

Diffusion in the head and neck: an assessment beyond the anatomy*

Aplicações da técnica de difusão por RM em cabeça e pescoço: um olhar além da anatomia

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Abstract DWI/ADC is a completely non-invasive technique that has been successfully conducted for many years in brain imaging and is currently being studied for the assessment of other organs, such as the abdomen and pelvis and in particular the head and neck structures. Even though DWI and the ADC measurement are able provide tissue information at the cellular level, most imaging centers have not yet adopted them as part of their routine evaluation of the head and neck. DWI has demonstrated usefulness to discriminate specific histological tumor types, especially to differentiate benign solid lesions from malignant masses, to evaluate lymph nodes, particularly to differentiate benign disease from malignancy, to differentiate postradiation changes from residual tumor and potentially to predict therapy success. Moreover DWI seems to be a safer and more affordable method considering the absence of radiation and to the higher cost of FDG-PET to localize tumors and to differentiate benign from malignant masses. Given all these advantages and strengths, DWI will certainly become part of the routine in the MR imaging of the head and neck.

Keywords: Head and neck; Tumors; Squamous cell carcinoma; Diffusion weighted imaging; Apparent diffusion coefficient map; Exponential diffusion weighted imaging.

Resumo DWI é uma técnica totalmente não invasiva que tem sido utilizada com sucesso por muitos anos em imagens do cérebro e recentemente incluída como parte da avaliação de outros sistemas, por exemplo, no abdome e pelve e na cabeça e pescoço. Apesar de a DWI e a medida dos valores de ADC serem capazes de fornecer informações de tipos histológicos específicos de tumores, a maioria dos centros de imagem ainda não os adotaram como parte da rotina na avaliação da cabeça e pescoço. A medida de ADC demonstrou ser útil para discriminar tipos específicos de tumores histológicos, especialmente para diferenciar lesões benignas sólidas de massas malignas, importante na avaliação de linfonodos cervicais, principalmente para diferenciar processos nodais benignos de malignos, para diferenciar as alterações pós-radioterapia de tumor residual e ter uso potencial para prever sucesso terapêutico. Além disso, DWI/ADC parece ser um método mais seguro e mais acessível, considerando a ausência de radiação ionizante e ao maior custo do FDG-PET na localização de tumores e diferenciar massas benignas de malignas. Com todas essas vantagens e potencialidades, DWI/ADC certamente fará parte da rotina na avaliação por imagem da cabeça e pescoço.

Unitermos: Cabeça e pescoço; Tumores; Carcinoma de células escamosas; Difusão; Mapa de ADC; Difusão exponencial.

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INTRODUCTION

Computed tomography (CT) and magnetic resonance imaging (MRI) have undoubtedly contributed to a better understanding of numerous diseases, particularly in the assessment of the central nervous system and head and neck regions^(1,2). As a result, there is a significant amount of responsibility on the shoulders of the diag-

nostic radiologist. Radiology is facing an escalating demand not only for structural imaging but also for physiological information. "Physiological radiology" is often sought out by clinicians, especially in the identification of early stage disease, as well as to follow treatment response and to discriminate tumor from inflammation, radiation changes or inactive scar tissue.

Physiological or functional imaging can be performed with both CT and MRI. Physiological information is also obtained by the use of fluorodeoxyglucose (FDG)-positron emission tomography, a well established method to assess tumoral re-

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sponse particularly in head and neck tumors⁽³⁾. Diffusion-weighted and diffusion-tensor imaging, spectroscopy and perfusion are the main functional modalities available in the MRI “toolbox”⁽⁴⁾. Diffusion-weighted magnetic resonance imaging (DWI) will be main focus of this review.

BROWNIAN MOTION AND DIFFUSION

Diffusion is a well-known phenomenon that occurs in water solutions of all normal living systems, and is responsible for the transport of metabolites into the cells. In 1828, Robert Brown first observed this phenomenon microscopically, perceiving that pollen grains suspended in water move in a rapid, random and irregular pattern. This random displacement of molecules in solution of uniform concentration is known as “Brownian motion”⁽⁵⁾.

In 1905, almost 80 years after Brown’s observations, Albert Einstein, in his PhD thesis and article entitled “*On the motion of small particles suspended in liquids at rest required by the molecular-kinetic theory of heat*”, elaborated further on this random motion⁽⁶⁾. According to Einstein’s theory, water diffusion in living tissues is less than in bulk water, the former occurring in a constrained environment by natural barriers such as wall membranes and by organelles. Water proton diffusion in biological tissues is complex and comprises the diffusion of extracellular water molecules, water protons passing through cell membranes, and intracellular water. Water motion can be disturbed by fibers, intracellular organelles and macromolecules in the tissues. Any change in tissue components, including a change in the ratio of extracellular to intracellular water protons, can alter the diffusion coefficient of the tissue. Hence, tissue DWI signal intensity is dependent on the microstructure and physiologic state of the tissues⁽⁷⁾.

HOW IS DIFFUSION-WEIGHTED MRI ACQUIRED?

Diffusion-weighted MRI (DWI) is highly sensitive to the motion of moving spins (water molecules). DWI is a T2 weighted technique that can be obtained by

the application of two magnetic field gradients in opposing directions about a refocusing T2 pulse. The first gradient will dephase the water molecules, which will then become rephased by the application of the second opposing gradient. Dephasing and loss of signal will occur if the water spins are moving freely. In cases of motionless spins, the water molecules will not dephase significantly and the signal will be maintained. The net signal is proportional to the strength of the gradients, known as “b-value” and to the bulk of water movement. The use of different b-values enhances the signal, which can be measured by using the apparent diffusion coefficient (ADC)⁽⁸⁾.

ROLE OF THE “b-value”

The term “b-value” refers to the strength of the diffusion-sensitizing gradient, which is proportional to the gradient amplitude, the duration of the applied gradient, and the time interval between paired gradients. “b-measure” is measured in seconds per square millimeter (s/mm^2)⁽⁹⁾. The choice of b-values is pivotal in DWI studies of the head. As for other systems, head and neck DWI requires at least three b-values, with maximum b-values at least of 500 s/mm^2 ⁽¹⁰⁾.

THE INSTITUTION PROTOCOL

The Montreal General Hospital head and neck diffusion protocol consists of axial diffusion EPI images, with minimum TE and 4000 TR, field of view of 28, slice thickness of 4 mm. All the images presented in the article were acquired using the aforementioned with b0 and b1000 protocol in a General Electric 1.5 T magnet.

DWI AND ADC IN THE CLINICAL PRACTICE

The clinical importance of DWI and the ADC measurement lies in its ability to provide tissue information at the cellular level. DWI has long been used in the evaluation of the brain in the assessment of acute infarct and hypoxic-ischemic encephalopathy. DWI has proven to be useful in central nervous system infections, particularly for the distinction between bacterial abscess

and necrotic tumor⁽¹¹⁾. Recently, DWI has also become the method of choice for the diagnosis of human prion diseases, especially for sporadic Creutzfeldt-Jakob disease⁽¹²⁾. Furthermore, ADC measurement can be used to improve the accuracy of grading astrocytic tumors^(13,14) and to differentiate solitary brain metastasis from primary glioblastoma multiforme⁽¹⁵⁾.

DWI has also been used in the abdomen, with the liver, kidney and prostate being the most studied organs. Taouli et al. studied liver DWI, reporting higher ADC values in benign hepatic lesions as compared to malignant lesions, with some degree of overlap. Liver cysts have the highest ADC values, followed by hemangiomas. The lowest values are found in HCC and metastases⁽¹⁶⁾. Kidney MRI can be used to assess diffuse renal disease as well as focal renal mass characterization. Namimoto et al. have found that patients with chronic kidney failure demonstrate lower renal ADC values as compared with patients with normal renal function⁽¹⁷⁾. DWI has been also used in the diagnosis of prostate cancer, which shows restricted diffusion as compared to normal prostatic tissue⁽¹⁸⁾.

In the musculoskeletal system DWI has proven to be worthwhile in the evaluation of vertebral fractures, osteomyelitis and tumors. One of the potential advantages of DWI is to facilitate the differentiation between metastatic tumor infiltration of vertebral bone marrow from benign fracture edema⁽¹⁹⁾.

DIFFUSION IN THE HEAD AND NECK

The first major paper on the usefulness of DWI in the head and neck dates back to 2001⁽⁷⁾. Since the release of this publication, there has been an increasing interest in this technology as evidenced by an increase in number of publications (Figure 1).

Most imaging centers have not yet adopted DWI as part of their routine evaluation of the head and neck. Recent publications will certainly encourage the use of this technique. According to Wang et al., DWI may be useful to discriminate specific histological tumor types in the head and neck. Following an evaluation of carcinomas, lymphomas, benign salivary gland

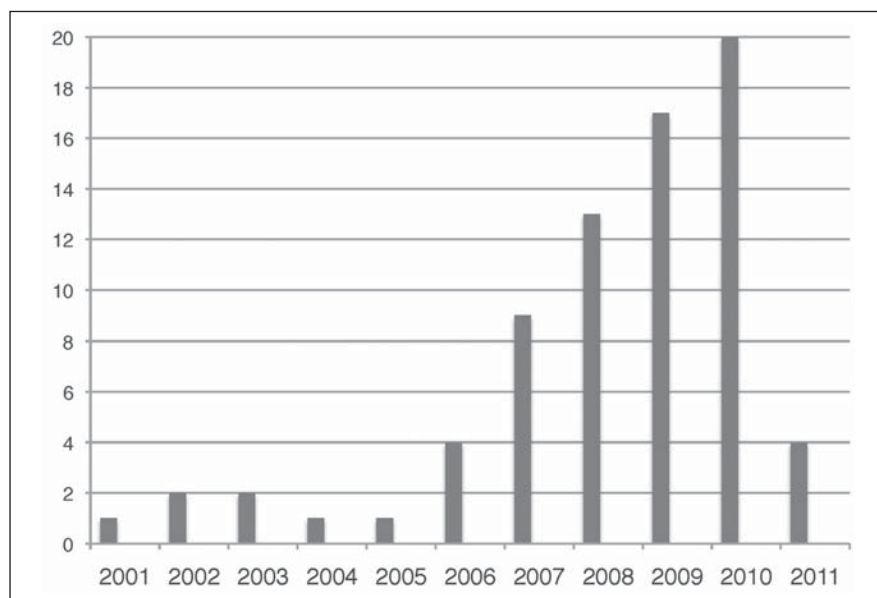


Figure 1. This chart demonstrates the number of publications per year since 2001. These publications were retrieved using the web-based Pubmed search engine with the terms: “diffusion MRI” and “Head and neck tumors”. This literature search retrieved at least 75 major papers. Note the steady growth in the number of publications since 2001. The data regarding 2011 only takes into account the period from January to April 2011.

tumors and cystic lesions of the head and neck, they concluded that ADC can be used to differentiate benign solid lesions from

malignant masses (see Figures 2 and 3). In ascending order, the authors have found that lymphomas demonstrated the lowest

ADC, followed by carcinomas with solid benign lesions demonstrating higher ADC values. A threshold of ADC values of $1.22 \times 10^{-3} \text{ mm}^2/\text{s}$ was used to differentiate benign from malignant tissue. This value was found to be 86% accurate, 84% sensitive and 91% specific to predict malignancy⁽⁷⁾. Lymphomas were the tumors that had lower ADC values according to Maeda et al.⁽²⁰⁾. Friedrich et al. also verified that DWI can be used for tissue characterization, specifically useful to differentiate squamous cell carcinoma (SCCA) from tumor-free tissue⁽²¹⁾. Even though head and neck DWI has been mainly been performed in 1.5 T machines, it can also be evaluated in higher field strengths without significant imaging degradation⁽²²⁾. Employing a 3.0 T magnet, Srinivasan et al. have encountered that SCCA had a mean ADC value of $1.101 \times 10^{-3} \text{ mm}^2/\text{s}$. This was lower than the measurement of the paraspinal and mastication muscles, the thyroid gland, the true vocal cord, the thyroid and the cricoid cartilages and the base of the tongue⁽²³⁾. A summary of the aforementioned studies can be found in Table 1.

Table 1 ADC measurements in head and neck tumors.

Authors	Subjects	MRI strength	b-value (s/mm ²)	Lymphomas	Carcinomas	Bening solid tumors	Benign cystic lesions	Tumor free soft tissue
Wang et al. ⁽⁷⁾	81	1.5 T	0-500-1000	0.66 ± 0.17	1.13 ± 0.43	1.56 ± 0.51	2.05 ± 0.62	N/A
Maeda et al. ⁽²⁰⁾	53	1.5 T	5-1000	0.65 ± 0.09	0.96 ± 0.11	N/A	N/A	N/A
Friedrich et al. ⁽²¹⁾	20	1.5 T	800	N/A	0.64 ± 0.28	N/A	N/A	2.51 ± 0.82
Srinivasan et al. ⁽²²⁾	20	3.0 T	0-800	N/A	1.101 ± 0.214	N/A	N/A	N/A

The ADC values are expressed in $10^{-3} \text{ mm}^2/\text{s}$. N/A, non available.

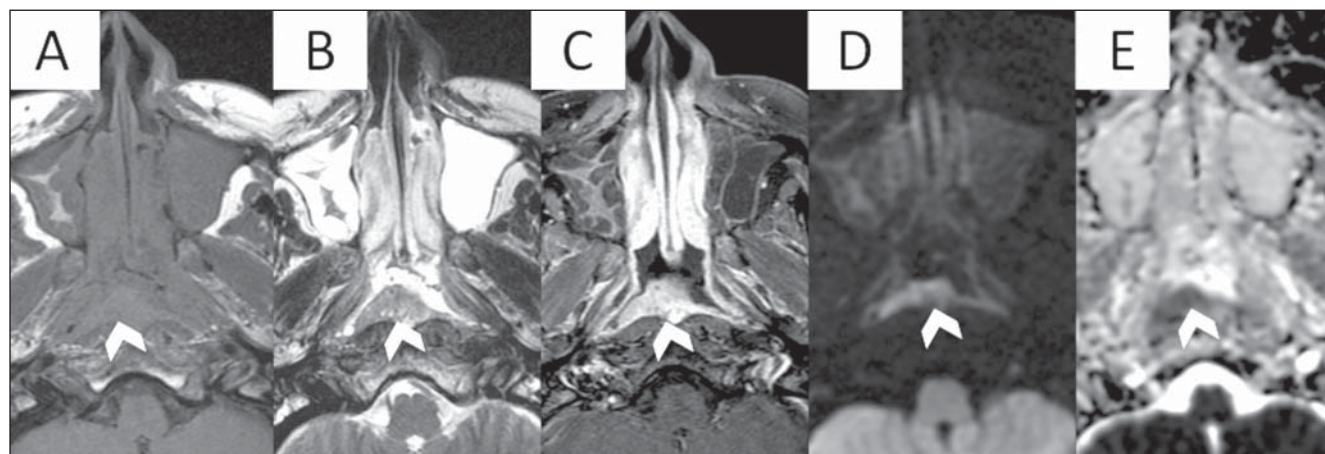


Figure 2. MRI of a 48 year-old patient with pathology proven nasopharyngeal SCCA. Axial T1, T2, T1 post contrast, DWI and ADC map at the level of the nasopharynx are presented from **A** to **E** respectively. Note an enhancing midline mass, which is extending slightly to the right, reaching the right lateral pharyngeal recess (arrowhead). Note the hyperintensity in DWI and low values on the ADC map (ADC measured at $0.93 \times 10^{-3} \text{ mm}^2/\text{s}$).

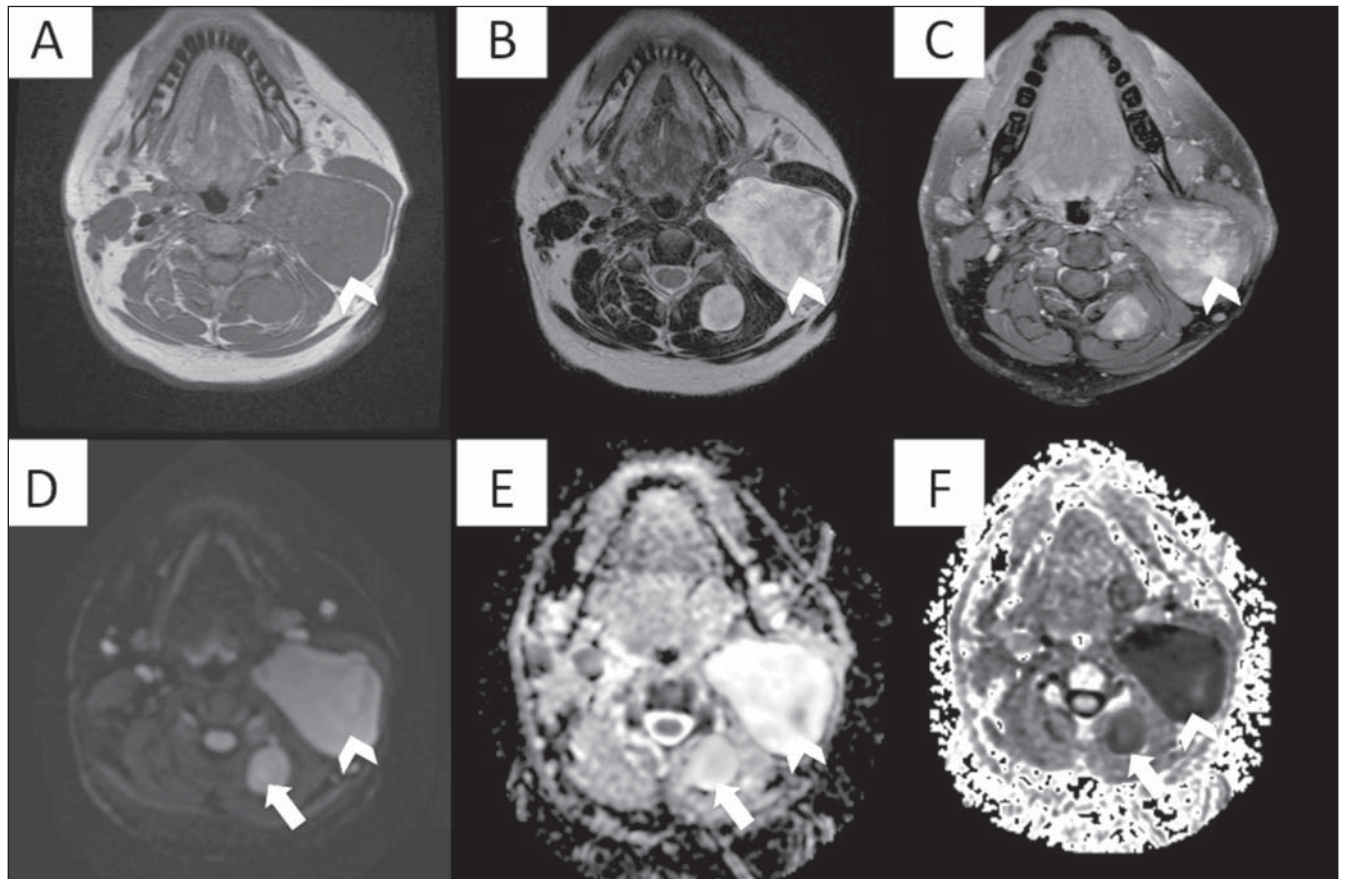


Figure 3. Multiplanar mutisequential MRI of a 24 year-old patient known for neurofibromatosis type 1. Note the large left sided suprahyoid neurofibroma (arrowheads) showing homogeneous T1 hypointensity (A), T2 heterogeneous hyperintensity (B), heterogeneous enhancement (C) and high signal on DWI (D). Note a small similar posterior cervical neurofibroma also on the left with high DWI signal (arrow). Without a companion ADC map, one may think these are potentially malignant. Nevertheless the ADC map reveals striking bright signal which is commonly seen benign lesions. Changes in the ADC values can potentially be used to assess malignant transformation of nerve sheath tumors. The combination of high DWI/ADC signal (D) and (E) and low signal in the exponential DWI (F) represents “T2 shine through effect” rather than real restricted diffusion.

DWI may be also useful in the evaluation of lymph nodes (LN) (see Figures 4 to 6). Holzapfel et al. studied 55 enlarged LN in 35 patients. These enlarged LN were either secondary to malignancy or were benign/reactive. In their study, DWI was able to depict all abnormal LN that were seen in other sequences. According to this study, malignant LN had lower ADC values, with mean of $0.74 \times 10^{-3} \text{ mm}^2/\text{s}$. ADC in LN with SCCA metastasis ranged from $0.62 \times 10^{-3} \text{ mm}^2/\text{s}$ to $0.93 \times 10^{-3} \text{ mm}^2/\text{s}$.

In LN with lymphoma, the mean ADC was $0.64 \pm 0.09 \times 10^{-3} \text{ mm}^2/\text{s}$. The ADC threshold to differentiate benign from malignant LN was $1.02 \times 10^{-3} \text{ mm}^2/\text{s}$ with accuracy of 94.3%, sensitivity of 100%, specificity of 87.0%, positive predictive value of 90.9% and negative predictive value of 100%⁽²³⁾. De Bondt et al. have also found that ADC is useful in the assessment of LN. They have demonstrated that LN metastasis had significantly lower ADC values as compared with benign LN. A cut off

of $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ had good sensitivity and specificity to differentiate them⁽²⁴⁾. According to Sumi et al., DWI successfully discriminated inflammatory from metastatic LN. LN lymphomas had the lowest ADC values⁽²⁵⁾. A summary of these studies can be found in the Table 2.

DWI also improves LN staging, with higher sensitivity and specificity (approx 90%) than conventional CT and MRI⁽²⁶⁾. DWI is particularly superior in detecting subtle metastatic LN. In cases of subcen-

Table 2 Differences in the ADC measurements in lymph nodes from benign and malignant origin according to multiple authors.

Authors	Lymph nodes	MRI strength	b-value (s/mm ²)	Metastatic lymph nodes	Lymphoma	Benign lymph nodes
Holzapfel et al. ⁽²³⁾	35	1.5 T	0-500-1000	0.78 ± 0.09	0.64 ± 0.09	1.24 ± 0.16
De Bondt et al. ⁽²⁴⁾	219	1.5 T	0-1000	0.85 ± 0.119	N/A	1.2 ± 0.24
Sumi et al. ⁽²⁵⁾	55	1.5 T	500-1000	0.410 ± 0.105	0.223 ± 0.056	0.302 ± 0.062

The ADC values are expressed in $10^{-3} \text{ mm}^2/\text{s}$. N/A, non available.

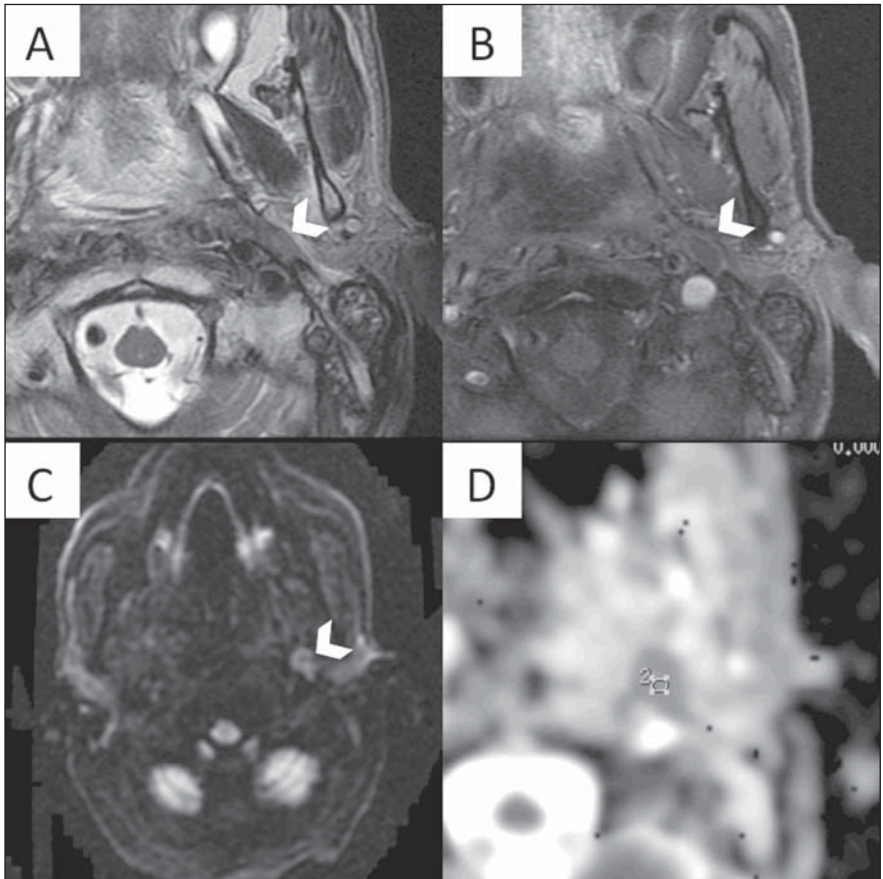


Figure 4. Multiplanar mutisequential MRI of a 69 year-old patient with SCCA of the soft palate, treated with myocutaneous flaps and chemoradiation. There is evidence of a left sided metastatic retropharyngeal lymph node (LN) in the four week post surgery follow-up MRI. **A:** Axial T2WI at the level of the oropharynx. Note an enlarged left retropharyngeal LN, which demonstrates hypointense signal (arrowhead). **B:** Axial T1WI post gadolinium administration. Note the irregular enhancement (mostly peripheral) of the LN. **C:** Axial DWI demonstrates markedly increased signal. **D:** The ADC shows low signal in the lesion. The ADC values were of $0.88 \times 10^{-3} \text{ mm}^2/\text{s}$, suggestive of recurrent metastatic lymph node.

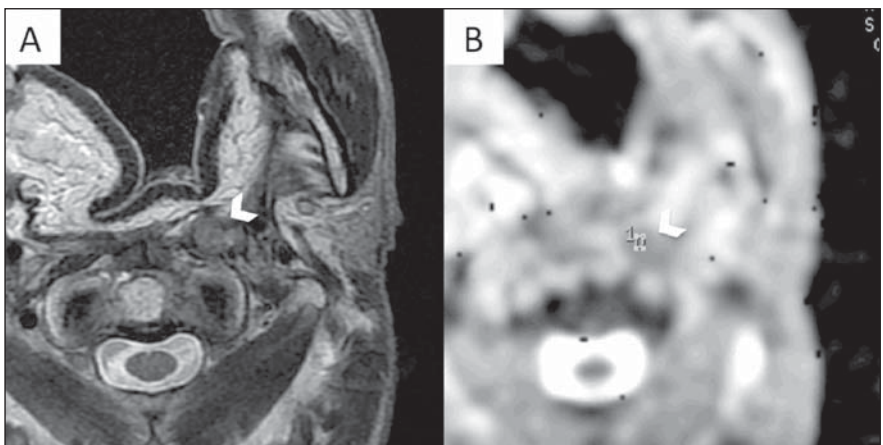


Figure 5. MRI examination of the same patient as Figure 4. **A:** Axial T2WI. Note the hypointense LN posteriorly to the flap. **B:** Note the values on the ADC map of $0.82 \times 10^{-3} \text{ mm}^2/\text{s}$.

timetric neoplastic LN, DWI was 76% sensitive as compared with only 7% sensitivity of conventional MRI⁽²⁶⁾.

DWI is potentially useful in the differentiation of postradiation tissue changes from residual tumor (see Figure 7). Accord-

ing to Vandercaye et al., who studied 26 patients with recurrent or suspected persistent SCCA, DWI is capable of accurately discriminating chemoradiotherapy-induced changes from persistent tumor. Persistent tumors demonstrated lower signal in the b0 and higher in the b1000 images with lower ADC values. As a qualitative marker, b1000 images were useful to localize suspicious lesions as these appeared brighter than nontumoral lesions. ADC values were significantly lower for SCCA than for in treatment-related changes ($1.11 \pm 0.029 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. $1.85 \pm 0.035 \times 10^{-3} \text{ mm}^2/\text{s}$; $p < 0.0001$)⁽²⁷⁾.

In more recent studies, Vandecaveye et al. demonstrated that DWI has the potential benefit of predicting therapy success in head and neck cancers. In the first study they applied DWI in the assessment of treatment response in head and neck SCCA. They measured ADC three weeks prior to treatment and subsequently on follow up. According to this group, an increase in the ADC after treatment is reflective of good treatment response. Cases of little or no ADC change are more likely to reflect treatment failure. In cases of complete remission, the difference in the ADC prior and subsequent to the treatment was 80%, as compared with 2% difference in cases of tumor recurrence^(28,29). Kim et al., who investigated 33 patients with head and neck SCCA, also concluded that ADC measurement is a potential marker for treatment response. In this study, ADC was measured prior to, during and subsequent to treatment. Patients with higher pre-treatment ADC values had better chances of treatment response. Complete responders (CR) had lower ADC values ($1.04 \times 10^{-3} \text{ mm}^2/\text{s}$) as compared to partial responders (PR) ($1.35 \times 10^{-3} \text{ mm}^2/\text{s}$), respectively⁽³⁰⁾.

PET-FDG can also be used to assess tumoral response to treatment. FDG however is not an entirely specific cancer tracer and PET suffers from low spatial resolution. As stated above, DWI can be used to differentiate malignancies from inflammatory changes. Anatomical MR images and DWI can be easily correlated allowing precise localization. DWI seems to be a safer and more affordable method considering the absence of radiation and to the higher cost of FDG-PET⁽⁸⁾.

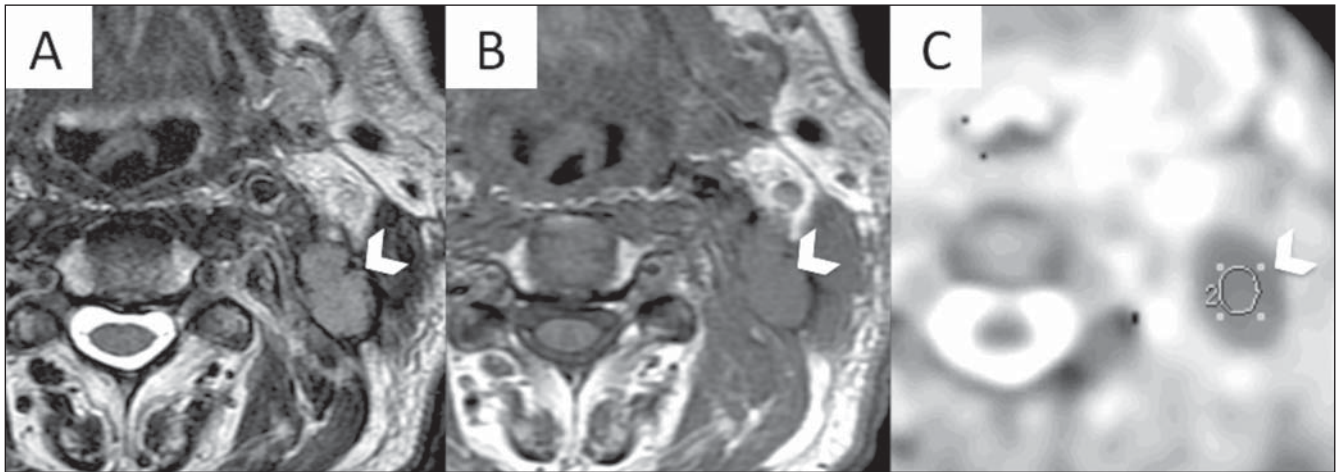


Figure 6. Multiplanar mutisequential MRI of a 48 year-old patient with SCCA of the left palatine tonsil showing ipsilateral metastatic lymph node (LN). **A:** Axial T1WI showing a large level 3 LN. **B:** Axial T2WI demonstrating the LN hypointense signal. **C:** ADC map. Note the low signal of the LN which measured $0.89 \times 10^{-3} \text{ mm}^2/\text{s}$, in keeping with a metastatic lymphadenopathy.

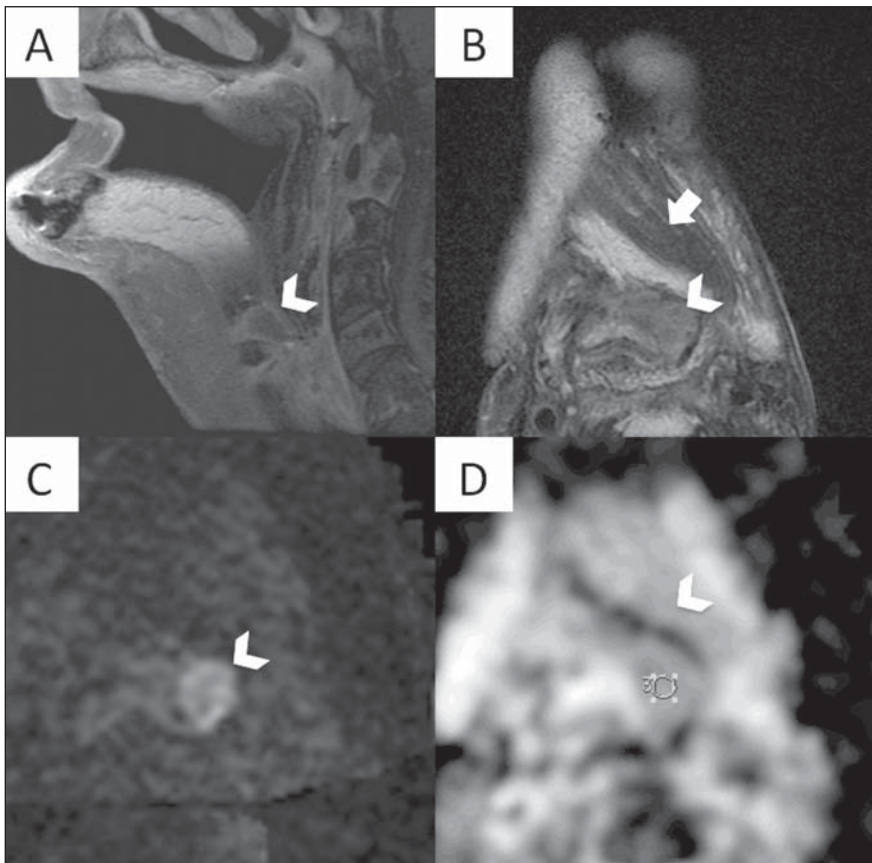


Figure 7. Multiplanar mutisequential MRI of a 65 year-old patient with SCCA of the oropharynx and tongue treated with extensive surgery, multiple myocutaneous flaps and chemoradiation with evidence of recurrent tumor. **A:** Sagittal T1WI post gadolinium. Note the major surgical changes of the oropharynx and also a neo tongue. At the base of the flap, above the level of the epiglottis, there is a small area of abnormal contrast enhancement (arrowhead). **B:** Axial T2WI. Note the same area which is hypointense (arrowhead) located just posterior to the myocutaneous flap (arrow). **C:** Axial DWI showing an area of increased signal (arrowhead) which is rather obvious in the background of low signal. The high contrast DWI properties was helpful and have clearly demonstrated the recurrent tumor in the base of the flap. **D:** The irregular abnormal area in the left pre epiglottic space is showing ADC of $1.05 \times 10^{-3} \text{ mm}^2/\text{s}$. This ADC value suggests recurrent tumor SCCA just in the inferior border of the flap.

DWI and ADC measurement in the head and neck region demands expertise, training and systematization. In the process of ADC measurement, the delineation of the tumor itself is typically performed on conventional images. In some situations however, the abnormalities may be only evident on the DWI. As ADC maps suffer from relatively poor spatial resolution, region of interest placement for ADC measurement should be referenced on the anatomical images. To avoid miscalculation, DWI and reference images (T2 or enhanced T1) should be performed using similar field of view, slice thickness and angulation⁽³¹⁾.

DWI has proven to be a multipurpose technique as it is: (1) capable of discerning between neoplastic and normal structures or tumor free tissue, (2) useful in the differentiation between post radiation changes and tumoral tissue, (3) advantageous in the assessment of LN even if they are subcentimetric and (4) valuable as a predictor of early therapy success. Finally, it may be potentially more affordable and safer than FDG-PET. Given all these advantages and strengths, DWI will certainly become part of the routine in the MR imaging of the head and neck.

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