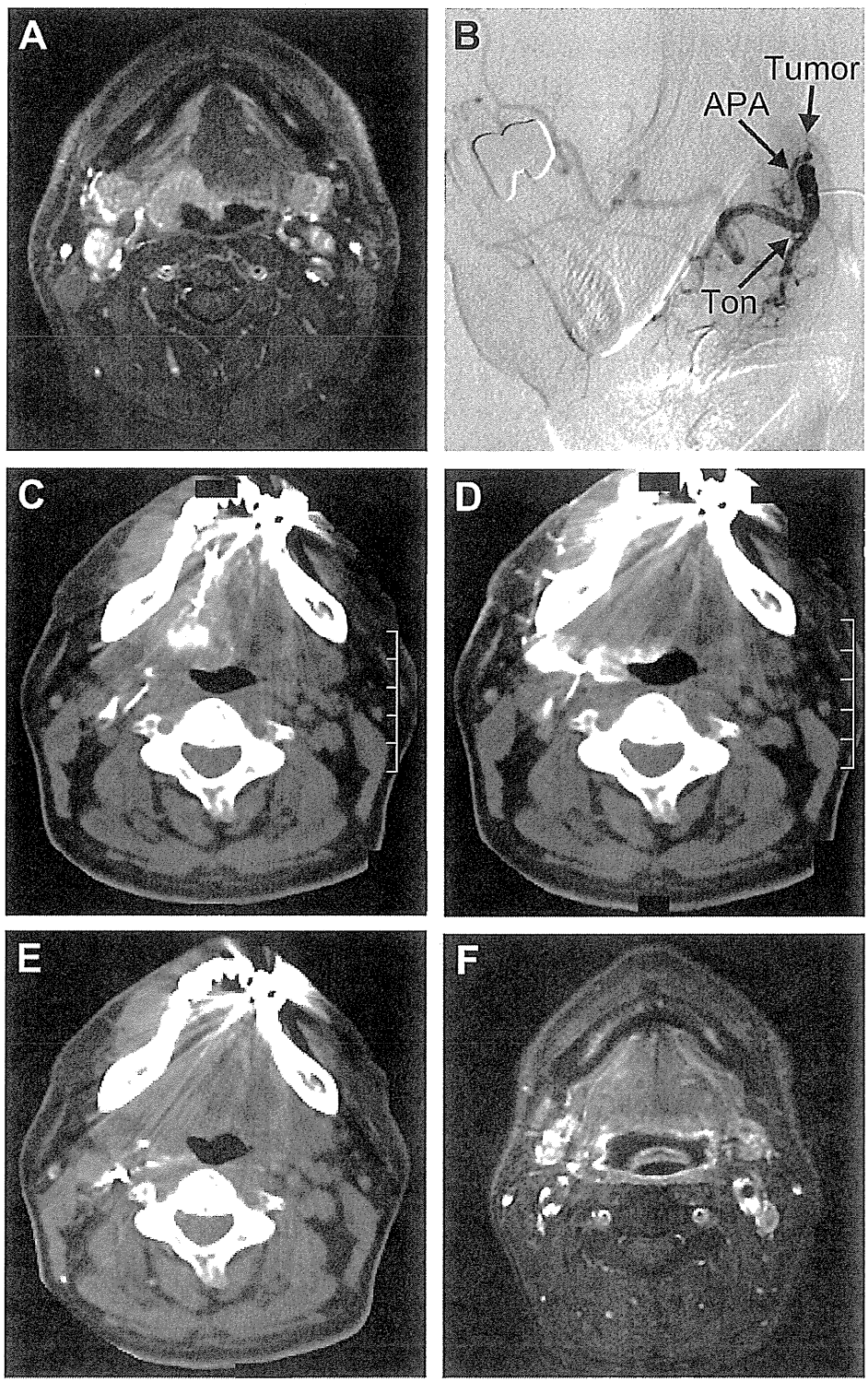

Figure 1 (A) MRI findings from a 58-year-old man with a right BOT cancer classified as T3N2bM0. (B) Lateral subtraction angiogram of right facial artery. Ascending palatine artery (APA) and tonsillar branch (Ton) supply tumor with blood. (C) Intra-artery computed tomographic arteriography (IA-CTA) of right tongue artery demonstrates tongue base tumor with enhancement in anterior but not posterior portion. (D) IA-CTA of right facial artery indicates that tumor in posterior of tongue base and tonsil was enhanced. (E) IA-CTA of right ascending pharyngeal artery indicates that residual of tonsillar tumor and posterior wall of pharynx were enhanced. (F) MRI indicates disappearance of tumor after therapy.

Osteonecrosis of the mandibule occurred in one patient as a late adverse reaction. This patient suffered grade 2 osteonecrosis despite prophylactic dental extractions prior to treatment, which was manageable with minor sequestrectomy.

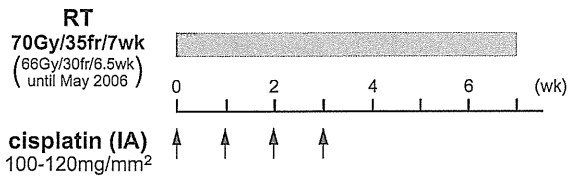

Figure 2 Treatment schedule of RADPLAT.

Table 1
T and N classification ($n = 13$).

T classification	Number of patients by N classification					Total
	0	1	2a	2b	2c	
2	1			2		3
3		1		3		4
4a	2			2	2	6
Total	3	1		7	2	13

Six patients required a feeding-tube (PEG or nasogastric tube) during treatment over a period of time that ranged from 0 to 47 days (median 15 days, mean 16 days). All surviving patients achieved normal swallowing without a feeding-tube after treatment.

Two patients received a tracheotomy during radiotherapy or at the time of salvage neck dissection. Both cases were able to decannulate.

Response of the primary disease and neck disease

All patients achieved a CR in the primary site. Three patients classified as N0 prior to therapy did not develop neck metastases after RADPLAT. Among the 10 patients with positive neck disease, six were well controlled by RADPLAT without surgery. Four patients underwent a neck dissection after treatment for a suspicious residual lymph node. As a result, viable tumors were seen in the surgical specimens of two patients.

Local control, overall survival and relapse

The 5-year local control and overall survival rate was 92.3% and 90.9% for all patients, respectively (Figure 3).

No patient has suffered distant metastasis to date. One patient had a recurrent tumor at the primary site and neck simultaneously. This patient did not wish to receive further therapy and later died.

Discussion

Historically, BOT cancer has been excised through complicated transmandibular or transpharyngeal approaches, sometimes resulting in the development of severe dysphagia and speech disorders. Total glossectomy with total laryngectomy is also frequently performed for advanced BOT cancers, and can result in difficulties with swallowing and speech. Moreover, the survival rate of patients with advanced BOT cancers treated by surgery is far from satisfactory.[13,14]

Recently, transoral laser microsurgery (TLM) has been used to treat BOT in several institutions.[15–17] TLM combined with neck dissection and postoperative radiotherapy achieved a good survival rate and improved the quality of life in patients with early stage cancers. Steiner et al. reported a 5-year overall survival rate of 52% among 48 patients including 28 (58%) with T4 disease,[17] while Grant et al. observed a 5-year overall survival rate of 38% in T4 patients.[16] Camp et al. reported a 2-year overall survival rate of 90% (T0–2 and T3–4 accounted for 74.6% and 25.3% of the patients treated, respectively).[15] However, this combined modality therapy was ineffective for patients with advanced stage cancer.

The advantages of radiation therapy over surgical therapy in the treatment of BOT cancer are controversial, with some studies showing improved swallowing and speech after radiotherapy compared with surgical therapy.[18,19] However, other studies found no significant difference in the survival rate between patients treated by surgery and radiation alone, including those patients with advanced stage tumors.[14,19–21]

CRT is a powerful tool for BOT cancer as well as other head and neck cancers. Several single-institution studies have reported a good outcome for patients treated with various regimens of CRT.[22–25] Among these, excellent 2-year overall survival rates of 90% were demonstrated in patients receiving high-dose cisplatin (100 mg/mm^2).[22] However, toxicity was much increased compared with other regimens, and some patients developed esophageal strictures or stenosis that required supportive feeding through a feeding-tube.

Combined therapy of external beam irradiation and brachytherapy has been reported to be effective by Cano et al. and Harrison et al., who showed a 3-year overall survival rate of 80.9% and a 5-year overall survival rate of 86%, respectively.[26,27] Not all BOT cancers have good indications for brachytherapy, however, particularly those tumors extending below the hyoid bone, into the preepiglottic space or posterior pharyngeal wall, or involving mandibular bone. Harrison et al. reported that 15–20% of cases are not oncologically suitable for brachytherapy.[27] Furthermore, a skilled radiation oncologist is required to accurately place the implant.

To date, we have performed RADPLAT for over 240 advanced head and neck cancers, including BOT cancers, and achieved good survival and local control rates.[12] In this study, we obtained an excellent 5-year overall survival and local control rate of 90.9% and 92.3%, respectively. Of the six patients with T4a tumors treated by RADPLAT, five (83.3%) survived with no recurrence. RADPLAT

Table 2
Acute toxicity ($n = 13$).

Toxicity	Number of patients by toxicity grade			
	1	2	3	4
Hearing	1		1	
Anemia	7	5	1	
Leukopenia	3	5	4	
Thrombocytopenia	4	1	1	
Fever	2	3	4	
Dermatitis	2	7	3	1
Nausea/vomiting	5	3	3	
Mucositis	1	6	5	1
Liver dysfunction	5	2		
Renal	1			

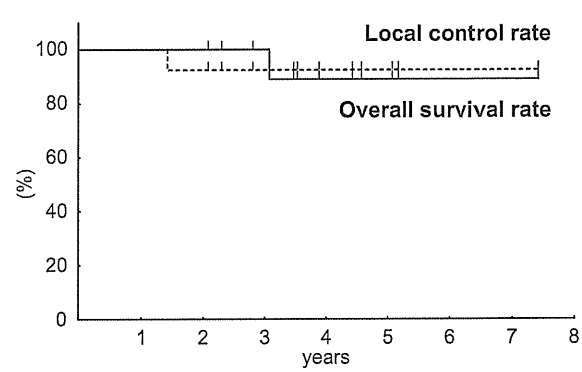

Figure 3 Local control and overall survival rate of 13 patients with BOT cancers.

was comparable to intravenous chemoradiation in toxicity and in functions of swallowing and speech after treatment. Furthermore, pharyngeal esophageal stricture, which is relatively common complication associated with many chemoradiation protocols, was not detected in this study. Although IA chemotherapy is sometimes regarded as dangerous because of the risk of catheter-related problems, cerebrovascular accidents and severe systemic compli cations, no treatment-related deaths or cerebrovascular accidents were encountered in the present study; indeed only one such case out of 240 has occurred at our institution, and this achieved a full recovery.

To demonstrate the maximum efficacy of RADPLAT and to prevent the risk of side effects, we suggest that the tumor should receive the simplest possible blood supply. BOT cancers are usually covered by the lingual artery, which is a good indication for RADPLAT. However, depending on the invasive area of the tumor, a more careful selection of the artery to be injected may be necessary. To determine which artery should be injected, we utilize IA-CTA, which is highly effective in determining the exact perfusion area of each artery and achieving flexible real time coordination of the cisplatin dose. For example, if the tumor has infiltrated over the midline, or progressed to an epiglottic vallecula, the patient should receive infusion into the contralateral lingual artery (7/13 patients of this study) or the superior thyroid artery (7/13 patients of this study), respectively. Similarly, if the tumor has progressed to a lateral pharyngeal wall, or posterior pharyngeal wall, the patient should receive infusion into the facial artery (8/13 patients of this study), or the ascending pharyngeal artery (2/13 patients of this study), respectively.

In this study, the response of the neck disease was good. Six patients with regional lymph node metastasis received direct infusion to lymph node through the occipital artery (4 cases) or the superior thyroid artery (2 cases). Five of the six patients achieved a CR in the neck disease, including one case of pathological CR after neck dissection. And the remaining four patients, who had relatively-small lymph nodes, without direct infusion to them were all controlled without neck dissection. This result suggests that the anticancer drugs flow to regional lymph node via the primary tumor.

A previous multicenter, randomized phase 3 trial of 239 patients with advanced head and neck cancer in the Netherlands concluded that IA chemoradiation was not superior to intravenous chemoradiation.[28] However, in an unplanned subgroup analysis, the authors observed a significantly higher local and locoregional control rate and disease free survival rate for IA treatment of large (>30 mL) lateralized tumors. This result is consistent with our experience. However, the Dutch study did not specify where and how cisplatin was administered intra-arterially, with no mention of the angiographic technique. This is of some concern, since the type of administration would obviously influence the treatment outcome.

Our study found that RADPLAT gave excellent survival rates and organ functions compared to systemic chemoradiotherapy. However, it was limited by a small sample size, a short follow-up period and a single institution experience, so a multi-institutional trial is needed to prove that this strategy is feasible and effective for patients with BOT cancer.

Conclusion

RADPLAT can result in good organ function and cure the majority of patients with advanced BOT cancers. Toxicity was manageable in the current study, and no patient died as a result of treatment toxicity. BOT cancer is a good indication for RADPLAT to enhance the efficiency of chemotherapy and minimize side effects. We fully expect RADPLAT to become a powerful alternative in the treatment of advanced BOT cancer.

Conflict of interest statement

None declared.

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References

1. Harrison LB, Ferlito A, Shaha AR, Bradley PJ, Genden EM, Rinaldo A. Current philosophy on the management of cancer of the base of the tongue. *Oral Oncol* 2003;**39**(2):101–5.
2. Malone JP, Stephens JA, Grecula JC, Rhoades CA, Ghaheri BA, Schuller DE. Disease control, survival, and functional outcome after multimodal treatment for advanced-stage tongue base cancer. *Head Neck* 2004;**26**(7):561–72.
3. Glick JH, Taylor 4th SG. Integration of chemotherapy into a combined modality treatment plan for head and neck cancer: a review. *Int J Radiat Oncol Biol Phys* 1981;**7**(2):229–42.
4. Marcial VA. Ninth annual del Regato lecture: optimal multidisciplinary management of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1987;**13**(3):393–401.
5. Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Werning JW, Villaret DB. Definitive radiotherapy for squamous cell carcinoma of the base of tongue. *Am J Clin Oncol* 2006;**29**(1):32–9.
6. Al-Sarraf M, Pajak TF, Marcial VA, Mowry P, Cooper JS, Stetz J, et al. Concurrent radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck. An RTOG study. *Cancer* 1987;**59**(2):259–65.
7. Merlano M, Benasso M, Corvo R, Rosso R, Vitale V, Blengio F, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 1996;**88**(9):583–9.
8. Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst* 1994;**86**(4):265–72.
9. Homma A, Furuta Y, Suzuki F, Oridate N, Hatakeyama H, Nagahashi T, et al. Rapid superselective high-dose cisplatin infusion with concomitant radiotherapy for advanced head and neck cancer. *Head Neck* 2005;**27**(1):65–71.
10. Robbins KT. The evolving role of combined modality therapy in head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2000;**126**(3):265–9.
11. Robbins KT, Kumar P, Wong FS, Hartsell WF, Flick P, Palmer R, et al. Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. *Head Neck* 2000;**22**(7):687–93.
12. Homma A, Oridate N, Suzuki F, Taki S, Asano T, Yoshida D, et al. Superselective high-dose cisplatin infusion with concomitant radiotherapy in patients with advanced cancer of the nasal cavity and paranasal sinuses: a single institution experience. *Cancer* 2009;**115**(20):4705–14.
13. Gourin CG, Johnson JT. Surgical treatment of squamous cell carcinoma of the base of tongue. *Head Neck* 2001;**23**(8):653–60.
14. Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB, et al. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. *Cancer* 2002;**94**(11):2967–80.
15. Camp AA, Fundakowski C, Petruzzelli GJ, Emami B. Functional and oncologic results following transoral laser microsurgical excision of base of tongue carcinoma. *Otolaryngol Head Neck Surg* 2009;**141**(1):66–9.
16. Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC. Carcinoma of the tongue base treated by transoral laser microsurgery, part one: untreated tumors, a prospective analysis of oncologic and functional outcomes. *Laryngoscope* 2006;**116**(12):2150–5.
17. Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. *Arch Otolaryngol Head Neck Surg* 2003;**129**(1):36–43.
18. Boscolo-Rizzo P, Stellin M, Fuson R, Marchiori C, Gava A, Da Mosto MC. Long-term quality of life after treatment for locally advanced oropharyngeal carcinoma: surgery and postoperative radiotherapy versus concurrent chemoradiation. *Oral Oncol* 2009;**45**(11):953–7.
19. Sessions DG, Lenox J, Spector GJ, Chao C, Chaudry OA. Analysis of treatment results for base of tongue cancer. *Laryngoscope* 2003;**113**(7):1252–61.
20. Jones AS, Rafferty M, Fenton JE, Jones TM, Husband DJ. Treatment of squamous cell carcinoma of the tongue base: irradiation, surgery, or palliation? *Ann Otol Rhinol Laryngol* 2007;**116**(2):92–9.
21. Yoshimoto S, Kawabata K, Mitani H, Yonekawa H, Beppu T, Fukushima H, et al. Treatment results for 84 patients with base of tongue cancer. *Acta Otolaryngol Suppl* 2007(559);123–8.
22. Lawson JD, Otto K, Chen A, Shin DM, Davis L, Johnstone PA. Concurrent platinum-based chemotherapy and simultaneous modulated accelerated radiation therapy for locally advanced squamous cell carcinoma of the tongue base. *Head Neck* 2008;**30**(3):327–35.

23. Nakamura T, Kodaira T, Tachibana H, Tomita N, Yokouchi J, Fuwa N. Clinical outcome of oropharyngeal carcinoma treated with platinum-based chemoradiotherapy. *Oral Oncol* 2009;**45**(9):830–4.
24. Oikawa H, Nakamura R, Nakasato T, Nishimura K, Sato H, Ehara S. Radiotherapy and concomitant intra-arterial docetaxel combined with systemic 5-fluorouracil and cisplatin for oropharyngeal cancer: a preliminary report – improvement of locoregional control of oropharyngeal cancer. *Int J Radiat Oncol Biol Phys* 2009;**75**(2):338–42.
25. Urba SG, Moon J, Giri PG, Adelstein DJ, Hanna E, Yoo GH, et al. Organ preservation for advanced resectable cancer of the base of tongue and hypopharynx: a Southwest Oncology Group Trial. *J Clin Oncol* 2005;**23**(1):88–95.
26. Cano ER, Lai SY, Caylakli F, Johnson JT, Ferris RL, Carrau RL, et al. Management of squamous cell carcinoma of the base of tongue with chemoradiation and brachytherapy. *Head Neck* 2009;**31**(11):1431–8.
27. Harrison LB, Lee HJ, Pfister DG, Kraus DH, White C, Raben A, et al. Long term results of primary radiotherapy with/without neck dissection for squamous cell cancer of the base of tongue. *Head Neck* 1998;**20**(8):668–73.
28. Rasch CR, Hauptmann M, Schornagel J, Wijers O, Buter J, Gregor T, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. *Cancer* 2010;**116**(9):2159–65.

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Concomitant Weekly Cisplatin and Radiotherapy for Head and Neck Cancer

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Objective: The most common chemoradiotherapy regimen is high-dose (100 mg/m^2) three-weekly cisplatin with concomitant radiotherapy; however, this protocol is associated with acute and late toxicities. Here, we reviewed the dose intensity and toxicity for concomitant weekly cisplatin and radiotherapy in patients with head and neck cancer.
Methods: Fifty-three patients with untreated head and neck cancer were enrolled and evaluated at our institution from April 2006 to April 2010. Weekly cisplatin (40 mg/m^2) was given on weeks 1, 2, 3, 5, 6 and 7 with radiotherapy, which comprised a standard dose of 70 Gy delivered in 35 daily fractions over 7 weeks.
Results: Fifty-one patients (96.2%) received the full dose of radiotherapy, while the course was disrupted by adverse events in two. Over the course of the chemotherapy, 31 patients (58.5%) received more than 200 mg/m^2 cisplatin. The toxicity was manageable in all except one patient, who died of sepsis after completing treatment. The 2-year overall survival rate and local progression-free rate for all patients were 93.7% and 88.0%, respectively. The primary site showed a complete response in 52 patients (98.1%) and a partial response in 1 patient (1.9%). The primary disease was well controlled by chemoradiotherapy in 47 patients (88.7%).
Conclusions: Weekly cisplatin could be easier to manage than three-weekly cisplatin, because patients can be monitored more regularly for toxicity allowing the schedule to be altered if required. This regimen appears to be a suitable alternative to three-weekly high-dose cisplatin with concomitant radiotherapy.

Key words: chemotherapy – cisplatin – radiotherapy – chemoradiotherapy

INTRODUCTION

Locoregionally advanced head and neck cancer (HNC) is generally treated with surgery followed by postoperative radiotherapy (RT). However, definitive concomitant chemoradiotherapy (CRT) is an alternative treatment option (1). Cisplatin is the most common agent used in combination with RT, and is one of the best studied. The standard regimen is three-weekly high-dose (100 mg/m^2) cisplatin (three cycles) concurrent with RT (2,3).

However, cisplatin at a dose of 100 mg/m^2 with concomitant RT is associated with significant acute and late toxicities (2,4,5). Furthermore, the completion rate for this regimen is relatively poor (2,3). The use of a lower cumulative cisplatin dose or a more fractionated cisplatin dose has therefore been suggested (6–8).

Renal function has been reported to decrease rapidly with aging in the Japanese population, although the underlying reason remains unclear (9). The recommended dose of cisplatin is 60–70 mg/m^2 for patients with HNC according to

the Japanese Ministry of Health, Labor and Welfare. A retrospective study of three Japanese patients with nasopharyngeal cancer receiving cisplatin and concurrent RT reported severe acute toxicities (10). By contrast, weekly cisplatin at a dose of 40 mg/m^2 was found to be well tolerated and to have acceptable toxicity, despite the large RT fields employed, for the treatment of nasopharyngeal carcinoma (11).

Weekly cisplatin at a dose of 40 mg/m^2 has been the standard schedule for HNC at our institution since 2006. In the present study, we calculated the dose intensity and evaluated the toxicity of this regimen in patients with HNC at our institution retrospectively.

PATIENTS AND METHODS

Patients

To be eligible for inclusion in this study, patients were required to have histologically proven Stage II–IV carcinoma of the oropharynx, hypopharynx or larynx. All patients were 75 years of age or younger, and had not received previous treatment for the tumor except neck dissection. Patients were required to be free of other active cancers, as well as distant metastases, and to meet the following criteria: a World Health Organization performance status of 0–2; a white-cell count of at least 4000/mm^3; a platelet count of at least 1 00 000/mm^3; a hemoglobin concentration of at least 9.5 g/dl; serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels of less than twice the upper limit of the normal range; a total bilirubin concentration of $<$2.0 mg/dl; a serum creatinine concentration of $<$1.5 g/dl; a blood urea nitrogen concentration of $<$25 mg/dl; and a creatinine clearance of more than 60 ml/min. The disease had to be measurable or amenable to evaluation, and had to be documented as precisely as possible before treatment by endoscopy, including computed tomography (CT) and/or magnetic resonance imaging (MRI). All patients were initially evaluated by a multidisciplinary team consisting of otolaryngologists and radiation oncologists, and the tumors were classified according to the 2002 Union Internationale Contre le Cancer (UICC) staging system. Written informed consent was obtained from all patients before entry into the study. Patients who were pregnant or breast-feeding were excluded from the study.

Chemotherapy

Weekly cisplatin was administered at a dose of 40 mg/m^2 on weeks 1, 2, 3, 5, 6 and 7 of the RT. Patients received prophylactic hydration (4 l) and $5HT_3$ antagonists plus dexamethasone for anti-emetic prophylaxis. The intended maximum total dose of cisplatin was 240 mg/m^2. The cisplatin dose was modified on a case-by-case basis according to the level of leucopenia and/or thrombocytopenia, the serum creatinine and/or creatinine clearance, the presence of liver dysfunction and/or infectious disease, and the patient's wishes. In addition, weekly cisplatin was altered to weekly carboplatin [area under the curve (AUC) = 1.5] in some cases based on the toxicity.

Preparation for percutaneous endoscopic gastrostomy feeding before treatment was recommended. The use of non-steroidal anti-inflammatory drugs was avoided, in order to prevent any synergistic toxic effects with cisplatin on renal function.

Radiotherapy

A standard dose of 70 Gy was delivered in 35 daily fractions over 7 weeks to all of the patients. All of the patients received external RT (40 Gy/20 fractions/4 weeks), in the form of 4 or 6 MV photons produced by a linear accelerator, to the primary sites and regional lymphatic area. The treatment was planned using a CT simulator and a three-dimensional dose-calculation computer. For patients who were suspected of having lymph-node metastases, the lower-neck region and supraclavicular fossa were prophylactically irradiated with a total of 40 Gy using an anterior single port. Electron beams were used to boost the dose delivered to the posterior cervical lymph nodes. The dose delivered to the spinal cord was kept below 40 Gy in all instances. After the initial dose of 40 Gy had been administered, an additional dose of 30 Gy was given with a shrunken field in 15 fractions over 3 weeks.

Evaluation of Toxicity and Response

Toxicities were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0. For measurable lesions, responses were evaluated by clinical examination and/or CT or MRI studies 6–8 weeks after the completion of therapy using the Response Evaluation Criteria in Solid Tumors (RECIST). CT and MRI were performed 6–10 weeks after the end of RT as a convenient means of determining target-lesion progress and identifying emerging new lesions.

Positron-emission tomography (PET) and PET-CT were used to support the diagnosis. Based on the radiographic changes related to treatment, it can be difficult to distinguish between the scar tissue and residual tumor tissue. Over time, however, the scar tissue will remain stable, whereas the remaining tumor tissue can progress. We designed the patient outcomes to reflect this uncertainty: a patient with radiological changes that remained stable over time, and no signs or symptoms of disease, was considered to be 'progression free'. Biopsy was performed only to document recurrence when indicated.

Statistical Considerations

Data on the disease site, Tumor-Node-Metastasis (TNM) stage, RT dose/fractionation and chemotherapy regimen were

collected. Incidences of delays to therapy, acute toxicity, dose reduction and missed treatments for both chemotherapy and RT were also recorded.

The primary endpoint was treatment compliance. Complete treatment delivery was defined as the administration of the 70 Gy RT dose within 63 days, and the completion of five or six courses of cisplatin. Treatment compliance was evaluated based on the rate of complete treatment delivery.

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

RESULTS

Patient Characteristics

Fifty-three patients (49 males and 4 females) were enrolled in the study and were evaluated from April 2006 to April 2010 (Table 1). The patients ranged in age from 40 to 75 years (median = 62 years). The most common site of the primary disease was the hypopharynx (22 patients), followed by the oropharynx (18 patients), larynx (12 patients) and oral cavity (1 patient). Two patients underwent bilateral neck dissection prior to CRT. One patient with T2N2b laryngeal cancer and synchronous esophageal cancer underwent esophagectomy and bilateral neck dissection prior to CRT in order to preserve the larynx. One patient with unknown primary bilateral neck cancer underwent bilateral neck dissection and panendoscopy with biopsies of the pharynx. A pathological examination revealed the base of the tongue as the primary site in this case, and the patient subsequently underwent CRT.

The clinical stages are listed in Table 2. In total, 30 patients had Stage IV disease, 6 had Stage III disease and the remaining 17 had Stage II disease.

All of the patients were closely observed during follow-up. The follow-up period of survivors ranged from 7 to 57 months (median = 29 months; mean = 29 months).

Table 1. Clinical characteristics ($n = 53$)

Age (years)	
Range	40–75
Median	62
Mean	61.1
Sex	
Male	49 (92.5%)
Female	4 (7.5%)
Performance status	
0	39 (73.6%)
1	12 (22.6%)
2	2 (3.8%)
Primary tumor site	
Oral cavity	1 (1.9%)
Oropharynx	18 (34.0%)
Hypopharynx	22 (41.5%)
Larynx	12 (22.6%)
Histology	
Squamous cell	51 (96.2%)
Adeno	1 (1.9%)
Lymphoepithelial	1 (1.9%)

Table 2. T and N stage ($n = 53$)

T stage	N stage						
	0	1	2a	2b	2c	3	Total
1		1		1	2		4
2	17	1		10	2	1	31
3	2	2	1	9		1	15
4a	1			1			2
4b				1			1
Total	20	4	1	22	4	2	53

Adverse Events

The acute adverse events observed, including hematological and non-hematological toxicities, are summarized in Table 3. One patient died of sepsis after completing the treatment; this patient exhibited Grade 3 leucopenia, anemia, fever and renal dysfunction, and Grade 4 thrombocytopenia, liver dysfunction and hypernatremia. Grade 4 hematological toxicities were not observed among the other patients. Grade 3–4 mucositis was observed in 21 patients (39.6%). Mild-to-intermediate renal dysfunction was observed in 15 cases: Grade 1 creatinine was present in 13 patients (24%), Grade 2 in 1 (2%) and Grade 3 in 1 (2%). The other Grade 3–4 non-hematological side effects observed included nausea/vomiting ($n = 3$), liver dysfunction ($n = 3$), dermatitis ($n = 18$), fever ($n = 4$), hyponatremia ($n = 1$), hypernatremia ($n = 1$), appetite ($n = 8$) and hyperglycemia ($n = 1$). None of the surviving patients showed evidence of disease, and all except one were able to achieve oral intake without feeding-tube support. Pharyngeal stenosis occurred in one patient with T3N1 hypopharyngeal cancer, who suffered from repeated pneumonia and underwent a total laryngopharyngectomy and free-jejunum transfer. One patient experienced osteonecrosis of the mandible, but did not require surgical treatment.

Total Treatment Compliance

In total, 51 of the patients (96.2%) received the full dose of RT (70 Gy) over a median period of 50 days (range = 46–62 days). The radiation course was disrupted in two of the patients by adverse events. The reasons for extension of the RT course beyond 50 days were holidays and machine maintenance, except in two patients. A total of 34 patients (64.2%) completed five (15 patients) or six (19 patients) courses of the chemotherapy; 11/17 (64.7%) with Stage II and 23/36 (63.9%) with Stage III/IV. However, in three of these patients, the dose of cisplatin was modified due to adverse effects. As a result, 31 patients (58.5%) received more than 200 mg/m^2 of cisplatin. The cisplatin treatment was stopped in 2 patients (3.8%) after one course, in 3 patients (5.7%) after two courses, in 4 patients (7.5%) after three courses and in 10 patients (18.9%) after four courses. Four of the five patients who received only one or two courses of cisplatin were switched to weekly carboplatin (AUC = 1.5). Finally, the average total amount of cisplatin administered was 185 mg/m^2 (median = 190 mg/m^2) when data from all patients were included in the analysis, and the average dose intensity of cisplatin was 26.5 mg/m^2/week.

Table 3. Toxicity ($n = 53$)

Toxicity	Grade				
	1	2	3	4	5
Leucopenia	11	23	14		
Neutropenia	10	17	10		
Anemia	22	17	9		
Thrombocytopenia	12	5	1	1	
Nausea/vomiting	14	4	3		
Mucositis	4	21	17	4	
Febrile neutropenia			2		1
Renal dysfunction	13	1	1		
Liver dysfunction	7	4	2	1	
Dermatitis	10	19	18		
Fever	16	2	4		
Appetite	22	3	8		
Hyponatremia	1		1		
Hypernatremia				1	
Hyperkalemia	2				
Hyperglycemia				1	
Hypercalcemia	1				

Overall Survival and Local Control

The 2-year overall survival and local progression-free rates for all patients were 93.7% and 88.0%, respectively (Fig. 1).

Response of the Primary Disease

Of the 53 patients who entered into the treatment program, complete responses at the primary site were observed in 52 (98.1%) and partial responses in 1 (1.9%). The primary disease was well controlled by CRT in 47 patients (88.7%). The remaining six patients (11.3%) had persistent or recurrent primary disease after completing CRT. All six of these patients underwent salvage surgery, and four subsequently survived and remained disease-free.

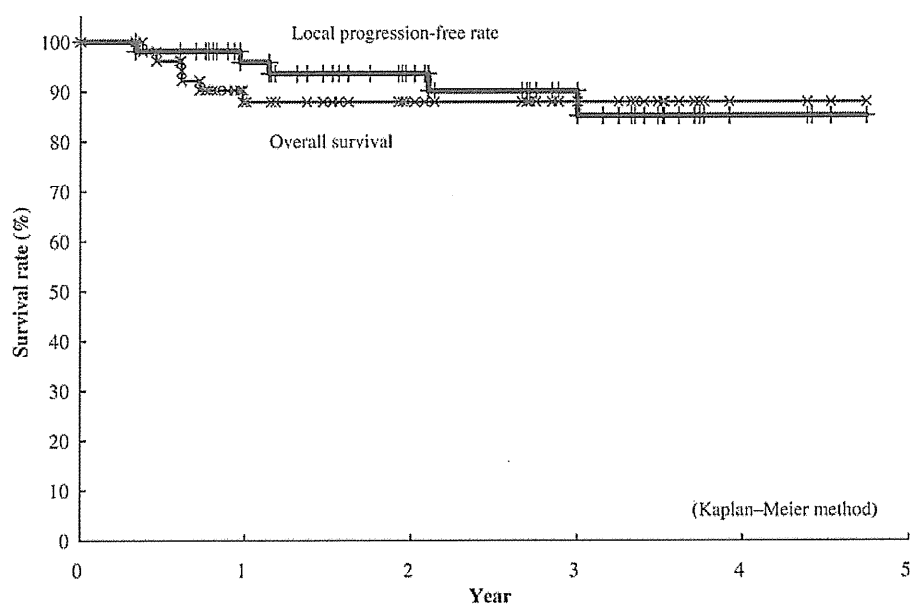

Figure 1. Overall survival and local progression-free rates.

Response of Neck Disease

Among the 33 patients with positive neck disease, two underwent neck dissection prior to CRT. Among the remaining 31 patients, the disease was well controlled by CRT without surgery in 20 patients (64.5%). Eight patients with obvious or suspected persistent neck disease after CRT were treated successfully by salvage neck dissection. In four of these patients, no viable cancer cells were observed in the surgical specimens. One patient with persistent neck disease after CRT received chemotherapy, which successfully treated the disease. Two patients underwent neck dissection when they received salvage surgery for recurrent primary disease. Both patients had no viable cancer cells in the surgical specimens, but one had recurrence in the primary and neck lesions. Thus, in 25 of the 31 patients (80.6%), the positive neck disease was well controlled by CRT. At the time of writing, 32 of the 33 patients had successfully controlled disease.

Sites of Uncontrolled Recurrence

The site of uncontrolled recurrence was identified whenever possible. Uncontrolled recurrence initially occurred at distant metastases in four patients, at the primary site in one patient and at the primary site and regional lymph nodes in one patient. One patient died of leukemia without recurrence in the head and neck region.

DISCUSSION

Three-weekly cisplatin at a dose of 100 mg/m^2 concurrent with RT is considered to be the standard of care for the non-surgical treatment of advanced HNC, based on several Phase III trials (2,3). However, this protocol has been associated with significant acute and late toxicities (2,4,5). Furthermore, the completion rate of this regimen has been reported to be relatively low, with 63–85% of patients in the CRT arm completing all three of the planned cycles of concurrent chemotherapy in several clinical trials (2,3,5). Poor compliance over three cycles of high-dose cisplatin was also reported in a series of patients at the Princess Margaret Hospital in Toronto. In this retrospective study of 75 patients, 42.7% underwent all three planned cycles of chemotherapy, and only 33.3% received the intended dose without a cumulative delay of at least 7 days throughout the three cycles (12). The death rate for patients undergoing this protocol was reported to be 4–5% in Phase III trial (2,3,13), and 10% in the community setting (13).

Ho et al. (14) retrospectively compared the differences in dose intensity, delays and toxicity between weekly and three-weekly cisplatin administered concurrently with RT to patients with locally advanced HNC. The authors concluded that three-weekly cisplatin at a dose of 100 mg/m^2 concurrent with RT was less well tolerated than weekly cisplatin at a dose of 40 mg/m^2, and resulted in less patients achieving a cumulative dose of more than 200 mg/m^2, thereby potentially lowering the chemotherapy dose intensity. Based on these results, high-dose cisplatin might not be suitable for routine use.

The Head and Neck Intergroup conducted a Phase III randomized trial comparing radiation therapy alone with radiation and concurrent weekly cisplatin at a dose of 20 mg/m^2 between 1982 and 1987 (15). Although the response rate was greater in patients treated with the concurrent regimen, the median survival was only 13 months and did not differ between the two treatment arms. Although the addition of concurrent weekly cisplatin at 20 mg/m^2 to daily radiation did not significantly improve survival, there was some evidence of an effect. Similarly, concomitant CRT using daily low-dose (4 mg/m^2) cisplatin showed disappointing results (16). A high dose of cisplatin was therefore considered necessary to achieve a good outcome (17,18).

CRT using weekly cisplatin at a dose of 40 mg/m^2 was found to be well tolerated in patients with advanced nasopharyngeal carcinoma in Hong Kong (11). The relatively low dose used in the investigation arm of the study resulted in no treatment-related mortalities, although this strategy could have led to suboptimal benefits. The progression-free survival rate significantly differed between the concurrent CRT arm and the RT-alone arm for patients with advanced T and N stages. Hence, after some consideration, we introduced this schedule at our institution.

The regimen appeared to be well tolerated, with low rates of severe toxicities: 62.3% of the patients completed at least five of the six planned chemotherapy cycles. A total cisplatin dose of 200 mg/m^2 or more was delivered to 58.5% of the patients in this study. The average dose intensity of cisplatin (26.5 mg/m^2/week) was equivalent to that of three-weekly regimen (28.9 mg/m^2/week) (19). With regard to toxicity, the rate of Grade 3 or greater leukopenia and mucositis in the three-weekly cisplatin regimen in patients with unresectable disease was reported to be 42.1% and 45.2%, respectively. Also in the same regimen for laryngeal preservation, the rate of Grade 3 or greater hematologic toxicity and mucositis was 47% and 43%, respectively. In the present study, the rate of Grade 3 or greater leukopenia and mucositis was 26.4% and 39.6%, respectively. Toxicity in the present study was similar or less than those in Phase III trial of three-weekly cisplatin regimen.

Weekly cisplatin could be easier to manage than three-weekly cisplatin because patients can be more regularly monitored for toxicity, and the schedule can be changed before the effects become severe, based on the patient's condition. Because the dose delivered in each cycle is smaller, the toxicity is reduced. In the current study, five of the patients stopped receiving cisplatin after one or two courses due to the toxicity. Four of these patients subsequently received weekly carboplatin (AUC = 1.5) instead of cisplatin: creatinine clearance measured by the Cockcroft–Gault formula dropped to <50 ml/min in three patients, Grade 3 liver dysfunction was present in the fourth patient. If these patients, who were considered unsuitable for cisplatin administration, had initially

received a dose of 100 mg/m^2, the toxicity would have been more serious and they might have not undergone further chemotherapy or RT. We therefore consider this regimen to be a reasonable alternative to three-weekly high-dose (100 mg/m^2) cisplatin concurrent with RT.

Molecular growth inhibitors such as cetuximab have recently been investigated in conjunction with radiation therapy for advanced HNC patients, and have shown promising results (20–22). The Memorial Sloan-Kettering Cancer Center reported a Phase II trial of concomitant boost RT, cisplatin (100 mg/m^2 in weeks 1 and 4) and cetuximab (400 mg/m^2 intravenously in week 1, followed by 250 mg/m^2 in weeks 2–10). The study was halted owing to significant adverse events, including two deaths (one from pneumonia and one from unknown causes), one case of myocardial infarction, one case of bacteremia and one case of arterial fibrillation (21). Cisplatin at a dose of 100 mg/m^2 concurrent with radiation therapy is an intensive regimen, and adding a molecular-targeted agent might have resulted in the unacceptable toxicity. The results of the French TREMPLIN trial indicated that only 43% of all patients receiving induction docetaxel, cisplatin, and 5-fluorouracil chemotherapy (TPF) followed by cisplatin (100 mg/m^2) CRT (Arm A) were compliant with the full course of treatment, in contrast to 74% of the patients receiving induction TPF and subsequent cetuximab-containing bioradiation (Arm B) (23). Three months after treatment, there was no significant difference in laryngeal preservation between Arm A (93%) and Arm B (96%). Further clinical trials of concomitant CRT using cisplatin with a molecular-targeted agent, with or without induction chemotherapy, are required.

In conclusion, it is unlikely that cisplatin at a dose of 100 mg/m^2 will be an acceptable standard CRT regimen because of the severe toxicity. However, radiation therapy concomitant with cisplatin is likely to remain a key regimen. Weekly cisplatin could be easier to manage than three-weekly cisplatin, because patients can be monitored more regularly for toxicity allowing the schedule to be altered if required. In addition, the average dose intensity of cisplatin of weekly regimen was equivalent to that of three-weekly regimen. Therefore, weekly cisplatin is predicted to play an important role in the future. We thus believe that there is a need for a randomized trial comparing high-dose (100 mg/m^2) three-weekly cisplatin and weekly cisplatin as a basic CRT regimen in the near future.

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Conflict of interest statement

None declared.

References

1. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology*. Head and Neck Cancers, 2010, version 2. http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf696.
2. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091–8.
3. Adelstein DJ, Li Y, Adams GL, Wagner H, Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003;21:92–8.
4. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol* 2008;26:3582–9.
5. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;16:1310–7.
6. Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *J Clin Oncol* 2000;18:1458–64.
7. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 2005;23:6730–8.
8. Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *J Clin Oncol* 2004;22:4665–73.
9. Nishimura G, Tsukuda M, Horiuchi C, Satake K, Yoshida T, Taguchi T, et al. Decrease of creatinine clearance rate with aging in patients with head and neck cancer in Japan. *Int J Clin Oncol* 2007;12:120–4.
10. Isobe K, Kawakami H, Uno T, Yasuda S, Aruga T, Ueno N, et al. Concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: is intergroup study 0099 feasible in Japanese patients?. *Jpn J Clin Oncol* 2003;33:497–500.
11. Chan AT, Leung SF, Ngan RK, Teo PM, Lau WH, Kwan WH, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2005;97:536–9.
12. Bahl M, Siu LL, Pond GR, Kim J, Tannock IF, Bayley A, et al. Tolerability of the Intergroup 0099 (INT 0099) regimen in locally advanced nasopharyngeal cancer with a focus on patients' nutritional status. *Int J Radiat Oncol Biol Phys* 2004;60:1127–36.
13. de Castro G, Jr, Snitcovsky IM, Gebrim EM, Leitao GM, Nadalin W, Ferraz AR, et al. High-dose cisplatin concurrent to conventionally delivered radiotherapy is associated with unacceptable toxicity in unresectable, non-metastatic stage IV head and neck squamous cell carcinoma. *Eur Arch Otorhinolaryngol* 2007;264:1475–82.
14. Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. *Acta Oncol* 2008;47:1513–8.
15. Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A. Phase III study of radiation therapy with or without cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). *Int J Radiat Oncol Biol Phys* (in press).
16. Homma A, Shirato H, Furuta Y, Nishioka T, Oridate N, Tsuchiya K, et al. Randomized phase II trial of concomitant chemoradiotherapy using weekly carboplatin or daily low-dose cisplatin for squamous cell carcinoma of the head and neck. *Cancer J* 2004;10:326–32.
17. Marcu L, van Doorn T, Olver I. Cisplatin and radiotherapy in the treatment of locally advanced head and neck cancer—a review of their cooperation. *Acta Oncol* 2003;42:315–25.

18. Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. *Head Neck* 2001;23:579–89.
19. Zenda S, Onozawa Y, Tahara M, Kawashima M, Shikama N, Sasaki S, et al. Feasibility study of single agent cisplatin and concurrent radiotherapy in Japanese patients with squamous cell carcinoma of the head and neck: preliminary results. *Jpn J Clin Oncol* 2007;37:725–9.
20. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;11:21–8.
21. Pfister DG, Su YB, Kraus DH, Wolden SL, Lis E, Aliff TB, et al. Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: a Pilot phase ii study of a new combined-modality paradigm. *J Clin Oncol* 2006;24:1072–8.
22. Langer CJ, Lee JW, Patel UA, Shin DM, Argiris AE, Quon H, et al. Preliminary analysis of ECOG 3303: Concurrent radiation (RT), cisplatin (DDP) and cetuximab (C) in unresectable, locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN). *Proc Am Soc Clin Oncol* 2008;26(Suppl): abstr 6006.
23. Lefebvre J, Pointreau Y, Rolland F, Alfonsi M, Baudoux A, Sire C, et al. Sequential chemoradiotherapy (SCRT) for larynx preservation (LP): preliminary results of the randomised phase II TREMPLIN study. *Proc Am Soc Clin Oncol* 2009;27(Suppl):303s.

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化学療法

分子標的薬治療の導入に向けて

KEY WORDS
- 頭頸部癌
- 分子標的薬剤
- セツキシマブ
- 化学放射線療法

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はじめに

頭頸部癌に対する治療は，従来から手術を中心に行われているが，手術が技術的に不可能な場合と拡大手術によっても治療成績が悪い進行例に対する治療や，喉頭や咽頭の温存を目指す場合は放射線治療と化学療法による集学的治療が広く行われている。化学療法は導入化学療法や放射線治療との併用，補助化学療法として施行される。放射線治療との併用ではシスプラチン(CDDP)単独が世界的には標準とされているが，そのほかでは多剤併用療法が中心で，CDDPと5-FUの併用療法が最も多く行われている。進行頭頸部癌の治療は放射線治療と化学療法を同時併用する化学放射線療法(CCRT)が高いエビデンスが証明されて標準的治療の1つとなっている。臨床では，欧米においてCCRTに関する多くの無作為比較試験が行われている。そして，1965年から1993年までに行われた63の無作為比較試験に対するメタアナリシスでは，放射線治療に化学療法を追加することにより5年生存率の向上が証明されており，化学療法を追加する場合は放射線治療と同時に施行した場合が最も生存に対する利得が大きいことが証明されている[1]。さらにこれ以降のランダム化比較第Ⅲ相試験でもさまざまな化学療法の併用療法が検討されている。これらの比較試験の大部分は切除不能例を対象としており，ほとんどが放射線治療単独と比較して化学療法併用療法の優位を報告している。しかし多剤併用療法による導入化学療法やCCRTは効果的ではあるが，強い毒性のために施行困難となる場合がある。近年のメタアナリシスでも70歳以上の進行癌症例では，放射線治療単独に比較してCCRTを施行する生存への上乗

For introduction of molecular-targeted agents to head and neck cancer
Masato Fujii (部長)

せ効果は認められていない[2]。

近年，さまざまな分子標的薬剤が開発され，乳癌，大腸癌，悪性リンパ腫，慢性骨髄性白血病などで画期的な成績が報告されるようになってきている。頭頸部癌に対しても欧米ではすでに多くの分子標的薬剤の臨床試験が進んでいる。その結果，分子標的薬剤による多剤併用療法や放射線治療との併用は，再発/転移症例やCDDPによるCCRTの施行が困難な高齢者に対する標準的治療としての役割を担いつつある。腫瘍の増殖に関与する上皮成長因子(epidermal growth factor；EGF)の受容体(EGFR)は頭頸部扁平上皮癌細胞に高率に発現しており，EGFRを阻害する薬剤の効果が期待される。EGFR阻害薬としての代表的分子標的薬剤であるセツキシマブはわが国でも頭頸部癌に対する保険適応承認が予定されていることなどから，分子標的薬剤の導入について十分な検討を行うことは，わが国の頭頸部癌治療にとって非常に重要な時期となっている。

Ⅰ．頭頸部癌に対する分子標的薬剤

頭頸部癌に対して欧米で臨床応用が開始されている分子標的薬剤のうち，EGFRを標的とする薬剤として，まずキメラ型抗体のセツキシマブがあげられる。これはEGFRの細胞外領域に特異的に結合するモノクロナール抗体である。頭頸部扁平上皮癌におけるEGFRの発現は80～90％と報告されており，その強発現は予後不良因子とされている[3][4]。セツキシマブ単剤の評価は主にCDDPなどのプラチナ製剤に対して耐性となった症例に対して行われており，奏効率は10％程度である[5]。ザルツムマブは，セツキシマブと異なりEGFRに対するヒト型モノクロナール抗体であるが，CDDP使用後に再発・転移した頭頸部癌に対してメトトレキサートを併用した緩和治療との比較試験において，無再発生存期間の延長が認められて注目されている[6]。EGFR阻害薬としてEGFRの細胞内シグナル伝達機構を阻害するチロシンキナーゼ阻害薬がある。それらのうちエルロチニブ，ラパチニブは海外では頭頸部癌に対する臨床試験が進んでいる。さらに，血管内皮成長因子(VEGF)を阻害して腫瘍の血管新生を抑制するベバシズマブやソラフェニブが開発され，頭頸部癌に対する検討が行われている[7]。

Ⅱ．抗癌剤との併用

頭頸部癌に対する化学療法におけるkey drugはCDDPであり，多剤併用化学療法はCDDPを中心にさまざまな抗癌剤が組み合わされている。一方，CDDPとセツキシマブの併用は基礎実験において相乗効果が示されており[8]，臨床では，さまざまな第Ⅱ相試験でその有用性が検討されてきた[9]。それらを踏まえて，Burtnessらは Eastern Coopetative Oncology Group(ECOG)グループにおいて転移・再発頭頸部癌症例に対してCDDPとセツキシマブを併用する効果を比較検討する大規模な第Ⅲ相試験を報告している[10]。それは，評価可能病変をもつ再発・転移扁平上皮癌症例をCDDP＋セツキシマブ群(arm A)とCDDP＋プラセボ群(arm B)に無作為に振り分ける二重盲検試験であるが，arm BでPDとなった症例はセツキシマブ併用療法を行うこととしている。arm A 57例，arm B 60例が登録され，65％が遠隔転移例となっている。奏効率ではarm Aが26.3％，arm Bで9.8％とセツキシマブ併用群で有意に勝っていたが，生存期間中央値はおのおの4.2ヵ月と2.7ヵ月で，無増悪生存期間中央値では4.2ヵ月と3.1ヵ月であり，有意差を認めなかった。セツキシマブ併用群では皮膚毒性が有意に増強するが，皮膚毒性が出現した症例については生存期間の有意な延長が報告されている。再発・転移癌に対する最も重要な臨床試験はVermorkenらが行ったExtreme Studyである[11]。これは，再発・転移頭頸部癌症例に対してCDDPまたはカルボプラチンと5-FUとの併用療法にセツキシマブの同時併用を行う群(A群)と行わない群(B群)との比較試験であり，欧州17ヵ国が参加し420例が登録された大規模比較試験である。化学療法は最大6コース行い，A群ではさらにセツキシマブ投与を継続し，腫瘍の増大や治療継続不可能な副作用発現まで治療を続けることとしている。副作用に関してはセツキシマブ併用によって皮膚発疹と投与時のアレルギー反応が出るが，その他の骨髄毒性などに関しては両群で差がなかった。一方，全体生存期間に関しては平均生存期間がセツキシマブ併用群で10.1ヵ月，非併用群で7.4ヵ月と有意に延長した。再発・転移癌に対する治療で生存期間の延長が証明された画期的な報告である(図)。近年では，セツキシマブなどと化学療法併用のさまざまな第Ⅱ相試験が報告されている。主に再発・転移癌に対するものであるが，なかには未治療例に対する臨床試験もあり，今後分子標的薬剤の併用が多剤併用療法のなかで標準的な位置を占め

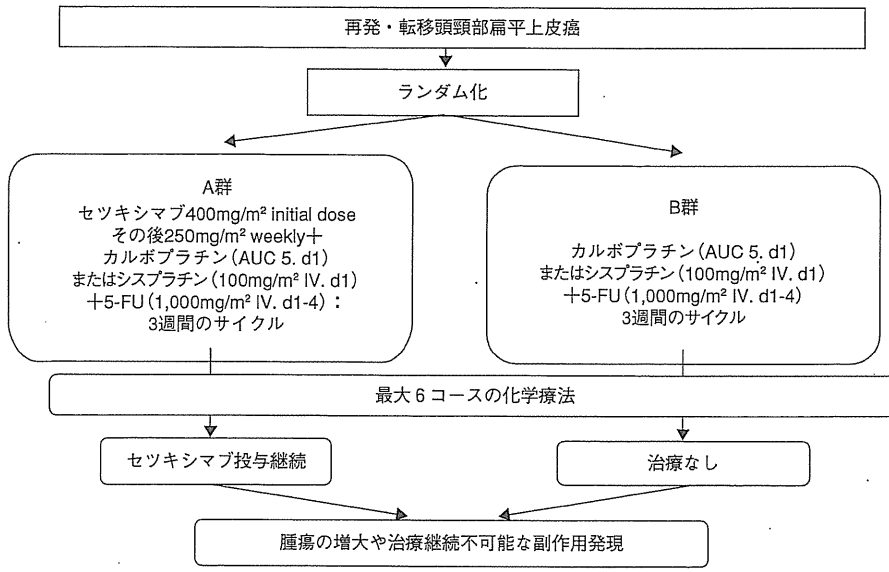

図. Vermorkenらの再発・転移癌に対するプラチナ製剤＋5-FU療法に対するセツキシマブ併用の第Ⅲ相試験

る可能性が大きい。

Ⅲ. 放射線治療との併用

局所進行頭頸部癌に対してAngらはRadiation Therapy Oncology Group (RTOG)で第Ⅲ相試験を試行し，EGFR発現は放射線治療による局所コントロールと生存期間に対して独立した予後不良因子であることを報告している[12]。そして，Robertらは放射線治療と併用するセツキシマブの投与量設定を行っている[13]。それによると，セツキシマブの投与量は照射前1週間に400mg/m²を投与し，照射中は毎週250mg/m²併用が推奨用量としている。そしてセツキシマブと放射線治療の比較第Ⅲ相試験がBonnerらによって報告されている[14]。これによると，セツキシマブ併用により副作用の増強はなく，治療成績は放射線治療単独と比較して50％生存期間は29ヵ月から49ヵ月に延長し，3年全体生存率は45％から55％に改善し，3年局所制御率も有意に向上している。Pfisterらは局所進行頭頸部癌に対するCDDPと放射線治療同時併用にセツキシマブを加えた第Ⅱ相試験を報告している[15]。それによると3年全体生存率，無増悪生存率，局所制御率はそれぞれ76％，56％，71％と良好な成績を報告し，さらに第Ⅲ相試験が現在行われている。今後はセツキシマブを中心とした分子標的薬剤と放射線治療併用レジメンは，毒性の強い化学放射線療法が施行困難な場合に用いられる重要なレジメンになると考えられる。

おわりに

これまで述べたように，海外では頭頸部癌に対する分子標的薬の臨床研究が非常に精力的に行われ，ランダム化比較第Ⅲ相試験によって高いエビデンスが生まれつつある。CCRTに対するメタアナリシスでも高齢者における化学療法の生存に対する上乗せ効果が明らかではないため，70歳以上の進行頭頸部癌に対しては，Bio-RADと称する放射線治療と分子標的薬剤の併用が標準となりつつある。そして，CDDPに不応となった再発転移癌に対する治療においても分子標的薬剤が重要となる。わが国では分子標的薬剤の承認が大幅に遅れているが，海外の第Ⅲ相試験のデータをもとに薬剤が承認され，実臨床に組み入れられる日も遠くないと考えられる。

わが国における頭頸部癌治療は腫瘍内科医の関与が少ないことなどさまざまな問題があり，分子標的薬剤の実臨床への導入に際しては十分な注意が必要である。現在までに確立したエビデンスに基づいた標準的治療をふまえ，

そのうえで分子標的薬剤投与の症例を選択すべきである。また，分子標的薬剤は化学療法薬と比較して，副作用が少ないと理解されがちであるが決してそのようなことはなく，化学療法では経験しないさまざまな副作用が発現する可能性がある。最も一般的なものは皮膚毒性であり，頻度が高く重症となる可能性もある。その他，薬剤によっては肺毒性，心毒性，中枢神経合併症や，infusion reactionを起こすものもある。

今後，分子標的薬剤の実臨床への導入の際には，対象症例の選択と副作用対策を十分に行って施行すべきであり，安易な使用や副作用に対する不十分な知識は大きな医療事故につながる可能性がある。頭頸部癌に対する分子標的薬剤の導入はわが国においても非常に期待されるところであるので，以上の事柄に注意して慎重に臨床導入されることが望まれる。

文　献

1) Pignon JP, Bourhis J, Domenge C, et al：Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma：three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 355：949－955, 2000
2) Pignon JP, le Maître A, Bourhis J；MACH-NC Collaborative Group：Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC)：an update. Int J Radiat Oncol Biol Phys 69(2 Suppl.)：S112－114, 2007
3) Grandis JR, Melhem MF, Barnes EL, et al：Quantative immunohistochemical analysis of transforming growth factor-alpha and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. Cancer 78：1284－1292, 1996
4) Dassonville O, Formento JL, Frncoul M, et al：Expression of epidermal growth factor receptor and survival in upper aerodigeative tract cancer. J Clin Oncol 11：1873－1878, 1993
5) Cohen EE：Role of epidermal growth factor receptor pathway-targeted therapy in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 24：2659－2665, 2006
6) Machiels JP, Subramanian S, Ruzsa A, et al：Zalutumumab plus best supportive care versus best supportive care alone in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after failure of platinum-based chemotherapy：an open-label, randomised phase 3 trial. Lancet Oncol 12：333－343, 2011
7) Fujita K, Sano D, Kimura M：Anti-tumor effects of bevacizumab in combination with paclitaxel on head and neck squamous cell carcinoma. Oncol Rep 18：47－51, 2007
8) Fan Z, Masui H, Altas I, et al：Blockade of epidermal growth factor receptor function by bivalent and monovalent fragments of 225 anti-epidermal growth factor receptor monoclonal antibodies. Cancer Res 53：4637－4642, 1993
9) Bourhis J, Rivera F, Mesia R, et al：Phase Ⅰ/Ⅱ study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 24：2866－2872, 2006
10) Burtness B, Meredith AG, Flood W, et al：Phase Ⅲ randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer：an easterncooperative oncology group study. J Clin Oncol 23：8646－8654, 2005
11) Vermorken JB, Mesia R, Rivera F, et al：Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359：1116－1127, 2008
12) Ang KK, Berkey BA, Tu X, et al：Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res 62：7350－7356, 2002
13) Robert FE, Zekiel MP, Spencer SA, et al：Phase 1 study of anti-epiidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer. J Clin Oncol 19：3234－3243, 2001
14) Bonner JA, Harari PM, Giralt J, et al：Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354：567－578, 2006
15) Pfister DG, Su YB, Kraus DH, et al：Concunent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregjonally advanced, squamous cell head and neck cancer：a pilot phase Ⅱ study of a new combined-modality paradigm. J Clin Oncol 4：1072－1078, 2006

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Ⅱ．TPF 療法の現状

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はじめに

頭頸部がんの治療は手術が中心に行われているが進行した場合には放射線治療や化学療法を組み合わせた集学的治療が行われる。さらに近年では喉頭や咽頭を温存し発声や嚥下機能をできるだけ残す試みが積極的に行われ，進行がんに対する化学療法の重要性が増している[1]。放射線療法に化学療法を同時併用する化学放射線療法（CCRT）は，進行頭頸部がんに対して標準的な治療として高いエビデンスが証明されている。しかし，強い効果と同時に急性毒性が強く十分に効果的な CCRT が施行できない場合があり，近年では遅発性毒性も問題となっている。また，CCRT は局所制御率の向上には寄与しているが，遠隔転移に対する抑制効果は十分に証明されていない。一方，放射線療法や化学放射線療法の前に施行する導入化学療法（Induction Chemotherapy; IC）は，局所の腫瘍体積を減少する目的と遠隔転移の抑制を目的として行われてきた。そのレジメンはシスプラチン（CDDP）と 5-FU の併用（FP）が標準的レジメンとされている。進行した頭頸部がんに対して IC が奏効した症例は予後がよいことが知られている。特に IC によって臨床的に complete response（CR）が得られた症例の予後は良好であり，そのような症例は放射線療法を追加することによって拡大手術を回避でき，その結果喉頭などの臓器が温存されることが注目されるようになってきた[2]。

したがって IC を効果的に施行するために奏効率の高い多剤併用療法の開発が求められている。特に CR 率の高いレジメンが求められる。CDDP と 5-FU の併用療法は奏効率，すなわち CR と partial response（PR）をあわせた割合は高いが CR 率は 10～20％の報告が多く必ずしも良好とは考えられない[3]。

一方，近年では頭頸部腫瘍に対するタキサン系抗がん剤を含んだ多剤併用療法の有効性が示されている。現在，頭頸部がんに対して保険適応があるのはドセタキセル（DOC）であるが，本邦における進行頭頸部がんを対象とした DOC の第Ⅱ相試験では 22.2％の奏効率を示し[4]，CDDP との併用第Ⅱ相試験において奏効率 45％，生存期間中央値は 10 か月と良好な成績が得られ，海外においても DOC と CDDP の併用療法の奏効率は 33～53％，生存期間中央値 9.6～11 か月と同様に良好な成績が得られている[5-7]。さらに DOC と CDDP，5-FU の 3 剤併用（TPF 療法; TPF）は高い奏効率を示し，CR 率も従来の CDDP と 5-FU の 2 剤併用と比較して高いことが Colevas らによって報告され注目されるようになった[8]。しかし CDDP と 5-FU に DOC を加えることにより副作用も増加すると考えられる。今回，TPF による進行頭頸部がんに対する IC の有用性と，現在行われている様々な臨床研究について検討し，TPF に関する今後の展望について考察する。

1．TPF 療法による IC の有用性

大規模なメタアナリシスが，2000 年に pignon らによって報告されている。63 の無作為比較試験で 10,741 例の症例を対象としたものであり，化学療法の同時併用は放射線療法単独と比較して 5 年生存率で 8％の上乗せ効果を認めている[9]。さらに，2009 年にはデータが更新され，CCRT は 6.5％の 5 年生存率向上がみられており，進行頭頸部がんに対する CCRT は標準治療として認識されている[10]。一方，IC については，生存に対する上乗せ効果が認められないとされているが，FP を施行した 15 試験について解析した結果では FP による IC は 5 年生存に対する 5％（p=0.1）の上乗せ効果があったと報告されている[11]。さらに，FP に DOC を加えた 3 剤併用の TPF は強力な化学療法として注目されるようになった。1999 年に Colvas らは頭頸部がんに適応となったタキサン系薬剤である DOC を CDDP と 5-FU に加えたレジメンを報告して注目された。彼らは CDDP，5-FU，DOC とロイコボリンを加えた 4 剤併用を外来化学療法にも応用して報告している[12]。その奏効率は 100％と非常に優れたものであるが毒性も強くそのために 5-FU の減量を行い，さらにロイコボリンを併用しないレジメンも発表している[13]。そして，TPF の IC としての有用性に関して 2 つの第Ⅲ相試験が相次いで発表された。それ

表 1　TPF 療法と FP 療法の効果

	TAX323		TAX324	
	PF（n=181）	TPF（n=177）	PF（n=246）	TPF（n=255）
Overall Survival				
中央値，（月）os	14.5	18.8	30	71
ハザード比（95% CI）	0.73(0.56～0.94)		0.70(0.54～0.90)	
p-value	0.02		0.006	
Progression-free Survival				
中央値（月）	8.2	11	13	36
ハザード比（95% CI）	0.72(0.57～0.91)		0.71(0.56～0.90)	
Log-rank p-value	0.007		0.004	
奏効率，%	59*	72*	64**	72**
p-value	0.006		0.07	

*: CCRT 後　**: 化学療法後

表 2　TAX324 試験の長期成績

	TPF（n=255）	FP（n=246）	ハザード比	p 値
Overall Survival				
生存	131	101		
死亡	124	145		
生存期間中央値（月）	70.6	34.8	0.74（0.58～0.94）	0.014
生存率				
2年	67%	55%		
3年	62%	49%		
5年	52%	42%		
ステージ別生存（月）				
Ⅲ	90.2	65.1	0.69（0.36～1.31）	0.26
Ⅳ	58.6	25.1	0.74（0.57～0.97）	0.03
Progression-free Survival				
無増悪例	113	87		
無増悪期間中央値（月）	38.1	13.2	0.75（0.60～0.94）	0.011
無増悪割合				
2年	54%	42%		
3年	50%	38%		
5年	45%	34%		
ステージ別（月）				
Ⅲ	71.2	21.4	0.65（0.37～1.15）	0.14
Ⅳ	25.1	12.2	0.76（0.60～0.98）	0.03

（文献 16 から改変）

らは同時に 2007 年の New England Journal に掲載された TAX323 試験と TAX324 試験である[14,15]（表 1）。まず，TAX323 試験はヨーロッパの共同研究グループ EORTC から報告されたものであり，358 例の初回治療例で切除不能な局所進行頭頸部がん症例が登録された。これらは，導入化学療法として FP と TPF に無作為割り付けが行われた。FP として CDDP は 100 mg/m^{2}で第 1 日目に投与し 5-FU は 1,000 mg/m^{2}で第 1 日目から第 5 日目まで 5 日間の持続投与とした。TPF 療法では CDDP は 75 mg/m^2，DOC は 75 mg/m^{2}でともに第 1 日目に投与し，5-FU は 750 mg/m^{2}で第 1 日目から 5 日間の持続投与とした。導入化学療法は 21 日ごとに 4 コース施行され，その後に通常の放射線療法 70 Gy または多分割照射 74 Gy が行われた。その結果，奏効率は TPF が FP に対して有意に良好であり，無増悪生存期間と全生存期間でも有意に勝っていた。副作用では，TPF は好中球減少が FP と比較して grade 3，4 の発現が高かったが，悪心・嘔吐，口内炎，聴力障害などはむしろ FP の方が高く，FP において CDDP，5-FU の投与量が多いことに起因し，骨髄毒性以外は DOC を加えることによる副作用の増強は大きな問題にはならないと考えられた。次に，TAX324 試験は，米国の Posner らのグループから発表されたものであり，やはり TPF 療法または FP 療法を導入化学療法としてその後に CCRT を施行する第

Ⅲ相比較試験である。対象は未治療で切除不能症例と機能温存を目指した症例も含まれた。501例の症例が登録されTPFまたはFPに割り付けられ21日ごとに3コースの化学療法が施行された。FP療法はTAX323と同様であるがTPFはCDDP 100 mg/m^2・day 1，5-FU 1,000 mg/m^2・day 1～4としてDOCは75 mg/m^{2}でday 1に投与した。ICの後，カルボプラチン併用で70～74 Gyの放射線療法を施行した。本試験は2011年2月に中央値で6年の観察期間による長期成績が報告されている[16]。経過観察の中間値は72.2か月で5年生存率はTPFで52%，FP療法で42%であり，生存期間は中間値で各々，70.6か月，34.8か月とTPFで有意に勝っていた。部位別やステージ別に長期成績が解析されており，TPFは機能温存治療例やstage Ⅳで有意に生存期間が長い結果となっている（表2）。このようにTPFは優れた効果を示すが毒性も強いことが問題である。しかし長期経過では，胃瘻に依存する割合や気管切開を行った割合では両者ともに差がなかったとしており，TPFの副作用は長期的なQOLの低下には結びつかないと述べている。これらのデータから，進行頭頸部がんに対する化学療法の標準的レジメンはTPFであることのエビデンスが証明されつつある現状である。

2．われわれが施行しているTPF療法

2000年1月から2003年8月までに国立病院機構東京医療センターおよび慶応義塾大学医学部耳鼻咽喉科において，stage Ⅱ以上で遠隔転移のない未治療の頭頸部扁平上皮癌症例に対してICとして化学療法を施行する症例を対象にretrospectiveに検討した結果について述べる。施行に当たって，症例の一般状態Performance Status（PS）は0～1で年齢は20歳以上とし上限は設けなかった。また，投与前検査で骨髄，肝，腎など主要臓器の機能が保持されている症例とした。すべての症例で文書による副作用等に関する説明と同意を取得した。効果判定は頭頸部癌取扱い規約第3版に従い，副作用基準は，National cancer institute toxicity criteria ver. 2.0 1998日本語訳JCOG版を使用した。本研究に先立って，3剤の投与量を検討した[8]。まず進行再発頭頸部がん症例3例に対して，標準的投与量であるCDDP 70 mg/m^2 day 1，5-FU 700 mg/m^2/dayでday 1からday 5持続投与に加えてDOCを60 mg/m^{2}でday 1に点滴投与した。その結果，3例すべてでgrade Ⅳの副作用（白血球減少と腎機能低下，血小板減少，白血球減少）がみられた。そのため，CDDPを60 mg/m^{2}とし5-FUを700 mg/m^2/dayでday 1からday 4として進行再発がん4例で検討した結果，grade Ⅳの白血球減少が1例のみで，G-CSF併用で安全に投与可能であった。そこで本研究の投与スケジュールは，DOCとCDDPはおのおの60 mg/m^{2}でday 1に点滴投与し，5-FUは700 mg/m^2/dayでday 1からday 4まで96時間の持続点滴投与とした。CDDPの腎毒性軽減のためday 0に2,000 mL，day 1に4,000 mL，day 2に2,000 mLの水分負荷を行った。また，制吐剤としてグラニセトロン（40 μg/kg）をCDDP投与の1時間前に30分で点滴投与した。好中球減少については，grade 3以上又は発熱性好中球減少に対してG-CSF製剤を使用した。今回の対象となった症例は51例で男性44例，女性7例，平均年齢は60.8歳であった。各症例のstageはstage Ⅱが6例12.3%，stage Ⅲが7例で14.3%，stage Ⅳが36例73.5%でstage Ⅲ以上が87.8%をしめた。ただしstage分類のない聴器がん症2例はstage別の検討からは除外した。効果ではCRが15例，29.4%，PRが24例で47.1%であり奏効率は76.5%となった。部位別での奏効率は中咽頭癌で奏効例6例75%，下咽頭癌で奏効例19例86.4%，舌・口腔癌で奏効例7例70%であった。Stage別での効果はstage Ⅱで奏効例5例83.3%，stage Ⅲで奏効例7例100%でありstage Ⅳでは奏効例26例72.2%であった。症例の予後に関してCRとなった症例15例では，1例のみ追加手術を行い，14例では放射線治療を追加しそのうち2例で再発し手術となった。副作用では白血球減少が主なものでGrade 1以上は96.1%発現しGrade 3は33例64.7%に発現した。G-CSFを使用したためGrade 4となった症例はみられなかった。そのほかの副作用としてgrade 1の脱毛がほぼ全例に認められ，2コース後には21例41%でgrade 2の著明な脱毛がみられたがいずれも投与後約2か月で回復した。下痢はgrade 2が12例24%に発症し，3例でgrade 3となり輸液を要した。粘膜炎は軽度でgrade 2以上の症例はなかった。以上のような治療効果と副作用であったが，予後解析は行っていない。ICのあと様々な治療が行われており解析には不適当と考えられ，予後については前向き試験を行って明らかにすべき

表3　TPF療法によるIC施行の推奨基準

1	良好なperformance status
2	各臓器機能が十分に保たれていること
	クレアチニンクリアランス　60 mg/min以上
	WBC　4,000/mL以上
	Hb　12.0 mg/dL以上　など
3	局所進行がん: Bulky mass
4	下深頸部転移
5	推奨される原発部位
	中咽頭癌
	下咽頭癌
	喉頭癌

（文献19から改変）