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Review

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Precision radiation oncology in head and neck cancer: beyond physical precision - a narrative review

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Abstract

Radiotherapy is an integral part of the management of head and neck cancers, both in radical and adjuvant settings. Traditionally, similar radiation dose and fractionation schedules have been used based on tumor stage with variable outcomes indicating "one size does not fit all". In the era of precision medicine, though we have achieved physical precision with technological advancements, we have yet to attain biologic precision. In the current review, we have highlighted the different aspects of precision oncology such as hypoxia targeting, radiomics and radiogenomics, radiobiologic targeting, and big data. The review also discusses various potential therapeutic targets and approaches in head and neck cancer management that might help to increase radiosensitization, which in turn increase survival, and quality of life. This can be incorporated into the armamentarium of radiation oncology in all the phases of radiation planning, from diagnosis to treatment to the prognosis and management of long-term side effects. Biologic precision can be applied in the clinic to provide individualized, personalized treatment in the future.

Keywords: Head and neck cancer, precision oncology, radiation oncology, radiomics, big data

INTRODUCTION

Since the discovery of X-rays by Wilhelm Roentgen in 1895, the clinical use of radiotherapy has evolved significantly[1]. The introduction of computed tomography (CT) scan in the 1980s has helped in visualizing the tumor 3-dimensionally (3D) instead of bony landmark 2-dimension (2D) and thus effective planning of radiotherapy in head and neck cancer (HNC). Since then, there have been progressive technological advancements in radiation oncology with the advent of intensity-modulated radiotherapy (IMRT) in the 1990s, image-guided radiotherapy (IGRT), stereotactic radiotherapy (SRT), particle radiotherapy, and adaptive radiotherapy. All these high-precision techniques are aimed at improving the therapeutic ratio, targeted delivery of very high doses, and reducing doses to the organs at risk (OAR), thus improving the outcome and providing better quality of life in HNC patients.

Even though anatomic or physical precision was achieved in the 21st century, still the whole world is preaching precision oncology in radiotherapy. Despite the advances, there continues to be a significant failure which may be due to unpredictable biological behavior of similar tumors in different individuals. Patients with the same stage and disease at the same site respond differently to the same treatment modality, reaffirming "one size does not fit all". Hence, requiring more to be integrated into the treatment approach than what is presently practiced. This has attracted the investigators to think and go beyond physical precision and attempt to incorporate biological precision. Precision oncology holds the promise of tailoring the spectrum of cancer care from diagnosis to risk assessment, predicting the outcome, and personalization of cancer care.

In this narrative review, we aim to highlight the different aspects of precision oncology in the present era, such as targeting hypoxia, incorporation of imaging as data and predictive models, radiobiologic targeting, and finally "Big Data" in achieving personalized precision therapy.

HYPOXIA TARGETING

Locoregional failure (LRF) is the major cause of disease progression and death in HNC patients. Hypoxia is one of the important tumor micro-environmental components associated with radioresistance, tumor progression, and metastasis, which poses a great clinical challenge as well as an attractive target for therapeutic manipulation in HNC. The impact of hypoxia has been known since the 1950s and there is extensive evidence of its impact on clinical outcomes[2,3].

Although the mechanism of hypoxia-induced radioresistance has been described in different models, it is more complex than what is understood. The normal stem cell niche not only has the capability to tolerate and survive hypoxia but also requires hypoxia for survival[4-6]. The tumor cells are generally considered to be more hypoxic than normal stem cells[7,8]. The same mechanism of survival of cancer stem cells can be replicated from normal cells. This is by the mechanism of "radical competition". The low oxygen tension protects the stem cell DNA damage from free oxygen radicals and the DNA radicals are reduced by hydrogen donation from the thiol compound, thus leading to survival and radiation protection[9]. There are several hypoxic-induced responsive mechanisms, which not only decrease the effectiveness of therapeutic radiation but also negatively influence the outcomes of chemotherapeutics and radiosensitizers. These mechanisms/molecules include hypoxia-inducible factor (HIF)-1α based mechanisms, hypoxia-induced reprogramming of energy metabolism, heat shock transcription factor 1(HSF1)-mediated heat stress response, and heat shock proteins (HSPs), endoplasmic reticulum stress, glucose-regulated proteins (GRPs), hypoxia-induced autophagy, hypoxia-induced formation of the radioresistant cancer stem cells (CSC) phenotype, hypoxia-Responsive microRNAs, long non-coding RNAs and circular RNAs and hypoxia-induced exosome generation. The hypoxic areas are more prone to develop into Epithelial Mesenchymal

Transition (EMT), where mobile invasive cancer stem cells invade the vessels and migrate to other organs, leading to distant metastasis. It is the site where cancer cells increase their invasiveness, motility, potential for metastases, stemness, and chemo-radio resistance. Hypoxia-adapted cancer cells are resistant to low as well as high linear energy transfer (LET) radiation due to certain phenotypes with specific regulation[10].

Despite the mechanism and effect of hypoxia being understood, the quantification of tumor hypoxia (TH) poses a diagnostic challenge for therapeutic manipulation. Different methods like polarographic technique, bioreductive agents, determination of HIF-1α, positron emission tomography (PET-CT) with hypoxic tracers (18F-labelled misonidazole (FMISO), fluoroazomycin arabinoside (FAZA), blood oxygen level-dependent magnetic resonance imaging (BOLD-MRI) have been used for determining tumor hypoxia. However, there is no standard, most acceptable method of determining hypoxia, leading to decreased reliability in its determination. MicroRNAs (miRNAs) are short, endogenous non-coding RNAs found to be involved in the regulation of many biological processes such as cellular proliferation, development, cell death, metabolism, and oncogenesis. These miRNAs may help to determine hypoxia[11]. Of the 11 different miRNAs dysregulated in HNC, miR-210 is the only miRNA consistently induced and regulated by hypoxia and hence can be used as a predictor of hypoxia[12,13].

Another novel approach to detecting hypoxia and predicting response to hypoxic modification is hypoxic gene signature profiling. Toustrup *et al*. developed a 15-gene hypoxic classifier for predicting the impact of hypoxic modification, which has been validated in the Danish Head and Neck Cancer Group (DAHANCA) 5 study cohort[14,15]. Another study of 26-gene hypoxia signatures in laryngeal cancer patients reported improved benefits with accelerated radiotherapy with carbogen and nicotinamide (ARCON) in tumors with higher hypoxia scores than those with lower scores[16]. Recently, P4HA1 has been proven to be a single gene surrogate of hypoxic signature in oral squamous cell carcinoma[17]. Different hypoxia markers can be detected in biopsy or resected specimens. The markers can be either endogenous such as HIF-1α, carbonic anhydrase IX (CAIX), glucose transporter 1 (GLUT-1), and vascular endothelial growth factor (VEGF) or exogenous such as pimonidazole and EF5, overexpression of which is associated with poor response/ treatment failure and thus poor prognosis in HNC patients.

Targeting hypoxia may lead to improved outcomes in HNC. Different strategies have been developed for targeting hypoxia, including vascular endothelial growth factor (VEGF) inhibitors, hyperthermia, hyperbaric oxygenation (HBO), erythropoietin stimulating agents, agents targeting tumor blood flow (pentoxifylline), use of bioreductive drugs, hypoxic cytotoxins, ARCON therapy and PR-104, CP-506. However, none of the methods have been widely accepted for clinical use as the basic idea of these methods is improving oxygen delivery[18,19]. However, there are some clinically useful and applicable strategies to target hypoxia, which are shown in Table 1. Phase II trials on ARCON reported it as the most promising therapy in improving tumor control of bladder and HN cancer[20,21]. A phase III randomized study showed that ARCON improves locoregional control and disease-free survival (DFS) in HNC patients with low expression of epidermal growth factor receptor (EGFR)[21-23]. Among the radiosensitizers, nimorazole is the only agent that has been adopted for clinical use, and that too only in Denmark. The confirmatory study, DAHANCA 29-EORTC 1219, done outside Denmark, to prove the efficacy of nimorazole in stage III-IV laryngeal, hypopharyngeal or p16-negative oropharyngeal SCC was not successful. The trial was closed prematurely due to the low conditional power associated with the hypothesized treatment effect. The 2-year locoregional control probability was not clinically different either in the entire population or in the subgroup of hypoxic-gene-positive patients[24]. However, DAHANCA 30, an ongoing non-inferiority trial, has gone one step further to evaluate the impact of hypoxia profile guided hypoxic modification with nimorazole in head and neck cancers (Clinicaltrials.gov Identifier: NCT02661152). Similarly, DAHANCA

Table 1. Selective strategies to target hypoxia in head and neck carcinoma

Strategy	Targeted mechanism/molecular target	Clinical trials [*n*]	Clinical outcome	Toxicity
HBOT (Hyperbaric Oxygen Therapy)	Physical increase in O_2 supply by enhanced amount of dissolved O_2	Benette *et al.*[31] Meta-Analysis [19 Clinical trials]	Reduced risk of death at 1 year and 5 year (RR = 0.83) Decrease local recurrence (RR = 0.66)	1. Claustrophobia 2. Increased risk of severe radiation tissue injury (RT + HBOT) 3. Risk of oxygen toxicity seizures
TPZ (Tirapazemine)	DNA strands breaks; HAP	Rischin *et al.*[32] (TROG 02.02, Head START)	No difference in failure-free survival/time to locoregional failure	More hematologic and GI toxicities in TPZ arm
ARCON	Carbogen (95% O_2; 5% CO_2) breathing can reduce chronic hypoxia Accelerated radiotherapy can counteract tumor cell repopulation Nicotinamide can decrease acute hypoxia	Kaanders *et al.*[21] [215 patients]	1. High local and regional control rates 2. For T3-T4 tumors, LC rate 80% for larynx 60% for hypopharynx, 87% for oropharynx, 29% for oral cavity 3. Regional Control rate 100% for N0, 93% for N1, 74% for N2 disease	1. Acceptable acute and late morbidity 2. Grade 4 morbidities developed in 5% of patients
		Janssens *et al.*[23] [345 patients]	Improved 5-year LRC (79% *vs.* 53%; *P* = 0.03) DFS (68% *vs.* 45%; *P* = 0.04) in patients with low pretreatment hemoglobin levels	1. Acceptable toxicities 2. Patients' stratification is required; especially useful for anemic patients
Nimorazole	Oxygen mimetic	Toustrup *et al.*[33] (DAHANCA 5; phase III) [323 patients]	Improved 5year LRC (49% *vs.* 18%; *P* = 0.001) DSS (48% *vs.* 30%; *P* = 0.04) in more head and neck cancer with hypoxia	Minor nausea and vomiting
Nelfinavir	Decreased HIF-1α and VEGF levels, suppresses angiogenesis, and suppresses Akt signaling	Hoover *et al.*[34] [15 patients]	No meaningful improvement in patients with recurrent ACC	1. Grade 3 or higher medical adverse events or toxicities experienced by 33% of the patients requiring dose modification 2. Radio-sensitizing effect

HBOT: Hyperbaric oxygen therapy; RR: risk ratio; RT: radiation therapy; HAP: hypoxia activated prodrug; GI: gastrointestinal; LC: local control; LRC: locoregional control; DFS: disease-free survival; DSS: disease-specific survival; HIF: hypoxia Inducible factor; VEGF: vascular endothelial growth factor; ACC: adenoid cystic carcinoma; ARCON: accelerated Radiotherapy with carbogen and Nicotinamide.

33 is evaluating functional image-guided dose-escalated radiotherapy in patients with hypoxic squamous Cell carcinoma of the head and neck (Clinical trial.gov Identifier: NCT02976051). So, hypoxia can be used as a potential therapeutic target in improving the outcomes through hypoxia modification in HNC patients treated with radiotherapy in the future. Recently, several molecular strategies have been proposed for hypoxia modification through direct or indirect modification of HIF-1α expression[25]. S-2-amino-3-(4′-N, N,-bis[2-chloroethyl] amino) phenyl propionic acid N-oxide dihydrochloride (PX-478) is one of the molecules assessed in phase I trials for direct modification of HIF-1α expression through the inhibition of glucose metabolism[26,27]. Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling axis and Janus kinase/signal transducer and activator of transcription (STAT) signaling pathway can be a target for hypoxia therapy through indirect regulation of HIF-1α[28]. In head and neck malignancies, the phosphorylation

and concurrent HIF-1α expression induce STAT3 activation. This activation can be inhibited by STAT3 inhibitor static, leading to suppression of tumor and enhanced tumor radio-sensitivity[29]. A DAHANCA 29 EORTC 1219 study data fails to show any significant benefits of Nimorazole in the whole population, or in the sub-group with hypoxic gene signature[24].

Despite the aforesaid strengths and potential use of hypoxia targeting, several caveats and limitations still remain. To effectively target hypoxia, several requirements must be met, including the use of expensive dedicated equipment, repeated biopsies, multiple injections at tumoral sites, exogenous drug administration, and the implantation of particulate paramagnetic materials. We need to validate the usefulness of these various biomarkers in large clinical trials[30]. There are clinical trials which study those selective Strategies to target hypoxia in Head and Neck Carcinoma such as using HBOT (Hyperbaric Oxygen Therapy)[31], tirapazemine[32], ARCON (Accelerated Radiotherapy with carbogen and Nicotinamide)[21,23], Nimorazole[33] and Nelfinavir[34] [Table 1].

RADIOMICS

HNC poses a major challenge in radiation oncology due to the anatomic location of a target, surrounding critical normal structure and the wide heterogeneity in the tumor as well as the radio sensitivity. HNC, like all other solid cancers, have significant temporal and spatial heterogeneity within tumors of the same site and stage, which may be the key to varying responses to the same treatment. The heterogeneity is attributed to the different subpopulations of cells within the tumor with differential growth kinetics, microvasculature, expression of biomarkers, immunological characteristics, genetic profile, and tumor microenvironment[35,36]. This heterogeneity leads to phenotypic heterogeneity, which can likely cause treatment resistance, progression, and metastasis[37]. Usually, biopsies provide genetic and phenotypic information, but with several limitations. Biopsy samples collected represent a specific subpopulation of cells within the tumor taken at a specific time point, and this procedure involves an invasive technique. It does not provide adequate pathophysiological and genetic information on the entire tumor. Conversely, radiomics, an emerging field of precision oncology, is a non-invasive representation of the virtual biopsy of the entire tumor in all 3 dimensions, providing integrative information on genetic alteration and phenotypic characteristics[38]. Thus, radiomics will help us with the implementation of personalized treatment. Biomedical imaging such as CT, Magnetic Resonance Imaging (MRI) and PET has the potential for unraveling the genotypic characteristics hidden behind the phenotypic expression and predicting the outcome[39-42]. Radiomics helps in the extraction of high throughput quantitative tumor heterogeneity data from these images, such as intensity, shape, texture, and wavelet, using a data-characterization algorithm and thus supporting and enhancing the clinical decision-making process[40,43].

Radiomics has its place in different steps of HNC, from diagnosis and prognosis to therapy response assessment/prediction [Table 2]. Texture analysis can accurately describe the tumor phenotype in HNC. CT radiomics can distinguish between human papillomavirus (HPV) positive and negative oropharyngeal cancer (OPC) without the need for immune histochemistry and in-situ hybridization[44]. Even it can distinguish between HPV-positive and negative non-oropharyngeal cancer[45]. PET CT can also be reliably used as another non-invasive modality for classifying HNC based on HPV status[46]. Radiomics can provide insight into the tumor microenvironment. Tumor resistance to radiation is the worst nightmare of the radiation oncologist and hypoxia is one major culprit for the resistance. PET-labeled nitroimidazole compounds can precisely locate the spatial distribution of hypoxic sub-volumes within the tumor and thus provide an opportunity to escalate doses to those specific sub-volumes and a promise for better local control[47-50]. Accurate prognostic and predictive models in radiomics are vital steps in widening its application to clinical oncology.

Table 2. Selected studies on applicability of radiomics in radiotherapy planning of head and neck cancer

Step	Study [*n*]	No of patients (*n*)	Sites	Features studied	Outcome prediction
Pretreatment					
HPV Status OPC	Buch *et al.*[44]	40	Oropharyngeal cancer	Extracted 42 texture features 13 histogram features, 5 gray-level co-occurrence matrix (GLCM) features, 11 gray-level run-length (GLRL) features, 4 gray-level gradient matrix (GLGM) features, and 9 Law's features	Significant difference in histogram parameters median (P = 0.006), entropy (P = 0.016), squamous cell carcinoma entropy (P = 0.043) based on HPV status
Non-OPC	Fujita *et al.*[45]	46	Oral cavity, Larynx, Hypopharynx (non-OPC)	42 texture features extracted	Significant differences between (HPV)-positive and HPV-negative non-oropharyngeal carcinoma (non-OPC) for 5 histogram features($P \leq 0.03$), 3 GLCM features($P \leq 0.02$), 1 GLRL features (P = 0.009), 2 GLGM features($P \leq 0.02$) and 5 law features ($P \leq 0.04$)
Extra-nodal extension	Kann *et al.*[61]	200# Lymph nodes	HN	ENE on pretreatment computed tomography (CT) imaging is identified by A deep learning algorithm	The algorithm achieved AUC of 0.9, outperforms the radiologists AUC
Distant Metastasis	Zhou *et al.*[62]	-	HN	Multifaceted Radiomics (M-Radiomics) Multiple base classifiers to build model	Outperforms current radiomic models in predicting distant metastasis
Prognosis	Aerts *et al.*[43]	1,019*	HN	Prognostic radiomic signature, capturing intra-tumor heterogeneity	These features are associated with underlying gene expression patterns. The routinely used imaging can improve decision support in cancer treatment at a low cost
Radiotherapy planning					
Target volumes Delineation	Lu *et al.*[63]	40	Nasopharynx	21 FO intensity features, 10 shape features 57 SO and HO textural features	Acceptable reproducibility and stability across manual and various automated segmentation techniques. Discretization generated larger effects on features than segmentation in both tracers. Features extracted from [^{11}C] choline were more robust than [^{18}F] FDG for segmentation
Organ at risk (OAR) Delineation 21 OAR	Nikolov *et al.*[64]	513	HN	21 computed tomography scans from clinical practice, each with 21 organs at risk segmented by 2 independent experts Surface Dice similarity coefficient, a new metric for the comparison of organ delineation	Deep learning model's segmentations and those of radiographers did not show any clinically meaningful difference It will improve the efficiency, consistency, and safety of radiotherapy pathways
Intra-treatment					
Daily CBCT and pCT	Bagher-Ebadian *et al.*[65]	18	Oropharynx	165 Textural features extracted, smoothing, sharpening of the images and noise to evaluate changes in features	Interchangeability of pCT and CBCT for investigating radiomics features as possible biomarkers for outcome
Treatment Verification	Park *et al.*[66]	20 + 20 Fluence Map of VMAT	HN+Prostate	Six textural features like angular second moment, inverse difference moment, contrast, variance, correlation, and entropy were calculated for fluence maps of VMAT	Contrast and variance showed considerable correlations (P < 0.003) with the plan deliverability Can be used as an indicator for degree of modulation of VMAT plans and is better than the conventional modulation indices
Treatment Delivery	Bogowicz *et al.*[67]	40	HN	From Two volumes including GTV-Recurrence and GTV-Control, we had extracted FO, SO and HO features. Bi-regional model was built.	The AUC of local radiomics for detection of noncontrolled sub-volumes in the training and validation sets was 0.66

				Local radiomics was implemented	(95%CI: 0.56-0.75) and 0.70 (95%CI: 0.53-0.86), respectively Local radiomics can detect sub-volumes with decreased radiosensitivity and dose escalation
Adaptive planning	Guidi *et al.*[68]	40 1,200 MVCT	HN	Support vector machine (SVM) and cluster analysis have identified cases where there are dose and volume discrepancies between fractions in certain treatment sessions	Whenever the patient needs a new dosimetric scan to adapt the volumes in head and neck cancer patients, these automated tools for adaptive treatment help to raise an alert
Post-treatment					
Survival	Parmar *et al.*[54]	101 (Training cohort) 95 (Validation cohort)	HN	440 features extracted. Different feature selection and classification methods were used, such as Minimum redundancy maximum relevance (MRMR), Mutual information feature selection (MIFS), Conditional infomax feature extraction (CIFE)	MRMR, MIFS, CIFE had high prognostic performance and stability. Identified prognostic and reliable machine-learning methods for the prediction of overall survival of head and neck cancer patients
Post treatment Toxicity (Xerostomia)	van Dijk *et al.*[59]	249	HN	Patient-specific characteristics, based on CT image biomarkers (IBMs) including geometric, CT intensity and textural characteristics of the parotid and submandibular glands	Prediction of Moderate-to-severe xerostomia and sticky saliva at 12 months was improved by including IBMs representing heterogeneity and density of the salivary glands

*1,019 includes Head Neck cancer and Lung Cancer. #A total of 200 lymph nodes were examined (not a number of patients). HPV: Human papilloma virus; CT: computed tomography; AUC: area under the receiver operating characteristic curve; CBCT: cone beam computed tomography; pCT: planning Computed tomography; HN: head and Neck; non-OPC: non oropharyngeal; LN: lymph node; LRC: locoregional recurrence; HNSCC: head and neck squamous cell carcinoma; CT: computed tomography; FO: first order; SO: second order; HO: higher order; MRMR: minimum redundancy maximum relevance; MIFS: mutual information feature selection; CIFE: conditional infomax feature extraction.

Different PET-CT and CT radiomic studies have been able to predict the risk of failure in different models. In a large study, Aerts *et al.* extracted 440 radiomic features in four phenotypes (tumor image intensity, texture, shape and wavelet formation) from the CT database of 1,019 patients of different cancers, including HNC, which showed a strong prognostic association of tumor heterogeneity and the underlying gene signature[43]. This radiomic signature was well validated externally in another cohort of 542 oropharyngeal cancer patients[51]. Besides the CT scan, it has been shown that texture analysis of PET-CT is a better predictor of outcome than the mere standardized uptake values (SUV)[52]. Radiomic machine learning classifiers have predicted the risk of local failure and distant metastasis in HNC[53,54]. This provides insights into treatment intensification or de-intensification on an individual basis, allowing for tailoring the treatment. Advanced tumor shape signature radiomics has also been shown to be a predictor of local recurrence in locally advanced HNC, which has also been validated in a cohort of 86 patients from TCGA databases[55].

An important and most challenging issue in head and neck radiotherapy is the critical location of normal organs. Radiomics has the potential to detect the physiologic and functional alteration in normal organs during radiotherapy. In a texture analysis study of nasopharyngeal cancer, Scalco *et al.* have shown a correlation between the dosimetric parameters and the structural changes in the parotid gland[56]. They have also shown that the early textural changes in the parotid gland can predict the final shrinkage with an accuracy of about 71.4%[57]. A similar study by Pota *et al.* has predicted parotid shrinkage and 12-month

xerostomia from CT radiomics[58]. van Dijk *et al.* suggested that the mid-treatment changes in the parotid gland are better predictors of late xerostomia as quantified by delta radiomic features[59]. Thus, for the implementation of personalized treatment, radiomics has a critical role to play in different stages of radiotherapy planning, from pretreatment patient section to intratreatment and post-treatment radiomics, which is beyond the scope of this review. However, radiomics-guided radiotherapy (RGRT) may lead to more effective radiation therapy and its usage in radiotherapy is increasing over the years[60]. The radiomics has been applied using different parameters in pretreatment[43-45,61,62], during radiotherapy planning[63,64], during treatment[65-68] and even in posttreatment setting[54] [Table 3].

Hybrid machine learning radiomics also helps in detecting molecular subtypes of Low-Grade Glioma (LGGs) using 726 raw features on MRI[69]. Radiomics-based models like eXtreme Gradient Boosting (XGBoost) help to detect molecular prognostic factors such as 1p/19q codeletion status on MRI[70].

The quantitative approach using radiomics has been widely investigated as a non-invasive and objective imaging biomarker in cancer patients; however, Because of a lack of standardization and validation of image acquisition protocols, features segmentation, extraction, processing, and data analysis, it is not applied as clinical routine practice. In the future, radiomics might be a reliable application in oncologic imaging for each type of cancer[71].

Artificial intelligence (AI), which uses deep machine learning to create "algorithms", has helped us to study image texture analysis, which is ultimately a part of radiomics. AI will help to facilitate pattern recognition in images, detection in biomarker data, and integration with non-imaging variables, which will flourish the field of radiomics. Though radiomics has greater potential in the field of precision oncology, there are several unmet challenges to be addressed. These include processing and reproducibility of large amounts of high-quality imaging data, application in the clinic and integration of genomics data. But these radiomics features do have some limitations due to their sensitivity to acquisition modes and reconstruction parameters. Hence, all of them are not recommended for use. We should investigate the topic such as the impact of harmonization and standardization on the quantification and predictive values of radiomic features. This still remains a challenging aspect[72].

BIOLOGIC ADAPTATION AND TARGETED THERAPY

Head and neck radiotherapy poses a great challenge subjecting to variation in the planned dose and dose delivered due to the ongoing anatomic changes related to tumor shrinkage and weight loss through the course of treatment delivery. With the advent of IGRT, adaptive radiotherapy (ART) has been the proposed solution to account for these changes with yet-to-be-proven benefits, given the subjective variations in the practice and indications of ART. ART would probably play a prominent role in controlling doses to the OAR without compromising the doses to the target volumes; however, there is significant uncertainty regarding the time of adaptation and is currently subject to physician discretion[73].

Although ART has been practiced for a long time and seems a logical step during radiotherapy based on volumetric (physical) changes, biological adaptation would play a more important role in precision oncology. Several trials have looked at trying to address the biological differences between oropharyngeal tumors based on HPV status and adapt the treatment accordingly. Different methods of dose de-escalation were evaluated in an attempt to treat this favorable group of relatively younger patients to reduce toxicity without compromising treatment-related outcomes. The different strategies include reduction in all the components of triple modality treatment[74].

Table 3. Selected studies on applicability of big data in head and neck cancer management

Study	No. of patients	Primary	Major findings
Robertson *et al.*[87]	684	Head and Neck cancer	Data-mining algorithm confirmed the following well-known OAR-dose/outcome relationships: • dysphagia/larynx, • voice changes/larynx, • esophagitis/esophagus, • xerostomia/parotid glands • mucositis/oral mucosa
Cavalieri *et al.*[89]	1,537	Stage III IV HNSCC	Represents the HNSCC largest available repository. It will allow for: • Developing/validating a decision support system integrating multiscale data to explore through classical and machine learning models their prognostic role
Resteghini *et al.*[94]	-	Head and Neck cancer	Computational strategies derived from big data science hold the promise • Identifying new prognostic and predictive factors • Discovering potential therapeutics • Identifying new molecular mechanisms driving head and neck cancer pathogenesis

HNSCC: Head and neck squamous cell carcinoma.

Besides treatment adaptation based on HPV status, radiobiologic tumor targeting is a new and emerging concept in precision oncology. Genome-based biologic targeting is being used in medical oncology to quantify the benefits of specific agents in specific groups of the population. Genome-adjusted radiation dose (GARD) is a relatively recent concept in radiation oncology, similar to genome-based targeting in medical oncology. Scott *et al.* used the gene-expression-based radiation-sensitivity index and the linear quadratic model to derive the GARD[75]. The postulation was that high GARD values predict a higher therapeutic effect with radiotherapy, which would relate to clinical outcomes. GARD is a genome-based model developed to predict the optimal radiation dose for a particular tumor using the linear quadratic model and radiosensitivity index; hence, the dose and fractionation schedule can be planned for each individual in the future.

The radiosensitivity index was developed as a molecular marker of cellular survival at 2 Gy[76]. This has been systematically validated as a predictor of clinical outcomes in HNC[77]. This multigene expression model of intrinsic radiosensitivity successfully proved to improve 2-year locoregional control (LRC) in the predicted radiosensitive group (86% *vs.* 61%, $P = 0.05$). Hence, the radiosensitive index could be used to segregate those patients who would benefit from radiotherapy *vs.* those who would not. Another study by Scott *et al.* demonstrated a wide variation in the radiosensitive index in HNC between the most sensitive and most resistant tumors, which indicates that the one-size-fits-all strategy is no longer applicable in radiation oncology and the radiation dose needs to be tailored in the era of precision oncology[75]. Another aspect of radiobiologic targeted therapy is combining the molecular-targeted agents with radiotherapy. Currently, the two targets for targeted therapy are epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR)[78]. Combining the EGFR monoclonal antibody, cetuximab, with radiation showed improved survival in HNC and has been approved by the Food and Drug Administration (FDA). VEGFR tyrosine kinase inhibitor (TKI), vandetanib, has been shown to enhance the antitumor efficacy of radiotherapy and restore the radiosensitivity of HNC cells by increasing the apoptosis and decreasing the microvessel density in HNC cells in preclinical studies[79,80]. A phase II trial is ongoing in advanced HNC to test the efficacy of vandetanib[81]. Similarly, sunitinib, sorafenib and linifanib have shown efficacy in preclinical studies and need to be tested in the future[81-83]. Restoring the p53 function is also another attractive area of manipulation in HNC[84] and several studies are ongoing. Several of these molecular-targeted therapies are under active investigation and the results may improve the effectiveness of current therapeutic strategies.

BIG DATA

Implementation of precision oncology needs the highest quality, evidence-based guidelines for application in patients. The more specific the approach, it decreases the pool of "like patients" to be tested for specific therapies. "Big Data" plays a major role in generating a pool of "like patients". Big Data is defined as a moving semi-quantitative target, and in computer memory terms, the total amount of data is in terms of terabytes or petabytes or more[85]. The patient data studied is much larger. Different sources of Big Data include the Surveillance, Epidemiology and End Results (SEER) database, the American College of Surgeon's National Cancer Database, other national cancer databases and different large completed clinical trials[86]. Most clinicians make decisions based on outcomes of available randomized control trials (RCTs), and patients and relatives are informed about the relative effectiveness of specific modalities over others based on the trial results. However, it may not always be possible to conduct large RCTs to answer clinical questions in a timely manner. Therefore, Big Data can be utilized for retrospective data analysis with large patient cohorts and at a faster rate. Data from large sources of Big Data can be generalized to the general population and can benefit the patients early and much before RCT proves the benefit. The benefit may be in terms of treatment adoption, improved efficacy, and fewer logistic issues. Big Data can overcome the problem of a smaller number of "like patients" when testing specific targeted therapy in these groups of patients. The result would be treating a smaller number of patients with specific therapy and sparing a large cohort of patients from unnecessary, ineffective treatments.

Big Data can be utilized for personalizing treatment plans for individual patients in radiation oncology. The quality and efficiency of treatment planning can be improved by previous patient treatment plans. Initiatives have been taken for collating large-scale data from dose-volume histograms for correlating and predicting toxicity[87,88]. Big Data provides greater hope for predicting normal tissue toxicities beyond the normal tissue complication probability (NTCP) models. To use multiparametric variables for predicting prognosis and guiding the optimal choice of treatment, the international European Consortium has built Bigdata to Decide (BD2Decide) project ("Big Data and Models for Personalized Head and Neck Cancer Decision (BD2Decide) Support; NCT02832102). This represents the largest available HNSCC repository of 1,537 patients with transcriptomic and radiomic data available for 1,284 (83%) and 1,239 (80%) of the patients. For patients who were enrolled prospectively, data were collected using quality of life questionnaires (QLQ) such as EORTC QLQ 30, EORTC HN 35, and EQ-5D-5L[89]. Big Data also plays a major role in basic and clinical research; the findings of Big Data research will reach the clinic in the coming 5-10 years[90]. The BD4QoL (Big Data for Quality of Life in Head and Neck Cancer), an ongoing study, aims to reduce and anticipate the proportion of HNC survivors experiencing a clinically meaningful reduction of QoL (Clinicaltrials.gov Identifier: NCT05315570). Though big data is not being routinely used in HNC research, specific applications like radiomics and genomics have leapt in recent years.

The features of data sets such as complexity, volume, velocity variety, and veracity determine the value of big data. We need to integrate these sources in order to improve biomedical research, patient care and monitoring the quality of care[91]. Big data is playing a big role in different steps of HNC radiation planning such as, OAR-dose/outcome relationships, identifying new prognostic and predictive factors and discovering potential therapeutics [Table 3].

Big Data requires the collection of large amounts of data from the patient at each patient encounter. It requires consent from the patients and their family, and a large effort to collect the data correctly from the patients and make them understand the need for it. This may also affect the patient-physician relationship as it puts their health information system in the public domain. These are the major challenges for big data[92]. These procedures call for different aspects of addressing ethical questions regarding patient information.

The large database has design and analysis issues such as selection bias, immortal time bias and several confounding factors during data collection[93]. Although Big Data poses some challenges to uniform data collection, it will provide a greater advantage of delivering better care for patients on an individual basis, extending patients' life expectancy and enhancing the quality of their years. The radiation oncologist will be able to use clinical, imaging, dosimetric, and genomic analyses for treatment recommendations, leading to a knowledge-guided radiotherapy approach and may become an indispensable component of precision oncology in the years to come.

CONCLUSION

Patients with the same TNM stage often have variable responses to the same therapy, which can be attributed to the large heterogeneity within the tumors of similar histology and even within a single tumor. Incorporation of precision and personalized medicine into clinical practice would be of great promise in improving the outcomes of HNC. Though there are lots of limitations and challenges in implementation, there is still a need to move beyond mere physical precision and adapt to biological precision with the application of hypoxia modification, radiomics, genomics, biologic treatment adaptation and Big Data whenever feasible.

DECLARATIONS

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Authors' contributions

Contributions to conception and design of the study: Swain M, Ghosh-Laskar S, Patil R
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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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