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Original Research

Influence of interval between biopsy and surgery on prognosis of patients with early-stage oral squamous cell carcinoma: A preliminary study

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ABSTRACT

Objective: Recent studies have suggested that preoperative interventions such as tooth extraction, incision and curettage may be associated with poor prognosis in patients with oral malignancies. Although biopsy is another preoperative intervention, its influence on the prognosis of patients with oral squamous cell carcinoma (OSCC) has remained unclear. We investigated the prognosis of stage I and II OSCC patients, with special reference to the influence of the interval between biopsy and surgery.
Materials and methods: The cases of 47 patients diagnosed with primary early-stage (T1 or T2N0M0) OSCC were reviewed retrospectively.
Results: Primary surgery was performed ≤ 21 days after biopsy for 17 patients, and > 21 days after biopsy for 30 patients. Incidence of local recurrence or delayed cervical lymph node metastasis was significantly higher among the long-interval group (p = 0.03). Patients with local or neck failure displayed a significantly longer interval (33.6 days) than patients who were stable (21.9 days; p < 0.01). Five-year survival rates in groups with and without recurrence or metastasis were 66.7% and 90.6%, respectively (p < 0.05).
Conclusion: Treatment delay can worsen the prognosis of patients with early-stage OSCC by increasing the incidence of local and neck failure. Prompt treatment after biopsy is thus recommended to optimize the outcomes.

1. Introduction

Oral squamous cell carcinoma (OSCC) accounts for 95% of all oral and oropharyngeal malignancies, and around 300,000 new cases are diagnosed every year, making this the sixth most common cancer in the world [1–3]. Despite advances in treatment strategy, the overall survival rate of OSCC remains poor, at approximately 50–60% [4,5]. This unfavorable prognosis generally stems from loco-regional recurrence and metastasis to cervical lymph nodes or distant organs. The majority of these problems take place within a year after primary treatment [6,7]. On the other hand, if surgical treatment is performed at an early stage, the 5-year disease-specific survival rate improves to around 80% [8]. Therefore, finding and treating OSCC at an early stage is considered particularly important [4]. Recent studies have suggested preoperative intervention such as tooth extraction, incision or curettage can possibly lead to poor prognosis in patients with oral malignant tumors [9,10].

However, biopsy before treatment is a preoperative intervention, the influence of biopsy on the prognosis of patients with OSCC has not been well documented.

The purpose of this study was to investigate the prognosis of early-stage OSCC patients, with particular reference to the influence on prognosis of the interval from biopsy through to primary operation.

2. Materials and methods

2.1. Patient characteristics

The cases of 47 patients diagnosed with primary early-stage (T1 or T2N0M0) OSCC at the Department of Dentistry, Oral and Maxillofacial – Plastic and Reconstructive Surgery, Yamagata University Faculty of Medicine, between 2011 and 2015 were reviewed retrospectively.

Patients who showed multiple cancers or metastasis to cervical

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lymph nodes or distant organs at the first visit were excluded from the study. Patient who had positive or close (< 4 mm) surgical margins were also excluded. The incidence of local recurrence or metastases was assessed as of 1 year after the primary surgery. Three oral surgeon performed submucosal biopsy, and the width of the specimens were about 5 mm.

Thirty of the patients were male and 17 were female. Mean age was 63.5 years (range, 23–93 years). The primary lesion was located as follows: tongue in 32 patients, upper gingiva in seven patients, lower gingiva in six patients, and buccal mucosa in two patients. The surgical methods comprised tumor resection alone in 40 patients, and resection with elective neck dissection in seven patients. Demographic and clinical characteristics, including age, sex, tumor site, T stage according to the TNM Classification of Malignant Tumours [11], presence of local recurrence or metastases and type of surgery were compared between groups with short and long intervals from biopsy to primary operation. The T stage of each tumor was determined based on the TNM Classification of Malignant Tumours [11]. The incidence of local recurrences or metastases were assessed by visual inspection, palpation, CT and magnetic resonance imaging examination. In addition, to clarify characteristics, patients with or without recurrence or metastasis were compared.

2.2. Statistical analysis

The significance of differences between background characteristics of the two groups were assessed using the chi square test, Student's independent t-test, and Fisher's exact test. Overall survival of patients in the two groups was calculated using the Kaplan-Meier method, and the significance of differences was computed using the log-rank test. The level of significance was set at the $P < 0.05$ level.

3. Results

Tumors were defined as T1 in 30 patients, and T2 in 17. Local recurrence or delayed cervical lymph node metastasis was observed in 12 patients, whereas 34 patients were free of both recurrence and metastases. Among these 34 patients, excisional biopsy was performed in three cases.

Of the 47 cases, 17 patients underwent primary surgery within 21 days after biopsy (short-interval group), and 30 patients at more than 21 days (long-interval group). These groups showed no significant differences in age, sex, tumor site, T stage, or type of surgery. However, the frequency of local recurrence or metastasis to cervical lymph nodes was higher in the long-interval group (p = 0.03; Table 1).

As shown in Table 2, patients with loco-regional failure showed a significantly longer interval from biopsy to surgery than those who were stable. Mean time from biopsy to primary surgery was 33.6 days (range, 19–61 days) for patients with loco-regional failure and 21.9 days (range, 0–48 days) patients without loco-regional failure (p < 0.01).

Overall survival curves are shown in Fig. 1. Five-year survival in the groups with and without loco-regional failure were 66.7% and 90.6%, respectively (p < 0.05).

Sites of recurrence or metastasis were as follows: local recurrence in two patients, metastasis to cervical lymph node in nine patients, and both local and neck failure in one patient. No distant metastasis was observed. The mean time from primary surgery to recurrence or metastasis was 4.1 months (range, 1–8 months; Table 3).

4. Discussion

Our results support the starting hypothesis by demonstrating a significantly higher incidence of local recurrence or cervical lymph node metastasis in the long interval group. Consequently, our findings offer evidence supporting early initiation of treatment after

Table 1
Clinical details of patients in short- and long-interval groups. Data are presented as number (%) unless otherwise stated.

Variable	Short-interval group (≤ 21 days) (n = 17)	Long-interval group (> 21 days) (n = 30)	P
Age (years)			0.32
Mean (range)	60.1 (29-91)	65.4 (23-93)	
Sex			0.05
Male	14 (82)	16 (53)	
Female	3 (18)	14 (47)	
Tumor site			0.61
Tongue	12 (71)	20 (67)	
Upper gingiva	2 (12)	5 (17)	
Lower gingiva	3 (18)	3 (10)	
Buccal	0	2 (7)	
T stage			0.05
T1	14 (82)	16 (53)	
T2	3 (18)	14 (47)	
Recurrence/Metastasis			0.03
+	1 (6)	11 (37)	
–	16 (94)	19 (63)	
Surgery			
Tumor resection	15 (88)	25 (83)	0.65
Tumor resection + neck dissection	2 (12)	5 (17)	

Table 2
Clinical details of patients in groups with and without recurrence or metastasis are compared. Data are presented as number (%) unless otherwise stated.

Variable	Group with recurrence/ metastasis (n = 12)	Group with no recurrence/metastasis (n = 35)	P
Age (years)			0.52
Mean (range)	66.3 (23–93)	62.5 (27–91)	
Sex			0.09
Male	5 (42)	25 (71)	
Female	7 (58)	10 (29)	
Tumor site			0.42
Tongue	7 (58)	25 (71)	
Upper gingiva	2 (17)	5 (14)	
Lower gingiva	3 (25)	3 (9)	
Buccal	0	2 (6)	
T stage			0.31
T1	6 (50)	24 (69)	
T2	6 (50)	11 (31)	
Time from biopsy to primary operation (days)			< 0.01
Mean (range)	33.6 (19–61)	21.9 (0–48)	
Surgery			
Tumor resection	11 (92)	29 (83)	0.66
Tumor resection + neck dissection	1 (8)	6 (17)	

intervention.

The above-mentioned outcomes are consistent with previous reports in terms of the deteriorating prognosis of oral cancer with preoperative procedures or diagnostic delay more than 1 month [9,10,12]. Regarding the influence of surgical procedure on OSCC, some reports have indicated neck failure and distant metastasis occur more frequently and rapidly when the cancer is repeatedly punctured in animal experimental models using OSCC and melanoma cell lines [13,14]. As for delayed treatment, the majority of patients with squamous cell carcinoma of the head and neck (SCCHN) develop significant signs of tumor
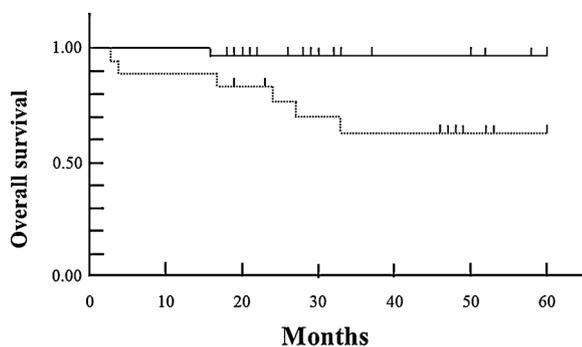
Fig. 1. Overall survival curve showing worse prognosis in the group with recurrence or metastasis than in the group without recurrence or metastasis (p < 0.05). Solid line, group without recurrence or metastasis; short dashed line, group with recurrence or metastasis.

Table 3
Site of recurrence or metastasis. Data are presented as number unless otherwise stated.

	Group with Recurrence/Metastasis (n = 12)
Site of Recurrence/Metastasis	
Local	2
Neck	9
Local + Neck	1
Time from primary operation to recurrence/metastasis (months) Mean (range)	4.1 (1–8)

progression within an average of 4 weeks [15], with the mean increase in the volume of primary SCCHN lesion reported as 38% [16]. In addition, the degree of tumor progression represents a strong prognostic factor [17]. In cases of OSCC, various prognostic factors have been suggested, including YK classification [18], which is based upon a pathologic assessment of the mode of invasion at the tumor-host borderline. Furthermore, tumor budding has also been reported as a useful prognostic factor in various cancers. Yamanouchi et al. reported that of the 8 patients with a high-grade budding classification, secondary cervical lymph node metastasis and/or locoregional recurrence were confirmed in 6 cases. On the other hand, of the 15 patients with a low-grade budding classification, secondary cervical lymph node metastasis and/or locoregional recurrence were confirmed in 6 cases [19].

Patients with local or neck failure showed a significantly lower 5-year overall survival rate (66.7%) than those without loco-regional recurrence (90.6%). Some authors have asserted that regional lymph node metastases is directly related to the risk of distant metastases [20]. Our results certainly suggest that the unfavorable prognosis of the long interval group results from neck failure. A large number of reports back this perspective [9,21].

Another notable finding of the study was that no local recurrence, neck failure, or distant metastases were seen in patients who underwent excisional biopsy. Although the sample size of our report was limited, this finding merits attention. Originally, this method was widely applied when treating malignant melanoma [10,22]. The favorable outcomes for patients treated with excisional biopsy in this study may indicate excisional biopsy for early-stage OSCC.

The present findings also offer a suggestion for the conventional treatment strategy. A recent study emphasized the benefit of elective neck dissection at the time of primary surgery, as compared with watchful waiting followed by therapeutic neck dissection for nodal relapse in patients with early-stage OSCC [23]. Considering our result that 11 of 30 patients (36.7%) who belonged to the long-interval group experienced local or neck failure, implementation of elective neck dissection can be considered when the interval grows longer. Naturally

enough, early initiation of treatment after biopsy should be considered first.

5. Conclusion

The results of this study document the harmful influence of late treatment after biopsy. Delays can worse the prognosis of patients with early-stage OSCC by increasing the incidence of local and neck failure. Prompt treatment after biopsy is strongly recommended to optimize outcomes.

Potential weaknesses of our study were as follows: the retrospective nature of the design, the limited sample size and the lack of uniform treatment. We reviewed patients who had been treated between 2011 and 2015, the determination of T stage is different from current classification in terms of considering depth of the lesion. Also, because there had not been enough evidence to support the benefit of elective neck dissection, not all the treatments we practiced were following the latest perception. Given these disadvantages, our findings cannot be considered indisputable. To enhance the level of evidence for the results, further prospective studies by multiple institutions against a large number of participants from a wider range of disease stages are warranted.

Ethical approval

Approval was obtained from the Ethics Committee of Yamagata University Faculty of Medicine. This study is a retrospective observational study, carried out by the opt-out method of our university website.

Conflict of interest

None.

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