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ORIGINAL ARTICLE

A new combined therapy for functional organ preservation and survival in lateral oropharyngeal wall cancer

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Abstract

Conclusion: The outcome of this treatment was good, indicating that it is safe and effective. A favorable outcome was obtained, especially in patients with T3, N0–1, and N2a–b cancer, while outcome remained unfavorable in patients with T4a and N2c cancer. Consideration should be given to the need for intensity-modulated radiation therapy (IMRT) and maintenance therapy. *Objective:* To improve the survival and functional organ preservation rates in patients with lateral oropharyngeal squamous cell carcinoma. *Methods:* The primary site was treated conservatively by neoadjuvant chemotherapy and/or concurrent chemoradiation therapy. Chemotherapy was administered by superselective intra-arterial infusion and cervical lymph node metastasis was treated by radical neck dissection. *Results:* Among 71 patients, the 5- and 10-year overall survival rates were 85.1% and 63.5%, respectively; and the 5- and 10-year functional organ preservation rates were 61.0% and 51.6%, respectively. The outcomes were especially good in patients with T3 N0–1, and N2a–b cancer. All patients with N2c cancer had poor outcomes.

Keywords: *Head and neck cancer, squamous cell carcinoma, neoadjuvant chemotherapy, concurrent chemoradiation therapy, neck dissection*

Introduction

The traditional treatment of advanced head and neck cancer is en bloc surgery, that is, total resection of the primary site together with any cervical lymph node metastases, and this has continued with little change in Japan. The causes of death due to head and neck cancer are broadly classified into three categories: failure to control the primary site, failure to control cervical lymph node metastasis, and distant metastasis. Head and neck surgeons and oncologists can contribute to functional organ preservation and survival by improving their knowledge and skills.

We previously reported improvement in functional organ preservation in patients with tongue cancer by considering the chemotherapy drugs used and their route of administration, and the timing of radiation therapy [1]. We also reported that concurrent chemoradiation therapy (CCRT) for laryngeal cancer was effective for organ preservation, but not useful for improving the survival rate [2,3]. However, CCRT in combination with docetaxel (DOC) improved both functional laryngeal preservation and overall survival [4].

Neoadjuvant chemotherapy (NAC) consisting of two courses of superselective intra-arterial infusion chemotherapy with DOC, cisplatin (CDDP), and 5-fluorouracil (5-FU), followed by CCRT consisting of two additional courses of superselective intra-arterial infusion chemotherapy in patients who did not achieve a complete response (CR) or partial response (PR) after NAC, achieved good outcomes

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in terms of functional organ preservation and overall survival in patients with advanced anterior oropharyngeal wall cancer, advanced laryngeal cancer, and advanced hypopharyngeal cancer, for whom laryngectomy was recommended [5–7]. The consistent concept underlying these treatments is to treat the primary site as conservatively as possible for functional organ preservation, but treat cervical lymph node metastasis with radical neck dissection for good overall survival.

In this article, the results of our treatment of advanced but operable lateral oropharyngeal squamous cell carcinoma with the aim of improving functional organ preservation and overall survival rates are reported.

Patients with T4b or N3 cancer were excluded from this study according to their request. In lateral oropharyngeal squamous cell carcinoma, however, the primary site is usually unilateral, but patients with advanced cases often have bilateral cervical lymph node metastasis. This significant clinical problem is discussed in this article.

Material and methods

Patients

The study group comprised a total of 71 patients with lateral oropharyngeal squamous cell carcinoma who were treated at Nihon University Hospital and related hospitals between April 2000 and March 2011. The patients were 60 males and 11 females aged 37–75 years (mean 63 years, median 64 years). None of the patients had previously been treated for their disease.

All patients were diagnosed with squamous cell carcinoma, which was well differentiated in 17 patients, well to moderately differentiated in 8 patients, moderately differentiated in 26 patients, moderately to poorly differentiated in 12 patients, and poorly differentiated in 8 patients (Table I).

The seventh edition of the UICC classification (2009) was used for TNM classification.

T classification was T3 in 31 patients and T4a in 40 patients; and N classification was N0 in 4 patients, N1 in 21 patients, N2a in 6 patients, N2b in 22 patients, and N2c in 18 patients. Twenty-four patients had stage III and 47 had stage IVA disease (Table II).

In this study, all 71 patients personally visited our hospital through the media that patients willingly received this treatment, despite the recommendation from their previous physicians for surgical treatment. Only patients with advanced cancer that was suitable for curative surgery were included. Patients with T1, T2, T4b, and N3 cancer were excluded from the study. Examination for human papillomavirus (HPV) infection was not performed.

Table I. Demographic characteristics of the patients (n = 71).

Characteristic	Value
Sex	
Male	60
Female	11
Age (years)	
Mean	63 (37–75)
Median	64
Treatment status	
Untreated	71
Previously treated	0
Recurrence	0
Histological type	
Squamous cell carcinoma	71
Well differentiated	17
Well to moderately differentiated	8
Moderately differentiated	26
Moderately to poorly differentiated	12
Poorly differentiated	8

Methods

The femoral artery was catheterized under fluoroscopic guidance, and an artery feeding the tumor was identified for intra-arterial administration of DOC (60 mg/m^2) and CDDP (60 mg/m^2) over 30–60 min. The neutralizing agent sodium thiosulfate was administered intravenously immediately before administration of CDDP. After administration of the anticancer drugs, hydrocortisone was administered intra-arterially to protect vascular endothelial cells and prevent vomiting. Starting on day 2, 5-FU (750 mg/m^2/day) was administered by continuous intravenous infusion over 120 h. During CCRT, the doses of DOC, CDDP, and 5-FU were reduced to 50 mg/m^2, 50 mg/m^2, and 600 mg/m^2/day, respectively (Table III).

Table II. TNM classifications* of the patients.

	N0	N1	N2a	N2b	N2c	N3
T1						
T2						
T3	4	20	3	4		
T4a		1	3	18	18	
T4b						

*UICC 7th edition, 2009.

Table III. Schedule for superselective intra-arterial infusion chemotherapy.

Before chemotherapy	Day 1	Days 2–6
Pre-hydration: 2000 ml i.v.	Hydration: 3000 ml i.v.	Hydration: 2000 ml i.v.
	Docetaxel hydrate: 50–60 mg/m^2 i.a.	5-FU: 600–750 mg/m^2/day i.v.
	CDDP: 50–60 mg/m^2 i.a.	
	Hydrocortisone: 300 mg/body i.a.	
	STS: 9 g/m^2 i.v.	
	STS: 12 g/m^2 i.v.	

CDDP, cisplatin; 5-FU, 5-fluorouracil; i.a., intra-arterial; i.v., intravenous; STS, sodium thiosulfate.

Two courses of superselective intra-arterial infusion chemotherapy were administered as NAC, followed by additional courses of superselective intra-arterial infusion chemotherapy in patients who achieved a CR or PR. Patients who did not achieve a CR or PR after NAC received CCRT with additional courses of superselective intra-arterial infusion chemotherapy, which was continued if a CR was achieved at 40 Gy. If a CR was not achieved at 40 Gy, patients underwent radical excision of the tumor with reconstructive surgery (Figure 1). Cervical lymph node metastasis unresponsive to this treatment was aggressively treated by neck dissection. Patients were carefully examined for the presence of recurrence, metastasis, and double cancers at regular intervals and followed up. If any of these symptoms was found, the patients received further treatment. No maintenance therapy was given.

Analysis

The antitumor efficacy (i.e. response) was assessed according to the World Health Organization (WHO) criteria. After the completion of treatment and resolution of secondary lesions such as mucositis, biopsy was performed in all patients except those who had gross residual tumor after 40 Gy of radiation therapy.

Statistical analyses were performed using the Kaplan–Meier method for the determination of overall survival and functional organ preservation rates. The log-rank test and generalized Wilcoxon test were used to determine the significance of differences between groups, and the Student's t test, Fisher's exact test, and χ^2 test were used to examine the population bias. Side effects were described using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (JCOG/JSCO version).

Evaluation of pharyngeal functions

The following tests were used in the evaluation of disorders of aspiration, articulation, and swallowing: (1) FEV1.0% (forced expiratory volume in 1 second percent), PaO_2 (partial pressure of arterial oxygen), and $PaCO_2$ (partial pressure of arterial carbon

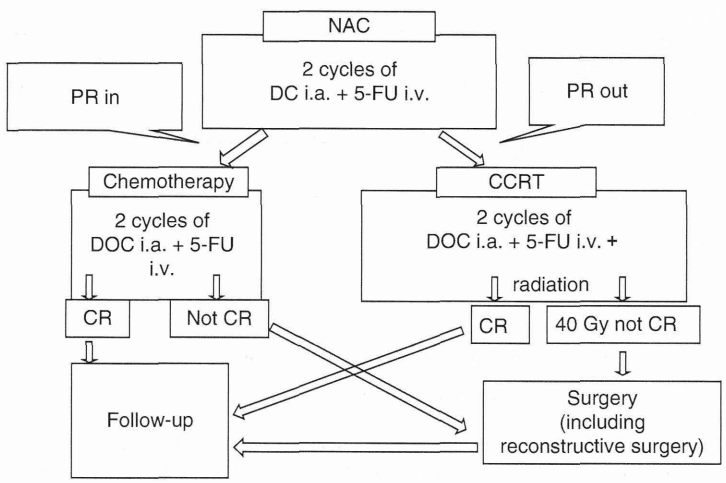

Figure 1. Flow diagram of treatment strategy. CCRT, concurrent chemoradiation therapy; CR, complete response; DOC, docetaxel; 5-FU, 5-fluorouracil; i.a., intra-arterial; i.v., intravenous; NAC, neoadjuvant chemotherapy; PR, partial response.

dioxide) (for aspiration); (2) word intelligibility testing using phonetic contrasts for Japanese speakers with articulation disorders (by speech therapist) (for articulation); and (3) video fluoroscopic examination of swallowing (VF) (for swallowing).

Results

Response to superselective intra-arterial infusion chemotherapy

Of the 71 patients, 56, 15, 0, and 0 showed CR, PR, no change (NC), and progressive disease (PD), respectively, with an overall response rate of 100% and a CR rate of 78.9%.

Radical surgery with reconstruction

Of the 71 patients, 24 patients (33.8%) underwent a radical operation including reconstructive surgery.

According to T classification, 3 (9.7%) of 31 patients with T3 cancer and 21 (52.5%) of 40 patients with T4a cancer underwent a radical operation including reconstructive surgery, showing that it was performed more frequently in patients with T4a cancer. Two of the 25 patients (8.0%) with N0–1 cancer, 7 of the 28 patients (25.0%) with N2a–b cancer, and 15 of the 18 patients (83.3%) with N2c cancer underwent a radical operation including reconstructive surgery, showing that it was performed in the dominant majority of patients with N2c cancer.

Overall survival according to T classification (Kaplan–Meier method)

The 5- and 10-year overall survival rates for all 71 patients were 85.1% and 63.5%, respectively. The follow-up period ranged from 471 to 4493 days (median 1991 days) (Figure 2). The 5- and 10-year overall survival rates for the 31 patients with T3 cancer were 98.5% and 90.5%, respectively (range of follow-up period 841–4493 days, median 2752 days). The 5- and 10-year overall survival rates for the 40 patients with T4a cancer were 51.3% and 45.7%, respectively (range of follow-up period 471–4300 days, median 1811 days). Overall survival was significantly better in patients with T3 cancer than in patients with T4a cancer ($p < 0.001$) (Figure 2).

Overall survival according to N classification (Kaplan–Meier method)

The 5- and 10-year overall survival rates for the 25 patients with N0–1 cancer were 95.8% and 89.8%, respectively (range of follow-up period 841–4493 days, median 2708 days). The 5- and 10-year overall survival rates for the 28 patients with N2a–b cancer were 85.6% and 83.6%, respectively (range of follow-up period 877–4300 days, median 2379 days). The 5- and 10-year overall survival rates for the 18 patients with N2c cancer were 22.2% and 0%, respectively (range of follow-up period 471–2605 days, median 1485 days) (Figure 3). There was no significant difference in overall survival between patients in the N0–1 and N2a–b groups ($p = 0.90$), but overall survival was

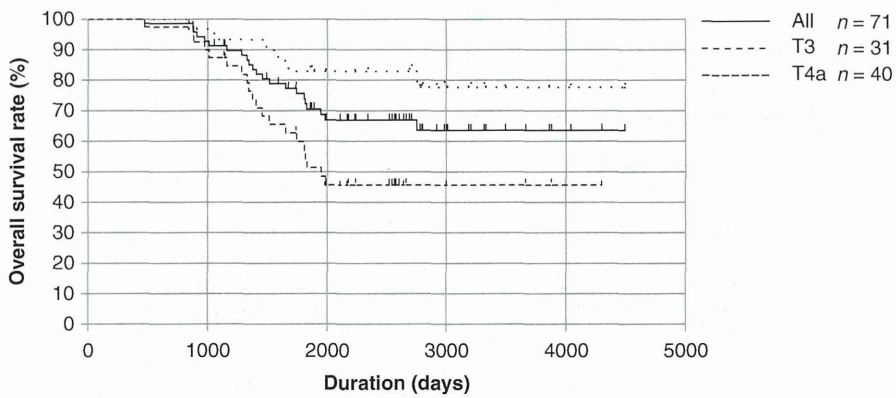

Figure 2. Overall survival according to T classification (Kaplan–Meier method). The 5- and 10-year overall survival rates for all 71 patients were 85.1% and 63.5%, respectively (range of follow-up period 471–4493 days, median 1991 days). The 5- and 10-year overall survival rates for the 31 patients with T3 were 98.5% and 90.5%, respectively (range of follow-up period 841–4493 days, median 2752 days). The 5- and 10-year overall survival rates for the 40 patients with T4a were 51.3% and 45.7%, respectively (range of follow-up period 471–4300 days, median 1811 days).

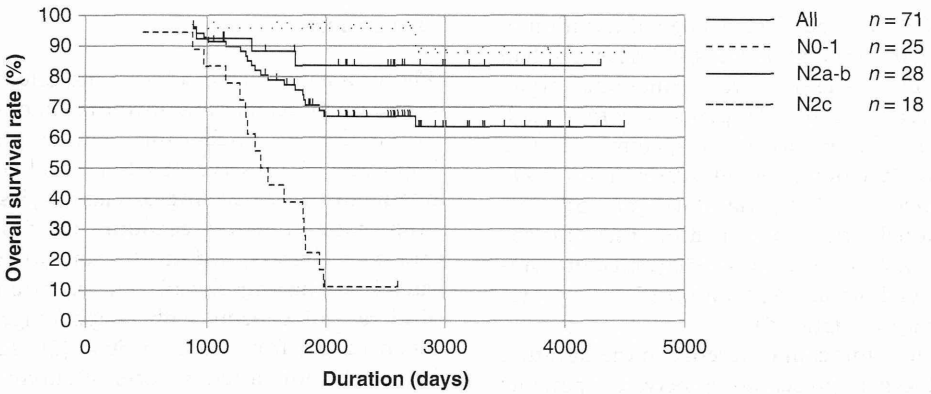

Figure 3. Overall survival according to N classification (Kaplan–Meier method). The 5- and 10-year overall survival rates for the 25 patients with N0–1 were 95.8% and 89.8%, respectively (range of follow-up period 841–4493 days, median 2708 days). The 5- and 10-year overall survival rates for the 28 patients with N2a–b were 85.6% and 83.6%, respectively (range of follow-up period 877–4300 days, median 2379 days). The 5- and 10-year overall survival rates for the 18 patients with N2c were 22.2% and 0%, respectively (range of follow-up period 471–2605 days, median 1485 days).

significantly better in patients with N0–1 than in patients with N2c cancer ($p < 0.001$), and in patients with N2a–b than in patients with N2c cancer ($p < 0.001$) (Figure 3).

Functional organ preservation according to T classification (Kaplan–Meier method)

The 5- and 10-year functional organ preservation rates for all 71 patients were 61.0% and 51.6%, respectively. The duration of functional organ preservation ranged from 52 to 4493 days (median 1769 days) (Figure 4). The 5- and 10-year functional organ preservation rates for the 31 patients with T3 cancer were 85.8% and 71.1%, respectively (range of duration of functional organ preservation 151–4493 days, median 2691 days). The 5- and 10-year functional organ preservation rates for the 40 patients with T4a cancer were 41.6% and 37.4%, respectively (range of duration of functional organ preservation 52–4300 days, median 1150 days (Figure 4).

The functional organ preservation rates significantly differed between the T3 and T4a groups ($p < 0.001$) (Figure 4).

Functional organ preservation according to N classification (Kaplan–Meier method)

The 5- and 10-year functional organ preservation rates for the 25 patients with N0–1 cancer were

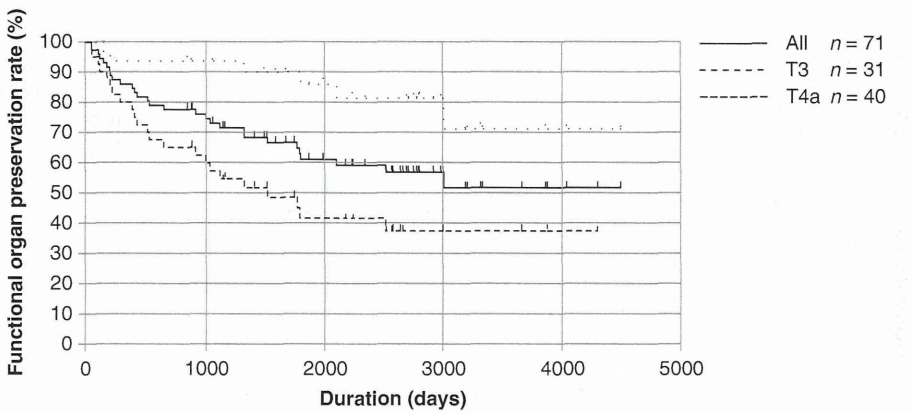

Figure 4. Functional organ preservation according to T classification (Kaplan–Meier method). The 5- and 10-year functional organ preservation rates for all 71 patients were 61.0% and 51.6%, respectively (range of duration of functional organ preservation 52–4493 days, median 1769 days). The 5- and 10-year functional organ preservation rates for the 31 patients with T3 were 85.8% and 71.1%, respectively (range of duration of functional organ preservation 151–4493 days, median 2691 days). The 5- and 10-year functional organ preservation rates for the 40 patients with T4a were 41.6% and 37.4%, respectively (range of duration of functional organ preservation 52–4300 days, median 1150 days).

84.7% and 66.4%, respectively (range of duration of functional organ preservation 52–4493 days, median 2343 days). The 5- and 10-year functional organ preservation rates for the 28 patients with N2a–b cancer were 74.5% and 69.0%, respectively (range of duration of functional organ preservation 109–4300 days, median 2376.5 days) (Figure 5). The 5-year functional organ preservation rate for the 18 patients with N2c cancer was 0% (range of duration of functional organ preservation 55–1791 days, median 717 days) (Figure 5).

There was no significant difference in the duration of functional organ preservation between patients with N0–1 and N2a–b cancer ($p = 0.62$), but the duration of organ preservation was significantly longer in patients with N0–1 than in patients with N2c cancer ($p < 0.001$), and in patients with N2a–b than in patients with N2c cancer ($p < 0.001$) (Figure 5).

Side effects and complications

Alopecia related to DOC was observed in 68 patients (95.8%). Side effects of grade 3 or more in severity included leukopenia in 18 patients (25.4%) and neutropenia in 18 patients (25.4%). Hypochromia, thrombocytopenia, and hepatic dysfunction were rarely observed. Mucositis (26 patients, 36.6%) and dermatitis (21 patients, 29.6%) were frequently observed, partly because 57 patients received CCRT. All of these side effects were reversible (Table IV). No puncture- or infusion-related complications such as thrombus formation, embolism, nerve paralysis, angiospasm, or hemorrhage were reported.

Discussion

The oropharynx is located at the bifurcation of the respiratory tract and digestive tract and is responsible for respiration, swallowing, and articulation. It is important to preserve oropharyngeal function after treatment of oropharyngeal cancer [8,9]. In Japan, oropharyngeal cancer accounts for 5–10% of head and neck cancers, and most frequently arises on the lateral oropharyngeal wall. The reported overall survival rate of patients with oropharyngeal cancer in Japan ranges from 40% to 50% [10–12], but there have been only a few reports of survival in patients with oropharyngeal cancer according to the subsite of the disease. Ebisumoto et al. [13] reported that the 5-year cause-specific survival rate in 47 patients with stage III or IV lateral oropharyngeal wall cancer was 55%.

The incidence of oropharyngeal cancer in relatively young patients is increasing in Western countries, and these cancers are associated with HPV infection [14]. In the abovementioned studies conducted in Japan, HPV infection was not assessed.

The oropharynx is a complex three-dimensional structure with no barrier against adjacent subsites, which allows a cancer to invade vertically and deeply in an unrestricted manner as it grows. In addition, it is difficult to determine the exact extent of invasion, recurrence rates are high, and patients may require further surgery or postoperative irradiation. Parsons et al. [15] reported that surgery ± radiation therapy was as effective as radiation therapy ± neck dissection in terms of tumor control, but was associated with a higher incidence of serious complications. On the other hand, Mowry et al. [16] reported that no significant

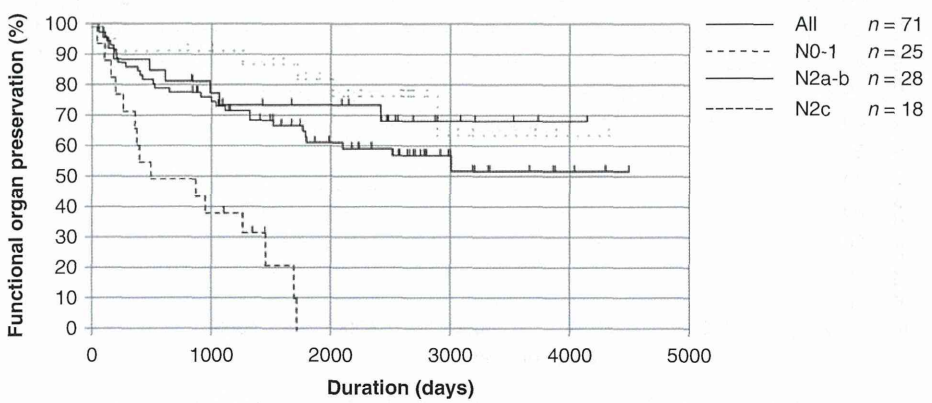

Figure 5. Functional organ preservation according to N classification (Kaplan–Meier method). The 5- and 10-year functional organ preservation rates for the 25 patients with N0–1 were 84.7% and 66.4%, respectively (range of duration of functional organ preservation 52–4493 days, median 2343 days). The 5- and 10-year functional organ preservation rates for the 28 patients with N2a–b were 74.5% and 69.0%, respectively (range of duration of functional organ preservation 109–4300 days, median 2377 days). The 5-year functional organ preservation rate for the 18 patients with N2c was 0% (range of duration of functional organ preservation 55–1791 days, median 717 days).

Table IV. Toxicity of treatment.

Adverse event	Common Terminology Criteria for Adverse Events grade			
	G1	G2	G3	G4
Decreased hemoglobin concentration	24	17	7	
Decreased leukocyte count	14	28	14	4
Decreased neutrophil count	14	28	13	5
Decreased platelet count	4	3		
Hepatic dysfunction	21	15	3	
Nausea	13	3		
Alopecia	5	63		
Mucositis	16	17	26	
Dermatitis	7	7	21	

differences were observed in pharyngeal, chewing, or laryngeal function between the CCRT and surgery groups, and Allal et al. [17] and Pignon et al. [18] reported that the quality of life was not affected by different treatments in early oropharyngeal cancer.

In Japan, en bloc surgery including neck dissection has generally been recommended for the treatment of advanced head and neck cancer. In the present study, we treated lateral oropharyngeal squamous cell carcinoma involving the oropharynx at the primary site and the lateral wall at the subsite with the aim of improving functional organ preservation and survival in response to strong requests from patients. The lateral wall of oropharyngeal cancer, which is the subsite, was treated by NAC and/or CCRT using superselective intra-arterial infusion chemotherapy in a conservative manner, and cervical lymph node metastasis, which is regional lymph node metastasis, was treated by radical neck dissection, resulting in good outcomes (Figure 1).

In other words, the primary site and cervical lymph node metastasis were separately treated as isolated lesions, rather than surgically treated as en bloc, because the figure and function of the lateral wall of oropharynx are completely different from those of the cervical area.

In this study, 56, 15, 0, and 0 of the 71 patients showed CR, PR, NC, and PD as the primary effect, respectively, with an overall response rate of 100% and a CR rate of 78.9%.

Despite a high local control rate in terms of the primary effect, some patients need to be radically treated with radical operation including reconstructive surgery during follow-up. In our study, 24 (35.8%) of the 71 patients underwent a radical operation including reconstructive surgery. More specifically, 3 (9.7%) of 31 patients with T3 cancer and 21 (52.5%) of 40 patients with T4a cancer underwent a radical operation including reconstructive surgery. In summary, 24 (35.8%) of the 71 patients underwent a radical operation including reconstructive surgery, resulting in impairment of oropharyngeal function, that is, impairment of respiration, swallowing, and articulation. Next, the overall survival rates are reviewed and assessed.

According to T classification, the 5- and 10-year overall survival rates of patients with T3 cancer ($n=31$) were as high as 98.5% and 90.5%, respectively. The overall survival rates of patients with T4a cancer ($n = 40$) were 51.3% and 45.7%, respectively, which seemed satisfactory. The overall survival rates significantly differed between patients with T3 cancer and those with T4a cancer ($p < 0.001$), and more patients with T3 cancer survived than those with T4a cancer.

According to N classification, the 5- and 10-year overall survival rates of patients with N0–1 cancer ($n = 25$) were as high as 95.8% and 89.8%, respectively. The overall survival rates of patients with N2a–b cancer ($n = 28$) were as high as 85.6% and 83.6%, respectively. However, the overall survival rates of patients with N2c cancer ($n = 18$) were as low as 22.2% and 0%, respectively. No significant difference was observed between the N0–1 and N2a–b groups ($p = 0.90$). However, the overall survival rates significantly differed between the N0–1 and N2c groups ($p < 0.001$) and between the N2a–b and N2c groups ($p < 0.001$), being lower in the N2c group.

Next, we discuss the functional organ preservation rate. According to T classification, the 5- and 10-year functional organ preservation rates in the 31 patients with T3 cancer were 85.8% and 71.1%, respectively, showing that good quality of life was achieved. The 5- and 10-year functional organ preservation rates in the 40 patients with T4a cancer were not very satisfactory at 41.6% and 37.4%, respectively. There were significant differences between the T3 and T4a groups ($p < 0.001$).

According to N classification, the 5- and 10-year functional organ preservation rates of patients with N0–1 cancer ($n = 25$) were as high as 84.7% and 66.4%, respectively. The functional organ preservation rates of patients with N2a–b cancer were also as high as 74.5% and 69.0%, respectively. However, the functional organ preservation rates of patients with N2c cancer were not satisfactory at 0% and 0%, respectively. No significant difference was observed between the N0–1 and N2a–b groups ($p = 0.62$). However, the functional organ preservation rates significantly differed between the N0–1 and N2c groups ($p < 0.001$) and between the N2a–b and N2c groups ($p < 0.001$), being lower in the N2c group.

Hence, it is thought that although the tumor size affects the overall survival rate and functional organ preservation rate, the critical factor is the presence of bilateral cervical lymph nodes metastasis. In fact, the overall survival rate and functional organ preservation rate were very poor in patients with N2c cancer, and this may be attributed to distant metastasis resulting from prolonged presence of cancer due to a failure to control contralateral cervical lymph nodes metastasis. The reason is that it is difficult to control cervical lymph node metastasis in patients with N2c cancer. When radical neck dissection is performed on both sides, bilateral internal jugular veins are ligated at the same time, being associated with risk of brain edema. If unilateral lymph node metastasis is not appropriately controlled, prolonged presence of cancer may cause distant metastasis. During follow-up, double cancer can develop.

Superselective intra-arterial chemotherapy was first described by Robbins et al. [19] as a rapid intra-arterial administration of CDDP alone. Based on the results of histoculture drug response assays, we modified it into superselective intra-arterial administration of CDDP and DOC, followed by continuous intravenous infusion of 5-FU over 120 h. We demonstrated that concomitant use of DOC and adjustment of the infusion rate further contributed to organ preservation [5].

The following should be kept in mind to achieve a good outcome with superselective intra-arterial chemotherapy: it should be administered anterogradely; minimal blood flow should be left between the catheter and the arterial intima; and anticancer drugs should be intra-arterially administered under approximately equal pressure to the systolic blood pressure. These aspects are also required to minimize complications, such as thrombus formation and nerve paralysis.

However, since superselective intra-arterial chemotherapy is highly useful for preserving the primary site, but it has been shown in contrast studies, etc., that anticancer drugs are not well distributed in cervical lymph node metastases, cervical lymph node metastasis is treated by complete neck dissection. In N2c cancer, it is very important to control cervical lymph node metastasis. The side effects of this treatment included bone marrow depression and alopecia, as well as severe mucositis and dermatitis in patients receiving CCRT. All of these changes were reversible. Some patients were withdrawn from treatment owing to a side effect. Completion of treatment is essential to achieve a good outcome.

There are several issues to be addressed for patients with N2c cancer, but this treatment is safe and very useful in terms of overall survival and functional organ preservation. To further improve functional organ preservation and overall survival rates, treatment of contralateral cervical lymph node metastasis in patients with N2c cancer, more specifically, radiation field in radiation therapy, method of postoperative irradiation, and necessity of maintenance therapy [20] should be addressed.

Conclusions

In 71 patients with lateral oropharyngeal squamous cell carcinoma, the primary site was treated conservatively by NAC and/or CCRT using superselective intra-arterial infusion chemotherapy, and cervical lymph node metastasis was treated by radical neck dissection.

This treatment resulted in good outcomes, with 5- and 10-year overall survival rates of 85.1% and 63.5%, respectively, and 5- and 10-year functional organ preservation rates of 61.0% and 51.6%, respectively. The outcome was especially good in patients with T3, N0–1, and N2a–b cancer. However, the overall survival and functional organ preservation rates of patients with N2c cancer were low. This may be due to ineffective treatment of contralateral cervical lymph node metastasis.

This treatment is safe and effective in treating the lateral type of oropharyngeal squamous cell carcinomas. For the improvement of outcome in patients with T4a and N2c cancers, the following approaches are expected to contribute to a better prognosis: introduction of IMRT; appropriate treatment of contralateral cervical lymph nodes metastasis (i.e. proper radiation therapy); and introduction of maintenance therapy. Consideration should be given to the need for these therapies.

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