Prognosis for Gingival Carcinomas With a Delayed Diagnosis After Dental Extraction

Prognosis for gingival carcinomas with a delayed diagnosis after dental extraction

Kenji Yamagata,DDS, PhD, * Hiroyuki Ito, DDS, * Kojiro Onizawa, DDS, PhD, §

Masanobu Yamatoji, DDS, PhD, † Toru Yanagawa, MD, DDS, PhD, ‡ Hiroki Bukawa, MD, DDS, PhD§

Department of Oral and Maxillofacial Surgery, Faculty of Medicine, University of Tsukuba

* Assistant professor

§ Professor

† Clinical Fellow

‡ Associate professor

The first two authors, K.Y. and H.I. were equally contributed to this work.

Correspondence: Kenji Yamagata

Department of Oral and Maxillofacial Surgery, Faculty of Medicine, University of Tsukuba

1-1-1 Tennodai, Tsukuba, Ibaraki, 305-8575, Japan

Tel: +81-29-853-3052, Fax: +81-29-853-3052

E-mail: y-kenji@md.tsukuba.ac.jp

Abstract

Purpose: In gingival squamous cell carcinoma (GSCC), the association between survival and history of dental extraction (DE) is controversial. The purpose of this study was to investigate the prognosis for patients in whom GSCC was detected after DE was performed.

Patients and Methods: DE for GSCC tumor symptoms was performed in 19 patients before diagnosis (DE group) and not in 58 patients (non-DE group). The clinical features, characteristics, and prognosis were evaluated statistically between the two groups.

Results: The interval between DE and the first visit to our hospital was 1.1-97 weeks (median 7.3 weeks). There was no significant difference in T status, N status, local recurrence, pathologically positive lymph nodes, or distant metastasis between the DE and non-DE groups. Bone invasion was observed radiographically in six patients with mandibular GSCC in the DE group (100%) and 13 in the non-DE group (68.4%). There was a significant difference in bone invasion between the DE and non-DE groups ($P<0.01$). Segmental mandibulectomy was performed in 11 patients (84.6%) in the DE group and 21 patients (61.8%) in the non-DE group. The extent of resection tended to be larger for the DE group. The 5-year overall survival rate was 84.6% for the DE and 65.8% for the non-DE patients with mandibular GSCC. For maxillary GSCC, the survival rates differed significantly between the groups (33.3% in the DE and 73.7% in the non-DE group).

Conclusions: For mandibular GSCC, the resection field was appropriate for the extent of bone invasion after DE, and the prognosis was similar to that in the non-DE group. For maxillary GSCC, a broad surgical field is suggested because of the potential for rapid spread in cancellous bony trabeculae.

Key Words: Dental extraction (DE), Gingival squamous cell carcinoma (GSCC), Survival rate, Prognosis, Surgical field

Introduction

Teeth that are in close proximity to a carcinoma can be associated with swelling, pain, and loosening, and may thus be erroneously extracted because of suspected periodontitis or pericoronitis by the dental general practitioner. Suzuki et al. reported that, compared to a group of patients in whom dental extraction (DE) was not performed, the incidence of pathologically positive lymph nodes was significantly higher and the five-year survival rate lower in a DE-treated group.[1] Moreover, when DE is performed for incorrectly diagnosed periodontitis or pericoronitis, the correct diagnosis and appropriate treatment may be delayed, resulting in a worse prognosis. Previous studies suggest that the risks of gingival squamous cell carcinoma (GSCC) recurrence, cervical lymph-node metastasis, and distant metastases are increased in patients with a history of DE. [1, 2]

However, the association between survival and a history of DE remains controversial. Other researchers have reported that DE does not influence local control, lymph-node metastasis, distant metastasis, or disease-specific survival prior to definitive treatment. [3-5] Lubek et al. reported that previous DE, which can potentially seed the open socket with cancer cells and allow deep bony involvement, was not a significant variable. [6] Thus, although the risks of DE have been emphasized, its effects on the metastasis and prognosis of patients have not been well documented. This study was carried out to investigate the prognosis of GSCC detected after DE was performed at the site of the carcinoma.

Patients and Methods

Subjects

Seventy-seven patients, 45 men and 32 women, in whom GSCC was diagnosed at the Department of Oral and Maxillofacial Surgery, University of Tsukuba Hospital, between 1997 and 2008, were retrospectively enrolled as subjects. All the cases were reviewed for an approximately 5-year period after each patient's first visit or radical treatment. Patients' ages ranged from 40 to 88 years, with a median of 70 years. The primary tumor site was the maxilla for 25 cases and the mandible for 52 cases. Each patient's cancer was staged according to the 1997 International Union Against Cancer (UICC) categories. The

treatment modality given for the primary tumor included surgery, radiotherapy, chemotherapy, or a combination. The primary tumor was excised with a safety margin greater than 10 mm in all directions. The extent of bone resection (marginal or segmental) was based on the extent of the soft-tissue tumor and of the radiographically determined bone invasion.

DE within the tumor was performed in 19 patients (24.7%) before diagnosis (DE group) and was not performed in 58 patients (75.3%) (non-DE group). The clinical features, characteristics, and prognosis were evaluated for statistical differences between the two groups. The patients' data were examined retrospectively by reviewing their medical records. Due to the retrospective nature of this study, it was granted an exemption in writing by the University of Tsukuba Hospital. The following information was obtained: age, sex, site of primary tumor (maxilla or mandible), locoregional treatment, history of DE before diagnosis, symptoms at first visit, and 5-year survival rate according to the primary tumor site.

Statistical analysis

Survival curves were calculated by the Kaplan-Meier method, and difference in the survival rate was determined with the Log-rank test. The Mann-Whitney U-test and Chi square test were used in statistical comparisons between the DE group and non-DE group. All statistical analyses were performed with the Stat View J 5.0 software package (SAS Institute Inc, Chicago IL). Differences with a *p*-value less than 0.05 were considered statistically significant.

Results

1. Patient characteristics

The tumor status in the DE group was T2 for 5 patients, T3 for 4, and T4 for 10; in the non-DE group, it was T1 for 3 patients, T2 for 22, T3 for 9, and T4 for 24. The node status in the DE group was N0 for 11 patients, N1 for 4, and N2b for 4; in the non-DE group, it was N0 for 37 patients, N1 for 6, N2b for 10, and N2c for 5. The cancer stage in the DE group was stage II for 3 patients, stage III for 4, and stage IV for 12;

in the non-DE group, it was stage I for 1 patient, stage II for 20, stage III for 8, and stage IV for 29. There was no significant difference in stage classification between the DE and non-DE groups (Table 1).

2. Patients undergoing DE before diagnosis and clinical features of both groups at first visit

DE within the tumor was performed in 19 patients before GSCC was diagnosed, at another hospital. The interval between DE and the first visit to our hospital was 1.1-97 weeks, with a median of 7.3 weeks. The extraction site was the maxilla in 6 patients (11 teeth) and the mandible in 13 patients (19 teeth). The tooth position was anterior in 3 patients (7 teeth) and molar in 16 patients (23 teeth).

The major symptom was swelling in both the DE and non-DE groups (52.6%, 53.4%). Pain (21.1%) and delay of extraction site healing (15.8%) were the next most common symptoms in the DE group. Poor denture fit (15.5%) and ulceration (12.1%) were the next most common symptoms in the non-DE group.

Radiographically, bone invasion was observed in all the patients in the DE group and in 37 patients (63.8%) in the non-DE group. Bone invasion of mandibular GSCC was observed in 6 patients (100%) in the DE group and 13 patients (68.4%) in the non-DE group. There was a significant difference in the bone invasion between the DE and non-DE groups ($P<0.01$) (Table 2).

3. Locoregional treatment and surgical procedure

The locoregional treatment in the DE group was surgery for 13 patients, pre-surgical radiotherapy and surgery for 4, surgery and post-surgical radiotherapy for 1, and radiotherapy for 1; in the non-DE group, the treatment was surgery for 31 patients, pre-surgery radiotherapy and surgery for 17, surgery and post-surgery radiotherapy for 2, and radiotherapy for 8 (Table 1). There was no significant difference in any of these factors between the two groups.

Surgery was performed in 21 patients with GSCC of the maxilla and 47 with GSCC of the mandible. Marginal mandibulectomy was performed in 2 patients (15.4%) in the DE group and 13 (38.2%) in the non-DE group. Segmental mandibulectomy was performed in 11 patients (84.6%) in the DE group and 21 (61.8%) in the non-DE group. Although the extent of resection tended to be larger for the DE group, the

difference between the groups was not statistically significant. The surgical procedure for the maxilla is shown in Table 3. Neck dissection was performed in 11 patients in the DE group and 25 patients in the non-DE group (Table 3).

Pathologically, the surgical margin was free of cancer in 16 patients (88.9%) in the DE and 43 patients (86.0%) in the non-DE group. Two patients in the DE and 7 patients in the non-DE group had a positive or close margin within 5 mm. Of the patients treated surgically, bone invasion was observed in 15 (83.3%) in the DE group and 30 (60.0%) in the non-DE group. There was difference in bone invasion between the DE and non-DE groups was not significant (Table 4).

4. Postsurgical course and survival rate of each group

Sixteen patients had a local recurrence during the postsurgical course (4 patients in the DE group and 12 in the non-DE group); 8 had late neck metastasis, and 9 had distant metastasis. The difference in postsurgical course between the DE and non-DE groups was not statistically significant (Table 5). Pathologically positive lymph nodes were observed in 5 patients (27.8%) in the DE group (range 1 to 3, median of 2 lymph nodes) and 12 patients (24.0%) in the non-DE group (range 1 to 4, median of 1.5 lymph nodes) (Table 4).

The 5-year overall survival rate was 68.4% in the DE group and 68.6% in the non-DE group among all the GSCC patients, which was not significantly different. For maxillary GSCC, the survival rate was 33.3% in the DE group and 71.8% in the non-DE group, which did reach significance ($p<0.05$) (Table 6, Fig 1). Among the mandibular gingival cancer patients, the survival rate was 84.6% in the DE group and 65.8% in the non-DE group, which was not significantly different (Table 6, Fig 2).

Discussion

Pain is reported to be the most common clinical feature of GSCC diagnosed after DE, present in all such cases. [7] In our study, pain was a symptom in 21.1% of the patients in the DE group, consistent with the previous report, and 8.6% in the non-DE group. The duration of symptoms before DE is reported to range

from 3 weeks to 20 months, with most patients seeking treatment at 3 months. [7] The mean time interval between DE and histologic diagnosis in a previous report was 63 days (9 weeks) with a range of 3 to 260 days (0.4-37 weeks). [1] In this study, the interval between DE and the first visit was 1.1-97 weeks, with a median of 7.3 weeks. Symptoms appeared in these patients about 2 months after DE, which was almost the same as in previous reports. This delay may be one of the factors that facilitate tumor dissemination. Suzuki et al. suggested that the delay in symptoms increases the risk of lymph-node metastasis and contributes to a poor prognosis. [1] In the present study, it was not clear whether this delay affected the lymph-node metastasis or prognosis.

The association between prognosis and history of DE remains controversial. It has been hypothesized that a history of previous DE worsens the prognosis, and neck node metastasis was reported to be more frequent in patients who underwent DE. [1] However, other authors reported that cervical lymph node metastasis was not significantly different between patients who underwent an invasive procedure and those who did not. [3, 5] In addition, statistically significant differences were not found in the tumor recurrence rate, cervical recurrence, distant metastasis, or 5-year survival rate. [3, 5] Lubek et al. reported that previous DE, which can theoretically seed the open socket and allow deep bony involvement, was not a significant variable for the prognosis for gingival carcinoma. [6] In the present study, we found no differences in the T status, N status, local recurrence, or distant metastasis with or without DE. Mandibular GSCC showed almost the same prognosis in the DE and non-DE groups. These results supported the latter opinions. On the other hand, there was a significant difference in the survival rate of patients with maxillary GSCC between the DE and non-DE groups. However, the sample size was small for the maxillary cases, and further studies with a larger number of cases at this primary site will be required to clarify the difference.

In a previous report, advanced clinical stage III and IV, previous DE, bony invasion, and invaded margins were associated with worse survival in a univariate analysis. [8] Only the difference in advanced stage was significant in multivariate analysis, but lymph-node involvement was not studied separately. [8] Although bone invasion is reported to be a predictive factor, a recent study showed that tumors with bone invasion limited to the cortex have a similar prognosis to those without bone invasion.[9] Surgical

invasiveness in oral cancer, including biopsy, causes the dissemination of cancer cells into the circulation, increasing the risk for metastasis. [2] In general, cervical lymph-node metastasis is one of the most significant factors affecting the prognosis of head and neck cancer. In the present study, the incidence of cervical lymph-node metastasis was 42.1% in the DE group and 36.2% in the non-DE group, which, although it was not significantly different, could have affected the overall survival rates of these two groups. On the other hand, another group reported that the disease-specific survival rates of two groups that had or had not undergone surgical procedures before GSCC treatment were not significantly different. This conclusion was based on the extent of resection needed for the primary tumor. [4] Cancer bone invasion is a well-known predictive factor for survival. [8] Hong et al. advised using more aggressive resection, when a GSCC in the dentate mandible remains undiagnosed for a few months after inadvertent DE or when a secondary surgical manipulation was previously carried out at the tumor site.[10] When the malignant tumor is related to previous DE or curettage, it tends to be more extensive than predicted from imaging. If mandibular invasion by GSCC is identified radiographically and clinically, segmental mandibulectomy is required for an adequate safety margin, considering the spreading pattern in the molar region. [10] In the present mandibular GSCC cases, previous DE did not affect the T stage. The resection field in the patients who received DE tended to be broader; for instance, the proportion of patients who received segmental mandibulectomy was 84.6% in the DE group versus 61.8% in the non-DE group. In addition, the extent of radiographically detected bone invasion was significantly greater in the DE group. Although the extent of bone resection was determined from clinical and radiographic criteria, surgeons may have believed that the DE patients had more locally disseminated microscopic disease, leading them to choose segmental mandibulectomy. This choice may have biased the data to some extent. Thus, the extended resection field might have been related to the lack of significant difference in the 5-year overall survival rate between the two groups.

In the cases of maxillary GSCC, there was a significant difference in the survival rates, 33.3% in the DE group and 73.7% in the non-DE group. Although the T status as detected by CT or MRI was not affected in the DE group, it is likely that microscopic GSCC extended into the cancellous bone of the maxilla. According to a report, the extent of bony invasion diagnosed clinically and radiographically often does not

correspond to that found histologically.[11] It is difficult to determine the appropriate resection margin, because bone invasion by cancer cells whose spreading is transmedullary is not radiologically identifiable. Moreover, tumor cells spread rapidly between cancellous bony trabeculae, since they meet no resistance or barrier. In our study, the sample size of maxillary cases was small, and further study with a larger number of cases at this primary site will be required to clarify the differences.

Choi et al. recommended that after invasive procedures, more aggressive treatment for gingival cancer, such as setting a broad surgical field and enforcing preventive neck dissection, are needed to improve the outcome. [5] In cases of maxillary GSCC, we agree with their recommendation, because of the possibility for rapid spreading between cancellous bony trabeculae in the maxilla, and because of our finding of a poor prognosis. However, the prognosis in the mandibular GSCC cases was not significantly different between the two groups, and the resection was performed according to the extent of the cancer based on radiographic findings. Moreover, the frequency of cervical lymph node metastasis between the DE and non-DE groups did not differ significantly in our study. Therefore, we believe that the extent of resection for mandibular GSCC and neck dissection corresponding to the usual field of resection, not aggressive resection, is appropriate.

GSCC mimics periodontitis and pericoronitis. DE performed without awareness of the carcinoma may cause a delay in reaching the correct diagnosis and starting appropriate treatment, and thereby worsen the prognosis. A larger lesion may raise the suspicion of neoplasm, thus resulting in a referral before extraction or treatment, whereas a smaller lesion may be suspected of being non-malignant. In the case of maxillary GSCC, we recommend setting a broad surgical field, because of the possibility of rapid spread between cancellous bony trabeculae. For mandibular GSCC, we set the resection field according to the extent of invasion for both groups, and the prognosis was almost the same for the DE and non-DE groups.

Conflict of Interest

All authors indicate they have no potential conflicts of interest.

References

1. Suzuki K, Shingaki S, Nomura T et al.: Oral carcinomas detected after extraction of teeth: a clinical and radiographic analysis of 32 cases with special reference to metastasis and survival. Int J Oral Maxillofac Surg 27:290, 1998

2. Kusukawa J, Suefuji Y, Ryu F et al.: Dissemination of cancer cells into circulation occurs by incisional biopsy of oral squamous cell carcinoma. J Oral Pathol Med 29:303, 2000

3. Shingaki S, Nomura T, Takada M et al.: Squamous cell carcinomas of the mandibular alveolus: analysis of prognostic factors. Oncology 62:17, 2002

4. Tomioka H, Omura K, Harada H et al.: A clinical study of patients with gingival cancer who received surgical procedures before our examination. Jap J of Head and Neck Cancer 37:18, 2011

5. Choi EJ, Zhang X, Kim HJ et al.: Prognosis of gingival squamous cell carcinoma diagnosed after invasive procedures. Asian Pac J Cancer Prev 12:2649, 2011

6. Lubek J, El-Hakim M, Salama AR et al.: Gingival carcinoma: retrospective analysis of 72 patients and indications for elective neck dissection. Br J Oral Maxillofac Surg 49:182, 2011

7. Obuekwe N, Akpata O, Ojo MA et al.: Malignant tumours presenting after dental extraction: a case series. East Afr Med J 82:256, 2005

8. Soo KC, Spiro RH, King W et al.: Squamous carcinoma of the gums. Am J Surg 156:281, 1988

9. Ebrahimi A, Murali R, Gao K et al: The prognosis and staging implications of bone invasion in oral squamous cell carcinoma. Cancer 117: 4460, 2011

10. Hong SX, Cha IH, Lee EW et al.: Mandibular invasion of lower gingival carcinoma in the molar region: its clinical implications on the surgical management. Int J Oral Maxillofac Surg 30:130, 2001

11. Nomura T, Shibahara T, Cui NH et al.: Patterns of mandibular invasion by gingival squamous cell carcinoma. J Oral Maxillofac Surg 63:1489, 2005

Table 1. Patient characteristics

Characteristics	No. of patients (%)	
	DE group, n= 19	Non-DE group, n=58
Sex		
Male/Female	11/ 8	34/ 24
Age (years)		
Median (range)	75 (40-84)	70 (47-88)
Primary tumor site		
Maxillary gingiva	6 (31.6)	19 (32.8)
Mandibular gingiva	13 (68.4)	39 (67.2)
Tumor status		
T1	0 (0)	3 (5.2)
T2	5 (26.3)	22 (37.9)
T3	4 (21.1)	9 (15.5)
T4	10 (52.6)	24 (41.4)
Node status		
N0	11 (57.9)	37 (63.8)
N1	4 (21.1)	6 (10.3)
N2a	0 (0)	0 (0)
N2b	4 (21.1)	10 (17.2)
N2c	0 (0)	5 (8.6)
N3	0 (0)	0 (0)
Stage classification		
I	0 (0)	1 (1.7)
II	3 (15.8)	20 (34.5)
III	4 (21.1)	8 (13.8)
IV	12 (63.2)	29 (50.0)
Locoregional treatment		
S	13 (68.4)	31 (53.4)
R+S	4 (21.1)	17 (29.3)
S+R	1 (5.3)	2 (3.4)
R	1 (5.3)	8 (13.8)

S: Surgery; R: Radiotherapy

Table 2. Clinical and radiographic features at first visit

Clinical feature	No. of patients (%) DE group, n= 19	Non-DE group, n=58	
Swelling	10 (52.6)	31 (53.4)	
Pain	4 (21.1)	5 (8.6)	
Delay of extraction site healing	3 (15.8)	0 (0)	
Poor denture fit	1 (5.3)	9 (15.5)	
Ulceration	0 (0)	7 (12.1)	
White lesion	1 (5.3)	2 (3.4)	
Tooth mobility	0 (0)	2 (3.4)	
Other	0 (0)	2 (3.4)	
Bone invasion by radiography	19 (100)	37 (63.8)	P<0.01
Maxilla	6	13	n.s.
Mandible	13	24	P<0.01

n.s.: Not significant

Table 3. Surgical procedure

		No. of patients (%)	
		DE group, n=19	Non-DE group, n=58
Maxilla (n=21)	Partial resection	5 (100)	14 (87.5)
	Total maxillectomy	0 (0)	2 (12.5)
Mandible (n=47)	Marginal resection	2 (15.4)	13 (38.2)
	Segmental resection	11(84.6)	21 (61.8)
No surgery (n=9)		1	8
Neck dissection (n=36)		11	25

Table 4. Association between pathological findings and dental extraction in patients treated with surgery

	No. of patients (%)	
	DE group, n= 18	Non-DE group, n=50
Positive lymph nodes (n=36)	5 (27.8)	12 (24.0)
Surgical margin <5mm (n=9)	2 (11.1)	7(14.0)
Bone invasion (n=45)	15 (83.3)	30 (60.0)

Table 5. Association between post-treatment factors and dental extraction

	No. of patients (%)	
	DE group, n= 19	Non-DE group, n=58
Local recurrence	4 (21.1)	12 (20.7)
Late neck metastasis	3 (15.8)	5 (8.6)
Distant metastasis	2 (10.5)	7 (12.1)

Table 6. Five-year overall survival rate of each group

Primary	5-year overall survival rate (%)		
	DE group	Non-DE group	P
Maxilla	33.3	71.8	<0.05
Mandible	84.6	65.8	n.s.
All	68.4	68.6	n.s.

n.s.: Not significant

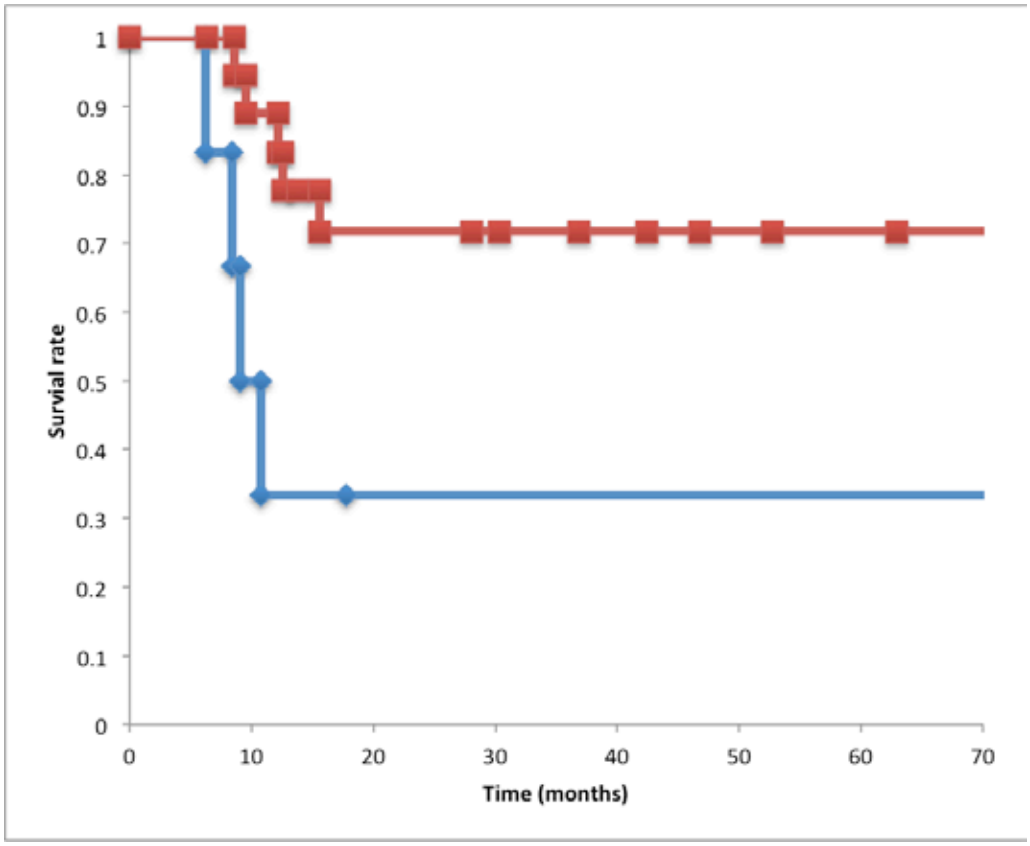

FIGURE 1. Survival rate of patients with maxillary GSCC. (Red line: Non-DE group, Blue line: DE group)

There was a significant difference in the survival rate between the DE and non-DE groups. ($P<0.05$)

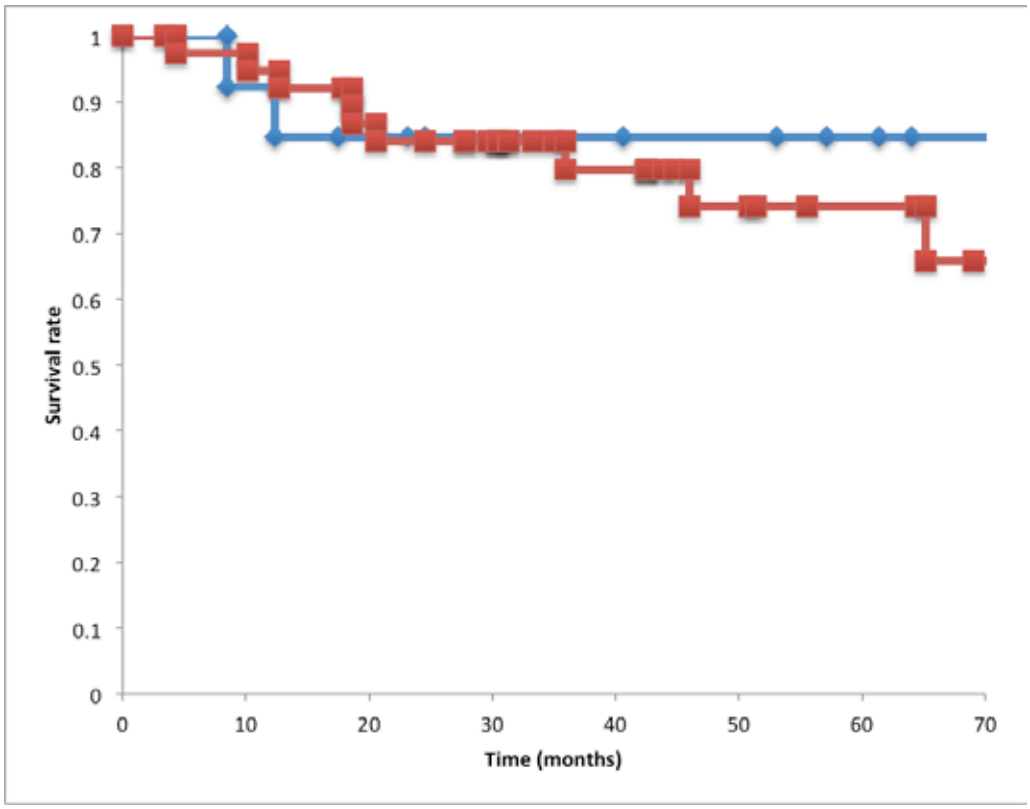

FIGURE 2. Survival rate of patients with mandibular GSCC.
(Red line: Non-DE group, Blue line: DE group)