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ORIGINAL RESEARCH

Clinicopathological Characteristics of Oral Squamous Cell Carcinoma at the Central Referral and Teaching Hospital in West Java, Indonesia

Irna Sufiawati[1], Alamsyah Piliang[2], Adi Ahmad Yusuf[2], Tenny Setiani Dewi[1], Hasrayati Agustina[3], Yohana Azhar[4], Adi Idris[5]

[1]Department of Oral Medicine, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia; [2]Oral Medicine Residency Program, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia; [3]Department of Anatomical Pathology, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Bandung, Indonesia; [4]Division of Oncology Surgery, Department of Surgery, Faculty of Medicine Universitas Padjadjaran//Dr. Hasan Sadikin General Hospital Bandung, Bandung, Indonesia; [5]Centre For Immunology and Infection Control, School of Biomedical Sciences, Queensland University of Technology, Brisbane QLD, Australia

Correspondence: Irna Sufiawati, Department of Oral Medicine, Faculty of Dentistry, Universitas Padjadjaran, Jalan Sekeloa Selatan I, Bandung, 40132, Indonesia, Tel +62-22-2504985, Fax +62-22-2532805, Email irna.sufiawati@fkg.unpad.ac.id

Purpose: This study aimed to investigate the clinicopathological characteristics of oral squamous cell carcinoma (OSCC) patients and analyze the relationship between the degree of differentiation and factors including age, sex, stage, and tumor location in West Java, Indonesia.

Patients and Methods: A retrospective cross-sectional study was conducted at the Central Referral and Teaching Hospital in West Java, Indonesia. The data were collected by reviewing medical records with International Classification of Diseases (ICD) codes C00-C06 from 2016 to 2023. Descriptive statistics were employed to summarize the clinicopathological characteristics of OSCC patients. Chi-square, rank Spearman tests, and contingency correlation coefficients were used to analyze the relationship between the degree of differentiation and various factors, such as age, sex, stage, and tumor location of OSCC.

Results: Out of the 627 oral cancer patients, 70.49% were diagnosed with OSCC with a gender distribution of 45.7% males and 54.3% females, predominantly within the age range of 30–49 (37.2%). Most OSCC cases were stage IV (37.7%), with the tongue identified as the most common site (68.8%). A consistent trend of higher well-differentiated and moderately differentiated OSCC by age and gender was observed. Statistical analysis revealed no significant correlation between age, gender, tumor location, and the degree of OSCC differentiation ($p>0.05$). However, a statistically significant correlation was identified between the degree of OSCC differentiation and stage ($p<0.001$, $r=0.460$).

Conclusion: There is a correlation between the degree of differentiation of OSCC and stage, suggesting significant prognostic implications that can aid in treatment planning and outcome prediction. However, further studies are needed due to the lack of comprehensive data on risk factors and survival rates of oral cancer patients, which is essential for enhancing prevention and treatment strategies for OSCC.

Keywords: degree of differentiation, epidemiology, oral cancer, oral squamous cell carcinoma, prognostic

Introduction

The global incidence of cancers of the lip and oral cavity was estimated to be 377,713 new cases and 177,757 deaths in 2020. However, there is regional variation in the incidence of oral cancer. Asia exhibited the highest incidence (65.8%), followed by Europe (17.3%) and North America (7.3%).[1] Southeast Asian countries are among the top 20 countries with the highest incidence of oral cancer globally, with an age-standardized incidence value of 9 per 100,000 people.[2] Notably, the global age-standardized rate (ASR) of oral cancer is 6.0 per 10,000 in males and 2.3 per 10,000 in females. The difference in incidence by sex is primarily attributed to the higher consumption of alcohol and tobacco among men than women. This ratio varies in countries where women share these same habits as men.[3]

Oral squamous cell carcinomas (OSCC) constitute more than 90% of all oral cancers, and their geographical prevalence varies globally. Notably, OSCC stands out as the most common oral cancer in Southeast Asian countries.[2]

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In Indonesia, national data on OSCC remains insufficient. Most studies are limited to specific hospitals, institutions, or regions, resulting in a fragmented understanding of OSCC epidemiology at the national level. The absence of a comprehensive national database further complicates efforts to obtain a complete overview. A cross-sectional study conducted at Dr. Cipto Mangunkusumo Hospital, a main referral hospital in Jakarta, Indonesia, analyzed 1093 documented OSCC cases from 2001 to 2020.[4] Additionally, research from Yogyakarta, a province in south-central Java, has highlighted an increasing trend in OSCC cases, with 91 cases recorded from January 2011 to December 2015.[5] By age, OSCC is more prevalent in men over 40 years old, with only about 0.4 to 3.9% of patients being under the age of 40.[6] The highest incidence of OSCC is observed in individuals over the age of 50 and is commonly diagnosed in individuals between the ages of 60 and 80. OSCCs are frequently identified at an advanced stage, primarily due to the lack of signs and symptoms in the early stages of the disease or insufficient public awareness and knowledge about oral cancers and their risk factors.[7,8]

The lateral border of the tongue exhibits the highest incidence of OSCC, accounting for an estimated 50% of all OSCC, followed by the floor of the mouth/ventral tongue, alveolar mucosa/gingiva, buccal mucosa, lips, and palate.[9–11] A positive trend in the incidence of OSCC on the tongue and buccal mucosa has been reported at a main referral hospital Dr. Cipto Mangunkusumo in Jakarta, Indonesia.[4] Similarly, a study performed at Dharmais Cancer Hospital, a national cancer referral hospital, documented an annual increase in tongue cancer cases.[12] These two studies may reflect the trend of increasing tongue cancer cases in Indonesia. The tongue cancer, in particular, is associated with a higher mortality rate compared to OSCC in other sites of the oral cavity.[11,13] The tumor-node-metastasis (TNM) classification of malignant tumors remains the standard for recording and classifying anatomical disease extent. The stage of cancer indicates the severity of the cancer, including tumor size (T), enlargement of nearby lymph nodes (N), and cancer metastases (M). Importantly, the survival rate for OSCC ranges from 10% to 82% depending on stage, age, treatment, comorbidity, and anatomical location in the oral cavity.[14]

OSCC is a cancer originating from the mucosal epithelium of the oral cavity with variable squamous differentiation.[3] Various histopathological scoring systems for OSCC have been reported.[6] Broder's assessment is a well-recognized reporting system, categorizing conventional histopathological evaluation into three groups, which include well-differentiated, moderately differentiated, and poorly differentiated. This degree of differentiation not only reflects severity but also aids in assessing the prognosis of OSCC. The simplicity and practicality of this system at the time of reporting have made it a routine choice, recommended by the World Health Organization (WHO) for uniformity in reporting.[3]

This study aimed to investigate the clinicopathological characteristics of OSCC patients attending the Central Referral and Teaching Hospital in West Java, Indonesia. Importantly, we analyzed the relationship between the degree of differentiation of OSCC and factors such as the patient's age and sex, as well as the stage and location of the tumors.

Material and Methods

The study employed a retrospective design, focusing on patients with oral cancer. Patient details were documented in the medical records of Dr. Hasan Sadikin General Hospital, the Central Referral and Teaching Hospital in West Java, one of the most densely populated regions in Indonesia. Details of the OSCC data include information on age, gender, anatomical location, cancer stage, and histopathological data, that were collected from patients' medical records over the past 8 years (2016–2023). Inclusion criteria comprised patients with ICD codes C00-C06, and the exclusion criteria were incomplete or duplicated medical records. Descriptive statistics, such as percentages and frequencies, were utilized to summarize categorical variables related to the clinicopathological characteristics of OSCC patients. The data were analyzed using the chi-square test, Spearman rank correlation, and contingency coefficients to determine the correlation between the degree of differentiation and factors including age, sex, stage, and tumor location of OSCC.

Results

The study included 627 oral cancer patients, where 442 (70.49%) of these patients were diagnosed with OSCC. The distribution of oral cancer types is illustrated in Table 1. Out of all the OSCC diagnoses, we obtained medical record data for 199 cases that met all the inclusion criteria. Table 2 shows the clinicopathological characteristics of OSCCs. OSCC was predominantly found in the 30–49 age group (37.2%). The youngest individual diagnosed was 19 years old, while

Table 1 Type Distribution of Oral Cancer

Type of Oral Cancer	Total n=627	Percentage (%)
Oral Squamous Cell Carcinoma	442	70.49
Parotid Carcinoma	102	16.27
Adenoid Carcinoma	57	9.09
Ameloblastoma	2	0.32
Fibrosarcoma	3	0.48
Salivary Gland Carcinoma	1	0.16
Malignant Melanoma	3	0.48
Schwannoma	1	0.16
Pleomorphic Adenoma	5	0.80
Rhabdomyosarcoma	3	0.48
B Cell Lymphoma	2	0.32
Epidermoid Carcinoma	2	0.32
Angiosarcoma	1	0.16
Mucoepidermoid	1	0.16
Synovial Carcinoma	1	0.16
Squamous Papilloma	1	0.16

Abbreviation: n, number of patients.

Table 2 Clinical Profile of Patients with OSCC and Management

Characteristics	Total n=199	Percentage (%)
Age (years)		
Median (52 years), mean ± SD (51.6 ± 12.0)		
- 15–29	7	3.5
- 30–49	74	37.2
- 50–59	64	32.2
- 60–69	45	22.6
- ≥ **70**	9	4.5
Sex		
- Male	91	45.7
- Female	108	54.3
Stages of OSCC		
- Stage II	9	4.5
- Stage III	26	13.1
- Stage IV	75	37.7
- Unknown	89	44.7

(*Continued*)

Table 2 (Continued).

Characteristics	Total n=199	Percentage (%)
Site		
- Tongue	137	68.8
- Labial mucosa	3	1.5
- Gingiva	15	7.5
- Buccal mucosa	19	9.5
- Palate	13	6.5
- Floor of the mouth	6	3.0
- Lips	6	3.0
Cancer differentiation grades		
- Well differentiated	88	44.2
- Moderately differentiated	78	39.2
- Poorly differentiated	33	16.6
Type of Treatment		
- Surgery	4	2.27
- Incisional biopsy	51	28.98
- Chemo-radiotherapy	16	9.09
- Surgery and chemotherapy	43	24.43
- Surgery and chemo-radiotherapy	58	32.95

Abbreviations: OSCC, oral squamous cell carcinomas; n, number of patients; SD, standard deviation.

the oldest was 78 years old. No data were available for the under-15 years old age group. In terms of gender distribution, there were 91 men (45.7%) and 108 women (54.3%). With regards to cancer stage, the majority of OSCC cases were diagnosed at stage IV, comprising 75 cases (37.7%), while the least common stage was stage II, with only 9 cases (4.5%) suggesting that the majority of these cases were not diagnosed until later stages of the disease.

Figure 1 shows the clinical features of OSCC. OSCCs were predominantly located on the tongue, accounting for 137 cases (68.8%), whereas the lips showed the least occurrence at 6 cases (3%). Figure 2 illustrates the histological grades of OSCC tumor differentiation. The results of the present study showed that well-differentiated and moderately differentiated tumor grades were the most prevalent, constituting 44.2% and 39.2%, respectively. Concerning treatment modalities, surgery combined with chemo-radiotherapy was the most frequently employed approach (32.95%), whereas the least common approach was surgery only (2.27%).

Table 3 demonstrates the results of the analysis on the relationship between the tumors' histopathological grade of OSCC and age, sex, staging, and tumor site. A Chi-square test and the contingency correlation coefficient revealed no significant relationship between age and sex with the degree of differentiation of OSCC ($p=0.123$, $r=0.245$; $p=0.975$, $r=0.016$, respectively). Based on the age distribution, within the 15–29 age range, half of the cases (57.1%) exhibited a moderately differentiated pathology. Furthermore, in the 30–49 age range, 48.6% were moderately differentiated, followed by 43.2% well-differentiated cases. In the 50–59 age range, the majority (43.8%) were well-differentiated. For individuals aged 60–69, 51.1% showed well-differentiated pathologies, while in the age range above 70, 55.6% were moderately differentiated. This consistent trend across the five age categories reveals a higher prevalence of well-differentiated and moderately differentiated pathologies, with poorly differentiated cases being the least frequent. Based on gender, the trend was also consistent between males and females, with a higher prevalence of "well-differentiated" and "moderately differentiated" pathologies and the least being poorly differentiated.

When observing OSCC stages, well-differentiated characteristics are more dominant in stage II cancer, followed by stage III cancer which is mostly moderately differentiated. In contrast, stage IV cancer shows a higher prevalence of both

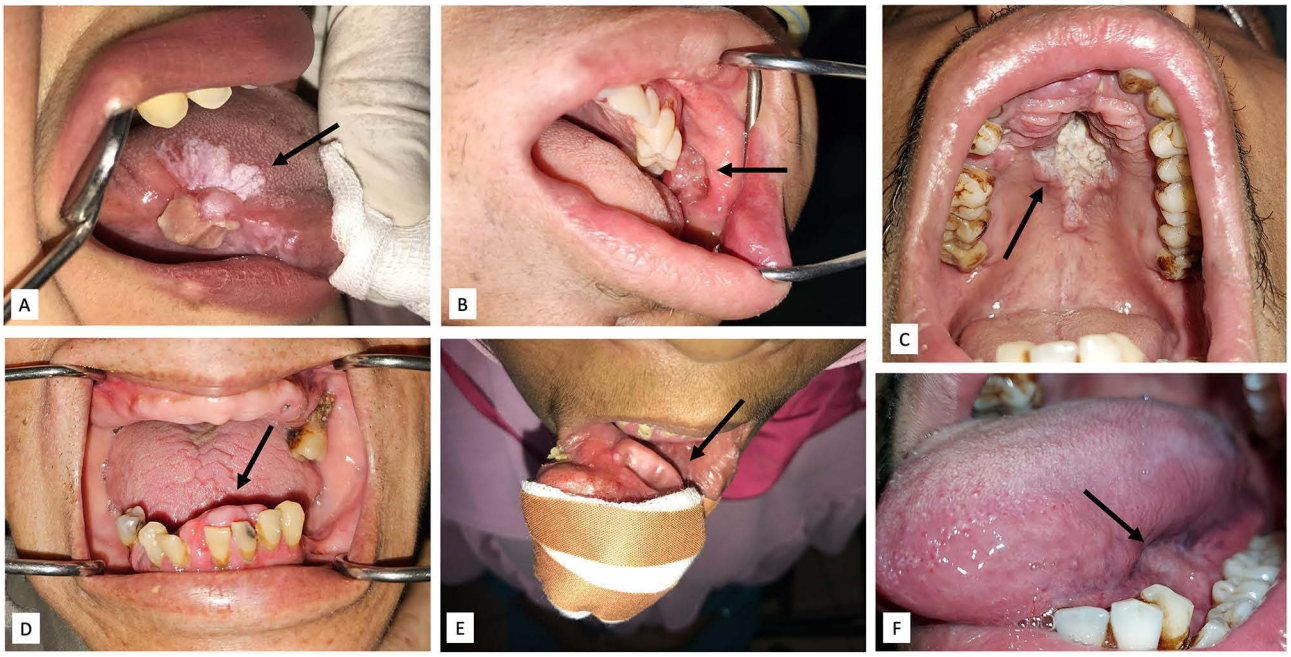

Figure 1 Clinical appearances of OSCC based on tumors site. (**A**) A mass on the lateral border of the tongue, accompanied by white plaques and ulcers covered with a yellowish-white pseudomembrane; (**B**) An exophytic mass with a granular, irregular surface on the upper posterior right buccal mucosa; (**C**) An exophytic lesion with a rough surface covered by a yellowish plaque located in the middle of the hard palate; (**D**) A lobulated mass with a smooth surface located on the anterior mandibular gingiva; (**E**) OSCC appears as a large mass on the lower lip; (**F**) An exophytic mass with a smooth surface, similar in color to the surrounding mucosa, located on the left side of the floor of the mouth.

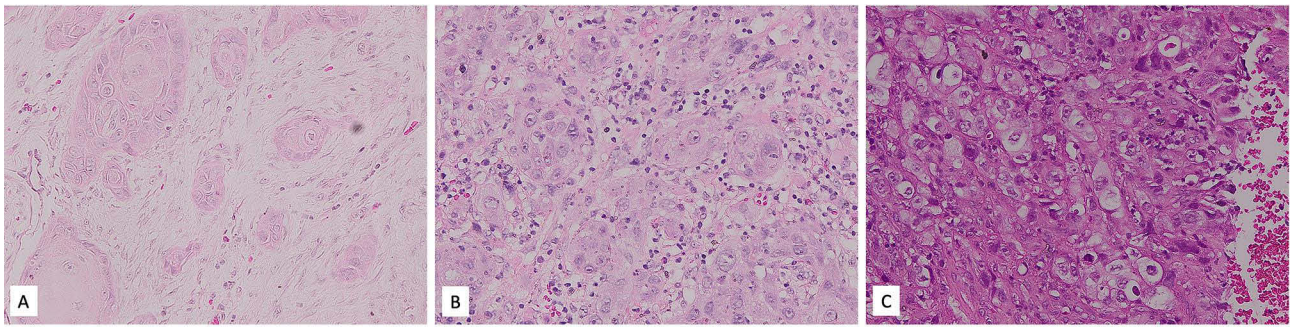

Figure 2 The histopathological features of different degrees of OSCC on the tongue. (**A**) Well-differentiated OSCC showing abundant keratin pearl formation. (**B**) Moderately differentiated OSCC with polymorphic nuclei, hyperchromatic and partly vesicular nuclei, and mitotic figures. Slight formation of keratin pearls is also observed. (**C**) Poorly differentiated OSCC displays a fibrocollagenous connective tissue stroma infiltrated with a fibrocollagenous connective tissue stroma infiltrated with numerous inflammatory cells, including lymphocytes and histiocytes, within the subepithelial layers. The tumor appears as a mass composed of large, round, oval, and polygonal cells that exhibit hyperplastic growth, condensation, and clustering. The cell nuclei are pleomorphic, hyperchromatic, and partly vesicular.

moderate and poor differentiation. A statistically significant association between tumor stage and OSCC differentiation grade was observed ($p<0.001$, $r=0.460$).

When analyzing the tumor sites, tongue cancer is predominantly found, exhibiting a higher prevalence of well and moderately differentiated phenotype. Additionally, gingiva tumors show a greater occurrence of well and poorly-differentiated phenotypes. Conversely, the lowest occurrences of well and poorly-differentiated phenotypes were in the palate, labial mucosa, and floor of the mouth. Moderately differentiated cases were more prevalent in these sites. For lip cancer, an equal distribution across well, moderately, and poorly differentiated cases was observed. Overall, our statistical analysis revealed no significant relationship between the tumor site and the degree of differentiation of OSCC ($p=0.303$, $r=0.256$).

Table 3 The Relationship Between the Degree of Differentiation of OSCC with Age, Gender, Cancer Staging, and Tumor Site

	Total n=165	The degree of differentiation			p-value	Coefficient r
		Well n (%)	Moderately n (%)	Poorly n (%)		
Age (years)						
15–29	7	2 (28.6)	4 (57.1)	1 (14.3)	0.123	0.245
30–49	74	32 (43.2)	36 (48.6)	6 (8.1)		
50–59	64	28 (43.8)	20 (31.3)	16 (25)		
60–69	45	23 (51.1)	13 (28.9)	9 (20)		
≥ 70	9	3 (33.3)	5 (55.6)	1 (11.1)		
Sex						
Male	91	41 (45.1)	35 (38.5)	15 (16.5)	0.975	0.016
Female	108	47 (43.5)	43 (39.8)	18 (16.7)		
Stages of OSCC						
Stage II	9	6 (66.7)	2 (22.2)	1 (11.1)	<0.001*	0.460
Stage III	26	10 (38.5)	15 (57.7)	1 (3.8)		
Stage IV	75	6 (8.0)	44 (58.7)	25 (33.3)		
Site						
Tongue	137	59 (43.1)	59 (43.1)	19 (13.9)	0.303	0.256
Labial mucosa	3	1 (33.3)	2 (66.7)	0 (0)		
Gingiva	15	7 (46.7)	2 (13.3)	6 (40)		
Buccal mucosa	19	8 (42.1)	6 (31.6)	5 (26.3)		
Palate	13	6 (46.2)	5 (38.5)	2 (15.4)		
Floor of the mouth	6	3 (50.0)	3 (50.0)	0 (0)		
Lips	6	4 (66.7)	1 (16.7)	1 (16.7)		

Notes: *p<0.05 was considered to be statistically significant.
Abbreviations: OSCC, oral squamous cell carcinomas; n, number of patients.

Discussion

Our study revealed no relationship between age and sex with the degree of OSCC differentiation, an observation aligning with that previously reported.[6,15–18] A previous study conducted in another region in Indonesia also showed no significant relationship between the distribution of histological features with age.[5] In our study, we adopted age grouping recommendations from the WHO. Troeltzsch et al categorized age into young (< 40 years), middle-aged (40–80 years), and very old (> 80 years),[16] whereas Tomo et al classified age into young adults (< 45 years), middle-aged (46–59 years), and older (>60 years).[17] On the other hand, Tandon et al delineated age categories as under 40 years, 40–60 years, and 60 years[15] while, Rikardsen et al divided age groups into 50 years, 51–60 years, 61–70 years, 71–80 years, and 81 years.[18] Despite differences in the distribution of age categories, our observation is consistent with the suggestion that age and the degree of OSCC differentiation are not correlated.

Our findings also revealed no significant association between gender and OSCC tumor differentiation, consistent with work done by Pires et al.[10] The study reported that males were predominantly affected by moderately and poorly differentiated tumors, while females were predominantly presented with moderately and well-differentiated tumors. Additionally, our study also aligns with a previous study by Wolfer et al, which also found no significant correlation between gender and tumor differentiation status.[19] Other studies conducted in two regions of Indonesia have similarly shown no significant relationship between the distribution of histological features and gender.[4,5] A lack of significant correlation between OSCC tumor proliferation and mitotic rates by gender has also been reported,[20,21] this could likely explain why OSCC tumor differentiation status is not related to gender status.

In the clinical and histopathological analysis, we found that well-differentiated OSCC tumors were predominantly associated with stage II cancer, moderately differentiated tumors with stage III, and stage IV exhibited a prevalence of both moderately and poorly differentiated tumors. Our statistical analysis revealed a significant relationship between the stage of the disease and the degree of differentiation of OSCC. These findings are in line with previous reports.[22,23] It has been suggested that immunological factors may play a role in OSCC tumor differentiation, as tumors produce factors that inhibit macrophage migration, suppressing and slowing down the immune system.[24,25] For instance, the induction of immunosuppressive cytokines, such as TGF-β, could inhibit the differentiation of lymphocyte cells involved in the mechanism of tumor destruction. This, in turn, reduces the likelihood of malignant cells being recognized by lymphocytes.[26,27]

The present study also revealed that the OSCC tumors on the tongue, gingiva, and buccal mucosa were more frequently associated with well and poorly-differentiated statuses, while tumors on the labial mucosa, palate, and floor of the mouth tend to be more moderately differentiated. However, we observed no significant relationship between the tumor location and the degree of OSCC differentiation. This study supports findings from other regions in Indonesia, which also show that there is no significant relationship between the distribution of histological features and anatomical location.[5] In contrast, several studies have reported that the relationship between the tumor location and its anatomical site is important. A prior study reported a link between the location of the dominant tumor on the lips and tongue with the degree of OSCC differentiation.[22] It has been considered the significance of the tumor location as an important prognostic indicator. Tumors located on the lips were generally associated with a histopathological picture of well-differentiated tumors, in contrast to poorly differentiated tumor locations on the tongue and floor of the mouth. This association was attributed to the higher occurrence of metastases in these locations and is linked to the degree of differentiation, indicating the presence of keratinization, cell proliferation, and mitosis. These factors are considered as prognostic indicators, providing insights into the potential course and outcome of the disease. Indeed, tongue OSSC has a poor prognosis and a high mortality rate if metastases have occurred.[13,28]

Our study has certain limitations. Firstly, this was a retrospective study that is dependent on accurate documentation. We found the presence of incomplete and duplicated medical records, making them ineligible for inclusion in this study. Additionally, the lack of data on risk factors and survival rates among OSCC patients leaves the prognosis of OSCC unknown. Prospective studies with larger numbers of patients and a more precise recording of the risk factors are required to eliminate these limitations and investigate this further.

Conclusion

This study found that OSCC is the most common type of oral cancer, with the tongue being the most frequently affected site. We identified a significant relationship between the degree of OSCC differentiation and the cancer stage but found no associations with age, sex, or tumor site. These findings have important prognostic implications for clinical practice, suggesting that the stage of OSCC could serve as a useful indicator of differentiation, aiding in treatment planning and predicting patient outcomes. This study highlights the need for further research to better understand the risk factors and survival rates associated with OSCC, particularly given the current lack of comprehensive national data. Enhanced epidemiological data and continued research are crucial for developing more effective prevention and treatment strategies for OSCC.

Ethics Approval

This study was approved by the Research Ethics Committee of Universitas Padjadjaran No. 942/UN6.KEP/EC/2021. Patient consent to review their medical records was not required by the Research Ethics Committee of Universitas Padjadjaran. The waiver was granted because this study involves a retrospective analysis of anonymized data. We ensured patient data confidentiality and complied with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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