Can diffusion-weighted imaging distinguish between normal and squamous cell carcinoma of the palatine tonsil?

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ABSTRACT. The utility of diffusion-weighted imaging (DWI) in the detection of squamous cell carcinoma (SCC) of the tonsils has not been previously investigated. This preliminary study compared DWI of apparent SCC tonsillar tumours with normal tonsils. DWI of the tonsils was performed in 10 patients with newly diagnosed tonsil SCC that was evident on conventional MRI and in 17 patients undergoing cranial MRI for other indications. Regions of interest (ROI) were drawn around each identifiable tonsil on the apparent diffusion coefficient (ADC) map and the mean ADC value for each tonsil was calculated. ADC values for normal and SCC tonsils were compared using the Mann–Whitney *U*-test. The median ADC and range ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) were found to be 0.814 and 0.548–1.312, respectively, for normal tonsils compared with 0.933 and 0.789–1.175, respectively, for SCC tonsils. ADC values were significantly higher for SCC tonsils than for normal tonsils ($p=0.009$). No SCC tonsil had an ADC less than $0.82 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ compared with 58% of normal tonsils. We conclude that there is a difference in the ADC between normal tonsils and SCC tonsils where the cancer is apparent on conventional MRI. These results are promising, although further studies are now required to determine whether DWI can be used to identify or exclude smaller foci of SCC within tonsils where the cancer is not evident on conventional MRI.

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Cancers in the palatine tonsil can be difficult to identify on conventional imaging using CT or MRI because they can have the same appearance as normal lymphoid tissue at this site. This leads to problems when imaging is used to search for the site of an “unknown primary” in head and neck squamous cell carcinoma (SCC) or to assess the extent of spread of SCC from adjacent sites in the oropharynx. Diffusion-weighted imaging (DWI) is an MR technique that shows potential for improving the detection of cancer. Early studies suggest that there are differences in the apparent diffusion coefficient (ADC) of metastatic nodes involved in SCC and normal nodes [1–3]. The aim of this preliminary study was to compare the ADC of normal tonsils with imaging-apparent SCC tonsils; to our knowledge, this has not been previously investigated. If it can be shown that there are differences in the ADC values of grossly infiltrated SCC tonsils and benign tonsils, this could provide justification for performing larger prospective studies to determine whether DWI can detect small occult cancers within the tonsil.

Methods and materials

Patient selection

The study was performed on a group of patients with biopsy-confirmed SCC who had undergone DWI at the time of diagnostic MRI. The DWI was part of a larger study into the role of DWI in head and neck cancer at our institute. To reduce the potential influence of any tonsillar biopsy prior to DWI, patients were included only if tonsil biopsy had been performed at least 4 weeks prior to the DWI. Patients with no history of head and neck cancer who were undergoing cranial MRI were also recruited prospectively for DWI of the normal palatine tonsil. The local ethics committee granted ethical approval for this study and informed consent was obtained.

MR technique

All MR examinations were performed on a 1.5 T whole-body system (Intera NT; Philips Medical Systems, Best, the Netherlands) with a 30 mT m⁻¹ maximum gradient capability. A standard receive-only head and neck coil was used for both conventional imaging and DWI. In all patients the protocol included axial *T*₂ weighted turbo spin-echo images with fat suppression

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(repetition time [TR] ms/echo time [TE] ms 2500/100; 4 mm slice thickness with no interslice gap; two signals acquired), axial T_1 weighted spin-echo images (TR/TE 477/12; 4 mm slice thickness with no interslice gap; two signals acquired) and contrast-enhanced axial T_1 weighted spin-echo images following a bolus injection 0.1 mmol kg^{-1} gadoteric acid (Dotarem; Guerbet, Aulnay, France) with utilisation of a 512 matrix. DWI was performed before the contrast-enhanced T_1 weighted sequence; 11 fat-suppressed diffusion-weighted images in the head and neck were acquired in the axial plane using a spin-echo single-shot echo-planar imaging sequence (TR/TE 2000/75; section thickness/gap 4/0 mm; field of view 230 mm; acquisition matrix 112×112 ; reconstruction matrix 256×256 ; signal averages 4) sensitised to incoherent motion by a pair of gradient pulses. Six diffusion-weighted images were acquired with b-factors of 0, 100, 200, 300, 400 and 500 s mm^{-2} . A relatively low maximum b-factor was selected to avoid the image distortion usually observed at higher b-factors and to prevent loss of signal. An isotropic diffusion-weighted image was calculated for each b-factor and an ADC map generated for each slice using an established six-point regression technique [4].

Image analysis

On the imaging workstation, regions of interest (ROIs) were drawn around the palatine tonsils on the ADC maps using both DWI and conventional MRI sequences, including T_1 and T_2 weighted images to assist in anatomical localisation (Figures 1 and 2). For each ROI, the cross-sectional area and mean ADC were documented. In the control group, ROIs were drawn around both tonsils. In tonsillar carcinoma patients, ROIs were drawn only around the grossly abnormal tonsil, as tumoral involvement of the contralateral tonsil could not be technically excluded and rare cases of bilateral synchronous tumours have been documented [5–9]. Tonsils with degraded ADC maps owing to marked motion or susceptibility artefacts were excluded.

Data and statistical analysis

An overall ADC value for the whole tonsil was calculated by weighting the ADCs of each ROI on each slice in proportion to their cross-sectional areas. In addition, the ADC value of the ROI with the largest cross-sectional area excluding any area of necrosis was recorded to determine whether this parameter could be a surrogate for the overall ADC. Statistical analyses were performed using SPSS 11.0 software (SPSS, Chicago, IL). Non-parametric analyses were used as indicated. Statistical tests were two-sided and a p -value of <0.05 was considered statistically significant.

Results

A total of 34 patients were initially recruited, although two patients with large SCCs and two patients with normal tonsils were excluded, one owing to motion artefacts and one because of susceptibility artefacts. A further three patients with normal tonsils that were too small to be delineated from the pharyngeal constrictor muscles on conventional MRI and DWI sequences were also excluded. Consequently, ADC maps were successfully generated for 33 normal tonsils in 17 patients (5 males and 12 females; mean age 43.8 years) and 10 SCC tonsils in 10 patients (6 males and 4 females; mean age 54.7 years). As a result of selection criteria for this study, tonsil tumours had been biopsied at least 4 weeks before DWI (range 4–13 weeks). Furthermore, all tonsil tumours were apparent in terms of tonsillar enlargement of asymmetry on conventional T_1 and T_2 weighted MRI sequences. None of the tonsillar tumours showed any areas of necrosis. The mean area of the largest ROI for SCC tonsils was 341 mm^2 (range $107\text{--}946 \text{ mm}^2$) and for normal tonsils was 95 mm^2 (range $34\text{--}194 \text{ mm}^2$).

The ADC results for normal and SCC tonsils are shown in Table 1 and Figures 3 and 4. The ADC of SCC tonsils was higher than that of normal tonsils using both the whole-tonsil ($p=0.009$, two-tailed Mann-Whitney U -test) and single-slice techniques ($p=0.006$, two-tailed Mann-Whitney U -test). The ADC using the single-slice

Figure 1. Axial (a) T_1 weighted MRI and (b) apparent diffusion coefficient (ADC) map in a patient without squamous cell carcinoma. The right tonsil is indicated between arrowheads in the MRI and outlined on the ADC map.

Figure 2. Left tonsillar carcinoma (arrow in a–d, contoured in e) on axial MRI. (a) T_1 weighted MRI. (b) T_1 weighted post-contrast MRI. (c) T_2 weighted fat-suppressed MRI. (d) DWI with an intermediate b-factor (200 s mm^{-2}). (e) DWI with an intermediate b-factor (200 apparent diffusion coefficient (ADC) map). On all conventional MRI sequences the signal intensity of the infiltrated left tonsil is similar to that of the contralateral uninvolved tonsil, which highlights the difficulty of detecting small tonsil tumours using conventional MRI.

technique correlated with the ADC using the whole-tonsil technique ($p < 0.001$, two-tailed Spearman rank correlation). In addition, receiver operating characteristic (ROC) analysis of ADC values to discriminate normal and SCC tonsils, with SCC indicating a positive result, produced similar areas under the curve of 0.785 and 0.770 for the single-slice and whole-tonsil techniques, respectively. There was no significant correlation between the ADC of pairs of normal tonsils (*i.e.* right and left side) in individuals ($p = 0.55$ for the single-slice technique, $p = 0.09$ for the whole-tonsil technique, Pearson correlation coefficient). Using the single-slice and

whole-tonsil techniques, no tonsils with SCC had an ADC less than 0.813×10^{-3} or $0.789 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, respectively, compared with 58% (19/33) and 49% (16/33) of all normal tonsils.

Discussion

The palatine tonsil is a relative blind spot for imaging. Tumours at this site are rarely necrotic and can have a homogeneous appearance similar to that of lymphoid tissue in the tonsil on contrast-enhanced CT

Table 1. ADC for normal tonsils and SCC tonsils using whole-tonsil and single-slice ADC measurement techniques

ADC measurement technique	Tonsil ADC median (sd; range) $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$		<i>p</i> -Value ^a
	Normal (<i>n</i> =33)	SCC (<i>n</i> =10)	
Whole-tonsil technique	0.81(0.19; 0.55–1.3)	0.93(0.10; 0.79–1.18)	0.009
Single-slice technique	0.71(0.20; 0.54–1.31)	0.95(0.10; 0.81–1.16)	0.006

^aAs determined using the Mann–Whitney *U*-test. ADC, apparent diffusion coefficient; SCC, squamous cell carcinoma; sd, standard deviation.

Figure 3. Box and whisker plot showing the apparent diffusion coefficient (ADC) for normal and squamous cell carcinoma (SCC) tonsils using the whole-tonsil ADC measurement technique. The horizontal bold black line denotes the median ADC, grey boxes denote interquartile values and the whiskers denote maximum and minimum values.

or conventional T_2 weighted and T_1 weighted pre- and post-contrast MRI. As a result, the detection of cancer by anatomical imaging often depends on the presence of tonsillar enlargement or asymmetry; however, this is unreliable because normal tonsillar size asymmetry is common and normal-sized tonsils can harbour small cancers [10–12]. These limitations are compounded by the fact that approximately 5% of patients presenting with cervical nodal metastases from head and neck

Figure 4. Box and whisker plot showing the apparent diffusion coefficient (ADC) for normal and squamous cell carcinoma (SCC) tonsils using the single-slice ADC measurement technique. The horizontal bold black line denotes the median ADC, grey boxes denote interquartile values and the whiskers denote maximum and minimum values.

SCC have a clinically silent primary, of which the tonsil and tongue base are the most common primary sites [7]. Functional imaging using fluorodeoxyglucose positron emission tomography (FDG-PET) and PET-CT has an important role in these cases, although false-positives and false-negatives can occur; for instance, small tumours might have insufficient FDG uptake or can be masked by high physiological uptake by lymphoid tissue at these sites [13–15]. Furthermore, pan-endoscopy and sampling biopsies identify up to 90% of all head and neck cancers, although false-negatives from blind sampling can occur [16]. As a result of these limitations, screening tonsillectomy is frequently performed in the work-up of occult SCC primary tumours [7, 17]. Clearly, there is a requirement for a test that can improve detection or exclusion of SCC non-invasively.

DWI is a widely available technique that is non-invasive and can be performed in only a few minutes. Our data indicate that the ADC of imaging-apparent tonsillar SCC is higher than that of normal tonsillar tissue: to our knowledge, this has not been documented previously. This difference could be a consequence of several factors, including a lowering of cell density in SCC tonsils compared with normal tonsils, the presence of microscopic necrosis and possibly an increase in the extravascular extra-cellular space [3, 18, 19]. In this context, although macroscopic necrosis can also influence ADC, there was no evidence of macroscopic necrosis on conventional MRI for all tonsillar tumours in our series. An increase in perfusion in SCC can alter ADC values when DWI is performed using low b-factors, but any perfusion effect was reduced in this study by using a range of intermediate b-factors. Although the direction of ADC change caused by tumour infiltration depends on the tissue that is being infiltrated, our findings are consistent with a study that documented higher ADC in non-lymphomatous nodal metastases, which included SCC nodes in comparison with benign nodes [2]. By contrast, it has been shown that nodes infiltrated by lymphoma have a lower ADC than both benign and SCC-infiltrated nodes; this is most likely because of the high cell density and relative lack of necrosis in lymphoma [2, 19].

In our study, there was a marginal improvement in the ability of ADC to differentiate normal tonsils and SCC tonsils if the ADC was derived from a single ROI with the largest axial tonsillar cross-sectional area, compared with averaging ADCs on multiple ROI for the whole tonsil. This finding could reflect the fact that the largest ROI in a tonsil is more likely to contain a higher proportion of a single type of tissue (*i.e.* either SCC or normal lymphoid tissue) and is less affected by volume-averaging with adjacent non-tonsillar tissues than smaller peripherally sited ROI.

There was a relatively wide range of ADC values in normal tonsils, despite a narrow interquartile range, which was mostly due to the presence of a few particularly high ADC values. It is possible that this scattering reflects heterogeneity in the histological constituents of normal tonsils, for instance in the ratio of lymphoid to non-lymphoid tissue, which in turn might reflect the presence of inflammation or scarring. Histological variation can also account for a lack of

significant correlation in ADC between pairs of tonsils (*i.e.* right and left side) in normal patients in our series. We found an appreciable overlap of the upper range of ADC values of normal and SCC tonsils, which suggests that a high ADC cannot be used to positively identify patients with diffusely infiltrating tonsillar SCC. Nevertheless, no tonsils infiltrated with SCC had an ADC less than 0.813×10^{-3} or $0.789 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ compared with 58% and 49% of all normal tonsils using the single-slice and whole-tonsil techniques, respectively.

This finding is encouraging as it suggests that ADC might be able to exclude SCC in a proportion of cases in which grossly enlarged tonsils are demonstrated on MRI. Moreover, this result suggests that there is merit in conducting further prospective studies to determine whether this applies to small tonsillar SCCs that are not apparent on conventional imaging. In this respect, it is possible that ADC techniques might be less accurate for smaller tumours: the small focus of tumour might not be included within the largest ROI using the single-slice technique, while its high ADC value might be averaged out by the lower ADC of surrounding normal tonsil using the whole-tonsil technique.

One limitation of DWI of the head and neck region is image degradation caused by motion and susceptibility artefacts. These can be particularly problematic for structures at air-tissue interfaces and in those structures affected by swallowing, which include the palatine tonsils. Nevertheless, several studies indicate that DWI can be successfully employed for head and neck lesions [1–3, 19–21]. In our study, susceptibility artefacts were reduced by using a relatively large bandwidth (1.833 kHz) together with low-to-intermediate b-factors (maximum of 500 s mm^{-2}); higher b-factors increase diffusion sensitivity but are more prone to susceptibility artefacts. We note that 10 out of the 12 patients with tonsil SCC initially selected for this study had successful ADC maps. This result is encouraging, but indicates that this technique might not be suitable for some patients.

In our study, we did not document the ADC of the tonsil opposite to the overtly infiltrated side because there was no histological confirmation for this side (contralateral tonsil biopsy is not performed at our institution as standard practice). This is relevant because synchronous contralateral tonsillar tumours have been documented in the literature [5–9]. In this context, in 1 of the 10 cases with tonsil SCC in our study there was suspected early contiguous tumour infiltration of the contralateral tonsil on conventional MRI, although histological confirmation was obtained only for the grossly abnormal side. Furthermore, this patient was subsequently treated by definitive chemoradiotherapy that included irradiation of both tonsils. Of the nine remaining patients with SCC, the contralateral tonsil was suboptimally demonstrated on ADC maps in four owing to their small size and susceptibility artefacts. Future large prospective studies could address this limitation, although it might be difficult to determine the status of the contralateral tonsil without performing tonsillectomy. This is because small synchronous tumours can be missed by biopsy and these might be inadvertently treated in radiotherapy portals centred on the grossly involved side.

Conclusion

Our study evaluated DWI in patients with normal tonsils and tonsillar SCCs that were apparent on conventional MRI; a higher ADC was demonstrated in the SCC group. In this context, no tonsil tumour in our series had an ADC less than $0.82 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ compared with 58% of normal tonsils. Further research is now required to determine if similar results can be achieved for smaller tonsil SCCs. This capacity could have practical utility in terms of non-invasively excluding the palatine tonsil as the primary site in patients referred with metastatic head and neck SCC from an unknown primary.

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