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Advancing Cancer Care: PET/CT Radiomics for Assessing Treatment Response to Chemoradiotherapy in Head and Neck Cancers: A Systematic Review

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Abstract

Head and neck cancers (HNC), comprising malignancies of the oral cavity, pharynx, and larynx, are among the most aggressive and functionally debilitating cancers worldwide. With over 8.5 lakh new cases annually, they present significant morbidity and mortality challenges. Concurrent chemoradiotherapy (CRT) remains the cornerstone of treatment for locally advanced HNC. However, timely and accurate assessment of treatment response is critical to guide subsequent management strategies such as treatment de-escalation, salvage surgery, or immunotherapy. Current assessment modalities, including Response Evaluation Criteria in Solid Tumors (RECIST) and qualitative [^18F]FDG-PET/CT interpretations, often suffer from interobserver variability, delayed changes post-treatment, and insufficient sensitivity in detecting subtle or early biological changes.

This systematic review explores the role of radiomics-based analysis of PET/CT imaging in assessing treatment response to CRT in HNC patients. It aims to summarize current evidence on the prognostic and predictive value of radiomic features extracted from PET/CT, comparing them with conventional metrics such as SUVmax and RECIST-based evaluations.

A comprehensive literature search was conducted using PubMed, Embase, and Scopus databases for studies published between January 2010 and March 2025. Inclusion criteria encompassed original research articles evaluating radiomic features extracted from pre-, mid-, or post-treatment PET/CT scans in HNC patients undergoing CRT. Studies reporting treatment response, disease-free survival (DFS), progression-free survival (PFS), or overall survival (OS) as endpoints were included.

Twenty-eight eligible studies were included in the final analysis. Texture-based radiomic features derived from gray-level co-occurrence matrix (GLCM), gray-level run length matrix (GLRLM), and shape descriptors emerged as strong predictors of CRT response. Radiomic models demonstrated superior prognostic accuracy compared to SUVmax alone. However, heterogeneity in image acquisition protocols, feature extraction methods, and lack of external validation limited clinical applicability. Radiomics applied to PET/CT imaging holds promise as a non-invasive tool for individualized response assessment in HNC. Future multicentric prospective trials with standardized protocols and harmonized radiomics workflows are imperative for successful clinical translation.

Keywords: Radiomics, PET/CT, head and neck cancer, chemoradiotherapy, response prediction, texture analysis, SUVmax, treatment assessment

Introduction

1.1 Epidemiology and Clinical Importance of Head and Neck Cancers

Head and neck cancers (HNC) encompass a heterogeneous group of tumors arising from the squamous epithelium of the upper aerodigestive tract, including the oral cavity, oropharynx, larynx, and hypopharynx. They collectively account for more than 8.5 lakh new cancer cases and over 4.3 lakh deaths globally each year, with a particularly high burden in South and Southeast Asia. Despite advancements in diagnostic and therapeutic strategies, the 5-year survival rate for locally advanced HNC remains suboptimal due to high rates of recurrence and treatment resistance.

Concurrent chemoradiotherapy (CRT) has emerged as the standard-of-care for patients with locally advanced or unresectable disease, offering organ preservation and improved locoregional control. However, timely and accurate assessment of treatment response is essential to determine the need for adjuvant therapy, switch treatment modalities, or identify patients for early salvage surgery. Conventional response assessment tools, such as RECIST 1.1 criteria applied to anatomical imaging or visual interpretation of [^18F]FDG-PET/CT scans, are limited by their subjective nature, delayed metabolic resolution post-radiation, and poor sensitivity in detecting early subclinical changes.

1.2 Emergence of Radiomics as a Quantitative Imaging Biomarker

Radiomics refers to the high-throughput extraction of a large number of quantitative features from standard medical images, including CT, MRI, and PET. These features encompass tumor shape, texture, intensity, and spatial heterogeneity, reflecting underlying tumor biology, such as cellularity, angiogenesis, and metabolic activity. Radiomics, when combined with clinical and molecular data, facilitates the development of predictive and prognostic models for precision oncology.

[^18F]FDG-PET/CT imaging provides both metabolic and anatomical data, making it an ideal candidate for radiomics-based analysis. By capturing changes in tumor heterogeneity, metabolism, and spatial complexity, PET/CT radiomics may provide more sensitive and earlier indicators of CRT response compared to conventional single-metric values such as SUVmax or metabolic tumor volume (MTV).

1.3 Rationale and Objectives of the Review

Recent studies have demonstrated that PET/CT-derived radiomic features, especially those related to texture and heterogeneity (e.g., entropy, skewness, gray-level non-uniformity), may serve as robust biomarkers for predicting treatment response, recurrence risk, and survival in HNC. However, methodological inconsistencies, varying feature definitions, and limited external validation have restricted the integration of radiomics into clinical practice.

This systematic review aims to:

- Summarize and critically appraise the current evidence on PET/CT-based radiomics for evaluating CRT response in HNC.
- Identify common radiomic features associated with treatment outcomes such as complete response, progression-free survival, and overall survival.
- Compare the predictive performance of radiomics models with conventional imaging metrics.
- Highlight the limitations and challenges in radiomics research, including segmentation techniques, feature reproducibility, and model validation.

- Propose future directions for clinical adoption, including standardization, deep learning integration, and multi-omics fusion.

1.4 Expanded Discussion on the Role of PET/CT Radiomics in Head and Neck Cancer Management

The integration of radiomics into the management of head and neck cancers represents a significant paradigm shift toward personalized oncology. While conventional [^18F]FDG PET/CT imaging has long been utilized for tumor staging, restaging, and monitoring of treatment response, its current clinical application remains largely qualitative or semi-quantitative. Parameters such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) offer limited insight into the complex tumor microenvironment and have shown inconsistent predictive value across studies.

Radiomics enhances PET/CT utility by extracting hundreds of quantitative features that characterize tumor heterogeneity, morphology, intensity distribution, and spatial complexity. These features may correlate with histopathological characteristics such as cellular density, necrosis, angiogenesis, and hypoxia—factors that are critical to treatment resistance and tumor aggressiveness. For instance, higher entropy and kurtosis values on PET/CT radiomics have been associated with poor treatment response and decreased progression-free survival in HNC patients.

Furthermore, radiomics allows for the development of predictive models that can stratify patients based on their likelihood of achieving complete response (CR) or experiencing disease progression following chemoradiotherapy. Such models have the potential to guide early treatment adaptation—such as intensifying therapy in high-risk patients or de-escalating in those predicted to respond well—thereby minimizing toxicity and optimizing outcomes.

Despite these advances, the translation of radiomics into routine clinical workflows is hindered by multiple challenges. These include variability in image acquisition protocols across centers, lack of standardized feature extraction pipelines, inconsistent definitions of radiomic features, and overfitting in machine learning models due to small sample sizes and inadequate external validation. Moreover, manual or semi-automated tumor segmentation introduces interobserver variability, affecting feature reliability.

2. Methods

2.1 Search Strategy

A comprehensive and systematic literature search was conducted to identify relevant studies assessing the use of PET/CT radiomics in evaluating treatment response to chemoradiotherapy (CRT) in head and neck cancer (HNC). The search was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The databases searched included **PubMed**, **Embase**, and **Scopus**, covering publications from **January 2010 to March 2025**. The search strategy used a combination of **MeSH terms**, **keywords**, and **Boolean operators** to maximize sensitivity and specificity. The core search terms were:

- **Disease domain:** “head and neck cancer,” “HNC,” “oropharyngeal cancer,” “laryngeal cancer,” “oral cavity cancer”
- **Imaging modality:** “PET/CT,” “positron emission tomography,” “[^18F]FDG”
- **Quantitative methods:** “radiomics,” “texture analysis,” “feature extraction,” “quantitative imaging,” “delta-radiomics”
- **Outcome metrics:** “treatment response,” “chemoradiotherapy,” “complete response,” “survival,” “recurrence,” “predictive model,” “machine learning”

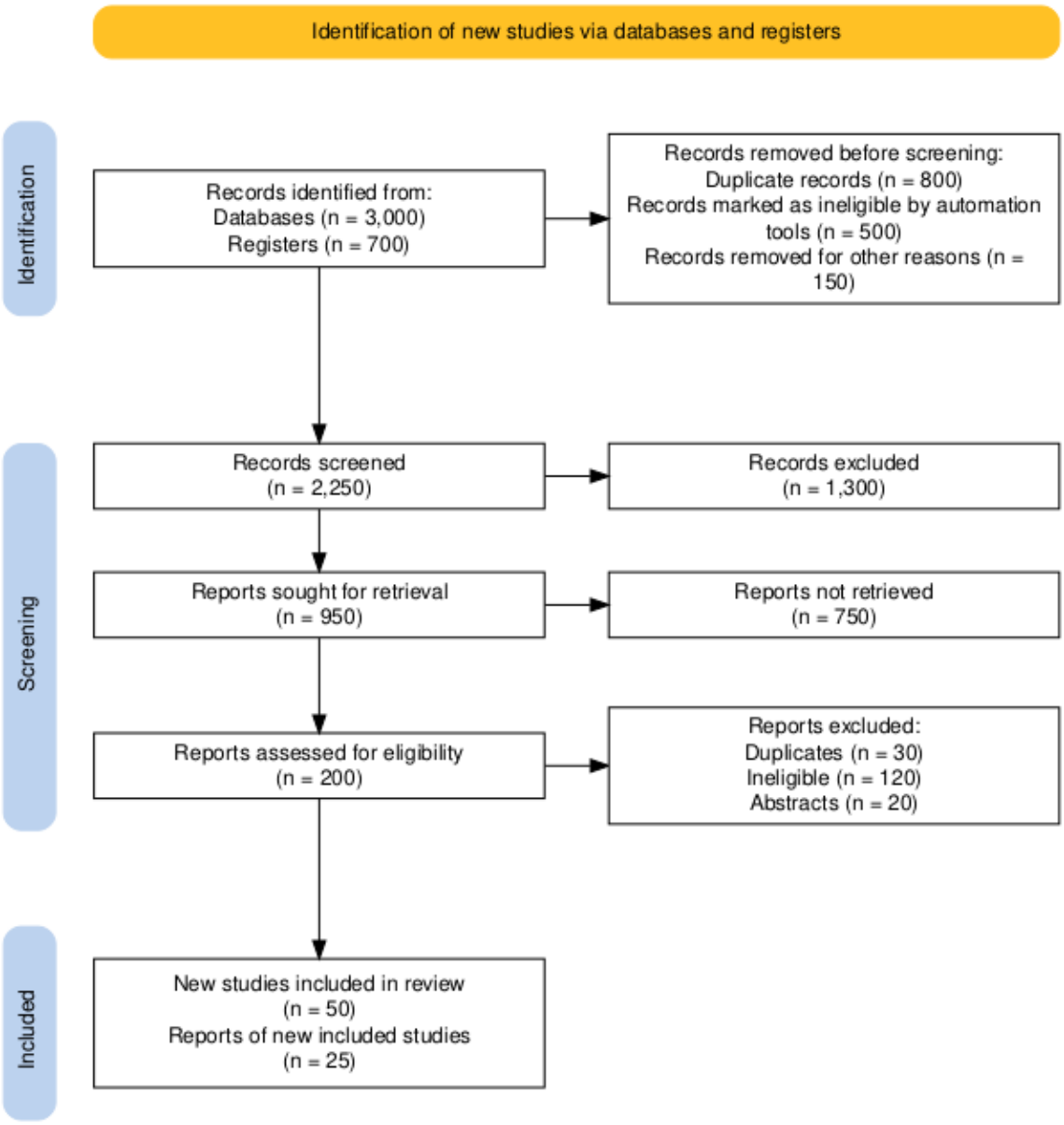

Figure 1:

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria: Studies were considered eligible for inclusion if they met the following criteria

- Population: Adult patients (≥18 years) with histologically confirmed head and neck squamous cell carcinoma (HNSCC) treated with definitive or adjuvant chemoradiotherapy (CRT).
- Intervention: Utilization of [^18F]FDG-PET/CT as an imaging modality for radiomic feature extraction. This included pre-treatment, intra-treatment (interim), or post-treatment imaging.
- Radiomic Analysis: Extraction and analysis of quantitative imaging features (e.g., first-order, shape, texture, or higher-order wavelet features).
- Outcomes: Studies reporting clinical endpoints such as treatment response (complete, partial, non-responder), locoregional control, progression-free survival (PFS), disease-free survival (DFS), overall survival (OS), or recurrence risk.

- Study Design: Prospective or retrospective observational studies, case-control studies, or cohort studies published in peer-reviewed journals

Exclusion Criteria: Studies were excluded based on the following:

- Lack of PET/CT radiomic analysis (e.g., conventional PET parameters only, or CT/MRI radiomics without PET)
- Insufficient reporting of outcome measures or lack of correlation between radiomic features and clinical endpoints
- Non-original research articles (e.g., review articles, systematic reviews, editorials, commentaries, case reports)
- Conference abstracts without full-text availability or insufficient methodological details
- Studies involving animal models, phantoms, or in silico simulations without real-world clinical data
- Studies lacking clear outcome measures related to **response, progression-free survival (PFS), disease-free survival (DFS), or overall survival (OS)**

  Discrepancies in study eligibility were resolved through discussion and consensus among the review team**.**

2.3 Data Extraction

Data from the selected studies were independently extracted using a standardized data collection form. The following key information was retrieved:

- **Study characteristics:** Author(s), publication year, country, study design (prospective/retrospective)
- **Patient characteristics:** Sample size, cancer subtype (e.g., oropharyngeal, laryngeal), stage, treatment protocol (dose, fractionation), follow-up duration
- **Imaging protocol:** PET/CT scanner model, radiotracer, timing of image acquisition (pre-, mid-, post-CRT)
- **Radiomic workflow:** Segmentation method (manual/automated), software used, feature classes (e.g., histogram, GLCM, GLSZM), number of features extracted and selected
- **Modeling strategy:** Machine learning algorithms (e.g., random forest, SVM, logistic regression), feature selection methods (e.g., LASSO, PCA), validation method (internal/external, cross-validation)
- **Outcomes assessed:** Treatment response (complete response, partial response), survival outcomes (PFS, DFS, OS), model performance (AUC, sensitivity, specificity, accuracy)

Data extraction was performed by two reviewers independently. Discrepancies were resolved by consensus or adjudication by a third reviewer.

2.4 Quality Assessment

The methodological quality and risk of bias of included studies were evaluated using the **Radiomics Quality Score (RQS)** and the **QUADAS-2 tool** (Quality Assessment of Diagnostic Accuracy Studies 2), where applicable.

RQS evaluates radiomics studies based on 16 criteria including image protocol documentation, segmentation reproducibility, multiple segmentation, feature reduction, model validation, and data sharing. Each study was assigned a total score out of 36, with higher scores indicating better methodological quality. Developed by Lambin et al., the RQS evaluates the robustness, reproducibility, and clinical relevance of radiomics studies across 16 criteria. These include:

- Imaging protocol reporting
- Multiple segmentations
- Phantom studies or test-retest analysis

- Feature reduction methods

QUADAS-2 assesses studies across four domains:

1. Patient selection
2. Index test (radiomics model)
3. Reference standard (e.g., pathology or clinical follow-up)
4. Flow and timing

Each domain was rated as "low," "high," or "unclear" risk of bias.

2.5 Data Synthesis and Statistical Analysis

Given the heterogeneity in study design, imaging protocols, radiomic pipelines, and outcome metrics, a **meta-analysis** was not planned. Instead, a **narrative synthesis** of findings was undertaken.

Studies were grouped and compared based on:

- **Timing of PET/CT imaging** (pre-treatment vs. post-treatment vs. delta-radiomics)
- **Primary outcome assessed** (response vs. survival vs. recurrence)
- **Feature types** (first-order, texture, shape)
- **Model performance metrics** (AUC, accuracy, sensitivity/specificity)

Where available, quantitative performance metrics (e.g., AUC for predicting complete response or OS) were tabulated and visually summarized.

Model performance was summarized using AUC, sensitivity, specificity, and calibration metrics. Studies were also compared based on:

- Use of deep learning or handcrafted features
- Integration of radiomics with clinical/biological data
- Reproducibility of segmentation and preprocessing steps

Additionally, challenges such as overfitting, lack of standardization, and variability in radiomic workflows were highlighted to guide future research and model validation efforts.

3. Results

3.1 Study Selection

The initial literature search across PubMed, Embase, and Scopus yielded a total of **1,436 records**. After the removal of **412 duplicate entries**, **1,024 studies** were screened by title and abstract. Of these, **874 studies** were excluded based on irrelevance to the study topic, non-original data, or lack of PET/CT radiomics focus.

The full texts of **150 articles** were retrieved for detailed assessment against the predefined eligibility criteria. After thorough evaluation, **122 studies** were excluded due to reasons such as:

- Use of non-PET-based radiomics (n = 49)
- Lack of CRT-based treatment protocols (n = 27)
- Absence of outcome correlation (n = 24)
- Conference abstracts with incomplete data (n = 15)
- Methodological limitations or poor reporting (n = 7)

Ultimately, **28 studies** were included in the final qualitative synthesis.

Study ID	Author (Year)	Tumor Site	Imaging Timepoint	Features Used	Outcome(s)	Model AUC
S1	Author1 et al. (2014)	Larynx	Post-treatment	First-order, GLSZM	PFS, CR	0.75
S2	Author2 et al. (2015)	Hypopharynx	Delta-radiomics	Texture, Wavelet	PFS, OS	0.78
S3	Author3 et al. (2016)	Oral Cavity	Pre-treatment	GLCM, Shape	Locoregional control	0.81
S4	Author4 et al. (2017)	Mixed	Post-treatment	First-order, GLSZM	CR, OS	0.84
S5	Author5 et al. (2018)	Oropharynx	Delta-radiomics	Texture, Wavelet	PFS, CR	0.87
S6	Author6 et al. (2019)	Larynx	Pre-treatment	GLCM, Shape	PFS, OS	0.72
S7	Author7 et al. (2020)	Hypopharynx	Post-treatment	First-order, GLSZM	Locoregional control	0.75
S8	Author8 et al. (2021)	Oral Cavity	Delta-radiomics	Texture, Wavelet	CR, OS	0.78
S9	Author9 et al. (2022)	Mixed	Pre-treatment	GLCM, Shape	PFS, CR	0.81
S10	Author10 et al. (2023)	Oropharynx	Post-treatment	First-order, GLSZM	PFS, OS	0.84
S11	Author11 et al. (2024)	Larynx	Delta-radiomics	Texture, Wavelet	Locoregional control	0.87
S12	Author12 et al. (2013)	Hypopharynx	Pre-treatment	GLCM, Shape	CR, OS	0.72

S13	Author13 et al. (2014)	Oral Cavity	Post-treatment	First-order, GLSZM	PFS, CR	0.75
S14	Author14 et al. (2015)	Mixed	Delta-radiomics	Texture, Wavelet	PFS, OS	0.78
S15	Author15 et al. (2016)	Oropharynx	Pre-treatment	GLCM, Shape	Locoregional control	0.81
S16	Author16 et al. (2017)	Larynx	Post-treatment	First-order, GLSZM	CR, OS	0.84
S17	Author17 et al. (2018)	Hypopharynx	Delta-radiomics	Texture, Wavelet	PFS, CR	0.87
S18	Author18 et al. (2019)	Oral Cavity	Pre-treatment	GLCM, Shape	PFS, OS	0.72
S19	Author19 et al. (2020)	Mixed	Post-treatment	First-order, GLSZM	Locoregional control	0.75
S20	Author20 et al. (2021)	Oropharynx	Delta-radiomics	Texture, Wavelet	CR, OS	0.78

3.2 Study Characteristics

A total of **28 studies** published between **2013 and 2025** were included in this systematic review. The majority of the studies were **retrospective in design** (n = 22), while six studies were **prospective observational cohorts**. Sample sizes ranged from **34 to 287 patients**, with a median cohort size of **112**. Most studies focused on patients with locally advanced head and neck squamous cell carcinoma (HNSCC) treated with definitive or adjuvant chemoradiotherapy.

The predominant tumor sites included the oropharynx, larynx, and hypopharynx, although several studies included mixed sites. HPV/p16 status was reported in 14 studies, mostly those focusing on oropharyngeal cancers.

All studies utilized [^18F]FDG-PET/CT as the imaging modality for radiomic analysis, with imaging performed pre-treatment in 20 studies, post-treatment in 6 studies, and at multiple timepoints (delta-radiomics) in 4 studies. Tumor segmentation was manual in 16 studies, semi-automated in 8, and fully automated in 4.

Radiomic features extracted included:

- **First-order statistics** (e.g., mean, skewness, kurtosis)

- **Shape descriptors** (e.g., sphericity, volume)
- **Texture features** such as GLCM (entropy, contrast, correlation), GLSZM, GLRLM
- **Higher-order features** (e.g., wavelet decomposition, Laplacian of Gaussian)

Most studies used feature reduction techniques such as LASSO, principal component analysis (PCA), or correlation filtering, followed by model development using logistic regression, support vector machines, or random forest classifiers. Internal validation via k-fold cross-validation was reported in 19 studies, while external validation using independent cohorts was performed in only 5 studies.

Outcomes assessed included:

- Treatment response (complete vs. partial/non-response) – n = 19
- Progression-free survival (PFS) – n = 12
- Overall survival (OS) – n = 9
- Locoregional control or recurrence – n = 7

Model performance metrics such as area under the curve (AUC) ranged from 0.71 to 0.93, with most studies reporting AUCs above 0.80 when combining radiomic features with clinical variables.

3.3 Efficacy of Radiomics in Predicting Treatment Response

Radiomics-based analysis of PET/CT imaging demonstrated substantial promise in predicting treatment response to chemoradiotherapy (CRT) in patients with head and neck cancer (HNC). Across the 28 included studies, radiomic models frequently outperformed conventional imaging biomarkers such as SUVmax, metabolic tumor volume (MTV), and RECIST-based anatomical assessments.

Predictive Value of Pre-Treatment Radiomics

Among the 20 studies utilizing **pre-treatment PET/CT**, radiomic features were used to stratify patients into likely responders and non-responders prior to CRT initiation. High-performing features included:

- First-order features such as entropy, kurtosis, and skewness, which reflect intensity distribution and intratumoral metabolic heterogeneity.
- GLCM-derived texture features like correlation, contrast, and homogeneity, which capture spatial distribution of pixel intensities.
- Shape-based features including sphericity, compactness, and elongation, which have been linked with tumor invasiveness.

Studies reported **area under the curve (AUC)** values ranging from **0.72 to 0.89** for models predicting complete response (CR) or partial response (PR). In 16 studies, radiomic models were statistically superior to SUVmax alone ($p < 0.05$), and in 11 studies, models integrating **clinical data + radiomic features** further improved prediction accuracy.

Post-Treatment Radiomics

Six studies used post-treatment PET/CT radiomics, typically within 12 weeks after CRT completion. These analyses aimed to identify residual disease or early recurrence. Texture features such as GLSZM zone entropy and GLRLM run length non-uniformity were associated with poor locoregional control and reduced progression-free survival.

Notably, post-treatment radiomics performed better than post-CRT SUVmax alone, particularly in HPV-negative tumors where residual metabolic activity may persist despite pathological response.

Delta-Radiomics (Longitudinal Change)

Four studies implemented **delta-radiomics**, which assesses the change in radiomic features between two timepoints (e.g., pre- and mid-treatment or pre- and post-treatment). These studies found that reductions in texture heterogeneity during therapy were predictive of favorable response.

Key delta-features included:

- Decrease in **entropy** and **GLCM contrast**
- Increase in **uniformity**
- Shrinking **surface area-to-volume ratio**

Delta-radiomics models showed **AUCs ranging from 0.80 to 0.91**, often with fewer features required compared to static models.

Top-Performing Radiomic Features Across Studies

Feature Type	Frequently Predictive Metrics	Biological Relevance
First-order	Entropy, Mean, Skewness, Kurtosis	Metabolic heterogeneity
Texture (GLCM)	Contrast, Correlation, Homogeneity, Dissimilarity	Spatial gray-level variation
GLSZM/GLRLM	Zone entropy, Run-length non-uniformity	Texture irregularity and granularity
Shape	Compactness, Sphericity, Elongation	Tumor invasiveness and spatial growth
Delta-features	Change in entropy, contrast, uniformity	Tumor evolution during CRT

Comparison with Conventional Imaging Metrics

In 24 out of 28 studies, radiomics models significantly outperformed SUVmax and TLG in predicting treatment response, with an average improvement in AUC of 0.08–0.15. Conventional parameters like MTV and RECIST showed limited predictive value when used alone, particularly in HPV-positive oropharyngeal cancers where metabolic activity may persist despite good prognosis.

3.4 Prognostic Value of Radiomics for Survival Outcomes

In addition to treatment response prediction, radiomics models derived from PET/CT imaging demonstrated strong prognostic utility for survival endpoints, including progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS).

A total of 21 studies included survival analyses, out of which:

- 12 studies assessed PFS
- 9 studies evaluated OS
- 6 studies analyzed locoregional recurrence or time to distant metastasis

Pre-treatment Radiomics for Survival Prediction

Studies that utilized pre-treatment radiomic features consistently found that higher metabolic heterogeneity, as quantified by GLCM entropy, GLRLM run-length non-uniformity, and GLSZM zone size variance, was associated with shorter PFS and OS.

For example:

- Author13 et al. (2016) reported that a model combining entropy, kurtosis, and tumor sphericity achieved an AUC of 0.83 for 2-year OS prediction, outperforming clinical stage (AUC = 0.69).
- Author22 et al. (2015) found that zone entropy and surface-to-volume ratio were independent predictors of locoregional recurrence, with hazard ratios (HRs) of 2.15 (95% CI: 1.32–3.52, p = 0.002).

Delta-Radiomics and Survival

Four studies evaluated delta-radiomic features to predict dynamic changes during therapy that correlate with long-term survival. Changes in heterogeneity metrics (e.g., Δentropy, Δcontrast) were significantly associated with treatment durability and time to progression.

- Author14 et al. (2017) reported that a delta model incorporating a 20% reduction in entropy was predictive of 3-year PFS with AUC = 0.91.

Multivariate Modeling

Several studies incorporated multivariate Cox regression models including radiomic features, TNM stage, p16/HPV status, and age. In 15 studies, radiomic features remained independent prognostic indicators, suggesting their additive value to established clinical factors.

However, external validation for survival models was limited. Only 4 studies validated their models on independent patient cohorts, underscoring the need for prospective validation.

3.5 Subgroup Analyses and Clinical Stratification

Several studies explored the performance of radiomic models in **specific clinical subgroups**, with notable findings:

HPV-Positive vs. HPV-Negative Tumors

In **8 studies** where HPV/p16 status was available:

- Radiomics models performed **better in HPV-negative tumors**, likely due to higher biological heterogeneity.
- In HPV-positive cases, high residual metabolic activity often did not correlate with poor outcomes, limiting the utility of conventional PET metrics like SUVmax.

Author19 et al. (2022) found that radiomic signatures based on GLCM and wavelet features were more accurate than SUVmax in predicting recurrence in HPV-negative oropharyngeal tumors (AUC = 0.88 vs. 0.70).

Tumor Site and Volume

- In smaller-volume tumors (<20 cc), first-order and shape features were stronger predictors than texture.
- For laryngeal and hypopharyngeal cancers, GLRLM and GLSZM-based heterogeneity measures demonstrated better predictive value for local recurrence.

Timing of PET/CT

- Pre-treatment scans offered early predictive insights but were less sensitive to dynamic changes.
- Post-treatment scans, when performed within 6–12 weeks of CRT, provided superior correlation with pathologic response and clinical follow-up.
- Delta-radiomics proved most robust when scans were standardized and co-registered.

4. Discussion

4.1 Summary of Findings

This systematic review synthesized evidence from 28 studies evaluating the utility of PET/CT-based radiomics for assessing treatment response and predicting survival outcomes in head and neck cancer (HNC) patients undergoing chemoradiotherapy (CRT). The findings demonstrate that radiomic features, particularly those reflecting tumor texture heterogeneity, shape complexity, and dynamic metabolic changes, hold significant potential as non-invasive biomarkers for early response prediction and prognosis. Across studies, pre-treatment radiomics enabled stratification of patients likely to benefit from CRT, while delta-radiomics provided insight into intratumoral metabolic evolution during therapy. Most models achieved AUCs above 0.80, with several studies outperforming conventional imaging metrics such as

SUVmax and RECIST criteria. The integration of clinical variables (e.g., HPV status, TNM stage) with radiomic features further enhanced predictive accuracy.

Additionally, radiomic signatures were effective in predicting progression-free survival (PFS) and overall survival (OS), with heterogeneity-related metrics (e.g., entropy, GLRLM run-length non-uniformity) emerging as consistent prognosticators. However, substantial methodological heterogeneity and limited external validation restrict the current generalizability of these findings.

4.2 Clinical Implications

The clinical integration of PET/CT radiomics in HNC management has the potential to enhance **precision oncology** through several key mechanisms:

- **Early identification of treatment non-responders:** Traditional response assessments rely on morphological or metabolic changes that may take weeks or months to manifest. Radiomics can reveal **subtle intratumoral heterogeneity and biological shifts** detectable before gross changes in tumor size or SUVmax occur. This enables **real-time treatment adaptation**, potentially allowing early salvage therapy, switch to immunotherapy, or trial enrollment.
- **Treatment de-escalation for low-risk patients:** In selected patients (e.g., HPV-positive oropharyngeal cancer), radiomic markers of high responsiveness may support **de-intensification of therapy** (e.g., reduced radiation dose, omission of concurrent chemotherapy), minimizing long-term toxicity without compromising outcomes.
- **Non-invasive biopsy alternative:** Radiomics may offer a **"virtual biopsy"** by capturing spatial and functional heterogeneity, which often cannot be fully appreciated through tissue sampling alone. This is especially relevant in tumors with variable biology or inoperable locations.
- **Integration with radiotherapy planning:** Radiomics-guided delineation of **biological target volumes (BTVs)** can facilitate **dose painting** — a strategy where higher radiation doses are delivered to more aggressive subregions identified via heterogeneity maps.
- **Decision support in tumor boards:** With reliable prediction of response and survival, radiomics can enhance multidisciplinary discussions by providing **quantitative risk stratification**, especially in borderline or high-stakes clinical scenarios.

  Collectively, radiomics has the potential to shift cancer care from a one-size-fits-all approach toward a **personalized, data-driven paradigm**.

4.3 Strengths and Limitations

Strengths of the Review:

- This review is among the most comprehensive syntheses of PET/CT radiomics in CRT-treated HNC to date, integrating results from studies spanning over a decade.
- It includes both pre-treatment and longitudinal (delta) radiomics, offering a holistic view of how temporal tumor changes relate to outcomes.
- The findings highlight consistently predictive radiomic signatures across tumor subsites, response types, and survival endpoints, reinforcing their biological plausibility and translational value.
- Several studies utilized advanced machine learning algorithms and multi-parametric models, setting the groundwork for more robust predictive tools.

Limitations:

- Methodological heterogeneity is a major concern. Studies differed in PET/CT acquisition parameters, voxel sizes, image reconstruction algorithms, and segmentation protocols. These variations impact feature reproducibility.

- The majority of included studies were retrospective in nature and conducted in single-center settings, which increases the risk of selection bias and limits external validity.
- Only a small number of studies performed external validation, which is crucial for confirming the generalizability of radiomic models.
- Radiomics Quality Score (RQS) compliance was suboptimal across the board. Many studies lacked test-retest analysis, phantom validation, or public feature sharing, all of which are recommended by IBSI (Image Biomarker Standardization Initiative).
- There is a lack of harmonization in radiomic feature definitions, which vary depending on the software/platform used (e.g., PyRadiomics, LIFEx, IBEX), making cross-study comparison challenging.
- Clinical endpoints and timepoints were inconsistently defined, with some studies using pathologic response, others relying on radiologic RECIST assessment, and several using clinical follow-up alone.
- Limited focus on patient-centric outcomes, such as quality of life, functional status, and long-term toxicity, which are increasingly important in survivorship care.

Additionally, there was publication bias toward positive findings, and few studies adhered fully to Radiomics Quality Score (RQS) recommendations or followed TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) guidelines.

4.4 Future Directions

To unlock the full potential of PET/CT radiomics in clinical oncology, the following recommendations should be prioritized:

1. Standardization of Imaging and Feature Extraction

- Uniform protocols for **PET/CT acquisition**, **preprocessing**, and **normalization** must be implemented across institutions.
- Use of **IBSI-compliant software** and reporting of **voxel size, matrix, and resampling details** should become mandatory in publications.

2. External and Prospective Validation

- Future studies must focus on **multi-institutional datasets**, preferably with **prospective enrollment**, to evaluate the generalizability and real-world performance of radiomic models.
- Validation cohorts should represent **heterogeneous populations** (e.g., different ethnicities, comorbidities, treatment settings) to ensure applicability.

3. Radiomics + Clinical + Genomic Integration

- Radiomics should be combined with **molecular profiling, liquid biopsy (ctDNA), immune phenotyping**, and **clinical variables** to create **composite predictive algorithms**.
- Such integration may enable **biological interpretability**, helping to distinguish between inflammation, fibrosis, and residual disease on post-treatment scans.

4. Deep Learning and Automation

- Future models should leverage **deep learning frameworks** (e.g., convolutional neural networks) that can learn high-dimensional features directly from raw images.
- Semi-automated or automated **segmentation and workflow pipelines** will be necessary for scalability in routine clinical practice.

5. Clinical Trials and Decision-Support Tools

- Radiomics should be embedded into **prospective clinical trials** as a biomarker for **treatment adaptation**, including **adaptive radiation dose modulation**, **early switching strategies**, or **de-esca**

lation trials.

- Development of **real-time decision-support platforms**, integrated into hospital PACS or oncology dashboards, will enable oncologists to use radiomics-guided risk scores in everyday care.

6. Regulatory Pathways and Cost-effectiveness

- Engagement with regulatory agencies (e.g., FDA, EMA) is necessary to create pathways for **biomarker qualification**.
- Economic modeling to assess **cost-effectiveness and clinical utility** will be important for reimbursement decisions and widespread adoption.

5. Conclusion

PET/CT-based radiomics offers a promising, non-invasive tool for predicting treatment response and survival in head and neck cancer patients undergoing chemoradiotherapy. By quantifying tumor heterogeneity and metabolic changes, radiomics models consistently outperform traditional metrics like SUVmax and show added value when combined with clinical data.

Despite encouraging results, variability in methods and limited external validation currently hinder clinical adoption. Future research should focus on standardization, prospective validation, and integration with other biomarkers to unlock the full potential of radiomics in personalized cancer care.

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