Radiomics and Radiogenomics in Prognostic Assessment of Head and Neck Cancer: A Systematic Review of Cutting-Edge Approaches

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AIM: The integration of radiomics and radiogenomics in the prognostication of head and neck cancer represents a rapidly evolving field within precision oncology. This systematic review aims to appraise advanced methods in radiomics and radiogenomics concerning prognostication in head and neck cancer, with a particular focus on methodological developments and clinical applications.
METHODS: A systematic literature search was conducted across seven major electronic databases: PubMed/MEDLINE, Embase, Web of Science, Scopus, Cochrane Library, CINAHL, and Google Scholar from January 2013 to December 2023. The search strategy incorporated database-specific syntax, controlled vocabulary such as Medical Subject Headings (MeSH) and Emtree terms, and supplementary free-text terms.
RESULTS: Twelve studies were included in the review, and the qualitative analysis revealed three distinct research clusters: prognostic applications, development of predictive models, and molecular-immunological characterization. In all scenarios, studies employing multi-modality modelling were significantly more competent than those relying on single-modality analyses. The area under the curve values of machine learning ranged across 0.71–0.86, outperforming traditional statistical approaches. Larger cohort studies exhibited superior validation metrics. While predictions of molecular characteristics varied, the prediction of immune phenotypes was superior to that of specific genetic alterations. Studies incorporating external validation provided stronger evidence supporting clinical usability. Although some studies presented moderate risk due to early-phase methodological variability, nearly half demonstrated low overall bias.
CONCLUSIONS: Our findings indicate significant advances in the prognostication of head and neck cancer through radiomics and radiogenomics approaches. Combined modelling strategies that integrate clinical, radiomic, and genomic features yielded enhanced performance. Despite the development of newer studies with greater methodological rigor and robust validation, variability in feature extraction, processing pipelines, and reporting metrics necessitates further consolidation of methodologies in this field.

Keywords: radiomics; radiogenomics; head and neck cancer; prognostic assessment; machine learning; artificial intelligence; molecular imaging

Introduction

Cancers of the head and neck represent a major global health issue, ranking among the most common malignancies, characterised by complex biological heterogeneity that significantly challenges clinical management [1–5]. Traditionally, diagnosis and prognosis have often been inadequate in capturing the molecular and phenotypic heterogeneity that influences treatment outcomes and patient survival [6–8].

Radiomics has initiated a new era in medical image analysis. It focuses on the high-throughput extraction of quantitative features from standard imaging modalities [9–11]. This computational approach transforms conventional medical images into repositories of mineable data, revealing pre-

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viously invisible characteristics of tumours through visual interpretation [12]. Advanced algorithms can now extract thousands of features that describe tumour texture, shape, size, and heterogeneity patterns from routine Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) imaging [13,14].

Radiogenomics takes this one notch higher by linking imaging phenotypes to the underlying genomic characteristics they represent. This connection [15] between the radiological features and molecular signatures enables non-invasive insights into tumour biology, often reducing the need for invasive biopsies and providing opportunities for monitoring [16–18]. There have been particularly promising results concerning the integration of radiomics with genomic data, primarily due to findings related to the identification of imaging biomarkers that reflect specific mutations, expression patterns, and molecular subtypes [19,20].

Recent technological advances in artificial intelligence and machine learning have enhanced the processing and analytical capabilities for large datasets [21–26]. Deep learning algorithms can currently auto-detect subtle imaging patterns that relate to clinical outcomes; advanced statistical approaches are feasible in radiomic signature validation. These computational methods have been held to very great promise in predictive ability for the pattern of response to therapy, survival, and recurrence of disease patterns [27].

However, significant challenges remain in the clinical implementation of radiomics and radiogenomics in head and neck cancer. Standardisation of protocols for image acquisition and robust methodologies for feature extraction and validated analysis pipelines are critical areas for improvement [28]. In addition, integrating data across different institutions poses challenges due to the heterogeneous imaging parameters frequently being heterogeneous. Other major concerns include the need for well-annotated datasets to build and validate predictive models [6,28].

This systematic review aims to discuss the most recent developments in radiomics and radiogenomics that can predict the prognosis of head and neck cancers by synthesising the available literature, highlighting recent methodological advances, clinical applications, and future research avenues.

Methods

Eligibility Criteria

The review protocol was developed in accordance with the PRISMA reporting guidelines (**Supplementary Material**) [29], incorporating the PECOS framework: Population (patients with Head and Neck Squamous Cell Carcinoma (HNSCC)), Exposure (radiomics and radiogenomics approaches), Comparator (conventional imaging assessment), Outcomes (prognostic assessment), and Study design (observational and interventional studies). The inclusion and exclusion criteria devised for the review are outlined in Table 1.

Search Protocol

The search strategy was employed across seven major electronic databases: PubMed/MEDLINE, Embase, Web of Science, Scopus, Cochrane Library, CINAHL, and Google Scholar. The search syntax was limited to database-specific syntax and controlled vocabulary, either in Medical Subject Headings (MeSH) terms for PubMed or Emtree for Embase, supplemented with free-text terms as detailed in Table 2. To ensure methodological rigor and the inclusion of peer-reviewed, high-quality evidence, grey literature was explicitly excluded from the review, including conference abstracts, theses, dissertations, white papers, and unpublished data.

Data Extraction Protocol

For each study meeting the inclusion criteria, the following variables were systematically recorded: Study ID (year of publication and first author), imaging modality employed for radiomics (e.g., MRI, CT, PET/CT, including technical details such as contrast, matrix size, or slice thickness), number and type of radiomic features extracted, and analytical pipeline employed (e.g., PyRadiomics, Imaging Biomarker Explorer (IBEX), in-house MATLAB scripts, or Computational Environment for Radiological Research [CERR] Toolbox). We also documented methodological information regarding feature selection or reduction methods employed—e.g., Least Absolute Shrinkage and Selection Operator (LASSO) regression, Principal Component Analysis (PCA), Support Vector Machine (SVM)-RFE, or recursive feature elimination—and validation methods, including cross-validation (3-fold, 100-fold Monte Carlo) or retrospective/prospective cohort validation.

Data on radiogenomic integration were meticulously documented, including genomic data sources (e.g., The Cancer Genome Atlas (TCGA), Affymetrix arrays, mRNA, or whole-exome sequencing), targeted gene or pathway-level changes (e.g., *CDKL2*, *TP53*, and *FAT1*), and the types of multi-omic associations reported. Types of prognostic models were also documented, such as machine learning models (e.g., Random Forest, SVM, XGBoost, and sparse logistic regression) and traditional statistical models (e.g., Cox regression and logistic regression), along with their corresponding performance measures such as Concordance Index (C-index), area under the curve (AUC), Coefficient of Determination (R^2) values, and hazard ratios.

Each study's clinical or molecular endpoints assessed were categorised and tabulated, including overall survival (OS), progression-free survival (PFS), loco-regional control (LRC), tumour heterogeneity, immune phenotype classification (hot vs. cold tumours), Human Papillomavirus (HPV) status prediction, *TP53* or *FAT1* mutation status, extracapsular spread, and other clinicopathologic features.

Table 1. Inclusion and exclusion criteria were devised for the review.

Criteria type	Inclusion	Exclusion
Study design	Original research articles, clinical trials, cohort studies	Case reports, reviews, meta-analyses, animal studies
Population	Adult patients with HNSCC	Pediatric cases, other cancer types
Language	English	Non-English publications
Time period	From January 2013 to December 2023	Not applicable

HNSCC, Head and Neck Squamous Cell Carcinoma.

Table 2. Detailed search strategies used for each database.

Database	Search string
PubMed	((“head and neck neoplasms” [MeSH] OR HNSCC) AND (radiomics OR radiogenomics) AND (prognosis OR survival))
Embase	(‘head and neck cancer’/exp AND (radiomics OR radiogenomics) AND ‘prognosis’/exp)
Web of Science	TS = (head and neck cancer AND (radiomics OR radiogenomics) AND (prognosis OR outcome))
Scopus	TITLE-ABS-KEY (head AND neck AND cancer AND radiomics AND prognosis)
Cochrane	“head and neck cancer” AND radiomics AND prognosis
CINAHL	(MH “Head and Neck Neoplasms+” AND (radiomics OR radiogenomics) AND (MH “Prognosis+”))
Google Scholar	(“head and neck cancer” OR “oral squamous cell carcinoma” OR “laryngeal carcinoma” OR “pharyngeal neoplasm” OR “HNSCC”) AND (radiomics OR “radiomic features” OR “quantitative imaging biomarkers”) AND (radiogenomics OR “imaging genomics”) AND (prognosis OR prognostic OR predictive OR “treatment response” OR “outcome prediction”) AND (imaging OR “Computed Tomography” OR CT OR “Magnetic Resonance Imaging” OR MRI OR PET OR “Positron Emission Tomography”)

MeSH, Medical Subject Headings; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography.

Bias Assessment Protocol

The ROBINS-I tool [30] was employed to assess bias in terms of confounding risk, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. Two independent reviewers assessed the risk, and any disagreements were resolved through consensus with a third reviewer.

Results

Study Selection Process

In the initial stage of the study selection process (Fig. 1), 392 records were identified through database searching. After removal of 36 duplicates, 356 records were screened. Nineteen records were excluded due to paywall restrictions. Of the 337 reports sought for retrieval, 45 could not be retrieved due to unavailability of full-text articles. Consequently, 292 reports were assessed for eligibility. Further exclusions were made for the following reasons: 54 did not address the PICO criteria, 38 were out of scope, 26 were individual case reports, 41 were animal studies, 33 were scoping reviews, 53 were literature reviews, and 35 were thesis articles. Ultimately, 12 studies [31–42] were included in the review.

Demographic Variables Analysed

There were notable demographic differences among the included studies regarding sample size and characteristics (Table 3, Ref. [31–42]). Liu *et al*. [34] reported the largest cohort of 761 patients, while Zwirner *et al*. [42] had the smallest sample size of only 20 patients. Mean ages varied between 47–63.6 years, except in the majority reporting an average of around 60 years. Gender distribution showed a notable male predominance across all studies. Follow-up periods varied significantly, with Tam *et al*. [39] reporting the longest duration of 5 years, while others, such as Spielvogel *et al*. [38], had median follow-ups of 25 months. Some studies, like Katsoulakis *et al*. [33], Wu *et al*. [40], and Zhu *et al*. [41], did not specify any follow-up period. Most studies employed retrospective designs; only Zwirner *et al*. [42] used a prospective method, while others, such as Corti *et al*. [31], employed both retrospective and prospective methods. In a few studies, for instance, Gao *et al*. [32] and Mukherjee *et al*. [35], separate training and validation cohorts were utilised.

Imaging Modalities Assessed

Table 4 (Ref. [31–42]) lists the radiogenomic characteristics assessed across the included studies. Corti *et al*. [31] applied MRI on a 1.5 T scanner using T1- and T2-weighted sequences. Gao *et al*. [32] used contrast-enhanced T1-weighted MRI with specific matrix parameters of 512 × 416 and 3 mm slice thickness. Katsoulakis *et al*. [33] focused solely on contrast-enhanced CT for pre-treatment imaging. Liu *et al*. [34] applied multiple MRI sequences, including T1, T2, and contrast-enhanced images. Mukherjee *et al*. [35] used contrast-enhanced CT data with variable acquisition parameters.

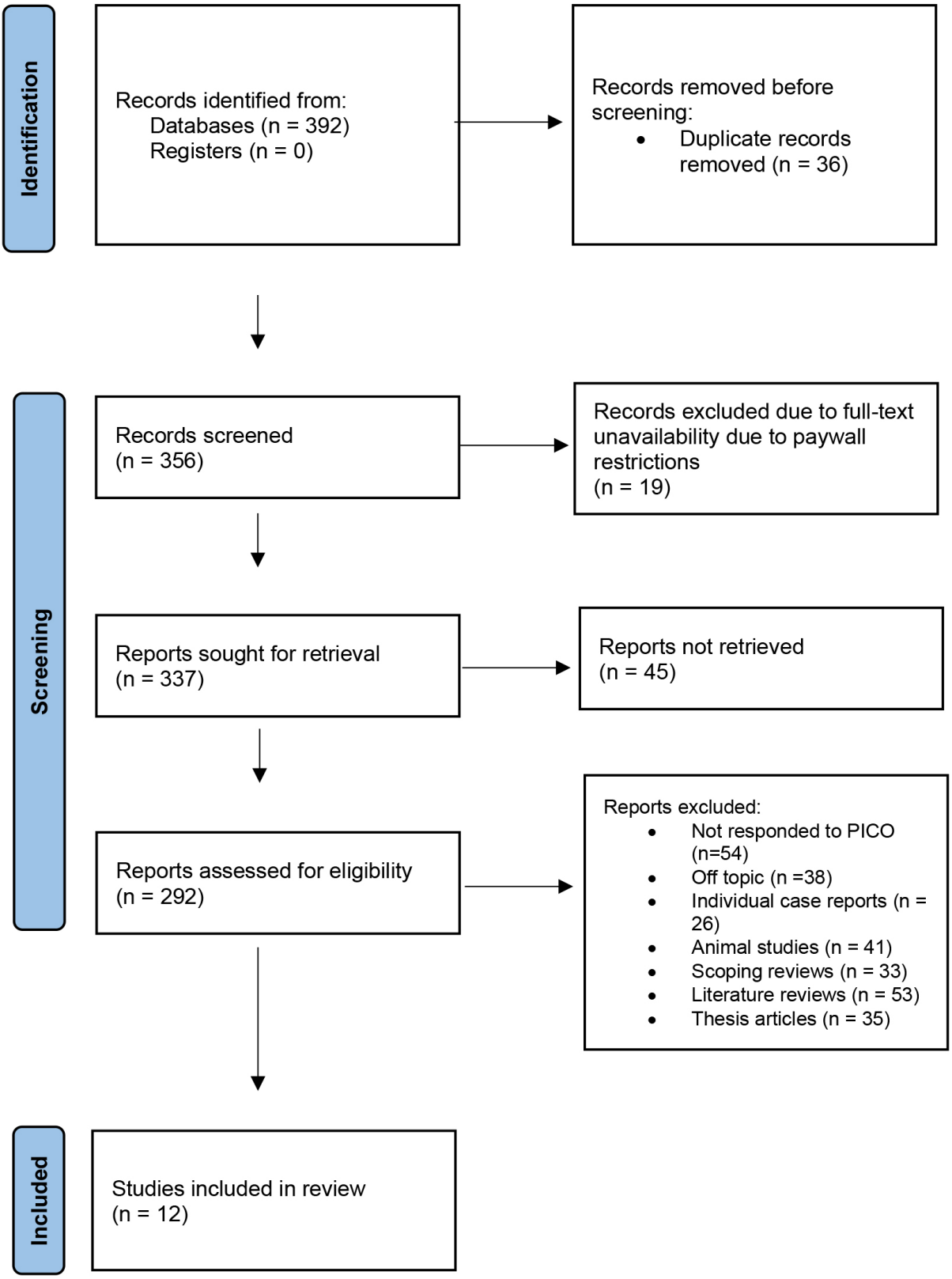

Fig. 1. Flow diagram of the study selection process. PICO, Population/Problem, Intervention, Comparison, and Outcome.

Table 3. Study characteristics of the included articles.

Study ID	Country	Year	Study design	Sample size	Mean age (in years)	Male: Female ratio	Follow-up period
Corti *et al*. [31]	Italy & Netherlands	2023	Retrospective/Prospective	231	60–61	~1.4:1	25–37 months
Gao *et al*. [32]	China	2021	Retrospective	316	47.6 (Training), 48.6 (Validation)	164:73 (Training), 56:23 (Validation)	~36 months
Katsoulakis *et al*. [33]	USA	2020	Retrospective Cohort	160	Not specified	Not specified	Not specified
Liu *et al*. [34]	China	2023	Retrospective	761	47–49	Approx. 3:1	Median 39–48 months
Mukherjee *et al*. [35]	USA	2020	Retrospective	113 (Training), 71 (Test)	59.8 (Training), 63.6 (Test)	Not specified	Not specified
Nguyen *et al*. [36]	France	2023	Retrospective Cohort	133	60.92	98:35	Not specified
Rabasco Meneghetti *et al*. [37]	Germany	2022	Retrospective Cohort	206	58	4:1	Not specified
Spielvogel *et al*. [38]	Austria	2023	Retrospective	62	57 (35–83)	45:17 (73% male)	Median 25 months (0–130)
Tam *et al*. [39]	USA (MD Anderson)	2024	Retrospective	299	57	Not specified	5 years
Wu *et al*. [40]	China	2021	Retrospective	106	60	79:27	Not specified
Zhu *et al*. [41]	USA	2019	Retrospective	126	59.81	97:29	Not specified
Zwirner *et al*. [42]	Germany	2019	Prospective	20	60 (49–75)	18:2	2 years

Table 4. Summary of radiogenomic models and outcomes in the included studies.

Study ID	Imaging modality	Radiomics features	Radiogenomics data	C-index (validation)	AUC values	Prognostic models	Outcomes	Conclusion assessed
Corti *et al*. [31]	MRI (T1w, T2w, 1.5 T)	1072 features, Stability analysis & Cox regression, Pyradiomics	Gene expression, Affymetrix arrays, 7 signatures	0.62 (IQR 0.58–0.64)	Not applicable (C-index only)	Cox model, Retrospective/Prospective validation, C-index, HR	OS stratification	MRI radiomics as a prognostic tool
Gao *et al*. [32]	MRI (CE-T1WI, 512 × 416 matrix, 3 mm slice thickness)	530 features, LASSO method, PyRadiomics	mRNA expression, Tumor samples, *CDKL2*, *PLIN5*, *SPAG1*	Not reported	Not reported	Radiomics, Clinical and Combined models, C-index, Calibration curve	PFS, Gene Expression Correlation	Radiomics signature predicts PFS and gene expression
Katsoulakis *et al*. [33]	CT (Pre-treatment, contrast)	104 features, Stability tests, CERR Toolbox	Genomic, TCGA, Molecular profiles	Not applicable (clustering analysis)	Not applicable (unsupervised clustering)	Random Forest, Cross-validation, R^2 = 0.30	HPV status, CD8+ T-cells	Radiomic analysis predicts molecular subtypes
Liu *et al*. [34]	MRI (T1, T2, Contrast-enhanced)	2106 features, Linear SVM, PyRadiomics	Transcriptomic, SYSUCC, Gene Sets	Not reported (only AUCs reported)	0.713–0.756 (PRNN prediction)	Random Forest, Internal/External, AUC 0.713–0.756	PRNN, G5-NFS, OS	Effective prediction of PRNN risk
Mukherjee *et al*. [35]	CT (Contrast-enhanced, various parameters)	2131 features, PCA for dimensionality reduction, in-house pipeline (MATLAB)	Genomic Data (TCGA), CT Imaging Archive, Histopathologic features	Not applicable (classification AUCs reported)	AUCs for features: 0.66–0.80	Sparse logistic regression, Cross-validation, AUC	Prediction of HPV status, tumor grade, extracapsular spread, etc.	Radiomics models show moderate prediction potential

Table 4. Continued.

Study ID	Imaging modality	Radiomics features	Radiogenomics data	C-index (validation)	AUC values	Prognostic models	Outcomes	Conclusion assessed
Nguyen *et al.* [36]	CT, Contrast-Enhanced, Slice Thickness ≤5 mm	1767 features, ICC >0.9, IBEX software	Gene Expression, TCGA & GHPS, HOT Score	Not reported	0.86 (XGBoost model in GHPS set)	XGBoost, 3-fold Cross validation (CV), AUC = 0.86	Hot/Cold Tumor Classification	Non-invasive prediction of immune phenotype
Rabasco Meneghetti *et al.* [37]	CT (Pre-treatment)	Morphological and texture, logistic regression, custom pipeline	Whole-transcriptome, Multicentre, Gene Signatures	0.63 [0.55–0.73] (combined model)	0.69 [0.53–0.83] (atypical subtype)	logistic regression, Validated, AUC and C-Index	Loco-regional control (LRC), overall survival (OS)	Multi-omics improves prognosis
Spielvogel *et al.* [38]	PET/CT ([18F] Fluorodeoxyglucose (FDG), Whole-body, Contrast-enhanced CT)	104 IBSI-compliant features, redundancy removal, in-house framework	Whole-exome sequencing, Formalin-fixed paraffin-embedded samples, Pathway-level disruption scores	Not reported	AUC 0.72–0.75	Machine learning (Random Forest, SVM), 100-fold Monte Carlo cross-validation, AUC 0.72–0.75	OS, Radiogenomic markers	Improved prognostic stratification with radiogenomic markers
Tam *et al.* [39]	CT, Radiotherapy (RT) planning	107 features, PyRadiomics, 3 Dimensional (3D) Slicer	Clinical data, TCIA, HPV status	Not reported (AUC only)	0.86 (PWEM combined model)	Machine learning (RF, SVM, etc.), VEML, PWEM, AUC	5-year overall survival	The combined model outperforms individual models
Wu *et al.* [40]	CT (Enhanced)	1022 features, SVM-RFE, Pyradiomics	Genetic alterations, TCGA, Pathway alterations	Not reported	0.70+ for 6 pathway predictions	SVM, Cross-validation, AUC	Predict pathway alterations	Radiomics can predict genetic alterations
Zhu *et al.* [41]	CT (contrast-enhanced, 120 kVp)	187 features, recursive feature elimination, IBEX	Multiomics, TCGA/TCIA, 5347 associations	Not reported	0.71 (HPV), 0.641 (*TP53* mutation)	Random forest, Cross-validation, AUC	HPV status, *TP53* mutation	Radiomic features are linked to genomic characteristics
Zwirner *et al.* [42]	CT (3 mm slice, 1.27 mm pixel)	Grey Level Nonuniformity, Run Length Nonuniformity, Wavelet Features	NGS (327 genes, *TP53*, *FAT1*, *KMT2D*)	Not reported	Not reported	Hypothesis-driven correlation	Tumor heterogeneity, survival outcomes	*FAT1* mutations linked to lower heterogeneity

Abbreviations: MRI, Magnetic Resonance Imaging; CT, Computed Tomography; PET, Positron Emission Tomography; CE-T1WI, Contrast-Enhanced T1-Weighted Imaging; T1w, T1-weighted; T2w, T2-weighted; SVM, Support Vector Machine; RF, Random Forest; LASSO, Least Absolute Shrinkage and Selection Operator; PCA, Principal Component Analysis; AUC, area under the curve; C-index, Concordance Index; OS, overall survival; PFS, progression-free survival; VEML, Voted Ensemble Machine Learning; PWEM, Probability Weighted Ensemble Model; PRNN, Prognostic Risk Neural Network; TCGA, The Cancer Genome Atlas; TCIA, The Cancer Imaging Archive; SYSUCC, Sun Yat-sen University Cancer Center; GHPS, Gustave Roussy Hospital Precision Score; HPV, Human Papillomavirus; NGS, Next-Generation Sequencing; R^2, Coefficient of Determination; ICC, Intraclass Correlation Coefficient; IBSI, Image Biomarker Standardisation Initiative; IBEX, Imaging Biomarker Explorer; IQR, Interquartile Range; HR, Hazard Ratio; CERR, Computational Environment for Radiological Research.

Nguyen *et al*. [36] obtained gated contrast-enhanced CT with a slice thickness not exceeding 5 mm. Rabasco Meneghetti *et al*. [37] conducted pre-treatment CT scans. Spielvogel *et al*. [38] employed a hybrid technique integrating Fluorodeoxyglucose (FDG) PET with contrast-enhanced CT. Tam *et al*. [39] used radiotherapy planning CT scans. Wu *et al*. [40] and Zhu *et al*. [41] both utilised contrast-enhanced CT, with Zhu specifically mentioning acquisition parameters of 120 kVp. Zwirner *et al*. [42] performed CT scanning with a slice thickness of 3 mm and a pixel size of 1.27 mm.

Radiomic Variables Assessed

Corti *et al*. [31] extracted 1072 radiomic features correlated with gene expression data from Affymetrix arrays across seven signatures. Gao *et al*. [32] extracted 530 features using the LASSO method and PyRadiomics, associated with the mRNA expression of specific genes (*CDKL2*, *PLIN5*, *SPAG1*). Katsoulakis *et al*. [33] used 104 features with the CERR Toolbox, integrating TCGA molecular profiles. Liu *et al*. [34] extracted 2106 features with Linear SVM, relevant to Sun Yat-sen University Cancer Center (SYSUCC) transcriptomic data. Mukherjee *et al*. [35] extracted 2131 features after PCA reduction with TCGA genomic data. Nguyen *et al*. [36] utilised 1767 features via IBEX software and correlated the HOT Score to TCGA and Gustave Roussy Hospital Precision Score (GHPS) gene expression data. Rabasco Meneghetti *et al*. [37] considered only morphological and texture features alongside whole-transcriptome data.

Spielvogel *et al*. [38] employed 104 Image Biomarker Standardisation Initiative (IBSI)-compliant features correlated with whole-exome sequencing data. Tam *et al*. [39] used 107 features through PyRadiomics, linking these features to the Cancer Imaging Archive (TCIA) clinical data and HPV status. Wu *et al*. [40] applied SVM-RFE to analyse 1022 features correlated with TCGA genetic alterations. Zhu *et al*. [41] extracted 187 features using IBEX, integrating multi-omic data from TCGA/TCIA. Zwirner *et al*. [42] highlighted specific texture features, namely Grey Level Nonuniformity and Run Length Nonuniformity, which correlated with the Next-Generation Sequencing (NGS) data of 327 genes, including *TP53*, *FAT1*, and *KMT2D*.

Prognostic Models and Outcomes Observed

Using Cox models alongside retrospective and prospective validation, Corti *et al*. [31] assessed overall survival stratification by C-index and hazard ratios. Gao *et al*. [32] employed several models developed with radiomics, clinical, and combined inputs to investigate the relationship between progression-free survival and gene expression. Katsoulakis *et al*. [33] utilised Random Forest cross-validation to assess the association of HPV status and CD8+ T-cell levels. Liu *et al*. [34] adapted the Random Forest algorithm with internal/external validation, achieving AUCs were obtained at 0.713–0.756 for Prognostic Risk Neural Network (PRNN), G5-NFS, and overall survival prediction. Mukherjee *et al*. [35] used sparse logistic regression to predict HPV status, tumour grade, and extracapsular spread. Nguyen *et al*. [36] applied XGBoost with threefold cross-validation, obtaining an AUC of 0.86 on the classification of tumours whether they are hot or cold. Rabasco Meneghetti *et al*. [37] employed logistic regression to assess loco-regional control and overall survival. Spielvogel *et al*. [38] utilised multiple machine learning approaches with Monte Carlo cross-validation, achieving an AUC range of 0.72–0.75 for overall survival prediction. Tam *et al*. [39] used machine learning approaches with Voted Ensemble Machine Learning (VEML) and Probability Weighted Ensemble Model (PWEM) to predict the 5-year survival rate. Wu *et al*. [40] applied SVM with cross-validation to predict pathway alterations. Zhu *et al*. [41] used Random Forest cross-validation to predict HPV status and *TP53* mutations. Zwirner *et al*. [42] conducted hypothesis-driven correlation analyses on tumour heterogeneity and survival outcomes.

Quality Assessment Results

The bias assessment revealed varying levels of heterogeneity across different domains (Fig. 2, Ref. [31–42]). Bias due to participant selection (D2) emerged as the most frequently observed source of methodological concern, with seven studies rated as moderate in this domain. All studies demonstrated a low risk in outcome measurement (D6). Selection of reported results (D7) was rated as low in all but one study (Zwirner *et al*. [42]]), suggesting strong consistency in outcome ascertainment and reporting. Additionally, bias due to missing data (D5) was uniformly low across all studies, indicating a high degree of data completeness and reliable follow-up. Regarding classification of interventions (D3), the majority of studies were judged to have a low risk of bias, although moderate concerns were noted in Zhu *et al*. [41] and Zwirner *et al*. [42]. Bias due to deviations from intended interventions (D4) showed moderate risk in five studies, indicating occasional discrepancies in protocol fidelity.

Sensitivity Analyses Observations

When classified by imaging modality, MRI-based studies (Corti *et al*. [31], Gao *et al*. [32], Liu *et al*. [34]) primarily focused on survival stratification, with some also examining gene expression profiles. These studies employed a wide range of features and often utilised Cox regression or Support Vector Machine-based models, yielding encouraging results in OS, PFS, or molecular risk profile prediction. CT-based studies (Katsoulakis *et al*. [33], Mukherjee *et al*. [35], Nguyen *et al*. [36], Rabasco Meneghetti *et al*. [37], Tam *et al*. [39], Wu *et al*. [40], Zhu *et al*. [41], Zwirner *et al*. [42]) examined a broader range of endpoints, including HPV status, immune phenotype, and pathway alterations. Their methodological heterogeneity was more pronounced,

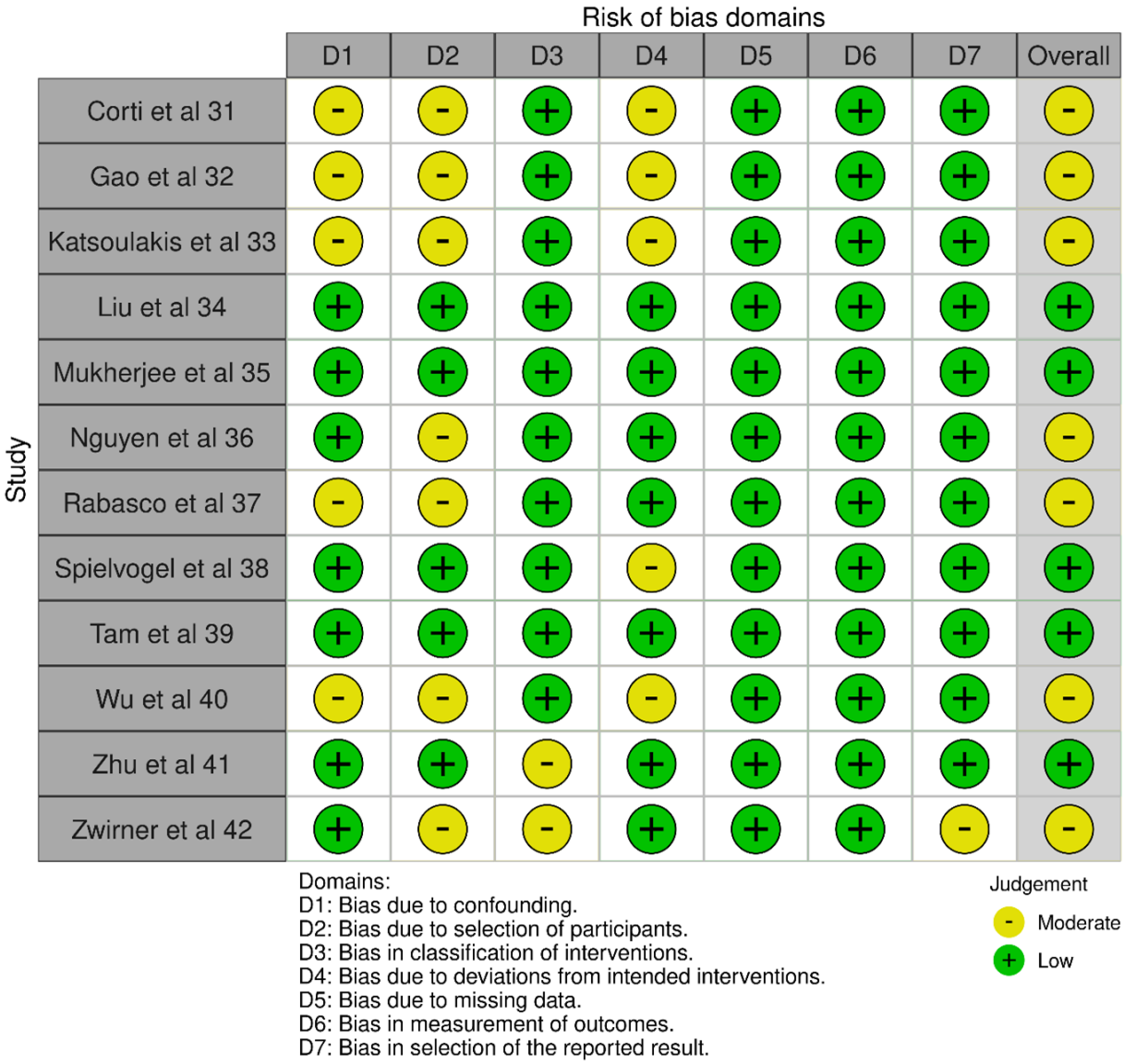

Fig. 2. Bias assessment using the ROBINS-I tool.

but performance metrics were generally high. The only PET/CT-based study (Spielvogel *et al.* [38]) combined both radiomic and genomic information, demonstrating promising machine learning-based prognostic stratification.

By analytical models, SVM or Random Forest analyses (e.g., Liu *et al.* [34], Nguyen *et al.* [36], Spielvogel *et al.* [38], Tam SY *et al.* [39], Wu *et al.* [40], Zhu *et al.* [41]) have exhibited greater accuracy (AUC $\geq$0.70), particularly when combined with dimension reduction techniques. More conventional models, such as logistic regression (Mukherjee *et al.* [35], Rabasco Meneghetti *et al.* [37]) and Cox regression (Corti *et al.* [31]) were employed where interpretability was paramount, although their performance was less consistent. In terms of radiogenomic integration, several studies (e.g., Gao *et al.* [32], Mukherjee *et al.* [35], Nguyen *et al.* [36], Spielvogel *et al.* [38], Zhu *et al.* [41], Zwirner *et al.* [42]) utilised genomic data, such as TCGA or Affymetrix arrays. These models tended to establish correlations between radiomic features and specific genetic mutations such as *TP53* or *FAT1*, and generally performed better in prognostic predictions than radiomics-only models. Furthermore, multi-omic investigations (e.g., Rabasco Meneghetti *et al.* [37], Zhu *et al.* [41]) appeared to enhance outcome predictions.

When clinical endpoints were stratified the analysis, OS was the most commonly evaluated endpoint (Corti *et al.* [31], Liu *et al.* [34], Rabasco Meneghetti *et al.* [37], Spielvogel *et al.* [38], Tam *et al.* [39], Zwirner *et al.* [42]), with the majority reporting adequate model performance. Others measured PFS (Gao *et al.* [32]), immune phenotype (Nguyen *et al.* [36]), HPV status (Katsoulakis *et al.* [33], Mukherjee *et al.* [35], Zhu *et al.* [41]), and pathway-level changes (Wu *et al.* [40]), indicating widespread application of radiomics for non-survival outcomes.

Discussion

A consensus analysis of the studies revealed contrasts and commonalities in radiomics and radiogenomics research, highlighting three major themes. The first theme focused on prognostic applications by Corti *et al.* [31], Gao *et al.* [32], and Rabasco Meneghetti *et al.* [37], which showcased unique methodological alignments despite variations in imaging modalities. Corti *et al.* [31] demonstrated the efficacy of MRI radiomics, Gao *et al.* [32] established predictions for progression-free survival, and Rabasco Meneghetti *et al.* [37] validated multi-omics approaches.

The second cluster, comprising Liu *et al.* [34], Spielvogel *et al.* [38], and Tam *et al.* [39], concentrated on developing predictive models. The PRNN risk prediction framework by Liu *et al.* [34] performed competitively with the radiogenomics markers of Spielvogel *et al.* [38] and the combined modelling approach of Tam *et al.* [39], whose AUC values ranged across 0.71–0.76.

The studies by Mukherjee *et al.* [35], Nguyen *et al.* [36], and Zhu *et al.* [41] were categorised into the third group, focusing on the evaluation of molecular and immunological characteristics. Among them, Nguyen *et al.* [36] achieved notable success in immune phenotyping, while Mukherjee *et al.* [35] and Zhu *et al.* [41] demonstrated moderate success in predicting molecular subtypes.

Katsoulakis *et al.* [33] and Wu *et al.* [40] formed a class targeting genetic alterations but employed different methodological approaches. Zwirner *et al.* [42] were somewhat isolated with their emphasis on *FAT1* mutations and heterogeneity, though conceptually related to the predictions of genetic alterations by Wu *et al.* [40].

Cross-study comparisons indicated that combined modelling approaches, such as those by Tam *et al.* [39] and Rabasco Meneghetti *et al.* [37], consistently outperformed single-modality analyses. Studies with larger cohorts, such as Liu *et al.* [34] and Tam *et al.* [39], exhibited stronger validation statistics compared to smaller studies, such as Zwirner *et al.* [42]. Predictions of molecular characteristics showed significant variability, with Nguyen *et al.* [36] demonstrating greater accuracy in immune phenotype prediction than specific genetic alterations, as seen in Wu *et al.* [40] and Zhu *et al.* [41].

Methodological heterogeneity was evident in the methods used for feature selection and modelling; contemporary machine learning techniques applied in most included studies [34,36,39] appeared superior to traditional statistical methods. Moreover, evidence for clinical application was more robust in studies with external validation [32,34] than in those relying solely on internal validation.

Molecular regulatory processes related to cell proliferation and survival involve intricately regulated signalling pathways determined by various genetic factors. Mutations in these regulatory pathways, reflected by genomic changes and epigenetic transformations, arise from selective pressure, environmental influences, and heredity [43]. The current head and neck cancer research emphasises characterising the tumour microenvironment (TME) to enhance diagnostics and prognostics [44]. The TME's role in maintaining cellular balance underlies its significance in both physiological and pathological conditions. Cellular changes in the TME often provide an opportunity for integrating neoplastic progression. Typically, alterations to the TME are assessed through targeted tissue sampling and molecular interrogation, alongside radiomics analyses [45].

Next-Generation Sequencing analysis [46] of HPV-negative HNSCC has revealed complex patterns of epigenetic changes and chromosomal aberrations, particularly disruptions of the CDKN2A/RB1 and TP53 pathways. Subsequent studies [47–52] have identified amplifications on chromosome 3q, including *PIK3CA*, *TP63*, and *SOX2*, with *PIK3CA* mutations being more common in both HPV-positive and HPV-negative subtypes. Further investigations indicated that inactivating mutations of tumour suppressor genes are favoured in the context of viral oncoproteins in HNSCC [48]. Biomarkers have been identified for predicting responses to immunotherapy in HNSCC, including *IFN-γ*, *PD-L1*, and *PD-L2* expression profiles [49]. Recent molecular studies have classified HPV33 as a prognostic marker in HNSCC and established p16 as an adequate surrogate marker in HPV-positive samples [50].

Although retrospective studies show positive results, the application of radiomic and radiogenomic methodologies to HNSCC treatment relies on prospective validation in actual clinical practice. This validation requirement has prompted efforts to establish a series of prospective trials aimed at integrating image-based biomarkers into treatment planning paradigms. For example, ClinicalTrials.gov Identifier NCT03422586 is currently investigating the prognostic relevance of radiomics in predicting resistant sub-volumes of tumours to guide adaptive radiotherapy strategies for HNSCC. This effort resonates with reports from Bogowicz *et al.* [43], who provided proof-of-concept that radiomic analysis at the CT scan-based level within tumour sub-regions would support the identification of intratumoral regions associated with radioresistance and facilitate the implementation of spatially adaptive dose escalation techniques.

Other trials, such as NCT03145077 and NCT03809052, are testing the use of radiomic and radiogenomic features to predict treatment responses, stratify patients based on immune phenotypes (i.e., hot tumours vs. cold tumours), and integrate these models with clinical and molecular biomarkers. These trials suggest a growing consensus that radiomics offers a readily available and reproducible means of tumour characterisation, particularly when coupled with molecular tests. Further research, such as that by Zhu *et al.* [41], has demonstrated that radiomic features derived from CT exhibit high correlations with central genomic alterations, such as *TP53* mutations and HPV status, using

large-scale multi-omics data from TCGA and TCIA. Similarly, Zwirner *et al*. [42] demonstrated high correlations between radiomic heterogeneity descriptors (e.g., grey-level nonuniformity, wavelet features) and somatic mutations in *FAT1*, highlighting the potential for radiogenomics to serve as a surrogate for molecular profiling in contexts of limited tissue availability. These findings underscore the biological plausibility of radiogenomic correlations and form the basis for predictive modelling in clinical trials.

Assessing these models is of significant interest due to the heterogeneity reported in radiomic workflows, imaging acquisition parameters, and machine learning techniques employed across various research studies. Feasibility trials represent a worthy approach to validate these models in diverse clinical settings, utilising standardised protocols, long-term follow-up durations, and multisite imaging archives. Such trials also facilitate easy comparison of radiomic and radiogenomic tools with conventional clinical risk assessments, thereby enabling informed decision-making regarding their ultimate clinical utility. A comparative analysis of our review findings with previous reviews [51–57] conducted on similar objectives revealed several key similarities and differences regarding the topic of radiogenomics in head and neck cancer. Our findings align with those of Ong *et al*. [51] and Bruixola *et al*. [52] concerning the potential of radiogenomics in precision medicine, particularly in tumour characterisation and treatment personalisation. Similar to van der Hulst *et al*. [55], this review emphasises the need for standardised imaging protocols and feature extraction methods. However, our analysis provides more detailed insights into specific ranges of selected radiomic features and the various software platforms employed in different studies.

While Illimoottil and Ginat [54] focused more on deep learning applications, our review encompasses a much larger set of analytical approaches, including traditional statistical methods and machine learning techniques. Likewise, Haider *et al*. [56] highlighted the importance of advancing computational capabilities in radiomics analysis. The preferred imaging modalities also differed somewhat from those of van der Hulst *et al*. [55], who concentrated primarily on MRI, whereas our review identified CT as the leading modality.

Our findings align with those of Tanadini-Lang *et al*. [57] in evaluating tumour heterogeneity through radiomics, but our review offers more specific performance metrics, with an AUC range of 0.71–0.86. The different approaches to prognostic modelling complement the emphasis placed by Shukla *et al*. [53] on their use in radiotherapy planning, although our review focuses more on applications for diagnosis and prediction.

Both our review and previous studies have highlighted similar issues, particularly the lack of standardisation and validation. Technical artefacts, such as dental artefacts, were also noted by Bruixola *et al*. [52], who were mentioned in some of our selected studies. Indeed, like Tanadini-Lang *et al*. [57], our review indicated a predominance of retrospective studies and the need for external validation.

Limitations

This review has several methodological limitations that must be acknowledged. The observed heterogeneity in validation strategies and reporting standards complicates direct comparisons of results. Divergent sample sizes and the predominance of retrospective analyses done retrospectively might affect generalisability. Limited standardisation of pipelines for selecting and processing radiomic features poses challenges for reproducibility assessment. Such deficiencies could introduce bias into outcome interpretations. Furthermore, technical variations arising from differences in imaging protocols, scanner parameters, and reconstruction algorithms across institutions may introduce variability related to the reproducibility of features.

Conclusions

Our assessments reveal that integrated approaches combining radiomics, genomics, and clinical features consistently outperform single-modality analyses in terms of prognostic performance. The results from machine learning implementations demonstrate superior predictive capabilities, particularly for molecular subtype and immune phenotype characterisation. While there has been substantial advancement in methodology during this period of developing radiomics in this field, standardisation of protocols for feature extraction and validation remains essential. The findings justify the promise of radiomics and radiogenomics in personalised cancer care, but further prospective validation and standardisation are required before entering routine clinical practice.

Availability of Data and Materials

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

Author Contributions

Conceptualization, ZQ and NSA; Methodology, MS and CS; Formal analysis, MMM and SS; Investigation, ZQ, NSA and CS; Writing—original draft, MMM, GM and SS; Data acquisition, writing—review & editing, GC and GM; Supervision, GC and GM. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Giuseppe Minervini was serving as one of the Editorial Board Members and Guest Editors of this journal. We declare that Giuseppe Minervini had no involvement in the peer review of this article and has no access to information regarding its peer review. Other authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4059.

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