Evaluation of Head and Neck Tumors with Functional MR Imaging

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DISCUSSION OF PROBLEM/CLINICAL PRESENTATION

Head and neck (HN) cancer is one of the major types of cancer, affecting 50,000 new patients in the United States every year.\textsuperscript{1} HN cancers typically originate from the mucosal epithelia of the oral cavity, pharynx, and larynx and can be linked to alcohol consumption and tobacco smoking.\textsuperscript{2} For early HN cancers, encouraging locoregional control can be reached through radiation or surgery treatment. However, for advanced HN cancer, the odds are less favorable, as with standard therapy, only 60\% of patients will survive 5 years.\textsuperscript{1} HN cancers frequently metastasize to (cervical) lymph nodes before they penetrate distant organs such as the lungs. In spite of recent advances in surgical and oncologic treatments, the overall survival rate of patients with HN cancer has unfortunately not improved much over recent years.\textsuperscript{1} Important causes for unfavorable outcome in advanced HN cancer can be a delayed diagnosis (followed by loco regional failure) and a tardy salvage treatment at the recurrence of the disease. A priori predictors of outcome and predictive biomarkers of treatment response are desperately needed to advance patient care and individualized treatment. For example, noninvasive imaging biomarkers could have an important role in the clinical decision-making process, thereby allowing oncologists to use interventions with alternative therapy strategies. Imaging has several benefits as a method for improving the tumor treatment evaluation, as it can sample the entire tumor noninvasively and can be repeated longitudinally to monitor changes at regular intervals.

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Functional MR imaging might provide the ideal tools yielding such noninvasive markers. This review focuses on the promises of diffusion- and perfusion-weighted MR imaging techniques in HN cancer. Diffusion-weighted (DW) MR imaging can quantify and map the diffusion of molecules (typically water), in biological tissues, whereas perfusion-weighted MR imaging can assess the passage of blood through vessels through tissue. Both MR imaging techniques have a rich history that extends decades, and the MR imaging tools available to assess the associated processes are currently very mature, providing excellent opportunities to study both diffusion and perfusion in HN cancer. Although some might consider magnetic resonance (MR) spectroscopy also to be a functional MR imaging technique, it falls beyond the scope of this review, and we refer the reader to an excellent review by Razek and Poptani.

**Diffusion**

DW imaging (DWI) is an MR technique that allows the measurement of water self-diffusivity. Because freedom of motion of water molecules is hindered by interactions with other molecules and cellular barriers, water molecule diffusion abnormalities can reflect changes of tissue organization at the cellular level (e.g., increase of extracellular space owing to cell death). These microstructural changes affect the (hindered) motion of water molecules and consequently alter the water diffusion properties and thus the MR signal. Apart from deriving a measure for the average extent of molecular motion that is affected by cellular organization and integrity (apparent diffusion coefficient (ADC)), it is also possible using diffusion tensor imaging (in which diffusion is measured in several directions) to measure the preferred direction of molecular motion, which provides information on the degree of alignment of cellular structures and their structural integrity (fractional anisotropy). Recently, also DWI techniques have entered the HN cancer clinic, in which images are acquired with multiple b values, yielding techniques such as intravoxel incoherent imaging (IVIM) or diffusion kurtosis imaging, techniques that aim to provide information that extends diffusion of water, such as perfusion (for IVIM) or non-Gaussian diffusion behavior (for diffusion kurtosis imaging).

**Perfusion**

Perfusion is physiologically defined as the steady-state delivery of blood to tissue. Two major approaches exist to assess perfusion with MR imaging. The first is the application of an exogenous contrast agent (usually gadolinium based), exploiting the susceptibility effects or relaxivity effects of the contrast agents on the signal, respectively, dynamic susceptibility contrast–enhanced MR perfusion or dynamic contrast–enhanced (DCE) MR perfusion. The second application involves the use of an endogenous contrast agent, namely, magnetically labeled arterial blood water, as a diffusible flow tracer in arterial spin labeling (ASL) MR perfusion. DCE and, to a lesser extend ASL, are currently being used to study HN cancer.

**Outline**

This review summarizes recent literature and provides an overview of the various studies in which diffusion- or perfusion-based MR imaging studies are applied to HN cancer. This review provides an overview of commonly used acquisition protocols and postprocessing methods, advanced data analysis, imaging findings regarding tumor characterization and differentiation, tumor risk stratification and staging, monitoring, and prediction of treatment response. Subsequently, limitations are highlighted followed by a conclusion with recommendations for future research.

**IMAGING PROTOCOLS**

**Diffusion-Weighted MR Imaging**

**Data acquisition**

- **MR imaging scanner and coil:** DW MR imaging studies for HN cancers are commonly carried out on 1.5-T or 3-T MR imaging scanners using dedicated neurovascular phase array coils.
- **Pulse sequence:** Clinical DW MR imaging is most commonly performed using single-shot spin-echo echo planar imaging (EPI), axial free breathing.
- **Acquisition parameters (Table 1):** Protocol optimization is a prerequisite for obtaining optimum signal-to-noise ratio in DW images. The number of b values for mono exponential modeling of the data are 2 to 3 and the b values are greater than 100 s/mm²; (usually between 500 and 1200 s/mm²), whereas the number of b values increases up to 10 or more (usually between 0 to 1500 s/mm²) including both the high and low b values for biexponential modeling of the data; slice thickness, 5 to 8 mm, gap thickness, 0 mm, field of view, 200 to 380 mm; acquired matrix, 128 x 128 or higher; number of averages, 2 to 4; parallel imaging (SENSE or ASSET), factor, 2; echo time (TE, ideal/target), minimum TE; acceptable,
less than 110 milliseconds; repetition time (TR), 2 to 4 seconds; receiver bandwidth, greater than 1000 Hz/voxel.

Diffusion-weighted MR imaging data processing

- **Region of interest analysis**: The regions of interest (ROIs) are usually drawn on the DW MR images by an experienced neuroradiologist based on the radiologic and clinical information. The ROI encompasses the entire tumor and node of interest.
- **Quantitative methods**: Mono- and biexponential models are usually used for quantifying diffusion either based on voxel by voxel or the ROI. For monoeXponential models, ADC value can be quantified using \( S/S_0 = \exp(-b \times \text{ADC}) \), where \( S \) and \( S_0 \) are the signal intensities with and without diffusion weighting, respectively, and \( b \) is the gradient factor (b value, seconds per millimeter squared). For biexponential models, metrics related to intravoxel incoherent motions can be calculated using

\[
S = S_0 \left( (1-f) \exp(-bD) + f \exp(-bD^*) \right)
\]

or

\[
S = S_0 \left( (1-f) \exp(-bD + \frac{1}{6}b^2D^2K) + f \exp(-bD^*) \right)
\]

where \( f \) is the vascular volume fraction or perfusion factor, \( D \) is the pure diffusion coefficient (millimeter squared per second), \( D^* \) is the pseudodiffusion coefficient (millimeter squared per second) associated with blood velocity and capillary geometry, and \( K \) is the diffusion kurtosis coefficient. Noise floor rectification schemes are commonly used in the above diffusion quantifications.

Dynamic Contrast-Enhanced MR Imaging Data Acquisition

- **MR imaging scanner and coil**: DCE MR imaging studies for HN cancers are commonly being carried out on 1.5-T or 3-T MR imaging scanners using dedicated neurovascular phase array coils.
- **Contrast agent**: The most commonly used contrast agent is paramagnetic gadolinium chelates, such as Gd-DTPA (gadopentetic diethylenetriamine pentaacetic acid) (Magnevist; Berlex Laboratories, Wayne, NJ). The bolus of contrast agent is typically delivered at 0.1 mmol/kg body weight at 2 mL/s followed by a 20-mL saline flush with a flow rate of 2 mL/s using an MR-compatible, programmable power injector (eg, Spectris; Medrad, Indianola, PA).
- **Pulse sequence**: Most of the DCE MR imaging data acquisition is performed using a fast 2-dimensional (D) or 3-D gradient-echo sequence because of its high T1 sensitivity and rapid image acquisition. A 3-D spoiled gradient-echo sequence is more widely applied than 2-D spoiled gradient-echo because of its ability to achieve higher spatial resolution and signal-to-noise ratio.

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Sequence</th>
<th>TE/TR (ms)</th>
<th>Slice Thickness (mm)</th>
<th>FOV (mm)</th>
<th>Matrix</th>
<th>Extras</th>
</tr>
</thead>
<tbody>
<tr>
<td>DW MR imaging</td>
<td>Single-shot spin-echo EPI</td>
<td>&lt;110/2000–4000</td>
<td>5–8</td>
<td>200–380</td>
<td>≥128x128</td>
<td>&gt;2 b values, 0–1500 s/mm²</td>
</tr>
<tr>
<td>DCE MR imaging</td>
<td>3-D spoiled gradient echo</td>
<td>~1.4/5.3</td>
<td>5–8</td>
<td>~220</td>
<td>≥128x128</td>
<td>Gd-DTPA bolus 0.1 mmol/kg at 2 ml/s, followed by a 20-mL saline flush</td>
</tr>
<tr>
<td>ASL</td>
<td>Multishot spin-echo echo-planar, pCASL</td>
<td>~20/4000</td>
<td>5</td>
<td>~230</td>
<td>~80x80</td>
<td>Labeling duration: 1650 ms; postlabel delay: 1280 ms; 2 shots; labeling just under the bifurcation</td>
</tr>
</tbody>
</table>
Acquisition parameters (see Table 1): The acquisition parameters can be tailored depending on whether the study design needs higher spatial resolution or higher temporal resolution. Approximate typical parameters on gradient-echo MR scanners are field of view (FOV), 22 cm; TR, 5.3 milliseconds; TE, 1.4 milliseconds; temporal resolution, 4 seconds; phases, 50; number of excitations (NEX), 1. Temporal resolution ranges from 3 to 6 seconds and acquisition time is generally in the range of 2 to 10 minutes.\(^{18,20,23}\)

Dynamic contrast–enhanced MR imaging data processing

- **Radiofrequency (RF) field inhomogeneity correction:** RF field nonuniformities often cause inhomogeneity in image profile. Image correction methods, such as an edge-completed low pass filter algorithm, can be used to correct this kind of image artifacts.\(^{19}\) Additionally, this inhomogeneity can result in deviation of the flip angles from nominal values when using gradient-echo sequences for data acquisition. This flip angle deviation has a great impact on the calculation of native T1 relaxation time values, further influencing the accuracies of the estimated pharmacokinetic parameters. A double-echo method can be used to correct this artifact.\(^{24,25}\)

- **Motion artifact correction:** DCE MR images in the HN region suffer from motion artifacts caused by the voluntary and involuntary motions of patients. The motions can cause in-plane and through-plane image artifacts. Image registration methods are commonly used to correct the through-plane image artifacts by realigning the DCE MR imaging time series image itself or coregistering DCE MR images with other image modalities, such as T1- or T2-weighted images.\(^{18,19,26}\) Rigid body alignments are more readily performed than nonrigid deformations.\(^{19}\)

Dynamic contrast–enhanced MR imaging data quantification

- **Semiquantitative methods:** Semiquantitative methods classify the signal intensity time curve of DCE MR imaging into different patterns or provide some simple summary descriptors about the curve. For curve pattern classification, the initial enhancement (1–2 min) of the curve is usually described as fast, medium, and slow uptake. The late enhancement (>2 min) of the curve is often classified as persistent, plateau, and washout.\(^{27}\) Normal tissues and tumor tissues with different degrees of malignancy could show different curve patterns. This feature can be used for tumor detection and tumor differentiation.\(^{28,29}\) For curve summary description, several summary parameters, such as maximum contrast index (CI), time to reach maximum CI, maximum slope, washout slope, area under the curve (AUC) at a specific time (eg, AUC90 means the area under the curve 90 seconds after contrast injection), are used.\(^{6,19}\)

- **Pharmacokinetic modeling methods:** Pharmacokinetic modeling methods provide characteristics of tumor microvasculature (related to endothelial permeability, the size of extracellular extravascular space [EES], and the size of intravascular space) by modeling tumor contrast kinetics into separate compartments and establishing the transport equation of the contrast agent. Commonly used models are the Tofts model, extended T model, shutter speed model, and the 2-compartment exchange model.\(^{18,20,26,30,31}\) Among these models, the Tofts model is used the most. From the Tofts model, kinetic parameters such as $K_{\text{trans}}$ (volume transfer rate between vascular space and EES, min\(^{-1}\)) and $v_e$ (volume fraction of the EES) can be characterized on a basis of tumor ROI or voxel by voxel.\(^{18–20}\) For these models, accurate estimation of the arterial input function (AIF) is required, and when this is not possible in individual cases, also averaged population-based AIF functions can be used.\(^{23}\)

Arterial Spin Labeling MR Imaging Data Acquisition

- **MR imaging scanner and coil:** ASL MR imaging studies for HN cancers\(^{32,33}\) have been reported using 3-T MR imaging scanners using dedicated neurovascular phase array coils.

- **Pulse sequence:** ASL can be acquired with a sequence using echo-planar MR imaging signal targeted by alternating RF pulses (EPI STAR).\(^{32}\) Magnetic labeling of in-flowing arterial blood can be achieved using section-selective 180° RF pulses in labeling slab. After the labeling, a Look-Locker readout of gradient-echo EPI with an excitation pulse of 30° can be used for image acquisition. Additionally, control images without labeling need to be acquired. Also, pCASL (Pseudocontinuous arterial spin labeling) techniques have
been reported.\textsuperscript{34} The acquisition of pCASL can be performed by using multishot spin-echo echo-planar imaging to obtain control and labeled images. The labeling slab can be placed just under the bifurcation of the internal and external carotid arteries.

- **Acquisition parameters** (see Table 1): Typical parameters on 3-T Philips MR scanners for EPI STAR are TR, 3000 milliseconds; TE, 24 milliseconds; FOV, 230 $\times$ 230 mm; matrix, 80 $\times$ 80; slice thickness, 10 mm; interslice gap, 30%; NEX 30. Label slab is 58.5 mm thick located 20 mm proximal to the imaging section. For pCASL, parameters are labeling duration, 1650 milliseconds; postlabel delay, 1280 milliseconds; TR, 3619 milliseconds; TE, 18 milliseconds; flip angle, 90$^\circ$; number of shots, 2; FOV, 230 $\times$ 230 mm; matrix, 80 $\times$ 80; slice thickness, 5 mm; number of slices, 15; acceleration factor for parallel imaging, 2.

### Arterial spin labeling data quantification

- Tumor blood flow (TBF) can be calculated using image processing software such as MatLab (MathWorks, Natick, MA). TBF can be calculated from analysis of magnetization difference obtained by subtracting the labeled images from the ASL control images.\textsuperscript{32,34} TBF maps can be created on a pixel-by-pixel basis.

### Advanced data analysis

In addition to using perfusion- or diffusion-based MR imaging contrasts for a better evaluation of HN cancer, on the data analysis side, improvements in the applicability of MR images in HN cancer are developing. Most of these techniques do not need specific MR imaging contrasts as input, because, in principle, they work on any quantitative map. For example, the parametric response map approach\textsuperscript{35} is a voxel-based approach that allows segmentation of a tumor volume based on regional intratumoral changes in the MR signal. It is ideally suited to accurately follow treatment-induced changes in tumors on a voxel-by-voxel basis. Another analysis method allows for accurate assessment of tumor heterogeneity. HN cancer can be very heterogeneous in nature, as the tumor vascular system is typically chaotic and poorly organized, and tumor heterogeneity itself is a well-recognized feature that is associated with tumor malignancy.\textsuperscript{36} In particular, tumor heterogeneity in the blood supply may prevent therapeutic efficacy and result in treatment resistance. Therefore, tumor heterogeneity may play an important role in assessing tumor malignancy and predicting treatment response. Most studies typically use summarizing characteristics, such as mean, median, or standard deviation of voxel-wise measures, to describe the nature of the whole tumor volume. However, these commonly used measures do not necessarily reflect the marked morphologic heterogeneity in nodal metastases of HN cancer. Image texture analysis may be an ideal candidate to assess tumor tissue heterogeneity in a reliable manner.\textsuperscript{37-39} In texture analysis, an algorithm that assesses spatial intensity coherence is applied to an image yielding several textural features (reflecting heterogeneity), independent of the image’s mean and variance. The gray-level co-occurrence matrix, or gray-level spatial dependence matrix, is one of the most important algorithms used for texture analysis.\textsuperscript{40}

### IMAGING FINDINGS

#### Tumor Characterization and Differentiation

Studies have found that DW MR imaging and DCE MR imaging can be used to differentiate tumor types. Sumi and Nakamura\textsuperscript{41} combined use of IVIM and time-signal intensity curve (TIC) analyses to diagnose HN tumors. IVIM parameters (f and D values) and TIC profiles in combination were distinct among the different types of HN tumors, including squamous cell carcinomas (SCCs), lymphomas, malignant salivary gland tumors, Warthin’s tumors, pleomorphic adenomas, and schwannomas; a multiparametric approach using both measures differentiated between benign and malignant tumors with 97% accuracy and diagnosed different tumor types with 89% accuracy. A combined use of IVIM parameters and TIC profiles may have high efficacy in diagnosing HN tumors.

Lee and colleagues\textsuperscript{6} used DCE MR imaging–derived parameters to differentiate SCC, undifferentiated carcinoma (UD), and lymphoma; they showed that $K^{\text{trans}}$, AUC60, and AUC90 were significantly different between UD and SCC and UD and lymphoma but not between SCC and lymphoma.

Similarly, Asaumi and colleagues\textsuperscript{42} attempted to differentiate malignant lymphomas from SCCs using DCE MR imaging with 17 lesions of malignant lymphoma and 30 cases of SCC. The results showed that there was a significant difference between SCC and malignant lymphoma in the time to reach the maximum CI.

Fong and colleagues\textsuperscript{43} found that DW MR imaging was successful in 45 of 65 with nasopharynx cancer (NPC), 5 of 7 with lymphoma, and 26 of 28 with SCC, and the mean ADCs ($\pm$ standard
deviation (SD) of NPC, lymphoma, and SCC were 0.98 ± 0.161, 0.75 ± 0.190, and 1.14 ± 0.196 (×10⁻³ mm²/s), respectively, which were significantly different (P < 0.001–0.003).

Srinivasan and colleagues⁴十四 in their DWI study found that HN squamous cell cancer (HNSCC) patients had a significantly lower mean ADC value (1.101 ±0.214) x 10⁻³ mm²/s) than paraspinal muscles, pterygoid muscle, masseter muscle, thyroid gland, and base of the tongue (P = 0.0006, 0.0002, 0.0001, 0.001, and 0.002, respectively). The tumor ADC values were not significantly different from ADC values of parotid and submandibular glands (P = 0.057 and 0.14, respectively).¹⁴ In their other study with 33 patients at 3-T MR scanner, they found that there was a statistically significant difference (P = 0.004) between the mean ADC values (10⁻³ mm²/s) in the benign and malignant lesions (1.505 ± 0.487; 95% confidence interval, 1.305–1.706, and 1.071 ± 0.293; 95% confidence interval, 0.864–1.277, respectively), and suggested that a 3-T ADC value of 1.3 x 10⁻³ mm²/s may be the threshold value for differentiation between benign and malignant HN lesions.

Tumor Risk Stratification and Staging
In a recent study by Lu and colleagues,¹⁵ the utility of DW MR imaging as a novel preoperative tool for risk stratification in thyroid cancer was evaluated. The study concluded that ADC values of papillary thyroid cancers (PTCs) with extrathyroidal extension (ETE; 1.53 ± 0.25 x 10⁻³ mm²/s) were significantly lower than corresponding values from PTCs without ETE (2.37 ± 0.67 x 10⁻³ mm²/s; P < 0.005), and the cutoff ADC was determined at 1.85 x 10⁻³ mm²/s with a sensitivity of 85%, specificity of 85%, and receiving operating characteristic curve area of 0.85 that had ETE from those patients that did not have ETE. ETE was assessed at pathology, making DW MR imaging a tool of choice for preoperative clinical workup.

Vandecaveye and colleagues,¹² investigated the role of DWI in nodal staging in HNSCC patients. In their study, DWI led to a correct change in nodal stage for 12 (36%) of 33 patients. The nodal stage of 2 patients was downgraded from N1 to N0 in one patient and from N2b to N0 in the other. In 4 patients, a contralateral metastasis that was initially undetected at preoperative MR imaging was diagnosed at DWI. The nodal stage of the lymph node in the neck of 6 patients was upgraded from N0 to N1 or N2b in 3 patients with laryngeal cancer, to N2b in 2 patients with tongue cancer, and to ipsilateral metastasis in 1 patient with mouth floor cancer. In the patient with mouth floor cancer, a contralateral lymph node at neck level 2 that was considered suspicious at turbo spin-echo imaging was correctly diagnosed as benign at DWI, and the extent of the contralateral neck dissection was consequently reduced. Compared with turbo spin-echo imaging, DW imaging performed with ADC < 0 to 1000 values had higher accuracy than MR imaging in nodal staging, providing added value in the detection of subcentimeter nodal metastases.

Monitoring of Treatment Response
To evaluate DWI for assessment of early treatment response in HNSCC after the end of chemoradiotherapy, Vandecaveye and colleagues¹² found that the ADC change between pretreatment and after treatment (ΔADC) of lesions with later tumor recurrence was significantly lower than that in lesions with complete remission for both primary lesions (-2.3% ± 0.3% vs 80% ± 41%; P < 0.0001) and adenopathies (19.9% ± 32% vs 63% ± 36%; P = 0.003). The ΔADC showed a PPV of 89% and an NPV of 100% for primary lesions and a PPV of 70% and an NPV of 96% for adenopathies per neck side. DWI improved positive predictive value and negative predictive value compared with anatomic imaging.

Kim and colleagues¹¹ investigated the ADC change in 40 newly diagnosed HNSCC, before, during, and after the end of chemoradiotherapy and found that pretreatment ADC value of complete responders (1.04 ± 0.19 x 10⁻³ mm²/s) was significantly lower (P < 0.05) than that from partial responders (1.35 ± 0.30 x 10⁻³ mm²/s). A significant increase in ADC was observed in complete responders within 1 week of treatment (P < 0.01), which remained high until the end of the treatment. The complete responders also showed significantly higher increase in ADC than the partial responders by the first week of chemoradiation (P < 0.01). These results suggest that ADC can be used as a marker for early detection of response to concurrent chemoradiation therapy in HNSCC (Fig. 1).

Prediction of Treatment Response
Shukla-Dave and colleagues²⁰ showed in a DCE MR imaging study performed on 74 HNSCC patients that in a stepwise Cox regression, skewness of Ktrans (volume transfer constant) was the strongest predictor for stage IV patients (progression-free survival and overall survival, P < 0.001). This study suggests an important role for pretreatment DCE MR imaging in prediction of outcome in these patients.

Baer and colleagues³⁵ reported the utility of DCE MR imaging in assessment of treatment response. They showed in 10 patients with locoregionally HNSCC who underwent definitive
concurrent chemoradiation therapy that the volume transfer constant and normalized area under the contrast-enhancement time curve at 60 seconds were predictive of survival in parametric response map analysis (volume transfer constant, $P = .002$; normalized area under the contrast-enhancement time curve at 60 seconds, $P = .02$) and in the percentage change analysis (volume transfer constant, $P = .04$; normalized area under the contrast-enhancement time curve at 60 seconds, $P = .02$). After appropriate validation, this method may find use in potentially guide treatment modification in patients with predicted treatment failure.

Bernstein and colleagues\textsuperscript{46} performed a study on 37 HNSCC patients undergoing induction chemotherapy (IC), and the median baseline tumor plasma flow ($F_p$) was $53.2\text{ mL/100 mL/min}$ in 25 responders and $23.9$ in 12 nonresponders ($P = .027$). Median baseline $F_p$ in lymph nodes was $25.8\text{ mL/100 mL/min}$ for 37 nodes in 25 responders and $17.1$ for 15 nodes in 12 nonresponders ($P = .066$), and frequency of IC response in 37 patients was $68\%$ overall, $83\%$ for tumor $F_p$ greater than the median ($40.6\text{ mL/100 mL/min}$) and $45\%$ less than the median, thereby concluding that pretreatment tumor $F_p$ determined by DCE MR imaging predicts IC response in HNSCC.

In a recent study, Fujima and colleagues\textsuperscript{32} used ASL in 22 patients with HN cancer and evaluated perfusion measures before and after nonsurgical treatment. The study found that the TBF reduction rate was significantly lower in patients with residual tumors ($0.54 \pm 0.12$) than in those without.

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**Fig. 1.** Upper row: patient with nodal metastasis (white arrow) on (A) contrast-enhanced T1-weighted image, (B) b1000 DWI, and (C) ADC map prior to chemoradiotherapy. Middle row: (D) contrast-enhanced T1-weighted image 3 weeks post-chemoradiotherapy shows persistent adenopathy >1.5 cm with intranodal heterogeneity. (E) The lymphadenopathy is hyperintense on the b1000 DWI. Bottom row: CT-scan, 2 years post-chemoradiotherapy, shows completely calcified, small remnant lymphadenopathy, without evidence of tumor recurrence. (From Vandecaveye V, Dirix P, De Keyzer F, et al. Diffusion-weighted magnetic resonance imaging early after chemoradiotherapy to monitor treatment response in head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2012;82:1098–107.)
(0.85 ± 0.06); therefore, ASL technique could accurately determine the effect of nonsurgical treatment (Fig. 2).

In a feasibility IVIM study on neck nodal metastases, Hauser and colleagues47 studied 15 HNSCC patients who received radiotherapy in combination with chemotherapy and/or immunotherapy. They found that the initial perfusion fraction (f) value was significantly higher ($P = .01$) in patients with loco-regional failure (LRF) compared to patients with locoregional control. LRF was present in 3 patients only. These preliminary findings need to be further validated.

Noij and colleagues48 performed pretreatment MR imaging on 78 HNSCC patients. ADC and contrast-enhanced T1-weighted images were evaluated, and the results showed that tumor volume (sensitivity, 73%; specificity, 57%) and lymph node ADC$_{1000}$ (sensitivity, 71% to 79%; specificity, 77% to 79%) were independent significant predictors of disease-free survival without and with contrast-enhanced T1-weighted images ($P < .05$).

In their HNSCC study, Srinivasan and colleagues44 found that a significant difference ($P = .03$) in mean ADC between patients showing positive and negative outcomes (1.18 and 1.43 * 10–3 mm$^2$/s, respectively) and patients with lower pretreatment ADC and with greater than 45% of volume less than ADC threshold of 1.15 × 10 to 3 mm$^2$/s may have better outcomes to chemoradiation at 2 years.

Lu and colleagues49 assessed the merits of texture analysis on parametric maps derived from pharmacokinetic modeling with DCE MR imaging for the prediction of treatment response in patients with HNSCC. In this retrospective study, 19 HNSCC patients underwent pre- and intratreatment DCE MR imaging scans at a 1.5-T MR imaging scanner. Image texture analysis was then used on maps of $K_{\text{trans}}$ and $v_e$, generating 2 texture measures: energy and homogeneity. No significant changes were found for the mean and standard deviation for $K_{\text{trans}}$ and $v_e$ ($P > .09$); however, texture analysis found that the imaging biomarker energy of $v_e$ was significantly higher in intratreatment scans relative to pretreatment scans ($P < .04$; Fig. 3).

PEARLS, PITFALLS, AND VARIANTS

Functional MR imaging techniques such as diffusion and perfusion MR imaging allow for quantifying tumor characteristics related to tumor cellularity and vascularity. Compared with anatomic imaging techniques such as T1-weighted and T2-weighted MR imaging, functional MR imaging techniques have shown their added values in tumor detection, characterization, staging, treatment response monitoring, and prediction. However, there are several limitations for these techniques. In DCE MR imaging, patient voluntary and involuntary motion is a major source of error in the derived metrics of tumor tissues;

![Fig. 2. T2-weighted and ASL-derived TBF maps of a patient (41-year-old woman) with tongue cancer before (A, B) and after (C, D) treatment. (B) Pretreatment TBF map shows high blood flow corresponding to the primary lesion. (D) The posttreatment TBF map shows that higher blood flow is not observed in the PTC area compared with the surrounding soft tissue. The 12-month follow-up confirmed that this lesion was not a residual tumor. Arrows in (A, C) indicate the primary lesion at the root of the tongue. (From Fujima N, Kudo K, Yoshida D, et al. Arterial spin labeling to determine tumor viability in head and neck cancer before and after treatment. J Magn Reson Imaging 2014;40:925; with permission.)](image-url)
therefore, images should be motion corrected before further analysis. The nonspecific nature of vessel leakage can lead to high false-negative and false-positive results, which require other imaging modalities to correctly interpret tumor characteristics. Lack of standardized protocols is another issue that needs consideration to compare the results in different studies. Moreover, the use of individual and population AIF is another source of variability among different studies. In DWI, images suffer from patient motions and susceptibility difference in HN cancers. The selection of b value is crucial to the ADC quantification, as too low and too high b values can lead to inaccurate estimation of ADC values. For IVIM and its variant modeling fitting, perfusion metrics are highly sensitive to image noise thereby limiting the benefits of such techniques. Therefore, to enable clinical applications of DW MR imaging and DCE MR imaging in HN cancers, the experiments of DW MR imaging and DCE MR imaging should be carefully designed, standardized, implemented, and interpreted. For most of the discussed techniques, state-of-the-art dedicated MR imaging hardware and software and knowledgeable personnel are needed to obtain reliable data that can be used in the clinic.

**SUMMARY**

Considering the diversity of applications and demonstrated potential of diffusion and perfusion imaging methods, the importance of these techniques in assessing HN cancer is expected to grow. Until now, most studies reporting on MR imaging diffusion and perfusion in HN cancer included relatively small populations (ie, n <100), but this number is likely to increase in the future. To obtain reliable biomarkers that extend beyond standard structural scans, however, one has to consider potential complicating factors with respect to both the data acquisition and processing. Yet most problems have been critically addressed and can be taken into account in a satisfying manner. Also, further progress in the development of (eg, automated) analysis methods has to be stimulated to make diffusion and perfusion imaging procedures more easily (ie, push button) applicable in clinical routine.

**REFERENCES**


