these patients are presently alive with disease, while two patients who underwent elective neck dissection are alive with no relapse. Finally, one patient developed distant metastasis to meninges 9.1 months after the start of treatment and was dead with disease.

## DISCUSSION

In the present retrospective study, we evaluated the efficacy of IC using TPS followed by PBT concurrent with cisplatin. Of the 10 patients who received PBT concurrent with cisplatin, 9 patients (90%) achieved CR, and the 5-year OS rate was 77.7%, with no brain damage or blindness recorded. Our study suggests that IC with TPS followed by PBT concurrent with cisplatin is well tolerated and displays reducing complication and promising antitumor activity.

The efficacy of chemotherapy for nasal and sinonasal malignancies is unclear (5), as it is generally used for palliative treatment of advanced or recurrent disease. However, favorable responses obtained with various chemotherapeutic regimens have prompted several institutions to modify standard therapeutic approaches in an attempt to improve treatment outcomes. Recently, chemotherapy has been evaluated as part of multimodality therapy delivered in either induction or concomitant settings (17,18). For example, Licitra et al. (17) reported the retrospective analysis of 49 patients with resectable sinonasal cancer who were treated with IC (cisplatin, fluorouracil and leucovorin) followed by surgery and post-operative radiotherapy. The objective response to IC and 3-year OS were 43 and 69%, respectively, suggesting that IC may play a role in surgery-sparing treatment approaches. In a similar study, Lee et al. (18) reported that a subgroup of 16 patients with Stage III or IV sinonasal carcinoma who received IC consisting of three cycles of cisplatin and fluorouracil achieved an 87% clinical response, indicating that IC could be an avenue for further improving the suboptimal results often encountered with reductions in tumors in close proximity with important structures. In the present retrospective study, after the completion of TPS, the overall response rate was 38.4% (5 of 13), with one patient achieving CR and four patients achieving PR. Neutropenia was the most common Grade 3 and 4 hematological toxicity (76.9%), while the most frequently observed non-hematological toxicity was nausea (23.0%). IC of TPS was well tolerated, feasible and showed good antitumor activity, which enabled the reduction in large tumor masses without severe toxicity.

Although squamous cell carcinoma is the most frequent pathology of HNC, olfactory neuroblastoma was most often observed in the present study. We speculate that the dominance of olfactory neuroblastoma among patients was due to referrals from institutions in the surrounding area with limited experience treating this type of carcinoma. Rosenthal et al. (19) reported that patients with olfactory neuroblastoma had excellent local and distant control rates with local therapy alone, but found higher rates of systemic failure for patients with neuroendocrine carcinoma, undifferentiated sinonasal carcinoma and small cell carcinoma. Although data concerning the response of nasal and sinonasal malignancies to IC are limited, several authors have reported the effectiveness of chemotherapy in the treatment of olfactory neuroblastoma, squamous cell carcinoma, undifferentiated carcinoma and adenocarcinoma. In the present study, about half of the patients had olfactory neuroblastoma, and the response rate after the completion of IC followed by PBT concurrent with cisplatin was high. This further emphasizes the need for accurate pathologic diagnosis of nasal and sinonasal malignancies, which may allow the use of separate IC as dictated by the histological analyses.

PBT approaches that would allow decreased irradiation doses to the surrounding critical organs while simultaneously delivering curative high-dose irradiation doses to tumors is critical for minimizing severe complications (5–7). Improvements of local control rates in treatment plans with lower doses to critical organs have been demonstrated when proton plans have been compared with photon plans in patients with nasal and sinonasal malignancies (13–15). Weber et al. (20) examined the long-term toxicity in patients with advanced sinonasal malignancies treated with proton/photon accelerated fractionated radiation and found that at a median dose of 69.6 GyE, 5.6% of the patients developed Grade 3 late visual/ocular toxicity, and no Grade 4–5 late visual/ocular toxicity, vascular glaucoma, retinal detachment or optic neuropathy were observed. Our group previously examined the clinical outcomes of 39 patients with unresectable malignancies treated with PBT at our institution between 1999 and 2006 and demonstrated that most patients experienced Grade 1–2 dermatitis in the acute phase, and 5 patients (12.8%) experienced Grade 3 or greater were observed (12). In the present study, 12 patients received PBT and no brain damage or blindness was recorded. When radiation is combined with concurrent chemotherapy, the acute and long-term side effects are occasionally more pronounced, and greater care and attention to the dose to normal surrounding organs is required for preventing complications. In the present study, 10 patients received PBT concurrent with cisplatin and no brain damage or blindness was recorded, suggesting that IC led to reduced tumor size and PBT could allow the delivery of tumoricidal doses with minimal complications.

Several limitations of the study warrant mention. First, this study includes the inherent limitations of a retrospective study. Second, only a small number of patients with biased histological types of cancer were examined. Here, sufficient doses of chemoradiotherapy without severe complications were achieved using IC and PBT; however, we cannot make definitive conclusions regarding the safety or side effect because of these limitations. Although it is difficult to conduct a prospective study as nasal and sinonasal malignancies are rare, additional patients are needed to confirm these results.

In conclusion, our retrospective analysis revealed that IC with TPS followed by PBT concurrent with cisplatin was well tolerated and effective in patients with locoregionally advanced malignancies of the nasal cavity and paranasal sinuses. This treatment approach demonstrated promising activity and minimal toxicity to warrant Phase II testing and may represent a suitable substitute for chemoradiotherapy alone for patients with T4b nasal and sinonasal malignancies.

## Conflict of interest statement

None declared.

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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 | O | O | O | O |
| Step 2: Moistened wound environment | | Δ | O | O |
| Step 3: Infection prevention | | Δ | Δ | O |

O, 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

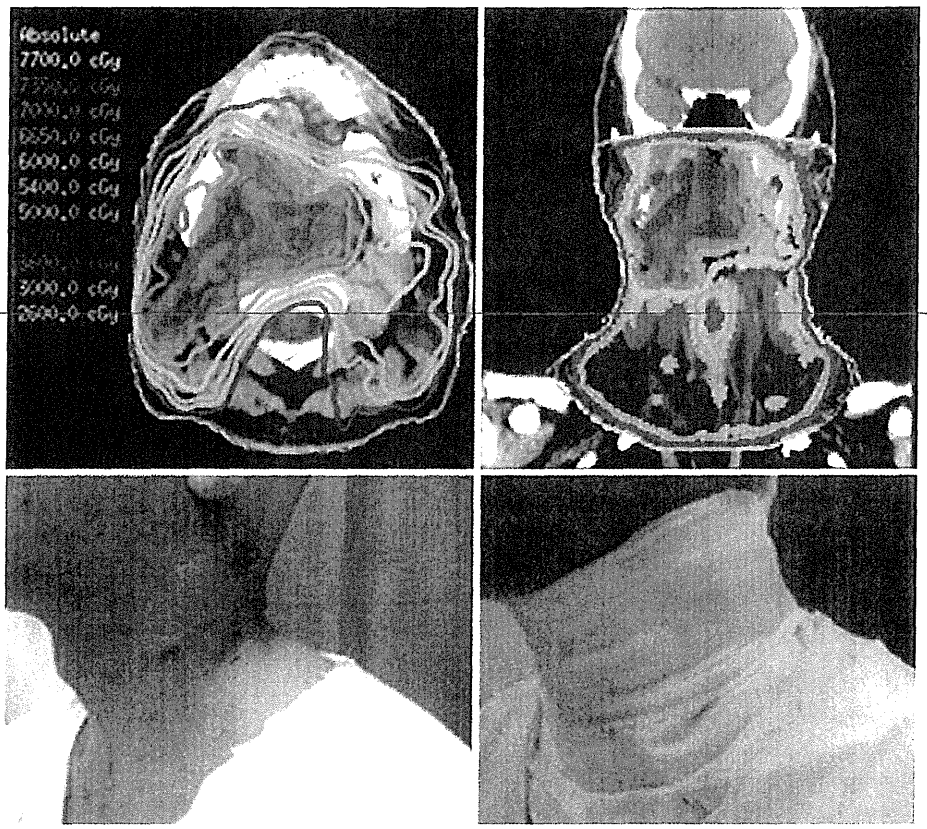


**Fig. 1** Dermatitis Control Program Step 2. The case was a 44-year-old-male with T4N2cM0 oro-pharyngeal cancer. He was treated with induction chemotherapy followed by chemoradiotherapy. The irradiated area was covered with gauze and moistened with dimethyl isopropylazulene. It is very important that 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

**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

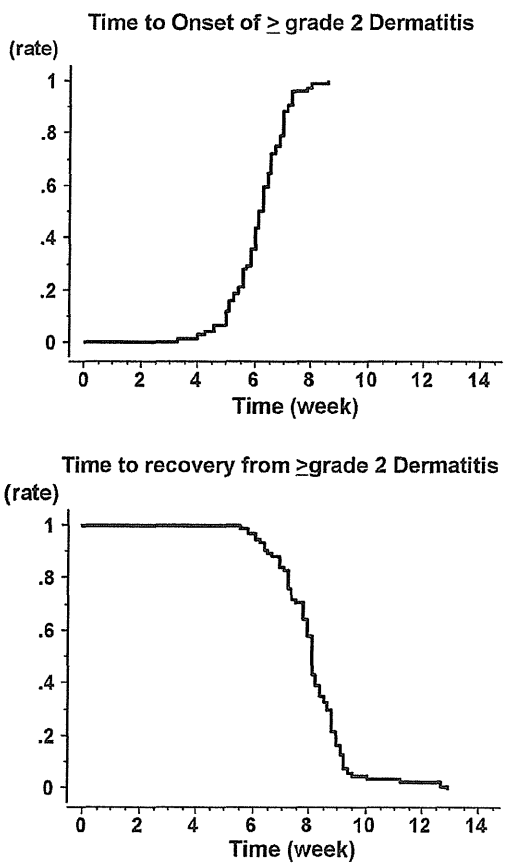


**Fig. 2** Time to onset (upper) and recovery (lower) of > grade 2 dermatitis. Median time to onset of grade 2 dermatitis from the initiation of radiotherapy was 43.5 days (range 23–60 days), and median radiation dose at onset was 61.5 Gy (range 36–70 Gy). In several cases, dermatitis became worse after 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

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.

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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# Radiotherapy for Stage I or II hypopharyngeal carcinoma

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Hypopharyngeal squamous cell carcinoma (HPSCC) is usually diagnosed at an advanced stage, and early-stage HPSCC is relatively rare. Because of the rarity of early-stage HPSCC, few reports have been published on the efficacy of radiotherapy (RT) in its treatment. We retrospectively reviewed the clinical records of 45 consecutive patients with Stage I and II HPSCC from May 1991 to June 2010. Patient characteristics were as follows: median age, 66 years (range, 44–90 years); male/female, 39/6; and T1/T2, 27/18. The irradiation dose ranged from 60 to 72 Gy (median: 70 Gy). Of the 45 patients, 21 underwent concurrent chemotherapy. With a median follow-up period of 62 months, the 5-year overall survival rate was 81%. Local failure occurred in 5 patients, and the 5-year local control rate was 83%. All local recurrences were successfully salvaged by surgery. The 5-year functional larynx preservation rate was 92%. Acute toxicity was manageable. Grade 3 laryngeal edema and Grade 3 hypothyroidism occurred in 1 patient each. No other late adverse events of Grade 3 or greater were observed. Based on these results, RT seemed to be an effective treatment modality for early HPSCC, with favorable organ preservation and acceptable adverse events. Early detection and accurate management of local recurrence and second malignancy was deemed to be critical.

**Keywords:** hypopharyngeal carcinoma; radiotherapy; chemotherapy; larynx preservation

## INTRODUCTION

Hypopharyngeal squamous cell carcinoma (HPSCC) is usually diagnosed in the advanced stage, and early-stage HPSCC is relatively rare. In recent years, mainly owing to the development of laryngeal and gastrointestinal fiberscopes, HPSCC has tended to be found in an earlier stage. Although optimal treatment for early HPSCC has not been established, treatment options have included surgery and radiotherapy (RT) with or without chemotherapy. RT may be the treatment of choice in terms of functional preservation. However, because of the rarity of early-stage HPSCC, few reports have been published on the efficacy of RT. Nakamura *et al.* reported the results of chemoradiotherapy for early HPSCC [1]. In that article, chemoradiotherapy was started in the preoperative setting, and patients who achieved complete response after 30 to 40 Gy irradiation underwent further definitive chemoradiation. The authors reported equivalent disease-specific survival rates for early responders and for patients who underwent chemoradiotherapy and surgery. However, the effectiveness of curative chemoradiotherapy for all patient cohorts remains unclear. Nakamura *et al.* also reported the analysis of questionnaires from 10 institutions regarding early HPSCC treated with curative RT [2]. The authors collected the questionnaires from 115 patients treated between 1990 and 2001. The

results indicated the efficacy of RT for early HPSCC. However, deviation of treatment strategy might have existed in the multi-institutional questionnaire study. In our institution, definitive RT was performed as a first line treatment for Stage I and II HPSCC. Salvage surgery was performed for patients with local recurrence or non-responders. In this study, we retrospectively reviewed our single-institution results for definitive RT in Stage I and II HPSCC.

## MATERIALS AND METHODS

### Patients

From May 1991 to February 2010, 238 patients diagnosed with HPSCC were treated in our Division. Of these, 35 were treated with palliative intent, 2 preoperative, 73 postoperative, and 127 with definitive intent (82 Stage III/IV and 46 Stage I/II) (Table 1). Among the 46 patients with Stage I or II HPSCC, one patient was lost to follow-up after 4 months without any events. In this study, the remaining 45 patients with early (T1–2N0M0) HPSCC who underwent definitive RT were analysed. All patients were followed for at least 12 months or until any events. All patients had histologically proven squamous cell carcinoma. Patient characteristics are summarized in Table 2. There were 39 men and 6 women, with median age of 66 years (range, 44–90 years). Staging work-up included physical examination, laryngoscopy and computed tomography. Esophagogastroduodenoscopy was included as of May 2002, and PET scan was added in November 2006. According to the TNM classification of malignant tumors, 7th Edition [3], there were 27 patients with Stage I (tumor limited to one subsite of the hypopharynx and to ≤2 cm in the greatest dimension), 18 patients with Stage II (tumor that had invaded more than one subsite of the hypopharynx or an adjacent site or measured >2 cm but <4 cm in the greatest dimension, without fixation of the hemilarynx). The primary sites were the pyriform sinus in 35, the posterior pharyngeal wall in 6, and the postcricoid region in 4.

**Table 1.** Patient accrual according to treatment strategy and decade of accrual

| | 1991–2000 | 2001–10 | Total |
|---|---|---|---|
| Preoperative | 2 | 0 | 2 |
| Postoperative | 10 | 63 | 73 |
| Palliative | 17 | 18 | 35 |
| Definitive (Stage III–IV) | 15 | 67 | 82 |
| Definitive (Stage I–II) | 13 | 33 | 46[a] |

[a]One patient was lost to follow-up after 4 months without any events and was excluded from this analysis.

**Table 2.** Patient characteristics

| Characteristics | No. of patients |
|---|---|
| Total no. patients | 45 |
| Gender | |
| Male | 39 |
| Female | 6 |
| Age | |
| Median (range) | 66 (44–90) |
| Tumor stage (from [3]) | |
| Stage I | 27 |
| Stage II | 18 |
| Tumor differentiation | |
| Well | 5 |
| Moderately | 15 |
| Poorly | 5 |
| Unknown | 20 |
| Subsite | |
| Pyriform sinus | 35 |
| Posterior wall | 6 |
| Postcricoid region | 4 |

### Radiotherapy and chemotherapy

All patients underwent RT with radical intent, using 4-MV linear accelerator X-rays. No patient was treated with preoperative intent. A conventional fractionation schedule of 2 Gy/day was used. All patients received prophylactic lymph node irradiation. A prophylactic nodal area (including the retropharyngeal region and supraclavicular nodes) was irradiated up to 40–50 Gy with parallel-opposed lateral fields with a matched anterior lower neck field. The primary lesion was boosted with reduced fields after prophylactic nodal irradiation. The median total irradiated dose was 70 Gy (range: 60 to 72 Gy). Prescriptions for irradiation dose varied in accordance with the treating physician's preference. Concurrent chemotherapy was administered in 21 patients (Table 3). Inclusion criteria for chemotherapy were expanded to T2 disease beginning in the year 2000, and 16 out of 18 patients with T2 disease were treated after 2000; all 16 underwent concurrent chemotherapy. The two patients with T2 disease who were treated before 1999 did not receive chemotherapy. Five out of 27 patients with T1 disease underwent concurrent chemotherapy as per physician's preference. The regimen of chemotherapy is summarized in Table 4. Four patients received adjuvant chemotherapy with TS-1 (Oral fluoropyrimidine consisting of three components: tegafur, a prodrug of 5-FU; 5-chloro-2,4-dihydroxypyridine; and oxonic acid) (80 to 100 mg per body) as a part of feasibility study.

## Follow-up

Patients were followed up monthly for the first year after completion of RT, every 3 months for the following 2 years, and then every 6 months until progression or death. Physical examination and laryngoscopy were performed at every visit. Computed tomography was performed 3 to 6 months after completion of RT, and thereafter performed annually. A PET scanner was installed in our Institute in 2005. PET scan was not performed routinely at follow-up examinations except in cases of suspected disease after computed tomography or physical examination. Esophagogastroduodenoscopy was performed at 1 to 2 year intervals, depending on the findings of routine follow-up examinations.

## Statistical analysis

Survival was calculated from the date of initiation of RT to the date of any events or date last visited. Patients alive without relapse at the time of analysis were censored at their last follow-up. The progression-free survival (PFS) rate was calculated from the date of initiation of RT to the date of histologically-confirmed local recurrence, date of radiographic diagnosis of distant or nodal metastasis, or date of death from any causes. Local control rates and functional larynx preservation rates were calculated from the date of initiation of RT to the date of histologically-confirmed recurrence or date of surgical removal of larynx. Any death without local recurrence was censored for local recurrence. Any death with functional larynx was censored for functional larynx preservation rate. Survival rates were estimated using the Kaplan–Meier method. Univariate analyses with log-rank tests were performed to identify prognostic factors. Radiation dose, treatment interruption, use of chemotherapy, treatment period, tumor location, tumor stage, histological differentiation, age and gender were evaluated. All $P$ values reported are 2-sided. For all statistical tests, differences were considered significant at the 5% level. Commercially available statistical software (StatView, 5.0; SAS Institute, Cary, NC) was used for analysis. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 [4].

**Table 3.** Irradiated dose and chemotherapy

| | 1991–2000 ($n = 13$) | 2001–10 ($n = 32$) | total |
|---|---|---|---|
| Irradiated dose | | | |
| 60 Gy | 5 | 4 | 9 |
| 66–70 Gy | 7 | 28 | 35 |
| 72 Gy | 1 | 0 | 1 |
| Chemotherapy | | | |
| Induction | 0 | 0 | 0 |
| Concurrent | 2 | 19 | 21 |
| Adjuvant | 0 | 4 | 4 |

# RESULTS

## Survivals and larynx preservation

Median follow-up periods for surviving patients and all patients were 62 and 53 months, respectively (range, 12–132 months and 8–132 months, respectively). The 5-year overall survival rate and PFS were 81% and 69%, respectively (Fig. 1). Causes of death were: primary disease (1 patient), other primary cancers (5 patients) and suffocation from aspiration (1 patient). Of the 5 patients who died of other primary cancers, 2 died of synchronous cancer (lung cancer and esophageal cancer), 1 died of recurrent metachronous cancer before treatment of HPSCC (lung cancer) and 2 died of metachronous cancer which arose after completion of the treatment for HPSCC (esophageal cancer and oropharyngeal cancer). Local recurrence occurred in 8 patients, and the 5-year local control rate was 83% (Fig. 2A). All patients with local recurrence were successfully salvaged with surgical resection. Of these 8 patients, 3 were salvaged with laryngeal preservation surgery and 5 were salvaged with laryngectomy. Another 2 patients underwent laryngectomy because of second primary head and neck cancers (cervical esophageal cancer and oropharyngeal cancer). The 5-year functional larynx preservation rate was 92% (Fig. 2B). Three of 7 laryngectomies were performed more than 60 months after initiation of RT (66, 68 and 125 months, respectively). The 6-year

**Table 4.** Chemotherapeutic agents for concurrent chemoradiotherapy

| Chemotherapeutic agents | 1991–2000 | 2001–06 | 2007–10 | total |
|---|---|---|---|---|
| Cisplatin (70–80 mg/m$^2$) | 0 | 4 | 6 | 10 |
| Nedaplatin (70–80 mg/m$^2$) | 0 | 6 | 1 | 7 |
| Cisplatin + 5-FU (Cisplatin, 70 mg/m$^2$ on day 1; 5-FU, 700 mg/m$^2$ on days 1–4) | 1 | 2 | 0 | 3 |
| Low-dose cisplatin (5 mg/m$^2$, daily) | 0 | 1 | 0 | 1 |

5-FU = 5-fluorouracil.

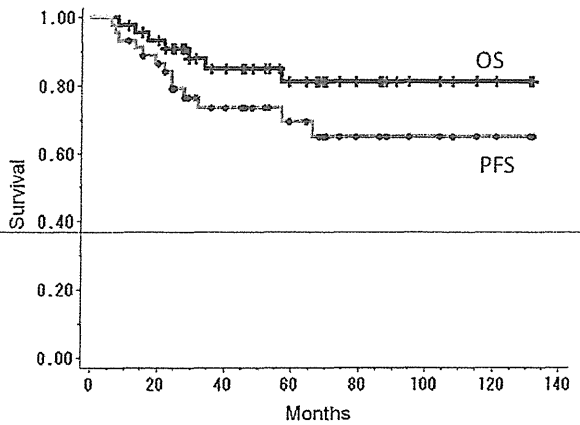


**Fig. 1.** Kaplan–Meier curves of overall survival rate (OS) and progression free survival rate (PFS). The 5-year overall survival rate and progression free survival rate for all patients were 81% and 69%, respectively.

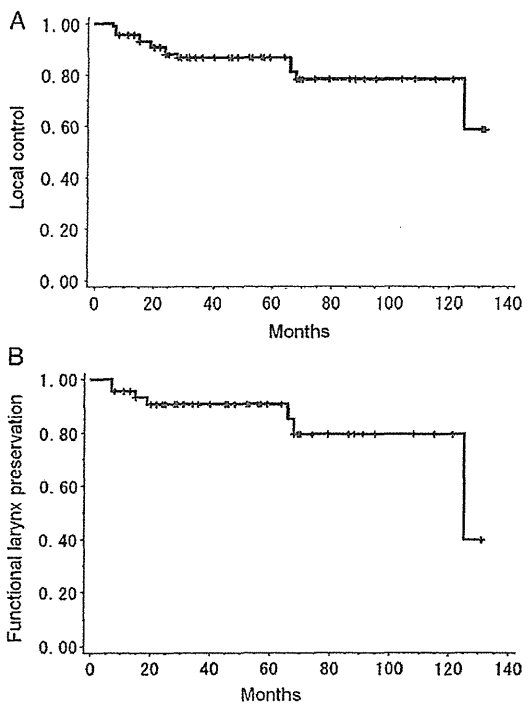


**Fig. 2.** Kaplan–Meier curves of (**A**) local control rate and (**B**) functional larynx preservation rate. The 5-year local control rate and functional larynx preservation rate for all patients were 83% and 92%, respectively.

functional larynx preservation rate was 79%. No cervical node metastasis was observed. Distant metastasis was observed in 1 patient.

## Metachronous malignancies

Eight patients had previously treated metachronous malignancies before initiation of RT for HPSCC. All of these metachronous malignancies were judged to be cured at the time of initiation of RT.

Seven patients had synchronous malignancies. All of these malignancies were diagnosed at non-metastatic stages and were suitable for curative treatment. Six out of 7 synchronous malignancies were treated with RT concurrently with the HPSCC. One synchronous malignancy (esophageal cancer) was treated with endoscopic mucosal resection after completion of RT for HPSCC.

Fourteen patients developed metachronous malignancies in 17 sites during the follow-up period. Two patients received best supportive care (BSC). Patients in whom the other 15 malignancies were diagnosed without disseminated disease were treated with curative intent. Among 14 patients with metachronous malignancies after RT, 1 died of HPSCC, 2 died of metachronous malignancies, 1 died of suffocation from aspiration and 10 were alive and well at the time of analysis (Table 5).

**Table 5.** Synchronous and metachronous malignancies after radiation therapy

| **Synchronous malignancies** | **No. of patients** |
|---|---|
| Esophagus | 4 |
| Larynx | 2 |
| Lung | 1 |
| Treatment | |
| RT | 6 |
| Endoscopic treatment | 1 |
| Metachronous malignancies after RT | No. of patients |
| Esophagus | 6 |
| Oropharynx | 3 |
| Lung | 3 |
| Prostate | 2 |
| Breast | 1 |
| Larynx | 1 |
| Hypopharynx[a] | 1 |
| Treatment | |
| Surgery | 11 |
| Endoscopic treatment | 2 |
| RT | 1 |
| Hormonal therapy | 1 |
| BSC | 2 |

RT = radiation therapy, BSC = best supportive care.
[a]*De novo* carcinoma arising from contralateral pyriform sinus.

**Table 6.** Prognostic factors

| Variable | | 5yr-PFS (%) | *P* value | 5yr-LC (%) | *P* value |
|---|---|---|---|---|---|
| Dose | 60 Gy | 75 | 0.75 | 88 | 0.66 |
| | 66–72 Gy | 68 | | 81 | |
| Interruption | < 5 days | 74 | 0.18 | 84 | 0.55 |
| | ≥ 5 days | 49 | | 74 | |
| Chemotherapy | yes | 67 | 0.96 | 77 | 0.35 |
| | No | 73 | | 87 | |
| Period | 1991–2000 | 62 | 0.41 | 68 | 0.16 |
| | 2001–10 | 72 | | 89 | |
| Subsite | PW | 50 | 0.12 | 50 | **0.01** |
| | Others | 72 | | 72 | |
| Stage | I | 67 | 0.84 | 80 | 0.93 |
| | II | 76 | | 86 | |
| Differentiation | w/d | 0 | **< 0.0001** | 0 | **< 0.0001** |
| | Others | 77 | | 91 | |
| Age | < 70 | 65 | 0.43 | 80 | 0.61 |
| | ≥ 70 | 81 | | 88 | |
| Sex | Male | 65 | NA[a] | 80 | NA[a] |
| | Female | 100 | | 100 | |

PFS = progression free survival, LC = local control rate, PW = posterior wall, w/d = well-differentiated squamous cell carcinoma, NA = not assessed.
[a]*P* value was not assessed because no event occurred in the female arm.

## Prognostic factors

We examined prognostic factors for PFS and local control, including radiation dose, treatment interruption, use of chemotherapy, treatment period, tumor location, tumor stage, histological differentiation, age and sex (Table 6). We found that well-differentiated squamous cell carcinomas ($n = 5$) were poor prognostic factors for PFS and local control ($P < 0.0001$). Tumors of the posterior wall ($n = 6$) were also associated with poor prognosis for local control ($P = 0.01$) (Fig. 3). The other factors did not show significant impact on PFS or local control.

## Morbidity

No patient required a feeding tube or intravenous hyperalimentation during and after treatment. In the late period, laryngeal edema of Grade 3 (requiring temporal tracheostomy) was observed in 1 patient, and Grade 3 hypothyroidism (myxedema) was observed in 1 patient. The Grade 3 hypothyroidism was treated with levothyroxine sodium (Thyradin S). No other late toxicity of Grade 3 or greater was documented (Table 7).

Twenty-one patients underwent concurrent chemotherapy. Renal and hematologic toxicities related to chemotherapy were manageable (Table 7). Only 1 patient experienced febrile neutropenia.

## DISCUSSION

Although several authors have reported the outcomes of RT for HPSCC, patients with Stage I and II hypopharyngeal cancer were relatively small cohorts in these studies [5–7]. In general, either RT or surgery with or without laryngeal preservation is selected as the initial treatment for T1–2 HPSCC. However, there have been only a few reports focusing on the efficacy of RT for early-stage hypopharyngeal cancer, and the optimal treatment approach remains controversial. RT has been recognized as an effective treatment modality for HPSCC. Mendenhall *et al.* achieved excellent local control in 80% of patients with T1–2 pyriform sinus carcinoma treated with RT alone [5]. Later, Amdur *et al.* also reported the results of RT for T1–2 pyriform sinus [6]. They included 101 patients with T1–2 carcinoma of the pyriform sinus and achieved local control rates for T1 and T2 tumors of 90% and 80%, respectively. However, of 101 patients, only 25 patients had Stage I or II disease. Their report showed relatively poor 5-year overall survival rates (57% for Stage I, 61% for Stage II, respectively). It was

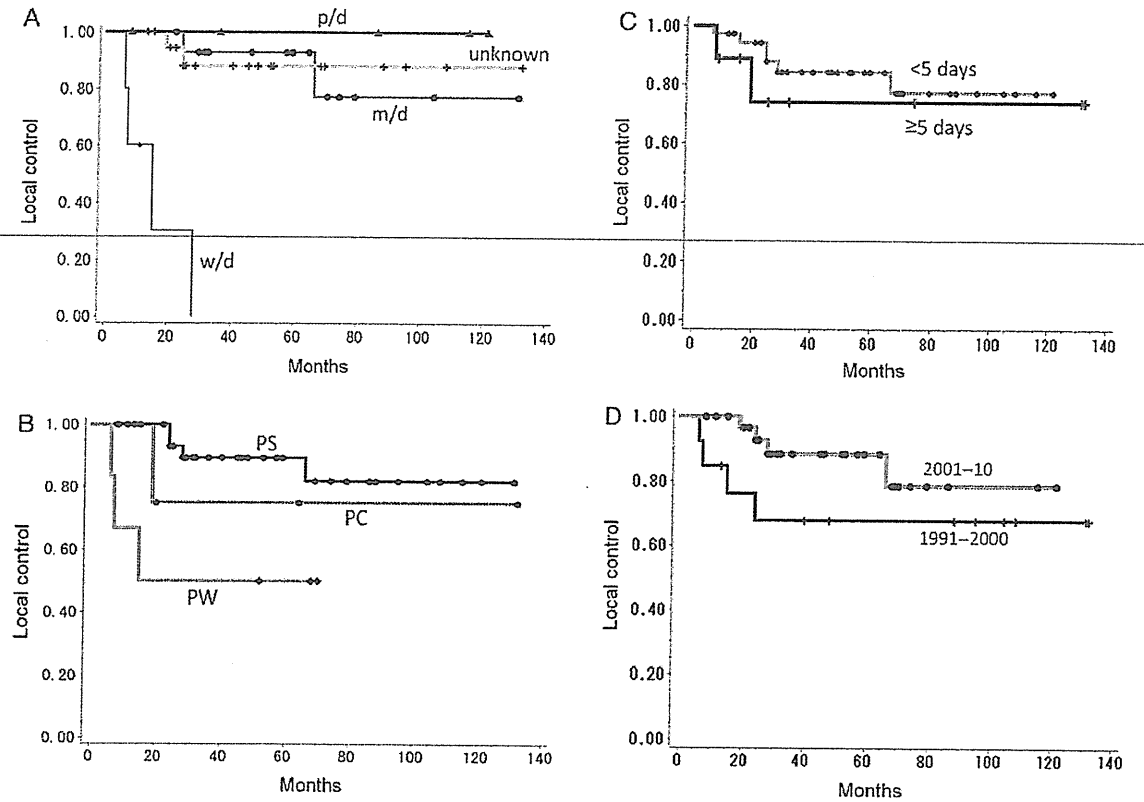


**Fig. 3.** Kaplan–Meier curves of local control rate according to (**A**) histological differentiation, ($P<0.001$), (**B**) tumor location ($P=0.01$), (**C**) treatment interruption ($P=0.55$), (**D**) treatment period ($P=0.16$). p/d = poorly differentiated squamous cell carcinoma, m/d = moderately differentiated squamous cell carcinoma, w/d = well-differentiated squamous cell carcinoma, PS = pyriform sinus, PC = postcricoid region, PW = posterior wall.

**Table 7.** Toxicity profiles (grade 3/4 toxicities)

| Concurrent Chemotherapy | yes ($n=21$) | no ($n=24$) |
|---|---|---|
| | No. of patients (%) | No. of patients (%) |
| Early | | |
| Renal dysfunction | 0 (0) | 0 (0) |
| Neutropenia | 4 (18) | 0 (0) |
| Anemia | 0 (0) | 1 (4) |
| Thrombocytopenia | 2 (9) | 0 (0) |
| Febrile neutropenia | 1 (4.5) | 0 (0) |
| Late | | |
| Thyroid dysfunction | 0 (0) | 1 (4) |
| Laryngeal edema | 0 (0) | 1 (4) |

difficult to determine the long-term efficacy of RT for early-stage HPSCC. Garden *et al.* reported that the 2-year actuarial local control rate for T1 and T2 tumors after RT alone was 89% and 77%, respectively [8]. These reports included patients with neck node metastasis, and neck nodes were managed with or without neck node dissection. Because these reports contained node-positive patients, the survival period was short. It may be difficult to elucidate the exact long-term benefit of RT for node-negative HPSCC, although these reports suggest the efficacy of curative RT for primary lesions. In our series, definitive RT resulted in a comparable local control rate (83%) in a neck node-negative patient cohort that achieved a relatively longer overall survival rate of 81% with a median follow-up period of 62 months.

In our series, all patients received prophylactic nodal irradiation and no patient experienced cervical node metastasis. Compared to other reported series for early stage HPSCC (Table 8), the nodal control rate in our study seemed to be favorable. There appears to be some potential benefit of prophylactic irradiation for early stage HPSCC. Local recurrence occurred in 8 patients. The incidence of local recurrence was comparable to other studies. All local recurrence was successfully salvaged with surgery. Early detection and adequate management for local recurrence seemed to be critical.

**Table 8.** Comparison of prophylactic irradiation, loco-regional control, and salvage surgery

| Series | Treatment period | No. of Pts | median f/u (M) | 5yr-OS (%) | Prophylactic RT yes/no | Prophylactic dose (Gy) | No. of nodal rec. | No. of local rec. | No. of salvage sx for local rec. |
|---|---|---|---|---|---|---|---|---|---|
| Nakamura[a] [1] | 1976–2002 | 43 | 52 | 70 | 35/8 (81%) | 30–50 | 3 (7%) | 2 (5%) | 2 (100%) |
| Nakamura[b] [2] | 1990–2001 | 115 | 47 | 66 | 90/25 (78%) | 36–50 | 14 (12%) | 30 (26%) | 26 (87%) |
| Yoshimura [10] | 1988–2007 | 77 | 33 | 47 | 66/11 (86%) | 20–50 | 11 (14%) | 16 (21%) | 12 (75%) |
| Current study | 1991–2010 | 45 | 53 | 81 | 45/0 (100%) | 40–50 | 0 (0%) | 8 (18%) | 8 (100%) |

[a]Eleven of 43 patients received surgery after 30–40 Gy irradiation.
[b]Questionnaire collected from 10 institutions.
Pts = patients, f/u = follow-up period, M = months, OS = overall survival rate, RT = radiation therapy, rec. = recurrence, sx = surgery.

In our series, 5 patients died of second primary cancers. Yoshimura *et al.* also reported a high incidence of synchronous and metachronous malignancies [9]. In their report, patients with metachronous malignancies had poorer survival outcomes. In our series most metachronous malignancies were diagnosed at non-metastatic stages, and curative treatments were performed. Out of 14 patients with second malignancies, 9 were successfully treated and were alive and well at the time of analysis. We believe close follow-up and accurate management of local failure and metachronous malignancies can provide better outcomes. Careful follow-up and early detection of local recurrences and other malignancies are critical for survival and larynx preservation.

Several authors have reported the additional benefit of chemotherapy for advanced head and neck cancers [10–13]. However, the additional benefit of chemotherapy for early HPSCC remains controversial. Use of concurrent chemotherapy for these tumors differed among the reported articles. While Yoshimura reported that only 16 of 77 patients received concurrent chemotherapy [9], Nakamura reported that 39 of 43 patients received concurrent chemotherapy [1]. Inclusion criteria for concurrent chemotherapy were not documented in these articles. In our series, the treatment strategy included concurrent chemotherapy for T2 disease beginning in the year 2000. Chemotherapeutic agents were varied during the two decades of our study period. Since 2007, cisplatin alone has been the mainstay in our Institute. Out of 18 patients with T2 disease in our series, 16 were treated after 2000. All 16 underwent concurrent chemotherapy. In our results, T2 disease had a local control rate comparable with that of T1 disease. Thus, there may be some potential benefit of chemotherapy for T2 disease. T2 disease has a relatively wide range of tumor sizes (2 to 4 cm) and it may prove that concurrent chemotherapy is beneficial for larger tumors. However, it is still difficult to address the exact benefit of chemotherapy because of small sample sizes and lack of randomized data. Though adverse events related to chemotherapy were manageable, it is important to avoid unnecessary use of chemotherapy in patients who are likely to have tumor control with RT alone.

Well-differentiated squamous cell carcinoma and posterior wall tumors had poor outcomes for local control. Though these patients were a small cohort in our series, the poorer local control in posterior wall tumors was compatible with the report of Yoshimura *et al* [9]. Exact reasons for the poorer outcome in posterior wall tumors and well-differentiated tumors remain unclear. We might consider a more aggressive treatment strategy for these kinds of high-risk tumors, such as concurrent chemotherapy or volume-reduction surgery prior to RT.

Several authors have reported results of laryngeal preservation surgery for selected patients [14–17]. Though these reports also include node-positive disease, and it would be difficult to compare the long-term efficacy and local control rate with our result, they seemed to obtain comparable local control rates. However, postoperative mortality and morbidity is not negligible. Postoperative death rates of 2 to 10% were reported, and persistent swallowing difficulties and speech impairment were also reported. Radical RT for early-stage HPSCC may have some mortality and morbidity advantage in treatment without reducing local tumor control.

No patients in our series were treated with intensity-modulated RT (IMRT). IMRT is a conformal RT technique that can spare the major salivary glands and may reduce the incidence of long-term radiation-induced xerostomia. All patients with preserved larynxes in our series maintained ability in speech and swallowing. However, lack of saliva affects quality of life (QoL). Recently, the result of a randomized trial comparing conventional RT and parotid-sparing IMRT for head and neck cancers was reported [18]. Parotid-sparing IMRT was found to reduce the incidence of xerostomia and improve QoL. Because of the expected longer survival for early HPCSS, IMRT may be beneficial and should be considered for these patients.

## CONCLUSION

In conclusion, RT for early HPSCC is deemed to be a feasible and effective treatment modality with minimal morbidity. In our cohort, 81% 5-year overall survival and 91%

functional larynx preservation rates were obtained during a follow-up period of 62 months. Salvage surgery with or without larynx preservation was reserved for recurrent disease. Early detection and adequate management of local recurrence and metachronous malignancies are critical in obtaining longer survival.

## ACKNOWLEDGEMENTS

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C 下咽頭がん

# 2. Planned Neck Dissection の EBM とは？

## 1 序論

Planned Neck Dissection（PND）は1986年にMendenhallら[1]が報告した頸部リンパ節転移陽性頭頸部がんに対する治療戦略である．原発巣が放射線療法により制御可能と判断され，なおかつ頸部リンパ節転移巣の制御が放射線療法では困難と推測される症例をその治療対象としている．リンパ節に対する治療が奏効したかどうかにかかわらず，放射線治療終了後に急性期反応の消退を待って，放射線治療前からの計画どおりに頸部郭清術を行うため，その戦略的側面からplanned neck dissectionとよばれる．本邦では計画的頸部郭清術という表現が用いられることが多い．

下咽頭がんに対する治療戦略として，同時併用化学放射線療法（concurrent chemo-radiotherapy: CCRT）の占める割合は近年増加しているが，従来より原発巣と比較して頸部リンパ節転移巣の制御は不良なことが知られている．下咽頭がんに対するPNDは，放射線治療の弱点を観血的に補完して頸部のコントロールを改善することを目的としており，CCRTと併せて行うことにより喉頭温存治療の一翼を担うものである．

## 2 指針

下咽頭がんにおいては，原発巣が比較的限局している状態でもすでに頸部リンパ節転移をきたしていることがまれではない．したがって下咽頭がんに対するPNDの最もよい適応となるのは，原発巣と頸部転移巣の組み合わせが下記のような症例である．

原発巣: 手術による喉頭温存は困難であるがCCRTによる制御が十分に期待される，T2症例と一部のT3症例，手術を希望しないT1症例．

頸部転移巣: 化学放射線療法での制御が困難と思われるN2-3症例．

T4症例では原発巣の制御が不安定であるため慎重にならざるを得ない．またN 0-1症例では一般的にPNDの必要性は指摘されていない．通常は原発巣がCCRTにより消失していることを確認したうえで，CCRT終了後4～12週目に奏効の有無を問わず頸部郭清術を施行する．

## 3 エビデンス

### 1 頭頸部がんに対するPNDの有用性

Grabenbauerら[2]は口腔がん，中下咽頭がんに対するCCRT後の頸部リンパ節再発は下咽頭がんで最も多く，下咽頭がんに関してはPNDを含めた積極的な治療が必要であると報告している．またArgirisら[3]は，N2-N3頭頸部がんに対してPNDを行うこ

とで少なくともlocoregional control rateを改善すると報告しており，さらにBrizelら[4]はPNDが生存にも寄与すると報告している．Mukhija[5]らは根治的な照射後であれば，選択的頸部郭清でも全頸部郭清と同等の成績が得られると報告している．

### 2 CCRT後完全奏効症例への対応

Lavertuら[6]の報告では，N2-3症例のPND切除標本で，照射後に完全奏効と判定された群で22%，非完全奏効群で47%にpathological positive nodeを認めたとしている．Corryら[7]は，頸部リンパ節のみに再発してくる症例は少なく，通常は遠隔転移を伴って再発してくる場合が多いと報告している．同様にFerlitoら[8]は，PNDが有用とする24の報告とPNDの有用性は低いとする26の報告を分析し，結論としてCCRTで完全奏効した症例では頸部単独で再発をきたす割合は低く大部分で遠隔転移を伴うため，PNDを漫然と施行するべきではないと結論づけている．

### 3 再発確認後に行う救済手術との比較

Mabantaら[9]は頸部リンパ節転移の増悪確認後では多くの症例（65%）で救済手術が行えないと報告しており，Stensonら[10]やLavertuら[11]はPNDの方が合併症は少なく，頸部再発後の救済手術のほうが合併症の頻度が高いとしている．

### 4 CCRT後の画像診断

Brizelら[4]は，臨床評価と病理学的結果は必ずしも相関しないと報告している．またFDG-PETについて，Schechterら[12]はCCRT後に腫瘍へのFDGの集積低下があるため偽陰性となることがあると報告しており，一方でTanら[14]はPETでの陽性所見よりもむしろ陰性所見が頸部コントロールの予測に重要であると報告している．Gourinら[15]は，SUV（standardized uptake value）と病理組織学的所見あるいはリンパ節サイズに関連は認められなかったと報告しており，CCRT後の画像評価法として支持されるには至っていない．

### 5 NCCN（National Comprehensive Cancer Network）ガイドライン（2009）

下咽頭癌T1, N＋; T2-3, any N症例において，同時併用化学放射線療法により原発巣と頸部リンパ節転移巣が完全奏効した場合，頸部リンパ節に対して最低でも12週毎のPET，CE-CTかMRI，診察を行い，転移が出現しなければ経過観察を，転移が確認されれば頸部郭清術を行うよう推奨している．ただしT1N1症例やT2-3N0-1症例もこのカテゴリーに含まれており，またPNDについては触れられていないため，参考にとどめる．

## ④ 根拠となった臨床研究の問題点と限界

そもそも大部分の報告においては検討の対象となる原発巣が多岐にわたっており，そのデータを下咽頭がんにそのまま当てはめることができない，また後向きの検討が大部分であり，前

向きの臨床研究も必要であろう．対象症例中に占める下咽頭がん症例の割合が低い報告では，特にその解釈に注意を要する．また放射線治療における技術的な問題として，中咽頭がんでは原発巣と頸部転移巣を含めた標的体積に均一に根治線量を投与することが比較的容易であるが，対側を含めた多領域への転移をきたしやすい下咽頭がんでは標的体積の凹凸や頭尾側方向の長さから線量分布が不均一となり，さらに危険臓器の線量制約から頸部転移巣への十分な線量投与が困難な場合があることもあげられる．

CCRT後の頸部再発症例では遠隔転移を伴っていることも多く，PNDが大きく生存率に寄与するというエビデンスを得ることは困難であろう．しかしながら非生存例に対する配慮が切り捨てられるべきではない．すなわち，PND施行例と非施行例では再発から死に至るまでの臨床経過やQOLが異なってくる可能性が浮かび上がってくる．頸部再発がもたらす本人・家族・医療従事者らの苦痛（疼痛・出血・悪臭・処置）については，臨床研究などでは通常あまり取り扱われず評価されない．

## ❺ 患者に適応する際の注意点

前述したように，文献によって対象患者が大きく異なっており治療強度も違うため，PNDの施行あるいは省略にあたっては各施設で行っている化学放射線療法がどの報告文献と合致あるいは類似しているかを十分に比較検討すべきである．また放射線治療は我々が漠然と想像しているほど均てん化されたものではなく，導入機材や放射線治療医によって照射野や照射線量の配分が異なることに注意を払う必要がある．一連の治療の中にPNDを組み込むのか，あるいはあくまで照射での完全奏効を目標とするのか，放射線治療医との協議をできれば十分に行いたいところである．併用する化学療法の種類や併用回数についてもしかりである．

明らかな頸部再発を確認した後に施行する救済手術では，照射後早期に施行するPNDと比較して線維化や瘢痕化が高度であり，合併症の増加のみならず手術手技的にも困難な傾向がみられる．PNDを施行するにあたっては，治療開始以前からその長所・短所を十分に理解しておく必要がある．

## ❻ コメント

近年の放射線治療では抗がん剤の併用や照射技術の向上に伴って局所頸部制御率は上昇し，画像診断技術の向上により照射後転移診断の精度も改善されつつある．今後はさらなる診断・治療技術の向上により，真にPNDを行うべき症例を絞り込んで不必要な手術は省略すべきとの方向に戦略は変換されていくであろう．しかしながらASCO（American Society of Clinical Oncology）の喉頭がんに対する機能温存治療ガイドライン[13]にある下記内容について，2006年の報告ではあるがその思考課程や患者対応を含めて治療者は十分に留意すべきと思われる．

「根治的放射線療法や化学放射線療法を受けたN2, N3症例に対する手術は，その反応いかんによらず推奨される．一部の外科医や患者は手術に伴う死亡リスクや大部分の症例で病理組織学的検索により転移がないことが見込まれることを根拠として頸部郭清術に対し意欲的ではないが，照射後という状況下の転移診断に関して意志決定に明確に寄与し得る標準的な画像評価法は確立されていない．またこのような状況下で頸部再発に対して行われる救済手術は，成

功に導かれる可能性が低い，上記の二点については，放射線治療もしくは化学放射線治療により臨床上完全奏効と判断されて希望的に経過観察を選択したすべての患者と討論しておくべきである.」

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