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Review

Radiomics-Guided Precision Radiation Therapy in Head and Neck Squamous Cell Carcinoma

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Simple Summary: Recent advances in artificial intelligence and automated image analysis have enabled clinicians to extract quantitative features from medical images, such as CT, MRI, or PET scans, beyond what is perceptible to the human eye. These features, known as radiomics, provide detailed information about tumor shape, texture, and heterogeneity, which are relevant to clinical outcomes. Radiomics information can help clinicians predict tumor response to specific treatments, assess the likelihood of recurrence, and estimate overall survival outcomes. In this article, we provide an overview of recent studies in the field of radiomics aimed at guiding personalized radiotherapy in patients with head and neck cancers.

Abstract: Radiomics and deep learning computer vision algorithms can extract clinically relevant information from medical images, providing valuable insights for accurate diagnosis of cancerous lesions, tumor differentiation and molecular subtyping, prediction of treatment response, and prognostication of long-term outcomes. In head and neck squamous cell carcinoma (HNSCC), growing evidence supports the potential role of radiomics and deep learning models in predicting treatment response, long-term outcomes, and treatment complications following radiation therapy. This is especially important given the pivotal role of radiotherapy in early-stage and locally advanced HNSCC, as well as in post-operative and concomitant chemoradiotherapy. In this article, we summarize recent studies highlighting the role of radiomics in predicting early post-radiotherapy response, locoregional recurrence, survival outcomes, and treatment-related complications. Radiomics-guided tools have the potential to personalize HNSCC radiation treatment by identifying low-risk patients who may benefit from de-intensified therapy and high-risk individuals who require more aggressive treatment strategies.

Keywords: head and neck tumor; oropharyngeal squamous cell carcinoma; radiomics; radiation therapy; machine learning

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1. Introduction

Most head and neck tumors arise from epithelial cells; consequently, squamous cell carcinoma accounts for approximately 90% of cancers in head and neck. Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer globally, resulting in more than 300,000 deaths annually [1]. In recent decades, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) form has been rising, particularly in Europe and USA, due to increased rates of Human Papillomavirus (HPV) infection [2,3]. The most recent

global incidence of OPSCC is estimated at approximately 93,000 new cases per year [4]. According to the most recent (8th) edition of the American Joint Committee on Cancer (AJCC) staging system, OPSCC is referred to as HNSCC in the posterior one-third and base of the tongue, tonsils, soft palate, uvula, and the posterior and lateral pharyngeal walls [5]. Due to their divergent prognosis, the 8th edition of AJCC has categorized OPSCC into HPV-associated and non-HPV-associated subtypes [5]. Given the favorable response of primary tumors and cervical lymphadenopathy in HPV-associated OPSCC, radiation therapy has become the primary treatment modality for small tumors, combined with surgery for larger or advanced disease, or along with chemotherapy in the case of locally advanced disease. Thus, there is active research focused at improving radiation treatment planning, post-therapy surveillance, prediction of locoregional recurrence, and accurate prognostication in HNSCC, and particularly OPSCC. Radiomics and computer vision have the capacity to guide precision radiation therapy by extracting biologically relevant imaging patterns from medical scans that are typically imperceptible to the human eye.

Recent advancements in imaging technology and statistical algorithms have given rise to radiomics, a field focused on extracting quantitative features, such as shape, intensity, and texture, from medical imaging modalities like computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound [6]. While radiomics extracts imaging features based on predefined algorithms, deep learning computer vision algorithms can identify novel patterns from medical scans through an iterative training process. A growing body of evidence highlights the capability of radiomics and deep learning computer vision algorithms in the diagnosis, molecular subtyping, differentiation, and prognostication of HNSCC [7]. In this article, we summarized the most recent advances in image-guided precision radiation therapy of HNSCC with emphasis on predicting treatment response, locoregional recurrence, post-radiation complications, and survival in OPSCC patients.

2. Methods

2.1. Literature Search Strategy

We performed a comprehensive search of the literature in PubMed and Google Scholar dataset. The primary key search terms included “radiomics”, “radiotherapy”, “oropharyngeal”, “head and neck”, and “squamous cell carcinoma”, which are directly related to the central theme of the review. Additionally, terms like “treatment response”, “post-radiation”, or “after radiation” were incorporated to target studies focusing on post-radiation outcomes and prognostic factors. Specific terms like “recurrence” and “locoregional” were employed to identify studies predicting locoregional recurrence, and terms such as “progression free survival” and “overall survival” were used to target studies about prediction of overall survival, adding the terms “complications”, “post-radiation”, and “xerostomia” to identify challenges occurring in patients due to radiation treatment. Finally, terms like “machine learning”, “deep learning”, “prediction”, and “hybrid model” were incorporated to identify different applications and techniques that were used. Boolean operators AND and OR were utilized to refine search results. For instance, the combination “(radiomics) OR (radiotherapy) AND ((oropharyngeal) OR (head and neck) OR (squamous cell carcinoma)) AND (treatment response)” identified papers focusing on radiomics related to oropharyngeal cancer and how it is affected by radiotherapy treatment. This search string was applied on the PubMed and Google Scholar databases to search for words in all fields.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria for our review were as follows: articles written in English, research-focused studies, specifically addressing HNSCC, and employing radiomics or

deep learning analysis of cross-sectional imaging modalities such as CT, MRI, or PET. Exclusion criteria were non-research article types such as abstracts, conference proceedings, or editorials, as well as studies utilizing ultrasound imaging, which lacks the resolution and detail required for radiomics analysis. Additionally, we excluded studies focused on metastatic head and neck cancer, as our aim was to explore primary tumors to maintain a clear and consistent scope. Exclusion criteria were abstract or conference article types, editorial, ultrasound imaging, and metastatic head and neck cancer. We collected over 43 related papers from 2014 to 2024 to summarize in this review.

2.3. Review Structure

In this review, we have summarized the findings of articles in each subsection and provided additional details in the corresponding tables. The tables include the year of publication, total number of subjects, and whether the study focused solely on the OPSCC subtype or included HNSCC from various subsites. They also summarize the total sample size, cross-sectional imaging modality, and results of the best-performing models. For radiomics studies, the machine learning models are listed, while models using deep learning are prefixed with "DL-". Additionally, we have clearly indicated whether the models were based solely on radiomics/image inputs or incorporated both radiomics/image and clinical variables as inputs.

3. Results

3.1. Tumor Characteristics

OPSCC accounted for the majority of HNSCC cases in the articles included in this review. Six studies focused exclusively on radiomics in OPSCC; two of these studies specifically examined HPV-associated OPSCC, with the largest sample size being 190 patients [8]. Other studies included patients with HNSCC, with the largest sample size reaching 2552 patients [9], involving two external collaborators. The smallest sample size was 21 patients with osteoradionecrosis, a condition related to radiation therapy, drawn from a cohort of 83 OPSCC patients [10]. Notably, one study included both lung and head and neck cancers [11], exploring a lung-derived radiomic signature for prognostication in head and neck tumors [11].

3.2. Imaging Modalities

Due to their widespread availability and relatively standardized image intensity values across different scanners, many studies have utilized CT images for HNSCC radiomics analysis and deep learning models. Many researchers have used contrast-enhanced CT, as it inherently provides better visual delineation of tumoral lesions. Additionally, cone-beam CT and Megavoltage CT scans, used for longitudinal treatment response assessments, can provide imaging input for prognostic models, although they tend to have lower signal-to-noise ratio [12,13].

Compared to CT images, which primarily capture the structural or morphological properties of tumors, PET radiomics provides quantitative metrics of tumor functional or metabolic activity using radiotracers such as fluorodeoxyglucose (FDG), fluoromisonidazole, and fluorothymidine [14–16]. Notably, one study demonstrated that 50% of the features extracted from 18-FDG PET achieved an intraclass correlation coefficient ≥ 0.8 between manual and various automated segmentation methods in OPSCC, indicating sufficient reproducibility for radiomics analysis [17]. In addition, PET/CT surveillance is commonly recommended for assessing treatment response, typically performed at baseline and during the 3-month post-treatment follow-up [18]. This sequential series of PET/CT scans provides a valuable resource for radiomics analysis of treatment response in HNSCC.

However, despite the high sensitivity and negative predictive value, PET/CT has the caveat of high false positive rates due to post-treatment inflammation [18]. Furthermore, studies have shown that combining PET and CT radiomic features can more accurately predict local recurrence than models based on either PET or CT alone [16], even when analyzing sub-volumes or subregions of tumors [19–21].

MRI is the preferred modality for evaluating soft tissue involvement in HNSCC. Radiomics features from pre- and post-contrast T1-weighted images have been used in HNSCC prognostication, predicting HPV status, and radiation-induced xerostomia [22–25]. Diffusion-weighted imaging (DWI), which reflects tumoral cellularity, has also been valuable. One study demonstrated that apparent diffusion coefficient (ADC) maps can detect significant changes in HNSCC heterogeneity and residual disease as early as 6 weeks post-chemoradiotherapy [26]

Finally, ultrasound scans can provide quantitative parameters that reflect detailed microstructural information of tissues. Radiomic features extracted from ultrasound images, such as the spectral intercept from metastatic lymph nodes, can predict treatment response after chemoradiation in HNSCC [27,28].

3.3. Input for Prognostic Models

Different studies have utilized 2D slices, 3D volume of interests or volumetric patches from CT, MRI, PET scans, and ultrasound to compute radiomic features or serve as input for deep learning algorithms in post-radiation prognostication of HNSCC. In radiation therapy, gross tumor volume (GTV) refers to the volume encompassing the primary tumor and any involved lymph nodes [19]. Many groups have used the GTV masks as input for their radiomics and deep learning models. In addition, the planning target volume (PTV) includes the additional margin besides GTV, considering physiologic organ mobility during therapy and uncertain positioning [29]. Some authors suggested that both GTV and PTV radiomics features can provide prognostic information regarding HNSCC recurrence and survival [30]. Many other studies have used manually or automatically segmented regions of interest (ROIs) on diagnostic scans as input for their models.

The inclusion of demographic information and clinical risk factors—such as age, gender, tobacco and alcohol use, HPV status, tumor site, T- and N-stage, and treatment paradigm—alongside imaging data improves radiomics or deep learning models' performance compared to using individual inputs alone [8,12,19,23,25,31]. Models using CT+PET+Clinical, CT+PET+Dose+Clinical, or CT+MR+Dose+Clinical data as input have demonstrated improved predictions of locoregional recurrence, radiation-induced oral mucositis, and xerostomia, offering potential for personalized radiotherapy in OPSCC patients [20,24,32,33].

3.4. Prediction of Early Post-Radiation Treatment Response

Post-radiation treatment response is typically evaluated 3 months after completing therapy using radiological scans. Locoregional failure is defined when there is less than a 25% decrease in lesion volume from pre-treatment to 3-month post-treatment evaluation scans, or when local, regional, or distant recurrence, or new disease is confirmed through histopathology, imaging, and clinical examination [34]. In contrast, locoregional control is achieved when there is no histopathologically proven local residual tumor, recurrence, metastatic lymphadenopathy, or metastases [23]. Patients with locoregional control and no residual disease at the primary tumor site or within lymph nodes are considered to have a "complete" treatment response. Patients who do not meet the criteria for complete response or locoregional failure are classified as "partial" responders.

Although OPSCC patients typically show a high rate of early treatment response to radiation therapy, a significant number of patients experience residual or recurrent disease, which can lead to considerable deterioration, toxicity, and mortality. As a result, there is growing interest in identifying radiomic features that can predict treatment response, with the goal of improving radiation treatment planning, increasing the rate of complete responses, and preventing locoregional failure.

Table 1 summarizes recent studies that utilized radiomics to predict early post-radiation treatment response. One study found that certain CT radiomic features were predictive of locoregional control, achieving a validation area under the curve (AUC) of 0.78, while none of the PET features reached this level of predictive accuracy [35]. Another study demonstrated that PET radiomic models, applied post-chemoradiotherapy, were predictive of locoregional control in HNSCC, with a validation AUC of 0.76 [36]. Additionally, an MRI-based radiomics model predicted post-radiation locoregional control with an AUC of 0.740 [23]. Combination of radiomics and clinical variables substantially improved the predictive performance of models [12,22,23].

Table 1. Prediction of early post-radiation treatment response.

Author, Year	Sample Size	Imaging Modality	Machine Learning Model	Input for Model with Best Performance
Bogowicz et al., 2017 [36]	178 HNSCC	18F-FDG PET	PCA, LASSO, Cox Regression	Radiom CV-CI: 0.76
Bos et al., 2021 [23]	177 OPSCC	contrast-T1W MRI	LR	Radiom+Clin Test-AUC: 0.745
Bos et al., 2023 [22]	157 OPSCC	contrast-T1W MRI	LR	Radiom+Clin CV-AUC: 0.68
Osapoetra et al., 2024 [28]	55 HNSCC	QUS	SVM, LDA, k-NN, ANN	Radiom Test-AUC: 0.77
Sellami et al., 2022 [12]	93 HNSCC	CBCT	LR	Radiom+Clin CV-AUC: 0.80
Starke et al., 2023 [35]	55 HNSCC	CT, FDG-PET	CPH	Radiom CV-CI: 0.78
Tran et al., 2019 [27]	32 HNSCC	QUS	k-NN, Naive-Bayes, LR	Radiom AUC: 0.91
Ulrich et al., 2019 [14]	30 HNSCC	FLT-PET	AP, Cox regression	Radiom CI: 0.86

ANN: artificial neural network; AP: affinity propagation; AUC: area under the receiver operating characteristics curve; CBCT: cone-beam CT; CI: concordance index; Clin: clinical model; CPH: Cox Proportional Hazards; CT: computed tomography; CV: cross-validation; FDG: fluorodeoxyglucose; FLT: fluorothymidine; HNSCCs: head and neck squamous cell carcinomas; k-NN: k-nearest neighbors; LASSO: least absolute shrinkage and selection operator; LDA: linear discriminant analysis; LR: Logistic Regression; MRI: magnetic resonance imaging; OPSCC: oropharyngeal squamous cell carcinoma; PCA: Principal Component Analysis; PET: positron emission tomography; QUS: quantitative ultrasound; Radiom: radiomics model; SVM: Support Vector Machine.

Among radiomic features, several common characteristics have emerged as predictive of early post-radiation treatment response. Regarding tumor size and shape, smaller and more spherical lesions at baseline have been associated with better treatment responses [14,34,37]. In addition, textural features such as coarseness and grey-level parameters of the primary tumor have shown promise in predicting treatment response across different imaging modalities [12,14,26]. Such textural features have also demonstrated higher sensitivity and specificity in distinguishing metastatic lymph nodes between complete and partial response groups in HNSCC [27]. Overall, rounder and more homogeneous tumors are generally associated with more favorable treatment response, while tumors exhibiting greater heterogeneity and irregularity are linked to poorer outcomes.

Notably, some studies have proposed delta-radiomics to assess treatment response, quantifying the temporal evolution of radiomic features by calculating the difference (delta) or relative change between pre-treatment and inter- or post-treatment scans [38]. Radiomic features that show significant relative differences—such as those with an AUC > 0.65 at each time point—are selected as delta-radiomics features. For example, one study found that HNSCC patients with high coarseness parameters from cone-beam CT images at the fourth week of treatment were the best responders to radiotherapy [12]. Another study, using pre-treatment and inter-treatment CT and FDG-PET imaging, demonstrated that CT and FDG-PET features performed differently in overall discrimination and patient stratification during weeks two and three of treatment [35]. Similarly, a quantitative ultrasound delta-radiomics model from four different classifiers showed improved performance in predicting 3-month post-treatment response after the first week of radiation in HNSCC patients [28]. These findings suggest that models trained on delta-radiomics features can provide earlier and more reliable prognostication, facilitating personalized and timely treatment strategy modification.

3.5. Prediction of Locoregional Recurrence

Locoregional recurrence refers to the return of HNSCC in the same anatomical region as the original tumor or in nearby lymph nodes within the regional lymphatic drainage zone. Table 2 summarizes recent studies utilizing radiomics or deep learning models to predict post-radiation locoregional recurrence in HNSCC.

Using radiomics from contrast-enhanced CT, Wu et al. achieved an AUC of 0.77 in predicting locoregional recurrence [39], while peritumoral radiomics from contrast-enhanced CT achieved C-index values ranging from 0.32 to 0.61 [40]. Wang et al. have developed a multi-classifiers, multi-objectives, and multi-modalities model using delta-radiomics for prediction of HNSCC locoregional recurrence with an AUC of 0.80 [33,41]. Another model with inputs from CT, PET, dose distribution and clinical factors has achieved an average AUC of 0.892 by deep learning [19]. One of the most accurate models for predicting HNSCC recurrence used deep learning artificial neural networks based on GTV and PTV radiomic features from treatment-planning CT images, reaching an AUC greater than 0.9 [30]. Furthermore, using an attention-based multiple instance risk prediction model, Pan et al. quantitatively assessed relevant highest and lowest weighted intratumoral subregions in HNSCC and predicted the risk of locoregional recurrence [19]. Such an approach can direct precision radiation therapy to high-risk subregions of the tumor.

Locoregional recurrence also refers to the reappearance of tumors in regional lymph nodes. A recurrent node is defined as a new pathological node emerging after an initial complete response, in contrast to residual disease, which refers to a persistent pathological node observed at least 12 weeks post-treatment [42]. By combining several clinical variables and radiomic features from lymph nodes on pre-treatment contrast-enhanced CT, Zhai et al. predicted locoregional lymph node recurrence with a C-index of 0.80 in HNSCC [42]. Patients identified as being at higher risk for locoregional recurrence may be candidates for intensified radiation therapy.

Table 2. Prediction of locoregional recurrence.

Author, Year	Sample Size	Imaging Modality	Machine Learning Model	Input for Model with Best Performance
Bogowicz et al., 2021 [21]	40 HNSCC	CECT, FDG-PET/CT	LR	Radiom CV-AUC: 0.88
Cong et al., 2021 [16]	298 HNSCC	18F-FDG PET/CT	RF	Radiom+Clin CV-AUC: 0.70
Devakumar et al., 2021 [34]	31 HNSCC	CT, PET	LASSO, LR, Ridge Regression	CT-Radiom CV-AUC: 0.79
Fh et al., 2021 [30]	188 HNSCC	planning CT	DL-ANN	Radiom AUC: 0.956
Gangil et al., 2022 [31]	311 HNSCC	CECT	RF, KSVM, XGBoost	Radiom+Clin Mean-AUC: 0.98
Goncalves et al., 2022 [43]	183 HNSCC	CT	XGBoost, LR, RF, DT, MTP	Radiom+Clin AUC: 0.74
Haider et al., 2021 [8]	190 OPSCC	CT, PET	RSF	Radiom CV-CI: 0.76
Han et al., 2022 [20]	157 HNSCC	CT, PET	DL-DNN	Radiom+Clin Mean-AUC: 0.892
Keek et al., 2020 [40]	444 HNSCC	CECT	CPH, RSF	Radiom CV-CI: 0.74
Pan et al., 2023 [19]	228 HNSCC	CT, PET	Wilcoxon	Radiom+Clin Test-CI: 0.766
Wang et al., 2020 [33]	277 HNSCC	CT, PET	SVM, DA, LR	Radiom+Clin Test-AUC: 0.77
Wang et al., 2023 [41]	224 HNSCC	FDG-PET/CT	SVM, DA, LR	Radiom+Clin AUC: 0.80
Wu et al., 2024 [39]	192 HNSCC	CECT	SVM	Radiom Test-AUC: 0.770
Zhai et al., 2020 [42]	277 HNSCC	CECT	CPH	Radiom+Clin CV-CI: 0.80

ANN: artificial neural network; AUC: area under the receiver operating characteristics curve; CECT: contrast-enhanced CT; CI: concordance index; Clin: clinical model; CPH: Cox Proportional Hazards; CT: computed tomography; CV: cross-validation; DA: discriminant analysis; DL: deep learning; DNN: deep neural network; DT: Decision Tree; FDG: fluorodeoxyglucose; HNSCC: head and neck squamous cell carcinoma; KSVM: Kernel Support Vector Machine; LASSO: least absolute shrinkage and selection operator; LR: Logistic Regression; MRI: magnetic resonance imaging; MTP: Multilayer Perceptron; OPSCC: oropharyngeal squamous cell carcinoma; PET: positron emission tomography; Radiom: radiomics model; RF: Random Forest; RSF: random survival forest; SVM: Support Vector Machine.

3.6. Survival Prognostication

In survival analysis, the time gap from treatment to the occurrence of locoregional recurrence, distal metastasis, or the last follow-up visit is used to define progression-free survival [44]. Overall survival (OS) is the time from the first day of treatment until death for any cause [44], and the proportion of patients surviving after treatment in some defined or interested year(s) is referred to as overall survival rate. These survival metrics are the main measures to define anti-cancer treatment efficacy. Image-based prognostic tools can guide personalized radiation treatment by tailoring the intensity and type of treatment based on the predicted survival outcomes. Table 3 summarizes recent studies utilizing radiomics or deep learning models to predict progression-free survival and overall survival after radiation in HNSCC.

Our team showed that combined CT and PET radiomics can predict OS and PFS more accurately than AJCC staging in both HPV-associated and non-HPV-associated OPSCC [45]. Notably, the radiomics models usually had more accurate prognostic performance in HPV-associated OPCSS than the non-HPV-associated form [23]. It is also noteworthy that HPV-associated OPSCC are more sensitive to radiation therapy, and radiomics-based predictors

of survival in HPV can guide (de)intensification of radiotherapy in low-risk cohorts [46]. Overall, models that combine CT/MRI/PET-based radiomics with clinical variables usually perform better for the prediction of OS than models based on clinical variables or radiomic features alone [43]. For example, combination of pre-treatment T1-weighted MRI-based radiomics features with clinical variables improved OS prediction [25]. It is also shown that radiomic features from both GTV and PTV provide prognostic information regarding post-treatment survival [29,30]. Finally, it is notable that one study showing shape features such as sphericity and elongation had higher prognostic importance than texture features on baseline contrast-enhanced CT [37].

Table 3. Prediction of survival outcomes.

Author, Year	Sample Size	Imaging Modality	Machine Learning Model	Input for Model with Best Performance
Abe et al., 2023 [13]	100 HNSCC	planning CT	LASSO, Cox regression	Radiom Test-CI: 0.685
Aerts et al., 2014 [11]	231 HNSCC	CT	CPH	Radiom CV-CI: 0.69
Bernatz et al., 2023 [37]	157 HNSCC	CECT	EN, RSF	Radiom Test-AUC: 0.811
Boot et al., 2023 [25]	249 OPSCC	T1W-MRI	LR, RF	Radiom+Clin CI: 0.72
Bos et al., 2021 [23]	177 OPSCC	contrast-T1W MRI	LR	Radiom+Clin Test-AUC: 0.744
Fh et al., 2021 [30]	188 HNSCC	planning CT	DL-ANN	Radiom AUC: 0.9460
Goncalves et al., 2022 [43]	183 HNSCC	CT	XGBoost, LR, RF, DT, MTP	Radiom+Clin AUC: 0.91
Haider et al., 2020 [45]	311 OPSCC	PET/CT	RSF	Radiom CI: 062
Kazmierski et al., 2023 [9]	2552 HNSCC	planning CT	DL-MTLR	Radiom+Clin AUC: 0.823
Miller et al., 2019 [46]	38 OPSCC	CECT	LDA	Radiom AUC: 0.80
Tang et al., 2022 [29]	135 HNSCC	planning CT	DT, RF, EB, SVM, GLM (Linear)	Radiom AUC $\geq$ 0.920

ANN: artificial neural network; AUC: area under the receiver operating characteristics curve; CECT: contrast-enhanced CT; CI: concordance index; Clin: clinical model; CPH: Cox Proportional Hazards; CT: computed tomography; CV: cross-validation; DL: deep learning; DT: Decision Tree; EB: Extreme Boost; EN: elastic net; GLM (Linear): Generalized Linear Model (Linear); HNSCC: Head and neck squamous cell carcinoma; LASSO: least absolute shrinkage and selection operator; LDA: linear discriminant analysis; LR: Logistic Regression; MRI: magnetic resonance imaging; MTLR: Multitask Logistic Regression; MTP: Multilayer Perceptron; OPSCCs: oropharyngeal squamous cell carcinomas; PET: positron emission tomography; Radiom: radiomics model; RF: Random Forest; RSF: random survival forest; SVM: Support Vector Machine.

3.7. Prediction of Post-Radiation Complciations

Prediction of radiation-induced toxicities, such as mucositis, xerostomia, and dysphagia, can enable tailored treatment plans that minimize exposure to critical organs. Such predictive tools can guide radiation oncologists to adjust radiation dosage and select treatment modalities, such as intensity-modulated radiation therapy (IMRT), with lower likelihood of complications. Additionally, in patients requiring re-irradiation, predictive models can inform the decision-making process by weighing the risks against the benefits of radiotherapy. Early identification of high-risk patients also allows for closer monitoring, timely interventions and supportive care following radiotherapy. Recent studies have shown the potentials of radiomics to predict post-radiation toxicity and treatment complications in HNSCC patients (Table 4).

Table 4. Prediction of post-radiation toxicity and complications.

Author, Year	Complication, Sample Size	Imaging Modality	Machine Learning Model	Input for Model with Best Performance
Abdollahi et al., 2023 [47]	Xerostomia, 31 HNSCC	CT	LASSO	Radiom AUC: 0.89
Agheli et al., 2024 [32]	Oral mucositis, 49 HNSCC	CT	RF	Radiom+Clin AUC: 91.7%
Barua et al., 2021 [10]	Osteoradionecrosis, 21 OPSCC	CECT	MFPCA	Radiom AUC: 0.74
Sheikh et al., 2019 [24]	Xerostomia, 266 HNSCC	CT, contrast-T1W MRI	LASSO	Radiom+Clin CV-AUC: 0.68

AUC: area under the receiver operating characteristics curve; CECT: contrast-enhanced CT; Clin: clinical model; CT: computed tomography; CV: cross-validation; HNSCC: head and neck squamous cell carcinoma; LASSO: least absolute shrinkage and selection operator; MRI: magnetic resonance imaging; OPSCC: oropharyngeal squamous cell carcinoma; Radiom: radiomics model; RF: Random Forest; MFPCA: Multivariate Functional Principal Component Analysis.

Radiation-induced oral mucositis is one of the most common treatment complications affecting more than 90% of HNSCC patients, which can result in severe dysphagia and weight loss and may limit further treatment [48]. Combining treatment-planning CT radiomics features with clinical variables, Agheli et al. could predict post-radiation oral mucositis with AUC = 0.91 [32]. High-risk patients may benefit from prophylactic supportive care to prevent or alleviate the mucositis symptoms.

Xerostomia is another acute radiation-induced toxicity with 50 to 80% incidence rate in HNSCC, likely from radiation to salivary glands [49]. In a study on radiotherapy-induced xerostomia, delta features between mid-treatment and pre-treatment CT combined with dose parameters achieved an AUC of 0.89 [47]. In another study, the best predictive performance for post-radiation xerostomia was based on inputs from clinical, dose–volume histogram, CT and post-contrast T1-weighted MRI radiomic features [24].

Comparatively, osteoradionecrosis is a late complication caused by radiation to the mandibular bone, followed by reduced blood supply and osseous devitalization with an incidence between 1 and 16% [50] and variable severity from Grade I to IV [51]. In a cohort of 21 OPSCC patients, the temporal trajectory of radiomics features from contrast-enhanced CT achieved an AUC of 0.74 in predicting osteoradionecrosis [10]. They showed that sequential pre- and post-radiotherapy CT follow-up can provide predictive markers for radiation-induced mandibular osseous necrosis with potential for earlier intervention [10].

4. Discussion

We summarized the latest advances in the application of radiomics for post-radiation surveillance and prognostication in HNSCC. Radiomics and deep learning models have demonstrated considerable accuracy in predicting early post-radiotherapy treatment response, locoregional recurrence or failure, progression-free and overall survival, post-radiation toxicities and complications. Once the generalizability and reliability of such models are established by external and prospective validation, they can serve as valuable tools in guiding personalized radiation treatment planning for HNSCC.

Radiotherapy plays a critical role in the treatment of HNSCC, especially HPV-associated OPSCC, either as a standalone therapy or in combination with chemotherapy and surgery. Radiotherapy plays a major role as definitive/curative therapy or as an adjunct to surgery in early-stage and locally advanced HNSCC. In patients with positive surgical margins or discovery of lymph node involvement in surgery, post-operative radiotherapy has been shown to improve survival. Concomitant chemoradiotherapy has been the mainstay treatment for advanced HNSCC. There is also ongoing research into combining

radiotherapy with newer immunotherapy to improve outcomes. Radiomics-based models can improve patients' selection for dose deintensification in low-risk HNSCC versus more aggressive treatment strategies in high-risk individuals. Predicting post-radiation complications can guide preventive care or modified treatment strategies. However, it should be noted that the primary determinant of post-radiation complications is the radiation dose. Many radiomics studies—cited in this review article—assume that patients receive the same radiation dose, suggesting that tissue characteristics captured by radiomics can predict complications. This assumption does not account for the real-world variability in radiation doses and other confounding factors, limiting the applicability of these findings to diverse clinical settings. Overall, radiomics-based models have demonstrated significant potential in guiding precision radiotherapy for HNSCC.

Heterogeneity, resulting from subclones associated with different gene expressions and molecular phenotypes within subregions of a tumor, is a characteristic of HNSCC and represents different radiosensitivity or resistance [21,52]. Radiomics features that measure tumoral lesion texture heterogeneity on medical images reflect such histopathological variations in tumor subregions [53,54]. Thus, the combination of tumor size and shape feature and textural heterogeneity can provide prognostic information about treatment response and long-term outcomes.

A notable trend in many studies is the added value of incorporating multi-modal inputs into predictive models. Multiple studies have shown that combining radiomics from different imaging modalities (e.g., CT and PET), integrating clinical variables with radiomic data, or utilizing changes in radiomic features over time (e.g., delta-radiomics) can improve the prediction accuracy for different outcome metrics. This approach aligns with the concept of multi-omics, where abundant information from imaging, laboratory tests, genetic data, and clinical sources collectively informs personalized treatment strategies for cancer patients.

Moreover, the choice of imaging modality and input plays a critical role in radiomics analysis, as it directly impacts the quality and type of features extracted. Modalities such as CT, MRI, and PET provide distinct information: CT scans offer structural details, MRIs capture soft tissue properties, and PET scans represent metabolic activity. The radiomics methodology, including preprocessing, feature extraction, and selection, is equally important for ensuring reproducibility and robustness. Standardized protocols are essential to minimize variability and enhance the comparability of results across studies. Optimizing the synergy between image modality and analysis methodology is crucial for unlocking the full potential of radiomics in guiding precision HNSCC radiation therapy.

However, there are significant limitations in the adoption of radiomics-based models in clinical practice. One significant challenge is the heterogeneity of imaging data, which reduces the generalization of models across different centers. Normalizing signal intensities to a reference organ has been shown to improve model performance [55]. Another major limitation is the variability in lesion segmentation, as most radiomics models rely on segmentation masks of the tumor. The accuracy and reliability of segmentation are crucial for reproducibility of model performance. Some researchers have addressed this by selectively including radiomic features with strong inter- and intra-reviewer consistency to improve model generalization [45]. Additionally, the development of radiomics-based machine learning models requires large training datasets. Models trained on smaller cohorts are prone to overfitting, which can lead to overestimated accuracy and reduced generalizability. Finally, the constantly evolving treatment paradigms for HNSCC add another layer of complexity, requiring training of new models for reliable prognostication of novel therapies.

Our article is inherently limited by the absence of a formal systematic review process. However, we employed a transparent search strategy and detailed our inclusion

and exclusion criteria. Despite this, our comprehensive review lacks the rigorous article selection methodology and the potential for quantitative synthesis characteristics of systematic reviews. Major challenges for conducting a systematic review on radiomics-guided HNSCC radiation therapy are heterogeneity in cancer subsites of patient samples, differences in statistical comparison methods, inconsistency in validation processes, and variable outcome metrics. Additionally, there are very few articles addressing radiomics-based prediction of post-radiation complications. Additionally, although OPSCC, particularly the HPV-associated subtype, represents a biologically distinct cancer from other HNSCC types with different treatment responses, many studies did not stratify their results by HNSCC subsite, as shown in Tables 1–4. This represents a major limitation of the available studies; however, it may reflect the delayed recognition of OPSCC and the HPV-associated subtype as distinct cancer entities by the AJCC until 2018 [5]. In addition, there is a general sparsity of multi-omics analysis in HNSCC. We found no research articles combining radiomics with transcriptomics or metabolomics addressing HNSCC radiation therapy. However, Zhi et al. applied spatial transcriptomics and metabolomics to map the spatial location of cancer cells, fibroblasts, and immune cells in oral submucous fibrosis-derived tissues of oral squamous cell carcinoma [56]. They found that fibrosis-derived oral HNSCC cells undergo partial epithelial–mesenchymal transition within in situ carcinoma, eventually acquiring fibroblast-like phenotypes and contributing to collagen deposition [56]. Additionally, Li et al. compared metabolomics and transcriptomics of 73 HNSCC patients with 51 healthy controls, identifying four genes associated with seven differential metabolites [57]. These findings highlight both the potential and the knowledge gap of multi-omics analysis in guiding radiation therapy for HNSCC.

5. Conclusions

In summary, the information extracted from medical scans as radiomics or via deep learning computer vision models offers valuable prognostic markers to guide precision radiation therapy in HNSCC. Integrating radiomics from multiple imaging modalities, pre- and post-treatment scans, and incorporating clinical variables can improve the prognostic performance of these models. However, challenges such as the harmonization of image processing, lesion segmentation, and feature normalization must be addressed to develop models that are generalizable to clinical practice. Additionally, these prognostic tools will require continuous retraining to stay aligned with the evolving treatment paradigms in HNSCC.

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