

Radiomic Application for Head and Neck Squamocellular Tumor: Systematic Review

D. Messineo^{1*}, F. Massaro¹, P. Izzo², A. Milani³, R. Polimeni³, G. Iannella³, S. Marinozzi⁴, F. Consorti⁵, S. Cocuzza⁶, A. Maniaci⁶, A. Mucchino³, M. Nannarelli³, A. Greco³, G. Magliulo³, M. Salducci³, A. Pace³⁻⁵

¹Radiological, Oncological and Anatomic-Pathological Sciences Department, Sapienza University of Rome, Rome, Italy; ²Pietro Valdoni" Surgery Department I, Sapienza University of Rome, Rome, Italy; ³Organi di senso Department, Sapienza University of Rome, Rome, Italy; ⁴Department of Molecular Medicine, Unit of History of Medicine and Bioethics, Sapienza University of Rome, Rome, Italy; ⁵Scienze Chirurgiche Department, Sapienza University of Rome, Rome, Italy; ⁶Otorinolaringoiatria Department, University of Catania, Catania, Italy

Abstract

Radiomics represents the convergence of artificial intelligence and radiological data analysis, primarily applied in the diagnosis and treatment of cancer. In the head and neck region, squamous cell carcinoma is the most prevalent type of tumor. Recent radiomics research has revealed that specific bio-imaging characteristics correlate with various molecular features of Head and Neck Squamous Cell Carcinoma (HNSCC), particularly Human Papillomavirus (HPV). These tumors typically present a unique phenotype, often affecting younger patients, and show a favorable response to radiation therapy. This study provides a systematic review of the literature, summarizing the application of radiomics in the head and neck region. It offers a comprehensive analysis of radiomics-based studies on HNSCC, evaluating its potential for tumor evaluation, risk stratification, and outcome prediction in head and neck cancer treatment. *Clin Ter* 2024; 175 (2):153-160 doi: 10.7417/CT.2024.5048

Keywords: radiomics, head and neck cancer, squamous cellular tumor, HPV

Introduction

Radiomics represents a novel frontier in precision medicine, first introduced by Lambin et al. (1) as an effective method for analyzing specific radiological images using artificial intelligence. This technique is particularly vital in oncology, where analyzing thousands of diagnostic images (such as CT, MRI, PET-CT) is essential to capture details that are otherwise challenging to discern.

Radiomics involves four primary steps. Initially, it requires the acquisition of images (X-ray, CT, MRI, PET). Subsequently, a secondary segmentation process is undertaken on the volume of interest, typically a potential pathological lesion. This segmentation is executed via an expert

system that outlines the volume, delineates its boundaries, and incorporates all the acquisition slices into its radiomic protocol for further processing (2).

The subsequent stages involve feature extraction and analysis, tailored to each individual image identified by the system. The final phase is modeling, where the selected and extracted features are compiled into a database. This database is then used to develop predictive models for clinical outcomes. In oncological radiomics, these features can aid in constructing models to assess risks of locoregional metastasis or recurrence, and to estimate cancer survival probabilities (3). These radiomic models may incorporate not only extracted features but also clinical variables such as patient age, cancer stage, and analyses on samples, including HPV detection.

Globally, over 550,000 cases of head and neck cancers are diagnosed annually, ranking as the sixth most common neoplastic disease worldwide (4). The majority of these tumors originate from epithelial tissue, with squamous cell carcinomas accounting for about 90% of diagnosed histotypes. Established risk factors for head and neck cancers include smoking, alcohol consumption, and human papillomavirus (HPV) infection. The treatment approach, which may involve surgery, radiation therapy (XRT), or systemic chemotherapy (CHT), is primarily dictated by the staging at diagnosis. It is estimated that approximately 75% of these patients will benefit from radiation therapy for locoregional control (5). Currently, the development of biomarkers based on tumor radiomics is underway, aiming to gauge the neoplasm's response degree both prior to and during treatment.

Recent radiomics studies, including the 2019 study by Dr. Zhu (6), have highlighted how specific bioimaging features correlate with various molecular characteristics of Head and Neck Squamous Cell Carcinoma (HNSCC), especially HPV. This correlation in HNSCC is characterized by a distinctive tumor phenotype, often involving younger

Correspondence: D. Messineo, Viale dell'Università 33, 00165 Rome, Italy. Tel. +393397917573; email: daniela.messineo@uniroma1.it

patients, where primary tumors are smaller and present with significant cervical adenopathy at diagnosis, and exhibit a favorable response to radiation therapy.

This study conducts a systematic literature review to encapsulate the role of radiomics in the head and neck region. It provides an extensive overview of radiomics-enhanced studies on HNSCC tumors, focusing on their potential for tumor evaluation, risk stratification, and outcome prediction in head and neck cancer therapy.

Materials and Methods

Search Strategy

Our research was executed across several databases: PubMed, Cochrane, Scopus, and Embase. We utilized keywords including “head and neck” AND “radiomics” OR “texture” OR “histogram”. Further keywords such as “lymph node”, “HPV” OR “Human Papilloma Virus”, OR “treatment” OR “prediction” were integrated following a meticulous selection of MeSH terms. This approach directed our systematic analysis towards two primary facets of radiomic application in head and neck oncology: the prediction of treatment response and assessment of HPV status.

Inclusion and Exclusion Criteria

The timeframe for the selected studies spanned from 2010 to 2022. Excluded were articles not addressing squamous cell tumors or those discussing them from a

non-radiomics perspective. We also excluded publications available only as abstracts or those with text deemed too brief or non-informative, as well as systematic reviews. The inclusion criteria focused on articles in English with full texts accessible.

Inclusion criteria encompassed: 1) patients diagnosed with squamous cell head-neck tumors; 2) application of radiomics in delineating disease characteristics and/or response to treatments, including predictive analysis for specific treatments and/or tumor status assessment; 3) availability of data demonstrating statistical significance of clinical-radiological and radiomic correlations, in terms of AUC, sensitivity, specificity, and accuracy, or as a correlation coefficient (r).

Quality Assessment

The study was conducted adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines(7) (review registration: 351769). However, meta-analysis was not included due to the limited number of studies that provided adequate data and exhibited significant methodological diversity.

Data Extraction, Collection, Analysis, and Review

The analyzed model had to encompass radiomics-related features, but could also integrate additional clinical or pathological aspects. Other considerations included potential genetic or histological characteristics of the tumor, patient sample size, image acquisition type, radiomic feature types, algorithms for result prediction, and when feasible, the Machine Learning classifier employed.

Results

We identified 885 studies through a systematic review of the literature (7) (Fig. 1). After removing duplicates and

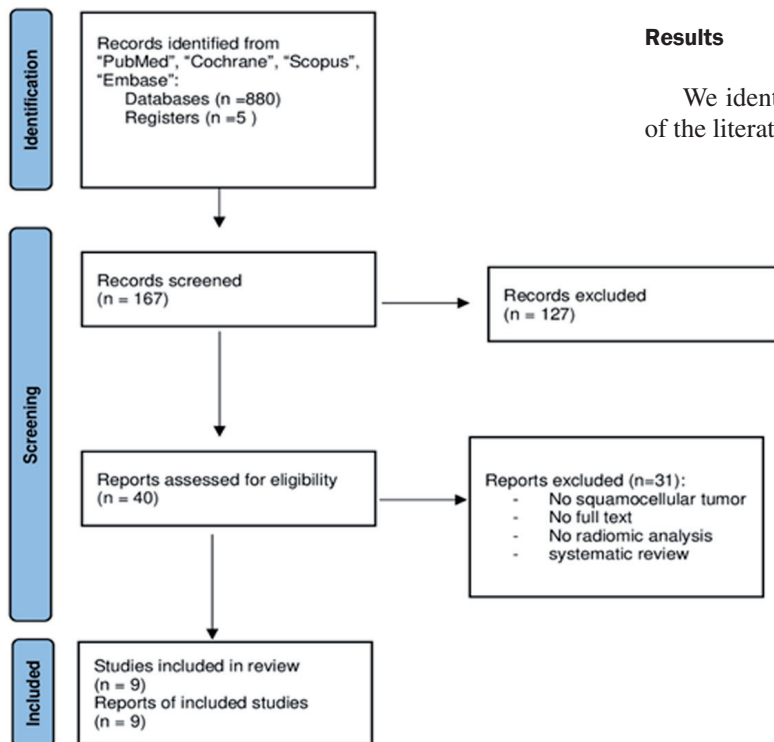


Fig. 1. PRISMA flow-chart

applying our specified criteria, 167 records were deemed potentially relevant. Subsequent record analysis and full-text screening excluded non-matching studies, leaving 40 articles. Studies reporting non-squamous cell tumors, lacking full texts, or not involving radiomic screening and systematic review were also excluded. Ultimately, 9 papers were included in the qualitative synthesis for data extraction(8-16).

Radiomic Analysis for Evaluation of Response to Therapy in Advanced Tumors and Lymph Node Metastases (Table 1)

Tran and Osapoetra et al.(8-10) conducted clinical trials to identify predictive markers of therapeutic response and radiosensitivity in patients with metastatic lymph nodes prior to radiotherapeutic treatment. The results showed promising AUC values indicating prediction accuracy of 80%, 86%, and 85% at 24 hours, 1 week, and 4 weeks, respectively. A three-feature model predicted treatment response with 87.5% accuracy.

Osapoetra et al.(10) analyzed 2-year recurrence-free survival in ER (early responders), LR (late responders), and PD (progressive disease) using an SVM model, achieving accuracies of 91%, 78%, and 27%, respectively.

Zhang et al.(11) conducted a retrospective study on 72 patients with locally advanced HNSCC, finding that primary mass entropy and asymmetry measurements, across multiple spatial filters, correlated with overall survival (OS) independent of tumor dimensions, N grade, and other clinical variables. This study lacked internal validation and included only patients treated with chemotherapy. The radiomic model showed a statistical difference in lymph nodal response to chemotherapy (AUC: 0.85).

Ou et al. (12) matched 120 patients with advanced HNSCC into two groups: concurrent chemo-radiotherapy (CRT) and brachytherapy (BRT). They found that a radiomic feature based on 24 characteristics significantly predicted OS and PFS. Multivariate analysis indicated that this 24-item feature significantly predicted OS (HR=0.3, P=0.02) and PFS (HR=0.3, P=0.01). Combining the radiomic signature with p16 status showed improved prognostic performance compared to p16 alone (AUC=0.78 vs. AUC=0.64 at 5 years, P=0.01) or the radiomic signature alone (AUC=0.78 vs. AUC=0.67, P=0.01).

Predictive Status on HPV

Bogowicz et al. (13) focused their analysis on primary tumor regions, estimating 317 CT radiomic features. Cox and logistic regression models were constructed to predict local control (LC) and HPV status. Features showing the best performance in univariate analysis were included in a multivariate analysis, excluding redundant features. The radiomic LC model was compared with models incorporating clinical parameters. A radiomic feature comprising 3 characteristics was significantly associated with LC (training CI = 0.75 and validation CI = 0.78), indicating that tumors with more heterogeneous CT density distribution had increased risk for LC reduction. Adding clinical parameters to the radiomic model improved the model in the training cohort but not in the validation cohort. Another radiomic signature showed good performance in predicting HPV status (training

AUC = 0.85 and validation AUC = 0.78), suggesting that HPV-positive tumors have a more homogeneous CT density distribution.

Huang et al. (14) studied several molecular phenotypes of HNSCC, including DNA methylation subtypes, HNSCC gene expression subtypes, and common somatic gene mutations. They employed the MethylMix algorithm and consensus clustering for subtyping, utilizing a large radiomic feature set of 540 features from pre-treatment CT scans of 113 patients. Feature selection and LASSO-penalized logistic regression were applied in nested cross-validation. Machine-learning classifiers showed moderate to good predictive performance in identifying HNSCC molecular phenotypes, outperforming models based solely on clinical variables.

In a cohort of 126 patients with HNSCC, Zhu et al. (15) examined correlations between radiomic features from contrast-enhanced CT images and whole-genome multi-omic data. They identified over 5000 significant associations, suggesting a widespread correlation between genomic markers and radiomic features. Random forest classifiers trained in 5-fold cross-validation were used to predict HPV status and TP53 disruptive mutation status, with the best model achieving an AUC of 0.641 (average over 30 cross-validation repetitions).

Min Park et al. (16) conducted a retrospective study on 155 patients with OPSCC (oropharyngeal squamous cell carcinoma), using machine learning to extract radiomic features from preoperative MRI. The logistic regression model showed an AUC of 0.792 in predicting HPV status. The LightGBM model had an AUC of 0.8333 for the same prediction. AUC values of 0.7871, 0.6713, and 0.6638 were reported for predicting lymphovascular invasion, extracapsular nodal spread, and metastatic lymph nodes, respectively. For predicting disease recurrence, the LightGBM model showed an AUC of 0.8571, while for predicting patient death, the AUC was 0.8175.

Discussion

Radiomics, a synergy of artificial intelligence and radiological data analysis, has emerged as a pivotal gateway to the future of precision medicine, particularly in the realm of oncological diagnosis and treatment. In the domain of head and neck oncology, squamous cell carcinoma represents the most prevalent tumor type. Recent advances in radiomics have elucidated the correlation between specific bio-imaging features and molecular traits of Head and Neck Squamous Cell Carcinoma (HNSCC), especially with regard to Human Papillomavirus (HPV). This correlation is characterized by a unique tumor phenotype, predominantly affecting younger patients, and exhibiting a notably favorable response to radiation therapy.

Effective Relevance of Radiomic Enhancement in Predicting Treatment Response in HNSCCs

Quantitative ultrasound (QUS) has proven to be a groundbreaking tool in detecting tumor treatment responses earlier than conventional imaging methods. It does so

Table 1. Selection of articles dealing with prospective studies or retrospective studies to delineate the role of radiomics in assessing the response to treatment of tumor or lymph node metastasis of HNSCC tumors.

First Author, year, Country	Study design	Aim	Intervention	Statistical evidence	Clinical setting	Radiol. Technique	N° pts	Predictive method	Limitations of the study
Tian WT ⁹ , 2020 Canada	PS	Monitor long term response to radical RT in pts with HNSCC and positive lymph node.	Study of QUS images obtained with RE. F-up 24h, 1- 4w.	Ranking naive-Bayes had the best results with prediction accuracy that were 80, 86 and 85% at 24h, 1w and 4w	QUS with RE predicts the response to treatment at 3m by performing it even at 24h after the start of therapy	QUS	36	Kaplan- Meier product-limit method to determine survival analysis K-nearest neighbor enaive- Bayes machine- learning for classification	Pilot study limited by a small sample size were the images of the primary tumor site were not performed since some of them were not explorable with QUS.
Tian WT ⁹ , 2019 Canada	PS	Identifying radiomic markers predictive of response to RT of metastatic lymph nodes of HNSCC tumors	Study of QUS images, spectral form and second-order texture parameters	Features extracted from the spectral intercept SI contrast AUC: 0.741. The three-feature model predicts treatment response with 87.5% accuracy	Suitable features for a priori prediction of treatment response are spectral- intercept SI contrast. Identification of "complete radiologic response" vs "partial radiologic response"	QUS	32	K-nearest neighbor and Naive Bayes machine learning	The sample size was small, and no lymph nodes were evaluated. There was a high heterogeneity in the tissue lesion and no complete information about HPV status.
Osapoetra LO ¹⁰ , 2021 Canada	PS	Assessing radiosensitivity in patients with HNSCC tumors by QUS preradiocal treatment with RT	Five spectral parameters, 20 textures and 80 features derived from the textures	An SVM classifier yielded the highest performance, achieving an accuracy of 92% and an AUC of 0.91, in a responsive manner to define the response at 3 months (ER vs LR/PD). The 2-year relapse-free survival for ER, LR, PD predicted using an SVM model were 91%, 78% and 27%, respectively (p < 0.01).	Pre- treatment QUS radiomics using plot derivatives in HNSCC can predict response to RT with more than 90% accuracy with a strong influence on survival	QUS	59	Automatic learning classifiers were used to develop a radiomic model for predicting the binary response with "leave-one- out" cross-validation	The study was conducted on a small sample treated with chemotherapy or radiotherapy. Moreover, not all of them presented HPV.
Zhang M ¹¹ , 2021, USA	RA	Develop a CT based radiomic biomarker to predict lymph node response to CT in LAHNSCC, HPV+	93 radiomic features of enlarged lymph node were extracted from CT for predictive model to evaluate lymph node response to induction ChT	Comparison between clinical model and combined radiomic-clinical model. The combined model had the best results (AUC = 0.85) on the training cohort and on the test cohort (AUC = 0.75)	Radiomic features of lymph node on pretreatment CT imaging can give information about the response of induction ChT.	CT	27	Multivariable logistic regression	Preliminary, retrospective study on a small patient sample, lacking validation by multi-center studies

<p>Ou D¹², 2017, France</p>	<p>RA</p>	<p>Identify a radiomic signature to estimate OS in LAHNSCC treated with BRT and CRT considering also clinical risk factor (HPV)</p>	<p>544 radiomic features were extracted from pre RT- CT imagines and Cox proportional hazard models were used to establish the association between survival and radiomic features.</p>	<p>MVA showed that both radiomics signature score and p16 strongly predicted OS. Spearman correlation coefficient did no show significant correlation between the radiomic signature score and p16 status. The AUC showed that incorporates radiomics score and p16 status was better to these scores alone during f-up (AUC=0.78 versus AUC=0.67, P=0.01)</p>	<p>Radiomic features associated with p16 status are prognostic and predictive biomarkers in LAHNSCC treated with CRT/BRT. Radiomic features provided additional information on HPV/p16 status to further stratify patients.</p>	<p>CT</p>	<p>120</p>	<p>Kaplan-Meier for Survival rates; Log-rank test for survival curves comparison; Cox proportional hazards models for association between survivorship and radiomics characteristics with false discovery rate correction.</p>	<p>Preliminary and retrospective study with a small and heterogeneous population. They did not perform combining test for HPV validation.</p>
<p>Bogowicz M¹³, 2017, Switzerland</p>	<p>RA</p>	<p>Evaluate prognostic value of contrast-enhancement CT-based radiomics in HNSCC regarding local tumor and HPV status in patients treated with RT-ChT</p>	<p>Predicting LC after RT-ChT HNSCC and HPV using CT radiomics</p>	<p>Cox regression analysis showed a good prognostic model for LC (validation cohort CI = 0.75; validation CI = 0.78) Radiomic and clinical parameters (HPV and T) had a high prognostic power (CI=0.80) HPV status: good performance (training cohort AUC=0.85; validation cohort AUC=0.78)</p>	<p>The heterogeneity of HNSCC tumor density, quantified by CT radiomics, is associated with LC after RT-ChT and HPV status</p>	<p>CT</p>	<p>149</p>	<p>Cox and logistic regression models; Wilcoxon test; G-rho test</p>	<p>The study used single-center data based on a non-standardized scanning protocol for the training cohort. Moreover, CT were performed with 3 different scanners with varied scanning grid size. Finally, the patients underwent o different types of systematic therapy (cisplatinum, cetuximab or associations).</p>

AUC: Area under curve; BRT: bioradiotherapy; CI: Concordance index; CT: Computed tomography; ChT: Chemio-therapy; F-up: follow-up; h:hour(s); HNSCC: Head and neck squamous cell carcinoma; HPV: human papillomavirus; LAHNSCC: locally advance Head and Neck squamous cell carcinoma; LC: local tumor control; m: month(s); ML: metastatic lymphnodes; MVA: Multivariate Cox regression analysis; OS: overall survival; PS: prospective study; pts: patients; QUS: quantitative ultrasound; RA: retrospective analysis; RE: radiomic enhancement; RT: radio-therapy; SVM: support vector machine; T: tumor volume; US: ultrasonographic; w: week(s).

by capturing the ongoing changes in the elastic properties of tissue, which are indicative of cellular death. Utilizing raw radiofrequency (RF) data, QUS provides insights into the tissue microstructure's elastic properties and underlying biology (17). The analyzed data, encompassing ultrasonographic studies that include quantitative analysis, microvascularization, and micronecrosis, were correlated with CT studies.

Previous studies have demonstrated the potential of QUS, obtained both before and during treatment, as a promising predictor of treatment response in head and neck tumors (6; 18). For instance, in a cohort of 32 patients, pre-treatment QUS predicted response at 3 months with an 88% accuracy rate. Moreover, in a subsequent study involving 36 patients, the performance classifier was enhanced when QUS features were acquired during radiotherapy, as early as after 1 week of treatment.

The management of head and neck malignancies has evolved significantly in recent decades. Radical radiotherapy (RT), often accompanied by concurrent chemotherapy, has been recognized as the standard of care for primary cancers of the pharynx and larynx. This approach has led to improved organ preservation rates, crucial for maintaining key functions such as swallowing, speech, and respiration, intricately coordinated by the head and neck anatomy. The advent of intensity-modulated RT and image-guided treatment has further reduced normal tissue toxicities, like xerostomia (19). Despite these advancements, a significant proportion of patients still experience disease recurrence, and many who are cured continue to suffer from long-term treatment-related toxicities that severely impact their quality of life. This challenge has fueled the pursuit of reliable biomarkers for real-time monitoring of cell death during treatment and for predicting overall treatment response.

Fatima K et al. were pioneers in proposing the use of delta-radiomic QUS during RT as a straightforward, rapid, and cost-effective imaging modality to predict response to radical RT treatment in head and neck malignancies. Delta-radiomics refers to the temporal changes in radiomic features linked to treatment-induced alterations in the tumor. This approach, targeting the largest metastatic lymph node (LN), demonstrated that changes in the biological structure of LN post-RT correlate with the patient's response, thereby establishing a link between LN response and locoregional control. The advantage of QUS radiomics lies in its ability to develop biomarkers from a non-invasive imaging modality, with rapid scan acquisition and excellent patient compliance. This makes it an attractive strategy for real-time monitoring of treatment response during the early stages of treatment.

Prediction of HPV Infection Based on Radiomic Features in HNSCC Tumors

In recent years, numerous studies have explored the association between radiomic features of HNSCC tumors and HPV infection status. Researchers like Buch et al. and Fujita et al. have investigated the relationship between individual texture features and HPV status (21-22). Meanwhile, other researchers have developed various machine learning models to predict HPV presence in HNSCC. Table 2 summarizes the reviewed studies focusing on radiomic intervention in HPV-positive tumor characteristics. These studies stand out because they demonstrate statistical significance superior to the other reviewed works.

While some studies omitted details of the HPV test used for diagnosis, others employed immunohistochemical testing to predict p16 status. Most studies utilized CT-based radiomics for HPV classification. However, few studies reported

Table 2. Prediction of HPV infection based on radiomic features in Head-Neck Squamo-Cellular Tumors (HNSCC).

First Author, year, Country	N° pts/ type of cancer	HPV p16	Radiol. Technique	Predictive status on HPV
Bogowicz M ¹³ , 2017, Switzerland	93 HNSCC	Positive	CT	Radiomic model evidenced a good prediction performance in both the training cohort (AUC=0.85) and validation cohort (AUC=0.78)
Zhu ¹⁵ , 2018 USA	126 HNSCC	ND	CT	Radiomic model did not show statistic difference between the average AUCs obtained with different numbers of features (higher AUC= 0.71)
Huang C ¹⁴ , 2019, China	113 HNSCC	Positive	CT	Radiomic models distinguished HPV+ from HPV- status (AUC= 0.73) Radiomic model had an high performance to discriminating MethylMix HPV+ from the other patients (AUC= 0,79).
Min Park UY ¹⁶ , 2022 South Korea	155 OPSCC	Positive	MRI	The logistic regression model showed AUC= 0.792 in predicting human papillomavirus (HPV) status.
Bos P ¹⁸ 2021, Netherlands	153 OPSCC	Negative	MRI-T1 after contrast agent	Radiomic models showed low performance for LC (AUC 0.587 to 0.66) and OS (t AUCs 0.559 to 0.600).

on the quantitative diffusion MRI approach(23), highlighting differences in apparent diffusion coefficient values between HPV-positive and HPV-negative OPSCC. Nevertheless, there has been no report on radiomic signatures based on MRI for predicting HPV status.

A notable limitation of this method is its resolution, which is not sufficient to accurately analyze lesions smaller than 1 cm in diameter. This limitation underscores the need for ongoing refinement in radiomic techniques and the integration of more advanced imaging modalities to enhance the precision and applicability of radiomic analysis in head and neck oncology.

Conclusions

Radiomics has emerged as a transformative tool in oncology, offering rapid, cost-effective, non-invasive, and comprehensive tissue and organ characterization. Its ability to extract features directly from both standard and specialized (preprocessed) medical images — such as specific sequences in MRI or elasticity measurements in QUS — positions it as a technology that complements traditional clinical predictors. This integration of radiomics is a stride towards personalized precision medicine in cancer care.

In oncology imaging, radiomics characterizes the attributes of pixels or voxels and their spatial relationships within an image. When these features are processed and compiled into big data, they yield high-dimensional imaging markers that provide insights into the cytobiology of tumors. Leveraging radiomic information, both pre- and intra-treatment, enables the development of tailored therapeutic programs and enhances the precision of radiotherapy treatments (24).

Tumor characterization, particularly in patients with squamous cell neoplasia of the head and neck, remains a challenge. Structural intratumoral heterogeneity, a manifestation of variations in tumor biology, often eludes traditional diagnostic techniques. Radiomics, offering a semi-quantitative assessment alongside traditional qualitative evaluation, can address this heterogeneity. It effectively allows for an internal assessment and examination of tumors, revealing morphological parameters and texture features derived from voxel or pixel characteristics. However, it's important to note that techniques like PET-CT and MRI face resolution limitations, particularly in analyzing lesions smaller than 1 cm in diameter (25).

Radiomic-based biomarkers for HPV status hold potential for aiding pathologists, especially when standard p16 immunohistochemical staining yields equivocal results or requires supplemental testing. In line with the 2018 guidelines of the College of American Pathologists, which recommend p16 immunohistochemistry as a surrogate marker for HPV in primary tumor specimens, radiomics can serve as an inexpensive confirmatory test for HPV status. Moreover, radiomic signatures for HPV classification could function as prognostic biomarkers in patients with oropharyngeal squamous cell carcinoma (OPSCC).

The integration of artificial intelligence, common software analysis, and imaging acquisition techniques opens up possibilities for developing oncological features predictive of therapeutic response. The future of radiomics lies in exploring the roles of other imaging modalities such as MRI or

FDG-PET and the application of advanced machine learning classifiers to enhance classification performance. Radiomics also has potential applications in detecting HPV-associated metastatic lymph nodes in carcinoma of unknown primary, guiding the search for oropharyngeal cancer sources.

While our research has highlighted various limitations of the current methodologies, technological advancements are expected to overcome these challenges, particularly the issue of dimensional limits. The evolving understanding of tumor necrosis heterogeneity through radiomic analysis is poised to yield highly useful features, marking a significant advance in the field of oncological imaging and treatment.

References

1. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012; 48:441-6
2. Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017; 14:749-762
3. Vallières M, Kay-Rivest E, Perrin LJ, et al. Radiomics strategies for risk assessment of tumour failure in head-and-neck cancer. *Sci Rep* 2017; 7:10117
4. Haider SP, Burtneß B, Yarbrough WG, et al. Applications of radiomics in precision diagnosis, prognostication and treatment planning of head and neck squamous cell carcinomas. *Cancers Head Neck* 2020, 4, 5:6.
5. Traverso A, Wee L, Dekker A, et al. Repeatability and Reproducibility of Radiomic Features: A Systematic Review. *Int J Radiat Oncol Biol Phys* 2018; 102:1143-1158
6. Zhu Y, Mohamed ASR, Lai SY, et al. Imaging-Genomic Study of Head and Neck Squamous Cell Carcinoma: Associations Between Radiomic Phenotypes and Genomic Mechanisms via Integration of The Cancer Genome Atlas and The Cancer Imaging Archive. *JCO Clin Cancer Inform* 2019; 3:1-9
7. Moher D, Liberati A, Tetzlaff J, et al. D.G. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097
8. Tran WT, Suraweera H, Quaiot K, et al. Predictive quantitative ultrasound radiomic markers associated with treatment response in head and neck cancer. *Future Sci OA* 2019; 6: FSO433
9. Tran WT, Suraweera H, Quaiot K, et al. Quantitative ultrasound delta-radiomics during radiotherapy for monitoring treatment responses in head and neck malignancies. *Future Sci OA* 2020; 6:FSO624
10. Osapoetra LO, Dasgupta A, DiCenzo D, et al. Assessment of clinical radiosensitivity in patients with head-neck squamous cell carcinoma from pre-treatment quantitative ultrasound radiomics. *Sci Rep* 2021; 11:6117
11. Zhang MH, Cao D, Ginat DT. Radiomic Model Predicts Lymph Node Response to Induction Chemotherapy in Locally Advanced Head and Neck Cancer. *Diagnostics (Basel)* 2021; 11:588
12. Ou D, Blanchard P, Rosellini S, et al. Predictive and prognostic value of CT based radiomics signature in locally advanced head and neck cancers patients treated with concurrent chemoradiotherapy or bioradiotherapy and its added value to Human Papillomavirus status. *Oral Oncol* 2017; 71:150-155

13. Bogowicz M, Riesterer O, Ikenberg K, et al. Computed Tomography Radiomics Predicts HPV Status and Local Tumor Control After Definitive Radiochemotherapy in Head and Neck Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2017; 99:921-928
14. Huang C, Cintra M, Brennan K, et al. Development and validation of radiomic signatures of head and neck squamous cell carcinoma molecular features and subtypes. *EBioMedicine* 2019; 45:70-80
15. Zhu Y, Mohamed ASR, Lai SY, et al. Imaging-Genomic Study of Head and Neck Squamous Cell Carcinoma: Associations Between Radiomic Phenotypes and Genomic Mechanisms via Integration of The Cancer Genome Atlas and The Cancer Imaging Archive. *JCO Clin Cancer Inform* 2019; 3:1-9
16. Min Park UY, Lim, Koh Y-L, Kim YW, et al. Machine learning and magnetic resonance imaging radiomics for predicting human papilloma virus status and prognostic factors in oropharyngeal squamous cell carcinoma. *Head Neck* 2022; 44: 897-903
17. Mourad M, Jetmore T, Jategaonkar AA, et al. Epidemiological Trends of Head and Neck Cancer in the United States: A SEER Population Study. *J Oral Maxillofac Surg* 2017; 75: 2562-2572
18. Bos P, van den Brekel MWM, Gouw ZAR, et al. Improved outcome prediction of oropharyngeal cancer by combining clinical and MRI features in machine learning models. *Eur J Radiol* 2021; 139:109701
19. Nutting CM, Morden JP, Harrington KJ, et al. PARSPORT trial management group. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011; 12:127-36
20. Fatima K, Dasgupta A, DiCenzo D, et al. Ultrasound delta-radiomics during radiotherapy to predict recurrence in patients with head and neck squamous cell carcinoma. *Clin Transl Radiat Oncol* 2021; 12:28:62-70
21. Buch K, Fujita A, Li B, et al. Using Texture Analysis to Determine Human Papillomavirus Status of Oropharyngeal Squamous Cell Carcinomas on CT. *AJNR Am J Neuroradiol* 2015; 36:1343-8
22. Fujita A, Buch K, Li B, et al. Difference Between HPV Positive and HPV-Negative Non-Oropharyngeal Head and Neck Cancer: Texture Analysis Features on CT. *J Comput Assist Tomogr* 2016; 40:43-7
23. Payabvash S. Quantitative diffusion magnetic resonance imaging in head and neck tumors. *Quant Imaging Med Surg* 2018; 8:1052-1065
24. Zhao B, Tan Y, Tsai WY, et al. Reproducibility of radiomics for deciphering tumor phenotype with imaging. *Sci Rep* 2001; 6:23428
25. Pinker K, Shitano F, Sala E, et al. Background, current role, and potential applications of radiogenomics. *J Magn Reson Imaging* 2018; 47:604-620