Functional imaging with diffusion and perfusion MRI in the evaluation of the response to CHT-RT therapy in head and neck cancer

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Summary

Background oropharyngeal squamous cell carcinomas (HNSCCs) have shown a significant increase in incidence. Currently, non image based clinical outcome metrics include morphology, clinical, and laboratory parameters. An imaging biomarker that would provide for an early quantitative metric of clinical treatment response in these cancer patients would provide for a paradigm shift in cancer care.
Method we selected and evaluated 24 original researches and 9 systematic reviews focused on the utility of dynamic contrast enhanced (DCE) and diffusion-weighted imaging (DWI) MR in cancer imaging.
Aim by discussing the current status of these advanced neuro imaging techniques the goal of this study is to evaluate the possibility of DCE- and DWI-MRI in the assessment of the functional aspects of tumor physiology pertaining to their application in the prognosis and monitoring of treatment response in tumors arising in the head and neck region.

KEY WORDS: head-neck tumors; diffusion MRI; perfusion MRI; dynamic contrast enhancement MRI.

Introduction

Head and neck cancers account for the sixth most common type of cancer worldwide, with tobacco and alcohol consumption being important risk factors causing significant morbidity and mortality (1). Squamous cell carcinoma (SCC) is the most common malignant histology in the head and neck region and originates from the epithelial lining of the upper aerodigestive tract (2, 3). Oropharyngeal squamous cell carcinomas (HNSCCs) have shown a significant increase in incidence. This rise is thought to be a result of an increase in the prevalence of HPV-related tumors (4). Approximately two-thirds of patients with head and neck cancers present with advanced stage disease, commonly involving regional lymphnodes, which require an amplified and aggressive treatment regimen consisting of neoadjuvant therapy and extensive surgery.
Treatment for advanced (Stage III or IV) head and neck tumors usually consists of combined chemo-radiation therapy (CHT-RT) or complete surgical resection followed by adjuvant chemotherapy (CHT) and/or radiation therapy (RT). Despite advances in the treatment options available, the overall survival rate of HNSCC patients with advanced disease has not improved substantially over the past decade (5, 6).
Reported tumor-based prognostic factors for loco-regional control of HNSCC include the presence and extent of nodal metastases, T-stage, tumor site, tumor size, human papilloma virus (HPV) tumor positivity, and other biological markers (1-8).
In advanced HNSCC, the T stage and nodal disease at initial presentation are the most important predictors of outcome. The use of individual and combined markers to predict outcome in HNSCC has shown conflicting results. Various investigators have recorded different degrees of correlation between tumor and suppressor gene p53 status or epidermal growth factor receptor (EGFR) over-expression (8, 9); recently, HPV positive HNSCC has been shown to respond to treatment better than non-HPV-positive HNSCC (5).
Imaging has a fundamental role in oncology, especially in the assessment of tumor response to therapy. By using tumor shrinkage as a standard endpoint of response, morphological imaging follow-up with changes in tumor dimension determines response or progression. New functional and metabolic imaging techniques that have the ability to integrate morphological changes, offer substantial potential as early predictors of therapy response.
These include diffusion-weighted MRI (DW-MRI), which assesses water motion and tumor cellularity, and dynamic contrast-enhanced MRI (DCE-MRI), which assesses the biodistribution of contrast medium within tumors (10, 12).
These techniques represent functional magnetic resonance images increasingly used as cancer imaging biomarkers for complementary tissue characterization and tumor diagnosis as well as for predicting and monitoring the response to treatments (10-12).

Methods

In this article we selected and evaluated 24 original researches and 9 systematic reviews focused on the utility of DCE and DWI-MR in cancer imaging. Specifically we discuss the current status of these advanced neuroimaging techniques pertaining to their application in the prognosis and monitoring of treatment response in tumors arising in the head and neck region.
We provide in this imaging array a brief technical overview of DCE and DW-MRI acquisition protocols, quantitative image analysis approaches and review those studies which have implemented these techniques for the purpose of early prediction of cancer treatment response.
We address those issues aimed to investigate relationships with hypoxia and VEGF expression and potential ways of DCE in characterizing tumor oxidative metabolism, tissue and microvascular parameters (tumor perfusion and permeability) in predicting treatment response and outcome in head and neck tumors.
At the same time, as regards DW-MRI, we referred to those studies focused on current research and clinical applications that hold promise for use as a cancer treatment response biomarker, as it is sensitive to macromolecular and microstructural changes which can occur at the cellular level earlier than anatomical changes during therapy. In particularly we reviewed and discussed the role and the efficacy of apparent diffusion coefficient (ADC) and its variations as a surrogate marker of treatment response to CHR-RT in HNSCC.
Finally we evaluated a less commonly applied aspect of DWI such as the intravoxel incoherent Motion (IVIM)-technique, first described by Le Bihan et al. for brain imaging and now undergoing somewhat of a rebirth application throughout the body, in order to verify its prognostic value in characterizing complex cancerous tissue.

Results

Preliminary evidence supports the potential role of such radiological biomarkers as DCE and DW-MRI in head-neck tumors management, but their value needs to be tested in prospective studies.

Perfusion MRI with Dynamic Contrast Enhanced (DCE)

DCE-MRI has the ability to non invasively characterize tissue vasculature, by providing additional insight into tumor perfusion and capillary permeability. This technique allows assessment of treatment response more readily than indirect and delayed assessments of tumor size.
DCE-MRI involves the acquisition of sequential images during the passage of a contrast agent through a particular tissue of interest. Gadolinium-based contrast agents, such as gadopentetate dimeglumine, have a sufficiently small molecular weight to allow assessment of vascular permeability. The DCE MRI will be performed acquiring dynamic volumes in the axial plane, during intravenous injection of 0.1 ml/kg of Gadolinium-DTPA to cover primary tumor and/or involved nodes. Dynamic imaging can depict the distribution of this agent by measuring variations in vessel and tissue enhancement over time. Analysis of DCE-MRI allows the generation of signal intensity *vs* time graphs, which enables measurement of various parametres as blood volume (BV) and blood flow (BF) that are related to the vascularity of the tissue and that indirectly provide information on the extent of hypoxia.
Based on a measurement of the signal intensity variation after bolus injection of contrast medium, DCE MRI may provide important information related to tumor-vessel permeability and extracellular-extravascular volume fraction. By dynamic contrast-enhanced (DCE) MRI or Perfusion Computed Tomography (CT) it is possible to characterize the tumor heterogeneity in terms of both blood volume (BV) and blood flow (BF) maps (11-15).
Using DCE-MRI, several studies suggested that both the baseline and the early changes in perfusion/permeability and/or blood volume parameters can predict for local regional control and also have prognostic value (13-16).
Biologically, these findings suggested that an HNSCC tumor with a poor baseline functional vasculature as reflected by its perfusion/permeability is at a higher risk for relapse. This relationship appears to be the same in both nodal metastases and primary tumors (17-21).
These data allowed to quantify both perfusion levels and extension of the hypoxic sub-volumes inside the lesion as functional imaging biomarkers related to outcome.
But not all authors have shown that report, for example Hermans et al. didn't observe the same relationship when evaluating nodal perfusion with DCE-CT imaging (15).
Zima et al. demonstrated that high pre-therapy tumor blood volume and perfusion are associated with large decreases in tumor volumes in response to induction CHT (13). In the HNSCC patient, clinical validation of the relationship between tumor perfusion/permeability and hypoxia has been elegantly demonstrated by Thorwarth D et al. (22) in a series of 18F- Fmiso dynamic and static PET imaging studies of HNSCC patients treated with RT.
A recent study reported correlations between tracer kinetic parameters and areas of tumor with high pimonidazole scores in 7 patients using DCE-MRI in head-and-neck cancer (23). Haris et al. (24) showed a significant positive correlation between VEGF expression and cerebral blood volume measured using DCE-MRI, whereas in another study, Newbold et al. (25) found no correlation between VEGF expression and any tracer kinetic parameters in breast tumors.
Donaldson et al. (9) estabilished that it is possible to obtain estimates of perfusion and permeability in head-and-neck tumors using a rapidly acquired DCE-MRI dataset and the two-compartment exchange tracer kinetic model (2CXM). Negative correlations between perfusion and both VEGF expression and hypoxia were observed, giving us informations on the physiologic interpretation of these tracer kinetic parameters.These findings support the theory that more-hypoxic tumors have poorer vascular function, resulting in VEGF expression to increase blood flow to the tumor (26, 27).
Cao et al. (20) argued that an increase of blood volume in the primary tumor volume during the early course of CHT-RT was associated with a better local control, suggesting that poorly oxygenated regions represent the

more aggressive portions of the tumor because resistant to conventional doses of RT (17, 18).
In a prospective study of DCE T1-weighted perfusion-weighted MRI in HNC, Cao et al. (20) were able to show that there was significantly increased BV (in the primary gross tumor volume) after 2 weeks of chemoradiation in patients who had local disease control (at a median 10 months) compared with those who had local or regional failure. Most surprising, reduction in tumor volume after 2 weeks of chemoradiation did not predict local disease control in this study. While this preliminary work suggested that DCE MRI could also have a role in monitoring therapy response, a more recent study investigating the efficacy of pretreatment DCE MRI parameters in predicting response has shown that the pretreatment permeability value was significantly higher *(P*_.001) in complete responders compared with partial responders (0.64_0.11 minutes_1 *vs* 0.21_0.05 minutes_1, respectively) (28).
Ktrans is thought to be a measure of the permeability surface area product per unit volume of tissue for endothelial transport between plasma and extracellular extravascular space, therefore it represents a key measurement in tumor neoangiogenesis (28).
Outside of the head and neck, Mayr et al. demonstrated that cervical cancers with high baseline perfusion/permeability and those with a significant increase in perfusion/permeability at week 2 of the RT were associated with higher local control, disease-specific, and overall survival rates. The improvement in local control rates in tumors demonstrating increasedperfusion/permeability during RT, would suggest that this may be due to tumor reoxygenation (29).

Diffusion MRI

DWIs, currently integral part of many standard MR acquisition protocols, are images sensitive to the thermally driven motion of water molecules along the axial orientations of additional diffusion gradients applied during the MR sequence (30). DW-MRI is sensitive to the microscopic motion of water molecules, and allows for non-invasive characterization of biological tissues on the basis of their water-diffusion properties. Thus, DWI may provides informations about the cellular architecture at a very short scale (tenths of μ), water motion in biological tissues being influenced by the presence of cellular membranes and macromolecular structures and by the compartmental tortuosity. The effect of water diffusive motions is to cause a signal amplitude attenuation that can be well described by an exponential decay.
The signal attenuation coefficient, known as apparent diffusion coefficient (ADC), can be analytically derived after a simple post-processing of DWIs.
As such, DWI plays an important role in characterizing the tumor microenvironment, usually to probe tumor cellularity, because the proliferation of cancer cells generally reduces the extracellular space, which in turn reduces ADC. Recent studies have shown that even the infiltrating cellularity itself can display diffusion anisotropy (31, 32). The sensitivity of DWI to the cellular structures of cancerous tissue is well documented and has played an increasingly important role in patient management (33).
Changes in ADC values are observed for tumors in, e.g., brain (34), liver (35), kidney (36), cervix (37), breast (38), and prostate (39). Conversely, ADC measurements have been shown to increase with tumor necrosis as tumor cells are treated using radiation or chemotherapy (40, 41).
At present, there are only limited data regarding the potential use of DW imaging for pretreatment prediction of tumor response. One recent study (41) with 33 patients and a median follow-up of 12 months showed a significantly lower pretreatment ADC in lymphnode metastases in complete responders than in partial responders, and a significant correlation was found between pretreatment ADC and local treatment failure in another study with 38 patients (42). However, these findings could not be corroborated in a larger study by King et al. (43) with 50 patients who had primary and nodal tumors and a median follow-up of 22 months.
There are additional published data that suggest the change in ADC over the course of treatment may indeed be a predictor of outcome. Cancers with more densely packed tumor cells and more cell membranes present a greater impediment to diffusion and consequently have a lower ADC, while a decrease in the number of cells and necrosis during treatment leads to an increase in ADC.
Moreover, Kim et al. (41) showed that changes in ADC during therapy served as better predictor than baseline ADC alone. The studies of Kato (44) and Vandecaveye (45) have also corroborated these findings showing good correlation between changes in ADC occuring early therapy and 2-year locoregional recurrence.
However, the efficacy of pre-treatment ADC values either in prediction or for detection of early treatment response (within one to two weeks of CHT-RT) in HNSCC has not been reported. Accurate and timely detection of treatment response or presence of non-responsive tumor can be critical in disease management since the optimal time window for successful surgery or alternative treatment methods may be limited.
A less commonly applied aspect of DWI is its sensitivity to vascularity, because active non-Brownian water motion processes such as blood flow can contribute to apparent diffusion.
Orientationally incoherent blood flow generates a "pseudodiffusion" effect that is known as "intravoxel incoherent motion (IVIM)" (30, 46, 47). Infact the water microscopic motions in each image voxel include both pure thermally driven molecular diffusion and blood microcirculation in capillary network. A totally non invasive technique was then developed to contemporary extract diffusion and perfusion information from DWIs, known as the Intravoxel Incoherent Motion (IVIM) imaging (30, 46, 47).
By a mathematical modeling of the signal decay with increasing b-values, within a region of interest (ROI) or in each image voxel, is possible to derive, besides ADC, two additional parameters: *f* the volume fraction of water flowing in perfused capillaries and *D* the diffusion parameter representing the pure molecular diffusion.
The IVIM approach, initially proposed only for brain applications, is based on the acquisition of multiple DW sequences with an extended range of b-values, being the b-value a factor depending on the gradient pulse sequence (as pulse duration and diffusion gradient strength) by which is possible to modulate the sensitivi-

ty of DWIs to different ranges of molecular velocity in tissues. In fact, signal from blood flow is rapidly attenuated at low b-value (b < 100-150 s/mm^2), while higher b-values (up to 800-1000 s/mm^2 or more) are required to suppress the perfusion contribution and identify the pure diffusion component.

Nevertheless IVIM imaging requires more sophisticated analyses, not yet included in standardized software and routine measurements, it has been recently proposed in different extracranial applications, demonstrating a clinical utility for improving tissue characterization and differentiation between benign and malignant tumors (48-51).

IVIM approach has been rarely investigated in HN region (52-54), probably because of strong susceptibility and motion artifacts and artifacts related to eddy currents and to Echo-planar-imaging (EPI) that easy decrease to quality of DWIs (12, 55).

IVIM, first described by Le Bihan et al. (30), is undergoing somewhat of a revival in applications throughout the body (30, 46, 47, 49). The IVIM technique has been applied in various cancer types, such as hepatic lesions (35), brain tumors (47), breast tumors (50) and animal models (28).

Some malignant lesions possess both high vascularity (significant pseudodiffusion) and high cellularity (restricted passive diffusion), which oppositely influence the DWI signal decay and can thus lead to confusion within the ADC model.

A compartmental analysis explicitly resolving vascular and parenchymal effects, would thus be beneficial both for avoidance of systematic error and for enhanced quantification ability.

Thus, we believe that the cellularity of tumors estimated by a single ADC value seems to be limited, and the measurement of additional parameters in characterizing complex cancerous tissue with IVIM MRI, such as *f* (volume fraction of water flowing in perfused capillaries) and *D* (pure diffusion) as diffusion parameter, could offer simultaneous biomarkers of vascularity and cellularity as well as exchange between them during CHT-RT therapy.

Such radiological tools may enable future studies that might individually monitor the effects of treatment on each of these properties of the microenvironment.

Discussion

Treatments' response (particularly the response to the radiotherapy) varies widely in head-and-neck squamous cell carcinoma (SCC). Various clinico-pathologic parameters for predicting outcome in HNSCC, such as hemoglobin (Hb) level, T-stage, tumor volume, comorbidity, primary site of the tumor, nodal involvement, tumor thickness, status of surgical margins, status of human papilloma virus infection, and histologic grade have been reported in previous clinical studies to be correlated with local control (5, 56-59). Despite a careful evaluation of these known clinical factors, it remains difficult to reliably predict outcomes after radiotherapy. Patients undergoing RT or CHT-RT will be classified as "responders" or "non-responders" based on the local control of disease, evaluated in basis of standard criteria for response assessment, using both diagnostic imaging (MRI 6/8 weeks after the end of RT and/or PET-CT scan 12 weeks after the end of RT and MRI follow-up for the next 2 years) and clinical evaluations. If an outcome can be predicted prior to treatment, patients who are unlikely to be cured with CHT could be selected for alternative treatments. Further improvement of current outcome rates could be achieved by carefully studying and targeting the factors that are related to treatment failure.

Advances in imaging technologies such as, DCE (9, 16, 25, 27, 28) and DW-MRI (11, 12, 49-55) have made it possible to assess the functional aspects of tumor physiology (Figs. 1, 2, 3). Among these, tumor hypoxia is an important factor determining treatment response (56, 57).

Intracellular oxygen is involved in increasing the DNA damage induced by radiation (58), but is also necessary for the tumor to maintain oxidative phosphorylation . Hypoxia is the result of irregularities/inadequacies in the blood and oxygen supply to the tumor (17, 56-59); moreover it has been shown the role of hypoxia either to characterize solid human tumors or to compromise the results of conventional cancer therapy (22, 57). Lack of oxygen resulting from insufficient perfusion would force the tumor cells to switch from cellular respiration toward anaerobic glycolysis for survival. Hypoxia stands out as an important explanation for the failure of traditional treatment modalities in the head-and-neck cancer. Hypoxic squamous carcinoma cells are resistant to RT, cytostatic drugs, and potentially, also to conventional surgery (21, 22, 60, 62, 63). However, hypoxia is a strong stimulus for angiogenesis (56, 58). High blood flow has consistently been found in experimental and human solid tumor. Since plenty of oxygen is available *in situ* when there is an high tumor blood flow (9) it was proposed that it could render tumor cells more susceptible to both RT and chemotherapy.

Thus, high flow might result as a consequence of the neovascularization elicited by angiogenic factors secreted by hypoxic tumor cells (59, 64). Infact at the cellular level, it is quite possible that hypoxia and high perfusion exist together.

The linkage among hypoxia, flow, and angiogenesis is crucial in the development of novel anticancer drugs and has been one of the main stimuli for the current protocol, which attempted to develop non invasive methods to assess tumor oxygenation status.

To overcome this notorious feature, hypoxia selective chemotherapeutic agents, chemical and physical modifiers of tumor oxygenation have recently been introduced in the clinical setting (60-63). However, for the optimal use of these modifiers and selective drugs, it is crucial to determine the hypoxic fraction individually. This is clearly not possible with the standard tools used in the diagnosis and staging of head-and-neck cancer; however, the impact of high blood flow on the sensitivity to oncologic therapy has been quite controversial.

DCE MRI is a technique that has a potential clinical utility in management of HNC, including detection of hypoxic tumor subvolumes, both early assessment and prediction of the treatment response and outcomes, and definition of a radiation boost target volume (9, 16, 25, 62, 65).

Skewness of Ktrans was a strong predictor of progression free survival (PFS) and overall survival (OS) in HNSCC patients with Stage IV nodal disease. This finding suggests an important role for this pretreatment DCE-MRI parameter as a predictor of outcome in HNSCC pa-

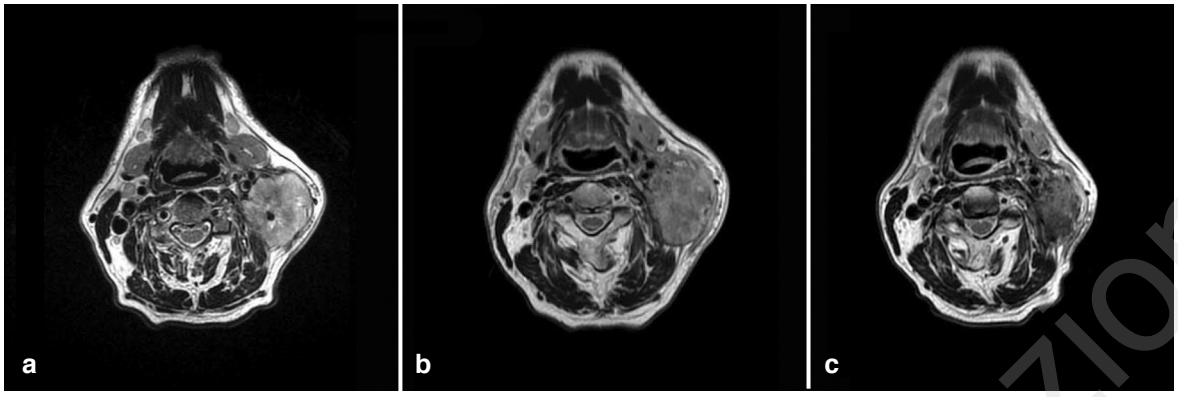

Figure 1 - MRI TSE T2 weighted images pre CHT-RT (a), during (b) and after therapy (c) in N3 node in patient with a small (T1) hypopharingeal tumor. There is an increase dimension of the node during therapy (b) and the reduction of the dimension of the node after therapy (c -same day of the end of radiotherapy).

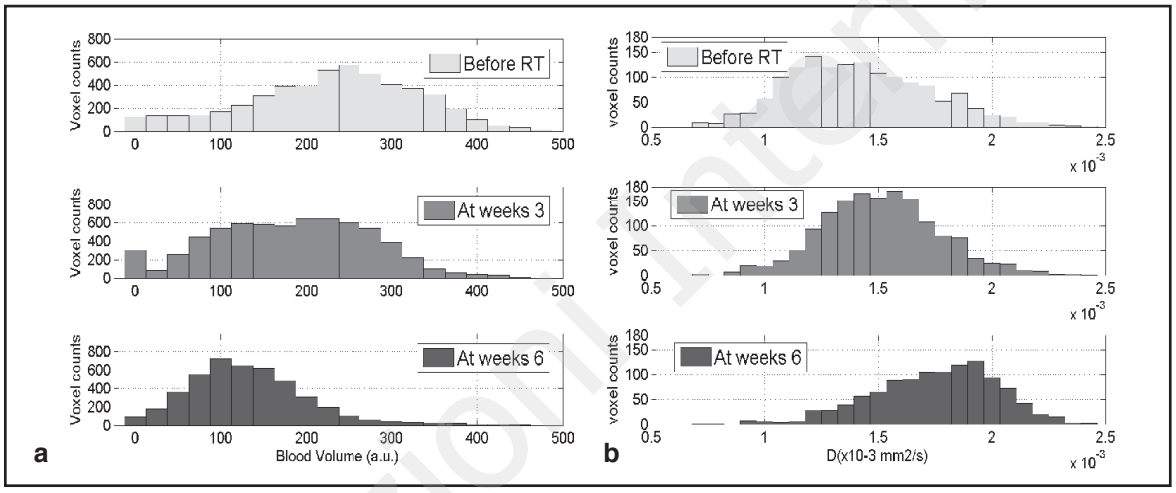

Figure 2 - Same patient. Analysis with histograms show that the blood volume (a) decreases progressively between the beginning and the end of the therapy, while the diffusion shows a progressive increase. These data appear in agreement with a good prognosis.

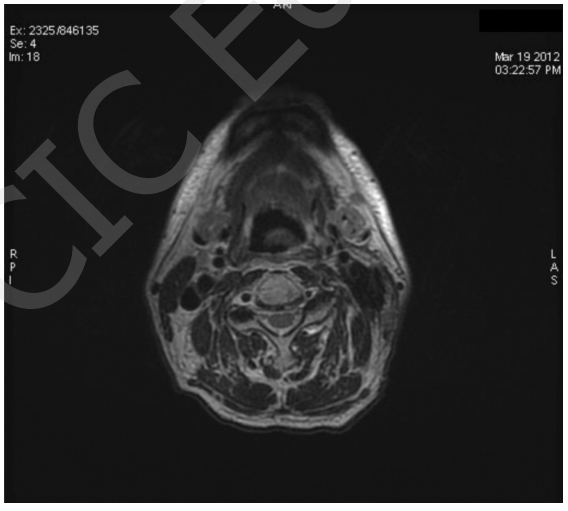

Figure 3 - Same patient. MR T2 weighted image, 8 weeks after CHT-RT shows a complete response to treatment with the presence of fibrous tissue.

tients with advanced disease (9, 16, 25 , 28). The sensibility and specificity of DCE MRI with Gadolinium-DTPA alone or in combination with Diffusion-MRI will be evaluated for prediction of local failure.

Infact one of the greatest potential benefits of DW imaging lies in the identification of the group of patients who fail to respond to therapy. At present, there are only limited data regarding the potential role of DW imaging for pretreatment prediction of tumor response.

It has been reported that an increase in ADC following therapy due to a decrease in cellularity suggests a positive therapeutic response (12), using a simple method based on the whole tumor mean ADC value.

Moreover, patients responding favorably to CHT-RT have significantly lower pre-treatment ADC than partial/non- responders. In addition, the change in ADC after the first week of CHT-RT, as compared to the pre-treatment value, showed the highest test accuracy along with a high sensitivity and specificity in separating complete responders from partial responders (12, 43-45, 52, 66).

Extracting ADC values from ADC maps by drawing ROIs around the margin of the tumor is relatively simple to per-

form. However, in this situation, competing factors would reduce the mean shift in ADC: if large cystic or necrotic regions are present within the tumor mass, these would also have the potential to reduce detectable changes in tumor ADC values following treatment. Therefore, the utility of an approach for detection of treatment response, based on summary statistics as mean or median values, can be attenuated by pre- and post-treatment spatial heterogeneity within the tumor (67, 68). More sophisticated techniques for quantitative evaluation of DW images that provide more information about the heterogeneity of tumors include ADC histogram analysis, based on voxel-by-voxel data, that are promising to an early detection of spatial changes during treatment (12, 67-69).

Furthermore, the ADC model (monoexponential), in the evaluation of tumors with significant vascularity, for any sampling, give an incomplete description of the tissue response and thus severely limit quantitative specificity or comparison with histology. Infact those malignant lesions that possess both high vascularity (high perfusion fraction and nonzero pseudodiffusion) and high cellularity (low tissue diffusivity), influence the DWI signal decay in opposite directions, confounding diagnosis and grading by DWI (50). In our opinion, even better diffusion parameters derived from intravoxel incoherent motion (IVIM) model with quantification of perfusion fraction (f), tissue diffusivity (D), and pseudo diffusivity (D*) in patients with HSCC, provides non invasive sensitivity to microenvironment properties. The compartmental analysis is thus beneficial both for avoidance of systematic error and for enhanced quantification ability.

We prefer finer quantitative analyses of DCE MRI and DWIs by using home-made scripts.

At our Radiology and Diagnostic Imaging Department an experienced radiologist identify lesions on parametric maps, both manually and with the aid of automatic segmentation instruments. In fact, a method based on the clustering analysis (70,71) is used to automatically identify inhomogeneous tumor subvolumes on both perfusion and diffusion images. This segmentation method is not based up on a user-defined threshold and analyzes the intrinsic properties of the parameter of interest by statistically grouping voxels into different feature classes. These applications have the potential to improve the specificity of MRI, therefore we believe that these tools are expected to enhance the role of MRI in diagnosis, monitoring, and treatment management of cancerous lesions and perhaps provide surrogate markers of biological properties key to effective treatment.

In conclusion, we think that the combination of morphological and functional imaging (DCE/DW-MRI) offers important means to define the prognostic elements before and during therapy.

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