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Original Research Paper

Dentistry

# REDEFINING THE DIAGNOSTIC ERA WITH REDIOGENOMICS - THE MODERN AGE TOOL.


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**ABSTRACT** Humankind has evolved a long way to finally enter an era of artificial intelligence; where machines aid in contemplating the given task to the utmost accuracy. Medicine, being as old as humankind, too, has evolved its way into modern age technologies for diagnosing and treating diseases. Today, Artificial Intelligence has become an integral part of our life and its various subsets are proving to be promising and efficient even in the field of healthcare. Radiogenomics is a subset of AI which holds the potential to accurately predict radiographic, genomic and molecular changes in completely non-invasive manner. It relies on obtaining image data from CT, MRI or PET scan which then is used to predict prognostic biomarkers. Due to its ability to assess changes tailored to a particular type of tumor, it is the most suitable model for precision medicine. In this article, we aim to elucidate the mechanism of Radiogenomics, its role in oral oncology along with challenges and future prospects.


**KEYWORDS :** Radiogenomics, artificial intelligence, oral cancer, diagnostics, oncology.

## INTRODUCTION

Head and neck cancer is the sixth most common cancer and cause of death worldwide. With revolutionizing advancements in the field of medical oncology and healthcare, cancer still remains as one of the most challenging entities to treat. The reasons attribute to its multifactorial etiology, high recurrence rates and insufficient information about the nature and spread of a particular type of cancer. Various imaging modalities such as PET, MRI, CT can give us salient information about extent of tumor, its invasive capabilities etc., but, are futile to give deeper insights into tumor microenviornment. The underlying molecular changes in specific type of cancer can dramatically alter the treatment regime and also increase the chances of survival.

Currently, to know the molecular changes underneath, we have to perform biopsy of the lesion which is invasive and traumatic to the patient. In addition, the specimen does not necessarily reflect the entire tumor burden. In this scenario, with changing faces of altering genetic events, the need for more sophisticated diagnostic techniques is indisputable.

In today's world, Artificial intelligence has entered almost every aspect of human life; and healthcare is no exception. One such subset of AI, a newly rising field at the horizon has the ability to overcome problems encountered in conventional techniques with great confidence. 'Radiogenomics' – an application of Artificial Intelligence, is a recently coined term which represents combination of two finest of AI algorithms – Radiomics and Genomics.

The conceptualization of Radiogenomics goes a long way in terms of its mechanism and applications. In this article, we attempt to throw light upon the concept of Radiogenomics and its role in revolutionizing diagnostic medicine. The aim of this article is to elucidate the mechanism of Radiogenomics, its role in oral oncology along with challenges and future prospects.

### Multiomics

Human health, whether oral or systemic, is examined from multiple prospects and layers. Various diagnostic investigations reveal specific aspects of (oral) health and diseases. However, over the past few years, the advent of AI has allowed clinicians to assess the disease from a bird's eye point of view. A new AI based perspective called 'Multiomics' has developed which helps in providing in depth information of any disease from any possible aspect.

So what exactly does multiomics comprise of? How does it function? In a nutshell, it is a collection of datasets which integrate all the technologies having suffix 'omics'. It includes radiomics, genomics, pathomics, proteomics, transcriptomics, etc. Each individual constituent of this entity uncovers a specific aspect of the target lesion hence, aiding in the diagnostic procedure. (Fig 1)

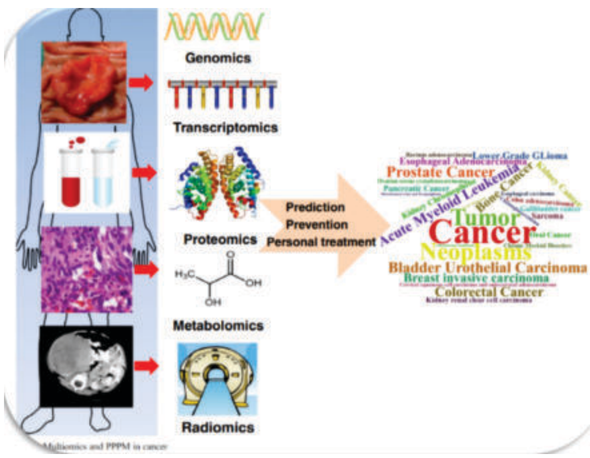



**Fig 1: Workflow Of Multiomic Approach.**[1]
(Image ref: Miaolong Lu et al.)

Let us consider the example of Oral Squamous Cell Carcinoma (OSCC) for instance. If one has to comprehensively understand the true nature, extent and malignant potential of the given OSCC in order to proceed, the clinician has to perform multiple radiological and histopathological tests including CT, PET, oral biopsy etc. These tests can be invasive, time consuming and extremely expensive. Multiomics provides the solution for these obstacles by presenting all the detailed analysis of the tumor including radiographic dimensions of the tumor, histological depth of invasion, ongoing molecular changes and protein composition of the tumor in one go. Because of its ability to assess these changes for each particular tumor, multiomics approach becomes the most suitable model for precision medicine.

There are multiple subtypes in the field of multiomics. In addition to single 'omic' dataset, two or more techniques can be combined and applied considering the clinical situation.

### What Is Radiogenomics And What Is Its Role In Multiomics?

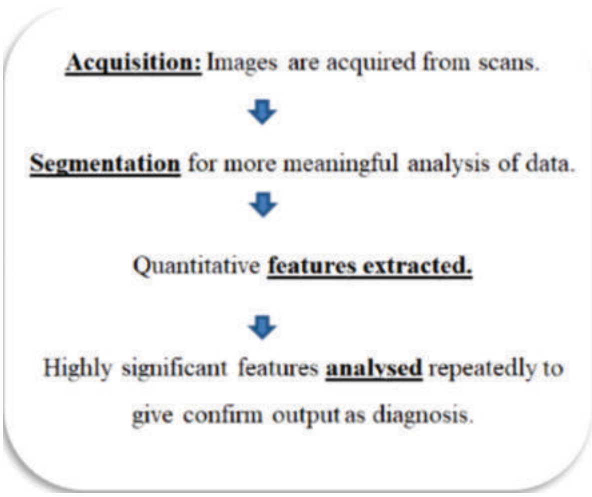
Multiomics approach can combine two or more techniques to correlate different aspects of tumor features and facilitate deeper understanding of the pathology. One such combination, which has given the diagnostics and therapeutics of medical oncology a new direction has emerged from combination of two different approaches of multiomics, called as "Radiogenomics".

Radiogenomics is recently discovered concept and the term was coined by Andreassen et al in 2002. The concept is basically aims to correlate imaging characteristics (imaging phenotype) with gene expression patterns, gene mutations and other gene related characteristics. It denotes direct relationship between imaging features of a particular disease and its underlying dynamic genetic or molecular features via discovery of imaging biomarkers such as shape, texture, histogram etc. that capture tumor heterogeneity.

The need to assess genomic biomarkers via radiographic images through radiogenomic approach arises from technical snags of biopsy procedure. The conventional approach to investigate any type of oral cancer includes various types of diagnostic imaging in order to assess soft tissue and osseous involvement and incising a small tissue specimen to analyze histopathologically for presence of dysplastic features or features of malignancy. Even if biopsy is considered as the 'gold standard' for diagnosis of carcinoma, it has certain limitations that tend to restrict its applications at times. Firstly, it is extremely traumatic to the patient, and, it also increases chances of overlapping secondary infections for the patient. Secondly, the specimen of biopsy does not reflect entire tumor burden. Hence, heterogeneity of tumor may not reproduce in the given biopsy sample.

## Workflow Of Radiogenomics

Radiogenomics symbolizes combination of radiomics and genomics. Out of these, Radiomics, an AI based diagnostic imaging method, identifies and analyzes features of heterogeneous tumors in a non-invasive way. The workflow of radiomics is given in flowchart 1. The concept of Radiogenomics is often confused with Radiomics, but both the terms differ from each other in the sense that while Radiomics signifies analyzing semantic imaging characteristics on radiographic images, radiogenomics expands its application in predicting histopathologic characteristics from the radiographic images, thus completely eliminating the need for biopsy.




**Flowchart 1: Workflow Of Radiomic Model**

## Image Acquisition

Various imaging modalities such as CT, MRI, PET etc. are acquired to gain a better insight about the nature and spread of tumor. For radiomic algorithm, only high-quality images operating in sophisticated computational tools are required in order to increase the accuracy of results.

## Tumor Segmentation

A gross region of interest (ROI) is needed to be identified from acquired images. This can be done either manually or with automated tools of AI. Multiple deep learning algorithms are available which contour the ROI with required robustness. (Ex. Seed points). However, in patients with metastatic tumors treated with RT previously, the lesions are already delineated by radiation oncologists manually. Such antecedent delineations can accelerate the radiomic analysis process further.

The segmented ROIs are then rendered in three dimensions to analyse the tumor features comprehensively.

## Feature Extraction

Rendering images in 3D facilitates the further step, i.e. feature extraction. High dimensional semantic and agonist features are considered from rendered three dimensional images. Semantic features include measures such as size, location, vascularity, speculation, necrosis etc. Agonist features entail more complex statistical features pertaining to inter relationship of voxel values. Together, these semantic and agonist features comprise high throughput mathematical feature set which is utilized for output in radiomics.

Feature selection is an important step in order to minimize errors such as overfitting and give as possible as accurate diagnosis.[2,3]

## Predictive Modeling

After the features are extracted, they are repeatedly analyzed to detect the patterns associated with clinical diagnosis. Several feature selection algorithms such as forward/ backward selection, Fischer score etc. cam be applied to identify most informative ones to fit the model.

In the final step, these repeatedly analyzed features give the most possible output in the form of diagnosis.

Thus, Radiomics gives us most significant feature based likely diagnosis of the lesion. However, utilizing radiomics alone is insufficient to achieve the goal of precision medicine. To tailor the diagnosis and treatment according to the need of each individual patient, a thorough understanding of tumor microenviornment including individual variability in underlying genetic composition is necessary. 'Genomics', another important 'omics' approach has shown a revolutionary progress in diagnostic oncology for studying genetic composition of tumors and analyzing them for confirmed diagnosis.

Hence, to combine radiomic features with genomics is imperative as it signifies the broadening of clinical imaging into genomic and molecular biomarkers and establishes the relationship between radiographic images and histological biomarkers.[4] (Fig 2)

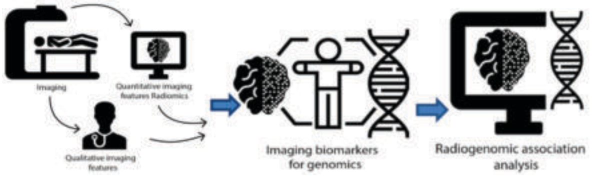



**Fig 2: Workflow Of Radiomics And Genomics Together To Give Radiogenomic Output.**

Pinker et al[5] reported that MRI scan of 10 patients having brain glioblastoma showed that ratio of enhancing to non-enhancing value on the scan correlated to increased expression of Epidermal Growth Factor Receptor and the enhancing phenotype was correlated with angiogenesis and tumor hypoxia related genes such as vascular endothelial growth factor. They have also reported that the Volumetric analysis of 76 TCGA glioblastomas showed that TP53 mutant tumors had smaller enhancing and necrotic volumes and RB1 mutant tumors had smaller edema volumes. Since all these oncogenes (TP53, RB1, EGFR etc. ) are commonly expressed in almost all oral cancers, similar imaging biomarkers can be correlated from diagnostic images. Jia wu et al[3] in their review have stated that Certain semantic radiomic features (texture intensity, rim enhancement, extent of necrosis) can be correlated with mutations of certain underlying genes (such as EGFR) expressed in that particular tumor. These and multiple other studies reported in the literature employ voxel based analyses and implement texture algorithms such as gray level co-occurrence matrix, local binary patterns,; to name a few, to correlate both types of findings. Many thousands of texture features are generated by advanced image analysis techniques and DL algorithms (Support vector classifiers, decision tree based random forests etc.) to study the intricate and dynamic micro environment of the entire tumor portion, and predict the metabolic genomic alterations underneath. [5] (Fig 3)

Approaches of radiogenomic technique can be exploratory or hypothesis driven. In exploratory studies, qualitative as well quantitative metrics are extracted (such as shape, extent of the tumor) and tested against various genomic metrics such as over expression of certain biomarkers. This type of radiogenomic approach allows clinicians to investigate correlating imaging features with expression of various genomic markers, leading to the recognition of imaging biomarkers – markers identified on X-ray images. Whereas in hypothesis driven approach, a specific hypothesis is assumed and features are correlated with specific genomic markers. [5,6]

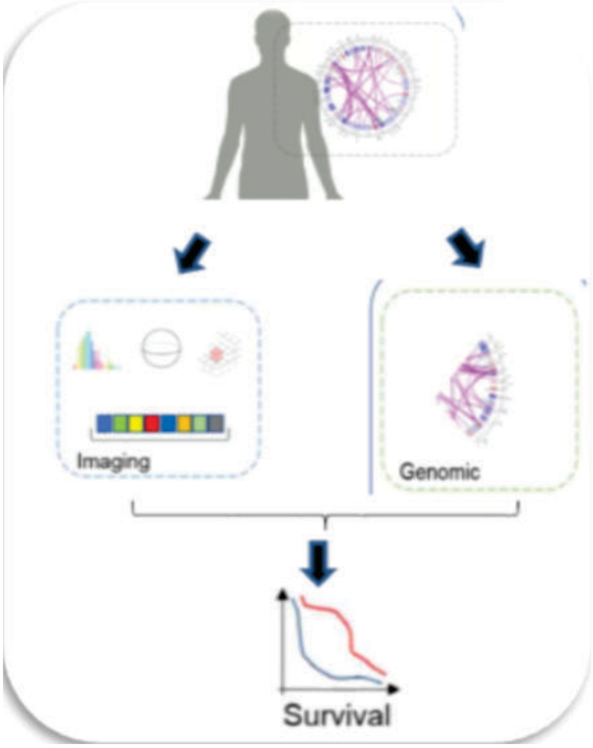



**Fig 3: Combining Imaging And Genomic Features In Radiogenomics To Predict Chances Of Survival.**

## CONCLUSION

To achieve the true concept of precision medicine, aligning the therapeutic regimen with dynamic changes of tumor microenviornment is of paramount importance. Hence, the diagnostic tests required for the same need to be equally equipped, multilayered and explicit to identify subtle changes underlying an active neoplastic lesion.

Such tests should encompass not one, but multiple possible aspects of investigation to support the precise prediction, guidance, and monitoring of treatment response. Radiogenomics is a novel field on the horizon owning the potential to revolutionize the field of diagnostic and therapeutic oncology. However, literature reports no studies or reviews on radiogenomic applications in oral cancer till today's date. This review summarizes mechanism of Radiogenomics and its future in the field of radiodiagnostics pertaining to oral cancer. To the best of our knowledge, this is the only review to overview the role of Radiogenomics into oral cancer. With correct direction of research, Radiogenomics can be the ray of hope to better diagnosis and therapeutics in oral and maxillofacial oncology.

## Conflict Of Interest

Authors declare no conflicts of interests.

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