical practice [6–8].

One of the most common and debilitating toxicities among head and neck cancer patients is radiation-induced mucositis [9,10], and severe acute mucositis often results in unplanned treatment breaks, clinic visits and hospitalizations [11,12]. Unplanned breaks in radiotherapy for head and neck cancer are associated with significantly worse locoregional control [13–15]. Even short breaks may have a negative influence: in one retrospective analysis of 2225 patients from four centers [13], for example, an unplanned break of only 1 day resulted in a 0.68% lower 2-year local control rate, while other authors estimated that the tumor control rate is at least 1% lower for every day that radiation treatment is interrupted [16,17].

To investigate whether a systematic pain control program might help decrease unplanned treatment breaks by suppressing radiation-induced pain, we developed an opioid-based pain control program for the systematic management of radiation-induced pain. The aim of this multicenter phase II study was to clarify the clinical benefit of this opioid-based pain control program for head and neck cancer patients during chemoradiotherapy.

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Patients and methods

This multi-center phase II trial was approved by the institutional review boards of all participating institutions before patient enrollment occurred.

Eligibility

Enrollment criteria included histologically confirmed squamous cell carcinoma of the head and neck, age 20–75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, normal organ function, scheduled receipt of definitive or postoperative radiotherapy (>50 Gy) with platinum-based chemotherapy, and no cancer pain at the time of recruitment. Written informed consent to treatment was obtained from all patients before the initiation of any treatment.

Treatment

All study patients were recommended to undergo percutaneous endoscopic gastrostomy (PEG) before the start of radiotherapy. The main protocol was called the 'opioid-based pain control program', which consisted of a three-step ladder (Fig. 1).

Prescription Step 1

The basic regimen for mild pain was acetaminophen at 500–1000 mg three times a day. Loxoprofen sodium or diclofenac sodium was avoided on the basis that their adverse effects on renal function might have influenced compliance with platinum-based chemotherapy.

Prescription Step 2

The basic regimen for mild-intermediate pain was fast-acting morphine e.g. anhydrous morphine sulfate at 5 mg three times a day before meals. The main aim of this prescription was to avoid full dependence on PEG at an early phase of CRT. This regimen could be used concurrently with Prescription Step 1. If oral intake became impossible soon after the initiation of CRT, this regimen could be skipped and the patient moved directly from Step 1 to Step 3.

Prescription Step 3

The basic concept in this step was the use of long-acting morphine around the clock. The starting dosage was 20 mg/day, and no upper limit was set. The rescue dose was set as 1–6 of the main morphine dosage. In principle, intravenous administration of morphine was not performed; in case oral intake became difficult, sustained-released morphine sulfate in fractional doses administered via PEG was recommended instead.

Appropriate use of medications to control side effects of morphine was strongly recommended in Steps 2 and 3. Pain strength was evaluated at least weekly by physicians or nurses using the grading system for mucositis/stomatitis (functional/symptomatic) in Common Terminology Criteria of Adverse Events version 3.

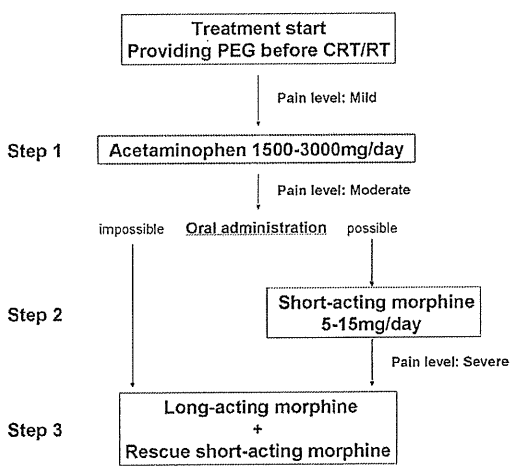

Fig. 1. Opioid-based pain control program. The main decision tree of the opioid-based pain control program is shown.

Toxicity

With regard to the acute toxicity of chemoradiotherapy, adverse events were coded according to the Common Terminology Criteria of Adverse Events version 3. Morphine-induced side effects were evaluated with regard to nausea, constipation, sleepiness, urinary retention, and respiratory depression.

Patient education about use of PEG

To allow CRT to be performed on schedule with minimum hospitalization, it was necessary that patients were able to use PEG alone at home. Expert nurses, including Wound, Ostomy and Continence (WOC) nurses, conducted educational sessions with all patients about how to use PEG during CRT.

PEG management ability was evaluated in each patient at the end of radiotherapy in a three-level score of perfect, possible with family support, and impossible.

Treatment evaluation and statistical analysis

The primary end point of this study was compliance with radiotherapy.

An unplanned treatment break in radiotherapy was defined as an interruption to radiotherapy of 1 day or more, excluding weekends or planned machine maintenance. In our group experience of definitive chemoradiotherapy from 2002 to 2006, 25% of all patients had treatment interruptions (unpublished data). With regard to postoperative radiotherapy, 24% of all patients had treatment interruptions which resulted in a total duration of treatment of more than 7 weeks in EORTC 22931 study [3]. On these basis, our present pain control program was considered worthy of additional study only provided that the true rate of interruption of radiotherapy was 20% or less, and not worthy of additional study if the true rate was 35% or more. With 80% power and a one-sided type-I error of 5%, the minimum number of patients required to evaluate the primary endpoint was 79.

We then calculated that 15% of patients might have a treatment break or cancellation due to reasons other than the failure of supportive management and that 10% might be excluded by violation of the protocol or other reasons. We therefore calculated a total sample size of 110 patients.

Patient demographic, pathologic, and clinical characteristics were described in terms of the mean, standard deviation, median, range, and percentage.

Results

Patient characteristics

One hundred and ten patients from 10 institutions were registered between February 2008 and May 2009. Nine patients were excluded from analysis because of patient discretion ($n = 5$) and change in strategy after registration ($n = 4$). The remaining 101 patients are characterized in Table 1. Median age was 60 years (range

Table 1
Patient characteristics.

No. of patients	101
Age	
Median (years, range)	60 (23–75)
Gender	
Male/female	89/12
Performance status	
0–1/2	101/0
Primary site	
Nasopharynx	24
Oropharynx	26
Hypopharynx	27
Larynx	6
Tongue, oral cavity	13
Unknown	5
Clinical stage	
II	12
III	10
IV	49
Recurrence	5
Postoperation	25
Radiotherapy setting	
Postoperative RT	25
Definitive RT	76
Treatment strategy	
IC → CRT	21
CRT	78
RT alone	2
Radiation dose	
Median (range)	70 (54–70)
Combination chemotherapy	
Cisplatin alone	77
Cisplatin and 5-FU	12
Cisplatin and docetaxel	1
Other platinum	9

Abbreviations: IC, induction chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy.

23–75). The major primary site was the pharynx (76%), followed by the nasopharynx (24%), oropharynx (26%) and hypopharynx (27%).

With regard to treatment strategy, 76 patients (75%) received radiotherapy as an initial approach, and the remaining 25 (25%) in a postoperative setting. Median radiation dose was 70 Gy (range 54–70) and the major combination chemotherapy regimen was cisplatin alone (77/101, 76%).

Treatment compliance

One hundred of 101 patients completed radiotherapy. The remaining patient was scheduled for irradiation with 66 Gy, but this was cancelled at 62 Gy because of patient discretion. The rate of unplanned breaks in radiotherapy was 13% (13/101, 90% confidence interval: 9.9–16.5%), owing to acute toxicity in 2, PEG trouble in 2, emergency tracheostomy in 1, gastric ulcer in 1, unplanned machine trouble in 2, patient discretion in 3, and other reasons in 2. Of these, the median interval of radiation interruption was 1 day (range 1–4 days), and no unplanned break of more than 1 week was seen.

Morphine regimen

Morphine use is shown in Table 2. From the initiation of treatment to 1 month after the end of radiotherapy, median total morphine use per patient was 815 mg (0–6284 mg), and median maximum use per day was 35 mg (0–150 mg). Median radiation dose at the start of morphine was 28.8 Gy. The frequency of morphine-induced side effects of nausea, constipation, sleepiness, urinary retention, and respiratory depression was 26%, 32%, 12%, 0%, and 0%, respectively.

Table 2
Toxicity.

	Grade (CTCAE ver.3.0)				
	1	2	3	4	% 3 and 4
Leucopenia	18	45	20	0	20
Neutropenia	21	41	11	1	12
Anemia	35	33	13	1	14
Thrombocytopenia	29	14	5	0	5
Nausea	32	33	10	0	10
Mucositis					
CE	13	33	54	0	53
FS	8	32	61	0	60
Neuropathy					
S	1	2	0	0	0
M	0	0	0	0	0
Xerostomia	46	39	3	0	3
Dermatitis	25	52	24	0	24
Febrile neutropenia	–	–	1	0	1
Weight loss	19	22	0	0	0

Abbreviations: CTCAE, Common Terminology Criteria of Adverse Events; CE, clinical exam; FS, functional/symptomatic; S, sensory; M, motor.

The rate of patient use of Step 2 or Step 3 programs to control pain during CRT was 83% (84/101), while the rate of use of morphine at one month after the end of radiotherapy was 26% (26/101). A schema of the frequency of use of each prescription is shown in Fig. 2.

Toxicity

Toxicity profile during CRT is shown in Table 3. No fatal hematological events were seen. With regard to non-hematological toxicity, mucositis/stomatitis and dermatitis were the most common acute toxicities. Grades 2 and 3 dermatitis events were seen in 52 (52%) and 24 patients (24%), respectively, while no fatal events were seen.

With regard to mucositis/stomatitis, grade 3 events in the categories 'clinical exam' and 'functional/symptomatic' occurred in more than half of the patients. Grade 2 weight loss was seen in 22 patients (22%), while no grade 3 weight loss was seen.

No treatment-related deaths were seen.

The data about PEG

Ninety-eight of 101 patients (97%) were provided PEG, mostly via the direct method. There were four events (4%) of PEG-associated infection or peritonitis during the observation period. At the end of radiotherapy, 92 patients had used PEG in daily life, of whom 84 (91%) were able to manage PEG by themselves, 5 could do so with family support, and 3 could not manage on an outpatient basis.

On the other hand, of 83 patients who survived over 1 year without primary tumor, the rate of PEG dependence at 1 year after RT was 8.4% (7/83).

Discussion

The aim of this phase II study was to clarify the safety and efficacy profile of a systematic pain control program for head and neck cancer patients during chemoradiotherapy. Results suggested that this program might contribute to improving compliance with CRT in these patients.

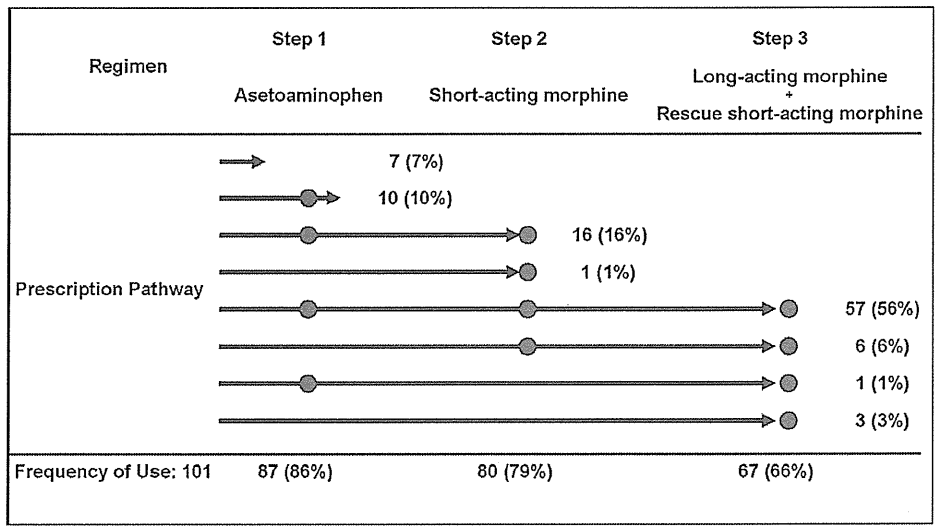

Fig. 2. The summary of prescriptions. Eight prescription pathway patterns were identified. Steps 1–3 was the most common route. Sixty-seven (66%) patients required Prescription Step 3 (long-acting morphine based regimen).

Table 3
Morphine use.

Rate of morphine use	84/101 (83%)
Median total quantity of morphine use per patient	815 mg (0–6286)
Median maximum quantity of morphine use per day	35 mg (0–150)
Morphine-free rate at 1 month after RT	75/10 (74%)
Morphine-induced SE	
Nausea	22 (26%)
Sleepiness	10 (12%)
Urinary retention	0 (0%)
Constipation	27 (32%)
Respiratory depression	0 (0%)

Abbreviations: RT, radiotherapy; SE, side effect.

The primary endpoint of this study was compliance with radiotherapy. Although many retrospective analyses have shown that unplanned treatment breaks have a significant negative impact on treatment outcome [13–15,18], only limited information about this is available from recent prospective trials. In the EORTC 22931 study [3], for example, 24% of all patients had treatment interruptions resulting in a total duration of treatment of more than 7 weeks. Lefebvre et al. [19] reported a randomized control trial which compared sequential chemotherapy and radiotherapy with alternating chemotherapy and radiotherapy, and showed that 23% of the alternating arm patients experienced an interruption to or delay in radiotherapy.

In our study, the rate of unplanned breaks in radiotherapy was 13% and the completion rate was 99%. Although therapeutic intensity in our study was not inferior to that of these two trials, our treatment compliance was better. These results suggest that systematic pain control programs may have a good impact on treatment compliance.

We consider that the provision of percutaneous endoscopic gastrostomy (PEG) before the start of radiotherapy was necessary to allow completion of the treatment schedule. However, complete dependence on PEG soon after starting CRT might result in a decrease in laryngo-pharynx function [20–23]. Taking fast-acting morphine three times a day preprandially at Step 2 might help avoid complete dependence on PEG at an early phase of CRT. In our study, the rate of PEG dependence at 1 year after RT was only 8.4% (7/83). We think the appropriate PEG use does not cause dysphagia in head and neck cancer patients treated with radiotherapy.

With regard to morphine use, the rate of patients using morphine to control pain during CRT was 83% (84/101), and the median maximum quantity of morphine use per day was 35 mg (0–150 mg). In contrast, the rate of patients using morphine at one month after the end of radiotherapy was 26% (26/101). These results suggest that radiation-induced pain worsened rapidly during radiotherapy but improved equally rapidly after the end of radiotherapy.

As an additional benefit of our systematic pain control program, the decrease in differences among physician orders facilitated the duties of nurses. Moreover, unusual changes in pain under this systematic program provided sensitive insight into the possibility of accidents, such as infection. We consider these changes as additional factors that also influenced our good results.

Finally, this program is relatively simple and can be easily implemented without special tools. Although few sustained-release morphine products suitable for administration via PEG are presently available, increased availability will facilitate broad application of the program. This opioid-based pain control program can therefore be widely used in other institutions.

Conclusion

Our opioid-based systematic pain control program during CRT may be helpful for improving compliance with CRT.

We are now planning a randomized control study to determine whether this program has a significant impact on treatment outcomes, including quality of life and overall survival.

Conflict of interest

We have no conflict of interest.

Acknowledgment

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ORIGINAL ARTICLE

A Dermatitis Control Program (DeCoP) for head and neck cancer patients receiving radiotherapy: a prospective phase II study

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Abstract
Purpose We speculated that a systematic program to manage radiation dermatitis might decrease the incidence of severe or fatal cases in head and neck cancer patients receiving radiotherapy. Here, we conducted a prospective phase II study to clarify the clinical benefit of a Dermatitis Control Program (DeCoP) that did not use corticosteroids.
Patients and methods Head and neck cancer patients scheduled to receive definitive or postoperative radiotherapy were enrolled. Radiation dermatitis was managed with a DeCoP consisting of a three-step ladder: Step 1, gentle washing; Step 2, gentle washing and moistening of the wound-healing environment; Step 3, prevention against infection, gentle washing and moistening of the wound-healing environment. The primary endpoint was the incidence of grade 4 dermatitis.
Results A total of 113 patients were registered between January 2009 and February 2010. Eighty patients received radiotherapy as an initial approach, while the remaining 33 received radiotherapy postoperatively. Grade 3 and 4 dermatitis events occurred in 11 (9.7%) and 0 (0%, 95% confidence interval 0–3.2%) patients, respectively. Median radiation dose at the onset of grade 2 dermatitis was 61.5 Gy (range 36–70 Gy) and median period between onset and recovery was 14 days (range 1–46 days).
Conclusion The Dermatitis Control Program has promising clinical potential. Radiation dermatitis might be manageable if gentle washing and moistening of the wound-healing environment is done.

Keywords Head and neck cancer · Cancer nursing · Dermatitis · Radiotherapy

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Introduction

Chemoradiotherapy is now commonly used in the treatment of head and neck cancer. For example, single-agent cisplatin concurrent with radiotherapy is now the nonsurgical standard care for locally advanced squamous cell carcinoma of the head and neck (SCCHN) patients [1–3], and is also considered the standard adjuvant therapy for high-risk postoperative patients [4–6]. Recently, induction chemotherapy using cisplatin, 5-fluorouracil, and docetaxel followed by chemoradiotherapy has shown promise for locally advanced head and neck cancer patients at high risk of distant metastases [7, 8].

However, as treatment strength increases, so too does the risk of toxicity. Acute skin reactions like radiation dermatitis are common, and not only risk interrupting treatment but can even be fatal. Although various topical medications have been used to manage and treat radiation dermatitis, there remains no agreement on the best treatment plan [9, 10].

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Among those being considered, there is strong evidence supporting the efficacy of a simple treatment plan that involves only gentle washing and moistening of the wound-healing environment [11, 12]. Here, we describe a prospective phase II study that uses a Dermatitis Control Program (DeCoP) incorporating a three-step plan, which includes gentle washing and moistening of the would-healing environment but no corticosteroid use, for head and neck patients receiving radiotherapy.

Patients and methods

This single institution prospective phase II study was approved by the institutional review board of the National Cancer Center Hospital before the start of patient enrollment. This trial was registered with UMIN-clinical trials registry (UMIN-CTR: UMIN000001579).

Eligibility

Patients fulfilling the following criteria were enrolled: histologically confirmed SCCHN; 20–75 years of age; Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2; normal organ function; and scheduled to receive definitive or postoperative radiotherapy (>50 Gy). Written informed consent for treatment was obtained from all patients before its initiation.

Treatment

The main protocol was the 'Dermatitis Control Program'. This systematic program consists of a three-step ladder (Table 1).

Supportive treatment for grade 0–1 radiation dermatitis (Step 1)

The basic concept of this step is 'watchful waiting'.

All treatments for radiation dermatitis prevention except gentle washing were avoided. All patients were instructed on how to wash with lukewarm water and mild soap for routine care. Physicians or expert nurses observed each patient for dermatitis at least twice a week.

Supportive treatment for grade 2 radiation dermatitis (Step 2)

The basic concept of this step is 'minimally required intervention'. The irradiated area was covered with gauze and moistened with either vaseline or dimethyl isopropyl-azulene. All outpatients and their families were instructed on how to cover and moisten the irradiated area. For inpatients, gauze coating was done by the patient or nurse. An example of Step 2 is shown in Fig. 1.

Supportive treatment for grade 3–4 radiation dermatitis (Step 3)

The basic concept for this step is similar to that of Step 2 except for the use of preventative action against infection. Physicians or experts including wound, ostomy, and continence nurses observed for dermatitis every business day. If no infection was noted, antibiotic drugs were not administered.

Table 1 Dermatitis Control Program steps

	Dermatitis grade (CTCAE ver. 3.0)			
	0	1	2	3
Step 1: Gentle wash	○	○	○	○
Step 2: Moistened wound environment		Δ	○	○
Step 3: Infection prevention		Δ	Δ	○

○, Treatment done unconditionally; Δ, treatment done if feasible

Toxicity

Adverse events related to acute toxicity by radiotherapy or chemoradiotherapy were coded according to the common terminology criteria of adverse events, version 3 (CTCAE ver. 3.0). According to these criteria, grade 2 radiation dermatitis includes moderate to brisk erythema, patchy moist desquamation mostly confined to skin folds and creases, and moderate edema. Grade 3 radiation dermatitis consists of moist desquamation other than skin folds or creases and bleeding induced by minor trauma or abrasion.

Radiation dermatitis was evaluated by physicians or nurses based on dermatitis grading according to the CTCAE ver. 3.0, followed by DeCoP performed according to the grading. The investigators' gradings were subsequently evaluated by a central review committee using photographs.

Irradiation methods

Irradiation dose and modality (conventional radiotherapy, intensity-modulated radiotherapy or proton beam therapy) varied according to primary site and tumor stage. Full-face immobilization (thickness 2 mm) was used for all patients to minimize set-up error. Target volumes were defined in accordance with International Commission on Radiation Units and Measurements Reports 50 and 62.

Treatment evaluation and statistical analysis

The primary endpoint of this study was the incidence of grade 4 dermatitis. Skin breakdown has the potential for

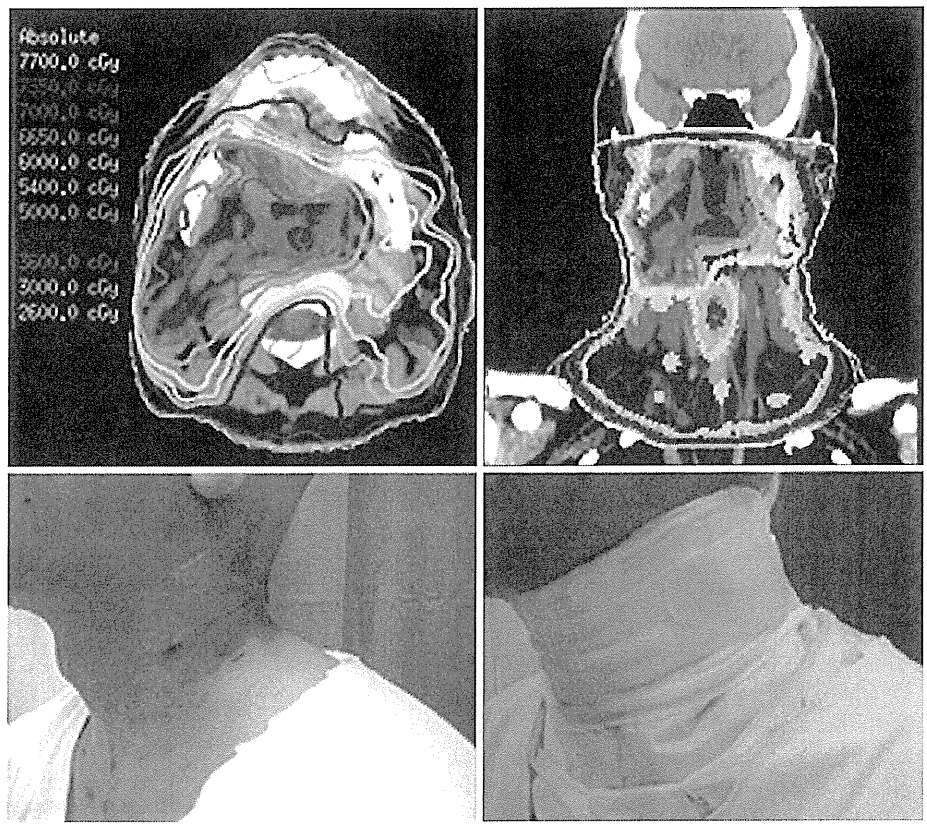

Fig. 1 Dermatitis Control Program Step 2. The case was a 44-year-old-male with T4N2cM0 oro-pharyngeal cancer. He was treated with induction chemotherapy followed by chemoradiotherapy. The irradiated area was covered with gauze and moistened with dimethyl isopropylazulene. It is very important that not only the physicians but also the co-medical staff understand where the radiation field is

infection, which risks disrupting radiotherapy treatment. Unplanned disruption was defined as one or more days of interruption, excluding weekends or days for planned machine maintenance.

If the true rate of grade 4 dermatitis was 7% or less and the true rate of disruption was less than 16%, the DeCoP was applied. To conduct statistical analysis with 90% power and a one-sided type-I error of 5%, a minimum of 104 patients were needed. However, we assumed that 15% of our patients would ultimately be excluded from analysis due to violation of the protocol or other reasons, and thus estimated that 120 patients were needed.

Descriptive statistics, including mean, standard deviation, median, range, and percentage, were used to describe patient demographics, and pathological and clinical characteristics.

Results

Patient characteristics

One hundred and twenty patients were registered between January 2009 and February 2010. Seven patients were excluded from analysis due to a change in treatment strategy (surgery for three patients, palliation for three patients) and refusal to participate after registration (one patient). The remaining 113 patients are characterized in Table 2.

With regard to treatment strategy, 80 patients (71%) received radiotherapy as an initial approach, and the remaining 33 (29%) in a postoperative setting. The major combination chemotherapy regimen was cisplatin alone (53/113, 47%).

Treatment compliance

All patients received the planned radiotherapy without any dose reduction. The rate of unplanned breaks in radiotherapy was 10.6% (12/113) owing to acute toxicity (two patients), PEG trouble (one patient), emergency tracheostomy (one patient), infection (three patients), unplanned machine trouble (one patient), patient discretion (two patients), and other reasons (two patients). Of these, the median interval of radiation interruption was 4 days (range 1–5 days), and no unplanned break of more than 1 week occurred.

Toxicity

The toxicity profile during radiotherapy/chemoradiotherapy is shown in Table 3. No fatal hematological events occurred.

Table 2 Patient characteristics

Characteristics	*n*
No. of patients	113
Age, years	
Median (range)	63 (22–87)
Gender	
Male/female	93/20
Performance status	
0–1/2	99/14
Primary site	
Naospharynx	13
Oropharynx	23
Hypopharynx	18
Larynx	33
Tongue, oral cavity	12
Unknown	14
Radiotherapy setting	
Postoperative RT	33
Definitive RT	80
Treatment strategy	
IC → CRT	25
CRT	43
RT alone	45
Radiation dose, Gy	
Median (range)	70 (54–70)
Combination	
Cisplatin alone	53
Chemotherapy	
Cisplatin and 5-FU	11
Cisplatin and S-1	2
Other platinum	1

CRT Chemoradiotherapy, *IC* induction chemotherapy, *RT* radiotherapy, *5-FU* 5-fluorouracil

Mucositis and dermatitis were the most common non-hematological toxicities.

Grade 2 and 3 dermatitis events were seen in 63 (56%) and 11 (9.7%) patients, respectively. No grade 4 dermatitis events were seen (0%, 95% confidence interval 0–3.2%). Median time until the onset of grade 2 dermatitis was 43.5 days (range 23–60 days) and the median radiation dose at onset was 61.5 Gy (range 36–70 Gy). Median period between onset and recovery was 14 days (range 1–46 days) and the median time until recovery from the initiation of radiotherapy was 57 days (range 39–91 days) (Fig. 2).

Grade 3 mucositis events in the categories 'clinical exam' and 'functional/symptomatic' occurred in about half of the patients for each. Weight loss was recorded in 22 grade 2 patients, but not in any grade 3 patients. No treatment-related deaths occurred.

Table 3 Toxicity

	Dermatitis grade (CTCAE ver. 3.0)				
	1	2	3	4	% 3 and 4
Leucopenia	23	34	4	1	4.4
Neutropenia	71	20	1	1	1.8
Anemia	13	30	1	2	2.7
Thromobocytopenia	16	6	3	0	2.7
Nausea	23	26	5	0	4.4
Mucositis					
CE	11	56	42	1	38.1
FS	15	44	47	0	41.6
Xerostomia	14	60	2	0	1.8
Dermatitis	39	63	11	0	9.7
Febrile neutropenia	–	–	1	0	0.9
Weight loss	19	22	0	0	0

CE Clinical exam, *FS* functional/symptomatic

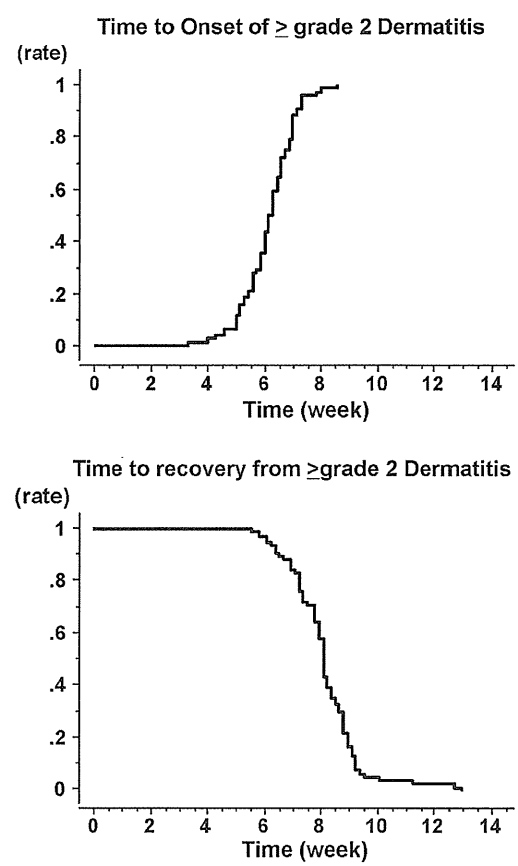

Fig. 2 Time to onset (upper) and recovery (lower) of > grade 2 dermatitis. Median time to onset of grade 2 dermatitis from the initiation of radiotherapy was 43.5 days (range 23–60 days), and median radiation dose at onset was 61.5 Gy (range 36–70 Gy). In several cases, dermatitis became worse after the end of treatment. Median time to recovery from grade 2 dermatitis from the initiation of radiotherapy was 57 days (range 39–91 days). Recovery did not take more than 6 weeks in any case

DeCoP data

All 113 patients received the planned dose of radiotherapy. The median radiation dose was 70 Gy (range 60–70 Gy) and the median duration of radiotherapy treatment was 49 days (range 33–63 days).

The frequency of using either Steps 2 or 3 to control dermatitis during radiotherapy was 63% (71/113), while at 2 weeks and 1 month after the end of radiotherapy it was 19% (21/113) and 2% (2/113), respectively.

Discussion

The primary endpoint of this study was the incidence of grade 4 dermatitis, which did not occur in any patient (0%, 95% confidence interval 0–3.2%). Grade 2 and 3 dermatitis events were seen in 63 (56%) and 11 (9.7%) patients, respectively. Given that radiotherapy is contraindicated in the presence of grade 4 dermatitis, these findings suggest that our DeCoP has good clinical potential.

To date, two randomized trials [11, 13] have assessed the effectiveness of washing. Roy et al. [13] conducted trials with 99 patients randomized to washing with soap and water or no washing, and found a significantly higher incidence of moist desquamation in the non-washing group; while Campell et al. [11] randomized 99 women receiving adjuvant radiotherapy for breast cancer into one of three groups with different washing practices, and found a significant reduction in itching score at the end of treatment and a reduction in erythema and desquamation scores at 6 or 8 weeks after treatment in patients who washed with soap and water independent of bolus dose.

Based on these results, we established Step 1 in our DeCoP as washing only.

Patients received elaborate instructions on how to wash properly. The median time to the onset of grade 2 dermatitis was 43.5 days (range 23–60 days). The frequency of Steps 2 or 3 at 2 weeks and 1 month after the end of radiotherapy was 19 and 2%, respectively. These results show that radiation dermatitis in head and neck lesions can be managed with minimal intervention.

This report has two major limitations. One is that, in our trial, we could not mention the prevention of dermatitis. Another is that it is not enough to mention whether corticosteroids are useful or not for the management of dermatitis because this trial is not a randomized study.

Given this minimal invasiveness, the DeCoP used here appears to be not only useful for clinical practice, but also effective as a control measure for large-scale randomized control trials investigating topical corticosteroids and other medications for dermatitis. Such studies are necessary because although corticosteroids remain frequently prescribed for the management of radiation dermatitis in clinical practice, the evidence for their effectiveness has been inconclusive [9, 12, 14–16].

To change our clinical practice, a further large-scale and qualified phase III study may play a great role.

In conclusion, the results above suggest that radiation dermatitis in head and neck lesions may be manageable if only gentle washing and moistening of the wound-healing environment is done during radiotherapy.

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Conflict of interest There is no conflict of interest.

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ORIGINAL ARTICLE

PROSPECTIVE TRIAL OF CHEMOTHERAPY-ENHANCED ACCELERATED RADIOTHERAPY FOR LARYNX PRESERVATION IN PATIENTS WITH INTERMEDIATE-VOLUME HYPOPHARYNGEAL CANCER

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Abstract: *Background.* Altered fractionation radiotherapy (RT) improves locoregional control in head and neck cancer without aggravation of late adverse events. To improve successful larynx-preservation rates in patients with resectable, intermediate-volume hypopharyngeal cancer, a prospective trial of chemotherapy-enhanced accelerated RT was conducted.

Methods. Patients with T2 to T4 hypopharyngeal cancer received 40 Gray (Gy)/4 weeks to the entire neck followed by boost RT administering 30 Gy/2 weeks (1.5 Gy twice-daily fractionation). Cisplatin and 5-fluorouracil were administered concomitantly only during boost RT.

Results. Thirty-five patients were enrolled in this study. All patients completed this protocol as planned. After a median follow-up period for surviving patients of 59 months (24–90 months), overall survival and local control rates at 3 years were 91% (95% confidence interval, 81% to 100%), and 88% (79% to 99%), respectively. All surviving patients maintained normalcy of diets.

Conclusion. This regimen was feasible with encouraging oncological and functional outcomes. © 2011 Wiley Periodicals, Inc. *Head Neck* **00:** 000–000, 2011

Keywords: hypopharyngeal cancer; accelerated fractionation radiotherapy; chemotherapy; larynx preservation; long-term swallowing function

Approximately one fourth of oral cavity or pharyngeal cancers in Japan originate from the hypopharynx, and the estimated incidence of patients with hypopharyngeal cancer is about 2500 per year.[1,2] Larynx-preserving approaches for hypopharyngeal cancer showed no obvious difference in overall survival compared to other surgical approaches in a randomized study[3] as well as in a large population-based study.[4] Conventional fractionation radiotherapy (RT) alone for patients with early-stage hypopharyngeal cancer with T2 disease achieved a local control rate of approximately 60%.[5,6] RT alone using altered fractionation significantly improved local control rates without deterioration of serious late adverse events.[7,8] This approach could achieve favorable larynx-preservation rates in selected patients with hypopharyngeal cancer with low-volume, T1 or T2 primary tumors which had tumor volumes of 7 mL or smaller.[9,10] However, less favorable results were expected for other patients with larger hypopharyngeal cancers that required total laryngectomy.[10,11] Therefore, the combination of chemotherapy with RT is required to improve larynx-preservation rates in these patients.[12]

Because hypopharyngeal cancer originates from the narrowest part of the upper digestive tract, late dysphagia and aspiration due to consequential late effects are not uncommon even after successful eradication of the disease after intensive chemoradiotherapy (CRT).[13–16] Therefore, special attention should be paid to minimize severity and duration of serious mucosal toxicity by a deliberate combination of altered fractionation RT and/or chemotherapy with meticulous patient selection according to the morphology and volume of the primary tumor.[10,17]

High incidence of distant metastasis in patients with hypopharyngeal cancer was mainly because of the high frequency of advanced nodal disease at the time of initial presentation.[18] If a patient has an intermediate-volume tumor without advanced nodal metastasis, tumor control above the clavicle instead of prevention of systemic tumor dissemination should be prioritized. We previously reported a favorable local cure rate after conventional fractionation RT in patients with intermediate-volume disease at the pharyngolarynx; however, further improvement of

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local control with good function is needed.[19] This study was based on the principle that use of chemotherapy as a radiation sensitizer should not compromise the benefit of altered fractionation RT alone in terms of long-term swallowing function in these patients.[7,8] Accelerated fractionation that delivers dose-dense RT during the latter part of the entire treatment is a reasonable strategy to overcome accelerated repopulation of the tumor, which is supposed to begin at approximately 4 weeks after commencement of RT.[8,20,21] The aim was to enhance the effect of treatment using both twice-daily RT and chemotherapy only during the period when acceleration of tumor repopulation is to be expected. Although the incidence of these patients was expected to be limited, and the true efficacy should be tested in multiinstitutional collaborative studies, preliminary results of this "chemotherapy-enhanced" accelerated fractionation RT were promising.[22] Therefore, matured results of a prospective, single institutional trial were reported here to demonstrate the safety and validity of conducting a larger trial of this regimen.

MATERIALS AND METHODS

Patient Population. Patients were required to have previously untreated, histologically proven squamous cell carcinoma of the hypopharynx that was judged amenable to margin-free resection with total laryngopharyngectomy and neck dissection by expert head and neck surgeons in our institution. Those who were considered as candidates for partial laryngectomy or who had T1 disease were ineligible for this study. In addition, the following eligibility criterion were required: age ranging from 20 to 75 years; no bilateral lymph node metastasis on CT and/or MRI scans; no evidence of distant organ metastasis (clinically M0); Zubrod Performance Status (PS) of 0 to 2; no history of RT for the head and neck area; adequate bone marrow and organ function; no history of other malignancies within 5 years before enrollment; and no history of ischemic heart disease and/or symptomatic cerebrovascular accident within 3 months before enrollment. Patients who had simultaneous superficial esophageal and/or gastric cancers that were judged amenable to margin-free resection using endoscopic mucosal resections were eligible for the study. All patients provided written informed consent. We received approval for this study from our institutional ethics committee.

Pretreatment Evaluation. Disease was staged according to the American Joint Committee on Cancer Staging Manual (6th edition). Staging procedures consisted of physical examination, head and neck fiberscope, CT and/or MRI of the head and neck region, chest X-ray, upper abdominal ultrasound, and gastroesophageal endoscopy. CT of the chest and bone scans were performed as indicated. Laboratory studies included a complete blood cell count, routine liver and kidney function tests, and electrocardiography. All patients underwent pretreatment dental examinations, and dental therapy was done as indicated before the start of RT. Nutritional support by using a nasogastric tube or percutaneous gastrostomy was not done in this protocol.

Radiotherapy. A total dose of 40 Gray (Gy)/4 weeks using 2 Gy once-daily fractionation was administered to the primary tumor, bilateral level II to IV lymph node stations, and retropharyngeal lymph nodes according to the American Joint Committee on Cancer Staging Manual (6th edition). This was followed by boost RT administering 30 Gy/2 weeks (1.5 Gy twice-daily fractionation) to the primary tumor with 2-cm margins. Interfraction interval was set as $\geq$6 hours. Maximum efforts were taken, if appropriate, to exclude the base of tongue and cervical esophagus at >2 cm below the caudal edge of the cricoid cartilage from irradiated volume of the boost RT. If a patient had gross nodal disease extending above the posterior belly of the subdigastric muscle and/or to level IV, which necessitated a larger irradiated volume than that described above during boost RT, neck dissection was performed before the start of RT. This was followed by a total of 55 Gy of RT that was administered to the surgical bed of this up-front nodal dissection, followed by additional 15 Gy to the primary tumor. Maximum dose to the spinal cord was restricted to 46 Gy/24 fractions. RT was delivered using 6 MV X-rays in all patients with 3-dimensional RT planning. Intensity-modulated radiotherapy was not used in this group of patients.

Chemotherapy. A single course of chemotherapy was concomitantly administered during the boost RT in expectation of a radiosensitizing effect.[23,24] Cisplatin 80 mg/m^2 was administered with intravenous hydration on the first day of chemotherapy, and 4-day continuous infusion of 5-fluorouracil 400 mg/m^2/day was started on the same day. Patients were hospitalized during the course of chemotherapy and received hydration and antiemetic therapy as indicated.

Dose Modifications. Grade 4 hematological toxicity or grade $\geq$3 dysphagia and/or swallowing pain required treatment break until these toxicities became grade $\leq$2. Chemotherapy was started only when the following criterion were fulfilled: white blood cell count $\geq$2000/mm^3, hemoglobin level $\geq$8.0 g/dL, platelet count $\geq$100,000/mm^3, any gastrointestinal toxicities of less than grade 3, serum bilirubin level $\leq$1.5 mg/dL, serum creatinine level $\leq$1.5 mg/dL, and dermal toxicity of less than grade 2. If patients did not meet these criterion, chemotherapy was postponed without RT break and administered only when patients satisfied the criterion within 7 days.

Outcome Measures and Statistical Considerations. Low accrual rate was expected in a single institutional setting, and experience of administering altered fractionation RT for hypopharyngeal cancer was limited in Japan at the time of protocol development.[6] Therefore, this trial was conducted as a feasibility study to plan a multiinstitutional trial of this regimen to evaluate the true efficacy with a sufficient number of patients. The primary endpoint was completeness of the protocol treatment without unplanned treatment break or dose modification. This trial used a 2-stage design wherein the expected rate of completeness was defined as 80%. This was tested against the threshold rate of 60% or lower with an alpha level of 5% and a power of 80%, which required an initial enrollment of 13 patients. If <8 of these 13 patients completed the protocol without unplanned break and dose modifications, the trial would be stopped. Otherwise, enrollment would be extended to 35 patients and the rate of completeness determined. Secondary endpoints were local control rate, progression-free survival, overall survival, and adverse events. Follow-up visits were requested monthly within 2 years after completion of RT, at least once per 3 months during the third year, and once per 6 months thereafter. Radiological examinations including CT and/or MRI of the head and neck were done at least twice within 6 months immediately after treatment, and at regular intervals of 6 to 12 months thereafter. Positron-emission tomography was not routinely done in this protocol. Time-to-event analyses from the start of RT were done using Kaplan–Meier estimates. Biopsy-proven recurrence of the primary tumor was considered as an event for calculating the local control rate, and patients who died without this event were censored at the time of last follow-up examinations. Death of any cause was defined as events in calculating overall survival. Also, recurrence at any site or death of any cause was used in estimating progression-free survival. Adverse events were estimated according to the National Cancer Institute Common Toxicity Criteria, version 2.0, and Radiotherapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme.

Although not required in the protocol, volumetry of the primary tumor was estimated from CT scans during RT planning in all patients retrospectively using RT planning software (Xio, version 4.4, Elekta CMS Software, St. Louis, MO) by the principal investigator (M.K.).

RESULTS

Patients. Between October 2002 and March 2008, 35 patients were enrolled. Patient characteristics are listed in Table 1. Thirteen of 15 patients with T3/4 disease had fixation of the vocal cord at presentation, and disease in 2 patients was defined as T3 because of estimated tumor diameter on CT/MRI scan that exceeded 4 cm. Among 20 patients with node-positive disease, 3 had lymph node metastasis at level IV, and the others were confined to level II and/or level III. Two patients had histories of esophagectomy due to esophageal cancer at 7 and 10 years before enrollment, and 2 other patients had simultaneous superficial esophageal cancers that were successfully treated with endoscopic mucosal resections thereafter. Three patients were classified as Zubrod PS 2, otherwise all patients were PS 1. At the time of this analysis, 1 patient was lost to follow-up at 24 months without evidence of disease recurrence. Otherwise, all patients were followed for more than 2 years or until death, and the median follow-up period for surviving patients was 59 months (24–90 months).

Table 1. Patient characteristics.

Characteristics	No. of patients	%
Sex		
Male	32	91
Female	3	9
Age		
Median (range), y	61 (46–73)	
Subsite		
Pyriform sinus	30	86
Post cricoid	4	11
Posterior wall	1	3
Differentiation		
Moderately	17	49
Poorly	6	17
Not specified	12	34
T/N classification		
T2	20	57
N0	7	20
N1	3	9
N2a	1	3
N2b	8	23
N3	1	3
T3	12	34
N0	6	17
N1	1	3
N2a	1	3
N2b	4	11
T4	3	9
N0	2	6
N1	1	3
Stage		
II	7	20
III	10	29
IV	18	51
Volume of the primary tumor (mL)		
Median (range)	15 (3–49)	
<10	5	14
≥10, <20	17	49
≥20, <30	9	26
≥30	4	11

Completeness of the Protocol. Eight patients received up-front nodal dissection at 8 to 25 days (median, 17 days) before start of RT without serious postoperative complications. All of the 35 patients

completed RT and chemotherapy as planned with a median overall treatment time of 44 days (range, 40–48 days). All prolongations of overall treatment time for more than 6 weeks were due to public holidays and/or maintenance of the RT machine. Adverse events that were observed within 90 days after start of the treatments are listed in Table 2. It should be noted that all of the grade 3 adverse events were observed after the end of the treatment and no patients required interruption of RT and/or chemotherapy. Five patients required transient parenteral hyperalimentation to supplement decreased oral intake. However, 24 (69%), 33 (94%), and 35 (100%) patients recovered their normalcy of diet within 2, 4, and 7 weeks, respectively, after completion of the treatments. Although 3 patients required tracheostomy before start of the treatments because of tumor-related airway stenoses, all of them were able to achieve complete resolution of the tumor and were decannulated within 2 months after completion of the treatments. One patient experienced transient grade 3 thrombocytopenia immediately after completion of RT but recovered spontaneously within a week without suffering a symptomatic hemorrhagic accident.

Patterns of Failure. Four patients experienced local persistence or recurrence with ($n = 3$) or without ($n = 1$) nodal metastases. Otherwise, 3 patients, all of whom had node-negative disease at presentation, experienced nodal recurrences as first sites of relapses within irradiated volume of the boost RT in 2 patients, and at the periphery in 1 patient. All but 1 patient with unresectable, isolated nodal failures underwent successful salvage without serious postoperative complications. However, 1 patient died of subsequent nodal failure. Two other patients experienced distant metastases in the lungs as first site of relapse without evidence of locoregional recurrence. Both of these 2 patients originally had node-negative disease (T2 in 1 patient and T4 in 1 patient). One patient died of ischemic heart disease without evidence of disease recurrence at 41 months. Overall survival rate at 3 years was 91% (95% confidence interval, 81% to 100%). All of the disease recurrences at the primary sites were observed within 2 years, and local control rate at 2 years was 88% (79% to 99%), as shown in

Table 2. Acute events.

Grade	0	1	2	3	4	5
White blood cell	18	12	5	0	0	0
Anemia	25	6	4	0	0	0
Thrombocytopenia	33	0	1	1	0	0
Mucositis due to radiation	0	6	17	12	0	0
Dysphagia-pharyngeal due to radiation	1	8	18	8	0	0
Creatinine	24	10	1	0	0	0
Nausea/vomiting	31	2	2	0	0	0
Worst overall	0	4	18	13	0	0

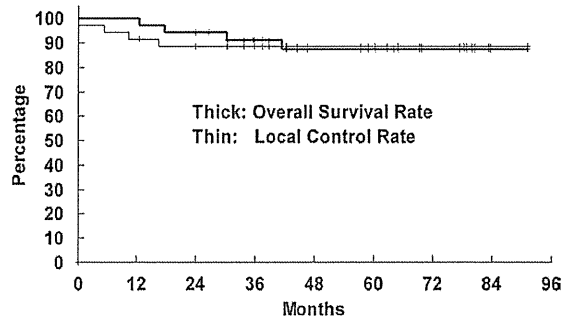

FIGURE 1. Kaplan–Meier estimates of overall survival and local control rates in patients with T2 to 4 primary tumor that was amenable to margin-free resection without bilateral or unresectable nodal metastasis who underwent chemotherapy-enhanced accelerated radiotherapy. Thick and thin lines represent overall survival and local control rates, respectively.

Figure 1. Nodal and distant metastasis rates at 2 years were 14% (3% to 26%) and 6% (0% to 15%), respectively. Progression-free survival at 2 years was 77% (63% to 91%). All of the 20 patients who had T2 disease did not experience local recurrence. However, 1 patient died of nodal recurrence at 13 months. On the other hand, 4 of the 15 patients who had T3/4 diseases experienced local recurrences. Local control rate at 2 years for patients with T3/4 disease was 73% (51% to 96%).

Primary tumors that showed superficial spread with an exophytic growth pattern had tumor volumes of less than 7 mL ($n = 5$), whereas patients that presented with endophytic tumors ($n = 30$) had tumor volumes of at least 10 mL on CT volumetry. Local control rate at 2 years for the former patients was 100%, contrasted to 87% (95% confidence interval, 74% to 99%) for the latter.

Late Adverse Events. One patient required 3 months of gastrostomy tube feeding and antibiotics for exposure of the thyroid cartilage to the pharyngeal cavity at 10 months, and another patient underwent repetitive balloon dilatation for pharyngeal stenosis without the need of taking a soft diet at 9 months. Both patients recovered their normalcy of diet thereafter and were alive and recurrence-free at 83 and 58 months, respectively. Otherwise, late radiation morbidities of grade 2 or greater were not observed. As a whole, all of the patients who were alive with their larynx retained their normal understandable speech without the need for a tracheostomy. Furthermore, all patients who were alive, including those who underwent salvage total laryngopharyngectomy, maintained their normal diets.

DISCUSSION

For laryngeal cancer, a clinical practice guideline for larynx-preserving approach was presented[17] based on

data accumulated from landmark studies.[25,26] The same principles are thought to be applicable to hypopharyngeal cancer. In this study, patients who had primary tumors that mostly localized within the hypopharynx and larynx without penetration of the thyroid cartilage and pharyngeal constrictor muscle were enrolled. These hypopharyngeal cancers had tumor volumes of approximately ≤30 mL, and better local control rate after RT than in patients with larger primary tumors as was suggested from retrospective studies.[19,27,28] Measurement of tumor volume is significantly influenced by interobserver variation and imaging modality used in volumetry.[29] However, the required precision for tumor volumetry to adequately predict radiocurability was considered as ±50% in a review of the literature.[30] Therefore, it is conceivable that most patients enrolled in this study had "intermediate-volume" tumors requiring total laryngopharyngectomy as a curative surgical approach and amenable to margin-free resections, but which were not categorized as having "low-volume" tumors.

When this study was being developed, however, a high percentage of patients with intermediate-volume hypopharyngeal cancers without advanced nodal diseases did not receive definitive CRT in many academic centers in Japan.[1,31] This was because the safety and efficacy of possible salvage surgery after CRT was empirically expected to be poor.[32,33] In addition, a recent multiinstitutional larynx-preserving trial using intensive CRT showed that, at 1 year, 23% of the patients were able to swallow only soft foods or liquids, and 3% could not swallow at all.[26] Other detrimental effects of concomitant high-dose chemotherapy with altered fractionation RT on long-term swallowing functions were also documented.[34,35] For patients with hypopharyngeal cancer with intermediate-volume primary tumors, clinical clarification of the following points were sought in this study: (1) altered fractionation RT alone is insufficient to satisfy the result; (2) however, 2 or more courses of concomitant chemotherapy not only could result in deterioration of function, but is unnecessary to achieve the outcome comparable to altered fractionation RT alone for early-stage, low-volume tumors[10,11]; (3) efforts to minimize the irradiated volume receiving CRT may be needed to prevent excessive vascular and/or connective tissue damage at the expected anastomosis site in possible salvage surgery; (4) for this purpose, up-front nodal dissection should be positively considered in patients with nodal disease spreading outside of the target volume for boost RT encompassing only the primary tumor with margins. Concomitant chemotherapy during the former part of RT was not done to eliminate unexpected local and/or systemic toxicity of chemotherapy that possibly interrupt timely administration of accelerated RT.[21] As a result, all patients completed the protocol treatment without an unplanned break, and all of the 4 patients who experienced local recurrences safely underwent salvage total laryngopharyngectomy.

More than 5 years were required to accumulate the 35 patients as expected at the time of protocol development. The principal conclusion of this study was the feasibility of this protocol. However, it should be emphasized that none of the 20 patients with T2 disease experienced local recurrence. Although 73% of local control rate at 2 years for T3/4 disease was observed in only 15 patients, the lower limit of the 95% confidence interval was 51%, which exceeded the results of a previous randomized study for larynx-preserving treatment in patients with resectable hypopharyngeal cancer.[3] Overall survival rate at 3 years was 91% with acceptable distant failure rate. These results showed that this regimen can become an alternative to more intensive CRT in patients who were eligible for this study.

This regimen is in contrast to the widely accepted benefit of concomitant chemotherapy delivered throughout RT. However, for certain patients with stage III/IV disease, low-volume disease could achieve satisfactory results after treatment without using intensive chemotherapy.[14,36] Incidence of grade ≥3 mucositis was 34% (12 of 35), which was comparable to results in previous studies regarding CRT with higher dose of chemotherapy.[26] However, it should be noted that all of the grade 3 mucositis occurred after completion of the protocol and most of the patients recovered their normalcy of the diet within 4 weeks, probably because of no additional injury to the mucous membrane after occurrence of serious mucositis in this regimen. In addition, grade ≥3 hematologic toxicity was observed in only 1 patient (3%). Given that bacterial colonization in patients with compromised immune reaction aggravates and prolongs severe acute mucositis,[37] lower bone marrow toxicity of this regimen is preferable to ameliorate chronic dysphagia as a consequential late effect.[16] As a result, no surviving patient experienced feeding tube dependency at ≥2 years in this study. Upfront nodal dissection followed by definitive RT with or without substandard chemotherapy for appropriately selected patients with small pharyngolaryngeal cancer with bulky N2/3 disease could achieve locoregional control rates equal to those who had N0/1 disease without compromise of survival.[38–41] Six percent of distant failure rate (none in patients who underwent up-front nodal dissection) in this study was in good agreement with these previous reports.[38,40,41] The survival benefit of adding intensive chemotherapy for the purpose of preventing distant failure had never been observed in patients with resectable disease and, at present, the value of intensive chemotherapy for these patients is recognized as improvement of locoregional control.[3,12,26] In this context, because of 88% preservation rate of functioning larynx with a low distant failure rate, this study including 20 patients with node-positive disease who were amenable to margin-free resections (8 required up-front nodal dissection)

should not be criticized based solely on substandard use of chemotherapy. Involvement of nodal metastasis outside of the sentinel area (ie, ipsilateral levels II and III) was reported as a significant factor of developing distant failure.[42] Because only 3 of 35 patients had gross nodal disease at the level IV, the results of this study might be relevant to a subsection of hypopharyngeal cancer patients having T2 or small T3/4 primary tumor with N0 to resectable N2 disease localized to the sentinel area (incipient N2), which should be considered in subsequent studies. The necessity of upfront nodal dissection only for prevention of excessive tissue damage may be negated in the intensity-modulated radiotherapy era.

Whether the results of this study were merely due to our patient selection in a single institutional setting, must be elucidated in larger, multi-institutional trials. However, the survival benefit of altered fractionation RT was already demonstrated in a meta-analysis.[43] Patients with hypopharyngeal cancer have relatively poor health status and high propensity of developing acute and/or late toxicities such as pneumonia and dysphagia. In this context, the benefit of intensive chemotherapy added to RT may be diminished and negated by its toxic effect when patients with hypopharyngeal cancer having relatively small tumor burdens are included in larynx preserving trials.[30] Therefore, testing separate strategies for patients with intermediate-volume primary tumor with N0 to incipient N2 disease was considered justifiable. Appropriateness of chemotherapy-enhanced accelerated RT was thought to be applicable even when intermediate-volume tumors were categorized as T3/4 disease in the current staging system with sophisticated imaging modalities. However, dosing of chemotherapy, role of induction chemotherapy, and molecular targeted therapy should be studied further with careful patient selection in these patients. In patients who have larger tumor burdens, reduced dose chemotherapy no longer achieved satisfactory tumor cure.[44,45]

In conclusion, accelerated fractionation RT with delayed concomitant chemotherapy as a radiation sensitizer was feasible and showed encouraging oncological and functional outcomes in patients with intermediate volume hypopharyngeal cancer who would otherwise have required total laryngopharyngectomy. Further study is warranted to test the appropriateness of this regimen for patients with hypopharyngeal cancer who have intermediate-volume, especially T2, primary tumor with N0 to incipient N2 disease in multi-institutional collaborations.

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Superselective arterial cisplatin infusion with concomitant radiation therapy for base of tongue cancer

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SUMMARY

The treatment of base of tongue (BOT) cancer is highly controversial with differing options according to individual institutions, or the primary surgical or radiation therapy bias. We aimed to determine patient outcomes and discuss technical aspects following treatment with concurrent radiation therapy and targeted cisplatin chemotherapy (RADPLAT).

We utilized RADPLAT for the definitive treatment of patients with BOT cancers.

The 5-year local control and overall survival rate was 92.3% and 90.9% for all patients, respectively, and all surviving patients achieved normal swallowing without a feeding-tube and normal speech without tracheostoma after treatment.

Our study found that RADPLAT gave excellent survival rates and organ functions for patients with BOT cancers. We consider that BOT cancer is a good indication for RADPLAT and that the angiographic technique and patient selection are keys to success.

Introduction

The management of base of tongue (BOT) cancer varies according to institution policies and the primary surgical or radiation therapy bias.[1] Although wide resection of the tongue base and adjacent pharynx and/or larynx in advanced disease has a profound impact on speech and swallowing,[2] radiotherapy alone is considered ineffectual for locally advanced, unresectable head and neck cancers,[3,4] especially T4.[5]

For this reason, there has been great interest in combined radiotherapy and chemotherapy. Prospective randomized trials have demonstrated improved survival rates in patients treated with chemoradiotherapy (CRT) compared with radiotherapy alone for unresectable squamous cell carcinoma of the head and neck.[6–8] Concurrent radiation therapy and targeted cisplatin chemotherapy (hereafter called RADPLAT) has also proved to be a promising treatment,[9,10] achieving a 90% complete response rate in advanced cases of head and neck cancer.[11]

The treatment program incorporates a novel technique for infusing cisplatin directly into the tumor bed, while minimizing the effects of the drug systemically. We previously reported our experiences of it in over 240 patients with cancer of the nasal cavity and paranasal sinus,[12] which gave improved results compared with alternative treatments of other studies.

In the present study, we utilize RADPLAT for the definitive treatment of patients with BOT cancer, and analyze and discuss the outcomes and technical aspects.

Patients and methods

Eligibility criteria

Thirteen patients were eligible for participation in the study, and written informed consent was obtained from all prior to entry. Patients were required to be younger than 75 years of age and to have a World Health Organization performance status of 0–2, adequate bone marrow reserve, and adequate liver and renal function. Patients also required histologic proof of squamous cell carcinoma of the tongue base. Patients who were pregnant or breast-feeding were excluded from the study.

All patients were initially evaluated by a multidisciplinary team consisting of head and neck surgeons and radiation oncologists, and tumors were classified according to the 2002 Union Internationale Contre le Cancer (UICC) staging system. The tumor stage was determined on the basis of patient history, physical examination,

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chest X-rays, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography.

Patients with a pathologic diagnosis of squamous cell carcinoma were eligible for the study, but were not if they had distant metastases or had received prior treatment of any kind for their cancer.

This work has been approved by the appropriate ethical committees of Hokkaido University Hospital, Sapporo, Japan.

Chemotherapy

All patients received concurrent intra-arterial cisplatin and intravenous sodium thiosulfate infusions in the following manner: cisplatin (100–120 mg/m^2 per week for four weeks) was infused through a microcatheter placed angiographically to selectively encompass only the dominant blood supply of the targeted tumor. Tumors of the anterior wall of the oropharynx are usually covered by the lingual artery, but in cases when the facial artery or the superior thyroid artery covered the tumor, part of the dose was administered through these alternative arteries.

At first, the catheter was positioned in the region of expected blood supply. Contrast agent was then injected as rapidly as possible until it refluxed slightly into the more proximal vessels during peak systole. Next, selective intra-arterial computed tomographic arteriography (IA-CTA) was performed to carefully identify the feeding arteries and their perfusion, and cisplatin was infused at the determined rate (Figure 1). Simultaneously, sodium thiosulfate (20–24 g) was given intravenously, as described by Robbins et al., to neutralize the cisplatin.[11] All arterial catheterizations were accomplished transcutaneously through the femoral artery, and the catheters were removed immediately after infusion. To ensure patients excreted the cisplatin rapidly, 8 L of lactated Ringer's solution were given over a 24 h period. A 5HT3-receptor antagonist was given to all patients before arterial infusion to minimize nausea and vomiting. Chemotherapy was completed during the first four weeks, provided that patients responded well in the early treatment period and had received three arterial infusions (Figure 2).

Radiotherapy

All patients were treated with external beam therapy without brachytherapy. Nine patients received conventional radiotherapy. Until May 2006, the irradiation schedule was 66 Gy in 30 fractions over 6.5 weeks. Since then, it has changed to 70 Gy in 35 fractions over seven weeks for all patients with advanced head and neck cancer. After the initial dose of 40–44 Gy was administered, an additional 22–30 Gy was applied to a more shrunken field, focusing on the primary tumor bed and the positive lymph nodes. Four patients received intensity-modulated radiotherapy (IMRT). The dose to the spinal cord was kept below 40 Gy in all instances.

Management of the neck

Patients with regional lymph node metastasis of the neck were treated with 65–70 Gy of radiotherapy and chemotherapy. If lymph node metastases remained or recurred, patients with resectable neck disease were referred for dissection.

Evaluation of response and toxicity

Responses were evaluated by clinical examination and/or CT or MRI studies 6–8 weeks after the completion of therapy. Standard criteria were used to assess the patient response. A complete response (CR) was defined as total resolution of the grossly visible tumor, and a partial response (PR) was defined as a 50% or greater reduction in the grossly visible tumor. As it is difficult to differentiate between radiographic changes related to the treatment and scar tissue from persisting tumors, we labeled patient outcomes to reflect this uncertainty. Over time, scar tissue remains stable, but persistent tumor tissue will progress, so a patient with radiologic changes that remained stable with no signs or symptoms of disease was considered to be "progression-free". A biopsy was performed only to document recurrence, if indicated. All toxicities encountered during therapy were evaluated according to the Common Terminology Criteria for Adverse Events v3.0 (2003).

Statistical analysis

The major endpoint of the study was overall survival. Additional endpoints included local control rate (local progression-free rate) and toxicity. All patients were closely observed during the follow-up period, the median of which was 4.2 years (range 2.5–8.0 years).

Cases of persistent or recurrent primary or neck disease after completion of RADPLAT were considered to be local or regional failures, regardless of whether salvage was successful. Probabilities of overall survival, which included death from any cause, and local control rates (local progression-free rates computed from the beginning of treatment to the time of local relapse) were calculated by the Kaplan–Meier method.

Results

Patient characteristics

Thirteen patients were entered in this study from February 2001 to June 2008 and were treated by RADPLAT at Hokkaido University Hospital. During the same period, two patients were treated by surgical therapy, three by radiotherapy alone and 12 by intravenous chemoradiotherapy. All patients were male, with a median age of 58 years (range 49–68 years). T and N classification is shown in Table 1. Three patients (23.1%) were diagnosed with T2, four (30.8%) with T3, and six (46.2%) with T4a disease. Lymph node stage was present in 10 patients (76.9%): one with N1, seven with N2b, and two with N2c. Two patients needed a few weeks to prepare to start radiotherapy for some reasons, therefore they received one course of induction chemotherapy prior to radiotherapy; one of these protocols was a combination of vincristine (1 mg/body on day 1 and 2), methotrexate (15 mg/body on day 3 and 4) and bleomycin (10 mg/body on day 5 and 6), while the other was docetaxel (20 mg/m^2). However, there was no remarkable change after induction chemotherapy in both tumors.

Compliance

RADPLAT (three or four infusions of IA cisplatin and a full dose of radiation therapy within 7 days of treatment interruptions) was feasible in 12 patients (92.3%). One patient received two cycles of IA chemotherapy, then pneumonia and poor general health resulted in a 16-day interruption of radiotherapy, which was later resumed.

Toxicity

Acute toxicity was manageable in most patients (Table 2) and none died as a result of treatment toxicity. Eleven patients (84.6%) experienced grade III to IV toxicity. Nonhematologic side effects included dermatitis ($n = 4$), mucositis ($n = 6$), and nausea/vomiting ($n = 3$). No patient had a cerebrovascular accident or neurologic problem. Hematologic toxicity consisted of leukopenia ($n = 4$), anemia ($n = 1$), and thrombocytopenia ($n = 1$).