

Comprehensive clinicopathological evaluation of malignant localized gingival enlargements in the Thai population

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Abstract. Malignant localized gingival enlargements (LGEs) are rare and often clinically mimic reactive or benign lesions, creating diagnostic challenges. The present study aimed to evaluate the prevalence and origins of malignant LGEs, assess clinicopathological diagnostic concordance, and identify the distinction of clinical features in a Thai population. A total of 96 malignant LGEs diagnosed over a 40-year period were retrospectively analyzed. Demographic data, clinical characteristics, and clinical and pathological diagnoses were collected. Malignant LGEs were categorized by origin, and diagnostic concordance was evaluated. Clinical features were compared between epithelial and non-epithelial malignant LGEs, and a decision tree model was constructed to identify predictive factors. Epithelial (60.4%) and non-epithelial (39.6%) malignant LGEs indicated a comparable distribution. Non-epithelial lesions demonstrated substantially lower diagnostic concordance and were frequently misdiagnosed as reactive or benign conditions. Significant differences between groups were observed in age ($P=0.004$), surface texture ($P=0.003$), color ($P=0.014$), and location ($P=0.044$). Decision tree analysis identified age ($P=0.018$) and surface texture ($P=0.03$) as key predictors of non-epithelial malignant LGEs. Non-epithelial malignant LGEs are particularly prone to clinical misdiagnosis. Lesions occurring in younger patients, notably those with smooth surface texture, should

raise suspicion for non-epithelial malignancy and prompt timely biopsy and referral. These findings may aid clinicians in improving early recognition of malignant LGEs.

Introduction

Localized gingival enlargement (LGE) is a clinical presentation that often poses a diagnostic dilemma in dental and clinical practice (1,2). In a recent study, the prevalence and clinical features of localized gingival enlargements (LGEs) were analyzed in Thai patients over a 20-year period. LGEs were categorized by nature and concordance between clinical and pathological diagnoses was assessed. Using key clinical factor including size, consistency, color, duration and patient age, a decision tree model was developed to help clinicians distinguish malignant from non-malignant LGEs (3). Among all groups of LGEs, malignant LGEs were the most critical due to their life-threatening potential. However, within the malignant LGE group, differences in patient demographics and clinical characteristics were observed. This observation is likely due to the wide spectrum of neoplastic origins of malignant LGEs, which include epithelial malignancies such as squamous cell carcinoma (SCC), verrucous carcinoma, hematologic malignancies such as lymphoma and plasmacytoma, salivary gland malignancies such as mucoepidermoid carcinoma, adenoid cystic carcinoma and even metastatic cancers (4,5).

With regard to a previous study conducted by our group, lesion size, consistency, color, duration and patient age were critical factors for distinguishing malignant from non-malignant LGEs. The proposed diagnostic guide may assist clinicians in assessing malignancy risk in LGEs (3). However, certain malignant LGEs remain challenging to diagnose due to their rarity and clinical resemblance to benign lesions (6-8). Further studies with larger sample sizes may improve the understanding of these conditions.

To the best of the authors' knowledge, the clinicopathological features of malignant LGEs in the Thai population has

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not been specifically analyzed. Therefore, the present study aimed to provide comprehensive clinical data to improve the clinical diagnostic accuracy of malignant LGEs by investigating their prevalence, origins and clinical information in a large sample of Thai patients. In addition, the diagnostic concordance between different origins of malignant LGEs and examined comparable clinical data among these cases. The present study focused exclusively on malignant LGEs over a 40-year period, analyzing differences between epithelial and non-epithelial origins, emphasizing the frequent misdiagnosis of non-epithelial malignant lesions, and identifying potential key clinical predictors.

Materials and methods

Data collection. The present retrospective single-center study was approved by the Faculty of Dentistry/Faculty of Pharmacy, Mahidol University, Institutional Review Board (approval no. COA.No.MU-DT/PY-IRB 2022/047.2209). All procedures performed in the present study were in accordance with the Declaration of Helsinki. Histopathological reports of LGEs were retrospectively retrieved from the archives of the Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, Mahidol University, between 1982 and 2021. All archived cases were systematically reviewed. To minimize temporal heterogeneity in the diagnostic criteria, pathological diagnoses were reassessed and where necessary, updated according to the 2022 World Health Organization classification (9). Only cases with a confirmed malignant diagnosis and documented clinical presentation as LGE were selected. Lesions originating from bony tissue or located on the alveolar mucosa, edentulous alveolar ridges, or other masticatory mucosa such as the hard palate or maxillary tuberosity were excluded. Thus, only lesions associated with the gingiva surrounding natural teeth were included. Patient demographic data, such as age and sex, clinical information, such as duration, location, color, consistency, surface texture and size, clinical diagnoses, including either a sole working diagnosis or the first-listed diagnosis in differential diagnoses and final pathological diagnoses were gathered from the pathological request forms and patients' medical records. Eligible cases were consecutively retrieved from the departmental archives during the study period. Case selection was based solely on histopathologic diagnosis and documented clinical presentation as LGE, without additional sampling or selective inclusion, thereby minimizing selection bias within the institution. Case selection and data extraction were performed using predefined criteria to ensure consistency across the study period.

Data analysis. For descriptive analysis, malignant LGEs were categorized into five origins: Epithelial, salivary gland, hematological, metastatic and others. The epithelial origin category refers specifically to malignant tumors arising from the surface squamous epithelium. All cases, except for metastatic tumors, originated primarily in the oral cavity. Diagnostic concordance between clinical and pathological diagnoses across different malignant LGE origins was assessed based on the sole working clinical diagnosis recorded at initial evaluation or the first-listed diagnosis in differential diagnoses. The results were presented as percentage concordance rates. To

facilitate concordance analysis, both clinical and pathological diagnoses were reclassified into distinct categories representing the nature of LGE diseases, including reactive lesions, benign tumors, infections and inflammation, malignant lesions and others. Diagnostic concordance was defined as a match between clinical and pathological diagnoses regarding their respective categories. Given the inherently limited sample size of this cohort, the present study elected to retain this case in all other analyses where complete data were available, in order to preserve statistical power and maximize data utilization. This decision resulted in differing denominators between the diagnostic concordance analysis and the remaining analyses. Comparison of patient demographic data and clinical information between epithelial and non-epithelial malignant LGEs was performed using the χ^2 test. The odds ratio was calculated using simple logistic regression analysis to identify an independent risk factor associated with non-epithelial malignant LGEs. A decision tree based on clinical characteristics for distinguishing between epithelial and non-epithelial malignant LGEs was constructed using the conditional inference tree methodology (10). The missing data were handled using pairwise exclusion. For each statistical analysis, cases with missing values for the variable under investigation were excluded only from that specific analysis, allowing all available data to be utilized without unnecessary listwise deletion. All statistical analyses were performed using R software (version 4.3.1). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Malignant LGEs based on their origins. Out of 19,505 total biopsy cases reviewed, 96 cases (0.5%) were identified as malignant LGEs presenting specifically in dentate areas. Among these, epithelial tumors were the most common (60.4%), followed by hematological tumors (14.6%), salivary gland tumors (10.4%), metastatic tumors (8.3%) and others (6.3%; Fig. 1A). The specific diagnoses of these malignant cases, categorized and color-coded by type, are shown in Fig. 1B. SCC was the most prevalent, comprising 55.2% of malignant LGEs, followed by non-Hodgkin lymphoma (13.5%) and mucoepidermoid carcinoma (7.3%).

Diagnostic concordances. Of the 96 malignant LGE cases, one case was excluded from the concordance analysis due to the absence of a recorded clinical or differential diagnosis, leaving 95 cases for evaluation (Table I). Concordance was determined based on whether the histopathological diagnosis matched either the sole working diagnosis or the first-listed diagnosis listed in the differential diagnoses. Concordance rates were higher in epithelial malignant LGEs (72.4%) than in non-epithelial malignancies (47.4%). Salivary gland malignancies exhibited the lowest concordance rate (20%), followed by metastatic tumors (25%).

Analysis of non-concordance malignant LGE cases. A total of 35 cases of malignant LGE were clinically misdiagnosed. When categorized by origin, over half of these misdiagnosed cases were non-epithelial malignant LGEs, accounting for 57.1% (Table II). Overall, most misdiagnoses were initially

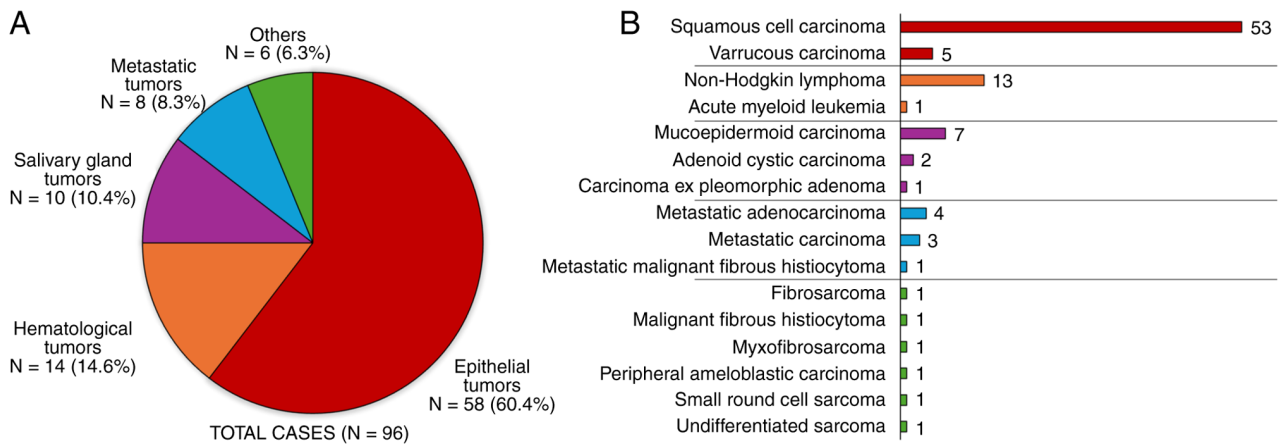


Figure 1. Distribution and diagnoses of malignant LGE Cases (n=96). (A) Pie chart illustrating the distribution of malignant LGE cases by tumor type. (B) Bar graph showing specific diagnoses, categorized and color-coded by tumor type: epithelial tumors (red), hematological malignancies (orange), salivary gland tumors (purple), metastatic tumors (blue), and other tumors (green). Data between 2002 and 2021 were previously published (3). The current figure has been updated to include newly reviewed cases between 1982 and 2001, while retaining the original diagnoses and case numbers between 2002 and 2021. LGE, localized gingival enlargement.

Table I. Diagnostic concordances among different types of malignant LGE cases.

Type of malignant LGE	No. of cases (n=95 ^a)	Concordance (%)
Epithelial tumors	57	42/57 (72.4%)
Non-epithelial tumors	38	18/38 (47.4%)
Hematological tumors	14	10/14 (71.4%)
Salivary gland tumors	10	2/10 (20.0%)
Metastatic tumors	8	2/8 (25.0%)
Others	6	4/6 (66.7%)

^aOut of 96 cases, one case was excluded due to the absence of a recorded differential diagnosis, leaving a total of 95 cases. LGE, localized gingival enlargement.

recognized as reactive lesions, notably in cases of hematological and metastatic malignancies. Furthermore, salivary gland malignancies were often misidentified as benign tumors.

Demographic data and clinical information. Age, site, surface texture and color are marked demographic and clinical factors that differ between epithelial and non-epithelial malignant LGEs (Table III). Epithelial malignancies were predominantly observed in patients >40 years old (mean=58.7 years), while non-epithelial cases included younger patients (mean=47.5 years; P=0.004). Epithelial malignant LGEs were more commonly located on the mandibular gingiva, while non-epithelial cases tended to occur on the maxillary gingiva (P=0.044). With regard to surface texture, the majority of epithelial cases exhibited a rough surface, whereas non-epithelial cases exhibited an equal mix of smooth and rough textures (P=0.003). For color, non-epithelial malignancies were most often red, followed by pink and other colors, while epithelial malignancies indicated an equal distribution of red and white (P=0.014). No significant differences were noted between the

two groups regarding sex, duration, consistency, or size. The two types indicated similar male-to-female ratios and typically presented with a duration of <3 months.

Simple logistic regression analysis and decision tree model. All clinical factors with significant differences in the χ^2 test were analyzed using simple logistic regression, revealing several significant predictors of non-epithelial malignant LGEs. Lesions with a smooth surface texture were strongly associated with non-epithelial malignant LGEs [Odds ratio (OR): 13.13, 95% confidence interval (CI): 2.27-75.86] followed by red-colored lesions (OR: 6.00, 95% CI: 1.12-32.28). Younger patients, notably those <40 years, indicated higher odds (OR: 4.90, 95% CI: 1.55-15.43), as did lesions located at the maxilla (OR: 2.36, 95% CI: 1.01-5.48).

A decision tree for differentiating epithelial and non-epithelial malignant LGEs was generated using a recursive partitioning process (Fig. 2). The analysis identified surface texture as the primary discriminating factor, followed by age. These findings confirm the strong predictive potential of this approach for distinguishing between epithelial and non-epithelial malignant LGEs. A non-epithelial origin was associated with LGEs that had a smooth surface (77.8%) or, if rough, occurred in patients younger than 40 years (66.8%). The matrix performance of the decision tree analysis demonstrated a sensitivity of 87.93%, specificity of 47.37%, precision of 71.83%, accuracy of 71.88% and F1 score of 79.07%.

Discussion

In the present study, a clinicopathological analysis of 96 malignant LGEs was conducted over a 40-year period at the Faculty of Dentistry, Mahidol University. Of the total biopsied specimens, malignant LGEs constituted 0.5% of cases, contrasting with the prior reported prevalence of 0.0006 to 0.005% (4,11). As our institution serves as a university-based referral center, the cases were obtained from biopsy records submitted by both internal faculty members and external dental clinics. Therefore, the potential impact of referral bias is considered

Table II. Analysis of non-concordant malignant LGE cases based on the nature of the disease.

Type of malignant LGEs	Non-concordance cases (n=35)	Nature			
		Reactive	Inflammation	Benign	Others
Epithelial tumors	15 (42.9%)	7 (46.7%)	4 (26.7%)	2 (13.3%)	2 (13.3%)
Non-epithelial tumors	20 (57.1%)	9 (45.0%)	3 (15.0%)	7 (35.0%)	2 (10.0%)
Hematological tumors	4 (11.4%)	3 (75.0%)	-	1 (25.0%)	-
Salivary gland tumors	8 (22.9%)	-	3 (37.5%)	5 (62.5%)	-
Metastatic tumors	6 (17.1%)	5 (83.3%)	-	1 (16.7%)	-
Others	2 (05.7%)	1 (50.0%)	-	-	2 (50.0%)

LGE, localized gingival enlargement.

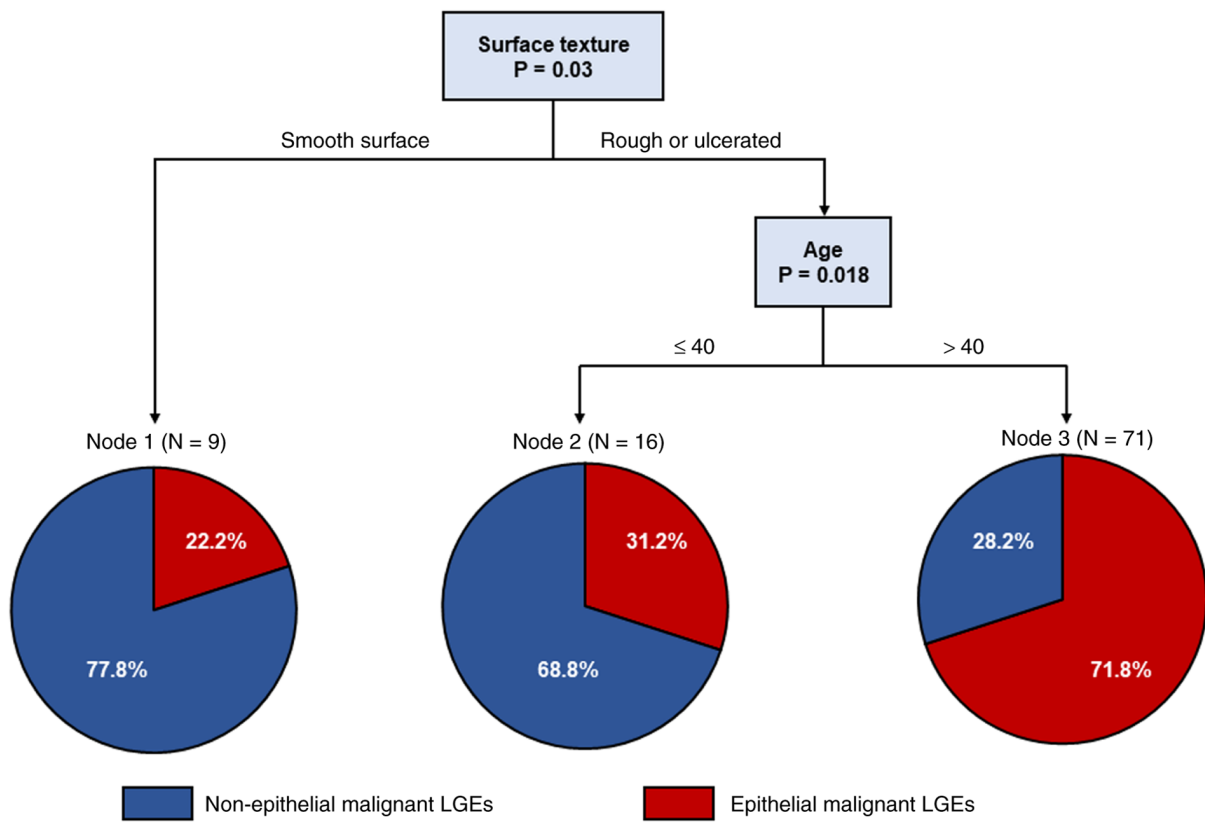


Figure 2. Decision tree model for differentiating epithelial and non-epithelial malignant LGEs. The model identifies key clinical predictors; age (in years) and surface texture, for distinguishing between epithelial and non-epithelial malignant LGEs. LGE, localized gingival enlargement.

minimal. Biopsy submissions included lesions with clinically benign appearances as well as those considered clinically suspicious, atypical, or persistent. Consequently, the spectrum of submitted cases is unlikely to have substantially influenced the observed proportion of malignant lesions. When focusing on gingival lesions, Li *et al* (12) reported a higher prevalence of 33.17% for malignant neoplasms in non-dental plaque gingival diseases among the Chinese population, while other studies have shown prevalence rates of gingival malignancies ranging from 3.69-8% (13-16). These studies included broader populations and did not focus exclusively on LGEs, making direct comparisons difficult. Such variations in study populations lead to inconsistent results and hinder direct comparisons.

In addition, most research on LGEs has focused on reactive lesions, primarily fibroma, pyogenic granuloma, peripheral ossifying fibroma and peripheral giant cell lesion (17-20). This underscores the limited knowledge of malignant LGEs. To the best of the authors' knowledge, this is the first study specifically focusing on this topic.

Of malignant LGEs, ~60% are of epithelial origin, similar to the 46% reported by Tamiolakis *et al* (4). This underscores the high proportion of malignant epithelial tumors, such as SCC, occurring at the gingival site. Non-epithelial malignant LGEs comprised 39.6% of cases, with hematological tumors (14.6%) being the most common, followed by salivary gland tumors (10.4%), metastatic tumors (8.3%) and others (6.3%).

Table III. Patient demographics and clinical data for epithelial and non-epithelial malignant LGE cases.

Clinical variables	Epithelial malignant LGE (n=58)	Non-epithelial malignant LGE (n=38)	P-value
Sex			
Male	26 (44.8%)	21 (55.3%)	0.317
Female	32 (55.2%)	17 (44.8%)	
Age (years)			
Mean (SD)	58.7 (15.1)	47.5 (16.0)	0.004 ^b
≤ 40	5 (8.6%)	12 (31.6%)	
>40	51(87.9%)	25 (65.8%)	
N/A	2 (03.4%)	1 (02.6%)	
Duration			
≤3 months	40 (69.0%)	27 (71.1%)	0.614
>3 months	9 (15.5%)	8 (21.1%)	
N/A	9 (15.5%)	3 (07.9%)	
Site			
Maxilla	24 (41.4%)	24 (63.2%)	0.044 ^a
Mandible	33 (57.0%)	13 (34.2%)	
N/A	1 (01.7%)	1 (02.6%)	
Surface texture			
Smooth	3 (05.2%)	7 (18.4%)	0.003 ^b
Rough	30 (51.7%)	8 (21.1%)	
Ulcerated	1 (01.7%)	-	
N/A	24 (41%)	23 (60.5%)	
Consistency			
Firm	13 (22.4%)	15 (39.5%)	0.151
Soft	25 (43.1%)	16 (42.1%)	
Others	-	2 (05.3%)	
N/A	20 (34.5%)	5 (13.2%)	
Color			
Pink	6 (10.3%)	6 (15.8%)	0.014 ^a
Red	13 (22.4%)	13 (34.2%)	
White	12 (21.0%)	2 (05.3%)	
Others	-	4 (10.5%)	
N/A	27 (46.6%)	13 (34.2%)	
Size			
≤2 cm	17 (29.3%)	18 (47.4%)	0.233
>2 cm	19 (32.8%)	11 (29.0%)	
N/A	22 (38.0%)	9 (23.7%)	

N/A=Missing data, ^aP≤0.05, ^bP≤0.01, P-value was calculated without N/A data. LGE, localized gingival enlargement.

Although Tamiolakis *et al* (4) did not identify any salivary gland malignant LGEs, they noted higher frequencies of hematological tumors (30.8%) and metastatic tumors (23.1%) in their study. Notably, these variations in prevalence may be influenced by ethno-geographical factors.

To further analyze the data, diagnostic concordance rates were evaluated between origins of malignant LGEs. The

findings revealed that non-epithelial malignant LGEs exhibited a lower concordance rate than epithelial LGEs. The majority of the diagnostic discordances were initially identified as reactive lesions, notably in cases of hematological and metastatic tumors. These findings align with prior reports describing oral metastatic malignancies and lymphoma mimicking reactive lesions (21-23). Notably, salivary gland malignancies presented the lowest concordance rate among non-epithelial malignant LGEs, with most cases being misdiagnosed as benign tumors. This may be attributed to their typical presentation as slow-growing masses (24).

The analysis indicated that surface texture, color, patient age and lesion location were key factors in distinguishing between epithelial and non-epithelial malignant LGEs, with surface texture being the strongest factor, followed by color, age and location. Non-epithelial malignant LGEs are 13 times more likely to have a smooth surface. These findings align with the decision tree of Mortazavi *et al* (25), which suggests that exophytic lesions with rough surfaces are more likely to be of epithelial origin, while those with smooth surfaces are indicative of non-epithelial lesions, including mesenchymal and salivary gland tumors. Therefore, surface texture may serve as a useful indicator in distinguishing between these two groups.

With regard to color, white coloration is frequently observed in epithelial malignant LGEs, often attributed to abnormal keratin formation on the surface, notably in SCC and verrucous carcinoma. In contrast to this observation, non-epithelial malignancies exhibited a wider range of colors other than white. Salivary gland malignancies may appear pink, bluish to red, or normal-colored nodular mass (25), while oral lymphomas typically present as normal, red or purple (26). The present study demonstrated that non-epithelial malignant LGEs are six times more likely to appear red. These color variations may be associated with the location of malignant cells or the vascularity of the tumors, influencing lesion appearance. It is interesting to note that while color appears to indicate general malignancy, it does not differentiate between epithelial and non-epithelial malignancies in diagnostic tree analysis. This finding is also consistent with the previous study conducted by our group, which indicated that color could distinguish benign from malignant LGEs but only with low to moderate malignancy risk (3).

It was shown that non-epithelial malignant LGEs are 4.9 times more likely to develop in patients <40 years old. Among these cases, sarcomas were the most prevalent, consistent with findings by Santos-Leite *et al* (27) who reported that gingival sarcomas commonly occur in the fourth decade of life. This also aligns with a prior study indicating that oral SCC, the most common epithelial cancer, typically occurs in older patients (>40 years) (28). The present study revealed that non-epithelial malignant LGEs are 2.3 times more likely to occur on the maxillary gingiva, which was consistent with previous reports on gingival malignancies. Non-Hodgkin lymphomas have demonstrated a higher prevalence in the maxillary gingiva, with twice the number of cases reported compared with the mandible (29). Similarly, oral metastases involving the gingiva are more commonly found in the maxilla than in the mandible (30). Conversely, the majority of gingival SCCs occur in the mandible (31). These findings highlight the

diagnostic challenge of non-epithelial malignant LGEs, which often mimic benign or reactive lesions and may lead to delayed diagnosis. Early recognition is critical, as certain lesions, such as sarcomas, require prompt and more aggressive management. The identified clinical features, particularly younger patient age and smooth surface texture, may help clinicians raise suspicion for malignancy and support earlier biopsy and referral, thereby improving diagnostic accuracy and patient management.

Given the diagnostic challenges associated with malignant LGEs, the present clinicopathological analysis provided clinically relevant insights; however, several limitations warrant consideration. This was a single-center study conducted within a defined population, which may limit generalizability to other geographic or ethnic groups. Future multicenter studies would help further evaluate the generalizability of these results. In addition, although the extended study period is an advantage, it also introduces potential heterogeneity in biopsy indications, clinical documentation and diagnostic standards. Clinical impressions were recorded during routine dental care by different clinicians over nearly four decades and may therefore reflect variability in individual judgment and documentation practices. Furthermore, the evolution of diagnostic frameworks, including updates in World Health Organization tumor classifications and the increasing availability of immunohistochemical techniques may have influenced case interpretation, notably in earlier years. To minimize temporal inconsistencies, all eligible cases were reassessed and confirmed according to current diagnostic standards at the time of the present study. A considerable proportion of clinical variables were unavailable, particularly in earlier cases, reflecting the retrospective nature of the present study and historical documentation practices. To avoid overfitting and loss of statistical power in this relatively limited cohort, univariable logistic regression analyses were performed to explore the association between each clinical factor and the outcome independently. Inclusion of all variables in a multivariable logistic regression model would have markedly reduced the effective sample size and potentially introduced instability and bias into the estimates.

To further explore potential confounding and interactions among variables (including age, location and clinical appearance), decision-tree analysis was also conducted. This approach allows simultaneous evaluation of multiple predictors, accounts for interactions between variables, and identifies hierarchical relationships that may not be captured in standard regression modeling. Accordingly, while the logistic regression analyses were exploratory and unadjusted, the decision-tree model provided a multivariable framework incorporating interrelated factors in outcome prediction. Despite these limitations, the available data allowed identification of clinically meaningful predictors. Nevertheless, the findings should be interpreted with caution and future studies with more complete and standardized data collection, ideally using prospective multicenter designs, are needed to validate and expand upon these results.

Furthermore, diagnostic concordance was defined based on agreement between clinical and pathological diagnoses according to reclassified 'nature of disease' categories. While this pragmatic approach enabled standardized comparison across a long retrospective period with variable documentation, it may oversimplify clinical diagnostic accuracy. Specifically,

it emphasizes recognition of biological behavior, such as malignant compared with non-malignant rather than exact entity level agreement. This approach may also influence concordance rates, notably for salivary gland and hematological malignancies that can clinically mimic reactive lesions. These findings should therefore be interpreted within this context. In addition, the use of simple logistic regression limits adjustment for confounding among interrelated variables such as age, site and clinical features. Given the limited sample size and missing data, multivariable modeling was not feasible. Although decision tree analysis was used to explore variable interactions, residual confounding cannot be excluded.

Among malignant LGEs, unsurprisingly, SCC was the most prevalent. However, nearly 40% of these malignancies originated from non-epithelial sources, which exhibited a notably low diagnostic concordance rate. Non-epithelial malignancies are more likely to have a smooth surface, appear red, occur more frequently in younger patients, and are predominantly located in the maxilla. By considering these clinical parameters, clinicians may be able to differentiate between epithelial and non-epithelial malignant LGEs more effectively, potentially leading to more accurate diagnoses and improved patient outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DR was responsible for the conceptualization, methodology, writing the original draft and project administration. PS was responsible for conceptualization, visualization, writing, reviewing and editing. NK was responsible for writing, reviewing, editing and supervision. TA was responsible for methodology, formal analysis, writing, reviewing and editing. NS was responsible for software, formal analysis and validation. VN, WA, SH and SA were responsible for formal analysis, investigation and visualization. PL was responsible for conceptualization, supervision, validation, writing, reviewing and editing. DR and PL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present retrospective study was conducted in accordance with the Declaration of Helsinki ethical standards and approved by the Faculty of Dentistry/Faculty of Pharmacy, Mahidol University, Institutional Review Board (COA.

No.MU-DT/PY-IRB 2022/047.2209). For this type of study, patient informed consent was waived by the Institutional Review Board due to its retrospective nature.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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