Effect of Celecoxib on Survival of Mobile Tongue Cancer

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Abstract. *Aim: The goal of the present study was to evaluate the effects of celecoxib on treatment outcomes of squamous cell carcinoma of the mobile tongue. Patients and Methods: Among 158 patients who were diagnosed with mobile tongue cancer, 19 received celecoxib during the preoperative, postoperative, or post-recurrence phase. Differences in disease-specific survival (DSS) and recurrence-free survival (RFS) between patients who received celecoxib (study group) and those who did not (control group) were analyzed. Results: For the entire cohort, DSS and RFS were not significantly different according to duration of celecoxib treatment (p=0.293 and 0.703, respectively). Among patients who received chemotherapy, DSS was significantly higher in the study group than in the control group (p=0.048), but RFS was not different between the two groups (p=0.117). Conclusion: When combined with chemotherapy, celecoxib may have a beneficial effect on the survival of patients with mobile tongue cancer.*

Cyclooxygenase (COX) is a rate-limiting enzyme in the synthesis of prostaglandins from arachidonic acid. There exist two structurally similar sub-types of this enzyme: COX1 and COX2. COX1 is extensively distributed *in vivo* and is involved in promoting the biosynthesis of prostaglandins, maintaining and regulating normal physiological activities of tissue cells, and preserving homeostasis. COX2 is overexpressed in oral pre-malignant lesions and in head and neck squamous cell carcinoma (HNSCC), and COX2 is believed to be correlated with decreased apoptosis and increased angiogenesis and invasiveness of cancer cells (1).

Experimental and clinical observations have confirmed that COX2 inhibition effectively prevents and treats gastrointestinal tumors and enhances the sensitivity of tumors to adjuvant chemotherapy. COX2 inhibition also reduces the occurrence of gastrointestinal complications and confers varied benefits in adjuvant radiotherapy for several types of tumors (2-4). Celecoxib, a COX2 inhibitor, is an effective treatment for arthritis and osteoarthritis (5). Preclinical animal studies have shown that celecoxib is an effective anti-inflammatory agent in a variety of animal models of chronic inflammation; celecoxib has excellent bioavailability and distribution and it is well tolerated. Additionally, celecoxib significantly suppresses tumor growth, angiogenesis, and metastasis in tumor-implanted mice with surgical wounds, which suggests that prophylactic use of celecoxib might be appropriate in many clinical situations, including in the treatment of residual tumors or the contamination of surgical fields by tumor cells (6-9).

Celecoxib has been used in clinical studies to improve response to therapy in cervical, esophageal, and breast cancer (10-14). However, no studies have been conducted with celecoxib in head and neck cancer, except for a single phase II trial of undifferentiated nasopharyngeal cancer (15). For this study, we conducted a retrospective review to evaluate the effects of celecoxib on the survival of patients with mobile tongue squamous cell cancer.

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Key Words: Tongue cancer, celecoxib, chemotherapy, survival.

Table I. *Patients' characteristics*.

	Study group (n=19)	Controls (n=139)	Total (n=158)
Age, years	49.0±13.5	54.7±13.8	54.0±13.8
Sex (M:F)	1.71:1	1.17:1	1.23:1
T Stage			
T1	10 (52.6%)	68 (48.9%)	78 (49.4%)
T2	6 (31.6%)	39 (28.1%)	45 (28.5%)
T3	0	13 (9.4%)	13 (8.2%)
T4	3 (15.8%)	19 (13.7%)	22 (13.9%)
N Stage			
N0	11 (57.9%)	89 (64.0%)	100 (63.3%)
N1	2 (10.5%)	18 (12.9%)	20 (12.7%)
N2	6 (31.6%)	31 (23.1%)	38 (24.0%)
Overall stage			
I	6 (31.6%)	60 (43.2%)	66 (41.8%)
II	3 (15.8%)	15 (10.8%)	18 (11.4%)
III	2 (10.5%)	21 (15.1%)	23 (14.6%)
IV	8 (42.1%)	43 (30.9%)	51 (32.2%)
Treatment modality			
OP only	4 (21.1%)	73 (52.5%)	77 (48.7%)
OP+RT or CCRT	4 (21.1%)	27 (19.4%)	31 (19.6%)
Induction chemo+OP	2 (10.5%)	5 (3.6%)	7 (4.4%)
Induction chemo+OP+RT or CCRT	5 (26.3%)	11 (7.9%)	16 (10.1%)
Induction chemo+RT or CCRT	2 (10.5%)	9 (6.5%)	11 (7.0%)
CCRT or RT	2 (10.5%)	10 (7.2%)	12 (7.6%)
CCRT or RT+OP	0	4 (2.9%)	4 (2.5%)

No significant differences were noted between the study group and the control group in age, gender, T- or N-stage, overall stage, or treatment modality. CCRT: Concurrent chemoradiation therapy; F: female; induction chemo: induction chemotherapy; M: male; OP: operation; RT: radiation therapy.

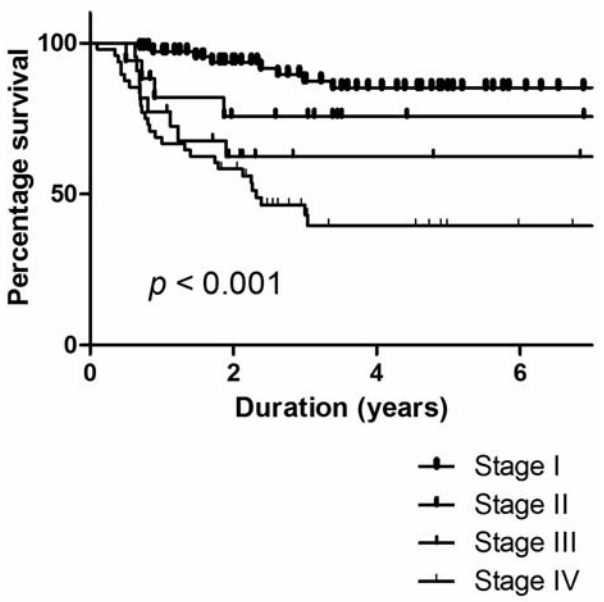

Figure 1. *Disease-specific survival (DSS) according to overall cancer stage. Five-year DSS was 63.4%. This rate was significantly different among each of the four stages.*

Patients and Methods

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1406-120-591). We reviewed clinical and pathological data of patients who were diagnosed with squamous cell carcinoma of the mobile tongue at Seoul National University Hospital from January 2003 to December 2012. Inclusion criteria were as follows: i) a diagnosis of squamous cell carcinoma of the tongue; ii) an initial diagnosis made in 2003 or later; iii) age older than 20 years at the time of diagnosis; and iv) no co-existing malignancy during the follow-up period. Patients with a pathological diagnosis other than squamous cell carcinoma, prior treatment for a malignancy other than tongue cancer, clinical and imaging evidence of distant metastasis at initial evaluation, or age younger than 20 years were excluded from the study. The disease diagnosis was based on a punch biopsy of the lesion and a histopathological examination of the surgically obtained specimen.

Among 158 patients included in the review, 19 received celecoxib treatment. These patients were named the study group. The choice of celecoxib treatment and duration of therapy was selected by the treating physicians. All patients in the study group received a celecoxib dose of 100 mg twice daily. The timing of celecoxib treatment was categorized as preoperative or postoperative in patients who underwent surgery, post-recurrence if celecoxib was initiated after a recurrence was detected, or during treatment in patients who received concurrent chemoradiation therapy. The control group consisted of 139 patients who did not receive treatment with celecoxib.

We retrospectively reviewed age at diagnosis, gender, TNM stage, treatment modality, treatment outcomes, and follow-up duration. The treatment modality for each patient was decided at the weekly tumor board conference of head and neck surgeons, radiologists, medical oncologists, and radiation oncologists. In patients who underwent operations, indications and modalities for adjuvant treatments varied over time and several findings required adjuvant radiotherapy or chemoradiation: positive or close margins found on resection, lymphovascular invasion, perineural invasion, multiple nodal metastasis, or extracapsular spread.

Cumulative recurrence and mortality rates were calculated by life-table analyses. Disease-specific survival (DSS) and recurrence-free survival (RFS) of each group were calculated according to overall disease stage, T-stage, N-stage, and celecoxib treatment. All statistical analyses were performed using SPSS V20.0 (IBM SPSS, New York, NY, USA). Statistical significance was defined as $p<0.05$.

Table II. *Characteristics and outcomes of the patients treated with celecoxib.*

Age, years	Sex	T	N	Overall stage	Treatment modality	Timing of celecoxib	Duration of celecoxib treatment (months)	Site of recurrence	Outcome
49	M	4a	2b	IVA	OP+RT	Post-recurrence	4.8	Neck	Death
42	F	1	1	III	Induction+OP	Preoperative	1.1	-	Survival
43	F	1	2b	IVA	OP+CCRT	Postoperative	5.0	-	Survival
41	M	2	0	II	OP	Postoperative	1.2	-	Survival
29	F	2	2b	IVA	Induction+OP+RT	Preoperative	10.3	-	Survival
60	F	2	0	II	OP+RT	Postradiation	1.0	-	Survival
74	M	1	0	I	OP	Postoperative	2.8	-	Survival
48	F	1	0	I	Induction+OP+RT	Preoperative	1.5	-	Death
46	M	2	0	II	OP+RT	Postoperative	8.9	-	Survival
21	M	1	1	III	Induction+OP+RT	Preoperative	7.8	-	Survival
67	M	1	2	IVA	Induction+OP+RT	Preoperative	3.8	Primary	Death
53	M	2	2b	IVA	Induction+OP+RT	Preoperative	1.0	Neck	Death
36	F	4a	0	IVA	Induction+OP	Preoperative	13.1	Primary/neck	Survival
55	M	1	0	I	OP	Postoperative	6.9	-	Survival
47	M	1	0	I	CCRT	During treatment	1.3	Primary	Survival
57	M	4a	0	IVA	CCRT	During treatment	1.0	Primary	Survival
70	M	2	2b	IVA	Induction+CCRT	During treatment	6.9	-	Survival
49	M	1	0	I	OP	Post-recurrence	2.4	Primary	Survival
46	F	1	0	I	Induction+CCRT	During treatment	1.4	-	Survival

CCRT: Concurrent chemoradiation therapy; F: female; induction: induction chemotherapy; M: male; OP: operation; RT: radiation therapy; Primary: primary lesion.

Results

Patients' characteristics. A total of 158 patients (87 men and 71 women) were included in this analysis. The mean patient age was 54.0±13.8 years, and the median follow-up duration was 42.7 months (range=1.2-134 months). Table I summarizes T-stage, N-stage, overall stage, and treatment modality of the study group and the control group. We observed no significant differences between the study group and the control group in terms of age, gender, T- or N-stage, overall stage, or treatment modality. The most prevalent T-stage in both groups was stage T1, followed by stages T2 and T4. The most prevalent N-stage was N0, with approximately 60% of patients in both groups receiving this classification. An overall stage of I was most prevalent in the control group and stage IV was most prevalent in the study group, though this difference was not significant. The most frequent treatment modality was operation-based therapy, which included operation-only and operation with adjuvant therapy. Twelve patients (63.2%) in the study group and 42 patients (30.2%) in the control group received chemotherapy, including induction or adjuvant chemotherapy combined with radiation therapy.

Table II summarizes the characteristics and treatment modalities of the 19 patients who received celecoxib. The mean age of this group was 49.0±13.5 years and 12 (63.2%) were male. Fifteen patients underwent operation and 13 patients received radiation therapy. All patients who received chemotherapy in the study group received celecoxib concurrently with chemotherapy. The mean duration of celecoxib treatment was 4.3±3.9 months.

Treatment outcomes. The five-year survival rate of the entire cohort was 63.4%; the rate was significantly different according to overall disease stage ($p<0.001$; stage I, 81.8%; stage II, 76.6%; stage III, 67.0%; stage IV 39.3%; Figure 1). DSS and RFS were not significantly different between the study and the control group ($p=0.293$ and 0.703, respectively; Figure 2A and B). The five-year survival rate was 73.9% in the study group and 61.8% in the control group. The overall recurrence rate was 42.4% and this rate was significantly different among the four stages ($p<0.001$). Among the patients with recurrence, the most frequent site of recurrence was the neck (18.3%), followed by primary lesion site (15.8%) and distant site (3.8%). The most frequent site of recurrence in stages I and II was the neck, while the most frequent site of recurrence in stages III and IV was the primary lesion ($p=0.003$). The recurrence rate in the study group was 36.8% and the most frequent site of recurrence was that of the primary lesion. The recurrence rate in the control group was 42.2% and the neck was the most frequent site of recurrence.

Among patients who received chemotherapy, DSS was significantly higher in the study group than in the control group ($p=0.048$; Figure 2C), but there was no difference in RFS

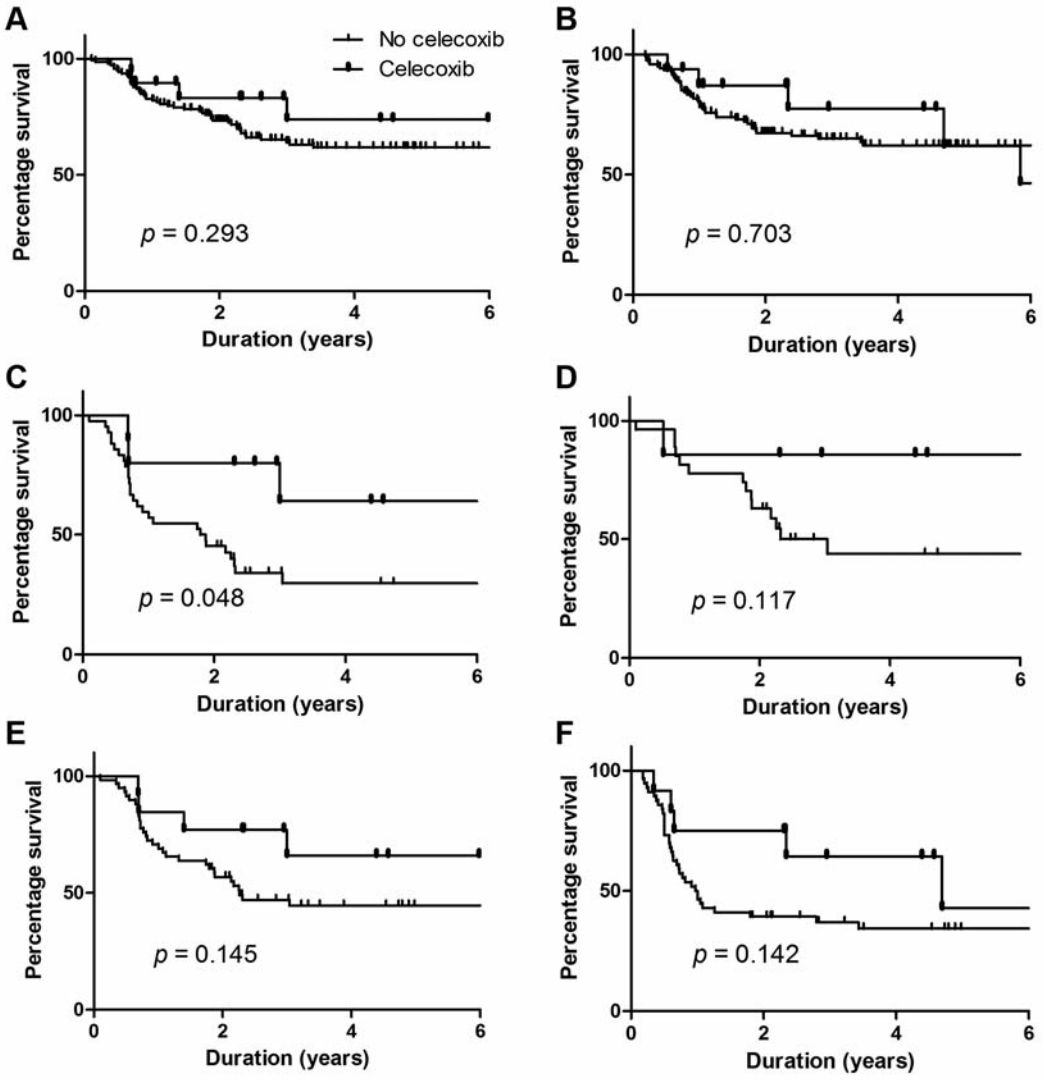

Figure 2. *Disease-specific survival (DSS) and recurrence-free survival (RFS) according to treatment modality. DSS and RFS were not significantly different according to celecoxib treatment (A, B). Among patients who received chemotherapy, DSS was significantly higher in the study group than in the control group (C), but RFS was not different between the two groups (D). Among patients who received radiation therapy, DSS and RFS were not significantly different according to celecoxib treatment (E, F).*

between the two groups (p=0.117; Figure 2D). Among patients who underwent radiation therapy, DSS and RFS were not significantly different between the study and control groups (p=0.145 and 0.142, respectively; Figure 2E and F). The DSS in the study and control groups were not significantly different according to T-stage, N-stage, or overall stage (Figure 3).

Discussion

Our study demonstrates that celecoxib treatment combined with chemotherapy for squamous cell carcinoma of the mobile tongue increased DSS. This is the first clinical study to define the effects of celecoxib on tongue cancer. Several *in vitro* studies have proven the anticancer effects of celecoxib, but the lack of clinical evidence in head and neck cancer has delayed clinical trials or application of this treatment modality. In the current study, celecoxib significantly increased DSS in patients who received chemotherapy. No difference in effect was observed according to disease stage (early or late) or radiation therapy.

The COX2 enzyme is overexpressed in many types of tumors, and its roles in tumorigenesis, angiogenesis, transformation, and metastasis have been reported in several studies (16-19). Many studies assessed the prophylactic role

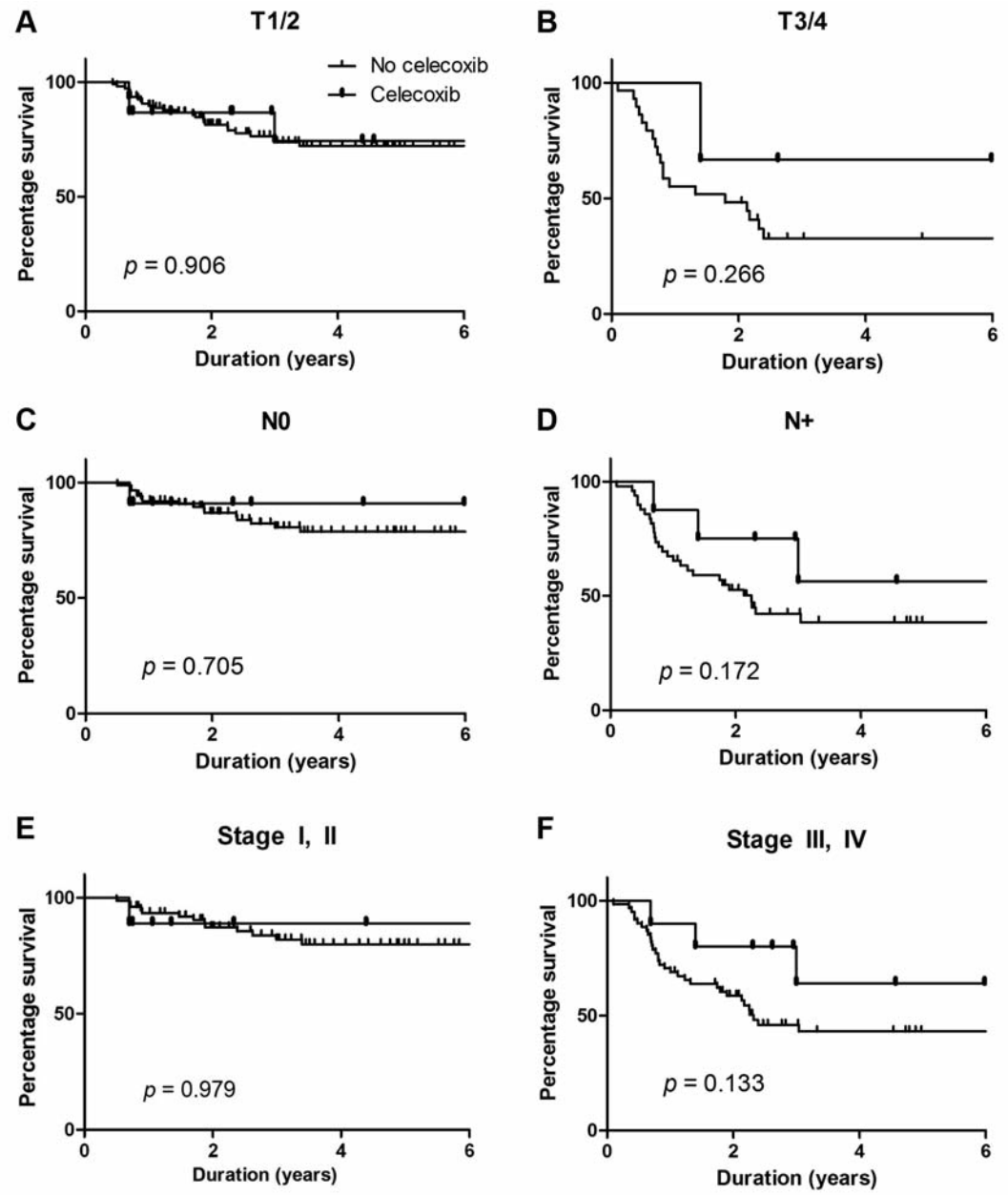

Figure 3. *Disease-specific survival (DSS) according to T-stage, N-stage, and overall cancer stage and celecoxib treatment. DSS in the study group and in the control group were not significantly different according to T-stage (A, B), N-stage (C, D), or overall stage (E, F).*

of COX2 inhibitors in various tumor types, such as colon and breast cancer, and showed that non-steroidal anti-inflammatory drugs and COX2 inhibitors decrease the incidence of colonic and breast cancer *via* inhibition of COX1 and COX2 enzymes (19). However, the anticancer effects of selective COX2 inhibitors, especially celecoxib, could result from various COX2-independent mechanisms, even in cancer cells without COX2 expression and activity (20). Additionally, this effect is observed with concentrations of celecoxib lower than those required for blocking COX2 activity in some cancer types (21, 22). In our own study with HNSCC lines, we observed that the tumor-killing effects of celecoxib might be evident even in HNSCC cells without COX2 expression, irrespective of the inhibition of prostaglandins produced by COX2 (8). Celecoxib has shown outstanding COX2-independent tumor-killing action in

several cancer models (23-25). Several different pathways of action have been described in cell lineages within the same type of cancer and, as such, the mechanism of action of celecoxib remains controversial (26). Nevertheless, the effects of celecoxib have been proven by several *in vitro* studies and its beneficial effects on various malignancies are now being studied in clinical trials (15, 27, 28).

Several clinical trials have evaluated the role of COX2 inhibitors in improving response to chemoradiation therapy for many cancer types. Herrera *et al*. evaluated the toxicity and efficacy of celecoxib in combination with definitive chemoradiation in locally advanced cervical cancer, and they reported that this combination was associated with acceptable acute toxicity (10). Govindan *et al*. reported that the addition of 400 mg celecoxib twice daily to chemoradiation in patients with resectable esophageal cancer was well-tolerated. They reported a pathological complete response rate of 22%, which was similar to that reported with the use of preoperative chemoradiation alone in other trials (11). In more recent trials, patients with high levels of COX2 in rectal cancer may benefit from celecoxib treatment after chemoradiation and surgery (27). In nasopharyngeal cancer, the addition of 100 mg celecoxib twice daily to concurrent chemoradiation improved the 2-year locoregional control rate (15). Therefore, celecoxib can be regarded as a relatively safe medication to be combined with a chemotherapeutic agent (*e.g*. cisplatin). The survival benefits of celecoxib need further evaluation.

An animal study reported that the combination of celecoxib and cisplatin inhibited the growth of tongue cancer in hetero-transplanted nude mice (29). Although several mechanisms of synergistic effects of celecoxib with cisplatin have been suggested, including the down-regulation of the phosphoinositide 3-kinase/Akt pathway and an endoplasmic reticulum stress response (9), none has been proven to be accurate. Although our current study did not clarify the mechanism of action, we demonstrated that celecoxib exerts its effect only when combined with chemotherapy. However, several studies found that COX2 inhibitors also significantly enhanced the response of tumor cells to radiotherapy (30-33). The exact mechanism responsible for the anticancer effects of COX2 inhibitors remains unclear but the anti-angiogenic effects of COX2 inhibitors are likely responsible for enhancing the effects of ionizing radiation (30) and COX2 inhibitors are believed to have a potential role for improving response to radiotherapy (31-33). In our study, celecoxib treatment was correlated with a small increase in survival, but the small number of patients in the study who received combined treatment with radiation therapy and celecoxib is probably the reason for the lack of statistical significance.

There are several limitations to our study. Firstly, this was a retrospective review and not a well-organized trial of celecoxib treatment. Therefore, there may be selection bias for initiating adjuvant treatment with celecoxib; the decision to start and finish celecoxib treatment was based on the surgeon's experiences and on previous *in vitro* studies. Secondly, the study group was small compared to the control group. As shown in Figure 3, celecoxib had a beneficial effect on RFS in patients who received chemotherapy, on OS of patients who received radiation therapy, and on survival of patients with advanced stages of disease (T3/4, N+, stage III/IV). However, these improvements did not reach statistical significance, which was probably due to the small number of patients in the study group. Moreover, the timing of the start of celecoxib treatment and the duration of treatment could not be evaluated because of the small number of patients in the study group.

Despite these limitations, our study is meaningful since as far as we are aware of it is the first to evaluate the effects of celecoxib in a clinical setting, not in an animal model or in an *in vitro* study. Despite the small number of patients included and the fact that this was a retrospective review, we believe that this study provides sufficient evidence to support a clinical trial of celecoxib treatment in mobile tongue cancer. In conclusion, celecoxib had beneficial effects on the outcomes of mobile tongue cancer in patients who received chemotherapy. A larger cohort and a well-organized protocol are required to clarify the effects of celecoxib.

Conflicts of Interest

No conflicts of interest exist. The Authors alone are responsible for the content and writing of this article.

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Received March 20, 2015
Revised April 3, 2015
Accepted April 8, 2015