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Original Article

Developing a Fused AI Model That Integrates 3D Radiomic Data From CBCT With Whole-Slide Images of Oral Biopsies

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ABSTRACT

Background: Oral squamous cell carcinoma grading remains clinically important for prognostic stratification and treatment planning, but conventional diagnostic workflows often evaluate radiological and histopathological data separately. Objective: To develop and evaluate a fused artificial intelligence model integrating three-dimensional CBCT radiomic features with whole-slide image–derived computational pathology features for improving OSCC grading accuracy. Methods: This cross-sectional diagnostic model-development study included 36 patients with histopathologically confirmed OSCC who had complete pre-treatment CBCT imaging and analyzable digitized biopsy slides. Radiomic features were extracted from segmented CBCT tumor volumes, while computational pathology features were derived from whole-slide hematoxylin and eosin images. Radiomics-only, whole-slide image–only, and fused feature-level machine learning models were evaluated using grading accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve. Results: The CBCT radiomics–only model achieved 69.4% accuracy and an AUC of 0.74, while the whole-slide image model achieved 77.8% accuracy and an AUC of 0.81. The fused AI model demonstrated the highest performance, with 86.1% accuracy and an AUC of 0.89. Fusion significantly improved accuracy compared with CBCT radiomics alone ($p = 0.012$) and whole-slide imaging alone ($p = 0.031$). Conclusion: Multimodal fusion of CBCT radiomics and whole-slide image analysis improved OSCC grading performance and may support more objective diagnostic decision-making. Keywords: Artificial Intelligence; Cone-Beam Computed Tomography; Oral Squamous Cell Carcinoma; Computational Pathology; Radiomics; Whole-Slide Imaging.

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Ethical Approval: Dow International Dental College, Karachi, Pakistan**. Informed Consent**: Written informed consent was obtained from all participants; **Conflict of Interest**: The authors declare no conflict of interest; **Funding**: No external funding; **Data Availability**: Available from the corresponding author on reasonable request; **Acknowledgments**: N/A.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) remains a major malignancy of the head and neck region and continues to impose substantial diagnostic, functional, and survival-related burdens. Prognosis and treatment planning are strongly influenced by histopathological grade, because tumor differentiation reflects biological aggressiveness, invasive potential, and expected clinical behavior. In routine practice, grading is primarily determined through microscopic examination of biopsy specimens, while radiological imaging is interpreted separately to assess tumor extent, cortical involvement, and anatomical relationships. Although this conventional pathway is clinically established, it may underuse complementary information distributed across radiological and histopathological domains, particularly in borderline cases where inter-observer variability and subjective interpretation can affect diagnostic consistency (1).

Cone-beam computed tomography (CBCT) is widely used in oral and maxillofacial diagnostics because it provides high-resolution three-dimensional visualization of osseous structures and local tumor-related changes with relatively accessible imaging infrastructure. In OSCC, CBCT can contribute information regarding tumor extension, cortical disruption, and invasion patterns, but conventional interpretation remains largely qualitative and dependent on observer expertise (2,3). Radiomics addresses this limitation by converting imaging data into quantitative descriptors of tumor shape, intensity, spatial heterogeneity, and textural complexity, thereby enabling extraction of patterns that may not be visually apparent during routine assessment (4). Three-dimensional CBCT radiomics may therefore provide biologically meaningful macro-scale information related to tumor aggressiveness, although its discriminatory ability may remain limited when used in isolation because CBCT does not directly capture cellular differentiation.

In parallel, whole-slide imaging has transformed histopathology by enabling high-resolution digitization of hematoxylin and eosin–stained biopsy specimens and supporting computational analysis of tissue architecture, cellular density, nuclear morphology, stromal organization, and textural variation (5,6). Machine learning and deep learning approaches applied to digital pathology have shown promise in tumor detection, grading, and outcome prediction across several cancers, including oral malignancies. However, histopathological images primarily represent microscopic tumor characteristics within the sampled biopsy region and may not fully reflect the volumetric growth pattern, anatomical invasion, and spatial heterogeneity visible on imaging (7). Thus, radiology and pathology represent complementary but traditionally separated perspectives of the same disease process.

Recent advances in multimodal artificial intelligence suggest that integrating heterogeneous diagnostic inputs can improve classification performance by capturing relationships across biological scales. In oncological settings, fused radiology–pathology models have demonstrated potential to enhance diagnostic and prognostic prediction compared with single-modality models (8–10). For OSCC grading, this concept is particularly relevant because tumor grade is influenced by both microscopic cellular features and macroscopic structural behavior. A fused model combining CBCT-derived radiomic features with whole-slide image–derived computational pathology features may therefore provide a more complete representation of tumor biology than either modality alone.

Despite this rationale, evidence remains limited regarding the fusion of three-dimensional CBCT radiomics and whole-slide histopathological image analysis for OSCC grading. Most available studies evaluate radiological or histopathological data independently, and relatively few have tested whether integrated feature-level modelling can improve clinically meaningful grading performance in oral cancer (11,12). This gap is important because CBCT is commonly available in dental and maxillofacial settings, making it a practical imaging source for translational AI workflows if its quantitative features can be combined with digital pathology in a reliable and reproducible manner. Therefore, the present study was conducted to develop and evaluate a fused artificial intelligence model integrating CBCT radiomic features with computational features extracted from whole-slide oral biopsy images. The primary objective was to determine whether multimodal feature fusion improves OSCC grading accuracy compared with CBCT radiomics–only and whole-slide image–only models.

MATERIALS AND METHODS

This cross-sectional diagnostic model-development study was conducted over four months in Lahore among patients with histopathologically confirmed oral squamous cell carcinoma. The study followed a multimodal analytical framework in which radiological data from pre-treatment cone-beam computed tomography and histopathological data from digitized oral biopsy specimens were analyzed separately and then integrated into a fused artificial intelligence model. The study population corresponded to a PICO structure in which the population comprised adult patients with confirmed OSCC, the index modelling approach was fused CBCT radiomics and whole-slide image analysis, the comparator

approaches were single-modality CBCT radiomics–only and whole-slide image–only models, and the primary outcome was agreement between AI-predicted grade and conventional histopathological reference grading.

Patients were selected from tertiary-care dental and medical centers where CBCT imaging and oral biopsy were performed as part of routine diagnostic work-up. Eligible participants were adults with newly diagnosed, untreated OSCC who had complete pre-treatment CBCT imaging, available hematoxylin and eosin–stained biopsy material suitable for whole-slide digitization, and complete clinical and histopathological records. Patients were excluded if they had recurrent disease, previous head and neck malignancy, prior radiotherapy or chemotherapy before imaging or biopsy, inadequate CBCT image quality, extensive imaging artifacts, incomplete tumor visualization, insufficient biopsy tissue, poor slide quality, or whole-slide artifacts that interfered with computational feature extraction. These criteria were applied to reduce measurement bias and minimize heterogeneity arising from previous treatment, poor image quality, or inadequate tissue representation.

A total of 36 eligible cases were included in the final analysis. The sample size was based on the exploratory nature of the study, the four-month recruitment window, and the feasibility requirements of paired multimodal data acquisition in patients who had both CBCT imaging and analyzable biopsy slides. To reduce the risk of overfitting relative to the available sample, dimensionality reduction was performed before model training, and model evaluation was conducted using stratified cross-validation rather than a single random split. Histopathological grade, categorized as well differentiated, moderately differentiated, or poorly differentiated OSCC, served as the reference standard and was determined through conventional microscopic evaluation by experienced oral pathologists.

CBCT scans were acquired using standardized maxillofacial imaging protocols used in the participating centers. Image datasets were reviewed for adequacy before analysis, and three-dimensional tumor regions were segmented using semi-automated medical image analysis software with manual refinement to ensure accurate delineation of tumor boundaries. From the segmented tumor volumes, 108 radiomic features were extracted, including first-order intensity features, shape descriptors, and texture-based features reflecting spatial heterogeneity and structural irregularity. Radiomic features were normalized before modelling to reduce scale-related effects. Features with low variance or high redundancy were removed through variance-based filtering and inter-feature correlation assessment, leaving 24 radiomic features for model development.

Histopathological slides were digitized as whole-slide images from hematoxylin and eosin–stained biopsy specimens. Whole-slide preprocessing included color normalization, artifact screening, tissue-region segmentation, and selection of analyzable tumor regions. Computational pathology features were then extracted to quantify nuclear morphology, cellular density, architectural organization, and textural heterogeneity. A total of 76 histopathological image features were initially generated, of which 31 features were retained after feature reduction for downstream analysis. These retained features were selected because they represented measurable cellular and tissue-level characteristics relevant to OSCC differentiation.

Three modelling strategies were evaluated. First, a CBCT radiomics–only model was trained using retained radiomic features. Second, a whole-slide image–only model was trained using retained computational pathology features. Third, a fused model was developed by integrating normalized radiomic and histopathological feature sets at the feature level before classifier training. Supervised machine learning classifiers, including support vector machine and random forest algorithms, were evaluated, and the final model was selected according to cross-validated classification performance and interpretability. Stratified cross-validation was used to preserve grade distribution across training and validation folds, and hyperparameter tuning was performed within the training process to minimize optimistic performance estimation.

The primary outcome was overall grading accuracy, defined as the proportion of cases in which the AI-predicted OSCC grade matched the reference histopathological grade. Secondary outcomes included class-wise sensitivity, class-wise specificity, and area under the receiver operating characteristic curve. Model performance was compared across the three approaches to determine whether fused multimodal modelling improved grading performance over single-modality models. Continuous variables were summarized using mean and standard deviation, while categorical variables were summarized using frequency and percentage. Normality of continuous variables was assessed before applying parametric procedures. Differences in model accuracy between paired modelling approaches were assessed using paired statistical testing, and correlations between selected CBCT radiomic features and computational pathology features were examined using Pearson's correlation coefficient. Statistical significance was set at $p < 0.05$.

To address bias and strengthen reproducibility, all eligible cases were screened using predefined inclusion and exclusion criteria, imaging and slide quality were assessed before feature extraction, segmentation was refined consistently, features were normalized before integration, and dimensionality reduction was applied before classifier development. The analysis used complete paired imaging–pathology data, and cases lacking either modality were not included in model training. Data integrity was maintained through anonymized case coding, separation of clinical identifiers from analytical datasets, and consistent linkage of CBCT, whole-slide image, and histopathological grade data for each participant. Ethical approval and informed consent procedures were followed according to institutional requirements for research involving patient imaging and biopsy-derived data.

RESULTS

A total of 36 histopathologically confirmed OSCC cases were analyzed. The mean age was 52.8 ± 9.6 years, with patients ranging from 34 to 72 years. Males represented 23 cases (63.9%), while females represented 13 cases (36.1%). Buccal mucosa was the most frequent tumor site, accounting for 15 cases (41.7%), followed by tongue involvement in 12 cases (33.3%) and gingival lesions in 9 cases (25.0%). Conventional histopathological grading identified 14 well differentiated cases (38.9%), 13 moderately differentiated cases (36.1%), and 9 poorly differentiated cases (25.0%) (Table 1).

Table 1. Demographic and Clinical Characteristics of Patients with OSCC (n = 36)

Variable	Value
Age, mean ± SD	52.8 ± 9.6 years
Age range	34–72 years
Male	23 (63.9%)
Female	13 (36.1%)
Buccal mucosa	15 (41.7%)
Tongue	12 (33.3%)
Gingiva	9 (25.0%)
Well differentiated OSCC	14 (38.9%)
Moderately differentiated OSCC	13 (36.1%)
Poorly differentiated OSCC	9 (25.0%)

Table 2. Comparative Diagnostic Performance of Single-Modality and Fused AI Models

Model	Retained Features	Accuracy (%)	Error Rate (%)	AUC	Absolute Accuracy Gain vs CBCT (%)
CBCT radiomics only	24	69.4	30.6	0.74	Reference
Whole-slide image only	31	77.8	22.2	0.81	+8.4
Fused AI model	55	86.1	13.9	0.89	+16.7

Radiomic feature extraction generated 108 CBCT-derived features per lesion, of which 24 were retained after feature reduction. Whole-slide image analysis generated 76 computational pathology features, of which 31 were retained. The CBCT radiomics–only model achieved 69.4% overall accuracy and an AUC of 0.74. The whole-slide image model showed better performance, with 77.8% accuracy and an AUC of

0.81. The fused AI model achieved the highest performance, with 86.1% accuracy and an AUC of 0.89 (Table 2).

Class-wise analysis showed that the CBCT radiomics–only model had sensitivity values of 71.4%, 69.2%, and 66.7% for well, moderately, and poorly differentiated tumors, respectively. The whole-slide image model improved sensitivity across all grades, reaching 78.6%, 76.9%, and 77.8%. The fused model showed the strongest class-wise performance, with sensitivity of 85.7% for well differentiated, 84.6% for moderately differentiated, and 88.9% for poorly differentiated OSCC. Specificity also improved with multimodal fusion, reaching 89.7%, 83.3%, and 86.4% across the three grades (Table 3).

Table 3. Grade-Wise Sensitivity and Specificity Across AI Models

Model	Grade	Sensitivity (%)	Specificity (%)
CBCT radiomics only	Well differentiated	71.4	72.5
CBCT radiomics only	Moderately differentiated	69.2	68.0
CBCT radiomics only	Poorly differentiated	66.7	70.1
Whole-slide image only	Well differentiated	78.6	80.6
Whole-slide image only	Moderately differentiated	76.9	75.0
Whole-slide image only	Poorly differentiated	77.8	78.4
Fused AI model	Well differentiated	85.7	89.7
Fused AI model	Moderately differentiated	84.6	83.3
Fused AI model	Poorly differentiated	88.9	86.4

Comparative analysis demonstrated that the fused AI model significantly outperformed the CBCT radiomics–only model and the whole-slide image–only model. The fused model improved accuracy by 16.7 percentage points compared with CBCT radiomics alone and by 8.3 percentage points compared with whole-slide image analysis alone. The accuracy improvement was statistically significant compared with the radiomics-only model ($p = 0.012$) and the pathology-only model ($p = 0.031$) (Table 4).

Table 4. Statistical Comparison of Model Accuracy

Comparison	Accuracy Difference (%)	p-value
Fused AI vs CBCT radiomics only	+16.7	0.012
Fused AI vs whole-slide image only	+8.3	0.031
Whole-slide image only vs CBCT radiomics only	+8.4	Not reported

Correlation analysis showed moderate associations between selected macro-scale radiomic and micro-scale histopathological features. CBCT texture features correlated with nuclear pleomorphism indices ($r = 0.46$, $p = 0.004$), while shape irregularity metrics correlated with cellular density measures ($r = 0.41$, $p = 0.009$). These findings suggest that radiomic heterogeneity may partially reflect underlying microscopic tumor characteristics (Table 5).

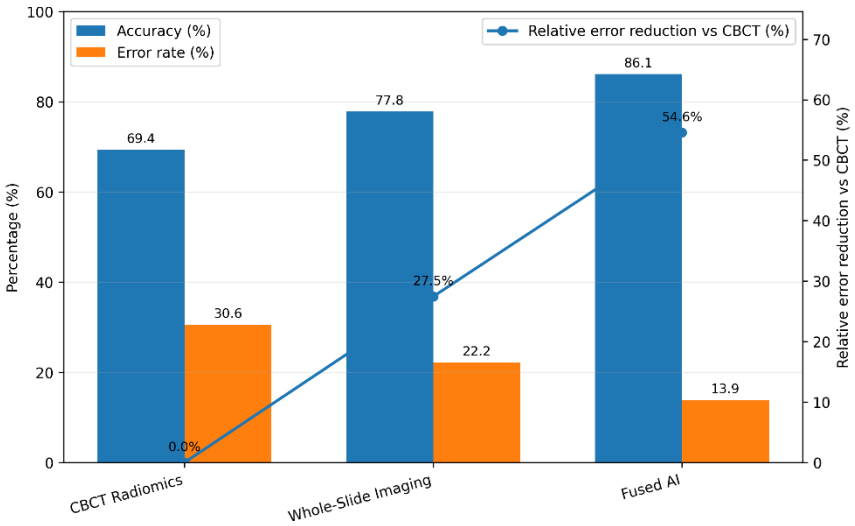

Figure 1. Diagnostic Accuracy Gain and Residual Misclassification Across AI Models

The fused AI model produced the most favorable diagnostic profile, increasing accuracy from 69.4% with CBCT radiomics alone to 86.1%, while reducing residual misclassification from 30.6% to 13.9%.

Table 5. Correlation Between Selected Radiomic and Histopathological Features

Feature Relationship	Correlation Coefficient (r)	p-value
CBCT texture features vs nuclear pleomorphism indices	0.46	0.004
Shape irregularity metrics vs cellular density measures	0.41	0.009

Relative to the CBCT radiomics model, whole-slide imaging reduced the error burden by 27.5%, whereas multimodal fusion reduced it by 54.6%, indicating that integration of macro-scale radiomic and micro-scale histopathological features provided a clinically meaningful improvement in OSCC grading performance.

DISCUSSION

The present study demonstrated that multimodal fusion of CBCT-derived radiomic features and whole-slide image–derived computational pathology features improved the grading performance for oral squamous cell carcinoma compared with either modality alone. The fused model achieved an accuracy of 86.1% and an AUC of 0.89, outperforming the CBCT radiomics–only model, which achieved 69.4% accuracy and an AUC of 0.74, and the whole-slide image model, which achieved 77.8% accuracy and an AUC of 0.81. This improvement suggests that OSCC grading is better represented through integrated macro-scale and micro-scale tumor features than through isolated radiological or histopathological assessment. The 16.7 percentage-point gain over CBCT radiomics alone and 8.3 percentage-point gain over whole-slide imaging indicate a clinically meaningful reduction in grading misclassification, particularly in a disease where differentiation status can influence prognostic stratification and treatment planning (13).

The comparatively lower performance of the CBCT radiomics–only model was expected because CBCT primarily captures three-dimensional structural and textural information rather than cellular differentiation. Although radiomic features can quantify tumor heterogeneity, shape irregularity, and spatial complexity, CBCT has limited soft-tissue contrast compared with conventional CT or MRI, which may restrict its independent discriminatory capacity for histological grading. Nevertheless, the moderate performance of the CBCT model supports the biological relevance of radiomic features in OSCC, particularly where tumor morphology, invasion pattern, and heterogeneity may reflect underlying aggressiveness (14). In contrast, the whole-slide image model produced higher accuracy, likely because computational pathology features directly quantify nuclear morphology, cellular density, tissue architecture, and textural characteristics that are closely related to tumor differentiation. This finding is consistent with the growing role of digital pathology and machine learning in objective histological assessment of malignant tumors (15).

The strongest finding was the superior performance of the fused AI model. The improvement observed with fusion supports the concept that radiological and pathological data provide complementary rather than redundant diagnostic information. The moderate correlations between CBCT texture features and nuclear pleomorphism indices ($r = 0.46$, $p = 0.004$), and between shape irregularity metrics and cellular density measures ($r = 0.41$, $p = 0.009$), further support the biological plausibility of multimodal integration. These associations suggest that macroscopic imaging heterogeneity may partially correspond to microscopic tumor disorganization, cellular crowding, and pleomorphic change. Similar benefits of radiology–pathology fusion have been reported in other oncological settings, where combined feature models improved classification or prognostic prediction beyond single-modality approaches (16).

From a clinical perspective, the findings suggest that fused AI systems may serve as decision-support tools for OSCC grading by providing objective, reproducible, and quantitatively derived outputs. Such tools would not replace expert pathologists or radiologists but could assist in difficult or borderline cases,

support consensus decision-making, and reduce observer-dependent variation. The use of CBCT is particularly relevant in oral and maxillofacial practice because it is widely available in dental diagnostic settings and may provide a practical entry point for radiomics-based decision support. When combined with digitized biopsy slides, CBCT radiomics could contribute to a more integrated diagnostic workflow that links anatomical tumor behavior with cellular morphology (17).

This study has several strengths. It evaluated a clinically meaningful three-class grading problem rather than a simplified binary classification task. It also compared radiomics-only, pathology-only, and fused models within the same patient cohort, allowing direct assessment of incremental diagnostic value. The use of feature reduction and stratified cross-validation improved internal methodological rigor and reduced, although did not eliminate, the risk of unstable model performance. The study also used routinely acquired clinical data sources, increasing translational relevance for real-world oral oncology workflows (18).

However, the findings should be interpreted within important limitations. The sample size was small, and the feature-to-sample ratio remained a concern despite dimensionality reduction. This increases the possibility of overfitting and limits generalizability. External validation was not performed, and the performance estimates should therefore be considered preliminary. Variability in CBCT acquisition parameters, segmentation boundaries, biopsy sampling, slide preparation, and digital pathology preprocessing may also affect feature extraction and model reproducibility. In addition, clinical covariates such as tumor stage, risk factors, anatomical subsite, nodal status, and treatment outcomes were not incorporated into the fused model, although these variables may improve future diagnostic and prognostic algorithms (19).

Future research should validate this fused modelling approach in larger, multi-center datasets with standardized CBCT acquisition, harmonized radiomic extraction, centralized digital pathology workflows, and independent external testing. Future models should also include explainability techniques such as feature importance mapping or SHAP-based interpretation to improve clinical trust and identify which imaging and histological features most strongly influence grading predictions. Integration of clinical, molecular, or outcome data may further improve model performance and extend its application from grading toward prognostic stratification and treatment planning. Overall, the present findings support continued investigation of multimodal AI as a clinically relevant framework for improving diagnostic precision in oral oncology (20).

CONCLUSION

This study showed that integration of CBCT-derived radiomic features with whole-slide histopathological image features improved the grading accuracy of oral squamous cell carcinoma compared with single-modality models. The fused AI model achieved the highest diagnostic performance, suggesting that combined macro-scale imaging heterogeneity and micro-scale cellular morphology provide complementary information for tumor grading. Although the findings are preliminary and require external validation in larger multi-center cohorts, they support the potential role of multimodal AI as an objective decision-support approach for improving reproducibility and precision in OSCC diagnostic workflows.

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