Review Article

Quantitative diffusion magnetic resonance imaging in head and neck tumors

Seyedmehdi Payabvash

Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, CT, USA

Correspondence to: Seyedmehdi Payabvash, MD. Department of Radiology and Biomedical Imaging, Yale School of Medicine, 20 York Street, PO Box 208042, Tompkin's East 2-209, New Haven, CT 06520-8042, USA. Email: sam.payabvash@yale.edu.

Abstract: In patients with head and neck cancer, conventional anatomical magnetic resonance imaging (MRI) scans are commonly used for identification of primary lesion, assessment of structural distortion, and presence of metastatic lymph nodes. However, quantitative analysis of diffusion MRI can provide added value to structural and anatomical evaluation of head and neck tumors (HNT), by differentiation of primary malignant process, prognostic prediction, and treatment monitoring. In this article, we will review the applications of quantitative diffusion MRI in identification of primary malignant tissue, differentiation of tumor pathology, prediction of molecular phenotype, monitoring of treatment response, and evaluation of posttreatment changes in patient with HNT.

Keywords: Diffusion weighted imaging (DWI); head and neck cancer; squamous cell carcinoma (SCC); intravoxel incoherent motion (IVIM)

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Biomedical imaging in head and neck tumors (HNT)

Worldwide, head and neck malignancies account for approximately 4% of the cancer patients, with 550,000 new cases and 380,000 deaths annually, making HNT the sixth most common cancer, globally (1,2). In 2016, the global 5-year prevalence rates for cancers of lip and oral cavity, nasopharynx, larynx, and other pharynx were 13.5, 4.4, 8.5, and 6.0 per 100,000, respectively (3). Notably, the highest age-standardized incidence rate for nasopharyngeal HNT are reported in the Asia-Pacific region, particularly in Indonesia, Micronesia and Eastern Asia, especially Southern China (3). Greater than 90% of HNT are squamous cell carcinomas (SCC) followed by lymphomas (4). While radiation therapy and surgical resection can achieve favorable results for early stage head and neck SCC, the odds are less favorable for advanced stages.

Biomedical imaging has a substantial role in diagnosis, and initial staging of HNT, as well as monitoring the treatment response and detection of local recurrence or distant metastasis. Nevertheless, accurate initial risk stratification, and predictive biomarkers of molecular subtypes are needed to improve patient care and pave the road for personalized treatment options in era of precision medicine (5). Noninvasive imaging biomarkers can play a crucial role in assessment of the entire tumor sample and can be repeated longitudinally to monitor treatment response, and guide decision-making process. This review focuses on the promises of quantitative diffusion MRI in assessment of patients with HNT.

Diffusion weighted imaging (DWI)

Diffusion MRI can assess cellular density and cytoarchitecture based on the measurement of water diffusivity. For the purpose of diffusion MRI, two strong opposed gradient pulses are applied along a certain diffusion direction, with the first diffusion-sensitizing gradient dephasing the water molecules, and the second

gradient completely rephasing the stationary molecules. In living tissues, the motion of water molecules is "restricted" by interactions with other macromolecules, and cell membranes, which is translated into a signal intensity decrease. Such a signal intensity decrease depends on the degree of molecule movement and respective speed along the diffusion-sensitizing gradient, as well as the strength of the gradient itself, and the duration of the diffusion-encoding gradients (b-value) (6,7). Thus, diffusion abnormalities of water molecules, captured by DWI, can reflect changes of tissue organization and impediments in water molecule motion at a cellular level.

The diffusion-sensitizing effects from the gradients are indicated by the b-value (s/mm^2), which represents the duration between gradient pulses that water molecules are allowed to diffuse before the distance is measured (6). The b-values are defined by the gradient strength, duration, and the time interval between the gradient pulses (8). Mono- and biexponential models can be used for quantifying the diffusion (9).

For monoexponential models, the apparent diffusion coefficient (ADC, expressed in mm^2/s) is calculated by means of the least-squares fit of signal intensities from images acquired with different b-values, where S(b) and S0 are the signal intensities on images with and without diffusion weighting, respectively, b is the gradient factor in s/mm^2, and D is the ADC:

$$\frac{S_{(b)}}{S_{(0)}}=e^{-b.D}$$

However, while fast-moving water molecules quickly lose their phase coherence and signal intensity, even at low b-values, slow-moving molecules will retain high signal intensities far into the higher ranges of b-values (10). Thus, low b-value (0 up to 200 s/mm^2) diffusion images reflect microvascularity and tissue perfusion; whereas, high b-value (800 or 1,000 s/mm^2) diffusion images represent tissue cellularity (11). Thus, mono-exponential ADC values cannot separate pure molecular diffusion from motion of water molecules in the capillary network; whereas, multi-exponential models using several b-values are more suitable for accurate quantification of diffusion without perfusion contamination (10,11).

The intravoxel incoherent motion (IVIM) and diffusion kurtosis imaging (DKI) assess the water molecule diffusivity with multiple b-values. The IVIM can distinguish pure molecular diffusion from motion of water molecules in the capillary network base on low b-value (<200 s/mm^2) and high b-value (>200 s/mm^2) diffusion image acquisitions (12,13). The relationship between signal intensities and multiple b-values can distinguish the real diffusion of water molecules (D) from the contribution of perfusion to the signal decay (D*, pseudodiffusion), and the contribution of perfusion to the diffusion signal (*f*, vascular volume fraction). For biexponential models, the metrics related to IVIM for each b-value are calculated using (12):

$$\frac{S_{(b)}}{S_{(0)}}=f\cdot e^{-b.D^*}+(1-f)e^{-b.D}$$

In DKI, multiple b-values are applied to assess the extent to which the diffusion pattern of water molecules deviates from a perfect Gaussian curve that is assumed when calculating monoexponential ADC values (14):

$$\frac{S_{(b)}}{S_{(0)}}=f\cdot e^{-b.D^*}+(1-f)e^{(-b.D+\frac{1}{6}b^2D^2k)}$$

There are limited number of studies examining the optimal combination and number of b-values for IVIM. Lemke *et al.* suggested that at least 10 b-values should be used for fitting the IVIM signal with assigning more weight to low b-value acquisitions (0 to 100 s/mm^2) (15). However, Gurney-Champion *et al.* found that 7 b-values would be enough for abdominal imaging purposes, and only 3 b-values for imaging of the liver (16). Sasaki *et al.* compared the traditional least-squares method with 11 b-values versus a geometric approach requiring only 3 b-values for differentiating between HNTs (10), and found that despite higher D values and lower *f* values, the geometric approach had similar accuracy to the least-squares method in differentiation of lymphomas from SCC, as well as different types of salivary gland tumors from each other (10). *Table 1* summarizes the IVIM metrics used in evaluation of HNT (10,17-29). Noij *et al.* recommend inclusion of at least 4 b-values below 200 s/mm^2 for optimal fit estimation of perfusion-related parameters (4).

Regarding the fit model used for estimation of diffusion parameters, the majority of studies listed in *Table 1* have applied bi-exponential with Levenberg Marquard algorithm for the IVIM fit—with the exception of Dikaios *et al.* applying maximum probability model nonlinear regression model (17), Ding *et al.* applying non-linear least-squares and simplified linear fit (18), and Sasaki *et al.* applying both traditional least-squares method and geometric approach (10), as mentioned above.

Table 1 Intravoxel incoherent motion (IVIM) acquisition details

Author	T	TR (ms)	TE (ms)	Slice (mm)	b values (s/mm^2)
Dikaios *et al.* (17)	1.5	8,700	88	4	0, 50, 100, 300, 600, 1,000
Ding *et al.* (18)	3	3,600	100	3.5	0, 20, 40, 60,80, 100, 120, 150, 200, 400, 600, 800
Guo *et al.* (19)	3	2,500	79	5	0, 10, 20, 30, 50, 70, 100, 150, 200, 400, 800, 1,000
Hauser *et al.* (20)	3	1,300	50	3	0, 50, 100, 150, 200, 250, 700, 800
Hejduk *et al.* (17)	1.5	3,200	88	4	0, 50, 150, 300, 500, 750, 1,000, 1,200
Lai *et al.* (21)	3	7,996	43	3	0, 10, 20, 30, 40, 60, 100, 120, 160, 200, 300, 500, 1,000
Lu *et al.* (22)	1.5	4,000	90	6-8	0, 13, 17, 23, 30, 40, 53, 70, 92, 122, 161, 212, 280, 369, 488, 644, 850
Marzi *et al.* (23)	1.5	4,500	77	4	0, 25, 50, 75, 100, 150, 300, 500, 800
Sakamoto *et al.* (24)	1.5	3,000	101	4-5	0, 20, 40, 60, 80, 100, 150, 200, 500, 1,000
Sasaki *et al.* (10)	1.5	1,625	81	4	0, 10, 20, 30, 50, 80, 100, 200, 300, 400, 800
Sumi *et al.* (25)	1.5	1,625	81	4	0, 10, 20, 30, 50, 80, 100, 200, 300, 400, 800
Xiao *et al.* (26)	3	4,495	69	5	0, 10, 20, 30, 40, 50, 100, 150, 200, 350, 500, 650, 800, 1,000
Xiao-ping *et al.* (27)	1.5	4,225	106	5	0, 50, 80, 100, 150, 200, 400, 600, 800, 1,000
Yu *et al.* (28)	1.5	4,225	106	5	0, 50, 80, 100, 150, 200, 400, 600, 800, 1,000
Zhang *et al.* (29)	3	3,000	58	4	0, 10, 20, 30, 50, 80, 100, 150, 200, 300, 400, 600, 800

Slice, slice thickness in mm; T, Magnet field strength in Tesla; TE, time to echo in ms; TR, repeat time in ms.

For routine head and neck DWI scan in clinical practice, single shot (SS) echo planar imaging (EPI) technique is most commonly used (30). The SS-EPI is relatively insensitive to motion but prone to susceptibility artifacts, chemical shift, and geometric distortion, with a limited spatial resolution and relatively thick sections (31). Compared to SS-EPI, turbo spin echo technique requires longer echo time but less susceptibility artifacts and better spatial resolution (32). The SS version of turbo spin echo is a diffusion-weighted HASTE sequence with lower sensitivity to motion and susceptibility artifacts as well as geometric distortion compared to the EPI sequence (33). Overall, the non-echo planar diffusion can improve image quality with lower susceptibility artifacts and higher spatial resolution; however, they non-EPI DWI scans take longer to acquire (which can introduce more motions) and have lower signal-to-noise ratio, which requires multiple averages and prolongs scanning time (11). Hence, non-echo planar diffusion is usually reserved for problem solving rather than routine clinical practice.

Differentiation of head and neck cancers

Tissue sampling and pathologic examination remain the gold standard for assessing the malignant nature of a head and neck lesion; however, tissue biopsy is not without risk, and cannot examine the whole lesion. Multiple studies have demonstrated the ability and reliability of quantitative diffusion MRI in distinction of benign from malignant lesions and differentiation of different HNT (34). Although there are many factors affecting the ADC, it is generally accepted that the ADC of a given voxel is inversely proportional to the cellularity of the tissue included in that voxel, and malignant tumors likely demonstrate lower ADC values compared with benign lesions owing to their relatively higher cellularity.

Some authors have focused on distinction of malignant from benign lesions using average ADC values. Using a

1.5 T magnet with split acquisition of fast spin-echo signals (SPLICE) and b-values of 0 and 771 s/mm^2, Sakamoto *et al.* have applied averaged ADC for differentiation of 16 cysts, 32 benign tumors, and 19 malignant tumors in head and neck (35). They found cysts to have higher mean ADC (2.41±0.48 ×10^{-3} mm^2/s), compared to benign (1.48±0.62 ×10^{-3} mm^2/s), and malignant (1.23±0.45 ×10^{-3} mm^2/s) tumors (P<0.001); and an ADC value of >2.10 ×10^{-3} mm^2/s could identify cysts, with 90% accuracy, 94% sensitivity, and 88% specificity (35). However, there was no significant difference between the ADC values of benign and malignant tumors (P=0.246) (35). Notably, when the same group applied (IVIM) technique and half-Fourier single-shot turbo spin-echo (HASTE) diffusion MRI for distinction of 23 malignant and 10 benign head and neck lesions, they found significantly lower average ADC (0.993±0.157 ×10^{-3} mm^2/s) and D values (0.813±0.172 ×10^{-3} mm^2/s) in malignant tumors compared to benign lesions (1.33±0.212 and 1.16±0.238 ×10^{-3} mm^2/s, respectively) (24). Using a 3 T scanner with a single-shot spin-echo EPI and b-values of 0 and 1,000 s/mm^2, Srinivasan *et al.* also found a lower average ADC (1.071±0.293 ×10^{-3} mm^2/s) in 16 malignant HNT compared to 17 benign lesions (1.505±0.487 ×10^{-3} mm^2/s) with a P=0.004 (36).

Quantitative diffusion MRI can also help with differentiation of various histopathologies; for example, differentiation of various salivary gland lesions. Accurate preoperative differentiation of a salivary gland tumor is important in establishing the surgical indication and preoperative planning. Fine needle aspiration cytology, which is currently used for diagnosis of a parotid gland lesion, can achieve 81% to 98% accuracy (37). While the majority of salivary gland tumors are benign (either pleomorphic adenomas or Warthin tumors), some can be malignant (adenoid cystic carcinoma or mucoepidermoid carcinoma). Prior studies suggest that pleomorphic adenomas (which contain myxoid tissue) have the highest ADC; whereas, Warthin tumors (which contain lymphoid tissue) have the lowest ADC values (38).

Using a 1.5 T scanner, with modified Sensitivity Encoding algorithm (SENSE) methods and b-values of 0, 500, and 1,000 s/mm^2, Habermann *et al.* found significantly different average ADC between pleomorphic adenomas (2.14±0.11 ×10^{-3} mm^2/s), Warthin tumors (0.85±0.1 ×10^{-3} mm^2/s), and mucoepidermoid carcinomas (1.04±0.3 ×10^{-3} mm^2/s) in 45 patients with parotid tumor (P<0.001) (39). Ikeda *et al.* have also shown that mean ADC of Warthin tumors (0.96±0.13 ×10^{-3} mm^2/s) was significantly lower (P<0.01) than that of malignant salivary gland tumors (1.19±0.19 ×10^{-3} mm^2/s) (40). And Kikuchi *et al.* proposed an average ≥1.5 ×10^{-3} mm^2/s for distinction of parotid pleomorphic adenomas from other tumors (41).

Quantitative diffusion MRI can also help with differentiation between benign and malignant thyroid nodules, with latter showing lower average ADC values (6). Using a 1.5 T scanner with SS EPI acquisition and b-values of 0, 250, and 500 s/mm^2, Razek *et al.* showed that mean ADC value of malignant solitary thyroid nodules (0.73±0.19 ×10^{-3} mm^2/s) was significantly lower than benign nodules (1.8±0.27 ×10^{-3} mm^2/s, P=0.0001) (42). They suggested that an ADC value of <0.98 ×10^{-3} mm^2/s could identify malignant thyroid nodules with an accuracy of 98.9%, sensitivity of 97.5%, and specificity of 91.7%. Using a 1.5 T scanner with SS EPI and b-values of 0 and 1,000 s/mm^2, Erdem *et al.* also found lower average ADC in malignant thyroid nodule (0.695±0.312 ×10^{-3} mm^2/s) compared to benign nodules (2.745±0.601 ×10^{-3} mm^2/s, P<0.001) (43). Similarly, using a 1.5 T scanner with SS EPI and b-values of 100, 200 and 300 s/mm^2, Bozgeyik *et al.* showed that malignant thyroid nodules had lower mean ADC (0.96±0.65, 0.56±0.43 and 0.30±0.20 ×10^{-3} mm^2/s) compared to benign lesions (3.06±0.71, 1.80±0.60, and 1.15±0.43 ×10^{-3} mm^2/s), respectively (44). They reported receiver operatic characteristic (ROC) areas under the curve (AUC) and cutoff values of 0.997 and 1.45 ×10^{-3} mm^2/s; 1.00 and 0.65 ×10^{-3} mm^2/s; and 0.884 and 0.36 ×10^{-3} mm^2/s, for differentiating benign from malignant thyroid nodules at 100, 200 and 300 s/mm^2 b-values, respectively (44).

Reactive versus metastatic lymphadenopathy

Nodal metastases herald poor prognosis in patients with head and neck cancer, and their detection is important for treatment planning, extent of radiation treatment field, or surgical neck dissection method. Currently, the differentiation of metastatic lymphadenopathy primarily relies on size criteria; however, nonenlarged nodes may harbor malignancy, and reactive nodes may be prominently enlarged (45). In addition, in patients presenting with suspicious cervical lymphadenopathy, differentiation of lymphoma from metastatic lymph nodes of unknown primary cancer site can be challenging. Distinction of metastatic from lymphomatous lymphadenopathy is particularly crucial since they demand radically different treatment approaches. Quantitative diffusion MRI can help with distinction of these entities.

Table 2 Differentiation of benign, metastatic and lymphomatous lymph nodes in head and neck

Study	T	b values (s/mm^2)	Average ADC (×10^{-3} mm^2/s)		
			Benign	Metastatic	Lymphoma
Abdel Razek *et al.* (46)	1.5	0, 1,000	1.64±0.16	1.09±0.11	0.97±0.27
Holzapfel *et al.* (47)	1.5	0, 500, 1,000	1.24±0.16	0.78±0.09	0.64±0.09
Sumi *et al.* (48)	1.5	0, 500, 1,000	0.302±0.062	0.410±0.105	0.223±0.056
Zhang *et al.* (49)	1.5	0, 800	1.01±0.11	0.93±0.16	0.64±0.13

Except Sumi *et al.* (who reported a lower average ADC in benign lymphadenopathy compared to metastatic lesions), other studies reported higher average ADC in benign lymph nodes compared to metastatic lesions. All studies reported higher average ADC in metastatic lesions compared to lymphoma. ADC, apparent diffusion coefficient; T, magnet field strength in Tesla.

Table 2 summarizes the results of studies comparing non-malignant, metastatic, and lymphomatous lymph nodes in head and neck (46-49). Except for Sumi *et al.* who found a lower average ADC in benign lymphadenopathy compared to metastatic lesions (48), other studies reported higher average ADC in benign lymph nodes compared to metastatic lesions (46,47,49); and all studies reported higher average ADC in metastatic lesions compared to lymphoma (*Table 2*). On the other hand, Hejduk *et al.* found not significant difference in the mean values of D, D*, and *f* between metastatic and non-metastatic lymph nodes (50).

Abdel Razek *et al.* suggested an average ADC value of 1.38 ×10^{-3} mm^2/s as a threshold value for differentiating malignant from benign lymph nodes, with an accuracy of 96%, sensitivity of 98%, and specificity of 88% (46). Holzapfel *et al.* suggested an average ADC value of 1.02 ×10^{-3} mm^2/s as a threshold value for differentiating malignant from benign lymph nodes, with an accuracy of 94.3%, a sensitivity of 100%, and a specificity of 87.0% (47). For distinction of lymphomatous from metastatic lymphadenopathy, Zhang *et al.* suggested an average ADC value of 0.77 ×10^{-3} mm^2/s as a threshold value, with an AUC of 0.94, a sensitivity of 83%, and a specificity of 89% (49).

Applying IVIM (*Table 1*), Yu *et al.* compared the diffusion characteristics of nasopharyngeal carcinoma with head and neck lymphoma (28), and found that the primary lesions in nasopharyngeal carcinoma had higher ADC, D, D*, *f*D* and *f* value compared to lymphomas. They proposed an ADC value threshold of 0.761 ×10^{-3} mm^2/s (0.781 AUC, 93.90% sensitivity, and 55.00% specificity); a D value threshold of 0.66 ×10 mm/s (0.802 AUC, 54.88% sensitivity, and 100.00% specificity); D* value threshold of 7.89 ×10 mm/s (0.898 AUC, 82.93% sensitivity, and 85.00% specificity); and *f* value threshold of 0.29 (0.644 AUC, 41.46% sensitivity, and 95.00 specificity) for distinction of nasopharyngeal carcinoma from lymphoma (28).

Prediction of human papilloma virus (HPV) status

HPV has recently emerged as a major causative risk factor for a subset of oropharyngeal SCC. The HPV-positive oropharyngeal SCC is related to sexual behavior; whereas, HPV-negative cancer is strongly associated with tobacco and alcohol use (51). The HPV-positive oropharyngeal SCC also has a different biology, and is associated with a better prognosis than HPV-negative SCC (52). Thus, in the updated eighth edition of the Cancer Staging Manual of the American Joint Committee on Cancer implemented in January 2018, the HPV-positive oropharyngeal SCC is staged separately from HPV-negative type (51).

The classical description of HPV-positive oropharyngeal cancer histology is non-keratinizing and basaloid differentiated SCC as opposed to keratinizing and poorly differentiated form which is commonly seen with HPV-negative forms (52). This histopathological difference has perhaps lent itself to the difference in ADC characteristics of HPV-positive versus HPV-negative oropharyngeal SCC (53-57). Recent studies have generally reported a lower mean ADC in primary lesion of HPV-positive oropharyngeal SCC compared to the HPV-negative form (*Table 3*). Chan *et al.* have also shown an ROC AUC of 0.8467 for the mean ADC values in primary oropharyngeal SCC for distinction of HPV status (53). Nakahira *et al.* has proposed a mean ADC cut-off value of 1.027 ×10^{-3} mm^2/s for prediction of HPV status in oropharyngeal SCC with 80.77% accuracy, 83.33% sensitivity, and 78.57% specificity (56).

If validated and standardized, the quantitative ADC

Table 3 The average ADC of primary oropharyngeal SCC based on HPV status

Study	T	b values (s/mm^2)	Average ADC (×10^{-3} mm^2/s)	
			HPV-positive	HPV-negative
Chan *et al.* (53)	1.5/3	0, 1,000	0.975±0.168	1.225±0.242
de Perrot *et al.* (54)	1.5/3	0, 1,000	1.014±0.178	1.184±0.168
Driessen *et al.* (55)	1.5	0, 150, 800	1.327±0.267	1.740±0.338
Nakahira *et al.* (56)	1.5	0, 1,000	1.218±0.214	0.987±0.156
Wong *et al.* (57)	1.5	0, 50, 400, 800	1.15±0.18	1.16±0.14

All studies except Wong *et al.* reported significantly lower average ADC in HPV-positive oropharyngeal SCC compared to HPV-negative form. ADC, apparent diffusion coefficient; T, magnet field strength in Tesla; SCC, squamous cell carcinoma; HPV, human papilloma virus.

analysis can offer a non-invasive imaging biomarker for HPV status of oropharyngeal SCC. This is particularly important since distinction of HPV status dictates the cancer staging and treatment strategy in patients with oropharyngeal SCC (51).

Histopathological and molecular biomarker correlates of ADC

In addition to prediction of HPV status, some studies have shown the application of quantitative diffusion MRI in evaluation of HNT microstructure and histopathological characteristics. Correlation studies have shown the association of quantitative ADC analysis with molecular biomarkers and histopathological findings in patient with SCC of head and neck.

Using a 3 T scanner with EPI DWI sequence and b-values of 0 and 800 s/mm^2, Surov *et al.* reported the associations of combined PET and ADC parameters with histopathological features in head and neck SCC (58). They examined the correlation between ADC and PET standard uptake value (SUV) with expression of Ki-67, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), tumor suppressor gene protein p53, hypoxia-inducible factor (HIF)-1α, and cell count (58). There was a significant correlation between cellularity with SUV-max/ADC-min; moreover, in grade 1 and 2 tumors, SUV-max/ADC-min correlated with HIF-1α expression. In separate studies, Surov *et al.* also examined the ADC histogram correlates of different molecular biomarkers in head and neck SCC (59,60). In grade 1 and 2 tumors, the ADC mode correlated with Ki-67; whereas, in grade 3 tumors, Ki-67 correlated with all ADC parameters except ADC mode. Cellularity correlated with all ADC parameters except ADC-max; and total nucleic had inverse correlation with mean, median, minimum, 25th, and 90th percentile of ADC (59,60).

Using EPI DWI sequence with b-values of 0 and 800 s/mm^2 (with undetermined magnet field strength), Meyer *et al.* also examined the ADC histogram correlates of Hif1-alpha, VEGF, EGFR, p53, p16, and Her 2 expression in patients with head and neck SCC (61). They found significant correlation between ADC-max with p53 expression and ADC mode with Her 2 expression (61). The p16 positive and p16 negative forms showed distinctive correlations between ADC histogram metrics with Hif1-alpha, P53, and VEGF expression (61).

These results promise a new role for quantitative diffusion metrics as imaging biomarkers for prediction of molecular biomarkers in patients with HNT. This is particularly important as we move toward application of personalized treatment strategies with chemotherapy agents targeting specific cellular receptors.

Risk stratification and prognostication

Many authors have examined the application of pretreatment ADC quantification for prediction of outcome in patients with head and neck SCC (62-68). The majority of these studies suggest that higher pretreatment ADC values in the primary SCC lesion are predictive of poor local control and treatment response (*Table 4*). Ohnishi *et al.* found that patients with an ADC value >0.79 ×10^{-3} mm^2/s had a significantly lower local control rate (44%) than those with a low ADC value (100%, P=0.0019) (64). Ng *et al.* suggested an ADC value >1.14 ×10^{-3} mm^2/s (P=0.003) as an independent prognostic factor for 3-year focal recurrence (66). Srinivasan *et al.*

Table 4 Prognostic application of the pretreatment ADC in primary head and neck SCC lesion

Study	T	b values (s/mm^2)	Main findings
Chawla *et al.* (68)	1.5	0, 500, 1,000	Higher ADC values in non-responders
Hatakenaka *et al.* (63)	1.5	0, 100, 200, 300, 500, 750, 1,000	High ADC (and tumor volume) correlate with local failure after radiotherapy
Kim *et al.* (62)	1.5/3	0, 500, 1,000	Higher ADC value in partial responders compared to complete responders
King *et al.* (67)	1.5	0, 100, 200, 300, 400, 500	Pretreatment ADC parameters showed no correlation with local failure
Lambrecht *et al.* (65)	1.5	0, 50, 100, 500, 750, 1,000	ADC value from high b-values (500–1,000) independent prognostic factor
Nakajo *et al.* (69)	1.5	0, 800	Low ADC predictive of poor 2-year disease free survival
Ng *et al.* (66)	3	0, 800	High ADC value was poor prognostic factor for 3-year focal control rate
Ohnishi *et al.* (64)	1.5	0, 300, 1,000	High ADC values in patients with lower local control
Srinivasan *et al.* (70)	3	0, 800	Lower ADC associated with better outcome at 2 years

T, magnet field strength in Tesla; SCC, squamous cell carcinoma; ADC, apparent diffusion coefficient.

found that an ADC >1.15 ×10^{-3} mm^2/s is associated with poor outcome after chemoradiation at 2-year follow-up (70). Notably, Lambrecht *et al.* found that primary lesion ADC values obtained with high b-values (500, 750 and 1,000 s/mm^2) but not those with low b-values (0, 50 and 100 s/mm^2) were predictive of treatment failure (65). On the other hand, Nakajo *et al.* found that low ADC values of primary lesion are associated with lower rate of 2-year disease free survival (69). Noij *et al.* also reported that lymph node ADC values at b value of 1,000 s/mm^2 were predictive of outcome, whereas primary lesion ADC values were not (71).

The IVIM studies also suggest that lower initial ADC and D values are predictive of positive response to treatment. Marzi *et al.* reported that head and neck SCC patients with regional disease control showed significantly lower pre-treatment D values compared to those with treatment failure (72). In separate studies, Guo *et al.* and Xiao-ping *et al.* found lower pretreatment ADC value, and D value in patients with response to therapy (19,27). Similarly, Xiao *et al.* reported lower baseline D value and higher DeltaD3, DeltaD21, DeltaD3*, DeltaD21*, and Deltaf21 in HNT lesions with positive response to treatment (26). In a cohort of HPV-positive oropharyngeal SCC, Ding *et al.* also found lower pretreatment ADC value, and D in lesions with complete response (18). However, Hauser *et al.* found significantly higher initial *f* value in patients with locoregional failure while the initial diffusion coefficient D was not significantly different between those with locoregional failure versus control (20).

Histopathological and molecular features such as high stromal content, low cellularity (lower proliferation), micronecrosis and negative HPV status are associated with resistance to treatment and poor outcome in patients with head and neck SCC (54,55,73,74). These prognostic characteristics are also associated with higher ADC and likely contribute to association of pretreatment high ADC (and D) values with poor outcome in patients with head and neck SCC. In the future, standardized quantitative diffusion MR metrics may be included in prognostic staging schemes of HNT to improve risk stratification and treatment planning.

Treatment response monitoring

After the start of chemotherapy and/or radiation therapy, it is desirable to monitor treatment response, and tailor further therapy to the individual patient. Quantitative diffusion MRI can evaluate the ADC or D value changes during the treatment, and predict therapy response. Notably, King *et al.* found no correlation between pretreatment ADC parameters with local failure (*Table 4*), while primary head and neck SCC with local failure had a lower percentage raise in the mean ADC, higher skewness, and higher kurtosis during treatment, compared with those

Table 5 Distinction of the posttreatment recurrent or residual tumor from fibrosis/granulation tissue based on average ADC in head and neck SCC

Study*	b values (s/mm^2)	ADC threshold**	Accuracy	Sensitivity	Specificity
Abdel Razek *et al.* (81)	0, 1,000	1.4 ×10^{-3} mm^2/s	87%	84%	90%
King *et al.* (80)	0, 100, 200, 300, 400, 500	1.3 ×10^{-3} mm^2/s	71%	45%	100%
Vandecaveye *et al.* (82)	0, 1,000	1.3 ×10^{-3} mm^2/s	95.5%	94.6%	95.9

Above studies have shown lower average ADC in residual/recurrent cancer compared to posttreatment benign tissue. *, all studies used 1.5 T scanners; **, average ADC of the posttreatment tissue. SCC, squamous cell carcinoma; ADC, apparent diffusion coefficient.

with local control (67).

The cumulative studies have reported a rise in ADC values of primary head and neck SCC tumors in the first few weeks after the start of treatment (62,67,69,75). These studies suggest that a smaller percentage rise (<14–25%) in the mean ADC values within the first to third weeks after the therapy initiation is predictive of treatment failure (62,67,69,75,76). For example, using a 1.5 T scanner and SS EPI sequence with b-values of 0, 90 and 800 s/mm^2, Matoba *et al.* found that fractional change in primary lesion and nodal ADC at pretreatment and 3 weeks after the start of treatment along with primary tumor volume, nodal volume, nodal stage, and tumor location had significant effect on locoregional failure and locoregional control (75). Primary lesion ADC factional change greater than 0.24 was predictive of locoregional control in their cohort (75). On the other hand, using 1.5 T scanner with spine echo EPI sequence and b-values of 50, 400 and 800 s/mm^2, Wong *et al.* found a tendency toward a larger but statistically nonsignificant increase in ADC values after the first and second rounds of induction chemotherapy (57).

Also in an IVIM study by Xiao-ping *et al.*, the percentage change of D value >25.25% within 20 days of induction treatment had an AUC of 0.859, sensitivity of 94.4%, and specificity of 76.5% to predict response to treatment as opposed to pretreatment ADC threshold of >0.879 ×10^{-3} mm^2/s with an AUC of 0.758, sensitivity of 76.5%, and specificity of 72.2%; and pretreatment D threshold of >0.711 ×10^{-3} mm^2/s with an AUC of 0.765, sensitivity of 64.7%, and specificity of 72.2% (27). Similarly, Paudyal *et al.* found that changes in D (within 3 weeks of treatment) was significantly different between head and neck SCC patients with complete response compared to incomplete responders (77). They could also identify subcategories of HPV-positive head and neck SCC patients with greater sensitivity to radiotherapy (77). On the other hand, Marzi *et al.* found that at mid-treatment time point, the patients with regional failure showed significantly higher D values, exhibited larger percent reductions in *f*, and product D* × *f* from the baseline (72).

Evaluation of ADC fractional changes in head and neck SCC is promising since the ratio changes could be more reproducible across different scanners and techniques compared to absolute ADC values. However, it should be noted that the optimal timing interval for early intra-treatment assessment of ADC values needs to be established given that development of post treatment mature scar tissues may "falsely" decrease ADC in patients with positive response to treatment (7,78). In the future prospective trials, serial quantitative assessment of diffusion MRI scans can be applied for close monitoring of treatment response in the early therapy phase and to guide personalized treatment decisions in patients with HNT.

Post treatment changes

Distinction of posttreatment fibrosis and granulation tissue from residual or recurrent tumor can be challenging (79). Quantitative analysis of diffusion MRI metrics can help distinguish between residual/recurrent malignant tissue and benign posttreatment changes similar to its application for distinction of primary malignant and benign lesions. Prior studies suggest that residual head and neck SCC tends to have lower average ADC compared to benign posttreatment tissue with optimal average ADC threshold of 1.3 to 1.4 ×10^{-3} mm^2/s for distinction of residual tumor (80-82), yielding 71–95.5% accuracy, 45–94.6% sensitivity, and 90–100% specificity (*Table 5*). These findings are likely reflective of difference in cellularity of malignant tissue compared to fibrotic posttreatment changes.

Applying IVIM, Lai *et al.* compared newly diagnosed nasopharyngeal carcinoma with biopsy-proven post-chemoradiation fibrosis (83). They found that D and *f* were significantly lower in nasopharyngeal carcinoma than in

posttreatment fibrosis; whereas, D* was significantly higher in tumoral tissue compares to fibrosis (83). Their proposed cut-off values and corresponding accuracy, sensitivity, and specificity were: D of 1.062 $\times 10^{-3}$ mm^2/s (100%, 100%, and 100%); *f* of 0.132 (78.3%, 66.0%, 100%); and D* of 85.283 $\times 10^{-3}$ mm^2/s (96.4%, 100%, 90.7%), respectively (83).

Challenges and limitations

Despite the proven value of quantitative diffusion MRI metrics for diagnosis, differentiation, and prognostication of HNT, its integration into clinical practice remains limited. The most obvious limitation in application of quantitative measures is the variety of b-values, pulse sequences, field strength, and imaging protocols that can influence ADC quantification. It will be cumbersome to validate ADC values for clinical use while different machines and imaging protocols yield various results. Lesion segmentation and selection of region of interest for quantification are another source of heterogeneity in reported results; for example, the ADC values of tumor lesion or metastatic lymph node are not easily comparable between different studies, when they consist of both highly cellular malignant component and poorly cellular necrotic portions. Image quality can also be an issue, as Schakel *et al.* have also reported severe distortions of DWI scans—up to centimeters—that can affect tumor volume measurements (84). Notably, Vidiri *et al.* suggested that reduced field of view can increase the accuracy of ADC value measurements (85).

Summary

Despite heterogeneity of prior studies in terms of applied b-values, imaging protocols, outcome measurements, and reference standards, the quantitative analysis of diffusion MRI proves to offer far ranging potential applications in patients with head and neck cancer. Quantitative analysis of diffusion metrics can help in distinguishing benign from malignant lesions, predicting tumor response to treatment based on pretreatment characteristics, monitoring and assessing the response to treatment as therapy progresses, and surveilling areas of prior treatment to detect posttreatment and recurrent malignant tissue. Overall, malignant lesions tend to have lower ADC values compared to benign lesions. In addition, ADC values can help with differentiation of potential HNT; for example, among salivary gland neoplasms, Warthin tumors have very low ADC values, and pleomorphic adenomas have very high ADC values, with carcinomas demonstrating midrange ADC values. Similarly, ADC values can distinguish lymphomatous, metastatic, and benign lymphadenopathy from each other (in order of increasing average ADC values). In addition, lower average ADC in primary lesion of patients with oropharyngeal SCC is predictive of positive HPV status. With regards to prediction of treatment response, a low ADC or D values in pretreatment lesions, and early interval increase in ADC and D values during the treatment are harbinger of favorable response to therapy and outcome. Eventually, for distinction of post-treatment changes from residual or recurrent head and neck SCC, the malignant tissue tends to demonstrate lower average ADC. Pending development of more standardized methods for image acquisition, quantitative calculation, and tissue segmentation, the diffusion MR metrics can be applied for HNT patients' selection, personalized treatment planning, and response monitoring in prospective trials.

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Footnote

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