e　ステージⅢ, ⅣA, ⅣB症例における手術治療群と化学放射線治療群との生存率比較は下表のとおりで、群間に生存率に有意差はなかった。

Stage	手術	CRT	p=
III	74% (n=47)	72% (n=55)	0.800
IVA	51% (n=151)	47% (n=141)	0.196
IVB	29% (n=7)	42% (n=29)	0.404

D．考察

PNDによる頸部リンパ節転移巣の制御については、その必要性や合併症に関する議論が賛否両論存在する。実際に、ICT/CCRT後の転移リンパ節内のviable cellの残存状況について検討した報告（米澤, 岩江ら 頭頸部癌 2007）では、CCRT後に腫瘍残存リンパ節を同定するのは困難であるとの結論であり、またリンパ節領域別に検討した照射線量因子の検討（藤井, 岩江ら 頭頸部癌 2009）でも、頸部後方のレベルVでは線量分布が低下しやすく注意を要するとの結論となっている。CCRT後のviable cellの残存率が比較的高率であったことを考慮すると、CCRTによる頸部制御の不十分さを補完する目的でのPNDはその妥当性が支持される結果となるが、PNDの安全性と利益・不利益については検討課題である。術後のQOLに関する検討を我々は以前にも行っているが（岩江ら 耳鼻と臨床 2009）、今回はそのさらなる詳細な検討となっている。

PND後のアンケートを主体とした後ろ向き調査では、自覚症状に関する内容でいくつかの有意差は認められたが, 嚥下や会話, 上肢挙上など多くの項目で有意差は認められなかった。術後の嚥下障害や上肢挙上障害などの有害事象は重篤なものではないと考えられ, 少なくとも有害事象を理由にPNDに対して消極的になる必要はないと考えられた（小松, 岩江ら 頭頸部癌 2011）。

下咽頭癌の後ろ向き観察研究で得られた結果の患者背景では、重複癌が47％と非常に高率に認められることがわかった。重複頻度の高い食道癌や頭頸部癌はいずれも喫煙や飲酒との関連が指摘されている癌腫であり、下咽頭癌の制御や全生存率の向上においては無視できない頻度であることから、後発重複癌を想定した治療の選択も重要になるものと推測され、治療の困難さが浮き彫りとなった。

初診時病期については、ステージⅢ・Ⅳの進行癌が計75.5％と大部分を占めており、早期に発見される頻度が低いことがうかがわれる。5年全生存率は、ステージ0/Ⅰ/Ⅱが86/68/79％に対して、ステージⅢ/ⅣA/ⅣB/ⅣCが69/45/40/0％と劣ることからも、早期発見の重要性は高い。ステージ0/Ⅰ/Ⅱでは手術や放射線治療で喉頭温存が可能な症例が多いことをふまえて考えても、下咽頭癌に関する啓蒙活動や禁煙指導などもさらに積極的におこなうべきであろう。ステージⅢ・Ⅳ症例のうち、原発巣がT2、T3、T4と進行していくにつれて、手術での喉頭温存は困難となっていく。したがって原発巣進行例で喉頭温存を希望する症例に対しては、通常化学放射線療法が選択される。ステージⅢ/Ⅳ症例について、手術症例と化学放射線治療症例との5年全生存率を比較してみると、どのステージに於いてもほぼ同等で有意差がないことがわかった。喉頭温存治療としての化学放射線治療が、根治治療として成り立つ治療法であるものと思われた。

E．結論

咽頭癌においては、CCRTでは頸部リンパ節転移巣の制御が困難であることが推測されるため、それを補完する目的でのPNDを効果的に取り入れることが重要となる。今回の検討より、術後の嚥下障害や上肢挙上障害などの有害事象は重篤なものではないと考えられ,少なくとも有害事象を理由にPNDに対して消極的になる必要はないと考えられた。

下咽頭癌の後ろ向き観察研究では、病期進行例が多くまた重複癌も多いことがわかった。ステージⅢ/Ⅳの病期進行症例における喉頭温存を目的とした化学放射線療法は、生存率の観点から手術と同等の治療成績が得られることがわかった。

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III. 研究成果の刊行に関する一覧表

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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.

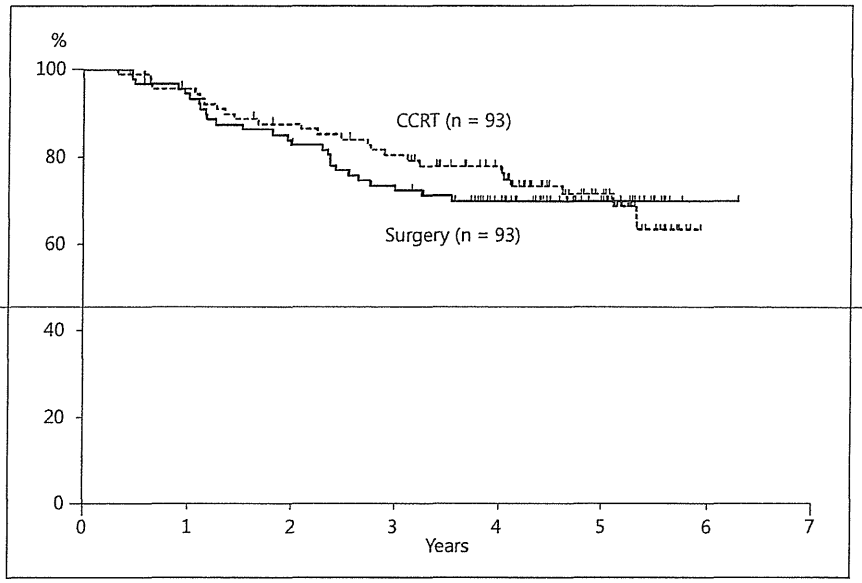

Fig. 1. Overall survival rate for patients initially treated with surgery or CCRT.

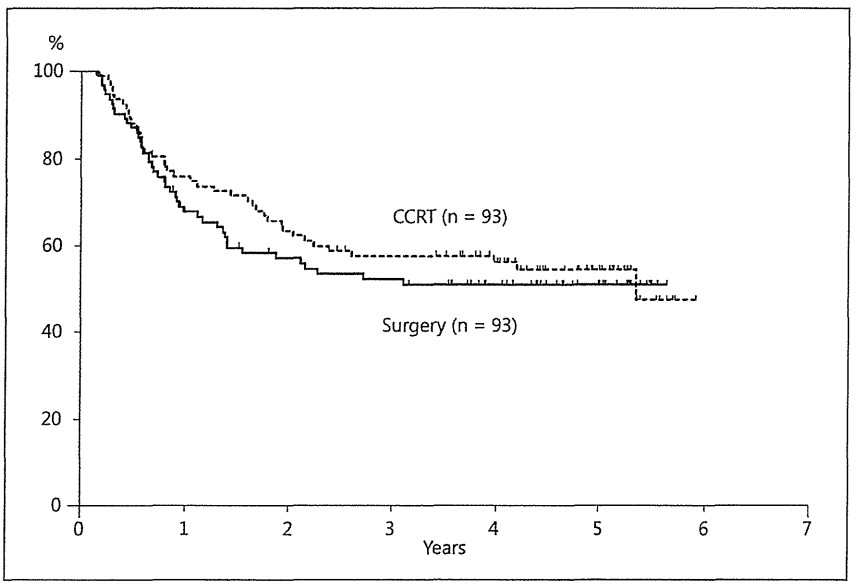

Fig. 2. Progression-free survival rate for patients initially treated with surgery or CCRT.

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

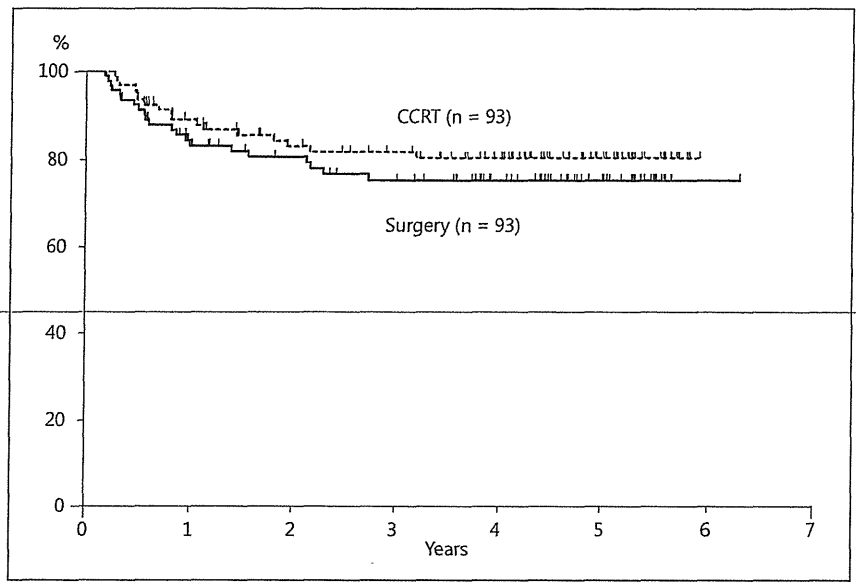

Fig. 3. Local control rate for patients initially treated with surgery or CCRT.

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

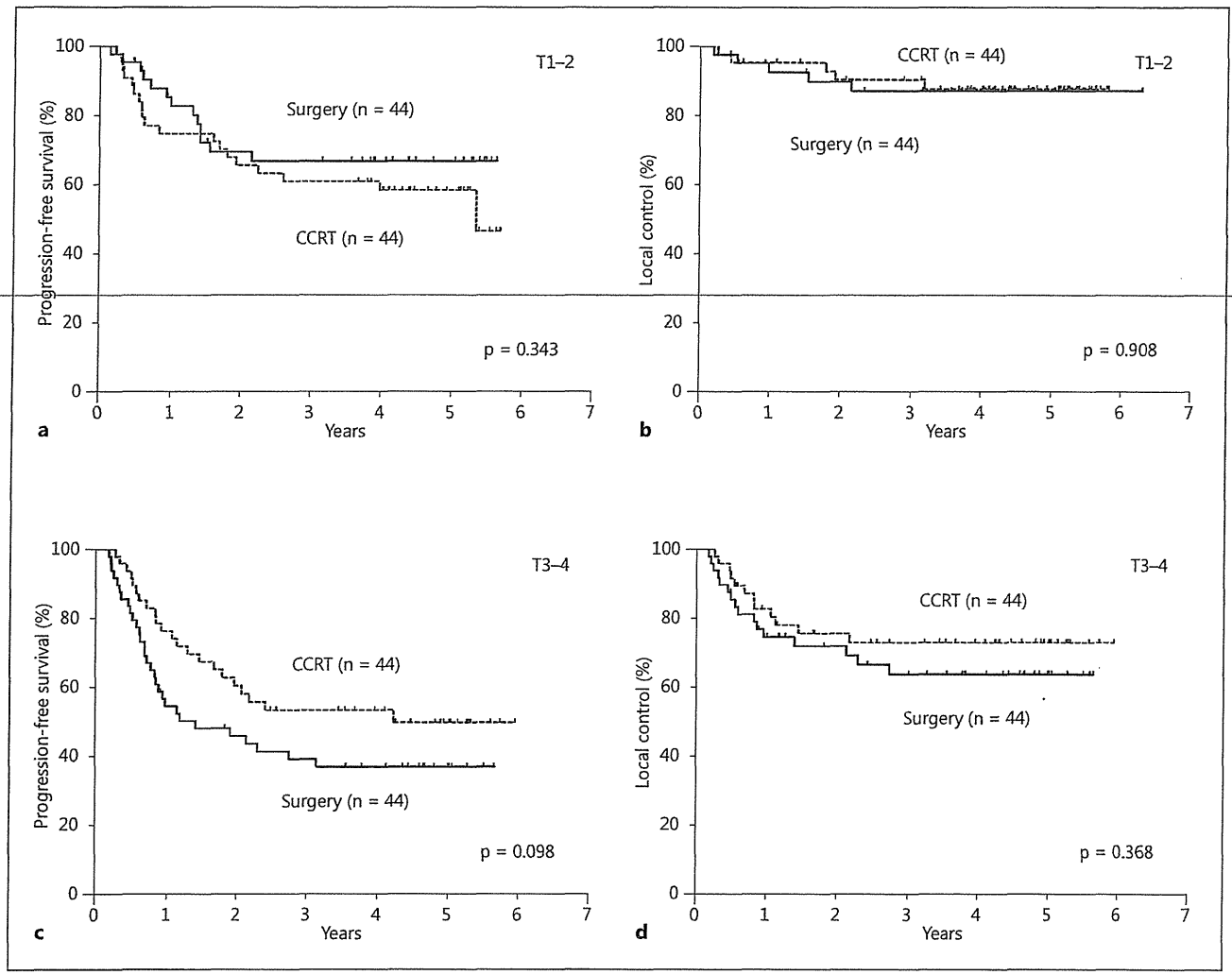

Fig. 4. Progression-free survival rate and local control rate based on the size of primary tumor for patients initially treated with surgery or CCRT. **a** Progression-free survival rate in T1–2 tumors. **b** Local control rate in T1–2 tumors. **c** Progression-free survival rate in T3–4 tumors. **d**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