Clinicopathological characteristics predicting advanced stage and surgical margin invasion of oral squamous cell carcinoma: A single-center study on 10 years of cancer registry data

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Abstract. The incidence profile of oral squamous cell carcinoma (OSCC) has not previously been comprehensively reported in Indonesia. The present study aimed to identify clinicopathological characteristics of patients with OSCC according to sex and age, to analyze histological differentiation patterns specific to tumor subsites, to highlight the role of lymphovascular invasion (LVI) in metastasis, and to develop a model to predict advanced stage and margin invasion. A retrospective cross-sectional study was performed using 581 medical records and pathological specimens from cancer registry data in the Dr Cipto Mangunkusumo Hospital (Jakarta, Indonesia), between January 2011 and December 2020. Clinicopathological characteristics were analyzed using parametric and non-parametric tests. Multivariate logistic regression analyses were performed for eligible parameters, identified using bivariate analysis, to predict advanced stage and margin invasion. Calibration of the prediction model was evaluated using the Hosmer-Lemeshow test, its discrimination value assessed using the receiver operating characteristic and area under the receiver operating characteristic curve (AUC). Sex-specific patterns in tumor subsites and differences in clinical staging according to age were demonstrated in the patients with OSCC. The proportion of well-differentiated cases was significantly higher in most tumor subsites, except in the buccal mucosa (more moderately differentiated cases) and floor of the mouth (well and moderately differentiated cases being equal). LVI was significantly associated with nodal metastasis but not distant metastasis. Multivariate analysis demonstrated that age ≤45 years [odds ratio (OR), 2.26] and LVI (OR, 8.42) predicted patients having advanced-stage OSCC among general populations (AUC, 0.773); however, LVI (OR, 8.28) was the sole predictor of advanced stage amongst young patients (AUC, 0.737). Margin invasion was predicted solely by tumor subsite, including mouth not otherwise specified (OR, 3.04) and palate (OR, 6.13), in the general population (AUC, 0.711). Furthermore, margin invasion was predicted by the palate subsite (OR, 38.77) and LVI (OR, 11.61) in young patients (AUC, 0.762). Investigating young patients thoroughly when finding SCC in the mouth and palate, and assessing LVI, especially among young patients, is critical to prevent advanced staging and margin invasion.

Introduction

Oral cancer is one of the 20 most common cancer types globally, accounting for 377,713 new cases and 177,757 deaths in 2020 (1). The high mortality rate and the disfigurement that survivors may suffer account for a rise in the global public health burden (1). Oral cancer is widespread in South, Central and Southeast Asia, including Indonesia (2). Global Cancer Observatory data reported that the prevalence of oral cancer in Indonesia ranked 17th among all cancer types and 15th for deaths due to cancer in 2020 (3). Identifying the incidence of oral cancer is essential for understanding the pattern of the disease within populations.

Oral squamous cell carcinoma (OSCC) constitutes >90% of all oral cancer cases (4). OSCC presents as an abnormal proliferation of cells in the squamous layer of the epithelium, with OSCC cells depicting varying grades of resemblance with normal epithelial cells (5). Evaluation of histological characteristics serves a vital role in diagnosing resected tumor specimens, and efforts have been undertaken to predict clinical outcomes and therapeutic responses using these (6). Numerous studies have reported that parameters involved include size and primary site of the tumor, Tumor-Node-Metastasis (TNM) staging, tumor differentiation and lymphovascular invasion (LVI) (4,6-8). Moreover, the increasing frequency of OSCC among young patients in several regions should attract

more attention to this disease (7). It has been reported that OSCC biological behavior in young patients differs from that in patients with advanced age (8). However, this concept remains controversial and requires further investigation into prognosis-related factors (9). Two of the most definite prognosis-related factors to have been reported are advanced stage and invasion of surgical margins (10,11), which can be predicted by understanding the role of clinicopathological characteristics of OSCC. However, these parameters have not been widely investigated.

Although the incidence of OSCC has been documented with considerable regional variations (12), Indonesian studies of OSCC epidemiology are still lacking. The increasing prevalence of OSCC among Asian countries (13-16) has demonstrated the value of profiling Indonesian OSCC epidemiology to give a new perspective on this disease and contribute to better prognosis and therapy planning. Previous studies in Indonesia (17-20) did not report a long study period and did not highlight the role of examining histopathological features. These studies did not assess contributing factors related to advanced-stage cancer and invasion of surgical margins in resected cases. Therefore, the present retrospective study aimed to identify the demographic, clinical and histopathological characteristics of patients with OSCC based on 10 years of cancer registry data in the largest referral hospital in Indonesia, and investigate distinct clinicopathological characteristics of OSCC according to sex and age. Furthermore, a comparative analysis was performed to obtain tumor subsite-specific patterns according to histological differentiation, and to assess the pivotal role of LVI in nodal and distant metastasis. A multivariate logistic regression analysis based on different clinicopathological characteristics of patients and tumors was performed to determine the predictors of advanced cancer staging and positive surgical margins in OSCC.

Materials and methods

Study design, patients, specimens and inclusion/exclusion criteria. A retrospective analysis of 581 cases of OSCC that underwent a histopathological examination was performed in the present study. Data on the characteristics of subjects with a primary oral cancer diagnosis defined as International Classification of Diseases (ICD) 10th revision (ICD-10) codes C01-C06 (21) between January 2011 and December 2020 were retrieved from the Dr Cipto Mangunkusumo Hospital (Jakarta, Indonesia). The data were collected from patient clinical records, slide archives, and hematoxylin and eosin-stained tissue blocks. To be included in the present study, patients had to be diagnosed with OSCC, have undergone primary surgery, and have had the diagnosis of OSCC confirmed by presurgical and postsurgical examinations. All data were then reviewed to confirm the inclusion of data on all of the investigated variables. Specimen slides were doubly reassessed to confirm the diagnosis independently and the final agreed diagnosis was used. Patients with recurrent disease on the initial presentation, those with changed diagnoses after re-examination and those whose slides were missing or duplicated due to multiple specimen-taking procedures on the same patient, were excluded from the study. Fig. 1 presents a flowchart of how samples were recruited and analyzed. All the included cases were subjected to the analysis of demography, clinicopathological characteristics and features associated with prognosis.

Ethical approval. The present study was approved by the Ethics Committee of the Faculty of Medicine of the University of Indonesia and Dr Cipto Mangunkusumo Hospital (Jakarta, Indonesia; approval no., KET-178/UN2.F1/ETIK/PPM.00.02/2021).

Patient demographic and clinicopathological characteristics. Patient demographic and clinicopathological characteristics were retrieved from histopathological reports, including registry year, age, sex, tumor subsites, keratinization status, World Health Organization (WHO) histological differentiation (22), Bryne's (1992) cellular differentiation score (23), clinical TNM staging (24), LVI (22), and invasion of surgical margins (22). Registry year was used to group patients per 5-year period and per year. The age of the patients was used to group patients into eight groups with a 10-year range. When specifically assessing OSCC in young patients, a cut-off age of ≤45 years was used to determine if a patient was of young, as reported in previous studies (25,26).

The procedure via which specimens were obtained was divided into three categories: Resection, biopsy and excision. Resection was classified as surgery to remove part or all of an organ, the tumor, adjacent tissues and surrounding lymph nodes (LNs). Biopsy was classified as the removal of cells or tissues; this could be an incisional biopsy where a cut was made in the skin to remove a sample of aberrant tissue or a portion of a lump or suspicious region, or a needle biopsy where a sample of tissue or fluid was extracted with a needle. However, the needle biopsy was not used to obtain a sample in this study. Excision included an excisional biopsy or wide local incision and was classified as a surgical procedure that entailed the removal of a whole lump or suspicious region that had to include some normal-appearing/healthy tissue around it. In our institution, not every patient was eligible to undergo optimal resection. Therefore, excision was occasionally preferable for specific reasons, such as a challenging and complicated location, advanced-stage cancer when the tumor was widespread, debulking to make a resection possible or in palliative care. To be noted, in the biopsy procedure, we could not fully assess margins and LN involvement.

The tumor subsites and keratinization status were coded according to ICD-10 and WHO classifications (21). The histological differentiation of lesions was classified into three categories: i) Well-differentiated; ii) moderately differentiated; and iii) poorly differentiated (27). The degree of cellular differentiation was classified using Bryne's (1992) system as 4-8 (Grade I), 9-12 (Grade II) and 13-16 (Grade III) (23). The surgical margins and LVI were only assessed using the resection specimen and not in the samples obtained from biopsy or excision. Negative margins were defined as those with resection margins of ≥5 mm, and positive margins as those with the tumor still involved (<1 mm) or close to (1-5 mm) healthy tissue, based on several previous studies (28-30). Clinical TNM staging of patients who underwent operative procedures were categorized based on the criteria published by the 8th American Joint Committee on Cancer (31). For multivariate analysis, cases were more simply ranked into early stage (I-II)
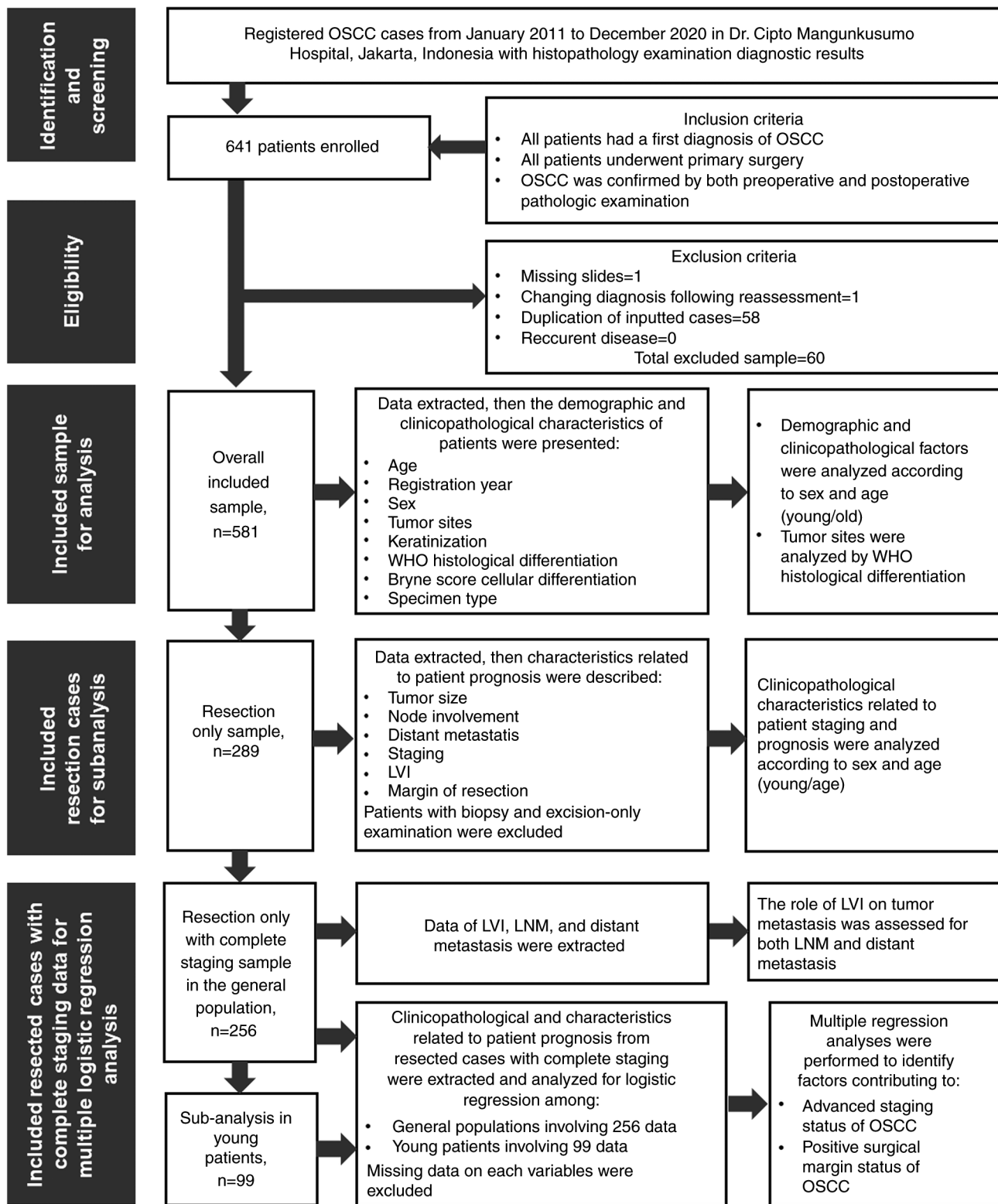
Figure 1. Flowchart describing the sample inclusion and study analysis. OSCC, oral squamous cell carcinoma; WHO, World Health Organization; LVI, lymphovascular invasion; LNM, lymph node metastasis.

and advanced-stage (III-IV) OSCC, using the same grouping method as in a previous study (32).

Statistical analysis. The data were analyzed using the χ^2, Fisher's exact test, or Kruskal-Wallis test with post hoc Mann-Whitney U test as appropriate, using SPSS v24.0

software (IBM Corp.). The demographic and clinicopathological profiles of the parameters assessed were made into frequencies and percentages for categorical parameters and mean ± standard deviations for continuous parameters; they were primarily presented as cross-tabulations to create descriptive statistics. The findings were then presented in

the form of frequency tables. The clinicopathological factors were analyzed via bivariate analysis using χ^2 or Fisher's exact tests with Mantel-Haenszel common odds ratio (OR) estimate. Variables that were significantly (P≤0.20) associated with the groups of interest (advanced-stage OSCC and invaded surgical margin status) in the bivariate analysis were analyzed using a stepwise and backward multiple logistic regression to produce an OR between the factors that contributed to the condition of the disease (33,34). P<0.05 was considered to indicate a statistically significant difference, with a 95% confidence interval (CI). To evaluate the performance and externally validate the risk-factor model, the fit of the data to the model was calibrated using the Hosmer-Lemeshow test and discrimination values were assessed using receiver operating characteristic (ROC) and area under the receiver operating characteristic curve (AUC) (33). The quality of the predictive model was classified based on the AUC value as excellent (0.9-1.0), very good (0.8-0.9), good (0.7-0.8), satisfactory (0.6-0.7) or unsatisfactory (0.5-0.6) (35). The research methods and results were written and presented according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cross-sectional studies (36).

Results

Characteristics and clinicopathological features of all included patients. The distribution of patient demographic and clinicopathological characteristics is presented in Table I. A greater number of OSCC cases occurred in the second interval of the assessed period (2016-2020), demonstrating an increase of 5.6% from the previous 5-year period. A total of 581 subjects with a mean age of 50.77±13.64 years were included (age range, 19-99 years old. The mean age of males was 49.74±14.18 years and for females the mean age was 50.99±13.75 years. Patients with stage I-II cancer had a mean age of 53.67±15.07 years and the mean age for patients with stage III-IV cancer was 49.74±13.66 years. Of the total cases, 36.1% were patients ≤45 years and 52.8% were male patients. The tongue was the most commonly affected subsite (68.7%), followed by mouth not otherwise specified (NOS; 14.1%) and the palate (6.7%). Most tumors demonstrated keratinization (84.7%). Based on histopathological parameters, the majority of tumors were well-differentiated (52.0%), with Bryne's score grade I (53.2%) and were resected (49.7%). The demographic and clinicopathological profiles between young and old patients were similar, yet a significant difference between the sexes was demonstrated with regard to tumor subsites (P=0.002).

Pathological characteristics of OSCC with regard to prognosis in patients who underwent resection. The clinicopathological characteristics of OSCC associated with staging and prognosis according to sex and age among patients who underwent resection are presented in Table II. The tumors diagnosed in the Dr Cipto Mangunkusumo Hospital tended to be extensive (T4: 62.9%), without LN involvement (42.2%) and had no distant metastasis (98.4%). Patients were more likely to present with advanced-stage disease (83.2%). Surgical results were positive, with 85.8% of cases demonstrating a primarily tumor-free resection margin; however, 54.7% of cases were

found to have LVI. There was no significant pattern for these characteristics according to sex; however, there was a significant difference between young and old patients with regard to the stage of disease (P=0.023).

Comparative analysis of tumor subsites with regard to WHO histological grading of all OSCC cases. The comparative analysis presented in Table III demonstrated that the specific histological differentiation patterns in different tumor subsites were significantly different from each other (P=0.017). In most anatomical origins, the proportion of well-differentiated cases was higher than other grades, except in the buccal mucosa, in which moderately differentiated OSCCs were more prevalent, and the floor of the mouth (FOM), for which the proportions of well-differentiated and moderately differentiated cancers were similar. In more detail, the pos hoc analysis elucidated a remarkable difference in grading between tongue and palate subsites (P=004), mouth NOS and palate (P=0.007), and palate and buccal mucosa (P=0.015), meanwhile other two subsites comparisons in pos hoc analysis revealed nonsignificant differences (P≥0.05).

Associations between lymphovascular invasion, lymph node metastasis and distant metastasis for all patients with OSCC who underwent resection with complete staging. A significant association between the presence of LVI and lymph node metastasis (LNM) (OR, 8.96; 95% CI, 5.06-15.88; P<0.0001) was found (Table IV). LVI was not significantly associated with distant metastasis (P=0.142); however, all cases with distant metastasis were also found to have LVI.

Multivariate logistic regression analysis of predictors for advanced-stage OSCC among general and young patients who underwent resection with complete clinical staging. The possible predictors of advanced-stage OSCC are presented in Table V. Multivariate logistic regression analysis elucidated two statistically significant predictors of advanced-stage cancer in the general population, such as younger age ≤45 years (OR, 2.26; 95% CI, 1.02-5.04; P=0.046) and the presence of LVI (OR, 8.42; 95% CI; 3.70-19.20; P<0.0001). LVI was also an independent predictor (OR 8.28; 95% CI; 1.65-41.47; P=0.010) in developing advanced-stage OSCC among young patients. The AUC was 0.773 (95% CI, 0.700-0.846; P<0.0001) for the predictor model of advanced-stage OSCC among the general population and was 0.737 (95% CI; 0.581-0.894; P=0.014) among young patients (Fig. 2). These AUC values demonstrated good discrimination and high-quality results, as a minimum value of 70% for AUC was considered clinically meaningful (33,37).

Multivariate logistic regression analysis of predictors for invaded surgical margin among general and young patients who underwent resection with complete clinical staging. The significant predictors for invasion of surgical margins in the general population are presented in Table VI. Significant predictors included particular tumor subsites, such as mouth NOS (OR, 3.04; 95% CI, 1.17-7.93; P=0.023) and the palate (OR, 6.13; 95% CI, 1.73-21.74; P=0.005). However, advanced-stage (stage III-IV) cancer status and Bryne score grade II were not statistically significant as risk factors in

Table I. Characteristics and clinicopathological features of all included patients (n=581).

Variables	Sex					Age					Total (n=581)	
	Male (n=307)		Female (n=274)		P-value	Young, ≤45 years (n=210)		Old, >45 years (n=371)		P-value		
	n	%	n	%		n	%	n	%		n	%
Year of registration					0.837[a]					0.598[a]		
2011	33	10.7	20	7.3		20	9.5	33	8.9		53	9.1
2012	24	7.8	25	9.1		15	7.1	34	9.2		49	8.4
2013	23	7.5	21	7.7		11	5.2	33	8.9		44	7.6
2014	28	9.1	19	6.9		17	8.1	30	8.1		47	8.1
2015	26	8.5	26	9.5		18	8.6	34	9.2		52	9.0
2016	18	5.9	21	7.7		12	5.7	27	7.3		39	6.7
2017	44	14.3	43	15.7		33	15.7	54	14.6		87	15.0
2018	41	13.4	37	13.5		36	17.1	42	11.3		78	13.4
2019	26	8.5	28	10.2		21	10.0	33	8.9		54	9.3
2020	44	14.3	34	12.4		27	12.9	51	13.7		78	13.4
Interval of registry year					0.445[a]					0.186[a]		
2011-2015	134	43.6	111	40.5		81	38.6	164	44.2		245	42.2
2016-2020	173	56.4	163	59.5		129	61.4	207	55.8		336	57.8
Age, years					0.150[a]							
11-20	1	0.3	1	0.4							2	0.3
21-30	22	7.2	18	6.6							40	6.9
31-40	46	15.0	49	17.9							95	16.4
41-50	79	25.7	60	21.9							139	23.9
51-60	76	24.8	86	31.4							162	27.9
61-70	65	21.2	37	13.5							102	17.6
71-80	14	4.6	20	7.3							34	5.9
>80	4	1.3	3	1.1							7	1.2
Age classification					0.858[a]							
Young, ≤45 years	112	36.5	98	35.8							210	36.1
Old, >45 years	195	63.5	176	64.2							371	63.9
Tumor subsites					0.002[a]					0.070[a]		
Tongue	203	66.1	196	71.5		157	74.8	242	65.2		399	68.7
Mouth NOS	39	12.7	43	15.7		19	9.0	63	17.0		82	14.1
Palate	31	10.1	8	2.9		16	7.6	23	6.2		39	6.7

Table I. Continued.

Variables	Sex					Age						Total (n=581)	
	Male (n=307)		Female (n=274)			Young, ≤45 years (n=210)		Old, >45 years (n=371)					
	n	%	n	%	P-value	n	%	n	%	P-value		n	%
Gingiva	20	6.5	8	2.9		11	5.2	17	4.6			28	4.8
Lip	8	2.6	9	3.3		3	1.4	14	3.8			17	2.9
Buccal mucosa	3	1.0	9	3.3		3	1.4	9	2.4			12	2.1
FOM	3	1.0	1	0.4		1	0.5	3	0.8			4	0.7
Keratinization					0.438[a]					0.803[a]			
Yes	265	86.3	227	82.8		180	85.7	312	84.1			492	84.7
No	35	11.4	37	13.5		25	11.9	47	12.7			72	12.4
Non-specific	7	2.3	10	3.6		5	2.4	12	3.2			17	2.9
WHO histological grading					0.451[a]					0.171[a]			
Well-differentiated	137	53.5	117	50.4		91	52.0	163	52.1			254	52.0
Moderately differentiated	64	25.0	63	27.2		42	24.0	85	27.2			127	26.0
Poorly differentiated	30	11.7	21	9.1		25	14.3	26	8.3			51	10.5
Undifferentiated	25	9.8	31	13.4		17	9.7	39	12.5			56	11.5
Missing data	51		42			35		58				93	
Bryne Score (1992) of cellular differentiation					0.513[a]					0.248[a]			
Grade I	149	55.0	128	51.2		92	48.4	185	55.9			277	53.2
Grade II	92	33.9	97	38.8		75	39.5	114	34.4			189	36.3
Grade III	30	11.1	25	10.0		23	12.1	32	9.7			55	10.6
Missing	36		24			20		40				60	
Specimen type					0.351[a]					0.978[a]			
Resection	145	47.2	144	52.6		105	50.0	184	49.6			289	49.7
Biopsy	158	51.5	125	45.6		101	48.1	182	49.1			283	48.7
Excision	4	1.3	5	1.8		4	1.9	5	1.3			9	1.5

[a]χ^2 test. WHO, World Health Organization; NOS, not otherwise specified; FOM, floor of mouth.

Table II. Pathological characteristics of oral squamous cell carcinoma related to prognosis in patients who underwent resection (n=289).

Pathological characteristics	Sex					Age					Total (n=289)	
	Male (n=145)		Female (n=144)		P-value	Young, ≤45 years (n=105)		Old, >45 years (n=184)		P-value		
	n	%	n	%		n	%	n	%		n	%
Tumor size					0.782[a]					0.225[a]		
T1	6	4.5	7	5.7		5	5.1	8	5.1		13	5.1
T2	22	16.5	24	19.5		12	12.1	34	21.7		46	18.0
T3	21	15.8	15	12.2		13	13.1	23	14.6		36	14.1
T4	84	63.2	77	62.6		69	69.7	92	58.6		161	62.9
Missing data	12		11			6		27			33	
Node involvement					0.266[a]					0.630[a]		
N0	51	38.3	57	46.3		40	40.4	68	43.3		108	42.2
N1	44	33.1	30	24.4		27	27.3	47	29.9		74	28.9
N2	38	28.6	36	29.3		32	32.3	42	26.8		74	28.9
Missing data	12		11			6		27			33	
Distant metastasis					0.353[b]					0.642[b]		
M0	132	99.2	120	97.6		97	98.0	155	98.7		252	98.4
M1	1	0.8	3	2.4		2	2.0	2	1.3		4	1.6
Missing data	12		11			6		27			33	
Staging					0.918[a]					0.195[a]		
I	5	3.8	5	4.1		2	2.0	8	5.1		10	3.9
II	15	11.3	18	14.6		8	8.1	25	15.9		33	12.9
III	22	16.5	17	13.8		15	15.2	24	15.3		39	15.2
IVA	77	57.9	67	54.5		58	58.6	86	54.8		144	56.3
IVB	12	9.0	13	10.6		13	13.1	12	7.6		25	9.8
IVC	2	1.5	3	2.4		3	3.0	2	1.3		5	2.0
Missing data	12		11			6		27			33	
Staging group					0.434[a]					0.023[a]		
I-II (early stage)	20	15.0	23	18.7		10	10.1	33	21.0		43	16.8
III-IV (advanced stage)	113	85.0	100	81.3		89	89.9	124	79.0		213	83.2
Missing data	12		11			6		27			33	
LVI					0.591[a]					0.105[a]		
Negative	68	46.9	63	43.8		41	39.0	90	48.9		131	45.3
Positive	77	53.1	81	56.3		64	61.0	94	51.1		158	54.7

Table II. Continued.

Pathological characteristics	Sex					Age						Total (n=289)	
	Male (n=145)		Female (n=144)		P-value	Young, ≤45 years (n=105)		Old, >45 years (n=184)		P-value				
	n	%	n	%		n	%	n	%				n	%
Margin of resection					0.229[a]					0.669[a]				
Negative	128	88.3	120	83.3		89	84.8	159	86.4				248	85.8
Positive	17	11.7	24	16.7		16	15.2	25	13.6				41	14.2

[a]χ^2 test; [b]Fisher's exact test. LVI, lymphovascular invasion.

Table III. Comparative analysis of anatomical tumor subsites with regard to age and WHO histological grading of all oral squamous cell carcinoma cases (n=581).

Tumor subsites	WHO histological grading										P-value
	Well-differentiated (n=254)		Moderately differentiated (n=127)		Poorly differentiated (n=51)		Undifferentiated (n=56)		Total (n=488)		
	n	%	n	%	n	%	n	%	n	%	
Tongue[b]	163	50.2	84	25.8	29	8.9	49	15.1	325	66.6	0.017[a]
Mouth NOS[c]	36	48.0	20	26.7	16	21.3	3	4.0	75	15.4	
Palate[d]	26	72.2	4	22.2	2	5.6	0	0.0	36	7.4	
Gingiva	15	65.2	8	17.4	3	13.0	1	4.3	23	4.7	
Lip	9	60.0	4	26.7	0	0.0	2	13.3	15	3.1	
Buccal mucosa	4	33.3	6	50.0	1	8.3	1	8.3	12	2.5	
FOM	1	50.0	1	50.0	0	0.0	0	0.0	2	0.4	

[a]Kruskal-Wallis test for all tumor subsites vs. all WHO histological grades. Significant results in post hoc analysis using the Mann-Whitney U test for every two subsites according to grading (well to undifferentiated). Other comparisons of subsites in post hoc analysis resulted in nonsignificant differences (P>0.05). [b]Tongue *vs.* Palate (P=0.004); [c]Mouth NOS *vs.* Palate (P=0.007); [d]Palate *vs.* Buccal mucosa (P=0.015). Missing data (n=93) were not included in the comparative analysis. WHO, World Health Organization; NOS, not otherwise specified; FOM, floor of mouth.

Table IV. Associations between LVI and LNM and distant metastasis of all oral squamous cell carcinoma cases that underwent resection with complete staging (n=256).

	LNM								Distant metastasis								
	Negative (n=108)		Positive (n=148)		Total (n=256)		OR (95% CI)	P-value	Negative (n=252)		Positive (n=4)		Total (n=256)		OR (95% CI)	P-value
LVI	n	%	n	%	n	%			n	%	n	%	n	%		
Negative	76	70.4	31	20.9	107	41.8	8.96 (5.06-15.88)	<0.0001[a]	107	42.5	0	0.0	107	41.8	n/a[c]	0.142[b]
Positive	32	29.6	117	79.1	149	58.2			145	57.5	4	100.0	149	58.2		

[a]Bivariate analysis using χ^2 test with Mantel-Haenszel common OR estimate; [b]bivariate analysis using Fisher's Exact test with Mantel-Haenszel common OR estimate. [c]No positive cases for the variable of distant metastasis, then the analysis of Mantel-Haenszel to yield the OR estimate could not be done. LVI, lymphovascular invasion; LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval.

multivariate analysis. For the young population, the palate tumor subsite (OR, 38.77; 95% CI, 3.36-447.66; P=0.003) and positive LVI (OR, 11.61; 95% CI, 1.34-100.61; P=0.026) were significant predictors for the invasion of surgical margins.

Furthermore, the AUC was 0.711 (95% CI, 0.619-0.804; P<0.0001) for the predictor model of OSCC with invaded surgical margins among the general population and 0.762 (95% CI, 0.645-0.880; P=0.001) among young patients (Fig. 3). These AUC values demonstrated good discrimination and quality for the predictive model results and showed that the predictive model had a good separability measure. The AUC was ~0.7 in the present study; which demonstrates that there was a 70% chance that the model would be able to distinguish between cases with invaded and clear surgical margins.

Discussion

Over the 10 years of the present study, an increase in the proportion of cases between the first 5-year interval (2001-2015) and the second 5-year interval (2016-2020) was demonstrated. It was possibly caused by the improvement of healthcare access and the advancement of healthcare in Indonesia due to the implementation of the National Health Insurance (Jaminan Kesehatan Nasional) scheme in 2014 (38) and the achievement of Universal Health Coverage in 2019 (39). It has been reported that the National Health Insurance scheme enhanced the pace of gaining diagnosis and equity in healthcare access. Nonetheless, it did not improve decrease the time before treatment was received due to limited expansion of healthcare facilities (40).

In the present study, males were more commonly diagnosed with OSCC than females, with a male/female ratio of 0.53:0.47. This result is consistent with earlier studies from numerous countries, including South Korea (males, 56.4%) (41) and Iran (males, 59.6%) (42), which reported a greater frequency of OSCC in men (8,43). By contrast, a study in Thailand reported a greater prevalence of OSCC in women, with a male/female ratio of 1.00:1.56 (44). Male patients are prone to habits such as frequent smoking and the consumption of tobacco products (45), which have long been recognized as risk factors for OSCC. Tobacco contains ~300 carcinogenic compounds, which can be converted to reactive metabolites that interact with DNA, resulting in oxidative stress. Continuous exposure of these agents to the heat from tobacco combustion further aggravates the stress placed on the oral mucosa (46). Data from Indonesia (2018) demonstrated that the percentage of males smoking on a daily basis was 47.3% compared with 1.2% in females (47).

The present study also demonstrated a sex-specific pattern in tumor subsites. Females were more commonly affected at the site of the lip, buccal mucosa, tongue and mouth NOS. However, the anatomical sites most prevalent in males were the palate, gingiva and FOM, in agreement with previous studies (48-50). Kruse *et al* (51) also reported sex-specific patterns. The exact reasons for this differential pattern of common sites for OSCC in males and females are still unknown; however, disparities in the prevalence of OSCC by sex may also be influenced by various factors such as genetic predisposition, altered immune and hormonal modulations, and HPV infection (52). Lip cancer affected more females than males in the present study,

Table V. Multivariate logistic regression analysis of predictors to advanced-stage oral squamous cell carcinomas among general (n=256) and young patients (n=99) who underwent resection with complete clinical staging.

A, General population (n=256)

Variables	Staging Early stage n	%	Staging Advanced stage n	%	Total, n	Bivariate analysis OR unadjusted (95% CI)	P-value	Multivariate analysis OR adjusted (95% CI)	P-value
Sex									
Female	23	53.5	100	46.9	123	Ref.	0.434[a]		
Male	20	46.5	113	53.1	133	1.30 (0.67-2.50)			
Age, years									0.046[c]
>45	33	76.7	124	58.2	157	Ref.	0.023[a,b]	Ref.	
≤45	10	23.3	89	41.8	99	2.37 (1.11-5.06)		2.26 (1.02-5.04)	
Tumor subsites									0.276[c]
Tongue	32	74.4	150	70.4	182	Ref.		Ref.	
Mouth NOS	5	11.6	26	12.2	31	1.11 (0.40-3.11)	0.843[a]		
Palate	1	2.3	13	6.1	14	2.77 (0.35-21.97)	0.472[d]		
Gingiva	1	2.3	12	5.6	13	2.56 (0.32-20.40)	0.700[d]		
Lip	4	9.3	5	2.3	9	0.27 (0.07-1.05)	0.066[d]	0.43 (0.09-1.98)	
Buccal mucosa	0	0.0	6	2.8	6	n/a	0.592[d]		
FOM	0	0.0	1	0.5	1	n/a	>0.999[d]		
Keratinization									
Yes	39	90.7	188	88.3	227	Ref.			
No	4	9.3	24	11.3	28	1.25 (0.41-3.79)	>0.999[d]		
NOS	0	0.0	1	0.5	1	n/a	>0.999[d]		
WHO histological grading									
Well-differentiated	22	75.9	86	62.3	108	Ref.			
Moderately differentiated	1	3.4	20	14.5	21	1.42 (0.57-3.54)	0.448[a]		
Poorly differentiated	1	3.4	12	8.7	13	2.02 (0.57-7.24)	0.271[a]		
Undifferentiated	5	17.2	20	14.5	25	1.34 (0.56-3.19)	0.515[a]		
Bryne score (1992)									
Grade I	27	62.8	105	49.3	132	Ref.			
Grade II	14	32.6	75	35.2	89	1.38 (0.68-2.80)	0.376[a]		
Grade III	2	4.7	33	15.5	35	4.24 (0.96-18.80)	0.041[a]		
LVI									
Negative	25	86.2	48	34.8	73	Ref.		Ref.	
Positive	4	13.8	90	65.2	94	11.72 (3.85-35.63)	<0.001[a,b]	8.42 (3.70-19.20)	<0.001[c]

Table V. Continued.

B, Young Patients (n=99)

| Variables | Staging | | | | Bivariate analysis | | Multivariate analysis | |
| | Early stage | | Advanced stage | | | | | |
	n	%	n	%	Total, n	OR unadjusted (95% CI)	P-value	OR adjusted (95% CI)	P-value
Sex									
Female	4	40.0	39	43.8	43	Ref.			
Male	6	60.0	50	56.2	56	0.86 (0.23-3.24)	>0.999[d]		
Tumor subsites									
Tongue	9	90.0	66	74.2	75	Ref.			
Mouth NOS	0	0.0	8	9.0	8	n/a	0.589[d]		
Palate	0	0.0	8	9.0	8	n/a	0.589[d]		
Gingiva	0	0.0	5	5.6	5	n/a	>0.999[d]		
Lip	1	10.0	1	1.1	2	0.14 (0.01-2.38)	0.244[d]		
Buccal mucosa	0	0.0	1	1.1	1	n/a	>0.999[d]		
FOM	0	0.0	0	0.0	0	n/a	n/a		
Keratinization									
Yes	8	80.0	82	92.1	90	Ref.			
No	2	20.0	7	7.9	9	0.34 (0.06-1.93)	0.225[d]		
NOS	0	0.0	0	0.0	99	n/a			
WHO histological grading									
Well-differentiated	5	50.0	49	55.1	54	Ref.			
Moderately differentiated	3	20.0	15	16.9	17	0.77 (0.13-4.36)	0.670[d]		
Poorly differentiated	3	20.0	11	12.4	13	0.56 (0.09-3.27)	0.614[d]		
Undifferentiated	2	10.0	14	15.7	15	1.43 (0.15-13.26)	>0.999[d]		
Bryne score (1992)									
Grade I	4	40.0	45	50.6	49	Ref.			
Grade II	4	40.0	31	34.8	35	0.69 (0.16-2.97)	0.714[d]		
Grade III	2	20.0	13	14.6	15	0.58 (0.09-3.52)	0.618[d]		
LVI									
Negative	8	80.0	29	32.6	37	Ref.		Ref.	
Positive	2	20.0	60	67.4	62	8.28 (1.65-41.47)	0.005[d,b]	8.28 (1.65-41.47)	0.010[c]

[a]Bivariate analysis using χ^2 test with Mantel-Haenszel common OR estimate; [b]$P \leq 0.20$ was deemed eligible to enter multivariate analysis after bivariate analysis; [c]multivariate logistic regression; [d]bivariate analysis using Fisher's Exact test with Mantel-Haenszel common OR estimate. OR, odds ratio; CI, confidence interval; LVI, lymphovascular invasion; NOS, not otherwise specified; FOM, floor of mouth; WHO, World Health Organization.
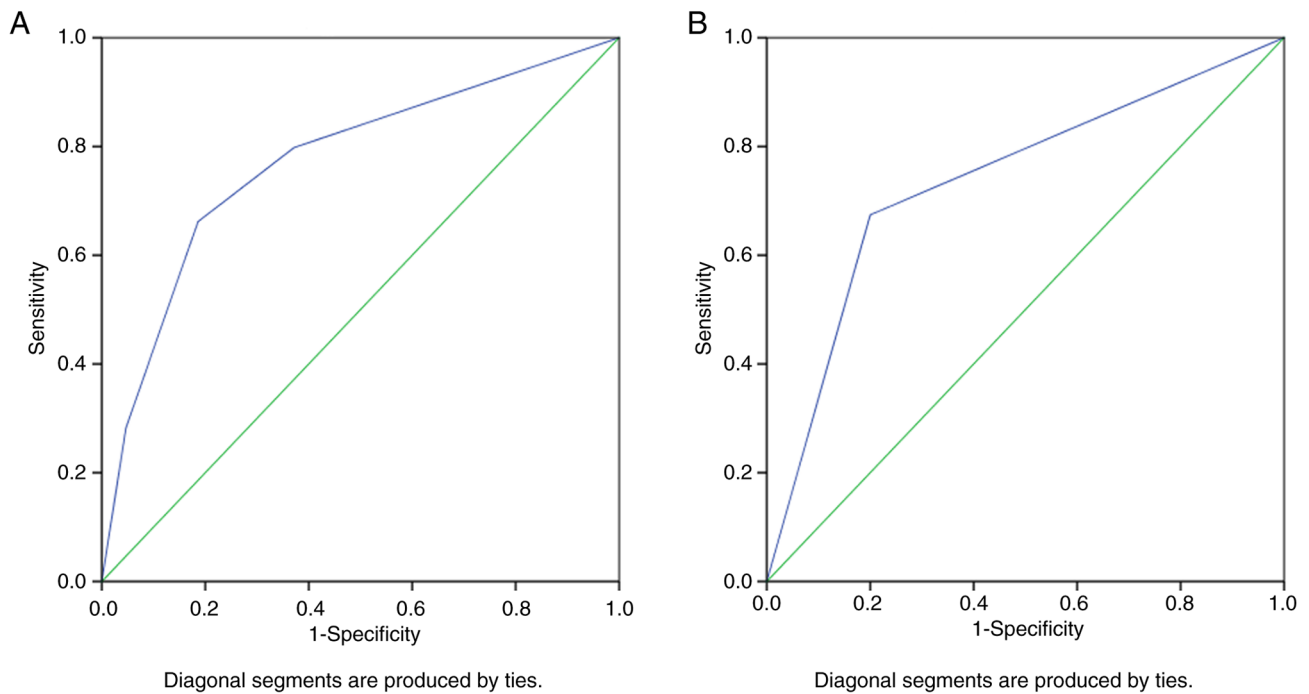
Figure 2. Receiver operating characteristic curve for predicting related factors of advanced-stage oral squamous cell carcinoma in the (A) general population, with an AUC of 0.773 (95% CI, 0.700-0.846; P<0.0001), and (B) in young patients, with an AUC of 0.737 (95% CI, 0.581-0.894; P=0.014). AUC, area under the curve.
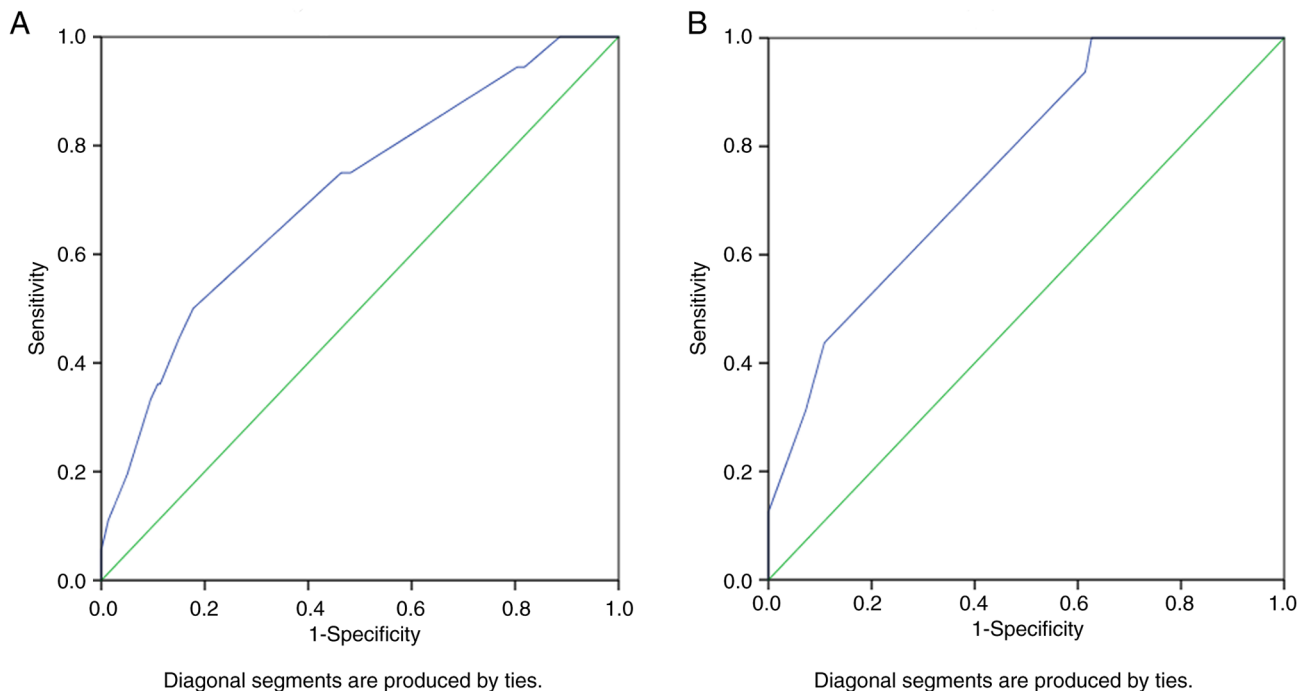

Figure 3. Receiver operating characteristic curve for predicting related factors of positive surgical margins oral squamous cell carcinoma cases in the (A) general population, with an AUC of 0.711 (95% CI, 0.619-0.804; P<0.0001) and (B) in young patients, with an AUC of 0.762 (95% CI, 0.645-0.880; P=0.001). AUC, area under the curve.

which was possibly due to the improper practice of using unsafe and unstandardized lipstick or other cosmetic products containing carcinogens, which are more common in adolescent girls (53,54). The lip epithelium has a thinner keratin covering, less melanin, less sweat and sebaceous gland secretions, and thus has less protection than the skin. Therefore, the use of

unsafe and non-standard lipsticks could put users at greater risk of developing cancer due to chronic local irritation and corrosion (53,54). Furthermore, the higher incidence of buccal cancer in the female population could have been linked to the prevalent practice of chewing betel nuts and consuming smokeless tobacco products in Asian women (55). Consuming

Table VI. Multivariate logistic regression analysis of predictors to invaded surgical margin among general (n=256) and young patients (n=99) who underwent resection with complete clinical staging.

A, General population (n=256)

Variables	Surgical margins				Total, n	Bivariate analysis		Multivariate analysis	
	Negative		Positive			OR unadjusted (95% CI)	P-value	OR adjusted (95% CI)	P-value
	n	%	n	%					
Sex									
Male	118	53.6	15	41.7	133	Ref.		Ref.	
Female	102	46.4	21	58.3	123	1.62 (0.79-3.31)	0.183[a]	1.95 (0.89-4.30)	0.097[b]
Age, years									
>45	137	62.3	20	55.6	157	Ref.		Ref.	
≤45	83	37.7	16	44.4	99	2.37 (1.11-5.06)		0.443[a]	
Tumor subsites									
Tongue	164	74.5	18	50.0	182	Ref.		Ref.	
Mouth NOS	23	10.5	8	22.2	31	3.17 (1.24-8.12)	0.032[c,d]	3.04 (1.17-7.93)	0.023[b]
Gingiva	10	4.5	3	8.3	13	2.73 (0.68-10.85)	0.151[c,d]	2.88 (0.70-11.82)	0.142[b]
Lip	9	4.1	0	0.0	9	n/a		>0.999[c]	
Palate	9	4.1	5	13.9	14	5.06 (1.53-16.75)	0.014[c,d]	6.13 (1.73-21.74)	0.005[b]
Buccal mucosa	4	1.8	2	5.6	6	4.56 (0.78-26.63)	0.124[c,d]	3.24 (0.54-19.41)	0.199[b]
FOM	1	0.5	0	0.0	1	n/a	>0.999[c]		
Keratinization									
Yes	39	90.7	188	88.3	227	Ref.			
No	4	9.3	24	11.3	28	1.25 (0.41-3.79)	>0.999[c]		
NOS	0	0.0	1	0.5	1	n/a	>0.999[c]		
WHO histological grading									
Well-differentiated	110	50.0	18	50.0	128	Ref.			
Moderately differentiated	40	18.2	8	22.2	48	1.22 (0.49-3.03)	0.665[a]		
Poorly differentiated	22	10.0	6	16.7	28	1.67 (0.59-4.67)	0.385[c]		
Undifferentiated	48	21.8	4	11.1	52	0.51 (0.16-1.58)	0.237[a]		
Bryne score (1992)									
Grade I	119	54.1	13	36.1	132	Ref.		Ref.	
Grade II	71	32.3	18	50.0	89	2.32 (1.07-5.02)	0.029[a,d]	2.17 (0.95-4.95)	0.066[b]
Grade III	30	13.6	5	13.9	35	1.53 (0.50-4.61)	0.539[c]		

Table VI. Continued.

A, General population (n=256)

Variables	Surgical margins Negative n	Negative %	Positive n	Positive %	Total, n	Bivariate analysis OR unadjusted (95% CI)	P-value	Multivariate analysis OR adjusted (95% CI)	P-value
Staging									
I-II (early)	41	18.6	2	5.6	43	Ref.	0.052[a,d]	Ref.	0.119[b]
III-IV (advanced)	179	81.4	34	94.4	213	3.89 (0.90-16.87)		3.29 (0.74-14.64)	
LVI									
Negative	94	42.7	13	36.1	107	Ref.	0.456[a]		
Positive	126	57.3	23	63.9	149	1.32 (0.64-2.74)			

B, Young patients (n=99)

Variables	Surgical margins Negative n	Negative %	Positive n	Positive %	Total, n	Bivariate analysis OR unadjusted (95% CI)	P-value	Multivariate analysis OR adjusted (95% CI)	P-value
Sex									
Female	37	44.6	6	37.5	43	Ref.	0.601[a]		
Male	46	55.4	10	62.5	56	1.34 (0.45-4.03)			
Tumor subsites									
Tongue	67	80.7	8	50.0	75	Ref.		Ref.	
Mouth NOS	6	7.2	2	12.5	8	2.79 (0.48-16.23)	0.246[c]	3.28 (0.50-21.41)	0.214[b]
Gingiva	3	3.6	2	12.5	5	5.58 (0.81-38.60)	0.115[c,d]	8.09 (0.90-73.09)	0.063[b]
Lip	2	2.4	0	0.0	2	n/a	>0.999[c]		
Palate	4	4.8	4	25.0	8	8.38 (1.75-40.17)	0.013[c,d]	38.77 (3.36-447.66)	0.003[b]
Buccal mucosa	1	1.2	0	0.0	1	n/a	>0.999[c]		
FOM	0	0.0	0	0.0	0	n/a	-		
Keratinization									
Yes	8	80.0	82	92.1	90	Ref.			

Table VI. Continued.

B, Young patients (n=99)

| | Surgical margins | | | | | Bivariate analysis | | Multivariate analysis | |
| | Negative | | Positive | | | | | | |
Variables	n	%	n	%	Total, n	OR unadjusted (95% CI)	P-value	OR adjusted (95% CI)	P-value
No	2	20.0	7	7.9	9	0.34 (0.06-1.93)	0.225[c]		
NOS	0	0.0	0	0.0	0	n/a	n/a		
WHO histological grading									
Well-differentiated	44	53.0	10	62.5	54	Ref.			
Moderately differentiated	14	16.9	3	18.8	17	0.94 (0.23-3.91)	>0.999[c]		
Poorly differentiated	11	13.3	2	12.5	13	0.80 (0.15-4.19)	>0.999[c]		
Undifferentiated	14	16.9	1	6.3	15	0.31 (0.04-2.68)	0.434[c]		
Bryne score (1992)									
Grade I	42	50.6	7	43.8	49	Ref.			
Grade II	29	34.9	6	37.5	35	1.24 (0.38-4.08)	0.721[a]		
Grade III	12	14.5	3	18.8	15	1.50 (0.34-6.70)	0.687[c]		
Staging									
I-II (early)	10	12.0	0	0.0	10	Ref.			
III-IV (advanced)	73	88.0	16	100.0	89	n/a	0.359[c]		
LVI									
Negative	34	41.0	3	18.8	37	Ref.		Ref.	
Positive	49	59.0	13	81.3	62	3.00 (0.80-11.36)	0.157[c,d]	11.61 (1.34-100.61)	0.026[b]

[a]Bivariate analysis using χ^2 test with Mantel-Haenszel common odds ratio estimate; [b]Multivariate logistic regression; [c]bivariate analysis using Fisher's exact test with Mantel-Haenszel common odds ratio estimate; [d]P≤0.20 was considered eligible to enter multivariate analysis after bivariate analysis. OR, odds ratio; CI, confidence interval; LVI, lymphovascular invasion; NOS, not otherwise specified; FOM, floor of mouth; WHO, World Health Organization.

these carcinogenic agents irritates the buccal mucosa and results in a greater risk of oral lesions compared with that in males (56,57).

The peak incidence in the populations were demonstrated in the 41-60 years age group; other studies have reported an older age range between 50 and 70 years (46,58-62). The present study demonstrated that OSCC in young patients was more prevalent in the Indonesian study population than in other parts of the world (36.1 vs. 4-6% of total cases) (48,63-67). The large proportion of OSCC cases presenting at a younger age in Indonesia should be a public health concern. In 2020, the productive age group (15-49 years) dominated the Indonesian population, totaling 145,571,000 or ~54% of the population, with a slight predominance of men compared with women (50.45%). This demographic bonus (also called as demographic dividend) will be less meaningful if non-communicable diseases, including cancer, contribute to the younger genera-tion's morbidity and mortality (68,69). Moreover, the present study demonstrated that the mean age for male patients is younger than that for their female counterparts, similar to the results of studies in Nigeria (70) and Thailand (48). This is socially important, as men have a leading role and are the main source of income in most families. Moreover, treatment may severely debilitate young patients, including disfigure-ment from surgery and the severe side effects of chemotherapy and radiotherapy. These effects may degrade a patient's quality of life.

In the present study, most tumors arose in the tongue, similar to previous studies (71,72). The population in the present study had fewer OSCCs starting from the FOM, possibly due to the difficulty of identifying the tumors originating from that subsite when a patient presents with extensive tumor growth occupying the entire oral cavity in advanced-stage disease. Factors affecting the location of OSCC could be linked to the geographical distribution of certain habitual risk factors. Tongue cancer is frequently correlated with the younger age group (73). In the present study an association between tumor topography and histological differentiation was demonstrated. Numerous well-differentiated tumors were identified in the lips, gingiva, tongue, palate and mouth NOS. However, moder-ately differentiated cases were significantly more frequently diagnosed on the buccal mucosa, and these are known to have less favorable prognoses (74,75). It was also demonstrated that the highest proportion of poorly differentiated tumors developed in the mouth NOS, followed by the gingiva, tongue and buccal mucosa. Pires *et al* (50) and Costa *et al* (76,77) also reported that histological differentiation was associated with the site of the tumors; however, the reason for this is still unclear.

In the present study, the tumors of most patients demon-strated keratinization and there was no significant difference between younger and older patients or the sexes. The existence of surface keratinization reflects the rapid rate of matura-tion of the epithelium. In OSCC, this is a genetically based process to increase the turnover rate by maintaining develop-ment or differentiation, which, enables the tumor to remain well-differentiated (78).

The present study demonstrated that well-differentiated OSCC was the most common histological subtype in both age groups, sexes, and clinical stages, which was in line

with previous studies (79-81). On the other hand, the least common subtype was diverse depending on the grouping. The least frequent subtype in both males and young patients was undifferentiated. Meanwhile, among females, old patients, and OSCC survivors at an advanced stage, poorly differenti-ated became the least prevalent subtype. Additionally, the joint least common histological subtype in the early stage was poorly differentiated and moderately differentiated. Well-differentiated SCCs almost resemble Malpighian cells of the normal epithelium. However, they disrupt the basal membrane and invade the underlying corium under various patterns of uncontrolled growth, with loss of polarity, develop-ment of dyskeratosis and the formation of 'keratin pearls' (82).

Histological grading has been used to predict the clinical behavior of OSCC for numerous decades, but its prognostic value is still controversial (83). WHO histological grading is well suited to the grading of tumors resembling the typical appearance of tissues, but cannot exclusively rate or reflect the aggressiveness of the tumor, thus leading to an inaccurate prognosis. The prognostic prediction from WHO histological grading can be difficult to derive because this characteristic typically relies on subjective inspection. Additionally, it will be more complicated if the specimen comes from a biopsy that serves a relatively small size of tumors but has high intratumor heterogeneity (75,84). To address the shortcom-ings of the WHO histological classification system, the Bryne score (1992) was introduced. It better reflects the idea of intratumor heterogeneity and cellular aggressiveness in differ-entiation (85). This system implied that the more invasive areas of the tumor, known as the invasive front, may have a different character compared to different areas of the same tumor. Hence this system is more relevant for the prognosis of OSCC (23,78). Based on this scoring system, more than half of the cases in the current study presented with grade I tumors. No significant differences between the subgroups of old and young patients, or between sexes, were demonstrated as being related to this parameter; however, the results did demonstrate that the proportion of grade II and III in younger patients was markedly higher than that in older patients.

Almost half of the patients in the present study underwent resection of their tumor and the remaining cases had speci-mens taken by biopsy or excision. The decision to resect was made on a case-by-case basis, as recommended by a multidis-ciplinary meeting. However, as the Dr Cipto Mangunkusumo Hospital is the leading referral hospital in Indonesia, the increasing volume and demand for surgery may have caused queues in operation schedules, making certain patients seek private healthcare facilities and therefore undergo resection outside of the data available to the present study. Moreover, 81.3% of the patients in the present study were at an advanced stage and so might not have survived the waiting time for surgery, as the overall survival (OS) rate of advanced-stage OSCC is poor (86). A prior study reported that the 1-year OS rate for OSCC in Indonesia was 60.6%, and that after 2 years it was 12.1%, with a median survival of only 20 months (95% CI, 9.07-30.9) (87). This scenario could be further complicated by a lack of health insurance. It has been reported that patients without medical insurance are more likely to present with metastatic head and neck cancer, and not receive definitive treatment (88). Differences in the type of samples obtained can

also impact the result of the analysis. Biopsy and excisional specimens may not represent all aspects of the tumor, such as LNM, LVI and surgical margins. Other important considerations in specimen analysis are the therapeutic approaches employed and the survival rates of the patients. Resection is the best choice of treatment for OSCC and was correlated with the highest survival rate for this malignancy in a previous study (89). Patients who underwent surgical procedures demonstrated higher survival rates (74.4±4.9 months) than those who did not (51.5±3.9 months), according to the study by de Barros Silva *et al* (89). Radiotherapy and chemotherapy are essential components of the management of OSCC. However, it has been reported that these modalities are not always correlated with a better prognosis (89).

Most patients were classified as clinical stage T4, N0 and M0 in the present study. These results were different to the results of a study by Elaiwy *et al* (90), which reported that patients with early T-stage disease made up more than one-half of the patient population sampled, but that half of the patients had no nodal metastases. More than 80% of patients in this study were diagnosed with OSCC at an advanced stage, consistent with the results in prior studies (91,92). The absence of pain in the early stages of OSCC may account for the late diagnosis. The late diagnosis could also be linked with the status of the Dr Cipto Mangunkusumo Hospital; as a national referral hospital (and thus a tertiary healthcare center), a large proportion of patients with the most advanced stage of disease development is expected. This result was similar to studies performed in referral hospitals in India (93) and Brazil (71,94), which reported that most patients also presented with late-stage disease (86.79 and 65.5% respectively). The late presentation of OSCC is most likely due to a combination of factors, including a lack of knowledge about the disease, poverty, the high expense of therapy, the seeking of alternative non-evidence-based medications by patients, professional delay in primary care and insufficient attention to oral health (93,95). Almost 90% of the younger population in the present study was diagnosed with advanced-stage disease, which was similar to findings in a previous study (64). The late diagnosis in younger patients is frustrating, as the prognosis of OSCC worsens with progressing TNM staging (96).

The presence of LVI indicates the initial steps in metastasis, and it can be assumed that the clinical staging of patients will be more advanced than that in those with no LVI (97). More than one-half of the patients were positive for LVI in the present study. This was similar to a study by Ting *et al* (98), which reported that most patients with T3-4 OSCC (44.9%) demonstrated LVI.

Almost 15% of cases in the present study demonstrated invaded surgical margins, similar to findings in previous studies (17-44% inadequate surgical margins) (11,99-101); however, one study reported a lower proportion of invaded margins (7.5%) (28). In OSCC, assessing surgical margins is a crucial part of determining the therapeutic outcome, while also considering tumor location, tumor stage, tissue shrinkage and mucosal elasticity (102).

Clinical TNM staging is the most reliable indicator of patient survival in OSCC (74,84), which also dictates the course of treatment (46). However, TNM staging alone is insufficient for optimal prognostication and needs histopathological features to maximize the accuracy of the prediction of outcomes (103). Due to the effects of staging and the lack of data on the clinicopathological contribution to prognosis, the present study focused on identifying several predictors contributing to the advanced stage of OSCC among general and young populations.

Multivariate analysis demonstrated that young age at diagnosis (≤45 years) and the presence of LVI significantly predicted patients having advanced-stage OSCC in the general population. Moreover, LVI was independently a significant predictor among young patients. However, other clinicopathological factors failed to predict advanced-stage OSCC among both the population in general and young patients. The role of young age as a predictor of advanced-stage status supported the hypothesis that that young age OSCCs are prone to be more aggressive because of their biological behavior and etiology, which differ from OSCC in older age groups (104). Consequently, younger patients have poorer survival (105-107). However, an alternative idea could be that LVI, not age, is a more significant predictor of advanced-stage disease and that LVI is more prominent at a young age (108). These findings reinforce the possibility that the worse prognosis of young patients, as demonstrated in the present study, is due to LVI.

LVI is a predictor of the progression of advanced-stage disease, as its presence is attributed to aggressive tumor behavior in head and neck cancer (109). The presence of LVI indicates that a significant amount of neoplastic cells have been accessing the lymphovascular flow to form tumor emboli, consequently increasing the chance of LNM, distant metastasis and recurrence (16,110,111). The present study demonstrated that the presence of LVI was significantly associated with LNM (OR, 8.96; P<0.0001). Furthermore, all metastatic OSCC cases in the present study had a positive LVI status, which is one of the earliest stages of metastatic development (97). Moreover, LVI significantly affects tumor size, histological grading, invasive front, prognosis and OS (109). A meta-analysis by Huang *et al* (97) also reported that LVI predicted poor OS [hazard ratio (HR), 1.55; 95% CI, 1.43-1.69; P<0.00001] and disease-specific survival (HR, 1.76; 95% CI, 1.48-2.09; P<0.00001). In the young patient group, among all proposed predictors, only LVI resulted in a significant possibility of patients developing advanced-stage OSCC, with markedly higher OR than in the general population. Thus, LVI can be identified as a critical pathological marker of tumor aggressiveness in OSCC (112).

The present study also revealed that sex did not significantly determine staging, prognosis or survival for a patient with OSCC. Even if there is a consensus that oral cancer is more common in males (113), whether sex significantly influences outcome has not been established and results are still conflicting (114-119). The model produced in the present study did not demonstrate that keratinization had valuable prognostic value in predicting advanced stage, similar to the results of a previous study (120). However, other studies reported that the degree of keratin expression was a predictor of prognosis (121,122) and that absent or minimal keratinization in OSCC was significantly associated with LNM compared with a high degree of keratinization (9,123,124). However, variables related to keratinization as a classification

degree by scoring were not analyzed in the present study. The association between WHO histological grading and the Bryne score (1992) cellular differentiation system as predictors of disease severity in OSCC is still controversial (75,84). Although Lin *et al* (6) reported that histologically, high-grade OSCC had a worse survival rate and a greater probability of recurrence than other groups, the present study did not demonstrate statistical significance between these factors to predict the advanced stage of OSCC cases. Further research on the role of these characteristics in OSCC is required.

A previous study reported that identified tumor subsite carried a prognostic value in the TNM clinical classification (74). However, the present study did not demonstrate a significant association between tumor subsites and TNM staging in general or young populations, confirming findings reported by Oliveira *et al* (91). In the general population, the present study demonstrated a tendency for patients with lesions in mouth NOS, palate, gingiva, buccal mucosa and FOM to be admitted with advanced-stage disease compared with those with tongue and lip OSCC, similar to findings in a prior study (74). These subsite patterns might relate to daily habits; a tongue lesion might be easier to detect as complaints in day-to-day eating use might be prominent, whereas a lip lesion is easily detected due to the cosmetic impact it brings to the appearance of the patient. Advanced-stage OSCC is often coded as being identified in the mouth NOS, as the extensive nature of advanced-stage disease means that an originating subsite of cancer cannot be determined in most cases.

Patients with positive and close margins should receive additional care (e.g., adjuvant therapy) and close monitoring since they are at an increased risk of local disease recurrence (102). Predicting the risk of positive surgical margins when treating the advanced-stage group is essential for local disease control (125). However, the effect of positive margins on the prognosis of OSCC is still debatable. In a prior study, the relative risk of death for involved and close surgical margins compared with clean margin status was 11.61 (P=0.0013) and 2.66 (P=0.002), respectively (126). Positive surgical margin status indicates the aggressiveness and likelihood of OSCC to recur (99,126). It also has been acknowledged as enormously impactful on the survival outcomes of patients treated surgically for oral cancer (127). In previous studies, the ability to achieve a wide free margin was linked with some clinical aspects, such as age, sex, the epicenter of the tumor, T and N status, and treatment modality (11,99,125,126,128,129). However, occasionally, oral surgeons cannot acquire an adequate surgical margin for OSCC, as the oral cavity has a complicated anatomy, and wider resection might cause more significant disfiguration or functional disability. The present study demonstrated that surgical margin invasion status was predicted solely by the particular subsite of the tumor (worse prognosis if the tumor was identified in the mouth NOS or palate) in the general population; however, in young patients, the location of the tumor (particularly in the palate) and the presence of LVI were predictors of invaded surgical margin status. The results of the present study aligned with those of several previous studies, which reported that the rate of inadequate (close or positive) margins was highest in palate tumors, followed by mouth NOS; moreover, tumors of the lip and FOM had the lowest proportions of positive surgical margins (28,84).

Tumor subsites are considered to be a related prognostic factor due to the particular gene expression profile, which differs according to tumor subsite, and the compact and complex anatomy of the oral cavity, which leads to variable tissue composition among distinct subsites, suggesting that these two explanations cause dissimilar vulnerability to tumor invasion in every subsite (130). Compared to the tongue as a reference, the present study demonstrated that based on the tumor subsite, mouth NOS and palate had a higher chance to result in poor tumor outcomes due to their likelihood to have invaded surgical margins. The tongue was used as a reference as it had the fewest amount of cases with positive surgical margins, and following other studies, which commonly used the tongue as a reference in OSCC analysis (11,28,99,102,131,132). The anatomy of the tongue permits the design and adaptation of a hemiglossectomy adequate for achieving clear margins (102). In the present study, the prevalence of positive margins in OSCC of the mouth NOS was high, linked to cases where the tumor has extended through the entire mouth area, demonstrating that it is undoubtedly complicated to free the margins. The palate was the most common area that resulted in positive margins due to the difficulty of entirely separating tumors from the superior aspect of the skull base and its surroundings during surgery, which may factor in a higher risk of recurrence (133). If cancer has grown into the hard palate, all or part of the involved bone (maxilla) will need to be removed (maxillectomy) and a wide local resection is therefore the preferred treatment (134).

The prediction model in young patients of the present study demonstrated that besides tumor subsites, LVI presence also contributed to positive margin status, a finding reported in other studies, such as those by Abbas *et al* (122) and Clark *et al* (135). The risk of locoregional recurrence and distant metastasis related to LVI can also be connected to margin status; however, to the best of our knowledge, no study has previously assessed the association between LVI and margin status in OSCC. However, similar results have been reported in prostate cancer, in which LVI increases the recurrence risk in patients with stage T3 tumors related to positive resection margin status (136,137). Moreover, the present study demonstrated that LVI was consistently associated as a predictor of advanced disease and invaded surgical margins for young patients with OSCC.

The present study has several shortcomings. First, as this was a retrospective cross-sectional study that relied heavily on the acquisition of proper documentation by the investigators, there may be certain missing data and a risk of bias. Second, the data were collected at a single institution, limiting external validity, and only a part of the recorded population had undergone resection due to the limited setting. However, these challenges have been addressed by performing several sub-analyses only for the resection specimen data. Third, evaluation of the histopathological features was performed by pathologists and individual disagreement is conceivable. To mitigate this, two independent pathologists were used to minimize bias. Furthermore, >80% of the patients diagnosed with OSCCs in the present study were in the late stages of the disease; therefore, the findings may not be generalizable to patients with early stage disease. Furthermore, thorough

histopathological assessment to predict staging and surgical outcomes is required.

An epidemiological study is essential for a comprehensive understanding of disease in the community. The present study demonstrated significant differences in clinicopathological characteristics of patients with OSCC according to sex with regard to tumor subsites and a significant difference in clinical staging between young and old patients. A tumor subsite-specific pattern in histological differentiation was also demonstrated, as well as a link between LVI and LNM, but not between LVI and distant metastasis. In developing a model to predict advanced stage and margin invasion, the presence of LVI and young age predicted advanced-stage OSCC among the general population, yet only LVI predicted advanced-stage disease in young patients. Mouth NOS and palate subsites predicted the invasion of surgical margins in the general population; however, the palate subsite and LVI were predictive factors for invaded margins in young patients. Given the importance of LVI as a predictive factor for advanced-stage disease and invaded surgical margins, pathologists should thoroughly examine the LVI status of patients with early stage OSCC, particularly young patients with lesions in the palate. Clinicians should also closely follow up with these patients to prevent morbidity and decline in quality of life.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NR conceived the study. NR, DRH, MS and EK interpreted data. The formal analysis was performed by NR and MH. NR acquired the funding and was project administrator. NR and MH performed the investigation. NR and MH were responsible for the methodology. NR, DRH, MS and EK provided resources. Software was used by MH. NR and EK supervised the project, NR, DRH, MS and EK validated the work. NR and MH wrote the original draft, NR, MH, DRH, MS and EK reviewed and edited the manuscript. NR and MH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of the Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital approved the study protocols (approval no. KET-178/UN2. F1/ETIK/PPM.00.02/2021).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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