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

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SUMMARY

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

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

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

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

Introduction

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

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

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

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

Patients and methods

Eligibility criteria

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

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

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

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

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

Chemotherapy

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

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

Radiotherapy

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

Management of the neck

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

Evaluation of response and toxicity

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

Statistical analysis

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

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

Results

Patient characteristics

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

Compliance

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

Toxicity

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

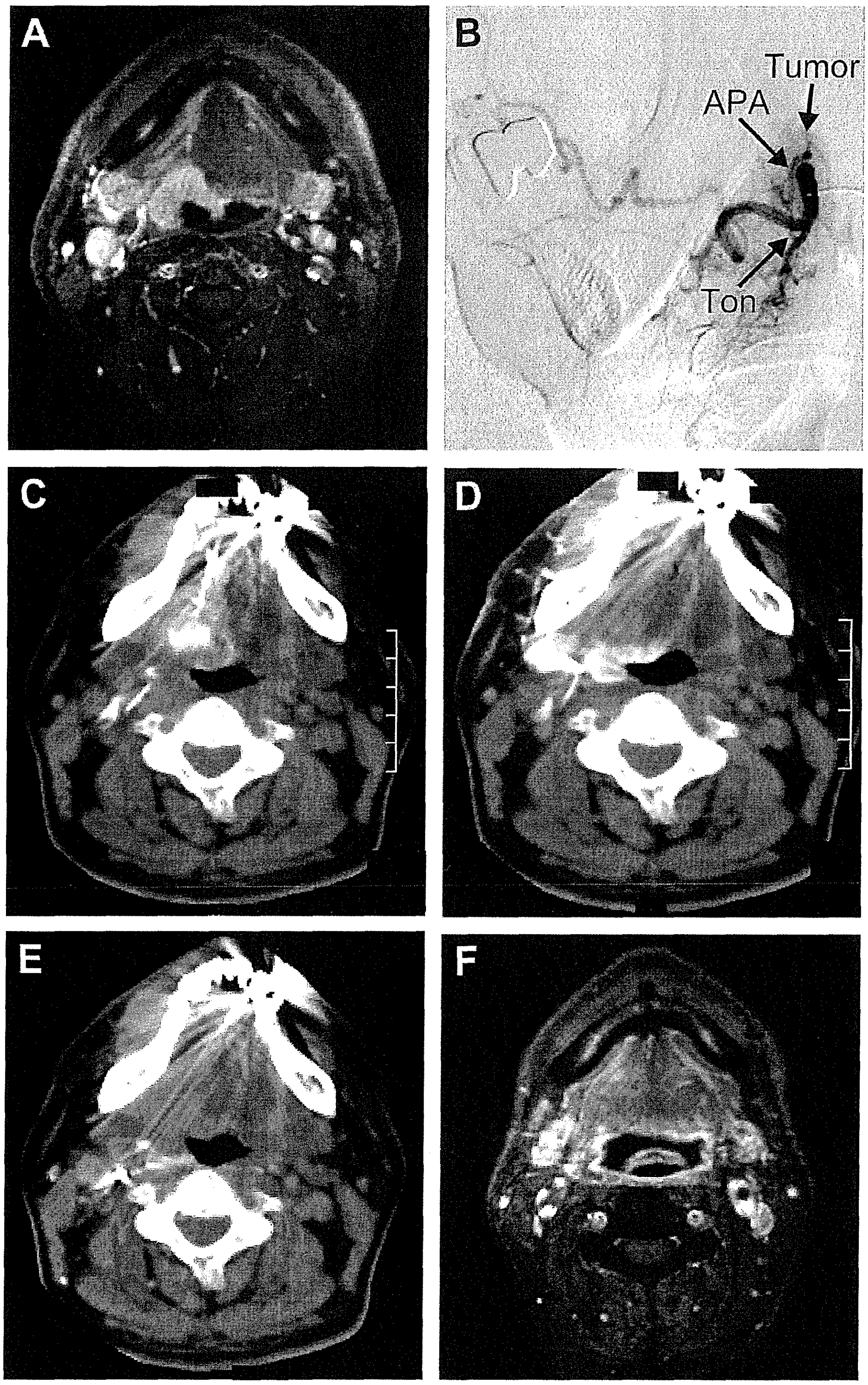

Figure 1 (A) MRI findings from a 58-year-old man with a right BOT cancer classified as T3N2bM0. (B) Lateral subtraction angiogram of right facial artery. Ascending palatine artery (APA) and tonsillar branch (Ton) supply tumor with blood. (C) Intra-artery computed tomographic arteriography (IA-CTA) of 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.

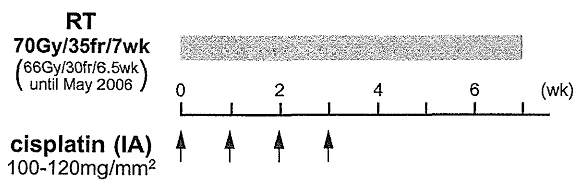

Figure 2 Treatment schedule of RADPLAT.

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 pre-epiglottic 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			

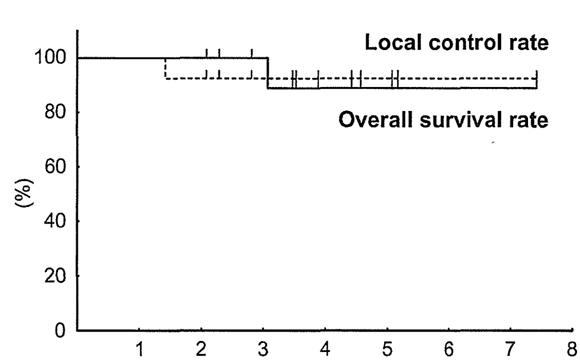

Figure 3 Local control and overall survival rate of 13 patients with BOT cancers.

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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Matched-Pair Analysis in Patients with Advanced Oropharyngeal Cancer: Surgery versus Concurrent Chemoradiotherapy

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Key Words
Oropharyngeal cancer · Chemoradiotherapy · Surgery · Matched-pair analysis

Abstract
Objective: The current study aimed to compare the therapeutic outcomes of surgery with those of chemoradiation for patients with advanced oropharyngeal cancer (OPC). ***Methods:*** The data for 523 patients with previously untreated OPC were obtained from 12 institutions belonging to the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group from April 2005 to March 2007. In this study, we matched a group of patients who underwent surgery with a second group treated with chemoradiation according to age, gender, subsite, and T and N classification, and analyzed the overall survival, progression-free survival, local control and swallowing function. ***Results:*** The final matched-pair analysis included 186 patients. The 5-year overall survival, progression-free survival and local control rates were 69.8 and 71.4% ($p = 0.762$), 51.0 and 54.4% ($p = 0.531$), and 75.2 and 80.3% ($p = 0.399$), respectively, in patients treated with surgery and those treated with chemoradiation. Swallowing function in patients treated with chemoradiation was significantly better than that in patients treated with surgery ($p = 0.015$). ***Conclusion:*** Although this study was not randomized, this matched-pair analysis of patients treated with surgery or chemoradiation showed that chemoradiation is as effective as surgery in the treatment of OPC.

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Introduction

In recent years, a significant increase in the incidence of oropharyngeal cancer (OPC) has been observed in the USA and Western Europe in people under 45 years of age [1]. Although tobacco and alcohol abuse are closely correlated with the carcinogenesis of OPC, as in other head and neck cancers, a relationship between human papilloma virus (HPV) and the risk of developing OPC has also been confirmed [2, 3]. OPC involves the tonsils, the base of the tongue, vallecula, soft palate and posterior pharyngeal wall. The majority of OPCs originate in the tonsils and the base of the tongue. In addition, more than 90% of OPCs are squamous cell carcinomas [4].

Surgery and radiotherapy (RT) alone are considered equally successful in the treatment of early-stage OPC. Recently, transoral laser microsurgery has been used to treat OPC, particularly base of tongue cancers, in several institutions [5, 6]. Furthermore, transoral robotic surgery using the da Vinci® Surgical System has been developed and its applicability to the treatment of OPC has been reported [7, 8]. Conversely, considerable controversy surrounds the appropriate treatment for advanced OPC. For many years, a radical open surgical approach followed by RT was considered the standard treatment for advanced OPC. Unfortunately, patients with advanced disease treated with surgical resection experience impairment of swallowing and speech function, leading to a decreased quality of life. Concurrent chemoradiotherapy (CCRT) has advantages over definitive surgery in terms of organ and function preservation, and over RT alone in terms of survival rate [9–11]. However, major concerns remain regarding the toxicity of CCRT, which sometimes requires long-term hospitalization and nutritional support.

Although the initial treatment strategy for advanced OPC has recently shifted from surgery toward CCRT [12, 13], no anatomic site-specific prospective randomized trials evaluating outcomes after surgery versus those after CCRT are available. Both surgery and CCRT are currently used as standard treatments for advanced head and neck cancer. However, there are marked differences in the levels of patient stress resulting from treatment, complications and hospitalization between surgery and CCRT; therefore, new randomized trials are difficult to perform.

Recently, a large-scale multi-institutional joint research program for OPC was performed in Japan for the first time. The aim of this research was to clarify the current status of OPC treatment in Japan and to help us to plan new clinical trials for OPC. Twelve institutions, all involved mainly in the treatment of patients with cancer, participated in this research and the data for 523 patients were obtained. In this study, we performed a matched-pair analysis following strict matching criteria. This design was chosen to provide the highest level of evidence obtainable without performing a randomized trial. We compared overall survival, progression-free survival, local control and swallowing function between patients with advanced OPC treated with surgery and those treated with CCRT.

Methods

Patients

The data for 523 patients with previously untreated OPC were obtained from 12 institutions belonging to the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group from April 2005 to March 2007. The subsites of primary tumor were defined based on the classification of the UICC. The anterior wall includes the base of the tongue and the vallecula, the lateral wall includes the tonsil, the tonsillar fossa, the tonsillar pillars and the glossotonsillar sulci, the superior wall includes the soft palate and the uvula, and the posterior wall includes the post pharyngeal wall from the plane of the hard palate superiorly to the plane of the hyoid bone inferiorly. The therapeutic strategy varied widely among the institutions, with the proportion of patients treated with surgery ranging from 6 to 59% and that of patients treated with RT with or without chemotherapy ranging from 41 to 94%. This study was a retrospective analysis, so the selection criteria for therapeutic modality were decided according to the policy of each institution or individual patient preference. This multi-institutional joint research has been representatively approved by the appropriate ethical committees of the National Hospital Organization Tokyo Medical Center, Tokyo, Japan.

This analysis was performed only on operable cases of locally advanced carcinoma. The number of patients with superior and posterior wall cancer or nonsquamous cell carcinoma was small, so such cases were excluded from the analysis. Of the 523 patients, 248 patients were included on the basis of the following criteria: (1) histological proof of squamous cell carcinoma; (2) clinical stage III or IV disease; (3) disease stage other than T4b; (4) no distant metastasis; (5) lateral or anterior wall cancer, and (6) surgery or CCRT as curative treatment.

To adjust for baseline differences between the two groups of patients who underwent surgery or CCRT, we performed a matched-pair analysis using propensity scores. The propensity score matching approach involved two steps. In the first step, the likelihood that a patient would receive surgery was assessed using a logistic regression model as a function of age, gender, subsite, and T and N classification. From this regression, the predicted probability of receiving surgery, or propensity score, was computed for each patient. In the second step, control patients were selected from among the patients undergoing CCRT and matched 1:1 to patients undergoing surgery according to their propensity score. In the case of ties, a control was selected at random from among all potential matches. Cases without a matched control were excluded.

Table 1. Matched patient characteristics

Variable	Patients, n (%)	
	surgery (n = 93)	CCRT (n = 93)
Age, years		
<62	49 (52.7)	49 (52.7)
≥62	44 (47.3)	44 (47.3)
Gender		
Male	82 (88.2)	82 (88.2)
Female	11 (11.8)	11 (11.8)
Subsite		
Lateral wall	68 (73.1)	68 (73.1)
Anterior wall	25 (26.9)	25 (26.9)
T classification		
T1, 2	44 (47.3)	44 (47.3)
T3, 4a	49 (52.7)	49 (52.7)
N classification		
N0–2a	29 (31.2)	29 (31.2)
N2b–3	64 (68.8)	64 (68.8)

Table 2. Unmatched characteristics

Variable	Surgery (n = 93)	CCRT (n = 93)	p
Median age (range), years	61 (36–84)	59 (37–80)	0.670
Comorbidity			
Diabetes	10 (10.8)	10 (10.8)	1.0
Hypertension	14 (15.1)	16 (17.2)	0.690
Cardiac disease	8 (8.6)	5 (5.4)	0.388
Pulmonary disease	1 (1.1)	1 (1.1)	1.0
Multiple primaries			0.744
Yes	25 (26.9)	27 (29.0)	
No	68 (73.1)	66 (71.0)	
Smoking status			0.698
Ever	76 (81.7)	78 (83.9)	
Never	17 (18.3)	15 (16.1)	
Alcohol consumption status			0.207
Ever	70 (75.3)	77 (82.8)	
Never	23 (24.7)	16 (17.2)	
T classification			0.562
T1	16 (17.2)	9 (9.7)	
T2	28 (30.1)	35 (37.6)	
T3	27 (29.0)	25 (26.9)	
T4a	22 (23.7)	24 (25.8)	
N classification			0.762
N0	8 (8.6)	8 (8.6)	
N1	14 (15.1)	15 (16.1)	
N2a	7 (7.5)	6 (6.5)	
N2b	41 (44.1)	32 (34.4)	
N2c	20 (21.5)	24 (25.8)	
N3	3 (3.2)	8 (8.6)	
Stage			0.448
III	15 (16.1)	19 (20.4)	
IV	78 (83.9)	74 (79.6)	
Follow-up of survivors, years			0.857
Median (range)	4.4 (0.2–6.2)	4.4 (0.3–5.9)	

Values in parentheses are either percentages or ranges.

Statistical Analysis

The major endpoint of this study was overall survival (death from any cause was considered as an event). Additional endpoints included progression-free survival (recurrence or progression and death were considered as an event), local control rate (persistent disease or local recurrence was considered as an event) and swallowing function after initial therapy. The median follow-up period for the survivors who initially underwent surgery or CCRT was 4.4 and 4.4 years (range 0.2–6.2 or 0.3–5.9), respectively.

Associations between the unmatched characteristics or swallowing function were tested using the unpaired Student t test or the χ^2 test, as appropriate. Overall survival curves, progression-free survival curves and local control curves were constructed using the Kaplan-Meier method and were analyzed using the log-rank test. A Cox proportional hazard regression model was used to assess the effect of each variable on overall survival. A two-tailed p value <0.05 was considered statistically significant. Statistical analyses were performed using XLSTAT 2011 (Addinsoft, New York, N.Y., USA).

Results

Patient Characteristics

The final matched-pair analysis included 186 patients (93 patients treated with surgery and 93 patients treated with CCRT). The matched characteristics of the two groups are listed in table 1. Sixty-eight patients (73.1%) had lateral wall cancer, 49 patients (52.7%) were diagnosed as T3 or T4, and 64 patients (68.8%) were diagnosed as N2b–3. Table 2 shows the unmatched characteristics of the two groups. The p value between the two groups for T classification was 0.562, that for N classification was 0.762 and that for clinical stage was 0.448. The two groups did not differ significantly with respect to any variables.

Details of Initial Treatment

Table 3 shows the details of initial treatment in the surgery group. Twenty patients (21.5%) underwent transoral surgery and 73 patients (78.5%) underwent open surgery. Of the 73 patients treated with open surgery, 64 (68.8%) underwent reconstructive surgery using pedicled or free flaps, and 17 patients (18.3%) underwent concurrent removal of their larynx. Neck dissection (ND) was performed in almost all cases (96.8%). Thirty-five patients

(37.6%) received postoperative RT and 15 patients (16.1%) received induction chemotherapy.

Table 4 shows the details of initial treatment in the CCRT group. The median irradiation dose was 67 Gy (range 60–72). Although the concomitant chemotherapy consisted of various regimens, about 77.4% of patients treated with those regimens received cisplatin and 90.3% received platinum-containing anticancer drugs. Intra-arterial cisplatin infusion was performed for 6 patients with anterior wall cancers and 1 patient with lateral wall cancer. Nineteen patients (20.4%) received induction chemotherapy. Two patients (2.2%) received ND followed by CCRT and 7 patients (7.5%) received planned ND after CCRT.

Swallowing Function after Initial Therapy

There was a statistically significant difference between the two groups (p = 0.015) in terms of swallowing function with 24 patients (25.8%) requiring tube-feeding support after initial surgery, whereas only 11 patients (11.8%) required tube-feeding support after initial CCRT (table 5).

Locoregional Recurrence and Salvage Surgery

In patients treated with surgery, 21 patients (22.6%) had local recurrence and 24 patients (25.8%) had regional recurrence. Eight patients with local failure underwent salvage surgery and 9 patients with regional failure underwent salvage ND. In patients treated with CCRT, 17 patients (18.3%) had local recurrence and 26 patients (28.0%) had regional recurrence. Six patients with local failure underwent salvage surgery and 10 patients with regional failure underwent salvage ND.

Survival and Local Control Rate by Initial Treatment

The 5-year overall survival rate was 69.8% for the patients treated with surgery and 71.4% for those treated with CCRT (p = 0.762; fig. 1). The 5-year progression-free survival rate was 51.0% for the patients treated with surgery and 54.4% for those treated with CCRT (p = 0.531; fig. 2), and the 5-year local control rate was 75.2% for the patients treated with surgery and 80.3% for those treated with CCRT (p = 0.399; fig. 3). No significant differences were found in the survival and local control rates between the two groups. Furthermore, the treatment outcomes were compared based on the size of primary tumor (fig. 4). There were no significant differences, although the progression-free survival rate in the CCRT group seemed to be better than that in the surgery group in T3–4 tumor. In addition, table 6 shows the multivariate Cox

Table 3. Details of treatment for patients initially undergoing surgery

Transoral surgery	20 (21.5)
Open surgery	73 (78.5)
With reconstructive surgery	64 (87.7)
Without reconstructive surgery	9 (12.3)
Laryngectomy	
Yes	17 (18.3)
No	76 (81.7)
Neck dissection	90 (96.8)
Ipsilateral	61 (65.6)
Bilateral	29 (31.2)
Postoperative radiation	35 (37.6)
Range of irradiation dose, Gy	44–70 (60)[1]
Induction chemotherapy	15 (16.1)

Values are n (%) unless otherwise indicated.
[1] Median dose.

Table 4. Details of treatment for patients initially undergoing CCRT

Range of irradiation dose, Gy	60–72 (67)[1]
Regimens of concomitant chemotherapy	
Cisplatin, 5FU	40 (43.0)
Cisplatin	20 (21.5)
Nedaplatin	6 (6.5)
Docetaxel	6 (6.5)
Cisplatin, 5FU, Docetaxel	5 (5.4)
Carboplatin, 5FU	3 (3.2)
S1	3 (3.2)
Nedaplatin, 5FU	2 (2.2)
Carboplatin	1 (1.1)
Cisplatin (IA)	7 (7.5)
Induction chemotherapy	19 (20.4)
ND followed by CCRT	2 (2.2)
Planned ND after CCRT	7 (7.5)

Values are n (%) unless otherwise indicated.
[1] Median dose.

Table 5. Swallowing function after initial therapy

	Patients, n (%)		p
	surgery (n = 93)	CCRT (n = 93)	
Nutrition			0.015
Oral feeding	68 (73.1)	81 (87.1)	
Tube feeding	24 (25.8)	11 (11.8)	

Data was not available for 1 patient in the surgery group and 1 patient in the CCRT group.

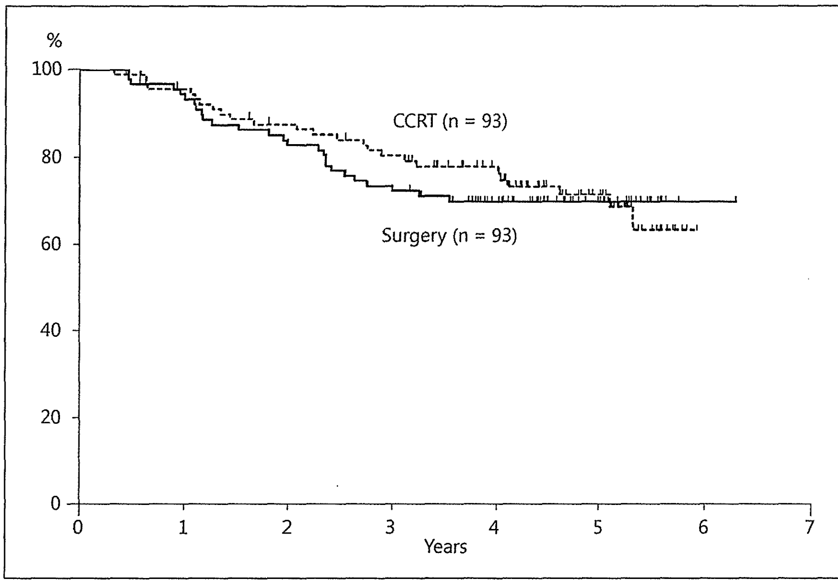

Fig. 1. Overall survival rate for patients initially treated with surgery or CCRT.

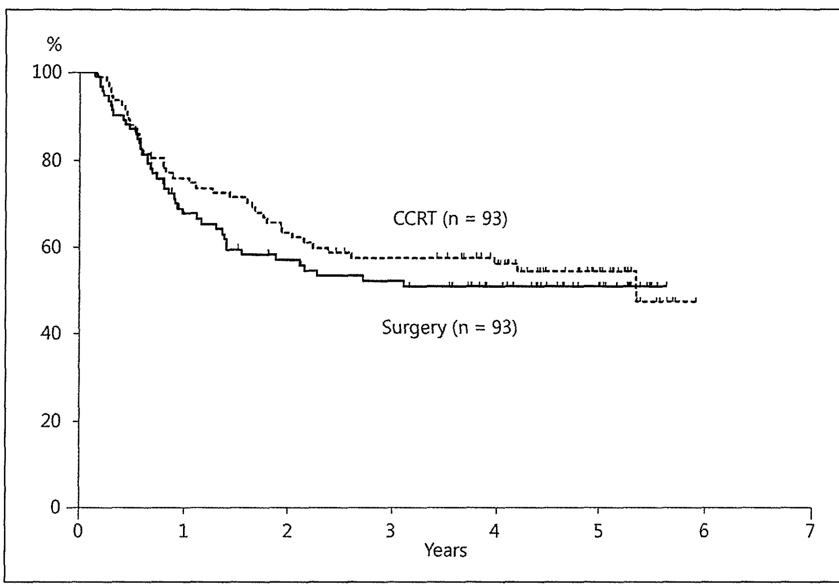

Fig. 2. Progression-free survival rate for patients initially treated with surgery or CCRT.

proportional hazard regression model analysis for overall survival. Results show that the difference in initial treatment was not associated with an increased risk of death.

Discussion

Most patients with OPC have advanced disease at presentation. In this multi-institutional joint research, 76.9% of patients with untreated OPC were categorized as stage III or IV. However, the treatment options for advanced OPC are various and controversial. In the past decade, several trials have shown a significant improvement in survival rates in patients randomized to receive CCRT compared with those receiving RT alone [14, 15]. Denis et al. [14] have reported that 5-year overall survival, specific disease-free survival and locoregional control rates were 22 and 16% (log-rank $p = 0.05$), 27 and 15% ($p = 0.01$), and 48 and 25% ($p = 0.002$), respectively, in patients undergoing CCRT and those undergoing RT alone. Olmi

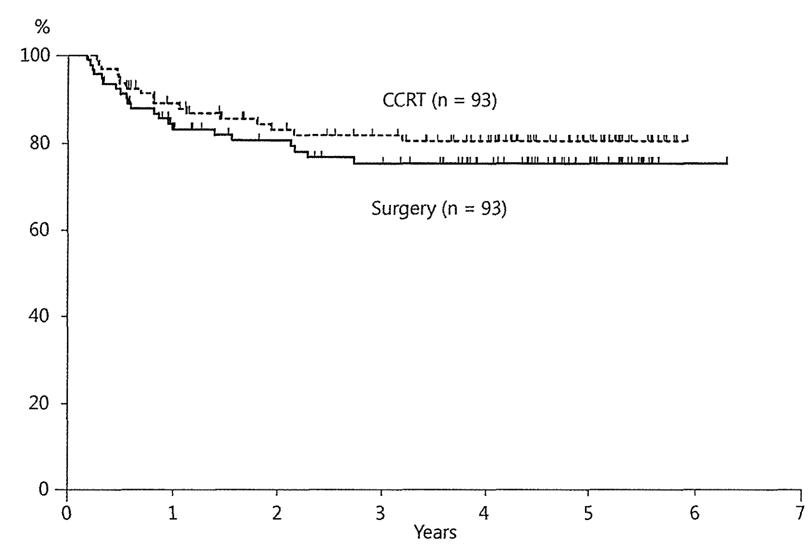

Fig. 3. Local control rate for patients initially treated with surgery or CCRT.

et al. [15] compared conventional fractionation RT, split-course accelerated hyperfractionated RT and conventional fractionation RT plus concomitant chemotherapy. Although there were no statistically significant differences in overall survival (p = 0.129), the 2-year disease-free survival differed significantly among the three regimens (p = 0.022), with CCRT showing the best results for 2-year disease-free survival.

However, no randomized trial has been conducted with which to compare the oncologic results of surgery and CCRT in patients with advanced OPC. Only one nonanatomic site-specific randomized trial, including 25 patients with OPC, has compared surgery plus RT with CCRT [16]. The 3-year disease-free survival rate was 54% for patients treated with surgery plus RT and 43% for those treated with CCRT (p = 0.425), and no subset analysis of patients with OPC was performed. Rades et al. [17] performed a matched-pair analysis in which 148 patients with advanced head and neck squamous cell carcinoma treated with CCRT were matched with 148 patients treated with surgery plus RT, including 134 patients with OPC. Although they reported that the outcomes after treatment with CCRT appeared similar to those after surgery plus RT, no subset analysis of patients with OPC was performed. In research limited to OPC, Parsons et al. [18] retrospectively compared the treatment results of surgery with or without adjuvant RT to RT with or without ND for patients with tonsillar cancer or base of tongue cancer. The rates of local control, locoregional control, 5-year overall survival and 5-year cause-specific survival were similar between patients treated with surgery and those treated with RT. Boscolo-Rizzo et al. [19] compared the outcome of a prospective case series of patients with resectable locoregionally advanced OPC treated with platinum-based induction chemotherapy and CCRT with that of matched historical control patients treated with surgery and postoperative RT. The matched-pair analysis indicated that the efficacy of induction chemotherapy and CCRT was equal to that of primary surgical resection and postoperative RT. In this study, we analyzed the difference in therapeutic outcomes between patients with advanced OPC treated with surgery and those treated with CCRT using a matched-pair analysis. Similar to the results reported from previous studies, our results showed that there were no statistically significant differences in overall survival, progression-free survival or local control rates between the two initial therapeutic modalities.

In our series, 35% of patients undergoing surgery received postoperative RT. Surgery with postoperative RT is a standard treatment for locally advanced OPC in Japan; however, this modality has actually been performed in an unexpectedly small number of patients. Then we analyzed patient characteristics between the groups undergoing postoperative RT and surgery alone, and found that there were no differences in T and N classification, subsite or surgical method (data not shown).

Recently, HPV has been reported to be related to the carcinogenesis of OPC, particularly in nonsmokers. In

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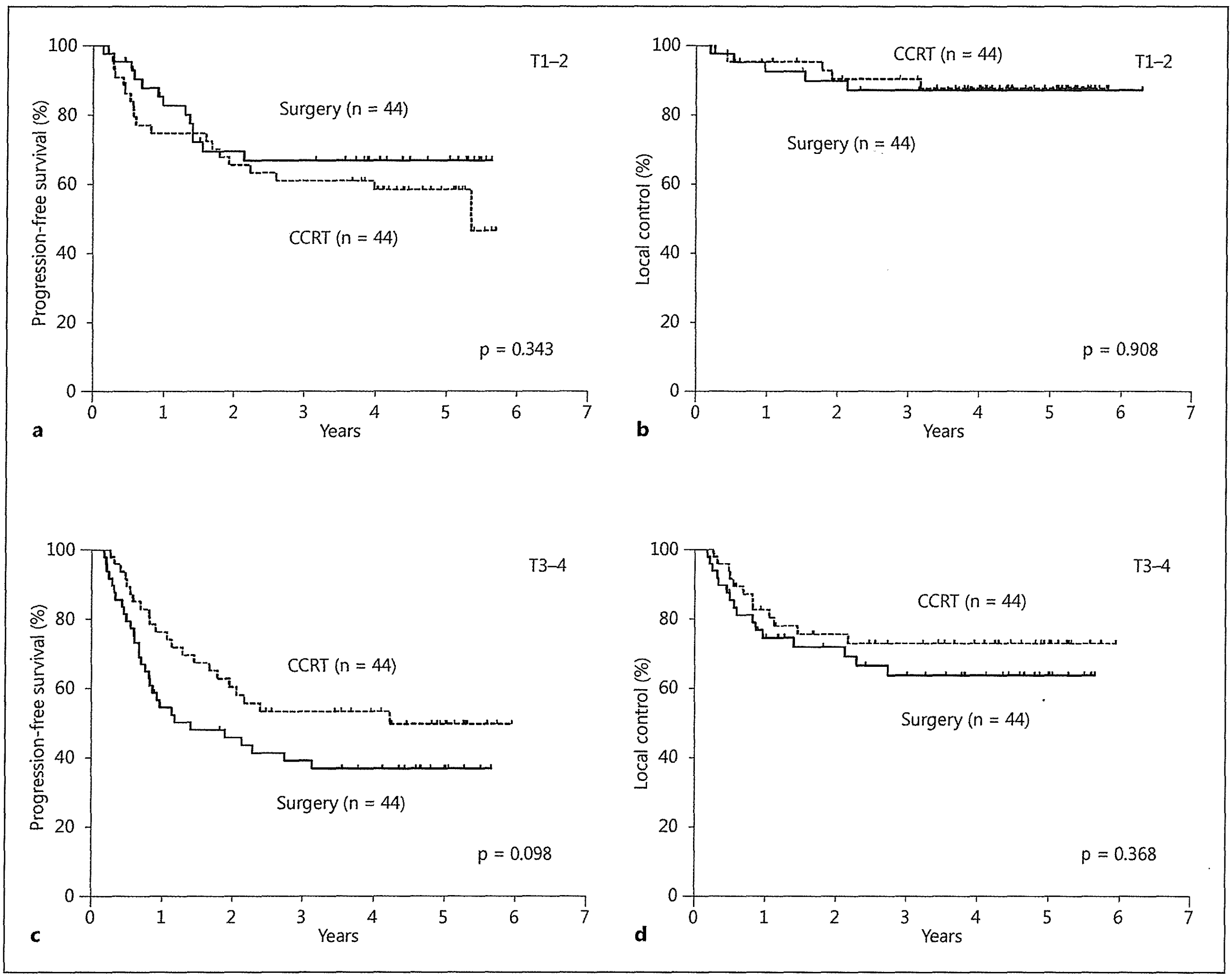

Fig. 4. Progression-free survival rate and local control rate based on the size of primary tumor for patients initially treated with surgery or CCRT. **a** Progression-free survival rate in T1–2 tumors. **b** Local control rate in T1–2 tumors. **c** Progression-free survival rate in T3–4 tumors. **d** Local control rate in T3–4 tumors.

addition, patients with HPV-positive OPC have been shown to have a significantly better prognosis than those with HPV-negative OPC, and this more favorable prognosis is thought to be due to its increased sensitivity to radiation and chemotherapy. Furthermore, several studies have reported that HPV-positive patients treated with surgery had significantly improved survival in comparison with HPV-negative patients [20, 21]. In this study, we did not detect any HPV DNA or p16 expression in the primary tumor of patients with OPC. Between 2005 and 2007 the analysis of HPV status was not yet common in Japan. Although we compared the overall survival rates for smoking patients with those for nonsmoking patients, there was no statistically significant difference in overall survival (table 6). If the data from this study were reanalyzed according to HPV status, some difference in outcome between surgery and CCRT might be observed.

Analysis of swallowing function after initial therapy revealed that 24 patients (25.8%) required tube-feeding support after initial surgery, whereas 11 patients (11.8%) required tube-feeding support after initial CCRT (table 5). Although the swallowing function of patients treated with CCRT seemed to be better than that of patients treated with surgery, these results only reflect tube

Table 6. Cox proportional hazard regression model analysis for overall survival

Variables	Hazard ratio (95% CI)	p
Age		
<62 vs. ≥62	0.708 (0.395–1.270)	0.247
Gender		
Male vs. female	0.941 (0.321–2.760)	0.912
T classification		
T1, 2 vs. T3, 4	0.298 (0.150–0.590)	0.001
N classification		
N0–2a vs. N2b–3	0.534 (0.277–1.029)	0.061
Subsite		
Lateral wall vs. anterior wall	0.566 (0.307–1.043)	0.068
Smoking status		
Never vs. ever	0.870 (0.335–2.261)	0.776
Alcohol consumption status		
Never vs. ever	0.973 (0.451–2.099)	0.945
Multiple primaries		
No vs. yes	0.726 (0.400–1.316)	0.291
Initial treatment		
CCRT vs. surgery	0.892 (0.514–1.548)	0.684

dependence immediately after initial treatment. For more accurate evaluation of swallowing function, detailed interviews with patients should be performed at several fixed times after treatment. On the other hand, Boscolo-Rizzo et al. [10] evaluated the long-term quality of life in patients with advanced OPC and compared the results of patients treated with surgery and postoperative RT with those undergoing CCRT. They reported that surgical patients showed a statistically higher incidence of problems with swallowing and social eating.

The matched-pair analysis method has been utilized for several reported retrospective cohort studies that included head and neck cancer research [22–24]. This method is based on retrospective analysis and the bias resulting from potential confounders can be limited using the matching procedure, especially in large-scale comparative studies. However, this method has some intrinsic limitations. Although the patients were matched for age, gender, subsite, and T and N status in this study, an imbalance was still present in variables that might become potential prognostic factors. Matched-pair analysis cannot replace prospective cohort studies and randomized clinical trials are required for proper comparisons between therapeutic strategies. However, it is unrealistically difficult to perform a randomized clinical trial comparing surgery versus CCRT. Furthermore, in a single institution analysis, even when matched-pair analysis is used, the selection of initial treatment can be biased by patient characteristics and clinician preferences. A large-scale multi-institutional joint research using the matched-pair analysis is thought to reduce such therapeutic bias and provide a feasible option to a randomized clinical trial comparing surgery with CCRT.

In conclusion, we compared the therapeutic outcomes for patients treated by surgery with those of patients receiving CCRT using a matched-pair analysis. Although overall survival, progression-free survival and local control rates for the CCRT group appeared similar to those for the surgery group, swallowing function based on the need for tube feedings immediately following treatment was significantly better in the CCRT group compared to patients treated with surgery ($p = 0.015$). A randomized prospective study comparing surgery with CCRT for the patients with advanced OPC is still required to confirm the reliability of the results of this study.

Disclosure Statement

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Salvage surgery for recurrent oropharyngeal cancer after chemoradiotherapy

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Abstract
Background The current study aimed to assess the role of salvage surgery for failure cases of oropharyngeal cancer (OPC) undergoing initial chemoradiotherapy (CRT).
Methods The data for 523 patients with previously untreated OPC were gathered from 12 institutions belonging to the Head and Neck Cancer Study Group in Japan Clinical Oncology Group (JCOG).
Results Of the 170 patients who received CRT, 35 patients (21 %) had local recurrence or residual disease. Only 11 patients underwent further salvage surgery, and 24 patients received nonsurgical treatment. There were statistically significant differences between the two groups in terms of patient age and the presence of a simultaneous regional recurrence. The 5-year overall survival rates for the patients who underwent salvage surgery were 49.1 %, whereas those for the patients who received nonsurgical treatment were 16.3 %.
Conclusion The initial treatment method for OPC should be decided carefully and the limitations of salvage surgery should be fully considered.

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Introduction

In recent years, the initial treatment strategy for advanced head and neck cancer has shifted from surgery toward chemoradiotherapy (CRT) [1, 2]. This paradigm shift is particularly marked for oropharyngeal cancer (OPC), because OPC has high sensitivity to radiation and chemotherapy, and extended resection of the oropharynx leads directly to swallowing and speech disorders. The meta-analysis reported by Parsons et al. [3] revealed that organ preservation protocols have comparable survival rates, improved functional outcomes, and decreased severe complications compared to open surgery. Additionally, the relationship between human papilloma virus (HPV) and carcinogenesis of the oropharynx has been confirmed, and its treatment sensitivity has expedited a further paradigm shift [4, 5]. Although CRT is reported to show good results, patients with OPC are at risk of recurrence after initial therapy. Bachar et al. [6] reported that 239 of 640 patients (37 %) with tonsillar cancer recurred post radiotherapy.

Salvage surgery is the only curative treatment for patients with recurrence. However, the rate of successful surgical salvage has remained modest. Previously, we analyzed the effectiveness of salvage surgery for local recurrence after CRT or radiotherapy (RT) in hypopharyngeal cancer and reported that the successful salvage rate was only 17.1 % [7]. Goodwin [8] conducted a meta-analysis of 532 patients with recurrent pharyngeal cancer undergoing salvage surgery after definitive radiotherapy and reported a recurrence-free survival rate of only 25 % at 2 years and a 5-year overall survival rate of 26 %. Furthermore, although reconstructive surgery for oral and pharyngeal surgical defects, such as microvascular reconstructive techniques, has developed over the past several decades, Agra et al. [9] reported that postoperative complications after en bloc salvage surgery for head and neck cancer occurred in 53.2 % of patients, including 42.7 % of patients with minor complications, 18.5 % of patients with major complications, and 3.2 % of patients who died within the postoperative period.

Recently, a large-scale multi-institutional joint research for OPC was performed in Japan for the first time. Twelve institutions, mainly treating patients with cancer, participated in this research, and the data for 523 patients were obtained. In this study, we focused on the patients initially treated with CRT, and retrospectively analyzed the treatment failures, salvage surgeries, and survival rates of these patients.

Patients and methods

Patients

The data for 523 patients with previously untreated OPC from April 2005 to March 2007 were gathered from 12 institutions belonging to the Head and Neck Cancer Study Group in Japan Clinical Oncology Group (JCOG). Therapeutic strategy varied widely among the institutions, with the proportion of surgical interventions varying between 6 % and 59 % and that of RT with or without chemotherapy being 41–94 %. This study was a retrospective analysis, so the criteria of selection of therapeutic modality was decided by the institutional policies or patients' preference. In all, 37 patients who received palliative therapy were excluded from further analysis, and the data for the remaining 486 patients were analyzed retrospectively. Of the 486 patients with OPC treated with curative intent, 199 patients (41 %) were treated with surgery, 117 (24 %) with RT alone, and 170 (35 %) with CRT (Table 1). Between each therapeutic modality, there was no statistical difference in age, gender, subsite, or histology. However, the patients with advanced disease tended to undergo CRT compared to surgery or RT alone. The rate of T3 or T4 disease was 48 % in the group of CRT (37 % in surgery, 29 % in RT alone), that of neck lymph node metastasis was 77 % in the group of CRT (60 % in surgery, 64 % in RT alone), and that of clinical stage III or IV was 88 % in the

Table 1 Characteristics of patients treated initially with surgery, radiotherapy (RT), or chemoradiotherapy (CRT)

Variable	No. of patients (%)		
	Surgery ($n = 199$)	RT ($n = 117$)	CRT ($n = 170$)
Age (years)			
Median (range)	64 (36–84)	66 (38–96)	60 (37–80)
Gender			
Male/female	167/32 (84/16)	100/17 (85/15)	147/23 (86/14)
Subsite			
Lateral/anterior/superior/posterior	106/52/34/7 (53/26/17/4)	78/21/11/7 (67/18/9/6)	105/45/8/12 (62/26/5/7)
T classification			
1, 2/3, 4	126/73 (63/37)	83/34 (71/29)	87/82 (51/48)
N classification			
0/1–3	80/119 (40/60)	42/75 (36/64)	39/131 (23/77)
Stage			
I, II/III, IV	64/135 (32/68)	35/82 (30/70)	21/149 (12/88)
Histology			
SCC/others	189/10 (95/5)	115/2 (98/2)	166/4 (98/2)

SCC squamous cell carcinoma

Table 2 T and N classification for patients treated with CRT

T classification	No. of patients by N classification						Total (%)
	0	1	2a	2b	2c	3	
1	4	0	2	5	2	5	18 (11)
2	17	9	9	22	8	4	69 (41)
3	9	7	1	10	8	3	38 (22)
4a	7	3	0	6	15	4	35 (21)
4b	2	0	0	1	2	4	9 (5)
X	0	0	0	0	1	0	1 (1)
Total (%)	39 (23)	19 (11)	12 (7)	44 (26)	36 (21)	20 (12)	170

group of CRT (68 % in surgery, 70 % in RT alone). The T and N classification for patients treated with CRT is shown in Table 2.

Time of assessment and evaluation method for tumors after CRT depend on the institution policies. It is difficult to differentiate between radiographic changes related to the treatment and scar tissue from persisting tumors. Over time, scar tissue remains stable, but persistent tumor tissue will progress, so a patient with radiologic changes that remained stable with no signs or symptoms of disease was considered to be progression free. Recurrence or persistent tumor was judged by apparent radiologic findings or proved by biopsy.

This multi-institutional joint research has been representatively approved by the appropriate ethical committees of National Hospital Organization Tokyo Medical Center, Tokyo, Japan, and written informed consent was obtained from all patients before entry into the study.

Statistical analysis

Associations between patient characteristics were tested using the unpaired Student's *t* test or the chi-square test, as appropriate. Overall survival curves were constructed using the Kaplan–Meier method and were analyzed using the log-rank test. A two-tailed *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using XLSTAT 2011 (Addinsoft, NY, USA).

Results

Details of initial treatment

Table 3 shows details of initial treatment in the CRT group. The median irradiation dose was 70 Gy (range, 55–72 Gy). Most patients received conventional radiotherapy and 2 patients were treated with brachytherapy. Although the concomitant chemotherapy consisted of various regimens, about 76 % of patients treated with those regimens received cisplatin and 92 % received platinum-containing anti-cancer drugs. Intraarterial (IA) cisplatin infusion was performed for 16 patients with OPC, including 13 with anterior wall cancer. Forty-one patients (24 %) received induction chemotherapy and 5 patients (3 %) underwent neck dissection (ND) followed by CRT.

Table 3 Details of initial treatment

Irradiation dose	55–72 Gy (median 70 Gy) No. of patients (%)
Concomitant chemotherapy regimen	
Cisplatin, 5-FU	64 (38)
Cisplatin	39 (23)
Nedaplatin	14 (8)
Docetaxel	11 (7)
Cisplatin, 5-FU, docetaxel	9 (5)
Carboplatin, 5-FU	5 (3)
Nedaplatin, 5-FU	4 (2)
Carboplatin	3 (2)
S1	3 (2)
Cisplatin, etoposide	2 (1)
Cisplatin (IA)	16 (9)
Induction chemotherapy	41 (24)
ND followed by CRT	5 (3)

IA intraarterial, *ND* neck dissection

Survival by initial treatment

The median follow-up period was 4.4 years (range, 0.3–5.9 years). The 3-year overall survival rate for patients treated initially with surgery, RT, and CRT was 81.8, 75.4, and 75.8 %, respectively. The 5-year overall survival rate for patients treated initially with surgery, RT, and CRT was 74.8, 66.0, and 67.1 %, respectively (Fig. 1).

Local recurrence and salvage surgery

Of the 170 patients who received CRT, 35 patients (21 %) had local recurrence or residual disease regardless of neck lymph node and distant metastasis. The median interval of local failure after CRT was 126 days (range, 0–715 days). Of the patients with local failure, 11 patients underwent salvage surgery. The most common surgical approach was open surgery, requiring microvascular free flap reconstruction (10 patients), whereas only 1 patient, who developed recurrence at the lateral wall, underwent transoral surgery. Following salvage surgery, 1 patient received postoperative reirradiation and 4 patients received adjuvant chemotherapy. Twenty-four patients received nonsurgical treatment, including reirradiation in 1, chemotherapy in 9, and best supportive care in 14 patients. Of 134 patients without local failure, 24 patients developed regional recurrences, 12 patients developed distant metastasis, and 7 patients developed both. Seventeen of the 134 patients were successfully salvaged. Additionally, there was 1 treatment-related death. The final outcome for each group is shown in Fig. 2.

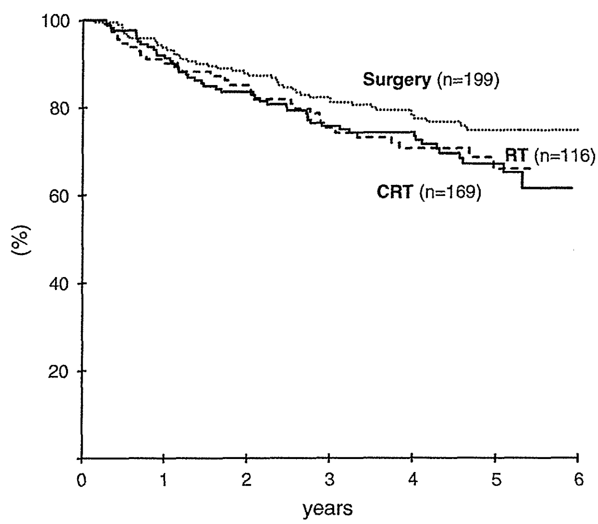

Fig. 1 Overall survival in 169 patients with oropharyngeal cancer treated with surgery, radiotherapy (*RT*), and chemoradiotherapy (*CRT*)

Characteristics of the patients undergoing salvage surgery or nonsurgical treatment for local recurrence or residual disease are summarized in Table 4. Statistically significant differences in patient age and the presence of a simultaneous regional recurrence were observed between the two groups. In addition, the patients who had more aggressive initial disease and developed distant metastasis tended to belong to the nonsurgical treatment group, although the difference was not significant.

Of the 35 patients with local failure, only 11 patients (31 %) underwent further salvage surgery, of whom only 8 (23 %) were successfully salvaged for local failure. Tables 5 and 6 show the successful salvage rates by T classification and subsite, respectively.

There was no perioperative death among the patients who underwent salvage surgery. As to swallowing function, two patients depended on a feeding tube just after CRT, whereas five patients required tube-feeding support after salvage surgery. Furthermore, three patients required the removal of their larynxes (Table 7).

For the patients treated with CRT, the 3- and 5-year overall survival rates for those without local failure were 83.8 % and 75.5 %, respectively (Fig. 3). For the patients with local failure, the 3- and 5-year overall survival rates for those who underwent salvage surgery were 61.8 and 49.1 %, respectively; those for the patients who received nonsurgical treatment were 24.4 and 16.3 %, respectively. The overall survival rate for patients treated with salvage surgery was significantly higher than that for patients

Fig. 2 Flowchart of 170 patients who received chemoradiotherapy for oropharyngeal cancer. *NED* no evidence of disease, *AWD* alive with disease, *DOD* dead of disease, *DOOD* dead of other disease

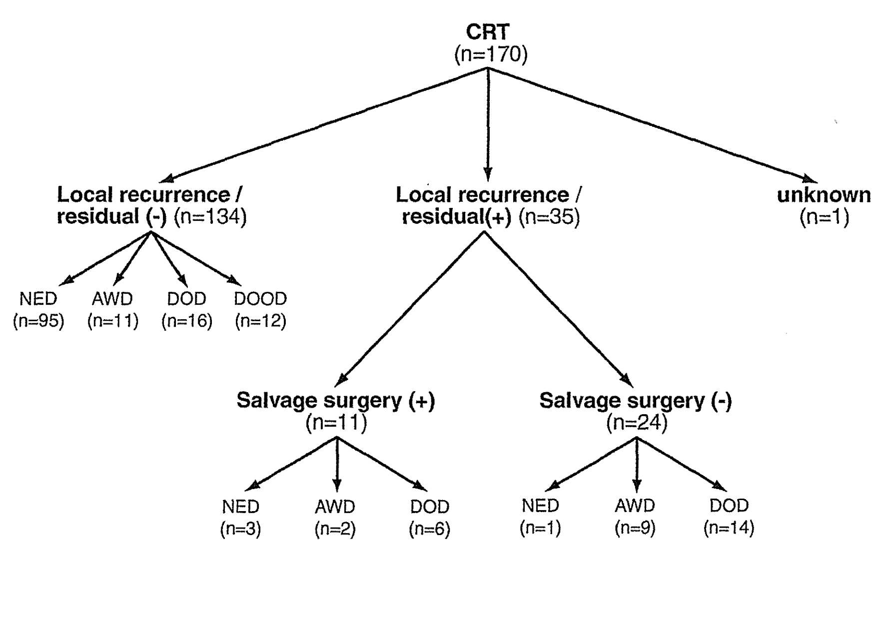

Table 4 Characteristics of patients who underwent salvage surgery or nonsurgical treatment for local recurrence or residual disease

Variable	No. of patients (%)		P
	Salvage surgery (n = 11)	Nonsurgical treatment (n = 24)	
Age (year)			
Median (range)	54 (42–75)	64.5 (46–78)	**0.04**
Gender			
Male/female	11/0 (100/0)	20/4 (83/17)	0.28
Comorbidity			
Diabetes	0 (0)	3 (13)	0.54
Hypertension	2 (18)	2 (8)	0.57
Cardiac disease	3 (27)	1 (4)	0.08
Pulmonary disease	0 (0)	2 (8)	1.00
Multiple primaries			
No/yes	5/6 (45/55)	16/8 (67/33)	0.41
Initial disease			
Subsite			
Lateral/anterior/superior/posterior	5/3/1/2 (45/27/9/18)	16/5/1/2 (67/21/4/8)	0.95
T classification			
1, 2/3, 4	6/5 (55/45)	5/19 (21/79)	0.11
N classification			
0/1–3	6/5 (55/45)	6/18 (25/75)	0.18
Stage			
I, II/III, IV	3/8 (27/73)	2/22 (8/92)	0.30
Completion of CRT			
Yes/no	8/3 (73/27)	15/9 (63/37)	0.71
Nutrition after CRT			
Oral/oral + tube/tube	9/2/0 (82/18/0)	13/4/2[a] (54/17/8)	0.90
Recurrent/residual disease			
Disease status			
Recurrent/residual	8/3 (73/27)	14/10 (58/42)	0.48
Regional recurrence			
No/yes	10/1 (91/9)	11/13 (46/54)	**0.02**
Distant metastasis			
No/yes	11/0 (100/0)	18/6 (75/25)	0.15

P values < 0.05 were shown in bold

[a] Nutrition data were not available for 5 patients in the nonsurgical treatment group

treated without salvage surgery ($P = 0.04$), whereas it was significantly lower than that for patients without local failure ($P = 0.02$).

Discussion

In the current study, the local failure rate among patients treated with CRT was 21 %, the salvage surgery rate was 31 %, and the 5-year overall survival rate after salvage surgery was 49 %. Roosli et al. and Zafereo et al. [10, 11] also reported an analysis of salvage surgery for the local recurrence of OPC. Their local failure rates were 12 and 29 %, their salvage surgery rates were 21 and 22 %, and their 5-year overall survival rates after salvage surgery were 28 and 25 %, respectively. It should be noted that salvage surgery was performed in only 20 to 30 % of patients with local failure. There were significant differences in patient age and simultaneous regional recurrence between the patients who underwent salvage surgery and those receiving nonsurgical treatment for local failure in the current study. In addition, the opportunity for salvage surgery tended to be more limited in patients who initially had advanced primary disease. Although 10 patients experienced only local failure without neck disease or distant metastasis, they received nonsurgical treatment. According to the analysis of their characteristics, their ages ranged from 56 to 76 years (median, 63 years), the rate of T4a disease was 50, and 50 % of patients had such poor performance status that they experienced swallowing