Review Article

Radiomics in head and neck cancer: from exploration to application

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Abstract: In the context of clinical oncology, a fundamental goal of radiomics is the extraction of large amounts of quantitative features whose subsequent analysis can be used for decision support towards personalized and actionable cancer care. Head and neck cancers present a unique set of diagnostic and therapeutic challenges by nature of its complex anatomy and heterogeneity. Radiomics holds the potential to address these barriers, but only if as a collective field we direct future effort towards investigating specific oncologic function and oncologic outcomes, with external validation and collaborative multi-institutional efforts to begin standardizing and refining radiomic signatures. Here we present an overview of radiomic texture analysis methods as well as the software infrastructure, review the developments of radiomics in head and neck cancer applications, discuss unmet challenges, and propose key recommendations for moving the field forward.

Keywords: Radiomics; head and neck cancer; texture analysis; machine learning; imaging biomarker

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Introduction

Radiomics is concerned with the high-throughput extraction of large amounts of quantitative features whose subsequent analysis and selection can be incorporated in clinical decision-making. Radiomics complements, facilitates, and accelerates the advancement towards cancer precision medicine, as it is able to (I) non-invasively characterize the overall tumor accounting for heterogeneity; (II) produce prognostic and/or predictive biomarker value derived from routine, standard of care imaging data as-is; and (III) allow for a fast, low-cost, and repeatable means for longitudinal monitoring (1,2). Head and neck cancer presents a unique set of diagnostic and therapeutic challenges, including but not limited to the complex regional anatomy, the minute scale of critical structures, the variable appearance of primary and recurrent tumors, significant anatomic changes related to tumor response, and high intratumoral heterogeneity that varies depending on anatomic site.

In turn, radiomics holds the potential to address these barriers to personalized therapeutics. Contrast-enhanced computed tomography (CT), magnetic resonance (MR), and positron emission tomography (PET) imaging are routinely acquired during the diagnosis and staging process in head and neck cancer, and the immense data volume gathered from multiple imaging modalities in existing clinical datasets can greatly facilitate exploratory radiomic analysis. Also, the heterogeneous composition of head and neck cancers can be captured non-invasively, which can serve as an essential adjunct to clinical decision-making.

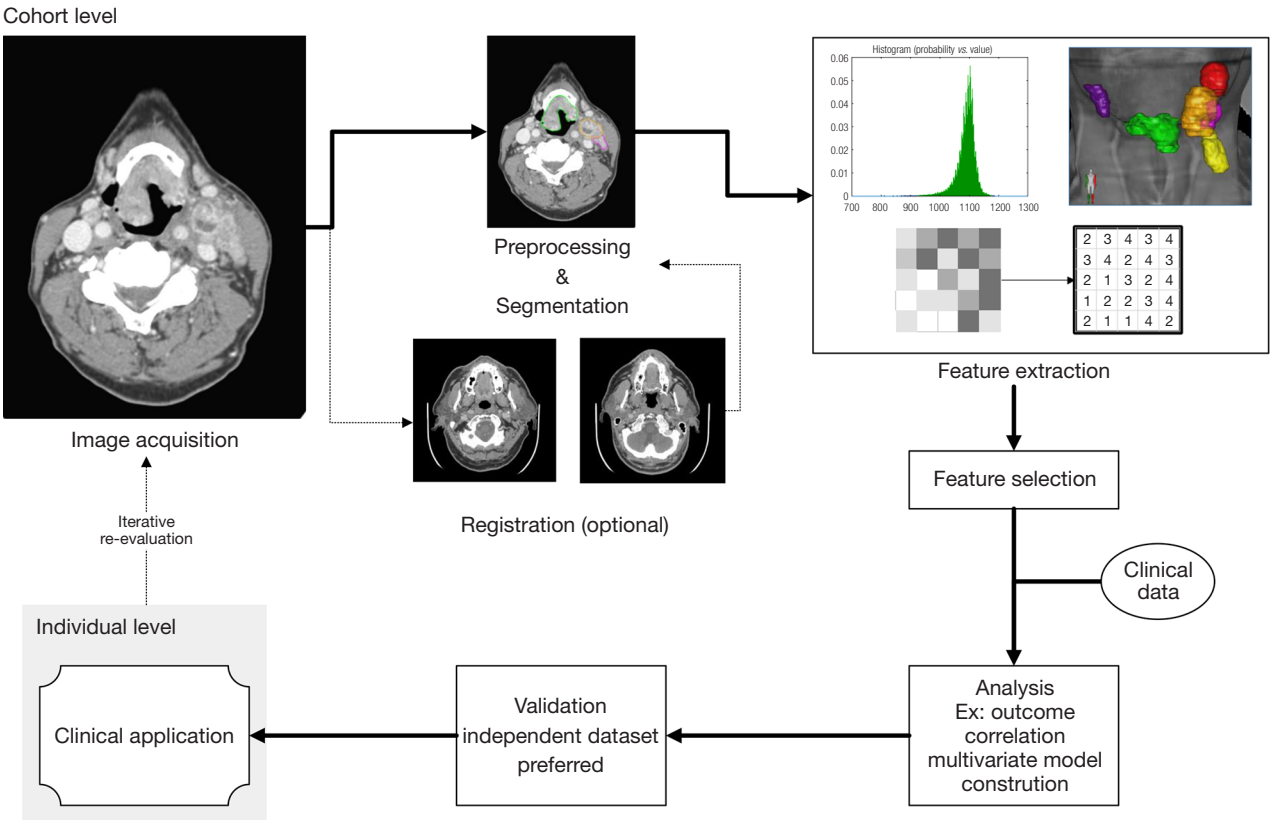

Figure 1 The "radiomics workflow" involves a series of iterative steps for reproducible and consistent extraction of imaging data. These steps include image acquisition, tumor segmentation, feature extraction, and feature selection. The selected features can then be analyzed for outcome correlation and potential incorporation into predictive models. Additionally, validations should be done against completely independent large datasets, preferably from other institutions.

In addition, radiomics can provide important day-to-day information regarding rapid anatomic change and tumor response during the course of treatment.

However, several key components are necessary to transition radiomics in head and neck cancers from exploratory studies to large-scale implementation as a clinical toolset. We first present an introductory overview of the radiomics workflow, texture analysis methods, and available software infrastructure. We then review key developments in head and neck cancer radiomics followed by a discussion of unmet challenges in its logistical and clinical application.

The radiomics workflow

To realize clinical application, an efficient series of iterative processes is required for reproducible and consistent extraction of radiomics data (*Figure 1*). This "radiomics workflow" begins with acquisition of high quality images with a standardized protocol. Segmentation of the tumor is then performed, followed by feature extraction from the defined tumor region. The extracted features that demonstrate the best performance, stability, or other defining metric are then selected for incorporation towards clinical applications (3).

An overview of texture analysis methods and available software infrastructure for radiomics exploration

Methods for texture analysis in head and neck cancers are more or less the same as those used in other organ sites. These include first- and second-order texture methods as well as various transform-based methods. The most "direct" features are those based simply on intensity values within a region of interest (ROI). Similar but unique features

may also be extracted from histograms of intensity values and Gaussian functions fitted to these histograms. Other "direct" features may be calculated from the shape of the ROI. Texture features in the head and neck are based on the same parent matrices that are utilized in other sites. Examples of these include the gray-level co-occurrence matrix (GLCM), the gray level run length matrix (GLRLM), the neighborhood intensity difference matrix (NIDM), neighborhood gray-level dependence matrix (NGLDM), and the intensity size-zone matrix (ISZM) (4-9). Other feature extraction methods are based on filters such as Fourier transform, Gabor transform, Laplacian of Gaussian filter (LoG), and multiscale wavelet decompositions (10-13). After processing the ROI according to the parent matrix or filter method, features such as coarseness, business, correlation, entropy, and energy are calculated. Details of these individual features are available in their respective references, and due to their multitude and complexity, will not be delineated in this article.

In addition to texture analysis methods, there exist multiple open-source, in-house developed, and commercial software solutions that facilitate the exploration and development of radiomics in head and neck cancer. A prime example of available open-source software is the Imaging Biomarker Explorer (IBEX) by Zhang *et al.*, described as an "*open infrastructure software platform that flexibly supports common radiomics workflow tasks such as multimodality image data import and review, development of feature extraction algorithms, model validation, and consistent data sharing among multiple institutions*." (14). IBEX is compatible with CT, PET, and MR modalities, and is available at http://bit.ly/IBEX_MDAnderson. MazDa is another open-source solution for texture analysis that has been validated through multi-institutional studies (15). This software is built primarily for magnetic resonance imaging (MRI) texture analysis and supports various feature selection methods for model generation. MazDa is available at http://www.eletel.p.lodz.pl/programy/mazda/index.php?action=mazda. CGITA is yet another open-source texture analysis tool, built in the MATLAB environment. The software supports numerous heterogeneity indices, user-defined calculations, and batch processing with a focus on molecular imaging. CGITA supports CT, PET, and MR images and is available at http://code.google.com/p/cgita (16).

Beyond open-source software tools, a number of groups have also developed in-house tools for radiomic analyses, most often in the MATLAB environment, but these softwares are not publicly available to our knowledge (17-21). One such example is a modified version of Computational Environment for Radiotherapy Research (CERR) used for texture analysis.

Lastly, numerous commercial solutions for radiomic analyses are also emerging. For instance, TexRAD is a commercial software which uses a LoG special filter to delineate fine, intermediate, and coarse textures in a ROI for subsequent analysis. This software contains various decision support tools for thoracic and gastrointestinal imaging and has also demonstrated applicability in head and neck cancer textural analysis (22).

Novel applications of texture analysis methods and the emergence of new software tools have both spurred on developments in radiomics for head and neck cancer.

A review of recent developments in radiomics for head and neck cancer

Specific applications for texture analysis and radiomics in head and neck tumors have, to date, demonstrated exciting promise in several distinct arenas. We elaborate on the preliminary applications of these techniques in the following areas for head and neck cancer:

(I) Tumor segmentation and pathologic classification;
(II) Risk stratification, as prognostic and/or predictive biomarker(s);
(III) Monitoring of alteration in normal tissue as a sequelae of radiotherapy dose deposition.

A summary of the mentioned studies in this section can be found in the *Table S1*.

Radiomics for tumor segmentation and classification

Textural analysis has demonstrated preliminary evidence suggesting clinical utility in the classification of and segmentation process for head and neck cancers (*Table 1*).

For instance, a number of studies have sought to classify head and neck cancers by human papillomavirus (HPV) status with textural analysis. Buch *et al.* investigated the use of texture analysis to distinguish between HPV(+) and HPV(–) status in 40 patients with primary oropharyngeal squamous cell carcinomas on contrast-enhanced CT (CE-CT) images. They identified three textural features (histogram median and entropy and GLCM entropy) that could make the distinction with statistical significance and concluded that textural analysis has the potential to be used as an adjunct to evaluate HPV status in squamous cell

Table 1 Studies on radiomics for segmentation and classification

Authors (study)	Publication date	Modality	# of patients	Anatomic site, if specified	Analyzed endpoint
Raja *et al.* (23)	Sep 2012	CT	21	Oral cavity	Tumor grade classification
Buch *et al.* (17)	Jul 2015	CT	40	Oropharynx	HPV status
Fujita *et al.* (24)	Jan 2016	CT	46	Oropharynx (25); larynx (17); hypopharynx (5)	HPV status
Yu *et al.* (26)	Mar 2009	FDG-PET/CT	20	–	Normal *vs.* abnormal tissue classification
Yu *et al.* (27)	Oct 2009	FDG-PET/CT	10	Oropharynx and nasopharynx	Normal *vs.* abnormal tissue classification
Vallieres *et al.* (25)	Oct 2013	FDG-PET	67	–	HPV status; loco-regional failure; distant metastasis
Fruehwald-Pallamar *et al.* (28)	Nov 2013	MRI	38	Parotid	Benign *vs.* malignant status; tumor type differentiation
Yang *et al.* (29)	Dec 2014	MRI	15	Parotid	Parotid *vs.* surrounding tissue differentiation
Brown *et al.* (15)	May 2015	DW-MRI	26 (training) 18 (validation)	Thyroid	Thyroid nodule classification
Jansen *et al.* (21)	Jan 2016	DCE-MRI	19	Oropharynx	Local control; local failure
Park *et al.* (30)	Feb 2016	MRI	27	Oropharynx	Tumor type differentiation
Fruehwald-Pallamar *et al.* (31)	Feb 2016	MRI	100	–	Benign *vs.* malignant status

CT, computed tomography; HPV, human papillomavirus; FDG-PET, fludeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging; DW, diffusion-weighted; DCE, dynamic contrast-enhanced.

carcinomas (17). A follow-up study by Fujita *et al.* sought to distinguish the HPV status of 46 patients with non-oropharyngeal carcinoma using texture analysis extracted from CE-CT images. They identified three features demonstrating statistical significance after false discovery rate (FDR) correction (GLCM contrast, GLCM correlation and law L8). Consequently, they suggested that there are morphologic feature differences based on HPV status even in non-oropharyngeal cancer (OPC) patients (24). Exploring beyond CE-CT, Vallieres *et al.* aimed to evaluate whether features derived from fludeoxyglucose-positron emission tomography (FDG-PET) could be used as non-invasive biomarkers of HPV status. The study, including 67 patients with head and neck squamous cell carcinoma (HNSCC) and known HPV status, demonstrated that multivariate models built via logistic regression (LR) and support vector machine (SVM) using five features could reliably classify HPV status [area under curve (AUC) of 0.64 and 0.72 for LR and SVM, respectively] and had the potential to predict treatment failure (AUC 0.66) (25).

In addition to classification methodologies, segmentation (in particular, distinguishing between normal and abnormal tissue) has been another application of textural analysis for head and neck cancers. For instance, Yu *et al.* conducted a study examining 20 patients with head and neck cancer with 20 matched controls and found that neighborhood gray-tone difference matrix (NGTDM) features including PET coarseness, PET contrast, and CT coarseness extracted from co-registered FDG-PET/CT images yielded good discriminatory performance. Their multivariate model, constructed via a decision tree-based K-nearest neighbor (DT-KNN) classifier, was able to successfully discriminate between normal and abnormal ROIs [receiving operator characteristic area under the curve (ROC Az) of 0.95±0.007, Az_{90} of 0.087±0.003]. It was found that the combination of PET and CT features outperformed either PET or CT

features individually in discriminatory ability. In addition, they found that features based on the NGTDM and SGLDM (spatial gray level dependence method) could classify ROIs with comparable accuracy to that of a human expert, suggesting that implementation of such analyses at the voxel level could lead to improvement in the accuracy of automated segmentation in head and neck cancer (26). To that end, Yu *et al.* published on such an implementation titled "co-registered multimodality pattern analysis segmentation system" (COMPASS) for ten head and neck cancer patients. They found that COMPASS outperformed other simpler PET-based thresholding methods for tumor segmentation and yielded contours that were quantitatively and qualitatively similar to those created manually by expert radiation oncologists (specificity 95%±2%, sensitivity 90%±12%) (27). In addition to studies that broadly examined segmentation of head and neck cancers, other studies have sought to segment tissue in specific anatomic regions, as Raja *et al.* aimed to do with regards to the buccal mucosa subsite of the oral cavity (23).

Much like the aforementioned studies performed in the CT and PET modalities, numerous investigations focused on the MR imaging modality have applied textural analysis towards classification and segmentation processes in head and neck cancer. Some of these MR imaging based studies (28-31) that differentiate between benign and malignant status and amongst different types of head and neck masses will not be elaborated upon in this text, but relevant findings and their statistical significance can be found in the *Table S1*.

MR imaging merits a distinct interest in radiomics. While CT Hounsfield units represent a standard physical phenomena, the dynamic range of information possible with distinct MRI sequences may allow greater imaging flexibility (in terms of voxel and subvoxel physiologic parameters) as well as the potential for multi-parametric texture/radiomics dataset acquisition in a single imaging series. Therefore, texture analysis of advanced MR sequences has generated interest for further investigation. For instance, in a multi-institutional study focused on preoperative stratification of thyroid tumors using diffusion-weighted (DW) MRI, Brown *et al.* reported that an algorithm constructed using linear discriminant analysis (LDA) with t21 features yielded an ROC AUC 0.97 (sensitivity 92%, specificity 96%) in a training dataset of 26 patients and correctly classified 89% of tumors in an 18 patient independent validation dataset (15). As expected, a significant difference in the ADC was observed between benign and malignant lesions, but ADC alone was not as effective in classification (AUC 0.73, sensitivity 70%, specificity 63%) as the model generated from radiomic analysis of the diffusion-weighted echo-planar imaging (DW-EPI) sequence. Furthermore, texture analysis of quantitative and semi-quantitative MRI data has also shown potential value. In a recent study of 19 HNSCC patients with pretreatment and intra-treatment dynamic contrast-enhanced (DCE), or DCE-MRI available, Jansen *et al.* analyzed the parametric maps of K_{trans} and v_e, which are measures of tumor vascularity. It was reported that the energy feature from the v_e map was significantly higher on intra-treatment scans (0.41±0.22 *vs.* 0.30±0.11; P<0.04). The findings suggest that texture analysis may provide complementary information in addition to standard DCE-MRI measurements that have been shown to be predictive of treatment response in head and neck cancer patients (21,32,33).

Radiomics as prognostic and predictive biomarkers

Another application of radiomics is the development and refinement of radiomic signatures that can improve upon prognostic and/or predictive models for specific cancers, including those of the head and neck (*Table 2*). Heading the effort in this area, Aerts *et al.* conducted a radiomic analysis of 440 features extracted from a pre-treatment CT database of 1,019 patients with either lung or head and neck cancer. The features described tumor phenotype in four categories (tumor image intensity, shape, texture, and wavelet decomposition) and the strongest radiomic features from each of the four feature groups were identified to create a signature: statistics energy, shape compactness, gray level non-uniformity, and wavelet (HLH) gray level non-uniformity. A multitude of features were found to have association with oncologic outcomes in independent datasets of lung cancer and head and neck cancer patients. Of interest, a radiomic signature that was trained using a dataset of non-small cell lung cancer patients was found to have impressive translatability in two independent head and neck cancer validation datasets. They also suggested that the prognostic significance of the features can capture underlying intratumor heterogeneity and is associated with gene-expression patterns (34).

In a subsequent study, the aforementioned radiomic signature was externally validated on an independent cohort of oropharyngeal squamous cell carcinoma patients (542 patients) (37). The signature validated well,

Table 2 Studies on radiomics for prognostic and predictive biomarkers

Authors (study)	Publication date	Modality	# of patients	Anatomic site, if specified	Analyzed endpoint
Zhang *et al.* (22)	Dec 2013	CT	72	Oral cavity (28); larynx (21); hypopharynx (14); oral cavity (8)	Overall survival
Aerts *et al.* (34)	Jun 2014	CT	474 (training); 545 (validation)	Lung or head and neck	Median survival
Parmar *et al.* (35)	Jun 2015	CT	878	Lung or head and neck	Survival; tumor stage; HPV status
Parmar *et al.* (36)	Dec 2015	CT	101 (training); 95 (validation)	–	Overall survival
Leijenaar *et al.* (37)	Aug 2015	CT	542	Oropharynx	Median survival
El Naqa *et al.* (20)	Jun 2009	FDG-PET	9	–	Overall survival
Dang *et al.* (38)	Jan 2015	MRI	16	Oropharynx	p53 status

CT, computed tomography; HPV, human papillomavirus; FDG-PET, fludeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging.

demonstrating good model fit and preservation of discrimination (Harrell's c-index 0.628; P=2.72e-9). Interestingly, it was also found that the signature retained discriminatory ability in the presence of visible CT artifacts, which are often present in head and neck CT sequences due to dental hardware (Harrell's c-index 0.647; P=5.35*e*-6).

In yet another application of radiomics as a predictive marker, Zhang *et al.* analyzed the predictive value of texture and histogram features in 72 HNSCC patients treated with induction chemotherapy. In multivariate Cox regression analysis incorporating both clinical and imaging variables, they found that in addition to expected factors such as tumor volume and N stage, primary mass entropy [hazard ratio (HR) =2.10 for each 0.5-unit increase; P=0.36] and histogram skewness (HR =3.67 for each 1.0-unit increase; P=0.009) were independent predictors of overall survival (OS) (22).

A common challenge in radiomics is to define a non-redundant set of imaging biomarkers from the vast amount of extracted features. An investigation by Parmar *et al.* examined the role of consensus clustering in reducing redundant features into a few robust and compact feature clusters. Upon analysis of features extracted from pre-treatment CT images from four independent lung and head and neck cancer cohorts (878 patients total), they showed that lung and head and neck radiomic clusters are significantly associated with patient survival and tumor stage. In addition to demonstrating prognostic value to clinical endpoints, their results revealed that clustering and the prognostic radiomic features are cancer specific (35).

Machine-learning methods have also been investigated for prognostic value as biomarkers for head and neck cancers. From two independent head and neck cohorts totaling 196 patients, Parmar *et al.* investigated 13 feature selection methods and 11 machine-learning classification methods chosen for simplicity, efficiency, and popularity in the literature. Specifically, they identified three classifiers and feature selection methods that demonstrated high performance and stability for predicting 3-year OS in head and neck cancer, suggesting that these machine learning methods should be the starting point for radiomics-based prognostic analyses due to their consistency. Identifying optimal machine-learning methods for radiomic analysis is a prerequisite to the development of a robust, clinically-applicable radiomic workflow. These findings provide valuable information for methodology selection in future radiomics investigations. Such methods could allow for improvements in cancer biomarker identification and personalized medicine in oncology (36).

In addition to CT, applying radiomics for prognostic and/or predictive purposes for head and neck cancer has been investigated in the PET, MR, and histopathologic imaging modalities as well. For example, one study by El Naqa *et al.* examined shape and textural features as well as intensity volume histogram metrics extracted from pre-treatment PET images on nine head and neck cancer patients. Using the highest predictive features, they were able to construct a two-metric LR model predicting OS with an AUC of 1.0 (20). In addition, certain studies aim

Table 3 Studies on Radiomics for longitudinal monitoring

Authors (study)	Publication date	Modality	# of patients	Anatomic site, if specified	Analyzed endpoint
Scalco *et al.* (43)	Dec 2013	CT	21	Parotid	Parotid volume
Scalco *et al.* (44)	Aug 2015	CT	37	Parotid	Various parameters

CT, computed tomography.

to predict p53 status, as a positive status is associated with poor prognosis in certain subsets of HNSCC patients (39-41). Dang *et al.* demonstrated that MRI texture analysis could predict p53 status in oropharyngeal squamous cell carcinoma with 81.3% accuracy (P<0.05). In a retrospective study of 16 patients, they identified and incorporated seven significant texture features into a predictive model. The variables featured significantly were those derived from post-gadolinium T1W1, T2W1, and ADC map, noted to be possibly due to differences in vascularity between p53(+) versus p53(–) status (38). In addition to PET and MR imaging, histopathological imaging coupled with textural analysis has demonstrated prognostic potential as well. For instance, a study of 53 cases of HNSCC was characterized by quantitative histologic texture analysis by generating a 2D planar tessellation of the tumor and then analyzing the reconstructed image using spatial statistics. Ultimately, mean nuclear area was found to be significant predictor of lymph node metastasis (42).

Radiomics for longitudinal monitoring of therapy response in non-tumor tissues

Several groups have compiled data indicative of the potential capacity for radiomics/texture techniques to afford longitudinal monitoring of tumor response. However, in addition to tumor imaging, the same approaches can readily be utilized to detect normal tissue physiologic alteration (*Table 3*). This is particularly beneficial for head and neck cancers, which exhibit significant anatomical changes with radiotherapy doses delivered to functional normal tissues. As an instance of this application, texture analysis has been applied to CT images to assess change in parotid gland structure during radiotherapy. In this study, a general decrease in parotid tissue complexity and heterogeneity was observed at different time points of radiotherapy. Also, volume and mean intensity variation were found to be correlated with pre-treatment dosimetric parameters, suggesting a relationship between dose plan and structural variation estimated after radiotherapy (44). The same group further investigated whether early variations of textural parameters [i.e., mean intensity and fractal dimension (FD)] could predict parotid shrinkage at the end of treatment. The study examined textural parameters extracted from CT images of 42 parotids of 21 nasopharyngeal cancer patients treated with IMRT. Using discriminant analysis based on volume and fractal dimensionality, they were able to predict final parotid shrinkage with 71.4% accuracy (43).

Unmet challenges for head and neck cancer radiomics

With respect to head and neck cancer radiomics, we first discuss the technical challenges inherent to the young field of big data, followed by the clinical challenges inherent to cancer medicine. The unmet technical challenges present today in the field of head and neck cancer radiomics are mostly similar to those in other disease sites. Technical challenges in radiomics for head and neck cancer include requirements for processing large amounts of high-quality imaging data, reproducibility in data processing, an assessment of radiogenomic associations, a suitable informatics infrastructure, and standardized reporting guidelines.

Radiomics inherently depends on large amounts of high quality imaging data. Results are highly dependent on segmentation, which can be a time-intensive process if carried out manually. However, manual segmentation adds a level of quality assurance and confidence in delineation that is not matched by auto-segmentation solutions, especially in the head and neck.

Reproducibility of results is another unmet need in this field. Not only do radiomic features need to demonstrate reproducibility in the same patient through test-retest studies, but these features need to be evaluated across different device manufacturers, imaging acquisition parameters, and institutions. Several studies have been done on test-retest variability of radiomic features in other

disease sites (19,45-48). Recently, Mackin *et al.* published a study on feature variability utilizing a phantom imaged by 16 CT scanners from four manufacturers at four separate facilities (48). They found that feature values tended to cluster by manufacturer and that the variability between manufacturers was not insignificant and even of comparable size to the variability among different non-small cell lung cancer tumors themselves. The findings highlight the need for collaboration among institutions to study the plethora of variables that may contribute to radiomic values and to develop a framework to minimize the variability.

Another major unmet goal specific to head and neck radiomics is in the radiogenomic assessment of head and neck cancers. In other disease sites including brain, breast, lung, and liver, studies have shown various associations between genomic expression patterns and radiographic features for a number of cancers (49-54). Such findings are supportive of the central hypothesis of radiomics that the genotype of a tumor is associated with the radiographic phenotype of a tumor. Researchers in other sites have leveraged genomic information from The Cancer Genome Atlas (TCGA) in combination with imaging data from The Cancer Imaging Archive (TCIA) for such studies. In the head and neck space, a radiogenomic assessment of the TCGA head and neck cohort is underway by the authors of this review.

From a practical standpoint, integration of radiomic data into the clinical workflow will require facilitation by software. An electronic health record (EHR) software and picture archiving communication system (PACS) that integrate radiomic analysis with all pertinent imaging metadata and clinical information will greatly enhance both the feasibility of a radiomics workflow and the potential value of acquired images. With respect to creating a standard methodology for analyzing and reporting radiomic data, two national collaborative efforts have been created to address this issue: the Quantitative Imaging Network (QIN), sponsored by the National Cancer Institute (NCI), and the Quantitative Imaging Biomarker Alliance (QIBA), sponsored by the Radiological Society of North America (RSNA) (55,56). In addition to these efforts, the NIH has required a plan for data sharing in all major research funding applications since 2003; ideally these efforts will spur sharing of datasets and methodologic transparency, in addition to increasing access to direct software resources developed for radiomics applications.

There are also several challenges unique to cancer medicine that must be addressed in radiomics. In clinical oncology, the ultimate goal of radiomics is to apply standardized signatures towards specific oncologic functions and outcomes, thereby enabling personalized cancer care that can be directly actionable. However, the literature investigating actionable radiomic signatures have not yet developed to a level sufficient for broad implementation. For instance, studies have examined the role of texture analysis in differentiating HPV status and p53 status in subpopulations of head and neck cancer patients. While the ability to infer oncology-specific parameters from imaging is promising, further investigations and collaborations are needed to incorporate these findings into a management scheme that can directly impact decision-making.

There is a need for radiomic signatures with specific oncologic function (i.e., defining oncologic pathophysiology such as metastasis). The complex management of each and every cancer patient also mandates radiomic signatures specific for clinical parameters tell-tale for different phases of treatment (i.e., pre- *vs.* post-procedure, during and after chemotherapy, and at different timepoints during radiation therapy). In addition, we must also refine clinical endpoints specific to oncology. For instance, in addition to investigating general outcomes like OS, radiomic signatures specific to the nodal metastasis probability would be clinically useful towards clinical management. In order to realize cancer-specific radiomics, we need extensive prospective multicenter trials and external validation to begin standardizing and refining radiomic signatures.

To that end, one fruitful and practical approach may be to leverage imaging data from ongoing and proposed randomized clinical trials which contain a well-defined imaging component. Validations should be done against completely independent large datasets, preferably from other institutions. A prime example of this process gaining ground is demonstrated in the efforts of Leijenaar *et al.* (37), whose group externally validated a prognostic radiomic signature on an independent cohort of oropharyngeal squamous cell patients. In addition, recent investigations revealing that radiomic signatures have translational capacity between cancer types, yet retain cancer-specific cluster features, are highly promising towards the effort to standardize and refine radiomic signatures (34,35). Finally, another means to accelerate developments in head and neck cancer radiomics takes the form of formal challenges posed to the research community to solve defined issues. The Medical Image Computing and Computer Assisted Interventions (MICCAI) challenge is one such challenge that bridges international solutions to user feedback. Their

challenges have sought solutions applicable to obstacles in cancer imaging, including those of head and neck cancer. The potential for radiomics to realize personalized cancer care has been demonstrated by numerous investigations. The field and its applicability to oncology promise to develop with time, but only if we direct our efforts to specific oncologic function and oncologic outcomes, with external validation through multi-institutional collaborative efforts.

Moving the field forward

The data summarized herein suggest cumulatively that there is great potential for radiomics and texture analysis techniques to improve upon multiple aspects of the tumor assessment, risk stratification, and outcome evaluation aspects in head and neck cancer therapy. However, at present the vast majorities of these studies are primarily exploratory, or at best, seek to perform model refinement and validation methods. At present, there is a fundamental need for several key efforts as an oncologic community which will solidify the role of radiomics in texture analysis techniques in a manner that can realize clinical utilization.

First, there needs to be a global effort towards standardization. This effort requires standardization not only of individual radiomics algorithms, but also of specific acquisition parameters. Fundamentally, performance quality assurance and quality improvement must be utilized such that a specific imaging acquisition protocol matched with a specific texture and analytic protocol (see *Figure 1*) can be shown to perform within an estimated error range as a diagnostic, predictive, and evaluative tool. It is only when such data are well defined that we will truly be able to implement radiomics and texture analytic techniques in the clinic.

Individual work at the level of algorithm standardization is already underway, with the recent publication by Parmar *et al.* (57) serving as an excellent model. In this seminal head and neck radiomics manuscript investigating the quality assurance/quality improvement methodology, Parmar *et al.* carefully and rigorously evaluated the process variability in their radiomics development process, discovering that the majority of performance variation could be identified in the classification process. Only by similar efforts in investigating the relative performance characteristics and error estimators in each individual step of the radiomics process will we achieve reliable and reproducible tools which can scale across institutions and imaging data sets. Additionally, individual image acquisition protocols should be standardized in a similar manner. For example, it is unclear at present whether there is comparability between individual predictive/prognostic features in inter-/intra-sequence MRI data sets, and between similar textural features in CT or PET-CT datasets. Ideally, multimodality data sets should be interrogated to determine whether similar and/or related textual features can be representative across imaging modalities.

Finally, the bulk of our efforts should be directed towards determining the underlying mechanistic underpinnings of the observed clinical findings demonstrated by radiomics and texture analyses. For example, it is unclear specifically which features are individually representative of what underlying physiological processes drive tumor response or normal tissue injury changes observed in the affirmation data sets. While the leading candidates represent measures of tumor heterogeneity, or vascular perfusion differentials across tumor lines, it is imperative that future efforts derived at clinical, radiologic, histopathologic, or genomic characterization interrogate the underlying molecular physiologic processes which drive the meso/macro-scale features observed in clinical datasets. One of the most compelling examples of how to approach such studies is that of Panth *et al.* (58), who grew colon cancer-derived xenografts with doxycycline-inducible (GADD34) cells in the flanks of nude mice. As GADD34 overexpression decreases hypoxic fraction, changes in gene function and hypoxia could be observed through serial CT imaging over time. Radiomics analyses were performed at 40 kVp and again at 80 kVp for validation, before and after radiotherapy. These data showed not only reproducible, robust changes seen at multiple kVp levels, but that specific temporal kinetic differences could be observed with regard to genotypic and phenotypic radiomics signatures. Work of this quality and scope will need to be undertaken in head and neck specific models to interrogate the mechanistic underpinnings of radiomics *in vivo*.

Conclusions

In summary, we believe that the preponderance of evidence suggests that radiomics is in fact revealing real information regarding tumor and normal tissue information that is above and beyond visual analysis However, these quantitative methods require further hardening of the underlying methodologic processes, as well as a greater coupling of quantitative imaging phenomena to the underlying biologic

processes. Our hope is that these needs can be met sooner than later.

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Footnote

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Supplementary

Table S1 Summary of studies on radiomics and head and neck cancer

Authors (study)	Modality	Findings pertinent to radiomics	Statistical findings
Brown *et al.* (15)	DW-MRI	Texture analysis can perform preoperative stratification of thyroid nodules with high sensitivity and specificity on multi-institutional DW-MRI datasets. Correctly classified 89% ROIs from 18 patients from an independent validation dataset	Training dataset stratification using LDA: AUC 0.97, sensitivity =92%, specificity =96%
Buch *et al.* (17)	CT	Identified two textural features that demonstrated significant differences after FDR correction in distinguishing HPV+ versus HPV– status in OPC patients	Histogram feature: median P=0.036; histogram feature: entropy P=0.048
El Naqa *et al.* (20)	FDG-PET	Using highest predictive features from IVH metrics, shape and texture features extracted from pre-treatment FDG-PET, constructed a two-metric LR model predicting overall survival with an AUC of 1.0. g(x) = –3566 × V90 + 78.5 × Shape_ Extent + 23.9	Rs =0.87 (P=0.0012)
Jansen *et al.* (21)	DCE-MRI	Texture analysis may provide complementary information in addition to standard DCE-MRI measurements which have been shown to be predictive of treatment response in HNC patients. Energy feature from the ve map was significantly higher on intra-treatment scans than pre-treatment scans (0.41±0.22 *vs.* 0.30±0.11)	P<0.04
Zhang *et al.* (22)	CT	Identified two texture and histogram features to be independent predictors of overall survival in HNSCC patients treated with induction chemotherapy	Primary mass entropy: HR =2.10 (0.5 unit increase); P=0.36; histogram skewness: HR =3.67 (1 unit increase); P=0.009
Fujita *et al.* (24)	CT	Identified three textural features that demonstrated significant differences after FDR correction in distinguishing HPV+ versus HPV– status in non-OPC patients	GLCM contrast q =0.004; GLCM correlation q =0.006; law L8 q =0.034
Vallieres *et al.* (25)	FDG-PET	Multivariate models built via LR and SVM using five features (textural entropy and homogeneity, SUV %inactive volume, volume, and solidity) could reliably classify HPV status and has potential to predict treatment failure	HPV status using LR: AUC =0.64; HPV status using SVM: AUC =0.72; treatment failure using: LR: 0.660±0.004
Yu *et al.* (26)	FDG-PET/ CT	NGTDM features including PET coarseness, PET contrast, and CT coarseness extracted from co-registered FDG-PET/CT images yield good discriminatory performance between normal and abnormal tissue. Multivariate model constructed via DT-based KNN classifier able to discriminate between normal and abnormal ROIs	Az of DT-based KNN: classifier: 0.950±0.007
Yu *et al.* (27)	FDG-PET/ CT	Extracting and selecting textural features from PET and CT voxels, COMPASS yielded contours that were quantitatively and qualitatively similar to manual segmentation by expert radiation oncologists and was able to distinguish HNC with variable (18)F-fluoro-deoxy glucose uptake from adjacent normal tissues with high physiologic uptake	COMPASS auto-segmentation: specificity 95%±2%; sensitivity 90%±12%
Raja *et al.* (23)	CT	Texture analysis on CT images of oral cancers involving buccal mucosa revealed no observed significant difference between the three grades of tumour for any of the parameters. Difference between mean FD and GLCM parameters of the lesion *vs.* the normal ROI were statistically significant	FD mean P=0.001; GLCM angular second: moment P=0.004; GLCM contrast P=0.02; GLCM inverse difference GLCM entropy P=0.002
Fruehwald-Pallamar *et al.* (31)	MRI	MRI 2D and 3D texture analysis can discriminate between benign and malignant HNC if performed on one scanner with the same protocol	–
Fruehwald-Pallamar *et al.* (28)	MRI	Texture analysis can differentiate benign from malignant parotid lesions, as well as pleomorphic adenomas from Warthin tumors based on standard T1-weighted sequences (+/– contrast). Mean ADC between Warthin tumors and pleomorphic adenomas (P=0.03) and between those of Warthin tumors and benign masses (P=0.042) are significantly different	–
Yang *et al.* (29)	MRI	Automated parotid segmentation method using feature-trained SVM can accurately quantify radiation-induced parotid gland change using pre- and post-treatment MRI. Successful parotid segmentation achieved for all 42 post-RT MRIs from 15 patients	–
Park *et al.* (30)	MRI	Histogram analysis of DCE-MRI parameters based on whole tumor volume can differentiate squamous cell carcinoma from malignant lymphoma of the oropharynx. Kurtosis of ve had best discriminative value	Kurtosis of ve: AUC =0.865 sensitivity =83.3% specificity =90.5%
Aerts *et al.* (34)	CT	Radiomic analysis of 440 features found that a large number of features have prognostic power in independent datasets of lung and HNC patients. Radiomic signature trained using a dataset of NSCLC patients was found to have translatability in two independent HNC validation datasets	–
Leijenaar *et al.* (37)	CT	Radiomic signature defined by Aerts *et al.* externally validated well on independent cohort of oropharyngeal squamous cell carcinoma patients, demonstrating good model fit and preservation of discrimination. Signature retained discriminatory ability in the presence of visible CT artifacts	Harrell's c-index 0.647; P=5.35e-6 (with artifact)
Parmar *et al.* (35)	CT	Consensus clustering resulted in 13 stable radiomic feature clusters for HNC. Clusters were externally validated using rand statistic. Lung and head and neck radiomic clusters are significantly associated with patient survival and tumor stage. Clustering and the prognostic radiomic features are cancer specific	HNC RS =0.092, P<0.001 HNC prognosis CI =0.68±0.01 HNC stage AUC =0.77±0.02
Parmar *et al.* (36)	CT	Identified prognostic and reliable machine-learning methods (three feature selection and three classifiers) for prediction of OS in head and neck cancer patients	–
Dang *et al.* (38)	MRI	MRI texture analysis could predict p53 status in oropharyngeal squamous cell carcinoma with 81.3% accuracy. Texture variables that featured significantly were derived from post-gadolinium T1W1, T2W1, and ADC map	P<0.05
Scalco *et al.* (44)	CT	A general decrease in parotid tissue complexity and heterogeneity was observed at different time points of radiotherapy. Volume and mean intensity variation were found to be correlated with pre-treatment dosimetric parameters	–
Scalco *et al.* (43)	CT	Using discriminant analysis based on volume and fractal dimensionality, final parotid shrinkage at end of RT treatment was predicted with 71.4% accuracy	–

DW, diffusion-weighted; MRI, magnetic resonance imaging; LDA, linear discriminant analysis; AUC, area under curve; CT, computed tomography; FDR, false discovery rate; HPV, human papillomavirus; OPC, oropharyngeal cancer; FDG-PET, fludeoxyglucose-positron emission tomography; IVH, intensity-volume histogram; LR, logistic regression; Rs, Spearman's rank correlation; DCE, dynamic contrast-enhanced; HNC, head-and-neck cancer; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; GLCM, gray-level co-occurrence matrix; FD, fractal dimension; SVM, support vector machine; SUV, standard uptake value; NGTDM, neighborhood gray-tone-difference matrix; ROI, region of interest; DT, decision tree; KNN, K-nearest neighbor; COMPASS, co-registered multimodality pattern analysis segmentation system; ADC, apparent diffusion coefficient; NSCLC, non-small cell lung cancer; IMRT, intensity-modulated radiation therapy; LRFS, loco-relapse free survival; OS, overall survival.