REVIEW ARTICLE
The emerging potential of magnetic resonance imaging in personalizing radiotherapy for head and neck cancer: an oncologist’s perspective

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ABSTRACT
Head and neck cancer (HNC) is a challenging tumour site for radiotherapy delivery owing to its complex anatomy and proximity to organs at risk (OARs) such as the spinal cord and optic apparatus. Despite significant advances in radiotherapy planning techniques, radiation-induced morbidities remain substantial. Further improvement would require high-quality imaging and tailored radiotherapy based on intratreatment response. For these reasons, the use of MRI in radiotherapy planning for HNC is rapidly gaining popularity. MRI provides superior soft-tissue contrast in comparison with CT, allowing better definition of the tumour and OARs. The lack of additional radiation exposure is another attractive feature for intratreatment monitoring. In addition, advanced MRI techniques such as diffusion-weighted, dynamic contrast-enhanced and intrinsic susceptibility-weighted MRI techniques are capable of characterizing tumour biology further by providing quantitative functional parameters such as tissue cellularity, vascular permeability/perfusion and hypoxia. These functional parameters are known to have radiobiological relevance, which potentially could guide treatment adaptation based on their changes prior to or during radiotherapy. In this article, we first present an overview of the applications of anatomical MRI sequences in head and neck radiotherapy, followed by the potentials and limitations of functional MRI sequences in personalizing therapy.

INTRODUCTION
Radical radiotherapy (RT) is integral to the management of head and neck cancer (HNC) in both the primary and adjuvant settings. Advances in computer-assisted radiological techniques over the past two decades have in turn revolutionized radiotherapy planning. Development of advanced radiotherapy planning techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy have allowed for better dose conformation to the tumour target and sparing of surrounding normal tissues. HNC was one of the first tumour sites where IMRT was widely implemented owing to a significant reduction in radiation-induced xerostomia in comparison with three-dimensional conformal planning.1

CT is currently the standard platform for radiotherapy planning. CT, however, provides a poor soft-tissue contrast, resulting in difficulty in identifying tumour and organs at risk (OARs) in the head and neck regions. On the contrary, MRI utilizes a strong magnetic field to provide high-resolution anatomical information by which blood vessels, masses and adjacent soft tissues are easily distinguishable. There is no increased risk of secondary malignancies with repetitive imaging, making MRI an attractive tool in the field of image-guided and adaptive radiotherapy.

The potential advantages of using MRI as a stand-alone radiotherapy planning platform have led to international collaboration to develop MR-Linac. MR-Linac aims to combine the two technologies in the MRI scanner and linear accelerator to address the current insufficiency in modern image-guided radiotherapy, i.e. to accurately define the tumour and tailor radiotherapy beams in real time. This would help eliminate the uncertainties related to patient setup, intrafraction and interfraction movements. However, there are several technical challenges with MR-Linac such as the lack of electron density data and the influence of magnetic field on radiotherapy dose distribution due to secondary electrons, which are currently being addressed during its development.
In addition, advanced MRI sequences, such as diffusion-weighted (DW), dynamic contrast-enhanced (DCE) and intrinsic susceptibility-weighted (ISW) sequences are capable of characterizing tumour biology further by providing quantitative functional parameters that are known to have radiobiological significance such as tissue cellularity, vascular perfusion/permeability and hypoxia. These sequences, also collectively referred to as functional MRI (F-MRI) in this article, are areas of ongoing research; but, there is increasing evidence to support the role of these F-MRI parameters as predictive and prognostic biomarkers.

In the first section of this article, we give an overview of the applications of anatomical MRI sequences in the management of HNC with specific focus on radiotherapy. For the purpose of this review, the term HNC refers primarily to squamous cell carcinoma, which accounts for over 90% of head and neck malignancies. Next, we elaborate on each F-MRI modality and discuss their potential utilities and limitations as imaging biomarkers to guide treatment individualization for HNC.

ANATOMICAL MRI SEQUENCES
Staging
MRI is increasingly used for defining the extent of tumour invasion into adjacent structures in HNC owing to its superior soft-tissue contrast. T1 weighted images are generally considered the best for gross structural information, whereas T2 weighted images distinguish abnormal pathology from surrounding tissues. In clinical practice, MRI is the imaging modality of choice for staging primary disease for nasopharyngeal and sinonasal tumours. It is also increasingly used to stage oropharyngeal (OP) cancer and detect cartilage invasion for laryngeal/hypopharyngeal cancer. Studies have shown MRI to be an independent poor prognostic feature, even for human papilloma virus (HPV)-driven OP cancer. Figure 1 shows an example of a metastatic retropharyngeal LN which was readily detectable on MRI, but not on CT.

Radiotherapy planning—tumour target and organ at risk delineation
Prior to the era of IMRT/volumetric-modulated arc therapy, head and neck radiotherapy planning has been historically based on compartmental volume, defined by anatomical boundaries. Consequently, radiation-induced toxicities were substantial with significant negative impact on patient quality of life. Advances in both diagnostic imaging and planning techniques have permitted a shift of practice towards volumetric contouring. This means that high-dose clinical target volume only includes the gross tumour volume (GTV) with a pre-determined margin for isotropic expansion, instead of the whole anatomical subsite. Importantly, no detrimental effect on locoregional control was observed with volumetric contouring.

Several planning studies have underlined the benefit of incorporating MR images in head and neck radiotherapy planning with improvement of tumour delineation and reduction in interobserver variations compared with CT. It also enables a more accurate delineation of neurological OARs such as the spinal cord, brain stem, optic chiasm and hippocampus, which is vital to avoid irreversible neurological sequelae. Nevertheless, the accuracy of MRI in this context is hugely dependent on the scanning position. Appropriate neck immobilization for planning MRI is necessary to reduce the risk of geographical miss, as deformable registration is unable to fully account for the differences in the position of the neck. Acquiring MRI in neck immobilization requires deviation from standard protocol owing to inability to use the standard head coil. However, this can be overcome by using a combination of flex and spine coils.

The majority of commonly used metallic implants, including dental objects, are MRI safe or conditional and can be imaged with MRI. However, these objects may cause local magnetic field

Figure 1. An example of axial T2 weighted MR image showing contralateral retropharyngeal node involvement (b) (indicated by arrow) in a patient with left tonsillar squamous cell carcinoma, which was not readily visible on CT (a).
inhomogeneity, resulting in regional signal loss and "pile-ups" depending on the implant material and geometry. In practice, these effects are often less problematic in comparison with CT streak artefact caused by beam hardening and photon starvation, thereby providing further advantage in radiotherapy planning. Furthermore, these artefacts can be greatly reduced for MRI by employing dedicated metal artefact reduction sequences, albeit at the expense of longer acquisition times.

In addition, it is feasible to quantify the magnitude of tumour motion using cine-MRI. This enables an individualized internal margin to generate a planning target volume for each patient. Cine-MRI is acquired through continuous real-time imaging, which historically posed limitations with poor image quality in terms of spatial resolution and signal-to-noise ratio, but this has vastly improved with newer techniques. A study assessing deglutition-induced organ motion with cine-MRI observed some tumour motion even in the absence of swallowing. The use of a customized intraoral immobilization device could help minimize tongue movement and prevent swallowing, but this service requires input from specialized orthodontics and is not widely available.

Radiotherapy delivery—adaptive approach
A patient anatomy changes throughout the course of radiotherapy, which may significantly alter the dose distribution to both planning target volume and OARs. This is a prominent issue for HNC owing to treatment-related weight loss. For example, parotids are known to shrink up to 30–40% of their original volume and tend to displace medially throughout the course of radiotherapy. Adaptive radiotherapy studies with CT have already demonstrated the benefit of such an approach in reducing cumulative dose to normal tissues throughout the radiotherapy without compromising long-term outcome.

MRI is naturally the imaging modality of choice for this approach owing to lack of additional radiation exposure and better soft-tissue contrast. Current imaging modalities available in the treatment room such as cone-beam CT or in-room CT provide limited soft-tissue contrast which precludes precise tumour tracking. One of the projected benefits with MR-Linac is that patients could be imaged daily to allow real-time online matching, dosimetric analysis and plan reoptimization if required. Moreover, GTV could be modified based on tumour response during radiotherapy, enabling further reduction in dose to adjacent organs (Figure 2). Efforts to develop automated OAR segmentation and rapid adaptive replanning are ongoing.

Functional MRI sequences
It is now evident that HNC represents a disease spectrum, which is divisible into different prognostic groups based on clinical variables such as clinical/radiological staging (Tumor, Node and Metastases), HPV status and smoking history. There is, therefore, a pressing need for a more personalized approach to treatment decision-making in order to optimize the balance between therapeutic efficacy and toxicity. However, biomarkers which could provide reliable information on the likely impact of a specific intervention at an early time point are required to guide treatment adaptation. F-MRI offers an attractive, non-invasive means to characterize the tumour biology by providing quantitative parameters with known radiobiological relevance. This has, in turn, led to a surge in the number of studies investigating the role of these parameters as imaging biomarkers for HNC over the past decade. In this section, we review the evidence and discuss the potential roles of these F-MRI sequences in the management of HNC.

Diffusion-weighted MRI
DW MRI utilizes the Brownian motion of water to assess tissue cellularity without the need of any exogenous contrast agent.

Figure 2. The coronal $T_2$ weighted MR images on the left are illustrating the early anatomical changes in primary gross tumour volume (GTV) observed following Week-1 and Week-2 radical chemoradiotherapy (CRT) in a patient with human papilloma virus-positive T3N0M0 left tonsillar squamous cell carcinoma. The axial image on the right is showing an overlay of co-registered MRIs between pre-treatment and Week-2 CRT for the same patient to illustrate the potential benefit of dose reduction to the pharyngeal constrictors and left parotid through GTV adaptation during radiotherapy with the shrinkage of the tumour away from these structures (filled contour—Week-2 CRT; dotted contour—pre-treatment).
The movement of the tissue water molecules during the course of the diffusion-encoding gradients results in dephasing, depicted as signal loss. The signal loss is proportional to the amount of water molecule displacement and the duration of the diffusion-encoding gradients (b-value). The voxel-based signal loss can be quantified to produce maps of apparent diffusion coefficient (ADC), which is inversely correlated with tumour cellularity.

DW sequences are increasingly incorporated in routine head and neck imaging owing to their additional values to anatomical sequences at diagnosing primary tumours (PTs), nodal involvement and detecting recurrences. Vandecaveye et al further reported the ability of DW MRI to differentiate between tumour and post-radiotherapy changes, thus enabling identification of residual tumour immediately after radiotherapy, in contrast to fludeoxyglucose-positron emission tomography (PET) which has a poor specificity in this situation. The high contrast between tumour and surrounding tissues in heavily DW images has also raised the possibility to use this technique as an adjunct to guide GTV delineation. Nevertheless, this is hampered by geometric distortions which are pronounced in the head and neck region owing to the large magnetic field inhomogeneity caused by the tissue–air interface. A study by Schakel et al found distortions up to 26 mm in the anteroposterior axis. This, however, can be minimized with dedicated acquisition and post-processing methods. DW distortion in HNC was shown to be greatly compensated using reduced-distortion readout-segmented echoplanar imaging and half-Fourier acquisition single-shot turbo spin echo (Figure 3). The latter, however, may not be optimal for qualitative tumour assessment owing to a low interobserver agreement for ADC values in lesions assessed with conventional echoplanar imaging vs half-Fourier acquisition single-shot turbo spin echo techniques.

There are now much published data that support the ability of DW MRI to assist in the early prediction of treatment outcomes following chemoradiotherapy in HNC. Overall, there were conflicting results over the value of pre-treatment ADC at predicting response to treatment (Table 1). Five studies failed to distinguish patients with unfavourable disease based on pre-treatment ADC, whereas six studies found high pretreatment tumour ADC to be predictive of poor outcome following RT. As illustrated in Table 1, there are heterogeneities between the studies in scanning protocol, analytical methods and measured clinical end points, which may be
Table 1. Summary of diffusion-weighted (DW) MRI biomarker studies in head and neck cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and treatment modalities</th>
<th>Scan time points</th>
<th>DW scanning protocol</th>
<th>Number of patients/ROIs analyzed/primary sites</th>
<th>End points (response criterion)</th>
<th>Results</th>
<th>Suggested ADC—thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al40 (2009)</td>
<td>Prospective, CRT</td>
<td>Pre-RT, Week 1 and Week 2 RT</td>
<td>1.5 T or 3.0 T; TR/TE: 4 s/89 ms ((b = 0, 500, 1000 \text{ s mm}^{-2}))</td>
<td>33 patients (all Stage IV)/LNs only 66% oropharynx</td>
<td>CR vs PR based on clinical and pathological evidence post-CRT</td>
<td>CR group has a lower pre-treatment ADC</td>
<td>(1.11 \times 10^{-3} \text{mm}^2\text{s}^{-1})</td>
</tr>
<tr>
<td>Kato et al43 (2009)</td>
<td>Retrospective, neoadjuvant CRT, IC and RT</td>
<td>Pre-RT only</td>
<td>1.5 T; TR/TE: 5 s/70–72 ms ((b = 0, 1000 \text{ s mm}^{-2}))</td>
<td>28 patients (Stage II–IV)/both PTs and LNs 40% larynx/hypopharynx</td>
<td>Tumour regression rate (RECIST) post-treatment</td>
<td>Inverse correlation of pre-treatment ADC with tumour regression rate (r = -0.384)</td>
<td>None</td>
</tr>
<tr>
<td>Vandecaveye et al49 (2010)</td>
<td>Prospective, CRT and RT</td>
<td>Pre-RT, Week 2 and Week 4 RT</td>
<td>1.5 T; TR/TE: 7.1 s/84 ms ((b = 0, 50, 100, 500, 750, 1000 \text{ s mm}^{-2}))</td>
<td>30 patients (Stage I–IV)/both PTs and LNs 53% larynx/hypopharynx</td>
<td>Locoregional control (median follow-up 2 years)</td>
<td>Lower increase in PTs and LNs ADC 2 and 4 weeks after treatment is associated with poor locoregional control at 2 years</td>
<td>PTs: 14% (Week 2) and 25% (Week 4) LNs: 14.6% (Week 2) and 19% (Week 4)</td>
</tr>
<tr>
<td>Hatakenaka et al41 (2011)</td>
<td>Retrospective, CRT and RT</td>
<td>Pre-RT only</td>
<td>1.5 T; TR/TE: 3 s/73 ms ((b = 0, 300, 1000 \text{ s mm}^{-2}))</td>
<td>38 patients (17 Stage III)/PTs only 60% hypopharynx/larynx</td>
<td>LC vs local failure (median follow-up approximately 10 months)</td>
<td>LC group has a lower pre-treatment ADC</td>
<td>(0.88 \times 10^{-3} \text{mm}^2\text{s}^{-1})</td>
</tr>
<tr>
<td>King et al36 (2010)</td>
<td>Prospective, CRT and RT</td>
<td>Pre-RT, Week 2 RT and 6 weeks post-RT</td>
<td>1.5 T; TR/TE: 2 s/75 ms ((b = 0, 100, 200, 300, 400, 500 \text{ s mm}^{-2}))</td>
<td>50 patients (Stage III–IV)/single-slice ADC analysis of tumour with largest diameter &gt;50% hypopharynx</td>
<td>Locoregional control (median follow-up 22 months)</td>
<td>No signal for pre-treatment ADC</td>
<td>N/A</td>
</tr>
<tr>
<td>Ohnishi et al48 (2011)</td>
<td>Retrospective, CRT and RT</td>
<td>Pre-RT only</td>
<td>1.5 T; TR/TE: 3 s/73 ms ((b = 0, 300, 1000 \text{ s mm}^{-2}))</td>
<td>32 patients, (Stage I–IV)/PTs only 53% hypopharynx, 47% larynx</td>
<td>LC (median follow-up 15 months)</td>
<td>Low pre-treatment ADC predicts for LC</td>
<td>(0.79 \times 10^{-3} \text{mm}^2\text{s}^{-1})</td>
</tr>
<tr>
<td>Berrak et al38 (2011)</td>
<td>Retrospective, IC + CRT</td>
<td>Pre-IC and 3 weeks post-IC</td>
<td>1.5 or 3.0 T; TR/TE: 4 s/89 ms ((b = 0, 500, 1000 \text{ s mm}^{-2}))</td>
<td>18 patients (Stage IV)/LNs only 72% oropharynx</td>
<td>OS (median follow-up approximately 19 months)</td>
<td>No signal for pre-treatment ADC</td>
<td>N/A</td>
</tr>
</tbody>
</table>

(Continued)
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<th>Study</th>
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<tbody>
<tr>
<td>Chawla et al(^{39}) (2013)</td>
<td>Prospective, CRT and IC + CRT</td>
<td>Pre-RT only</td>
<td>1.5 T or 3.0 T; TR/TE: 4 s/89 ms ((b = 0, 500, 1000 \text{ s mm}^{-2}))</td>
<td>24 patients (Stage III–IV)/ both PTs and LNs 94% oropharynx</td>
<td>Responders vs partial/ non-responders (median follow-up 23.7 months)</td>
<td>No signal from pre-treatment ADC alone (LN and PTs) N/A</td>
</tr>
<tr>
<td>Matoba et al(^{37}) (2014)</td>
<td>Prospective, CRT</td>
<td>Pre-RT and Week 3 RT</td>
<td>1.5 T; TR/TE: 4 s/86 ms ((b = 0, 90, 800 \text{ s mm}^{-2}))</td>
<td>35 patients (Stage III–IV)/ both PTs and LNs 57% larynx/ hypopharynx</td>
<td>Locoregional control (median follow-up 30.8 months)</td>
<td>No signal from pre-treatment ADC N/A</td>
</tr>
<tr>
<td>Ng et al(^{42}) (2014)</td>
<td>Prospective, CRT</td>
<td>Pre-RT only</td>
<td>3.0 T; TR/TE: 8.2 s/84 ms ((b = 0, 800 \text{ s mm}^{-2}))</td>
<td>69 patients (Stage III–IV)/ LNs only (largest) 53% oropharynx, 47% hypopharynx</td>
<td>3-year neck control (median follow-up 31 months)</td>
<td>Higher pre-treatment LN ADC is an independent predictor of poor neck control 1.14 × 10^{-3} mm² s⁻¹</td>
</tr>
<tr>
<td>Ng et al(^{41}) (2016)</td>
<td>Prospective, CRT</td>
<td>Pre-RT only</td>
<td>3.0 T; TR/TE: 8.2 s/84 ms ((b = 0, 800 \text{ s mm}^{-2}))</td>
<td>86 patients (Stage III–IV)/ both PTs and LNs 52% oropharynx, 48% hypopharynx</td>
<td>PFS and OS (median follow-up 36 months)</td>
<td>Lower LN ADC is an independent predictor of longer PFS but not OS 1.14 × 10^{-3} mm² s⁻¹</td>
</tr>
<tr>
<td>Wong et al(^{40}) (2016)</td>
<td>Prospective, CRT and IC + CRT</td>
<td>Pre-IC, post-1st and 2nd cycle IC</td>
<td>1.5 T; TR/TE: 13 s/61 ms ((b = 50, 400, 800 \text{ s mm}^{-2}))</td>
<td>20 patients (Stage III–IV)/ both PTs and LNs 90% oropharynx and 10% larynx/ hypopharynx</td>
<td>Complete remission 3 months post-CRT (median follow-up 14 months)</td>
<td>No signal from pre-treatment ADC or changes post-IC N/A</td>
</tr>
</tbody>
</table>

ADC, apparent diffusion coefficient; CR, complete response; CRT, radical chemoradiotherapy; IC, induction chemotherapy; LC, local control; LN, lymph node; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PR, partial response; PT, primary tumour; ROI, region of interest; RT, radical radiotherapy; TE, echo time; TR, repetition time.

accountable for the discrepancy in their findings. Some investigators used different magnetic field strengths (1.5 T or 3.0 T) even within the same study and the number of b-values used ranged from 2 to 5. Whilst almost all studies excluded apparent tumour necrosis from ADC calculation, there is a lack of consensus on the analytical methods: some studies only chose the tumour with the largest diameter (primary or LN), whereas others analyzed them in isolation. However, the pre-treatment ADC thresholds suggested by the positive studies appear to be fairly concordant with primary ADC <0.79–0.88 × 10^{-3} mm² s⁻¹ and nodal ADC <1.11–1.14 × 10^{-3} mm² s⁻¹ to be predictive of favourable outcome following radiotherapy.\(^{40,41,44,45}\) A contradictory result by Nakajo et al\(^{46}\) where they found patients with low pre-treatment primary ADC <0.88 × 10^{-3} mm² s⁻¹ to have an unfavourable 2-year outcome, somewhat highlighted the potential negative influence of including inhomogeneous tumour sites and treatment modalities in the study findings: 54% patients undergoing primary surgery instead of radiotherapy, with higher recurrence rate in patients undergoing surgery.
Another noteworthy observation by Wong et al. is that HPV-positive OP tumours in patients who achieved complete remission following chemoradiotherapy exhibited a wide range of pre-treatment ADC (0.9–1.54 × 10⁻³ mm² s⁻¹), thereby undermining its predictive value. HPV-positive OP cancer (tonsil and base of tongue) is known to exhibit unique histopathological features such as indistinct cell borders and comedo necrosis, unlike other subsites or HPV-negative disease. These features may have contributed to the high ADC in some HPV-positive tumours but, importantly, they do not have the same negative biological impact on treatment outcome as on a patient who is HPV negative. The potential impact of HPV status on ADC measurements in OP cancer has not been explored in other published studies; hence, caution should be exercised when interpreting pre-treatment ADC alone.

Whilst the value of pre-treatment ADC remains unclear, treatment-induced changes of ADC during radiotherapy have been more consistently demonstrated in several clinical studies. The cumulative results suggest that tumours that show a lower increase or even a decrease in ADC 1–4 weeks into radiotherapy (ΔADC <14–24%) are more likely to fail treatment. It is speculated that tumours with a good treatment response show a higher frequency of apoptosis or necrosis earlier in the course of treatment than those with a poor response. Thus, the ADC tends to increase in responding tumours because of the presence of fewer barrier structures to the movement of tissue water such as cell membranes. The optimal timing for early intratreatment assessment using DW MRI, however, still needs to be established (between Week 1 and Week 4 of RT), as development of mature scar tissues may “falsely” decrease ADC in responders.

The majority of published studies have calculated mean or median ADC from defined regions of interest to quantify the observed differences in DW MRI between patients at baseline and during treatment. More sophisticated analyses of DW MRI data are possible and may enable DW MRI to be used as a more sensitive and specific biomarker to provide an early prediction of response to chemoradiotherapy. Galban et al. described a voxelwise approach to the evaluation of ADC changes during treatment that involves the calculation of parametric response maps (PRM) in 12 patients. This approach uses registered baseline and intratreatment ADC maps to calculate regional tumour response and they concluded that PRM may be more sensitive to cellular changes than measurements of the change in the mean ADC over whole regions of interest. One lingering uncertainty, however, is how well deformable image registration accounts for volumetric or positional changes in tumour between the scanning time points to allow confident per-voxel analysis. Moreover, deformable image registration itself remains a matter of research with lack of clinical validation. Further studies on larger numbers of patients are, therefore, required.

**Dynamic contrast-enhanced MRI**

DCE MRI assesses changes in signal intensity following the injection of a paramagnetic contrast agent, e.g. gadolinium that shortens the longitudinal relaxation time ($T_1$). This leads to increased signal intensity in perfused tissue regions in $T_1$ weighted images. The temporal changes in signal intensity obtained by DCE MRI are related to the underlying permeability and perfusion of tumour microenvironment, all of which are known to influence treatment response. The gadolinium concentration–time curve can also be fitted to a two-compartment pharmacokinetic model to yield various kinetic and volumetric parameters such as the transfer coefficient from plasma to the interstitial space ($K_{trans}$), the extracellular vascular volume fraction ($V_e$) and plasma volume fraction ($V_p$).

Enhancement patterns of DCE MRI have shown correlations with malignancy, angiogenesis, proliferation and hypoxia. One of the first studies to evaluate the relationship between tumour perfusion and local control (LC) using DCE MRI in patients with HNC was published by Hoskin et al. 13 patients underwent DCE MRI before and on completion of accelerated radiotherapy. LC was found to be related to maximum tumour enhancement following radiotherapy and the difference in time taken to reach maximum tumour enhancement pre- and post-radiotherapy. These results suggested that tumours with lower perfusion at the end of radiotherapy were most sensitive to treatment and those with greater tumour enhancement were likely to fail locally.

Since then, several other groups have evaluated the ability of pre-treatment DCE parameters to provide prognostic information for patients with HNC undergoing radical chemoradiotherapy (CRT). These studies have been summarized in two systematic reviews published in recent years. The most commonly reported pre-treatment DCE parameters with predictive or prognostic value are $K_{trans}$ followed by $V_e$ and $V_p$. Two earlier clinical studies have shown low pre-treatment nodal tumour $K_{trans}$ to be correlated with poor locoregional control and disease-free survival. No threshold was suggested, but non-responders in both studies have an average $K_{trans}$ value of 0.15–0.21 min⁻¹. However, one of the larger study to date by Shukla-Dave et al. reported that it was the skewness rather than the mean value of nodal tumour $K_{trans}$ which was the strongest predictor of progression-free survival (PFS). The authors therefore recommended calculation of skewness to be a better measure of tumour heterogeneity, but did not indicate whether a positive or negative skew predicted for a better outcome.

Another large multimodality, parametric functional imaging study of 69 patients by Ng et al. reported low pre-treatment nodal $V_e$ (<0.23) to be an independent poor prognostic factor for 3-year neck control for patients undergoing CRT. This is one of the first study reported in HNC to incorporate multimodality functional imaging in fluorine-18 fluoro-deoxyglucose-PET/CT, DCE and DW MRI, given emerging evidence from correlation studies that these modalities provide different, but complementary biological tumour information, thereby improving predictive power. It is noteworthy that none of these studies reported DCE parameters for PTs and this may be related to technical difficulties, e.g. motion caused by swallowing or susceptibility artefacts. A more recent study by King et al. in 49 patients assessed the predictive value of pre-treatment DCE...
parameters in both primary and nodal tumours but failed to show any correlation with response to chemoradiotherapy. Ng et al\textsuperscript{45} also provided an update on their previous study after recruiting additional 17 patients and including PT in analysis. This showed a similar result, i.e. low pre-treatment nodal V\textsubscript{e} independently predicted for shorter PFS and overall survival (OS).

It is possible to conclude from the cumulative results shown above that pre-treatment DCE-derived K\textsubscript{trans} or V\textsubscript{e} in LNs could predict for outcome following radiotherapy in HNC. However, it is impossible to deduce which are the optimal pre-treatment parameters and the inconsistencies in the reported results are invariably attributable to the differences in DCE scanning protocols, pharmacokinetic models and arterial input function used. For example, there are up to four methodologies available to estimate arterial input function, e.g. population averaged,\textsuperscript{65} reference tissue based,\textsuperscript{66} contrast concentration in adjacent arteries\textsuperscript{67} and independent component analysis.\textsuperscript{68} Consequently, large collective efforts are required to optimize and standardize DCE protocols for future studies.

In contrast, there is a paucity of data on the role of intratreatment DCE MRI to assess and predict response to radiotherapy. The number of patients in these studies are very small (n < 15), precluding any definitive conclusion or clinical translation. One of the first study by Cao et al\textsuperscript{69} reported an increase of blood volume (BV) in PT 2 weeks into chemoradiotherapy to be associated with LC. Wang et al\textsuperscript{70} subsequently reported on a cluster analysis method to identify biologically relevant tumour subvolumes using DCE MRI. The sizes of the cluster analysis-defined tumour subvolumes with low BV, before and during Week-2 radiotherapy, were significantly greater in the patients with local treatment failure (LF) than that in those with LC. Whilst the total PT volumes were reduced from baseline to Week 2 to a similar extent for both patients with LF and LC, the percentage decreases in the subvolumes of the PTs with low BV in the same time interval were significantly smaller for the patients with LF than that for those with LC (p < 0.05).\textsuperscript{71} This illustrates the potential utility of DCE parameters to identify a biological target volume for radiotherapy dose escalation and using it to monitor response.

Baer et al\textsuperscript{71} investigated the feasibility of using PRM of DCE MRI to predict survival following CRT in 10 patients. They found that the reduction in K\textsubscript{trans} per voxel measured through PRM after 2 weeks of radiotherapy was a better predictor of OS in comparison with the whole tumour mean or median signal changes. Similar to the DW PRM study, this needs to be validated with more patients. The authors themselves acknowledged that the process to analyze PRM is complex and requires special attention during delineation owing to limitations in image resolution.

Intrinsic susceptibility-weighted MRI

Hypoxia is a well-recognized factor of resistance to chemotherapy and radiotherapy in HNC. A meta-analysis has demonstrated hypoxia modification to be a valid therapeutic strategy;\textsuperscript{72} thus, a non-invasive mean to detect tumour hypoxia is highly desirable to guide identification of patients who are likely to benefit from such a strategy. PET-based techniques using tracers such as fluorine-18 fluoromisonidazole are currently the most widely studied functional imaging to characterize hypoxia in HNC. However, these PET techniques are expensive, time consuming and suffer from a poor spatio-temporal resolution and signal-to-noise ratio.\textsuperscript{73}

An alternative hypoxia-specific imaging technique is ISW MRI, also known as blood oxygen level-dependent MRI. It exploits the paramagnetic properties of deoxyhaemoglobin in erythrocytes to create contrast. Essentially, deoxyhaemoglobin creates magnetic susceptibility perturbations around blood vessels and the transverse MR relaxation rate R\textsubscript{2}/* (R\textsubscript{2}/* = 1/T\textsubscript{2}*) of water in blood and the surrounding tissues increases in proportion to tissue deoxyhaemoglobin concentration. Because oxygenation of haemoglobin is proportional to arterial blood polarographic oxygen levels, tumour R\textsubscript{2}/* is a sensitive index of tissue oxygenation and a surrogate marker of hypoxia.

ISW MRI has been typically performed by measuring changes in R\textsubscript{2}/* with hyperoxic gas challenge such as carbogen. Clinical studies conducted in patients with HNC have consistently demonstrated that the tumour R\textsubscript{2}/* decreases following inhalation of hyperoxic gas, indicative of improved blood oxygenation which may further increase the radiosensitivity.\textsuperscript{74,75,76} The use of hyperoxic gas breathing in clinical practice remains limited owing to added complexity and side effects such as breathlessness. However, there are now emerging data that suggest that useful information may still be obtained from ISW MRI, even in the absence of oxygen challenge. A study in cervical cancer by Li et al\textsuperscript{77} was one of the first studies to demonstrate the ability of using baseline tumour R\textsubscript{2}/* alone to predict response to chemoradiotherapy: responders had a lower baseline R\textsubscript{2}/* than non-responders. This study also found baseline R\textsubscript{2}/* to be an independent prognostic factor for PFS and OS. However, these results are yet to be replicated in other tumour sites.

A study by Panek et al\textsuperscript{77} has demonstrated tumour R\textsubscript{2}/* measurement to be a sensitive and reproducible quantitative imaging technique in detecting clinically relevant changes in tumour oxygenation for HNC. However, reliable interpretation of R\textsubscript{2}/* as a stand-alone parameter is not possible without additional information such as tumour BV.\textsuperscript{77} This is supported by other observations that hypoxic tumours with high blood flow had high R\textsubscript{2}/*,\textsuperscript{78} whereas hypoxic tumours with low BV were found to have low R\textsubscript{2}/* instead.\textsuperscript{78} Serial weekly changes in R\textsubscript{2}/* alone throughout chemoradiotherapy in patients with HNC also did not appear to show any clear pattern.\textsuperscript{80} Therefore, a better understanding of how to interpret R\textsubscript{2}/* measurements with BV needs to be ascertained to improve its performance as an imaging biomarker.

Challenges with integration of functional MRI into clinical practice

Whilst there is little doubt that F-MRI can provide predictive and prognostic information for HNC, its integration into clinical practice remains limited. One of the main reasons is the lack of consensus of optimal modalities, scanning protocols and analytical methodologies, leading to discrepancy in the reported results (as described above). This is partly due to the constant...
evolution of machinery and acquisition techniques over the years. Consequently, a meta-analysis of F-MRI studies is not possible for the same reason. Efforts to standardize these protocols for clinical trials are under way and may be further facilitated through collaboration between MR-Linac consortiums.

Another important issue to consider is that physiological parameters, such as perfusion and oxygenation, are dynamic and potentially unstable parameters that may fluctuate significantly in the absence of therapy. Only limited data exist on the stability of F-MRI parameters in patients with cancer prior to treatment and there are no data on this aspect that are specific to patients with HNC receiving primary CRT. However, two studies in patients with a variety of cancers enrolled in Phase 1 clinical drug trials do provide some reassuring data on the reproducibility of F-MRI parameters. Koh et al. found ADC measurements from DW-MRI to be highly reproducible, with a coefficient of repeatability of 13.3%. Messiou et al. also reported the intrapatient coefficients of variation (CVs) for all DCE-derived parameters to be within the range of 8–30%, except for $V_p$. The most reproducible DCE-derived parameters were the enhancing fraction (CV = 8.6%), followed by $K_{trans}$ (CV = 13.9%) and initial area under the time-concentration curve over 60 seconds (CV = 15.5%). The stability of these parameters in HNC need to be established further prior to clinical implementation.

Furthermore, integration of F-MRI into radiotherapy treatment planning requires special attention in terms of image quality and geometrical accuracy, which means that image acquisition with immobilization in the radiotherapy treatment position is essential. This approach was lacking in most earlier F-MRI studies, which precluded the analysis of PT owing to gross motion artefact. Consequently, tolerability may be an issue for some patients owing to the additional discomfort with immobilization and scanning time required in comparison with standard anatomical MRI. Considerations should also be given to the potential pressure on the hospital resources, e.g. time on scanners and additional expertise required to process F-MRI images.

CONCLUSION

Anatomical and functional imaging capabilities offered by MRI provide potential opportunities to optimize radiotherapy strategies for HNC through improved target delineation, high-risk disease subvolume identification, early intratreatment monitoring and adaptation based on response. Based on current evidence, baseline tumour vascular permeability/hypoxia and early cell apoptosis during radiotherapy, as measured by DCE and DW MRI, respectively, appear to be the most promising biomarkers to predict radiotherapy outcome and tailor treatment strategies for HNC. The studies conducted to date have laid a solid foundation for the exciting prospect of integrating functional imaging into MR-Linac in the future. This added dimension will further enhance the appeal of using MRI as a single platform for radiotherapy planning and delivery in HNC. However, an important next step to bridge the translational gaps for F-MRI is a collective effort to determine the optimal methodology to allow standardization and perform clinical validation through a large multicentre study.

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