

Role of Dynamic Contrast Enhanced-MRI In Predicting and Evaluating Treatment Response in Patients with Head and Neck Cancers: Our Experience and Perspective



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Abstract

Despite advances in multimodality treatment strategies for locally advanced squamous cell carcinomas of head and neck (HNSCC) and improvements in loco-regional control, there still exists a considerable variation in response to chemoradiotherapy (CRT). Therefore, early patient stratification is clinically important for optimized and individualized therapeutic regimens necessitating the development of prognostic imaging biomarkers that can accurately predict and assess treatment outcomes. Dynamic contrast enhanced- magnetic resonance imaging (DCE-MRI) allows generation of several imaging parameters from the tracer kinetic analysis of a series of MRI images. These imaging biomarkers provide physiologic information and are promising for noninvasive prognostication and prediction of response in patients with HNSCC. The purpose of this review is to summarize the basic physical principles of DCE-MRI technique and provide an overview of potential utility of DCE-MRI derived parameters in predicting and evaluating treatment response in patients with HNSCC. We will also discuss the existing challenges and limitations of using DCE-MRI in evaluating HNSCC in clinical settings and will discuss possible solutions to avoiding pitfalls in study design, data acquisition, and analysis in future studies.

Keywords: Head and Neck Squamous Cell Carcinoma; Chemoradiation Therapy; Prognostic Biomarkers; Dynamic Contrast Enhanced-MRI; Generalized Kinetic Model; Shutter Speed Model; Volume Transfer Constant; Mean Intracellular Water Molecule Lifetime

Keywords: ADC: Apparent Diffusion Coefficient; AIF: Arterial Input Function; CRT: Chemo-Radiation Therapy; DCE-MRI: Dynamic Contrast Enhanced -MRI; DWI: Diffusion Weighted Imaging; GKM : Generalized Kinetic Model; HNSCC: Squamous Cell Carcinomas Of Head And Neck; K^{trans} : Volume Transfer Constant; SSM : Shutter Speed Model; V_e : Extravascular And Extracellular Volume Fraction; V_p : Plasma Volume Fraction; τ_i : Mean Intracellular Water Molecule Lifetime

Introduction

Head and neck squamous cell carcinoma (HNSCC) represent the sixth most prevalent cancer worldwide [1]. Patients with HNSCC are usually associated with a poor prognosis and the presence of metastatic cervical lymphadenopathy is considered a negative prognostic indicator in the treatment of HNSCC [2]. Radiation therapy and concurrent chemotherapy is the standard of care for patients with non-resectable HNSCCs [3]. However, the efficacy of chemoradiation therapy (CRT) relies on effective delivery of therapeutic agents and oxygen to neoplastic cells that is often impeded by abnormal blood vessels and the presence of tumor cells farther away from functional vasculature [4]. Thus, development of non-invasive and reliable imaging-based biomarkers offers the promise of investigating the biology of HNSCC and nodal metastases. These physiologic imaging parameters may also serve as biomarkers for early prediction of treatment failure that may enable thera-

peutic modification, including earlier salvage surgery and upfront intensification of CRT in these patients.

Fundamentals of Dynamic Contrast Enhanced- MRI

Dynamic contrast enhanced (DCE)-MRI is a functional MRI technique that enables the assessment of vascular physiology of tumors [5-8]. DCE-MRI involves rapid and sequential acquisition of fat-suppressed T1-weighted fast gradient echo images before, during and after the intravenous injection of a gadolinium based contrast agent within a tissue of interest. The contrast agent enters the tumor microcirculation through feeding arteries, passes through capillary beds, and extravasates from the intravascular to the extravascular and extracellular space (EES), at a rate, which is determined by tissue perfusion and the permeability of the capillary wall. This extravasation of contrast agent can be quantified either with a semi-quantitative or quantitative analysis.

The semi-quantitative analysis is also based on the premise that tumors demonstrate more rapid and more intense early enhancement. This method involves placing a region of interest (ROI) and tracking the time-intensity curves. There are three types of dynamic contrast enhancement curves: type 1 demonstrates progressive enhancement, type 2 demonstrates rapid enhancement and then plateaus, and type 3 demonstrates rapid enhancement and then washout. Earlier [9] heuristic DCE-MRI parameters such as peak enhancement, maximum upslope, time-to-peak enhancement, and washout slope have been used to characterize head and neck cancers and for predicting and monitoring treatment response. These semi-quantitative parameters are widely used because they are easy to compute without the need of any tracer kinetic modeling. However, these heuristic parameters are highly affected by the gain factor of the acquisition systems, contrast agent volume and injection rate. As a result, these factors can easily change the shape of the signal-intensity time curves precluding accurate estimation of the true concentration of contrast agent in the tissues, and thus making comparison and quantification difficult. Moreover, these descriptive parameters provide no physiologic information about the lesion of interest.

On the other hand, numerous pharmacokinetic models [10-15] have been proposed to extract parameters related to tumor microcirculation by using DCE-MRI. The more commonly used generalized kinetic model (GKM), proposed by Tofts et al. [12] assumes that the water exchange between intravascular and EES compartments is infinitely fast, and that a linear relationship exists between longitudinal relaxation rate (R_1) and the concentration of contrast agent in tissues. The Tofts model fits various parameters to the contrast agent concentration-time curve and it also incorporates an arterial input function. This pharmacokinetic model allows estimation of forward volume transfer constant (K^{trans}) determining the flux of gadolinium contrast agent from intravascular space to EES, efflux rate constant (K_{ep}) measuring the rate of efflux of contrast agent back into the plasma from tissue EES, fractional volume of plasma (V_p) and fractional volume of extravascular-extracellular space (V_e). K^{trans} is the most investigated DCE-MRI derived quantitative parameter. Physiologically, the parameter K^{trans} reflects tumor perfusion and vascular permeability. In fact, K^{trans} predominantly represents vascular permeability in a permeability-limited (high flow) situation but represents the blood flow into the tissue in a flow-limited (high permeability) situation. While the parameter V_e is an indirect measure of cellular density and necrosis of a tissue, V_p provides quantification of the plasma volume.

Alternatively, shutter speed model (SSM) [14,15] considers the rate of water exchange between these two compartments is not fast enough (especially in tumors) to equilibrate the effects of contrast agent in the time scales of the MRI acquisition. Under this situation, a linear relationship between R_1 and concentration of the contrast agent in the tissue no longer holds true. It has also been reported that SSM provides a more accurate fit to the measured DCE-MRI data than GKM [16]. Moreover, SSM provides

a novel imaging parameter known as mean intracellular water molecule lifetime (τ_i), in addition to the conventional parameters derived from GKM such as K^{trans} and V_e . The parameter τ_i provides unique information related to tumor cell characteristics such as cell size, and cell membrane permeability [17]. Earlier studies [17-19] have also reported that τ_i is inversely correlated with cell membrane ion-pump activity, a measure of mitochondrial metabolism suggesting that τ_i may be a sensitive indicator of cellular energy turnover.

Some studies have reported that increased metabolic activity is associated with lower τ_i in regions of prostate, [20,21] and esophageal cancer [22] when compared to the normal tissues. In yet another study, [23] lower τ_i was observed from normal liver parenchyma (a metabolically more active region) compared to hepatocellular carcinomas. An inverse correlation of τ_i with EF5, a marker of hypoxia, and a direct correlation of elevated τ_i regions with high blood flow have also been reported. [24] The unique strength of τ_i also lies in the fact that it is less sensitive to arterial input function (AIF) scaling variations than K^{trans} indicating that τ_i values are more likely to be reproducible and reliable [25].

Prediction of Treatment Response

While neovascularization is necessary for the growth and spread of HNSCC, it also influences the response to CRT. Therefore, pre-treatment evaluation of HNSCC is important as this would be valuable not only for the radiation oncologist, to target specific sites for a radiotherapy boost, but also for the radiologist to identify sites with a higher likelihood of residual cancer, to determine if these sites need to undergo post-treatment biopsy or can be closely monitored by follow-up imaging. The potential of pretreatment K^{trans} in predicting short-term treatment response [26] as well as survival [27-30] in patients with HNSCC has been reported earlier. These studies suggested that CRT-treated patients with high baseline K^{trans} from metastatic nodes were associated with better prognosis and prolonged survival compared to patients with low baseline K^{trans} . Taken together, these studies support the notion that tumors associated with elevated blood flow and permeable vasculature had higher oxygenation levels, resulting in better access to the chemotherapeutic drug and better radiosensitivity. Shukla-Dave et al. [28] examined the distribution of K^{trans} and showed that high skewness of K^{trans} was associated with lower progression-free and overall survival. The investigators indicated that more heterogeneous tumors, as estimated by high skewness of K^{trans} , were associated with poor prognosis. However, the standard deviation of K^{trans} , another marker of heterogeneity, was neither a significant predictor of progression-free survival nor overall survival.

Most of these studies have focused only on the metastatic cervical lymph nodes because the nodal region is less susceptible to motion-induced artifacts. In a study,[31] from our group, we reported the combined use of diffusion weighted imaging (DWI) and DCE-MRI from primary tumors and metastatic nodes in predicting response to CRT therapy in patients with HNSCC. When apparent

diffusion coefficient (ADC) and DCE-MRI parameters (K^{trans} , V_e and V_p) from both primary tumors and nodal masses were incorporated into multivariate logistic regression analyses, a considerably higher discriminative accuracy was observed in differentiating responders from non-responders. In a related study, Bernstein et al. [32] also observed significantly higher baseline tumor plasma flow from both primary tumors and lymph nodes in HNSCC patients treated with induction therapy. While these studies indicate that DCE-MRI derived K^{trans} has the potential to guide treatment in HNSCC, our group recently [33] observed that τ_i may be a better independent prognostic biomarker than K^{trans} . However, incorporation of both pretreatment τ_i and K^{trans} from metastatic lymph nodes in the multivariate analysis provided the best model to predict overall survival in patients with HNSCC. Taken together, these studies suggest that τ_i and K^{trans} may serve as potentially useful imaging biomarkers for predicting therapeutic effects of CRT in patients with HNSCC.

The parameter V_e reflects the extravascular extracellular space, which consists of interstitial fluid and connective tissue arranged in a supportive frame structure and is restricted by blood vessel walls and cell plasma membranes. In normal tissues, the extracellular space is balanced in size and shape to ensure adequate supply of nutrients and oxygen to the tissue. However, the composition of the extracellular space of neoplastic tissues is significantly different from that of most normal tissues [34]. In general, the tumor extracellular space is characterized by a large interstitial space, higher collagen concentration, higher interstitial fluid pressure, and higher effective interstitial diffusion coefficient of macromolecules compared with normal tissues. Although the V_e and V_p parameters are physiologically important, previous studies of different cancers [35,36] and our studies [26-31] in HNSCC have failed to show significant differences in V_e and V_p values between responders and non-responders. However, one study has indicated the importance of V_e and V_p as prognostic biomarkers of clinical outcome in patients with osteosarcoma who underwent chemotherapy [37]. Collectively these studies imply that V_e and V_p may not be considered to be reliable as independent parameters. However, given the inherently different physiologic information that V_e and V_p provide, we believe these parameters may play complementary roles in the overall prediction of treatment response when used in conjunction with other parameters.

Evaluation of Treatment Response

Post-treatment DCE-MRI of a residual mass in the primary or nodal bed may improve the diagnostic ability to ascertain if the residual mass still contains viable neoplasm so that primary or nodal resection can be performed before the cancer becomes inoperable. Several studies have shown the utility of DCE-MRI in monitoring for early treatment response in HNSCC. In a previous study [38], an increase in K^{trans} from baseline to a follow-up period was found to be associated with good response to CRT in patients with HNSCC. Similarly, in a prospective study [39], tumor blood volume was significantly higher in patients who went on to

achieve local control than in patients who had local failure after two weeks of CRT. In another study [40], post-treatment DCE-MRI demonstrated potential for accurate characterization of residual masses that had failed treatment. Using a large cohort of patients, Lerant et al. [41] also reported the potential of DCE-MRI in analyzing the post-CRT environment in HNSCC.

Current Challenges and Limitations of DCE-MRI

DCE-MRI technique is becoming increasingly common in studying HNSCC. DCE-MRI derived parameters facilitate better understanding of underlying tumor microenvironment. However, there are still some unresolved issues when implementing DCE-MRI in routine clinical practice. DCE-MRI data from head and neck region is sensitive to voluntary and involuntary motion such as breathing and swallowing, therefore, motion-correction algorithms should be used on the raw DCE image data to correct for any in-plane rotational motion artifacts. It has been observed that DCE-MRI parameters are inevitably influenced by various hemodynamic factors, types of contrast agents, signal to noise ratio and spatial resolution of images. For instance, K^{trans} is determined by blood flow and vascular permeability.

In conditions of high leakage or low-molecular-weight contrast agent administration, K^{trans} depends almost entirely on blood flow. Increased acquisition time with low temporal resolution results in underestimation of K^{trans} . In multicenter clinical trials, even minor differences of benchmarked standards may result in significant changes in parameters. These variables include (1) MR scanners (field strength, performance of gradient system, and selection of pulse sequences); (2) imaging acquisition protocols (acquisition parameters, spatial and temporal resolution, and coverage); (3) contrast agent administration (dynamic bolus, injection dose and rate, and timing); and (4) postprocessing methods (semiquantitative or pharmacokinetic model selection, AIF determination, and region of interest/histogram/voxel-wise analysis). Collectively, these factors across institutions hamper the accuracy and reproducibility of findings and thus inhibit translation of this powerful and useful imaging modality into a routine clinical setting [42].

To address these issues, the Quantitative Imaging Biomarkers Alliance (QIBA) of the Radiological Society of North American (RSNA) established an updated technical guideline for DCE-MRI data acquisition and analysis in 2015. We believe that these proposed recommendations will significantly reduce variability and will allow interpretation of imaging results from different centers with more reliability and confidence.

Conclusion and Future Perspectives

Despite some clinical limitations and unsolved issues, DCE-MRI is a valuable imaging technique that provides quantitative and biologically relevant information related to tumor microenvironment that can help to predict and evaluate treatment outcome and survival in patients with HNSCC. However, it is critical to standardize imaging protocols for fast-tracking the translation

of DCE-MRI into routine clinical applications. Follow-up studies should be performed using the same equipment and DCE-MRI acquisition and processing methods. Further progress in this field requires data sharing and large multi-center collaborative validation studies.

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