Prognosis of tongue squamous cell carcinoma related with individual surgical margin, pathological features

외과적 절제연과 병리적 양상에 따른
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이 논문을 치의과학석사 학위논문으로 제출함

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조 성 지 의 석사학위논문을 인준함

2022 년 6 월

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Abstract

Introduction: The specific muscular structure of the tongue greatly affects margin shrinkage and tumor invasion, making the optimal surgical margin controversial. This study investigated surgical margin correlated prognosis of TSCC (Tongue squamous cell carcinoma) according to margin location and its value, and the histopathologic factors which are suggestive of tumor invasion. We propose defining of the surgical margin for TSCC via prognosis according to location and margin values.

Materials and methods: We reviewed 45 patients diagnosed with TSCC who visited Seoul National University Dental Hospital (Seoul, Republic of Korea, SNUDH) from 2010 to 2019, who were managed by a single surgical team. Patient clinical and pathological data of patients were retrospectively reviewed, and in 36 out of 45 patients, the pathologic parameters had the worst pattern of invasion (WPOI) and tumor budding was investigated via diagnostic histopathology slide reading.

Results: There was no significant difference in disease specific survival (DSS) or loco-regional recurrence free survival (LRFS), which are standardized with as 0.25 cm anterior margins, as 0.35 cm deep margin.

Additionally, there was a non-significant difference in DSS and LRFS at the nearest margin of 0.35 cm (p_{DSS} = 0.276, p_{LRFS} = 0.162). Aggressive WPOI and high tumor budding showed lower survival and recurrence-free survival, and there were significant differences in close margin and involved margin frequencies.

Conclusion: In TSCC, the value and location of the surgical margin did not have a significant relationship with prognosis, but WPOI and tumor budding suggesting the pattern of muscle invasion affected survival and recurrence-free survival. WPOI and tumor budding should be considered when setting an optimal surgical margin.

Keywords: Tongue squamous cell carcinoma (TSCC), surgical margin, worst pattern of invasion (WPOI), tumor budding
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Introduction

Oral squamous cell carcinoma (OSCC) is a malignant tumor accounting for more than 90% of oral cancers and the tongue is the most common OSCC site, which accounts for about 50% or more[1]. The tongue, unlike other tissues in the oral cavity, has a characteristic structure including a high content of muscle bundles and a rich lymphatic chain[2]. A high proportion of muscles in the tongue make so that it can be a routes for tumoral spread through muscle fibers, thus local recurrence could be higher with muscle invasion[3]. In addition to creating a specific tumor microenvironment, it can also induce lots of shrinkage at resection[4] (Table 1, Fig. 1). Shrinkage, which is affected by tissue composition and tumor cells cohesiveness. has a greater effect in the tongue than in other oral structures. The microenvironment of the medial side which is adjacent to the muscular tissue of the tongue, neurovascular bundle, and mesenchymal tissue makes the boundary of the tumor unclear, irregular. Also it causes spreading and invasion of tumor cells from the mass, inducing epithelial to mesenchymal transition and infiltration5. These aspects make it difficult to set the surgical margin during surgery and obtain a sufficient surgical margin, and the interaction between cancer cells and the surrounding

microenvironment acts as an important factor in tumor development, invasion and metastasis[5].

In addition to perineural and lympho-vascular invasion and depth of invasion, current literatures hypothesize that histopathologic parameters like pattern of invasion (POI) and, tumor budding should be predictors of invasion, nodal metastasis and prognostic criteria[2,6-8]. POI is a pathologically classified invasion pattern of the resection margin to evaluate tumor aggressiveness[6-8] (Table 2), and to identify the worst pattern of invasion (WPOI). Tumor budding indicates loss of cellular cohesion and, active invasive movement and was defined as a single cancer cell or a cluster of less than five cancer cells in the stroma of the invasive front. According to the guideline published by the International Tumor Budding Consensus Conference, tumor budding should be assessed using × 20 objective within the hotspot at the invasive front, and graded as low (0 - 4 buds), intermediate (5 buds) or high (≥ 5 buds)[7].

Because radical resection is the fundamental treatment for tongue squamous cell carcinoma (TSCC), and considering the characteristics of the tongue, it could be expected that setting the surgical margin with consideration of tumor invasion is directly related to good prognosis.

In this study, we assumed that the size of the recommended surgical margin would vary depending on margin location and the anatomical specificity of the tongue, and we analyzed TSCC prognosis, according to the value of each location of the surgical margin. Additionally, by estimate the correlation between histopathologic prognostic factor like WPOI, tumor budding, prognosis, and surgical margin, we suggest the surgical margin of TSCC should consider anatomical specificity, tumor environment of tongue, and histopathologic prognostic factors.

Materials and methods

2.1 Study cohort

We reviewed 45 patients diagnosed with TSCC who visited Seoul National University Dental Hospital (Seoul, Republic of Korea, SNUDH) from 2010 to 2019 and who were, managed by a single surgical team. This study and its access of patient records were ethically approved by the Seoul National University Institutional Review Board (S-D20170026). These patients fulfilled the following inclusion criteria: (1) complete clinical evaluation, (2) mass ablation surgery with or without radiotherapy, and exclusion criteria: (1) did not undergo surgical treatment (2) did not receive adequate follow-up.

The following clinical information of patients was retrospectively reviewed, timing of surgery, tumor stage, surgical approach, survival and local recurrence, and the adjuvant therapy after surgery. Pathologic reports were also reviewed and summarized.

2.2 Pathologic evaluation

  The pathological features, including perineural invasion, lymphovascular invasion, and depth of invasion, which were reviewed by oral and maxillofacial pathologist, were collected.

Among 45 patients, a total of 340 diagnostic histological slides from 36 patients were scanned using an Aperio CS2® (Leica Biosystems, Nussloch, Germany) and read by Case viewer® software (3DHISTECH Ltd, Budapest, Hungary). POI was marked in all hematoxylin-and-eosin-stained slides, and the worst pattern was selected as a WPOI in each patient (Fig. 2). Tumor budding was defined as a single cell or a cluster of < 5 tumor cells present in the stroma at the invasive tumor front. Slides were viewed with × 5 magnification to select the highest tumor budding area at first, and at × 20 magnification. A 0.785 mm^2 standard file size was used for the budding counts (Fig. 3). Images were graded as low (0-4 buds) and high (≥5 buds). Critical reviews with confirmed evaluation were carried out by an oral and maxillofacial pathologist.

2.3 Surgical margin evaluation

Surgical margins were evaluated based on pathology reports and diagnostic histological slides (Figs. 3B and 3C). Margin status was evaluated in 5 directions: (1) anterior; (2) posterior; (3) superior; (4) inferior and (5) deep resection margin.

2.4 Statistical analysis

Surgical margin differences were evaluated by Student's t-test, Kruskal-Wallis test, and the Mann-Whitney U test. Cut-off values of each direction of surgical margin were calculated by ROC curve and Youden's J statistic. DSS and LRFS were analyzed according to the surgical margin, WPOI, and tumor budding. Univariate and multivariate regression was carried out with logistic regression and Cox-regression and hazard ratio and 95% confidence intervals(CI) were calculated for each survival and recurrence predictor. Statistical analyses were performed using SPSS® version 26.0 (SPSS Software Company, Chicago, IL, USA) and p values < 0.05 were considered statistically significant.

Results

3.1 Demographics

A total of 45 patients were investigated, and according to the T-stage classification of the American Joint Committee on Cancer (AJCC) classification, T_1 (16 patients), T_2 (24 patients), T_3 (2 patients), and T_4 (3 patients) were included. Fifteen patients underwent transoral partial glossectomy only and 30 patients underwent neck dissection and glossectomy. Among patients who underwent neck dissection, 23 patients were also treated with free flap reconstruction. The mean invasion depth value was 0.886±0.61 cm and statistically significant difference according to T-stage was observed ($p = 0.001$). Seventeen patients were treated with adjuvant therapy after surgery; 11 patients were treated with post-operative radiotherapy (PORT); 3 patients were treated with post-operative concurrent chemo-radiotherapy (POCCRT); and 3 patients were undergoing further resection surgery. There was a statistically significant difference in postoperative adjuvant therapy strategy according to T-stage ($p = 0.010$). Also, the group that received adjuvant therapy showed a higher disease-specific survival rate than the group that did not, and the difference

was a statistically significant. ($p = 0.045$). There were 3 patients who received neo-adjuvant therapy, all 3 died due to disease, and 2 had recurrence.

Recurrence occurred in 19 patients, among whom local recurrence occurred in 3; regional recurrence occurred in 12 patients; and distant recurrence occurred in 4 patients. The mean follow-up period for the patient group was 58.60 months, the mean 3-year disease-free survival was 75.56%, and the mean 3-year loco-regional recurrence free survival was 46.67%. There was a statistically significant difference in DSS according to T-stage ($p = 0.004$).

3.2 Surgical margin

The mean surgical margins values were 0.78±0.36 cm (anterior), 0.98±0.73 cm (posterior), 0.86±0.41 cm (superior), 0.65±0.38 cm (inferior), and 0.60±0.39 cm (medial) (Table 4). There was no significant difference except nearest margin according to T-stage and WPOI ($p_T = 0.012$, $p_{WPOI} = 0.091$) (Table 5). Also, comparing the size of the surgical margins of the survivor group and the deceased group, there was a statistically significant difference between the anterior and the medial sides of the surgical margins ($p_{Ant} = 0.013$, $p_{Deep} = 0.014$), and there was no

significant difference surgical margin between recurrence free patients and recurrence patients (Tables 6,7). The cut-off value for survival was calculated and was not statistically significant, however the cut off value for recurrence was significantly different for anterior surgical margins (Table 8), although the ROC curve showed little utility (Fig. 4). Based on these cut-off values, DSS and LRFS were calculated according to the value of the surgical margin. In nearest margin of 0.35cm, the group over 0.35cm showed higher DSS and LRFS than the group below 0.35cm, but the difference was not significance (Figs. 5 and 6) ($p_{DSS} = 0.276$, $p_{LRFS} = 0.162$). Also, there was no statistically significant difference in DSS and LRFS according to the location of the individual surgical margin.

3.3 Pathologic parameters

In the 36 patients, 2 were WPOI 2, 8 were WPOI 3, 15 were WPOI 4, and 11 patients were WPOI 5. Seventeen patients were classified into the low-tumor budding group, and 19 patients were classified into the high-tumor budding group.

In neck metastasis patients who were diagnosed during the first surgery with neck dissection or who later experienced recurrence at neck, 50% of patients ($n = 9$) were WPOI 5, and just one patient had non-

aggressive invasion (WPOI 1,2,3), which is a significant difference according to WPOI (p = 0.012). Also, regarding recurrence and survival there was a significant difference between non-aggressive invasion and aggressive invasion (WPOI 4,5) (Table 9). Among the tumor budding group, there was a significant difference in recurrence (p = 0.009), with inclusion of 70.6% patients who were in the with tumor budding group (Table 10).

Regarding margin status, incidence according to WPOI and tumor budding is a shown in Tables 11 and 12. In both cases, more aggressive WPOI or higher budding is significantly associated with, worse margin status (p_{WPOI} = 0.031, $p_{budding}$ = 0.035). DSS and LRFS according to WPOI were shown in Figs. 7 and 8. All Kaplan-Meier graphs showed significantly poorer DSS and LRFS in aggressive WPOI (p_{DSS} = 0.03, p_{LRFS} = 0.05). Also, DSS and LRFS according to tumor budding, are shown in Figs. 9 and 10. Similar to WPOI, it showed significantly poorer DSS and LRFS in high tumor budding cases, as shown, in the LRFS graph (p_{DSS} = 0.271, p_{LRFS} = 0.024).

3.4 Univariate and multivariate analysis of DSS and LRFS

In disease specific survival, advanced T-stage, surgical margins

<0.35cm, high tumor budding, and aggressive WPOI had high hazard ratio, but there was only significant value for advanced T-stage (T_3, T_4), in multivariate analysis (Table 13) (p = 0.016). Similarly, in locoregional recurrence free survival, advanced T-stage was classified as a prognostic factor in univariate and multivariate analysis (Table 14) (p = 0.035, p = 0.09).

Discussion

The optimal surgical margin of conventional OSCC has been considered to be 5 mm[9.10], but this designation is controversial[11-14]. However, because tongue muscle invasion impact on tumor progression and has a relatively poor TSCC prognosis, and the optimal surgical margin of TSCC is still controversial and values have been proposed, including tongue compartment surgery[3,12-16]. Zanoni et al. suggested 0.22 cm as the optimal surgical margin for the TSCC cases, where the proportion of T_1 and T_2 stages reached 87%[12]. Singh et al. determined that a surgical margin of 0.76cm was appropriate for TSCC in a patient group, where the proportion of early stage (T_1 and T_2) was about 40%[13]. From the point of view of individual surgical margins which we expected would have different values depending on location, Lee et al. reported that the posterior margin and deep margin have significant differences related to survival and recurrence. In early stage (T_1, T_2), the cut-off value of the posterior margin was 0.45 cm and, deep margin was 0.25 cm. In advanced stage (T_3, T_4), the cut-off value of the posterior margin was 0.95 cm and deep margin was 0.80 cm[14]. In this study, in which T_1, T_2 stages account for 88.9% of cases,

DSS, and LRFS were different at the nearest 0.35 cm margin but not significantly ($p_{DSS} = 0.276$, $p_{LRFS} = 0.162$). And there was no significant difference in DSS and LRFS which is standardized with an anterior margin of 0.25 cm, which showed to be a significant for the cut-off value, and a 0.35 cm deep margin, and was significantly different between the survivor group and the death group. Because of characteristic anatomical features, significantly different prognoses according to location of the surgical margin value, especially deep margin, was expected, however, there was no statistically significant difference in prognosis according to location of the surgical margin.

WPOI and tumor budding are known as parameters that reflect tumor invasiveness, and they especially correlate with loss of cellular cohesion, active invasive movement, and recurrence[6-8]. In this study, WPOI and tumor budding were evaluated as pathological parameters to evaluate the effect of invasion due to the tongue's special muscular structure in setting the surgical margin and surgery plan. According to WPOI grade, there was a significant difference in neck metastasis ($p = 0.012$), recurrence ($p_{recur} = 0.023$) and survival ($p_{surv} = 0.016$) between non-aggressive WPOI and aggressive WPOI. Similarly, we found a significant difference in recurrence according to grade of tumor budding, it showed

significant difference in recurrence ($p = 0.009$). Additionally, more aggressive WPOI and higher tumor budding was associated with, increased frequency of closed and involved margins 83.3% of involved margins were WPOI 5, and high tumor budding occurred in 100%. Tumor budding or satellite is often difficult to judge clinically or radiologically. Consequently, the frequency of closed or involved margins relatively increases, making it difficult to obtain sufficient surgical margins, resulting in poor prognosis. This tendency could also be also being observed in that the nearest margin decreases as WPOI increases (Table 5). Considering these facts, estimation of WPOI and tumor budding before surgery is important in setting the surgical margin, and when the WPOI grade is high, a larger surgical margin is recommended and surgical planning accompanied by elective neck dissection is necessary. Because it is difficult to identify WPOI before surgery, it is necessary to infer WPOI through biopsy pattern of invasion (BPOI), and for this, biopsy results from various sites could be helpful[17].

The patient group who received adjuvant therapy showed a higher DSS than the patient group who did not receive adjuvant therapy ($p = 0.045$), because, in most cases of closed margin patients or involved margin patients, the PORT or POCCRT procedures were performed

according to AJCC guidelines. It cannot be excluded that the relationship to value, location of surgical margin and TSCC prognosis may have been influenced by this. Further studies on these aspects, with additional patient groups, are needed.

Figures

Figure 1. Schematic drawing showing margin shrinkage of the tongue mass after detachment.; When tumor mass was dissected from adjacent tissue, tissue shrinkage occurred. Shrinkage occurred differently according to tissue composition and anatomical site, and varied between the tongue, other oral cavities, and the medial and lateral sides of tongue.
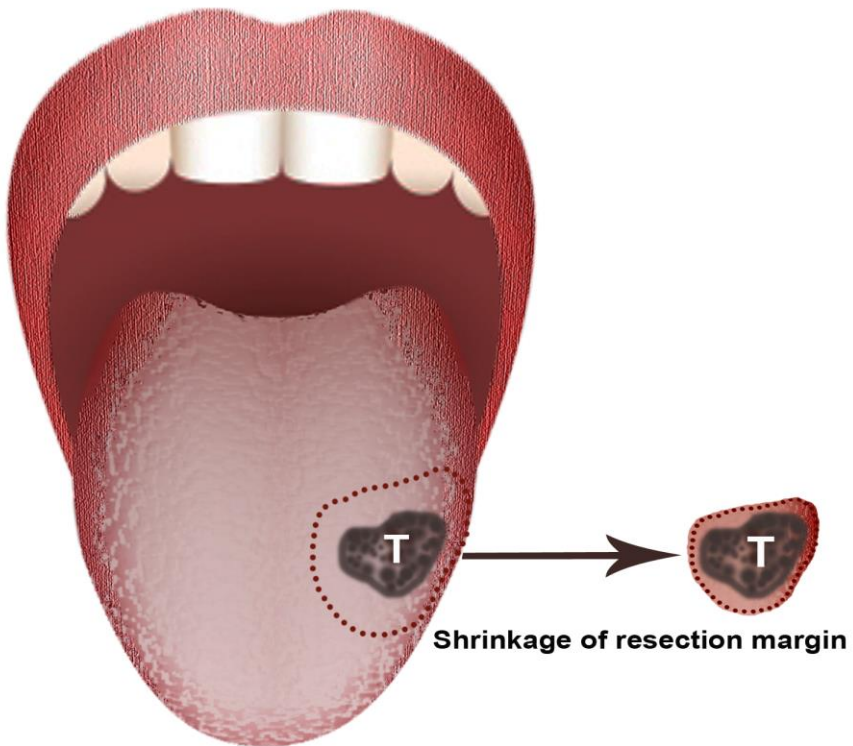
Figure 2. Classification of pattern of invasion: POI classified into 5 categories. Type 1 shows a broad pushing front. Type 2 shows a finger-like front (A, × 20 magnification). Type 3 shows a larger cell group (>15-cell island) (B, × 10 magnification). Type 4 shows smaller cell groups, strands, or even single cells (within 1 mm from main tumor) (C, × 20 magnification). Type 5 shows satellite patterns that detached the island from the main tumor or island by >1 mm (D, × 10 magnification), large cell island >1 mm away from the main tumor).
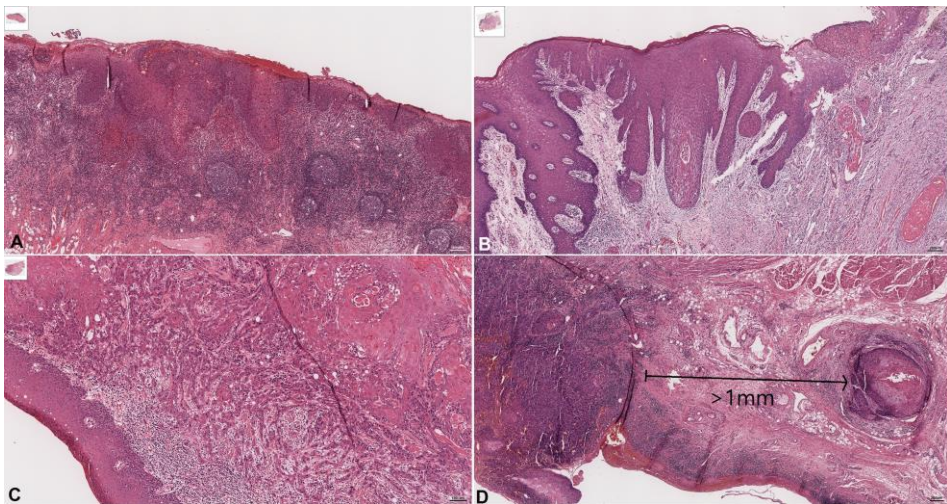
Figure 3. Histologic finding of tumor budding at invasive front area. Tumor budding was defined as a single cancer cell or a cluster of <5 cancer cells in the stroma of the invasive front (A, graded as low = 0-—4 buds, intermediate or high = ≥5 buds, ×40 magnification). Posterior surgical margin of tongue mass, dyed green, showing distance from green pointed tumor margin more than 13.0 mm (B, ×40 magnification). Red arrow indicates involved surgical deep margin of tongue, dyed with green C).
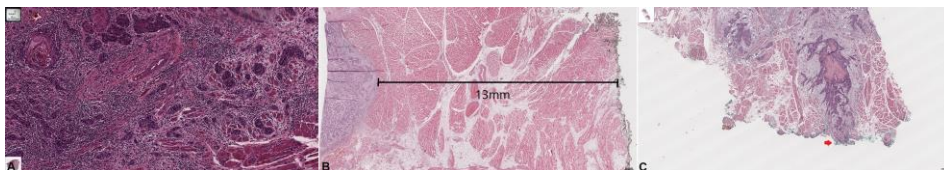
Figure 4. ROC curve of cut-off value with LRFS; anterior margin showed significant value, (0.25 cm, $p = 0.013$), but also a downward trend compared with the reference line, indicating low utility.
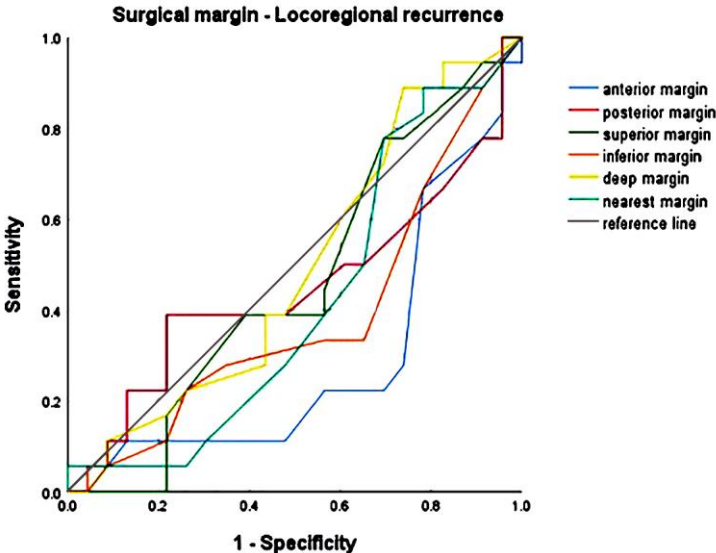
Figure 5. Kaplan-Meier curve of DSS according to nearest margin 0.35cm. For disease-specific survival, the group with the nearest margin greater than 0.35 cm in the survival curve showed higher survival, but it was not statistically significant ($p = 0.276$).
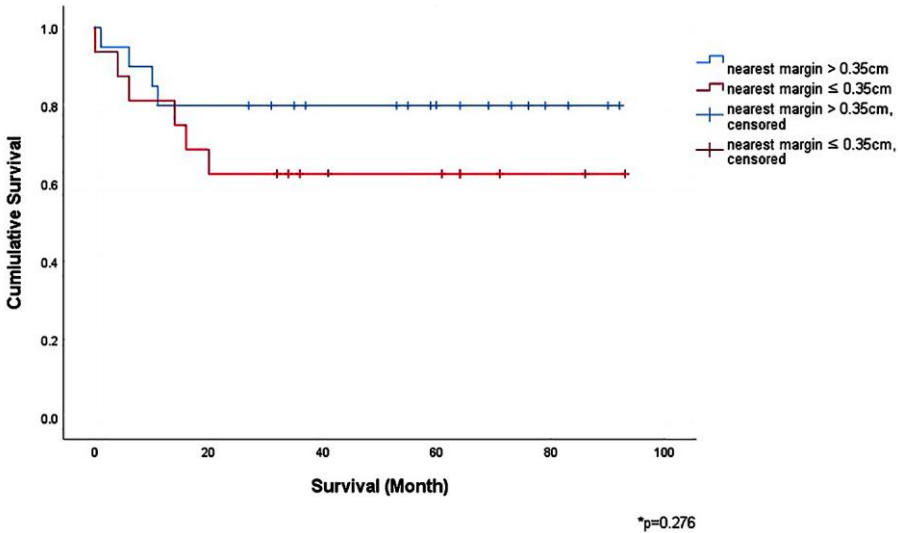
Figure 6. Kaplan-Meier curve of LRFS according to nearest margin 0.35cm. In loco-regional recurrence-free survival, the group with the margin nearest >0.35 cm in the recurrence-free survival curve showed higher recurrence-free survival, but it was not statistically significant ($p = 0.162$).
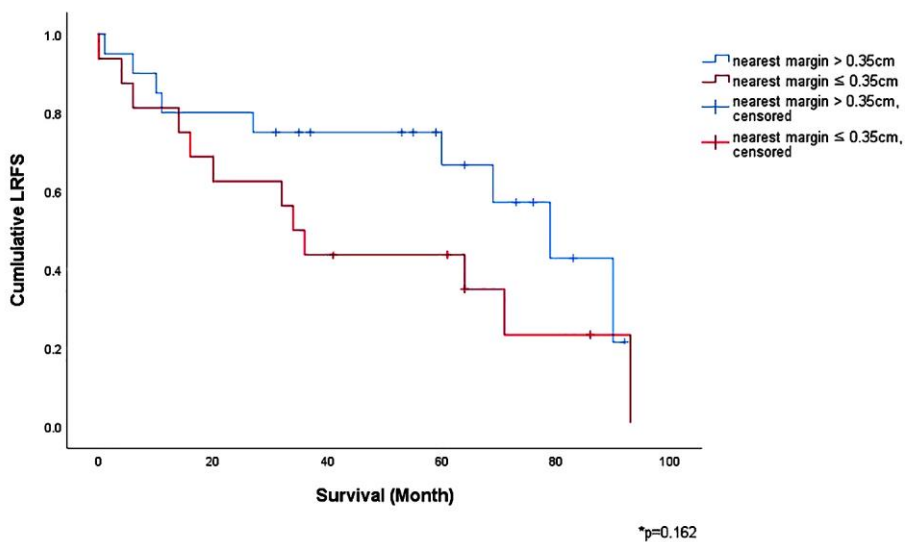
Figure 7. Kaplan-Meier curve of DSS according to WPOI. Non-aggressive WPOI (WPOI type 1,2,3), aggressive WPOI (WPOI type 4,5). In disease-specific survival, the non-aggressive WPOI group showed a 100% survival rate and showed a statistically significant difference compared with the aggressive WPOI group ($p = 0.03$).
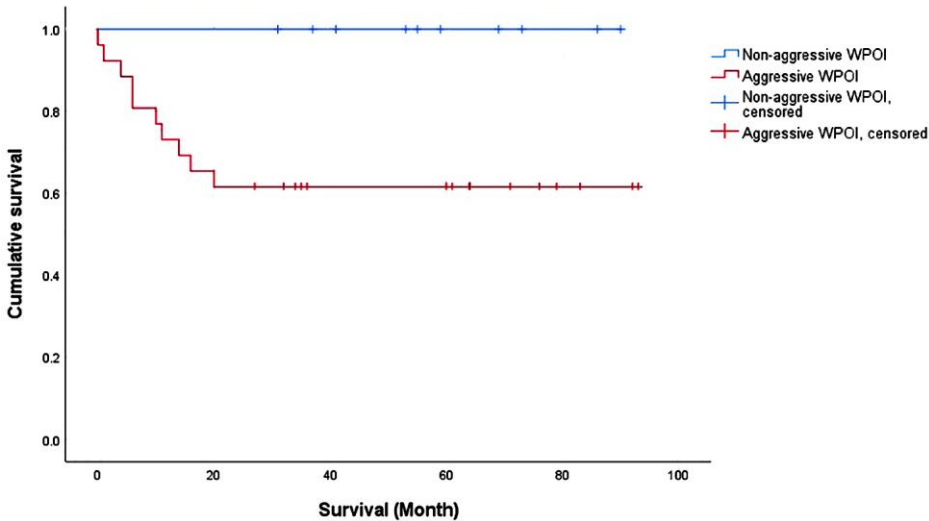
Non aggressive WPOI: WPOI 1,2,3 ; Aggressive WPOI: WPOI 4,5
**p=0.03

Figure 8. Kaplan-Meier curve of LRFS according to WPOI. Non-aggressive WPOI (WPOI type 1, 2, 3), aggressive WPOI (WPOI type 4, 5). In loco-regional recurrence-free survival, the group with non-aggressive WPOI group showed higher recurrence-free survival in the curve ($p = 0.05$).
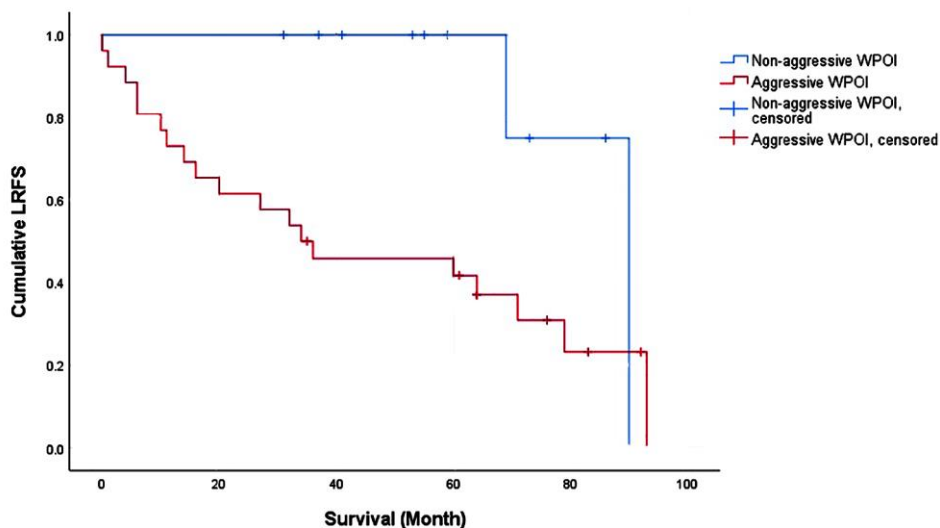
Non aggressive WPOI: WPOI 1,2,3 ; Aggressive WPOI: WPOI 4,5
**p=0.05

Figure 9. Kaplan-Meier curve of DSS according to tumor budding: low tumor budding (less than 5 buds), high-tumor budding (≥5 buds). Buds defined as a single cancer cell or a cluster of less than 5 cancer cells in the stroma of the invasive front. In disease-specific survival, the group with low-tumor budding in the survival curve showed higher survival, but it was not statistically significant. ($p = 0.271$).
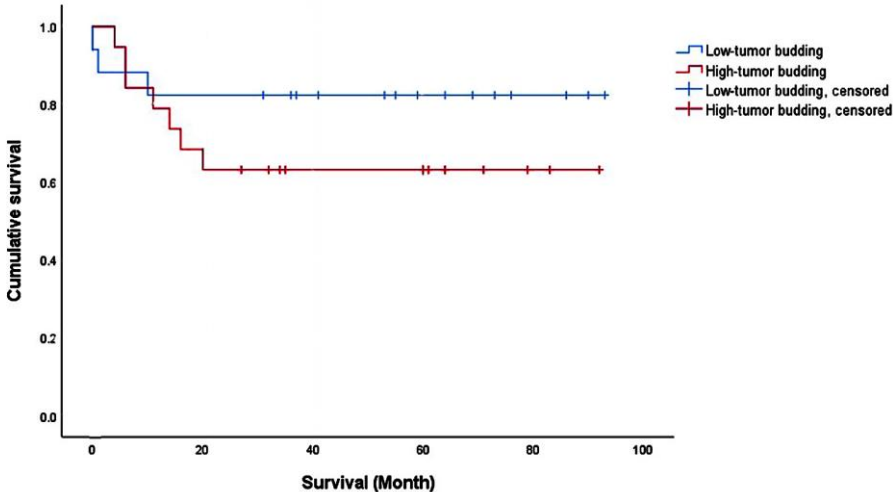
* Low-tumor budding: less than 5 cells ; High-tumor budding: equal or more than 5cells
**p=0.271

Figure 10. Kaplan-Meier curve of LRFS according to tumor budding: low-tumor budding (<5 buds), high-tumor budding (≥5 buds). Buds defined as a single cancer cell or a cluster <5 cancer cells in the stroma of the invasive front. In loco-regional recurrence-free survival, the group with low-tumor budding had higher recurrence-free survival in the curve ($p = 0.024$).
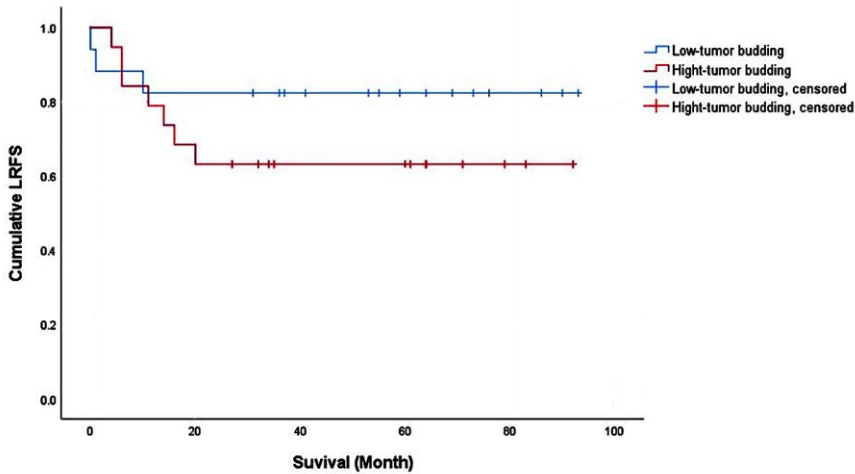
Low-tumor budding: less than 5 cells ; High-tumor budding: equal or more than 5cells
**p=0.024

Tables

Table 1. Degree of shrinkage of surgical margins according to
anatomical sites.[4]

Paper	Sample size	Anatomic location	Shrinkage (%)
Mistry et al.; 2005	27	Buccal mucosa	21.2
		Tongue	23.5
Cheng et al.; 2008	41	Buccal mucosa, Retromolar trigone, Alveolar ridge (Mn)	71.9
		Palate, Alveolar ridge (Mx)	53.33
		Tongue	42.14
El-Fol et al.;2015	61	Buccal mucosa	66.7
		Tongue	35
		Floor of mouth	33.3
		Retromolar trigone	16.7
		Alveolar ridge (Mn)	15.4

Table 2. Classification of pattern of invasion (POI).[6-8]

Pattern of invasion	Definition
Type 1	Pushing border
Type 2	Finger-like growth
Type 3	Large separate island (>15cells)
Type 4	Small separate island (≤15cells)
Type 5	Tumor satellites, ≥1mm to main mass or closest satellite

Table 3. Demographic details according to comparison with T-stage.

Characteristics	Overall (%) N = 45	T1 (%) N =16	T2 (%) N = 24	T3 (%) N = 2	T4 (%) N = 3	P
Sex, M:F	1:1.37	1:1.29	1: 1.67	1: 1.00	1: 0.50	0.650
Age	60.20	57.13	64.44	71.00	70.33	0.212
N stage						**0.021**
N0	30 (66.7%)	13 (81.3%)	16 (66.7%)	1 (50.0%)		
N1	4 (8.9%)	1 (6.3%)	3 (12.5%)			
N2	11 (24.4%)	2 (12.5%)	5 (20.8%)	1 (50.0%)	3 (100%)	
Surgery						
Only Transoral	15 (33.3%)	9 (56.3%)	6 (25.0%)			
With ND	30 (66.7%)	7 (43.7%)	18 (75.0%)	2 (100%)	3 (100%)	**0.032**
With Recon	23 (51.1%)	6 (37.5%)	12 (50.0%)	2 (100%)	3 (100%)	**0.054**
Depth of invasion (cm)	0.886	0.459	0.875	1.45	1.733	**0.001**
Meta lymph node ratio	0.10	0.03	0.21	0.05	0.24	
ENE	6 (13.3%)	1 (6.25%)	3 (12.5%)	0	2 (66.7%)	
PNI	9 (20.0%)	0	7 (29.1%)	1 (50.0%)	1 (33.3%)	
LVI	2 (4.4%)	0	0	0	2 (66.7%)	
WPOI *	36					**0.017**
WPOI 2	2 (5.6%)	1 (7.7%)	1 (5.6%)			
WPOI 3	8 (22.27%)	6 (46.2%)	2 (11.1%)			

WPOI 4	15 (41.7%)	5 (38.5%)	7 (38.9%)	1 (50.0%)	2 (66.7%)	
WPOI 5	11 (24.4%)	1 (7.7%)	8 (44.4%)	1 (50.0%)	1 (33.3%)	
Tumor budding *	36					**0.027**
Low (< 5 cells)	17 (47.2%)	10 (71.4%)	5 (27.8%)	1 (50.0%)	1 (33.3%)	
High (≥5 cells)	19 (52.8%)	4 (28.6%)	13 (72.2%)	1 (50.0%)	2 (66.7%)	
Additional Tx	17 (37.8%)	2(12.5%)	11(45.8%)	1(50.0%)	3(100%)	**0.010**
PORT	11 (24.4%)	2(12.5%)	7(29.2%)	1(50.0%)	1(33.3%)	
POCCRT	3(6.7%)		1(4.2%)		2(66.7%)	
Further resection	3(6.7%)		3(12.5%)			
Recurrence	19(42.2%)	5(31.3%)	11(45.8%)	1(50.0%)	2(66.7%)	0.305
Local	3(6.7%)	1(6.3%)	1(4.2%)	1(50.0%)		
Regional	12(26.7%)	4(25.0%)	7(29.2%)		1(33.3%)	
Distant	4(8.9%)		3(12.5%)		1(33.3%)	
Follow up period (month)	58.60	69.93	59.54	6.00	25.67	**0.021**
3Y- DSS (%)	75.56	93.75	75.00	0	33.33	**0.004**
3Y- LRFS (%)	46.67	62.5	41.67	0	33.33	0.201

Tx: treatment, ND: neck dissection, ENE: extracapsular nodal expansion, PNI: perineural invasion, LVI: lympho-vascular invasion, WPOI: worst pattern of invasion, PORT: post-operative radiotherapy, POCCRT: post-operative concurrent chemoradiation therapy, DSS: disease-specific survival, LRFS: locoregional recurrence free survival

Table 4. Individual surgical margin according to comparison with T-stage.

Characteristics	Overall	T1 stage	T2 stage	T3 stage	T4 stage	P value
Surgical margin						
Anterior	0.78±0.36	0.75±0.34	0.69±0.41	1.25±0.07	1.00±0.46	0.122
Posterior	0.98±0.73	1.21±0.89	0.76±0.56	1.75±0.64	1.13±1.10	0.082
Superior	0.86±0.41	0.73±0.19	0.80±0.48	1.25±0.35	0.67±0.55	0.342
Inferior	0.65±0.38	0.65±0.34	0.55±0.49	1.05±0.21	0.33±0.21	0.925
Deep	0.60±0.39	0.91±0.34	0.49±0.33	0.90±0.28	0.30±0.26	**0.013**
Nearest	0.39±0.24	0.50±0.16	0.22±0.17	0.80±0.14	0.27±0.26	**0.012**

The data is depicted as mean ± standard deviation. P value was calculated between early stage (T_1,T_2) and advanced stage (T_3,T_4). Unit: cm

Table 5. Individual surgical margin according to comparison with WPOI.

Characteristics	Overall	WPOI 1, 2, 3	WPOI 4	WPOI 5	P value
Surgical margin					
Anterior	0.78±0.36	0.67±0.32	0.88±0.37	0.83±0.42	0.317
Posterior	0.98±0.73	0.72±0.21	0.85±0.56	1.00±0.95	1.000
Superior	0.86±0.41	0.67±0.28	1.01±0.41	0.74±0.68	0.808
Inferior	0.65±0.38	0.64±0.37	0.61±0.31	0.49±0.62	0.164
Deep	0.60±0.39	0.84±0.37	0.79±0.38	0.53±0.39	0.055
Nearest	0.39±0.24	0.47±0.22	0.40±0.20	0.24±0.28	**0.031**

WPOI 1,2,3: Non-aggressive invasion; The data is depicted as mean ± standard deviation. Unit: cm

Table 6. Comparison of surgical margin, survivor and dead group.

Characteristics	Alive	Death	P value
`Surgical margin			
Anterior	0.83±0.26	0.71±0.48	**0.013**
Posterior	0.96±0.75	1.01±0.73	0.59
Superior	0.84±0.37	0.89±0.48	0.67
Inferior	0.73±0.40	0.52±0.31	0.89
Deep	0.71±0.43	0.65±0.31	**0.014**
Nearest	0.41±0.24	0.37±0.24	0.86

The data is depicted as mean ± standard deviation. Statistical significance was marked

with bold, Unit: cm

Table 7. Comparison of surgical margin, recurrence free and recurrence group.

Characteristics	Recurrence-free	Recurrence	P value
Surgical margin			
Anterior	0.86±0.38	0.67±0.33	0.25
Posterior	0.94±0.80	1.03±0.66	0.947
Superior	0.90±0.49	0.80±0.26	0.057
Inferior	0.71±0.40	0.57±0.34	0.891
Deep	0.67±0.44	0.73±0.31	0.176
Nearest	0.40±0.26	0.40±0.21	0.128

The data is depicted as mean ± standard deviation. Unit: cm

Table 8. Cut off value of surgical margin according to survival and recurrence.

Cut off value (Cm)	Survival	Recurrence
Surgical margin		
Anterior	1.35	**0.25 ****
Posterior	1.25	0.90
Superior	0.85	0.56
Inferior	0.13	0.13
Deep	0.25	0.35

Statistical significance was marked with bold, ** p = 0.022

Table 9. Incidence of neck metastasis, recurrence, survival according to

WPOI.

Characteristics	Non-aggressive invasion (WPOI 1,2,3)	WPOI 4	WPOI 5	P value
Neck metastasis				
(n= 18)				
	1 (5.56%)	8 (44.4%)	9 (50.0%)	**0.012**
Recurrence				
(n=17)				
	2 (11.8%)	7 (41.2%)	8 (47.1%)	**0.023****
Survival				
(n=26)				
	10 (38.4%)	9 (34.6%)	7 (26.9%)	**0.016****

neck metastasis includes patients with metastatic lymph node at first surgery, Statistical
significance was marked with bold
** This p-value was calculated between non-aggressive WPOI (1, 2, 3) and aggressive
WPOI (4, 5)

Table 10. Incidence of neck metastasis, recurrence, survival according to budding.

Characteristics	w/o tumor budding	w/ tumor budding	P value
Neck metastasis (n= 18)			
	6 (33.3%)	12 (66.7%)	0.100
Recurrence (n=17)			
	5 (29.4%)	12 (70.6%)	**0.009**
Survival (n=26)			
	14 (53.8%)	12 (46.1%)	0.206

* neck metastasis includes patients with metastatic lymph node at first surgery,
Statistical significance was marked with bold

Table 11. Incidence of margin status according to WPOI.

Margin status	Non-aggressive invasion (WPOI 1,2,3)	WPOI 4	WPOI 5
Clear margin (n= 8)			
	3 (37.5%)	4 (50.0%)	1 (12.5%)
Closed margin (n=22)			
	7 (31.8%)	10 (45.5%)	5 (22.7%)
Involved margin (n=6)			
		1 (16.7%)	5 (83.3%)

$** \ p_{\text{WPOI}}=0.031$

Table 12. Incidence of margin status according to WPOI.

Margin status	Low tumor budding	High tumor budding
Clear margin (n= 8)	5 (62.5%)	3 (37.5%)
Closed margin (n=22)	12(54.5%)	10(45.5%)
Involved margin (n=6)		6(100%)

$**p_{budding} = 0.035$

Table 13. Univariate and multivariate DSS analysis using Cox-

proportional hazards model.

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
T stage						
T1	1 (reference)			1 (reference)		
T2	0.40	0.01-1.61	0.197	0.61	0.23-1.62	0.316
T3,T4	1.38	0.16-11.79	0.768	*5.11*	*1.35-19.26*	*0.016*
Nearest margin						
≤0.35	1 (reference)			1 (reference)		
>0.35	3.81	0.55-26.58	0.178	2.80	0.51-15.36	0.235
Tumor budding						
<5	1 (reference)			1 (reference)		
≥5	3.86	0.37-40.66	0.260	1.18	0.43-3.26	0.75
WPOI						
WPOI 1,2,3	1 (reference)					
WPOI 4,5	2.00	0.30-13.17	0.471	1.67	0.2-18.35	0.68

HR: hazard ratio, CI: confidence interval, DSS: disease specific survival, WPOI: worst pattern of invasion, Statistical significance was marked with bold

Table 14. Univariate and multivariate LRFS analysis using Cox-

proportional hazards model.

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
T stage						
T1	1 (reference)			1 (reference)		
T2	0.32	0.25-3.822	0.363	0.67	0.23-1.91	0.45
T3,T4	*18.66*	*1.23-286.2*	*0.035*	*4.90*	*1.47-16.26*	*0.09*
Nearest margin						
≤0.35	1 (reference)			1 (reference)		
>0.35	2.15	0.30-15.55	0.45	1.24	0.51-3.01	0.632
Tumor budding						
<5	1 (reference)			1 (reference)		
≥5	1.65	0.28-9.86	0.58	2.06	0.41-10.47	0.38
WPOI						
WPOI 1,2,3	1 (reference)					
WPOI 4,5	0.82	0.38-1.79	0.62	0.91	0.48-1.73	0.78

HR: hazard ratio, CI: confidence interval, LRFS: locoregional recurrence free survival,
WPOI: worst pattern of invasion, Statistical significance was marked with bold

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국문초록

외과적 절제연과 병리적 양상에 따른
혀 편평상피세포암종의 예후

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1. 목 적

　　구강의 다른 해부학적 구조와는 차별점을 갖는 혀의 근육 구조는
특수한 미세종양환경을 조성하여 종양의 침투 양상에 영향을 주고, 절제된
종물의 수축량에 영향을 미쳐 혀 편평상피세포암종(TSCC)의 외과적
절제시에, 통상적인 외과적 절제연을 두고 절제하는 것에 의문을 갖게
했다. 본 연구에서는 절제면의 위치 별 외과적 절제연의 크기와 종양의
침투양상을 시사하는 조직병리학적 인자에 따른 TSCC 의 예후를
알아보고자 하였다. 이러한 요인들에 따른 예후를 종합하여 본 연구는
TSCC 의 적절한 외과적 절제연 설정에 대하여 제언하고자 한다.

2. 방 법

　　2010 년부터 2019 년까지 서울대학교 치과병원을 내원한, TSCC 로
진단받은 45 명의 환자군을 조사하였다. 환자의 임상 및 병리학적 정보를
후향적으로 검토하였고, 45 명의 환자 중 36 명의 환자군에 대해서는

조직병리 슬라이드 판독을 통해 WPOI(worst pattern of invasion), tumor budding 을 조사하였다.

3. 결 과

전방(anterior) 0.25cm, 내측(deep) 0.35cm 각각의 외과적 절제연을 기준으로 통해 조사된 질병 특이 생존율(Disease specific survival, DSS), 무국소구역재발 생존율(Loco-regional recurrence free survival, LRFS)에서는 유의한 차이가 없었다. 또한 절제연의 최소값이 0.35cm 이상인 군이 그렇지 않은 군보다 높은 DSS, LRFS 를 보였으나 통계적으로 유의하지 않았다(p_{DSS} = 0.276, p_{LRFS} = 0.162). WPOI 양상이 침투적인 양상을 보이는 군 (p_{DSS} = 0.03, p_{LRFS} = 0.05), tumor budding 이 많은 군에서 (p_{DSS} = 0.271, p_{LRFS} = 0.024) 더 낮은 DSS 와 LRFS 를 보였고, 더 많은 근접 절제연(close margin)과 양성 절제연(positive margin)의 빈도를 보였으며, 통계적으로 유의한 차이를 나타냈다 (p_{WPOI} = 0.031, $p_{budding}$ = 0.035).

4. 결론

TSCC 에서 외과적 절제연의 크기, 절제연의 위치가 그 예후에 끼치는 영향은 분명하지 않았다. 이에 반해 WPOI 와 tumor budding 의 경우에서 DSS 와 LRFS 에 미치는 영향이 통계적으로 유의한 값을 나타내었고, TSCC 의 외과적 절제연 설정 시에 단순한 절제연의 크기를 넘어 조직병리학적 양상이 충분히 반영되어야 함을 시사한다.

주요어 : 혀 편평세포암종, 외과적 절제연, WPOI, tumor budding

학번: 2020−29090

감사의 글

4 학기의 석사과정을 뒤로 하고 이렇게 학위 논문을 제출하게 되었습니다. 미흡하고 부족하기만 한 저를 이렇게 이끌어 주신 분들께 감사를 드릴 부분이 너무나도 많습니다.

가장 먼저 저의 나태함을 채찍질해주시고, 올바른 구강악안면외과학도의 길로 인도해주신 김성민 교수님, 부족한 부분에 아낌없이 조언과 가르침을 주시고 가르침을 주셨던 서울대학교 치과병원 구강악안면외과학 교실의 모든 교수님들께 무한한 감사를 올립니다.
이 논문이 나오기까지 세세한 부분에 까지 도움과 조언을 주셨던 서울대학교 치과병원 구강악안면외과 미세수술재건연구실 어미영 선생님, Buyanbileg Sodnom-Ish 선생님, Kezia Rachellea Mustakim 선생님, 조윤주 선생님께 심심한 감사의 마음을 전합니다.
걱정만 드리는 아들을 위해 기도로, 넘치는 사랑으로 챙기시는 아버지, 어머니께 죄송스러운 마음과 감사의 마음을 함께 전합니다.

끝으로, 지혜를 허락하시고 겸손한 마음으로 인도하시는 하나님 아버지께 영광과 감사를 올립니다.

2022 년 8 월

조성지 올림