Dorsal tongue versus ventrolateral tongue leukoplakia: An anatomical perspective on clinicopathological characteristics and treatment outcomes

Shih-Wei Yang (sweeyang@gmail.com)
Chang Gung Memorial Hospital Keelung Branch https://orcid.org/0000-0002-0979-7912
Yun-Shien Lee
Ming Chuan University - Taoyuan Campus
Liang-Che Chang
Keelung Chang Gung Memorial Hospital of the CGMF
Cheng-Han Yang
Keelung Chang Gung Memorial Hospital of the CGMF
Cheng-Ming Luo
Keelung Chang Gung Memorial Hospital of the CGMF

Research article

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Abstract

Background

Among the risks of malignant transformation of oral leukoplakia, tongue has been identified as a high-risk site. Only little information exists on the clinicopathological characteristics and treatment outcomes specific to leukoplakia of the dorsum of the tongue. The comparison of clinicopathological characteristics of the dorsal tongue and ventrolateral tongue leukoplakia is not available in the literature. The purpose of this study is to investigate the clinicopathological characteristics and treatment outcomes between dorsal and ventrolateral tongue leukoplakia.

Methods

The demographic data and pathological results of the patients who received carbon dioxide laser surgery for tongue leukoplakia from 2002 to 2019 were retrospectively reviewed and analyzed statistically.

Results

Of 144 enrolled, there were 108 males and 36 females with a mean age 52.17 ± 11.72. The follow-up time was 4.58 ± 4.53 years. Thirty patients had postoperative recurrence (20.83%). Twelve patients developed malignant transformation (8.33%). Annual transformation rate was 2.28%. In comparison of dorsal and ventrolateral tongue leukoplakia, there were no differences in the time to the development of carcinoma (2.62 ± 1.69 VS 3.98 ± 2.77 years), overall cumulative malignant transformation rates (7.50% VS 7.69%), and annual transformation rates (2.86% VS 1.93%). The prevalence of ventrolateral tongue leukoplakia is higher than the dorsal tongue leukoplakia ($P < 0.001$)

Conclusions

Dorsal tongue leukoplakia is not as frequently encountered clinically as ventrolateral tongue leukoplakia. The response to laser therapy of dorsal tongue and ventrolateral tongue leukoplakia are comparable in postoperative recurrence and postoperative malignant transformation.

Background

The tongue occupies the major portion of floor of mouth and is divided by the circumvallate papillae into the anterior two-thirds (mobile tongue or body) and the base of the tongue [1, 2]. Dorsal tongue and ventrolateral tongue are different parts of the mobile tongue, and the morphological outlook, development, structure, function, and histology are different [3, 4]. There isn't research on the dorsal tongue leukoplakia thus far, so the aim of the study is to investigate and compare the similarities and

differences between the dorsal tongue and ventrolateral tongue leukoplakia in the perspectives of histopathology, clinical characteristics, and treatment responses.

Methods

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (License No.: 201901384B0). Medical records of patients with oral tongue leukoplakia that received carbon dioxide laser (CO_2 laser) excision at the Department of Otolaryngology from Sept 2002 to Oct 2019 were retrospectively reviewed.

All the patients received thorough oral cavity examination by an otolaryngology specialist. Written informed consent was signed by every patient before conducting surgical intervention. The procedure of transoral laser excision was performed as previously described [5–7]. All the specimens were sent for pathological examination and the pathological diagnosis was confirmed and agreed by 2 different pathologists. A binary grading system proposed by WHO was adopted to diagnose the pathology [8]. Before surgery, the types of leukoplakia of every patient, including homogeneous and non-homogeneous [9, 10] were first evaluated and photographed by the author (S.-W.Y.). The images were later reviewed by two specialist of otolaryngology and a consensus on the clinical appearances were reached. The inclusion criteria consisted of a clinical diagnosis of leukoplakia on the mobile tongue with or without leukoplakia on the other parts of oral cavity mucosa, patients' age older than 20, treatment with CO_2 laser. Other kinds of OPMDs except leukoplakia (such as submucous fibrosis, lichen planus, erythroplakia etc.), previous treatment of oral leukoplakia (OL) at other medical facilities, no agreeable pathological diagnosis made, initial pathological diagnoses being carcinoma or malignancies, papilloma with a gross papillary appearance, obvious ulceration, overt carcinoma on inspection, or treatment with laser vaporization were excluded. The history of betel nut or areca chewing, alcohol drinking, and cigarette smoking were obtained by detailed questioning at the patients' first visit to the outpatient department [7]. The surface area of the leukoplakia was measured on the excised specimen immediately after the laser operation.

Postoperative recurrence is defined as OL regrows on the same site after confirmation of no evidence of any OL lesion for a definite period of time [11]. If a lesion of tongue leukoplakia occurred on the different location from the previous surgically treated site, it was defined as a second lesion instead of recurrence. If a patient had one or more than one lesion of leukoplakia exclusively on the mobile tongue, the situation was defined as "single". "Multifocal condition" described leukoplakia involving the oral mucosa in addition to the mobile tongue. The area of tongue leukoplakia in a patient would be added up for all tongue leukoplakia lesions if more than 1 lesion occurred. When the patient had more than 1 lesion, the highest degree of pathology and most severe form of clinical presentation were documented for analysis and statistical calculation on a per capita basis.

All the surgical procedures were performed by a doctor (S.-W.Y.) under local anesthesia [5–7]. The postoperative follow-up course was uneventful. All the patients were able to come back to office as

scheduled without any major morbidities, including wound infections causing systemic septicemia, massive hemorrhage, paresthesia, impaired mobility of tongue, change of taste sensations, and so forth.

Statistical Analysis

Results are presented descriptively, with factors related to postoperative recurrence and malignant transformation of tongue leukoplakia. For univariate analysis, the Fisher's exact test, and one way analysis of variance between groups were performed. The survival analyses were made using Kaplan-Meier curves with log rank tests (for factor with two groups of subjects) and logistic regression model (for continuous variable such as body mass index, area of leukoplakia, or combined calculations of factors). Odds ratio (OR), hazard ratio (HR), and 95% confidence intervals (CIs) were calculated using a 2-tailed test of significance ($P < 0.05$) for each factor. We followed the following parameters: (1) if the 95% CI excludes the null value (1.0), and the p-value of OR (or HR) of the risk factor must be < 0.05; (2) if the value of the OR (or HR) was greater than 1.0, the risk was increased, and (3) if the value was less than 1.0, the risk was reduced or protective. Comparison of the prevalence was calculated by the method of incidence rate ratio [12]. The Fisher's exact tests were calculated using the MATLAB version R2015a (Mathworks Inc., Natick, Mass., USA).

Results

Seven hundred and fifty-three patients with 1,591 OPMD lesions underwent CO_2 laser surgery for tongue leukoplakia at the department from 2002 to 2019 were recruited. Excluding patients with OPMDs occurring not on the oral tongue, clinical tongue OPMDs other than leukoplakia, and initial diagnosis of carcinoma, 144 patients with 241 lesions of tongue leukoplakia was enrolled, including 40 patients with 54 lesions of dorsal tongue leukoplakia and 117 patients with 187 lesions of ventrolateral tongue leukoplakia (Figs. 1–3). Among the 144, 13 patients had both dorsal tongue and ventrolateral tongue leukoplakia (Fig. 4).

Among the 144 patients, 108 were male and 36 were female, whose age ranged from 25 to 83 years with an average 52.17. The average follow-up time was 54.9 ± 54.41 months. Multiple lesions could occur both on the tongue or other locations of the oral cavity in some of the enrolled patients. Different clinical presentation, such as homogeneous and non-homogeneous leukoplakia, could happen on the different sites of the oral cavity or on the same site in cases with postoperative recurrence. Histopathological examinations of different severity also possibly happened in the different or recurrent locations of lesions in the same patient. It's not possible to correlate every patient with a single morphological appearance or pathological examination unless the patient had only one lesion. Therefore, the most severe form of morphology and highest degree of pathological severity were documented on a per capita basis. In this series, 78 out of 144 patients (54.17%) had multi-focal lesions, or other sites of OL in addition to tongue leukoplakia, including buccal leukoplakia in 71 patients, retromolar leukoplakia in 16, gum leukoplakia in 9, labial leukoplakia in 5, floor of mouth leukoplakia in 3, and palate leukoplakia in 2. Among the 66 patients (45.83%) with only tongue leukoplakia, 53 patients had solitary tongue leukoplakia during the

cohort study. Ninety-seven patients had homogeneous tongue leukoplakia and 47 had non-homogeneous tongue leukoplakia (67.36% VS 32.64%). The number of case of squamous hyperplasia, mild dysplasia, moderate dysplasia, and severe dysplasia/carcinoma in situ (CIS) was 37, 62, 22, and 23, respectively. If a binary classification was adopted,[8] the number of low-risk lesions (99 cases, including squamous hyperplasia and mild dysplasia) surpassed that of high-risk lesions (45 cases, including moderate dysplasia and severe dysplasia/CIS). The average area of tongue leukoplakia was 1.66 ± 1.84 cm^2. There were 30 patients (20.83%) who had postoperative recurrence and 12 patients (8.33%) had postoperative malignant transformation of tongue leukoplakia. The mean time for development of recurrence was 3.62 ± 3.65 years. The annual recurrence rate was 5.76%. The average time for malignant transformation was 3.65 ± 2.54 years. The annual transformation rate (ATR) was 2.28%. The demographic and clinicopathological data are demonstrated in Table 1.

Table 1
Characteristics of patients who received laser surgery for tongue leukoplakia (n = 144)

	Case No.	%
Gender		
Female	36	25.00%
Male	108	75.00%
Age (mean ± standard deviation: 52.17 ± 11.72 years old)		
< 65	121	84.03%
≥ 65	23	15.97%
History of head and neck cancer		
No	111	77.08%
Yes	33	22.92%
History of radiotherapy		
No	131	90.97%
Yes	13	9.03%
Alcohol drinking		
No	93	64.58%
Ex-drinker	37	25.69%
Current drinker	14	9.72%
Smoking		
No	40	27.78%
Ex-smoker	44	30.56%
Current smoker	60	41.67%
Betel quid chewing		
No	74	51.39%
Ex-chewer	62	43.06%
Current chewer	8	5.56%
Diabetes mellitus*		
No	112	77.78%

	Case No.	%
Yes	30	20.83%
Metformin taken†		0.00%
No	114	79.17%
Yes	26	18.06%
Occurrence of leukoplakia in addition to tongue‡		
No (single)	66	45.83%
Yes (multi-focal)	78	54.17%
Candida infection§		
No	128	88.89%
Yes	16	11.11%
Subsites of tongue leukoplakia§		
Dorsal tongue mucosa	40	25.48%
Ventrolateral tongue mucosa	117	74.52%
Morphological outlooks		
Homogeneous	97	67.36%
Non-homogeneous	47	32.64%
Histopathological diagnosis		
Squamous hyperplasia	37	25.69%
Mild dysplasia	62	43.06%
Moderate dysplasia	22	15.28%
Severe dysplasia / carcinoma in situ	23	15.97%
Postoperative recurrence		
No	114	79.17%
Yes	30	20.83%
Postoperative malignant transformation		
No	132	91.67%
Yes	12	8.33%
Body mass index	27.26 ± 15.06	

	Case No.	%
Area (cm^2) of the lesion(s)‖	1.66 ± 1.84	
Cumulative malignant transformation rate	8.33%	
Time to develop carcinoma (year)	3.65 ± 2.54	
Duration of follow-up (year)	4.58 ± 4.53	
Time to develop recurrence (year)	3.62 ± 3.65	
Annual recurrence rate¶	5.76%	
Annual transformation rate¶	2.28%	
*Two pieces of missing data in the group of diabetes mellitus (n = 142).		
†Four pieces of missing data in the group of metformin taken (n = 140).		
‡If a patient has other sites of oral leukoplakia in addition to tongue, the patient will be categorized as "Yes".		
§Thirteen patients had both dorsal and ventrolateral tongue leukoplakia.		
‖ If the patient has more than 1 site of tongue leukoplakia, the area is the sum of all tongue leukoplakia lesions.		
¶The annual recurrence rate and annual transformation rate is calculated by the recurrence rate and malignant transformation rate divided by the average time of development of recurrence or carcinoma (year).		

In the comparison of the clinicopathological characteristics and treatment outcomes of dorsal tongue and ventrolateral tongue leukoplakia, only 1 factor (prevalence of the lesions, $P < 0.001$, Table 2) was significantly different between the two sites of tongue leukoplakia. There were no statistical differences in postoperative recurrence, malignant transformation, cumulative malignant transformation rate and annual transformation rate between the dorsal tongue and ventrolateral tongue leukoplakia (Table 2). The postoperative malignant transformation of dorsal tongue and ventrolateral tongue leukoplakia was analyzed with the Kaplan-Meier survival analysis model and a log rank test, which showed no significant difference ($P = 0.397$, Fig. 5).

Table 2
The comparison of clinicopathological characteristics and treatment outcomes in patients with dorsal and ventrolateral tongue leukoplakia (n = 144)

		Dorsal tongue leukoplakia (n = 40)*	Ventrolateral tongue leukoplakia (n = 117)*	Odds ratio	*P* value
CLINICOPATHOLOGICAL DATA					
Gender					0.41
	Female	8	32	1.0	
	Male	32	85	0.66 (0.27 – 1.59)	
Age					1.00
	< 65	34	99	1.0	
	≥ 65	6	18	1.03 (0.38 – 2.81)	
Body mass index		24.94 ± 4.01	26.1 ± 4.71†	1.06 (0.98 – 1.16)	0.17
History of head and neck cancer					0.21
	No	27	91	1.0	
	Yes	13	26	0.59 (0.27 – 1.31)	
Alcohol drinking					0.34
	No	23	78	1.0	
	Yes (ex-drinker or current drinker)	17	39	0.68 (0.32 – 1.41)	
Smoking					0.25
	No	7	36	1.0	
	Ex-smoker	15	34	0.44 (0.16 – 1.21)	
	Current smoker	18	47	0.51 (0.19 – 1.35)	

	Dorsal tongue leukoplakia (n = 40)*	Ventrolateral tongue leukoplakia (n = 117)*	Odds ratio	*P* value
Betel quid chewing				0.36
No	17	63	1.0	
Ex-chewer	21	46	0.59 (0.28 – 1.24)	
Current chewer	2	8	1.08 (0.21 – 5.56)	
Diabetes mellitus‡				0.25
No	33	91	1.0	
Yes	5	26	1.89 (0.67 – 5.32)	
Metformin taken§				0.23
No	34	92	1.0	
Yes	4	23	2.125	
Prevalence (%)‖	3.85% [54 in (1591 – 187)]	12.17% [187 in (1591–54)]	3.25 (2.40 – 4.39)	< 0.001
Occurrence of leukoplakia in addition to tongue¶				0.59
No (single)	16	53	1.0	
Yes (multi-focal)	24	64	0.80 (0.39 – 1.67)	
Candida infection#				0.76
No	37	104	1.0	
Yes	3	13	1.54 (0.42 – 5.72)	
Morphological outlooks				0.71
Homogeneous	25	77	1.0	
Non-homogeneous	15	40	0.87 (0.41 – 1.82)	

		Dorsal tongue leukoplakia (n = 40)*	Ventrolateral tongue leukoplakia (n = 117)*	Odds ratio	*P* value
Area (cm^2) of the lesion(s)**		1.49 ± 1.75	1.53 ± 1.52	1.01 (0.80 – 1.27)	0.92
Pathology					0.74
	Hyperplasia	8	31	1.0	
	Mild dysplasia	19	51	0.69 (0.27 – 1.77)	
	Moderate dysplasia	5	18	0.93 (0.26 – 3.27)	
	Severe dysplasia / carcinoma in situ	8	17	0.55 (0.17 – 1.72)	
TREATMENT OUTCOMES					
Postoperative recurrence					0.66
	No	33	92	1.0	
	Yes	7	25	1.28 (0.51 – 3.24)	
Postoperative malignant transformation					1.00
	No	37	108	1.0	
	Yes	3	9	1.03 (0.26 – 4.00)	
Cumulative malignant transformation rate		7.50%	7.69%	1.03 (0.28 – 3.79)	0.49
Time to develop malignant transformation (year)		2.62 ± 1.69	3.98 ± 2.77	1.72 (0.80 – 3.70)	0.16
Annual transformation rate††		2.86%	1.93%	0.67 (0.21 – 2.14)	0.28
Duration of follow-up (year)		5.42 ± 4.64	4.69 ± 4.72	1.00 (0.99 – 1.00)	0.399

	Dorsal tongue leukoplakia (n = 40)*	Ventrolateral tongue leukoplakia (n = 117)*	Odds ratio	*P* value
*There were 13 patients who had leukoplakia both on the dorsal and ventrolateral tongues.				
†Four pieces of missing data in the group of body mass index of patients with ventrolateral tongue leukoplakia (n = 133).				
‡Two pieces of missing data in the group of diabetes mellitus (n = 155).				
§Four pieces of missing data in the group of metformin taken (n = 153).				
‖The prevalence of lesions is calculated by the number of tongue leukoplakia divided by that of all oral cavity leukoplakia in this study. There were totally 54 dorsal and 187 ventrolateral tongue leukoplakia lesions, including recurrent lesions.				
¶If a patient has other sites of oral leukoplakia in addition to the tongue, the patient will be categorized as "Yes".				
#The diagnosis of candida infection is made by pathology.				
**If the patient has more than 1 site of tongue leukoplakia, the area is the sum of all tongue leukoplakia lesions.				
††The annual transformation rate is calculated by the malignant transformation rate divided by the average time of development of carcinoma (year).				

Discussion

The sandpaper-like dorsal surface of mobile tongue is covered by the lingual papillae while a lack of these papillae is noted on the mucosa of the ventrolateral tongue and base of the tongue [2, 13]. Four types of lingual papillae, including filiform, fungiform, foliate, and circumvallate papillae, are found on the dorsal tongue. The taste buds of foliate papillae degenerate by the third year of age. From a study of microanatomy of the tongue at autopsies of 22 individuals within 12–16 hours after death, it's demonstrated that the dorsal tongue epithelium was orthokeratinized or parakeratinized and the epithelium on the ventral and lateral tongue was nonkeratinized, and the cell layers of the epithelium of the ventral tongue is considerably less than the remaining part of tongue epithelia [4]. In addition to the presence of keratinized corneum, cytokeratin analysis can define the type of epithelium in the different sites of mobile tongue more clearly. Keratins are a family of polypeptides that serve as markers for epithelial differentiation. Non-keratinized ventrolateral tongue epithelia participating in motion and deformation express cytokeratins 4 and 13 in suprabasal cell layers, and cytokeratins 5 and 14 in basal cell layers, and cytokeratins 6 and 16 known as markers of hyperproliferation, while the keratinized dorsal tongue epithelia mainly engaging in friction express cytokeratins 1, 2, 10, and 11 [2]. Most of the papillae protrude from the dorsal surface of tongue and have a masticatory mucosa whose highly keratinized stratified squamous epithelium allows the papillae to scrape food off a surface [13]. The characteristics of dorsal and ventrolateral tongue epithelia are summarized and the differences of the dorsal and

ventrolateral tongue with regard to the morphology, histology, and physiological functions are clearly shown in Table 3.

Table 3
Summary of the characteristics of dorsal and ventrolateral tongue epithelia with regard to the morphology, histology, and physiological functions

	Dorsal tongue	Ventrolateral tongue
Morphological appearance	Sandpaper-like surface covered with papillae	Smooth and shiny
Histology		
Keratinization	Yes	No
Papillae	Filiform, fungiform, circumvallate papillae	Nil
Cell layers	More	Less
Cytokeratins	Cytokeratins 1, 2, 10, 11	Cytokeratins 4, 5, 6, 13, 14, 16
Functions	Taste, scrape off food, friction	Motion, deformation

Only limited information exists on the clinicopathological characteristics and treatment outcomes specific to leukoplakia of the dorsum of the tongue. In fact, dorsal tongue leukoplakia wasn't specifically addressed in the research of the past and usually incorporated into the OL of all parts of oral cavity. Therefore, the present study is the first one to analyze the clinicopathological features and therapeutic effects of CO_2 laser on the dorsal tongue leukoplakia. In addition, we make a comparison between the dorsal and ventrolateral tongue leukoplakia to investigate if there are differences, which is also addressed for the first time in literature. Our series showed that there was no significant differences of clinicopathological features between the dorsal and ventrolateral tongue leukoplakia, including genders, age, body mass index, history of head and neck cancer, alcohol drinking, cigarette smoking, betel quid chewing, diabetes mellitus, taking metformin, concomitant occurrence of leukoplakia on the other parts of oral mucosa, *Candida* infection, area of the lesions, and pathology, except prevalence ($P < 0.001$). In Table 2, 40 cases with 54 lesions (3.85%, Fig. 4) of dorsal tongue leukoplakia were enrolled in our series over a period of 17 years. Compared with the cases of ventrolateral tongue leukoplakia (12.17%, 117 patients with 187 lesions, Fig. 4), the prevalence of dorsal tongue leukoplakia was significantly less than the ventrolateral leukoplakia ($P < 0.001$, odds ratio 3.25, 95%CI 2.40–4.39, Table 2). In other words, the dorsal tongue leukoplakia isn't as frequently encountered clinically as the ventrolateral leukoplakia. A similar finding was also noted in another study, where only 3 dorsal tongue leukoplakia was found among the all 38 lesions [14]. The same phenomenon seems to exist in in the patients with tongue squamous cell carcinoma. Carcinoma of the dorsum of the tongue occurs in 3–5% of all the cases of tongue carcinoma, which is far less frequently seen than ventrolateral tongue carcinoma [3, 15, 16]. The prognosis of dorsal tongue carcinoma was worse in a study carried out in Hong Kong on the 65 tongue

cancer patients treated by surgery. The 5-year survival of patients with ventrolateral tongue cancer was 51%, whereas the 5-year survival rate for the dorsal tongue cancer was 0% [17]. On the contrary, as for the treatment outcomes of mobile tongue leukoplakia in the present study, the prognosis in these two sites was not significantly different, including the postoperative recurrence rate (17.5% VS 21.37%, $P = 0.66$), cumulative malignant transformation rate (7.5% VS 7.69%, $P = 0.49$), and ATR (2.86% VS 1.93%, $P = 0.28$, Table 2).

In a meta-analysis of 24 studies of OL treated with CO_2 laser, the overall cumulative malignant transformation rate was 4.5% [18]. In another systematic review of 24 articles about malignant development of carcinoma of OL, the estimated overall cumulative malignant transformation rate was 3.5% [19]. The overall cumulative malignant transformation rate of the oral tongue leukoplakia was 8.33%, and the individual cumulative transformation rates of dorsal tongue and ventrolateral tongue leukoplakia were 7.50% and 7.69%, respectively (Tables 1,2). The rate of malignant change of tongue leukoplakia in the present study, regardless of the subsites, seemed to be higher than the rate of OL of all subsites of oral cavity in combination in previous studies. It's not possible to predict when OL will undergo malignant transformation, but it's agreeable that the longer the follow-up is, the higher rate of malignant change will happen. ATR, which is calculated as transformation rate divided by the time needed to develop carcinoma from OL, could be a more scientific method to investigate the issue of malignant transformation. The time for developing carcinoma from OL is a critical factor. If the follow-up time is short, it may not be able to collect those cases who will transform in the future and it's likely to underestimate the cumulative transformation rate. In a nationwide population-based retrospective cohort study of 1,898 OL patients in Taiwan, the mean time to develop oral cancer was 2.5 years [20]. A study done in the US showed that the time to the event of malignant change could be shortened because of the patient selection bias in a tertiary center [21]. Among the research of OL across the globe, the mean time for malignant transformation ranged from 2 to 8.1 years [21–28]. In the present study, the ATR of dorsal tongue and ventrolateral tongue leukoplakia was 2.86% and 1.93%, which is similar to the previous studies of OL. The time to develop carcinoma from the dorsal tongue leukoplakia was shorter than the ventrolateral tongue leukoplakia and ATR of dorsal tongue leukoplakia was higher than the ventrolateral location, however, these 2 factors weren't statistically significant (Table 2). The ATR of the published works of OL was between 1.2% and 2.9% [29–31]. Whitish patches on the tongue are usually asymptomatic but they are not easily overlooked, so delayed diagnosis seems not to happen on the oral tongue leukoplakia, regardless of the subsites. Even dysplasia isn't infrequently seen in lesions of leukoplakia, the epithelial changes are still confined above the basement membrane. Although there are differences in the incidence, morphology, histology architectures, and functions between the dorsal and ventrolateral tongue, we speculate that the relative benign nature of leukoplakia of both subsites is well subject to laser surgery so the treatment outcomes weren't different. Dorsal tongue leukoplakia isn't commonly seen clinically, the reasons why the occurrence of leukoplakia on the specialized epithelium of dorsal tongue remains an interesting and unsolved topic which needs more investigations in the future.

The tongue is an exceptionally mobile, muscular organ that assists in mastication by positioning bolus on the occlusal plane and functions in the formation and swallowing of the food. Since the depth of tongue leukoplakia is above the basement membrane, laser excision could hardly injure the bundles of muscles of tongue. Repair of oral mucosa in response to disease or infection is much more efficient than that of skin [32], as there is almost no scar formation after injury. In the present study, there was no change of taste, no paresthesia, no tethering of the tongue, no functional deficits such as dysarthria, dysfunction of swallowing or articulation. From the postoperative recovery of the patients, CO_2 laser excision is a safe intervention with few complications for the tongue leukoplakia.

The nationwide database, including Taiwan's Health Insurance Research Database, has been retrieved to undertake research over the past years. From the registry for contracted specialty services, the coding of ICD-9 (528.6) is "Leukoplakia of oral mucosa, including tongue". The corresponding coding of ICD-10 (K13.21) is the same description. Based on the coding rule of the ICD-9 and ICD-10, it's not possible to sort out the tongue leukoplakia from other OL, let alone distinguish the dorsal site from the ventrolateral site of tongue leukoplakia. At present it's not feasible to find more cases from the registry of big data resources. Concerning the current research conditions, a design of multi-center studies with larger sample sizes is warranted to overcome this dilemma. The results may help us to gain more knowledge and better understanding of leukoplakia of dorsal and ventrolateral tongue. Our results still needs to be validated by more researches in the future to set up a standard site-specific treatment guidelines for tongue leukoplakia.

There are some limitations in this study. First, the sample size of dorsal tongue leukoplakia was relatively small compared with the ventrolateral tongue leukoplakia. Large-scale, multicenter, prospective cohort studies are warranted to further investigate the disease. Second, there were some missing data in the variables due to its retrospective nature. Third, the quality histopathological diagnosis on the tissue might be more or less affected due to the thermal injury of CO_2 laser. Although we chose excision of the whole tongue leukoplakia lesion instead of vaporization, the case(s) would be excluded when the pathologists could reach a consensus on the pathological diagnosis.

Conclusions

The prevalence of ventrolateral tongue leukoplakia was higher than dorsal tongue leukoplakia. The treatment outcomes and other clinicopathological characteristics of dorsal tongue and ventrolateral tongue leukoplakia were not different. The time to develop carcinoma for dorsal tongue leukoplakia was shorter than the ventrolateral tongue leukoplakia and the ATR of dorsal tongue leukoplakia was higher than the ventrolateral site, but these 2 factors were not statistically significant. Dorsal tongue leukoplakia isn't clinically common and more studies are indicated for further investigation.

Abbreviations

CO_2: carbon dioxide; OL: oral leukoplakia; OR: odds ratio; HR: hazard ratio; CIs: confidence intervals; CIS: carcinoma in situ; ATR: annual transformation rate

Declarations

Ethics approval and consent to participate: The Institutional Review Board of Chang Gung Memorial Hospital has approved this study (certificate number: 201901384B0). Due to the retrospective nature of this study, the ethical committee waived the need for informed consent from the every enrolled patients.

Competing interests

The authors declare that they have no competing interests.

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Study concepts: SWY, YSL, CML

Study design: SWY, YSL

Data acquisition: SWY, LCC, CHY, CML

Quality control of data and algorithms: SWY, YSL, CML

Data analysis and interpretation: SWY, YSL

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Figures

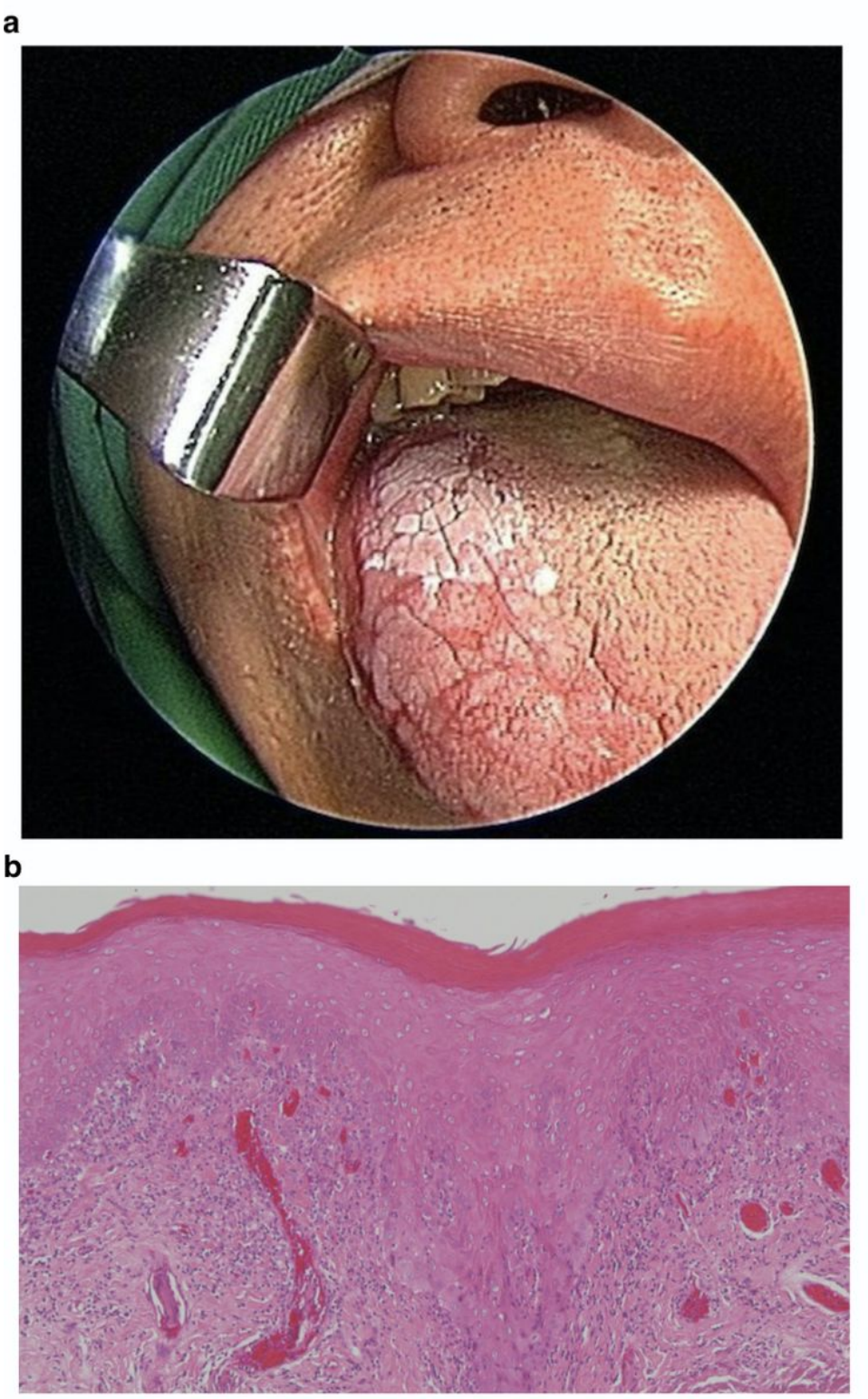

Figure 1

a. Right dorsal tongue non-homogeneous leukoplakia of a 48-year-old male patient. b. Pathology revealed moderate dysplasia. Architectural changes extended into the middle third of the squamous epithelium (hematoxylin-eosin stain, magnification 100x).

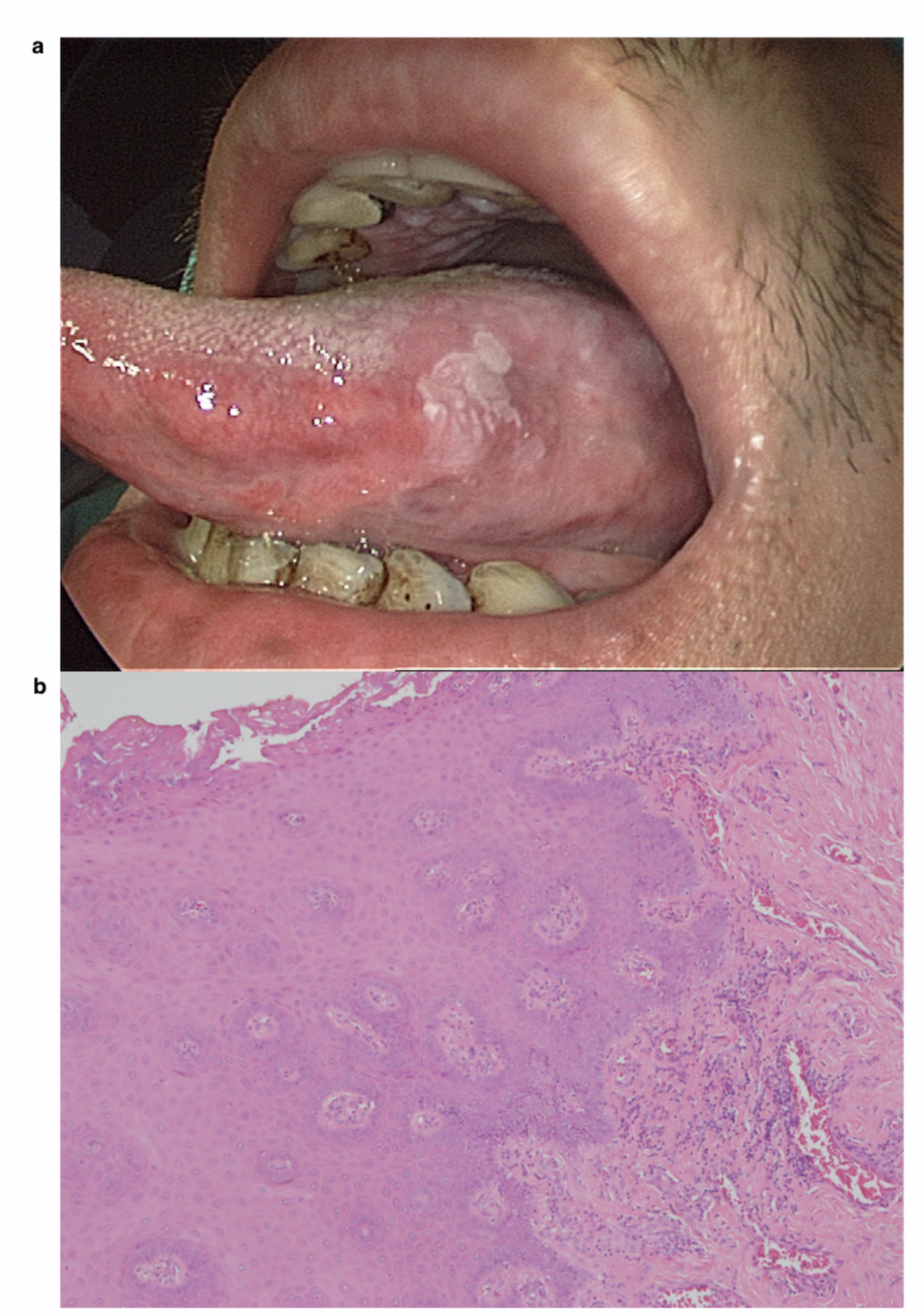

Figure 2

a. Left lateral tongue non-homogeneous leukoplakia of a 38-year-old male patient. b. Pathology showed mild dysplasia. Architectural changes with mild cellular atypia limited to the lower third of the squamous epithelium (hematoxylin-eosin stain, magnification 100x)

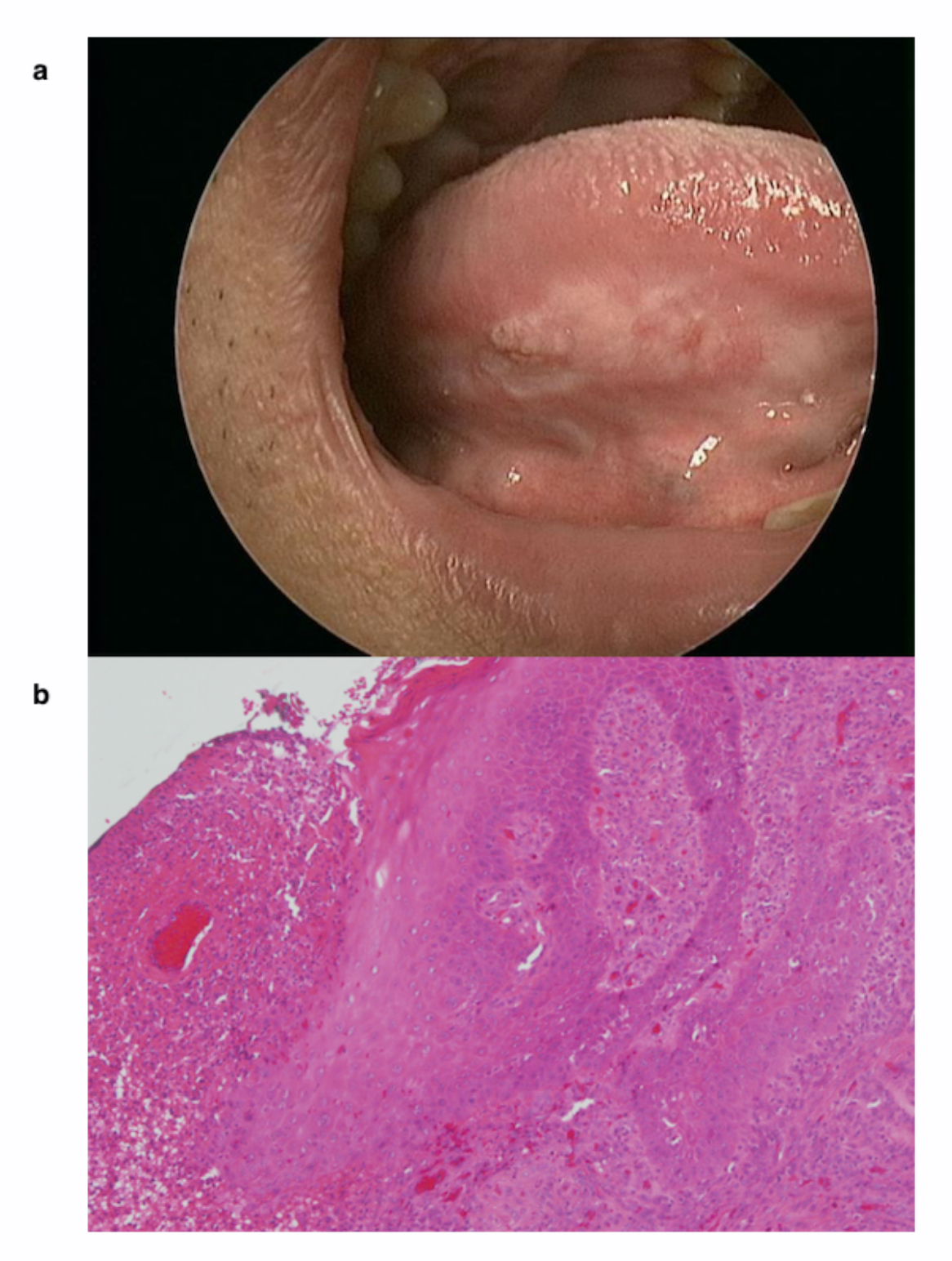

Figure 3

a. Right ventral tongue non-homogeneous leukoplakia of a 52-year-old male patient. b. Pathology demonstrated moderate dysplasia. Architectural changes with mild cellular atypia limited to the lower third of the squamous epithelium (hematoxylin-eosin stain, magnification 100x)

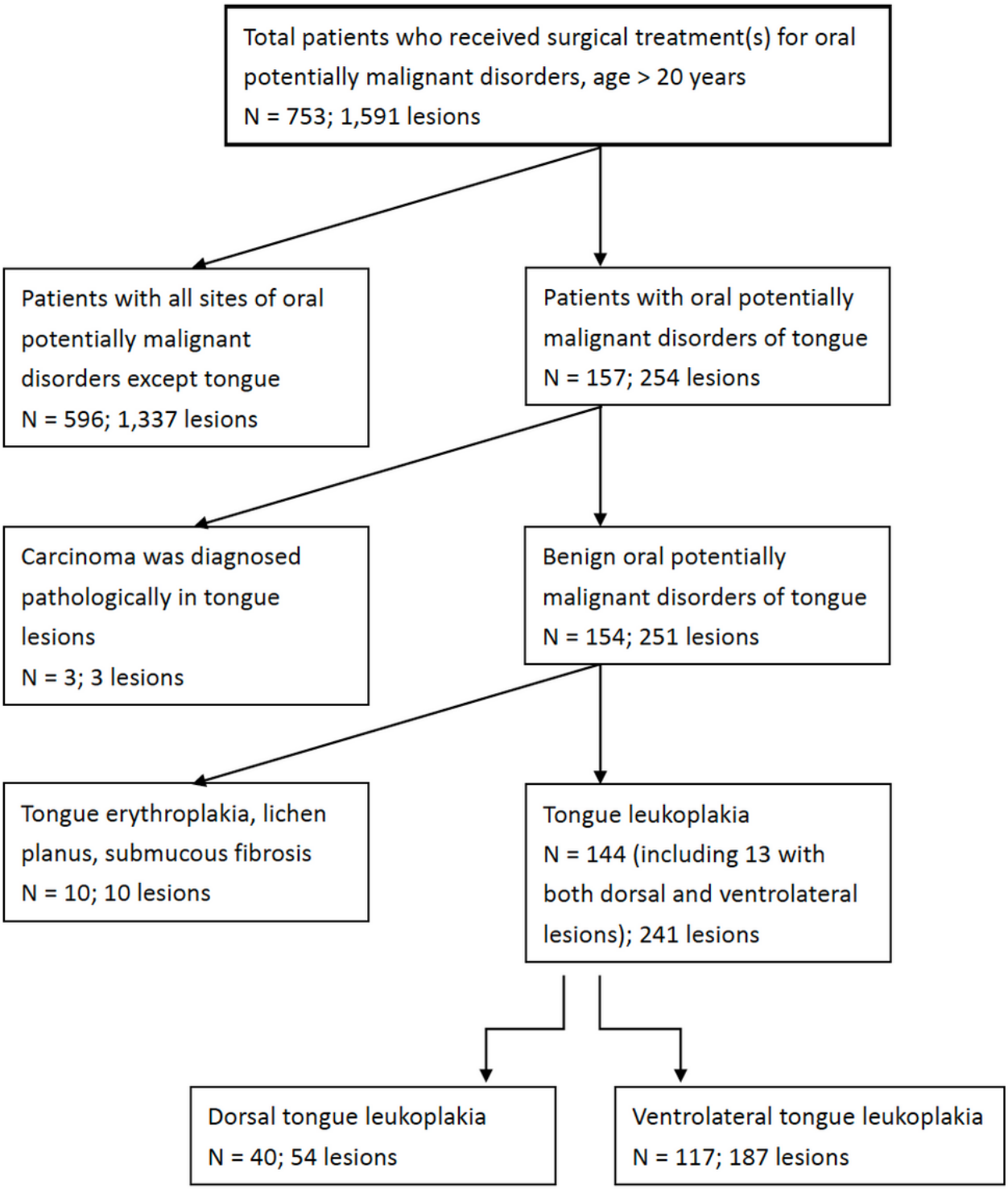

Figure 4

Algorithm for identifying study cohorts

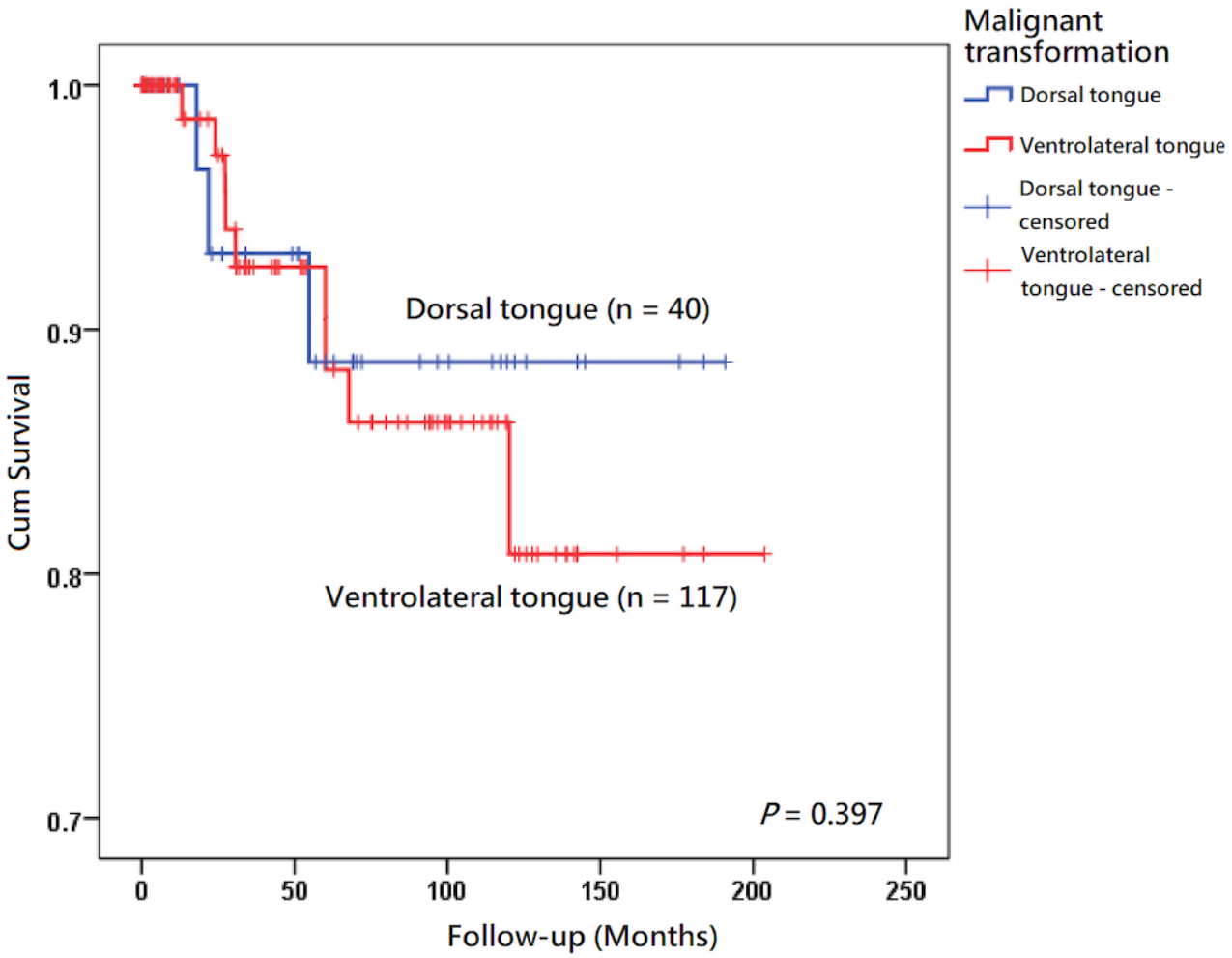

Figure 5

Kaplan-Meier analysis with a log rank test of annual transformation