Induction chemotherapy with docetaxel, cisplatin, fluorouracil and *l*-leucovorin for locally advanced head and neck cancers: a modified regimen for Japanese patients

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Combination chemotherapy with docetaxel (T), cisplatin (P), fluorouracil (5-FU) and leucovorin has been reported to have major activity against squamous cell carcinoma of the head and neck (SCCHN) administered as a 4-day (TPFL4) or 5-day (TPFL5) regimen. The purpose of this study was to evaluate the efficacy and toxicity of a modified TPFL regimen (m-TPFL) for locally advanced SCCHN, consisting of a modified dosage with docetaxel, cisplatin, 5-FU and *l*-leucovorin (*l*-LV) designed for Japanese patients. Organ preservation of the primary tumor site was also assessed. Thirty-four Japanese patients with locally advanced SCCHN were eligible. Docetaxel was administered as a 1-h i.v. infusion at 48 mg/m^2 on day 1; cisplatin, 24 mg/m^2/day; 5-FU, 560 mg/m^2/day and *l*-LV, 125 mg/body/day were delivered on days 1–4 by continuous i.v. infusion. This regimen was administered every 28 days. Patients who achieved a complete response (CR) after induction chemotherapy underwent radiation therapy alone. Ninety-one cycles were administered. The main hematological toxicity was neutropenia, classified as grade III or IV in 18.7% of cycles. The most common non-hematologic toxicities included anorexia, stomatitis and alopecia. The clinical overall response rate to m-TPFL was 88.2%, with 58.8% CRs and 29.4% partial responses. After definitive locoregional therapy, 25 of 34 patients were disease-free with preserved primary tumor site anatomy. Overall and progression-free survival rates at the 2-year follow-up are 92.8 and 75.3%, respectively. Our m-TPFL regimen designed for Japanese patients yielded excellent response rates with an acceptable toxicity profile in good-performance-status patients. *Anti-Cancer Drugs* 14:801–807 © 2003 Lippincott Williams & Wilkins.

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is a potentially curable tumor when treated adequately. However, approximately two-thirds of patients with SCCHN present with locoregionally advanced disease [1]. Advanced SCCHN frequently recurs after optimal local treatment and 3- to 5-year survival rates remain in the range of 20–40% [2,3]. Standard therapy for advanced SCCHN has been focused on local and regional approaches such as surgery and/or radiation therapy, but surgical management is associated with significant morbidity and no change with respect to survival has been noted in the last two decades. Some randomized trials have shown that induction chemotherapy followed by radiation therapy is equivalent to surgery in survival rates, with the significant advantage of organ preservation of the primary tumor site in a subset of patients. A recent meta-analysis on chemo-radiotherapy in head and neck cancer reported by Pignon *et al.* [4] showed that only concurrent treatment results in a survival benefit.

Although chemotherapy plays a central role in combination induction therapy for SCCHN, optimal combination remains controversial. The standard regimen for induction chemotherapy consists of cisplatin and 5-fluorouracil (5-FU), which has been associated with a complete response (CR) rate between 23 and 43% [3,5–7]. The survival rate of patients with advanced SCCHN remains poor in spite of the combination chemotherapy with cisplatin and 5-FU (PF). Based on these results, a combination of cisplatin, 5-FU and leucovorin (PFL) was developed as an induction regimen for SCCHN and has led to increased CR rates when compared with the results of the PF regimen [8,9].

Recently, docetaxel (Taxotere) has been shown to possess significant single-agent antitumor activity in patients with SCCHN in multiple phase II studies [10,11]. Combination chemotherapy with the addition of docetaxel to the PFL regimen (TPFL) has been reported to have major activity against SCCHN administered as a 4-day (TPFL4) or 5-day (TPFL5) regimen [12,13]. Since

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the standard dosage of TPFL4 or TPFL5 regimen was thought to be high for Japanese patients, we designed a modified TPFL regimen (m-TPFL) for locally advanced SCCHN, consisting of decreased dosages of docetaxel, cisplatin, 5-FU and *l*-leucovorin (*l*-LV). The purpose of this study was to evaluate the efficacy and toxicity of m-TPFL regimen in Japanese patients with locally advanced SCCHN. Organ preservation of the primary tumor site was also assessed.

Patient and methods

Eligible patients were required to have histologically confirmed SCCHN. All patients were required to have measurable or evaluable disease, a WHO performance status (PS) of 0–2 and a life expectancy of >3 months. Patients were also required to have adequate renal function (24-h creatinine clearance value >50 ml/min), and normal cardiac and hematologic functions. All patients signed informed-consent statements before chemotherapy was started.

Patients were staged by physical examination according to the 1997 International Union Against Cancer (UICC) classification [14]. Antitumor responses were assessed by physical examination, computed tomographic (CT) scan and laryngoscopy in some patients after every cycle. Criteria of CR, partial response (PR), no change (NC) and progressive disease (PD) were based on the standard definitions established by the WHO [15]. Toxic effects were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [16]. The survival curves were estimated using the Kaplan–Meier technique [17].

TPFL therapy consisted of 2500 ml prehydration of normal saline on day 0, and 16 mg of dexamethasone and 10 mg of azasetron hydrochloride administered before docetaxel. Docetaxel 48 mg/m^2 was administered i.v. in 250 ml of normal saline solution (NS) over 1 h on day 1. Three hours after the completion of the docetaxel infusion, cisplatin 24 mg/m^2/day on days 1–4 (total dose 96 mg/m^2), 5-FU 560 mg/m^2/day on days 1–4 (total dose 2240 mg/m^2) and *l*-LV 125 mg/body/day on days 1–4 (total dose 500 mg/body) were delivered by continuous i.v. infusion with 2.5 l of NS per day. These doses were determined according to the doses of PF regimens employed in Japan. Patients received additional prophylactic antiemetics including hydrocortisone 100 mg and haloperidol 5 mg i.v. on days 2 through 4 of chemotherapy. Subcutaneous granulocyte colony stimulating factor for patients was administered until the absolute neutrophil count exceeded 10 000 cells/μl. Antibiotic cephalosporin was administered i.v. twice daily on days 5–10. Through chemotherapy and post-chemotherapy, patients received furosemide 10 or 20 mg when they had weight gain over 0.5 or 1 kg, respectively. This regimen was repeated every 28 days until the patient exhibited dose-limiting toxicity. There were no dose reductions in docetaxel or *l*-LV. Cisplatin was reduced by 20% after episodes of serum creatinine levels in excess of 25% above the pre-treatment value and creatinine clearance measured by 24-h urine collection to less than 40 ml/min. 5-FU was reduced by 10% after episodes of grade 4 NCI-CTC mucositis and diarrhea.

Patients who achieved a CR after TPFL chemotherapy underwent radiation therapy alone. Using a Scanditronix Microtron MM-22 (Hitachi, Tokyo, Japan) radiation therapy was performed at an exposure of 2.0 Gy/fx 4 times per week. The total radiation dose to the primary site was between 60 and 66 Gy. The radiation dose to neck lymph nodes was 60 Gy if metastasis to those lymph nodes was positive at initial diagnosis, otherwise the dose to neck lymph nodes was 40 Gy. Those who had a PR or NC or PD after chemotherapy underwent definitive local treatment (surgery and/or radiation) based on the physician's preference.

Results

Between May 2000 and October 2002, 34 patients with locally advanced SCCHN were enrolled in the study. The results were analyzed on 1 March 2003, with a median of 21 months (range 6–35 months). The median age of patients at enrollment was 59 years, with a range of 30–78 years. At enrollment, we assessed 28 patients to be of WHO PS 0, two to be of PS 1 and four to be PS 2. The distribution of the primary tumor sites was as follows: oral cavity, $n = 7$; nasopharynx, $n = 1$; oropharynx, $n = 11$; hypopharynx, $n = 11$; and larynx, $n = 4$. All patients had stage III or IV disease, and 70.6% had stage IV disease (Tables 1 and 2).

Ninety-one cycles of TPFL were administered. One patient received five cycles of TPFL, three patients received four cycles, 16 patients received three cycles, 12 patients received two cycles and two patients received one cycle.

Table 1 Patient characteristics

No. registered	34
Sex	
male	31
female	3
Age (years)	
median	59.0
range	30–78
WHO PS	
0	28
1	2
2	4
Primary tumor site	
oral cavity	7
nasopharynx	1
oropharynx	11
hypopharynx	11
larynx	4

Table 2 Primary and nodal staging

	N0	N1	N2			N3	Total
			a	b	c		
T1							0
T2		8		1	1	1	11
T3	1	1	2	2	2		8
T4	2	3		6	2	2	15
Total	3	12	2	9	5	3	34
Stage III	10						
Stage IV	24						
Total	34						

Table 3 Response rates to TPFL

Sites	CR		PR		PR+CR	
	N	%	*N*	%	*N*	%
Primary tumor ($n=34$)	23	67.6	9	26.5	32	94.1
Neck lymph nodes ($n=31$)	21	67.7	6	19.4	27	87.1
Overall ($n=34$)	20	58.8	10	29.4	30	88.2

Table 4 Hematological toxicity per cycle

Toxicities	Grade 1		Grade 2		Grade 3		Grade 4	
	N	%	*N*	%	*N*	%	*N*	%
Anemia	24	26.4	14	19.0	1	1.1	0	0
Leukopenia	34	37.4	31	34.1	7	7.7	0	0
Neutropenia	19	20.9	31	34.1	16	17.6	1	1.1
Thrombocytopenia	11	12.1	8	8.8	2	2.2	0	0

$N=91$ cycles.

Response to m-TPFL

Overall, 20 of 34 patients (58.8%) achieved a CR and 10 of 34 (29.4%) achieved a PR, for an overall response rate (ORR) of 88.2% (30 of 34) to TPFL. At the primary tumor site, 23 of 34 patients achieved a CR and nine of 34 achieved a PR. In the neck lymph nodes, 21 of 31 patients achieved a CR and six of 31 achieved a PR (Table 3).

Toxicity

Toxicity was assessed in all 34 patients. Complete toxicity data were available for 91 cycles and complete hematologic toxicity data were available for 91 cycles. Hematologic toxicity is detailed in Table 4. Grade 3–4 neutropenia occurred in 18.7% of the course. The onset of neutropenia was quite rapid, with the nadir occurring between day 5 and day 10 after docetaxel administration, followed by a very rapid recovery. Thrombocytopenia was mild, with two episodes (2.2%) of grade 3 thrombocytopenia and no clinically significant bleeding. There was one episode of grade 3 anemia and 20 cycles were associated with red blood cell transfusions. The most common acute non-hematologic toxicities included anorexia, stomatitis and diarrhea. Alopecia was nearly universal, observed in 33 of 34 patients. Non-hematologic toxicities are listed in Table 5.

Table 5 Non-hematological toxicity per cycle

Toxicities	Grade 1		Grade 2		Grade 3		Grade 4	
	N	%	*N*	%	*N*	%	*N*	%
Anorexia	29	31.9	26	28.6	20	22		
Stomatitis	35	38.5	30	33.0	5	5.5		
Diarrhea	26	28.6	11	12.1	2	2.2		
Vomiting	13	14.3	3	3.3				
Fever	12	13.2	4	4.4				
Febrile neutropenia					4	4.4		
Neuropathy (sensory)	3	3.3						
Creatinine			2	2.2				

$N=91$ cycles.

Treatment outcome after induction chemotherapy and definitive local therapy (Fig. 1)

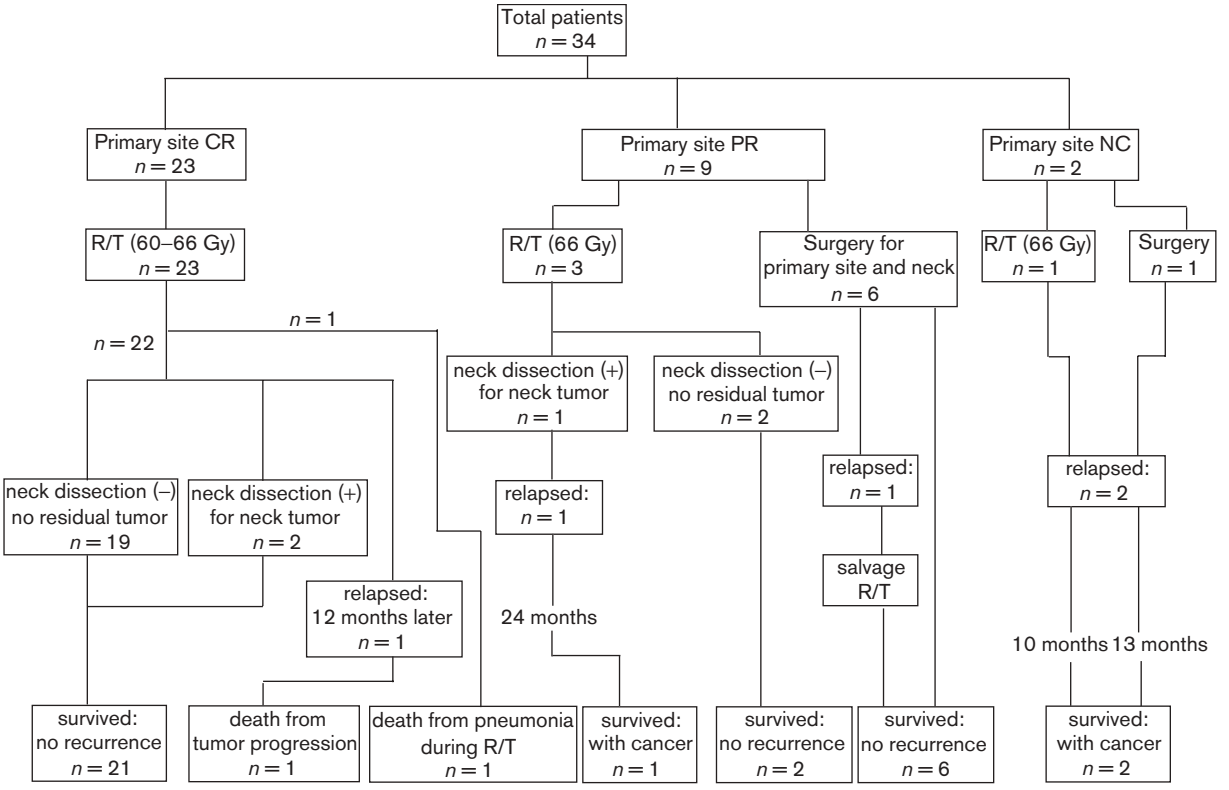
Twenty-three patients whose primary tumor sites achieved a CR with TPFL chemotherapy underwent a definitive dose (60–66 Gy) of radiation therapy alone to the head and neck sites. Twenty-one patients showed no evidence of disease and none of these patients has had recurrent disease to date. Two patients underwent neck dissection for residual neck disease after radiation therapy. One patient died from pneumonia during radiation therapy. The other patient whose neck site achieved a PR with TPFL chemotherapy demonstrated neck-site relapse 12 months after start of therapy and then died of tumor progression.

Three of nine patients whose primary sites achieved a PR with TPFL chemotherapy underwent radiation therapy, with one of them undergoing neck dissection for residual neck disease. One of three patients relapsed in the primary site, but was alive with cancer 24 months after treatment. Six patients received surgical therapy both in the primary tumor and neck sites. One of six patients demonstrated relapse in the contralateral neck, but was rescued by salvage radiation therapy and was alive at 30 months without evidence of metastatic disease or another locoregional recurrence.

There were two patients whose primary sites achieved a NC with TPFL chemotherapy. One patient with a T3N2c base of tongue tumor received radiation therapy because he refused surgical treatment including total laryngectomy, but achieved no response after radiotherapy. He was alive at 10 months with disease. The other patient with a T4N2c laryngeal tumor underwent surgery after only one cycle of TPFL chemotherapy because he refused chemotherapy. He relapsed with lung metastases at 13 months, but he is alive at 20 months.

Adverse reaction after definitive locoregional therapy included a prolonged laryngeal edema lasting for 3–5 months in three patients (two in hypopharyngeal cancer and one in laryngeal cancer) and prolonged oral ulceration lasting for 5 months in one tongue cancer patient.

Fig. 1



Treatment outcome after induction chemotherapy. R/T: radiation therapy; CR: complete response; PR: partial response; NC: no change.

However, these patients responded to the usual conservative therapy and recovered well.

Primary site pathologic findings after TPFL chemotherapy

Twenty-seven patients who were destined to receive radiation therapy after the completion of TPFL chemotherapy underwent biopsy of the primary tumor site. The other seven patients underwent surgical treatment for primary and neck sites. Of 27 patients, biopsy specimens of the primary site of 23 patients who achieved a clinical CR were pathological negative. The remaining four patients who achieved a PR or NC had pathological positive biopsies. One of the seven patients who underwent surgery for the primary site had a pathologic CR. The remaining six patients had pathologic PRs.

Organ preservation

Among the 34 assessable patients for organ preservation, seven patients underwent surgical resection of the primary organ sites after TPFL chemotherapy. After definitive locoregional therapy, 25 of the 34 patients (73.5%) had a functional primary organ site without disease. With a median follow-up of 21 months, 23 of the 34 patients (67.6%) showed no evidence of disease and had organ preservation at the primary site.

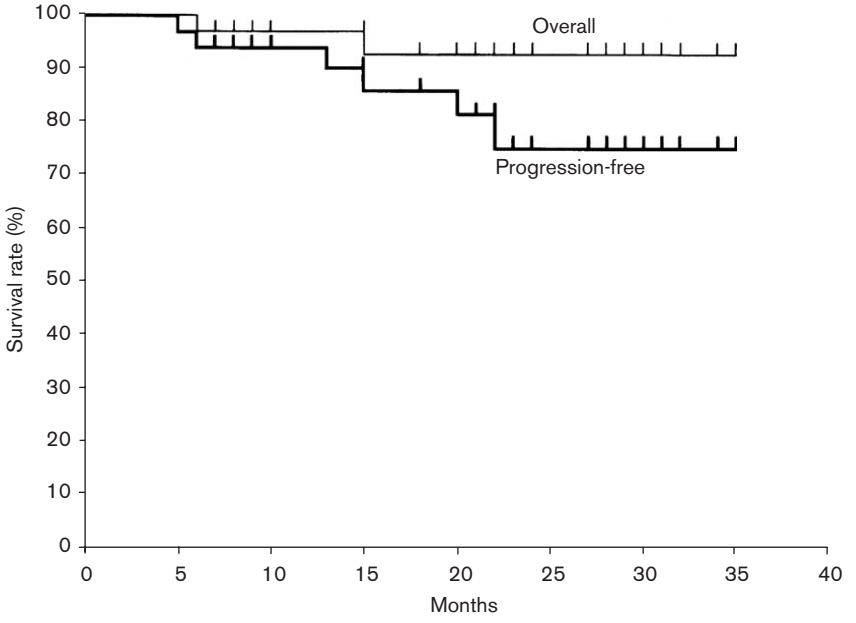
Survival

Although survival was not a primary end point in this study, as of 1 March 2003, the 2-year actual survival rate was 92.8% [95% confidence interval (CI) 82.9–100%]. Progression-free survival at 2-year was 75.3% (95% CI 56.8–93.8) (Fig. 2).

Discussion

Induction chemotherapy for advanced SCCHN with cisplatin and 5-FU (PF), the gold standard combination in the world, has been effective in preserving the primary tumor site anatomy without compromising survival. However, this regimen has failed to increase survival of patients with locally advanced SCCHN over the last decade. In randomized trials, the ORRs of PF-based regimens in untreated patients with locally advanced SCCHN ranged from 70 to 88%, but CR rates ranged from only 23 to 43%. Since previous data obtained from clinical studies suggested that improved survival could be achieved depending on obtaining a pathologic CR, new regimens have been investigated in an attempt to acquire

Fig. 2



Overall and progression-free survival.

a high CR rate in the treatment of locally advanced SCCHN.

TPFL, the regimen with the addition of docetaxel and leucovorin to PF, is one of the most promising regimens against advanced SCCHN. Colevas *et al.* reported a high CR rate (61–63%) in patients with advanced SCCHN when a 4-day (TPFL4) or 5-day (TPFL5) regimen was administered [12,13]. These results prompted us to employ induction chemotherapy with a modified TPFL regimen (m-TPFL), designed for treatment-naive Japanese patients with advanced SCCHN. The doses of docetaxel, cisplatin and 5-FU used in our study were relatively reduced in comparison to those used in Europe and America. This is due to the data obtained from previous clinical studies in Japanese patients. Although the recommended dose of docetaxel was 100 mg/m^2 every 3 weeks in Europe and America, doses of 70 mg/m^2 or higher were rejected in a Japanese phase I study, which resulted in a reduction in the dose of docetaxel to 60 mg/m^2 every 3 weeks in many studies undertaken in Japan [10,11,18,19]. The dose of cisplatin used in the TPFL4 regimen is 120 mg/m^2, but the recommended total dose of cisplatin per course ranged from 80 to 100 mg/m^2 on the basis of pharmacokinetics of cisplatin in PF therapy [20], which is consistent with the dose in the present study. Doses of 5-FU used in many studies for Japanese patients with SCCHN have ranged from 700 to 800 mg/m^2/day, whereas the dose of 1000 mg/m^2/day is employed in Europe and America [3,5,6,21–24]. This is mainly due to the adverse effects that occurred in Japanese patients receiving relatively lower doses of 5-FU [25], although the reported enzymatic activity of dihydropyrimidine dehydrogenase, the rate-limiting enzyme in FU catabolism, is not reduced in the Japanese [26–28]. The reason for a high incidence of adverse effects of 5-FU in Japanese patients has not been well determined, but we decided the doses of our TPFL regimen from these reports describing adverse effects of 5-FU. The modification of doses resulted in approximately 0.8 times the dose of docetaxel, cisplatin and 5-FU reported in the TPFL4 regimen [13]. In spite of the decreased dose of the m-TPFL regimen, patients in the present study achieved an ORR of 88.2% and a CR rate of 58.8%, which were almost equivalent to those obtained from the TPFL4 regimen [13].

The m-TPFL regimen was generally well tolerated. The most common toxicity was myelosuppression, in particular neutropenia with the nadir count predictably observed on days 5–10. We observed 18.7% of cycles with grade 3–4 neutropenia and 4.4% suffered from febrile neutropenia. There was no chemotherapy-related death. Colevas *et al.* reported an 8% incidence of grade 3–4 neutropenia and 2% febrile neutropenia in patients receiving the TPFL4 regimen. Other myelosuppression in the present study was mild to moderate, including 1.1% grade 3–4 anemia and 2.2% grade 3–4 thrombocytopenia, which would be acceptable. In non-hematologic toxicities the most common grade 3–4 toxicities included anorexia (22.0%) and stomatitis (5.5%).

The preservation of organ function is one of the major treatment goals in patients with SCCHN. The high feasibility of organ preservation of the primary tumor site has been the advantage of induction chemotherapy over surgical treatment, without compromising overall survival. This goal has been achieved by the PF-based regimen, as was reported by the Veterans Affairs Laryngeal Cancer Study Group [5]. The European Organization for Research and Treatment of Cancer has also reported that the 3- and 5-year estimates of retaining a functional larynx for patients treated with induction chemotherapy were 42 and 35%, according to their prospective, randomized study in which 194 patients with advanced cancer of the hypopharynx were enrolled [3]. In the present study, 23 of 34 patients (67.6%) with advanced SCCHN were disease-free with preserved primary tumor site anatomy. This result is similar to those reported previously [5]. Since definitive radiation therapy was administered in principle to patients who achieved a CR in this study, a higher primary organ preservation rate might be expected if it had been administered to all patients who achieved CR or PR.

The present study also suggests that a high CR rate would be essential to the survival of patients with SCCHN. Of 23 patients who achieved primary-site CR, 19 patients achieved a clinical CR. All but one who achieved a clinical CR did not suffer from tumor recurrence in any regional or distant field. The other patient who achieved a CR died from pneumonia, but was tumor-free. These data suggested that high CR rates with induction chemotherapy would be essential not only for the preservation of the primary tumor site, but also for the improvement of survival rates. Pathologic CR is more important as a predictor of survival than clinical CR [8,12]. In this study, pathological assessment of biopsy specimens taken from primary sites after induction chemotherapy was equal to the clinical assessment. This is probably because patients received periodical otolaryngological examinations including CT, magnetic resonance imaging and laryngopharyngoscopy at the primary tumor site by the same experienced otolaryngologist. It is often difficult to detect the primary tumor site correctly in patients who have achieved a clinical CR. In these patients, sampling errors may possibly occur in post-treatment tumor biopsies. Thus biopsy specimens should be taken from two or more sites, which are identified from the endoscopic photography taken before the start of treatment, to reduce the incidence of sampling errors.

Induction chemotherapy may also predict the effectiveness of subsequent radiation therapy [5,29]. Since patients with SCCHN may have a high risk of primary treatment failure and death, induction chemotherapy associated with a high CR rate before definitive local therapy appears to be an attractive approach for the preservation of organ function. Although the median follow-up was relatively short, the high rate of organ preservation with an excellent survival rate is highly encouraging.

In conclusion, our m-TPFL regimen designed for Japanese patients yielded excellent response rates with an acceptable toxicity profile in good-performance-status patients. A high CR rate obtained with the m-TPFL regimen possibly contributed to the organ preservation of the primary tumor site without apparently compromising survival. Although preliminary data concerning response rate and survival are promising, longer follow-up and greater experience are necessary. Further evaluation of combination chemotherapy with these agents is justified in Japanese patients with locally advanced SCCHN.

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