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ORIGINAL RESEARCH

Cholesteatoma: multishot echo-planar *vs* non echo-planar diffusion-weighted MRI for the prediction of middle ear and mastoid cholesteatoma

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Objective: We aimed to compare a newer readout-segmented echoplanar imaging (RS-EPI) technique with the established single shot turbo spin echo (SS-TSE) non-EPI diffusion-weighted imaging (DWI) in detecting surgically validated cholesteatoma.
Methods: We retrospectively reviewed 358 consecutive MRI studies in 285 patients in which both RS-EPI and non-EPI DWI sequences were performed. Each diffusion sequence was reviewed independently and scored negative, indeterminate or positive for cholesteatoma in isolation and after reviewing the T_1W sequence. Average artefacts scores were evaluated and the lesion size measured as a distortion indicator. The imaging scores were correlated with surgical validation, clinical and imaging follow-up.
Results: There were 239 middle ear and central mastoid tract and 34 peripheral mastoid lesions. 102 tympanomastoid operations were performed. The positive predictive value (PPV), post-operative PPV, primary PPV, negative predictive value were 93%, 95%, 87.5%, 70% for RS-EPI and 92.5%, 93.6%, 90%, 79% for non-EPI DWI. There was good agreement between the two techniques (k = 0.75). Non-EPI DWI is less susceptible to skull base artefacts although the mean cholesteatoma measurement difference was only 0.53 mm.
Conclusion: RS-EPI has comparable PPV with non-EPI DWI in both primary and post-operative cholesteatoma but slightly lower negative predictive value. When there is a mismatch, non-EPI DWI better predicts the presence of cholesteatoma. There is good agreement between the sequences for cholesteatoma diagnosis. The T_1W sequence is very important in downgrading indeterminate DWI signal lesions to a negative score.
Advances in knowledge: This is, to our knowledge, the first study to compare a multishot EPI DWI technique with the established non- EPI DWI in cholesteatoma diagnosis.

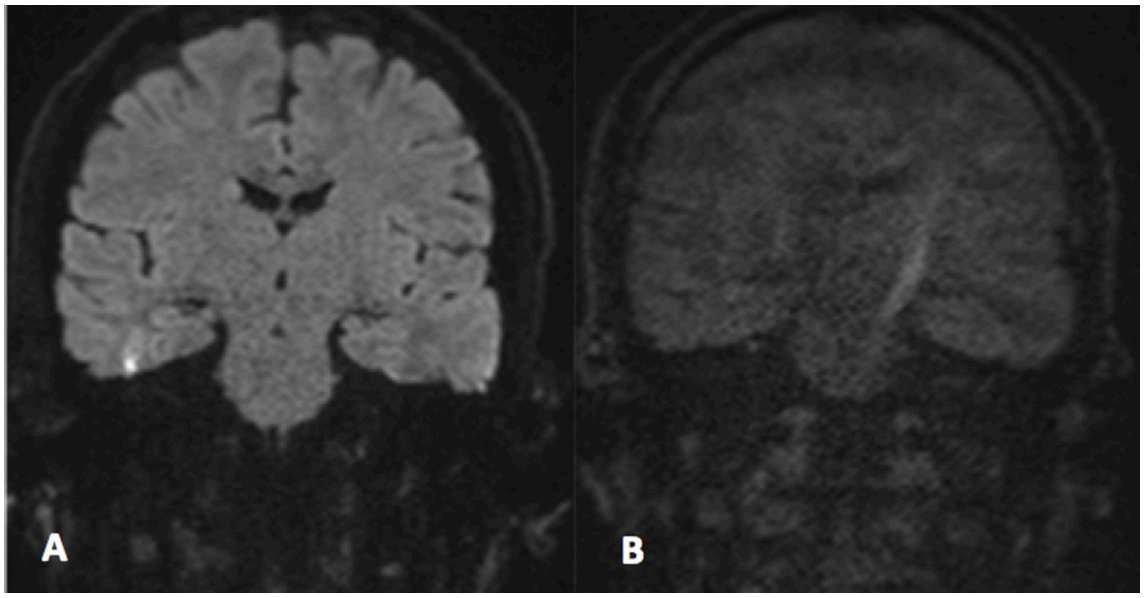
INTRODUCTION

Diffusion-weighted MRI (DW-MRI) is a powerful tool for the detection of cholesteatoma. Over the past decade, numerous imaging studies have been performed looking into detection of cholesteatomas, investigating both echo planar imaging (EPI) and non-EPI DWI sequences.[1–3]

The single shot EPI (SS-EPI) DWI sequence is a standard, fast and relatively insensitive to motion artefact technique, however, limited by a poorer resolution due to the single shot.[3–7] Furthermore, it is very sensitive to B0 inhomogeneities such as those arising at bone–tissue and air–tissue interfaces, with resulting susceptibility artefacts and geometric distortion masking areas of restricted diffusion.[8] Cholesteatomas of smaller size can be missed using SS-EPI, with the limit of detection of 5 mm in a study by Vercruysse et al.[3]

Non-EPI DWI sequences are turbo spin echo (TSE)-based techniques and have been most extensively evaluated with a single shot TSE (SS-TSE) sequence. These generally have a lower SNR than EPI (Figure 1) but are much less sensitive to magnetic susceptibility mismatches and geometric distortion, leading to better lesion detection.[9–12] In a study by De Foer et al[13] the detection of cholesteatomas

Figure 1. Matched slice thickness images demonstrate higher SNR for RS-EPI DWI (A) *vs* SS-TSE non-EPI DWI (B). DWI, diffusion-weighted imaging; RS-EPI, readout-segmented echoplanar imaging; SNR, signal-to-noise ratio; SS-TSE, single shot turbo spin echo.



measuring 2–3 mm has been possible using non-EPI DWI. A recent meta-analysis by Li et al[14] calculated an overall sensitivity and specificity of 94% for non-EPI DWI techniques, with more recent literature reviews also concluding a strong recommendation of using non-EPI DWI for clinical detection of cholesteatomas.[15]

Multishot-EPI (MS-EPI) is an alternative echo planar approach in which signal-intensity acquisition can be divided into several "shots" or repetition time periods, with substantially shorter echo-spacing than SS-EPI, greatly reducing the sensitivity to the effects of magnetic susceptibility mismatches. This results in reduced image distortion and a similar signal-to-noise ratio (SNR) compared with SS-EPI, at the expense of a longer imaging time.[16,17] Yamashita et al[18] found MS-EPI superior to the SS-EPI techniques in diagnosing recurrent or residual cholesteatoma, with increased accuracy from 74.1 to 87.9% when comparing 29 patients prospectively. More recently, Algin et al[19] also found better sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) as well as fewer artefacts and better visibility scores when comparing MS-EPI with SS-EPI in 30 patients.

However, non-EPI DWI remains the standard for the MRI diagnosis of cholesteatoma, and there is currently no study directly comparing MS-EPI with non-EPI DWI.

Our primary aim was to compare the PPV of a readout segmented EPI (RS-EPI) (RESOLVE = REadout Segmentation Of Long Variable Echo trains) which is a type of MS-EPI DWI sequence, with a SS-TSE non-EPI DWI sequence (HASTE = Half-Fourier Acquisition SS-TSE) in detecting primary and postoperative cholesteatoma.

Secondary objectives were to evaluate the PPV in primary vs post-operative residual cholesteatoma, estimate NPV of the two techniques, assess the likelihood of cholesteatoma when there is a mismatch between the DWI signal on the two sequences, investigate the impact of additional T_1W MRI sequence on the DWI based diagnosis, evaluate percentage agreement between the two sequences and investigate the effects of image distortion on cholesteatoma size measurements.

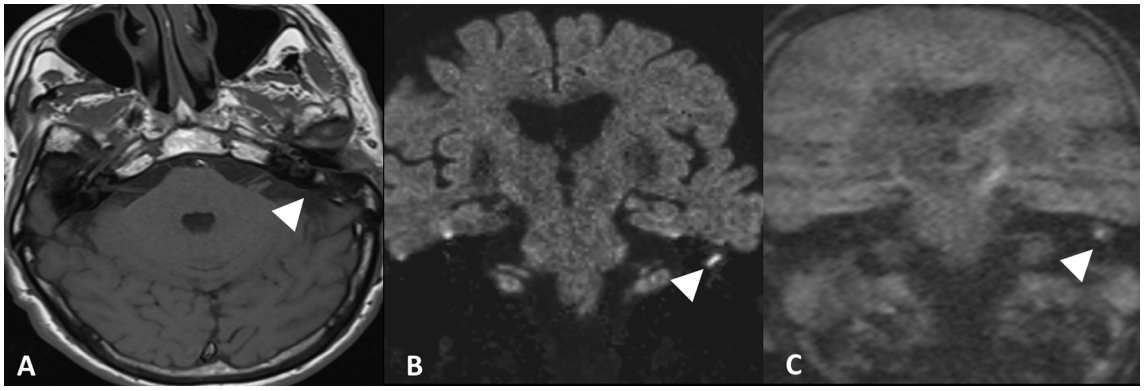
METHODS AND MATERIALS

Institutional review board approval with waiver of informed consent was obtained for this retrospective analysis. The radiology management system (CRIS^{TM}; Healthcare Software Solutions; Mansfield, UK) was retrospectively interrogated over a 40 months period from 2013 to 2017. MR studies were included if the clinical request for imaging or the report text contained "cholesteatoma". Studies that did not have both non-EPI and RS-EPI DWI sequences (11) were excluded. Some patients had multiple studies performed and several patients had more than one lesion analyzed.

MRI was performed using a 1.5 T Aera MR imaging system (Siemens, Erlangen, Germany). The sequence parameters (TR/TE/acquired spatial resolution/acquisition time) were 3240/68/1.2 × 1.2 × 2 mm/1.45 s for RS-EPI and 2000/103/1.15 × 1.53 × 3/278 s for non-EPI DWI. Both sequences were acquired in coronal plane with *b*-values of 0 and 1000 s mm^{-2}. RS-EPI had seven segments.

The studies were viewed on a GE Centricity PACS workstation (GE Medical Systems, Milwaukee, WI). Each diffusion sequence was reviewed independently from the other sequence by one of two neuroradiologists with 2 and 3.5 years of experience and was

Figure 2. Hyperintensity score. T_1 hyperintensity (A) downgrades the DWI reading on both RS-EPI (B) and non-EPI (C), arrows. RS-EPI, readout-segmented echoplanar imaging.



scored according to the signal intensity relative to that of white matter. The score was negative if there was hypointense DWI signal, indeterminate if there was DWI isointense signal and positive for cholesteatoma in the presence of hyperintense DWI signal. Each scoring was performed twice on separate occasions, both in isolation and after reviewing the T_1W sequence, when some lesions were "downgraded" to negative if shown to be T_1W hyperintense (Figure 2). Only a final positive score was considered to represent cholesteatoma.

The lesion size was recorded on each sequence as the maximum coronal diameter of maximal hyperintense signal, without penumbra, on standardized unadjusted non-magnified window settings. The presence of artefact and the susceptibility score were also documented (0–3: 0, no artefact; 1, artefact at the skull base; 2, artefact below the skull base; 3, artefact interfering with diagnosis; Figure 3). The lesion location was designated as involving the middle ear and central mastoid tract (MECMT) or the peripheral mastoid air cells (PM). In the case of the PM, only the largest lesion was considered. Lesions of the external auditory meatus and petrous apex (10) were excluded. If a lesion was extending between two compartments, it was placed into the compartment that contained the majority of the lesion. Clinical and demographic information was recorded. For patients undergoing subsequent tympanomastoid surgery, the intraoperative diagnosis of cholesteatoma was recorded and correlated with the imaging findings. Where surgical validation was not performed, the clinical and imaging follow-up was recorded in order to determine whether cholesteatoma was felt likely at follow-up. A lesion was deemed clinically stable if there was no upgrade in lesion size or suspicion score on follow-up imaging and there was no clinical suspicion of recurrence. Primary and postoperative cholesteatomas were analyzed both together and separately.

Statistical analysis was performed with JMP software (JMP 14.0, SAS Institute, Cary, NC). Cohen's κ was used to calculate the lesions score agreement and the paired *t*-test for calculating the mean difference between lesion measurements, ($p < 0.01$). The impact of T_1W sequence on downgrading the two diffusion sequences scores was compared using χ^2.

RESULTS

There were a total of 285 patients, 59 of whom had more than one study performed and 43 patients had more than one lesion analyzed; a total of 358 MRI studies were reviewed, in which 426 entries were scored.

Figure 3. Susceptibility artefact scores for RS-EPI, examples: 0, no artefact (image A thin arrow); 1, usual artefact at the skull base (image B and image C, arrowheads); 2, artefact below the skull base (image A thick arrow); 3, artefact interfering with diagnosis (image C dash arrow). RS-EPI,readout-segmented echoplanar imaging.

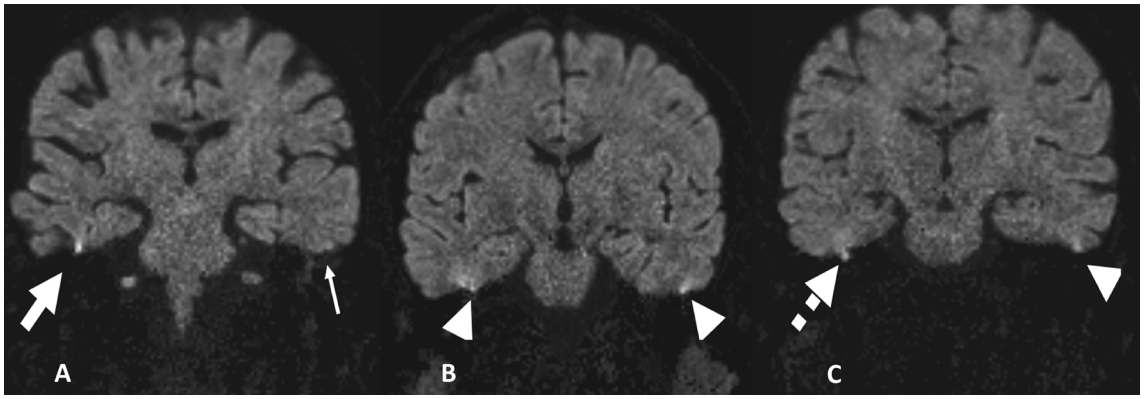


Table 1. PPV, NPV and combined NPV for the 97 MECMT lesions

	RS-EPI	Non-EPI
Positive	57	67
Primary	16	20
Secondary	41	47
True positive	53	62
Negative	40	30
True negative	28	24
PPV	93%	92.5%
NPV	70%	80%
Negative on both	25	
True negative on both	21	
Combined NPV	84%	

NPV, negative predictive value; PPV, positive predictive value.

The mean age was 43 years (7–87), M:F ratio 1.13:1.

There were 239 MECMT and 34 PM lesions detected on either RS-EPI and/or non-EPI DWI while 153 studies were negative for cholesteatoma on both sequences.

Documented surgical validation allowed evaluation of PPV in 97/239 MECMT lesions (Table 1) and in 5/34 PM lesions. The mean interval between imaging and surgery was of 250.3 ± 20.3 days.

The PPV of RS-EPI in the 57 positive surgical validated cases was 93%, with post-operative and primary cholesteatoma PPVs of 95 and 87.5% respectively.

Non-EPI DWI had an overall PPV of 92.5% when analyzing the 67 positive surgically validated cases, with PPVs of 93.6% in post-operative and 90% in primary cases.

For the selected group of 40 operated negative RS-EPI cases, the NPV was 70%, while for the 30 operated negative non-EPI DWI cases, the NPV was 80%. The combined NPV for the 25 operated cases which were negative on both techniques was 84% (Table 1).

Only one out of the five operated PM lesion was found to have cholesteatoma.

There were 10/114 "mismatch" cases in which the RS-EPI sequence was positive but non-EPI DWI was either indeterminate or negative (Figure 4 and Figure 5). Conversely, there were 20/124 mismatch cases which were non-EPI DWI positive but RS-EPI indeterminate or negative (Figure 6 and Figure 7). Non-EPI DWI positive but RS-EPI negative scores were more likely to demonstrate cholesteatoma (12/20, 60%) on surgical and clinical follow-up than RS-EPI positive but non-EPI DWI negative scores (2/10, 20%).

None of the non-operated RS-EPI positive mismatched lesions and only one of the non-operated mismatched non-EPI positive cases was clinically suspected to have cholesteatoma over 469 ±

Figure 4. Mismatched definite RS-EPI lesions and surgical validation. DWI,diffusion-weighted imaging; RS-EPI, readout-segmented echoplanar imaging.

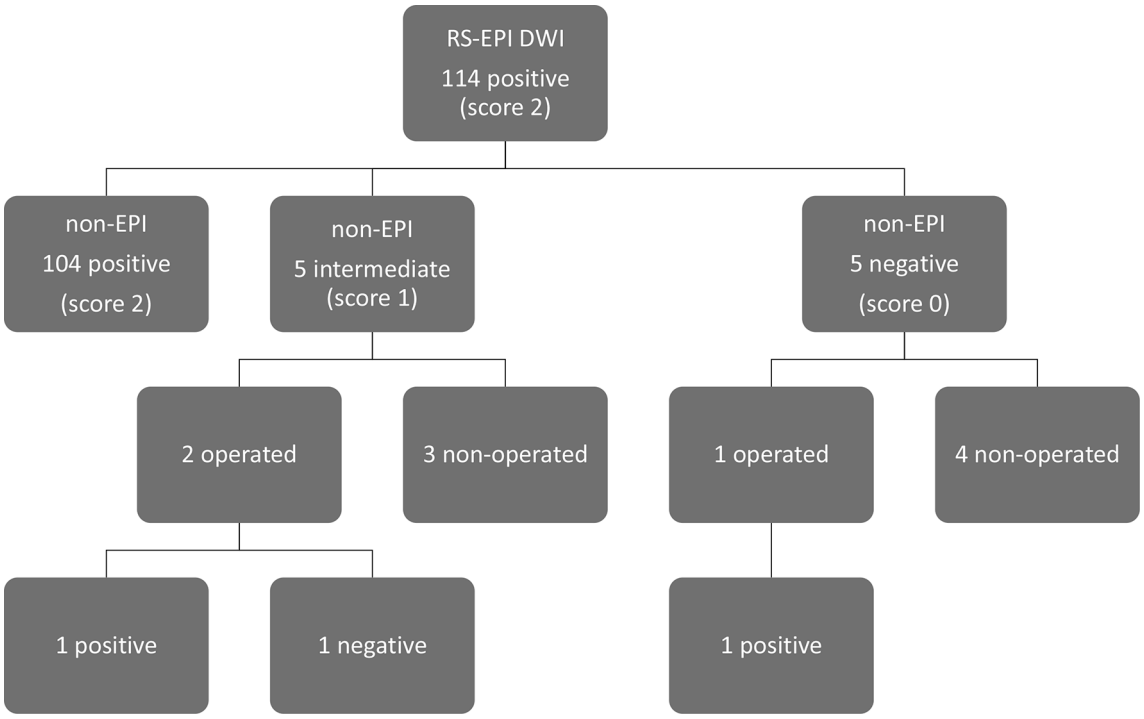
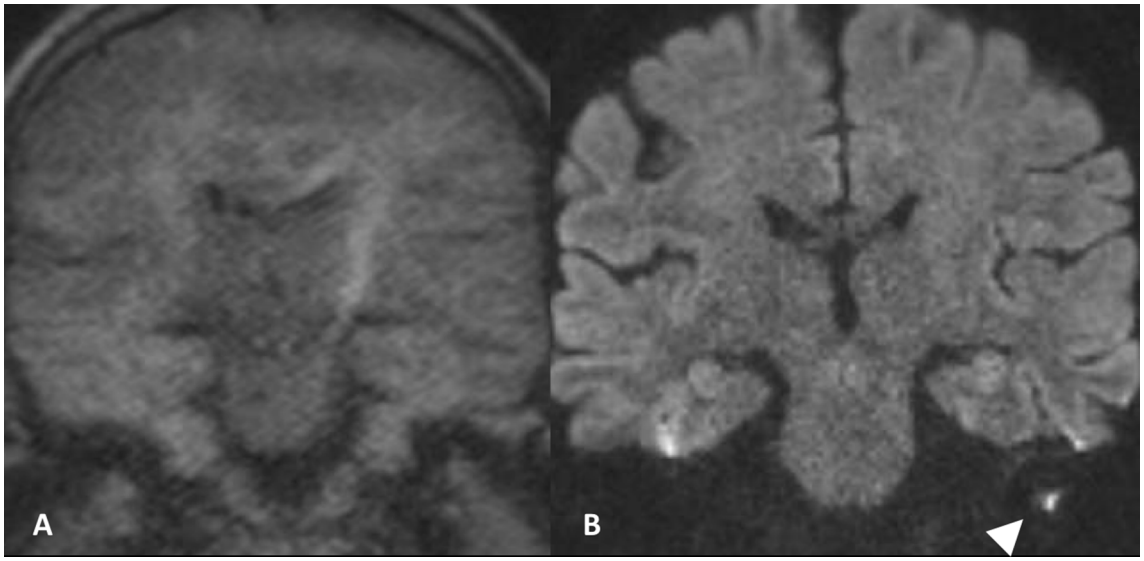


Figure 5. Mismatch cases in which the non-EPI DWI sequence was negative (A) but RS-EPI was positive (B, arrowhead). DWI, diffusion-weighted imaging; RS-EPI, readout-segmented echoplanarimaging.



162 days of follow-up. There was no further imaging performed for the non-operated mismatched cases.

Of the 171/273 non-operated studies, 94.8% of negative studies on RS-EPI (n = 163) and 96.7% of negatives (n = 147) showed stability/no clinical suspicion of recurrence over a clinical follow-up of 458.8 ± 20 days. 76 RS-EPI and 78 non-EPI DWI studies had no clinical data available. 33 lesions with one or more further follow-up imaging studies remained stable and negative by both techniques, including two lesions clinically suspicious for cholesteatoma.

The evaluation of the impact of subsequent T_1W image review on the DWI diagnosis of cholesteatoma (Table 2) revealed similar percentages of intermediate scored MECMT lesions by each sequence, 27.5% of RS-EPI and 32.2% of non-EPI DWI cases on initial assessment, respectively. After T_1 signal assessment, 58.7% indeterminate lesions were downgraded to negative on RS-EPI and 62.5% indeterminate studies were downgraded to negative on non-EPI DWI. When looking at the mastoid studies only, the T_1 sequence contribution was even greater, dismissing 78.6% indeterminate RS-EPI lesions and 66.7% indeterminate non-EPI DWI lesions. There was no statistical difference in downgrading

Figure 6. Mismatched definite non-EPI DWI lesions and surgical validation. DWI, diffusion-weighted imaging; RS-EPI, readout-segmented echoplanar imaging.

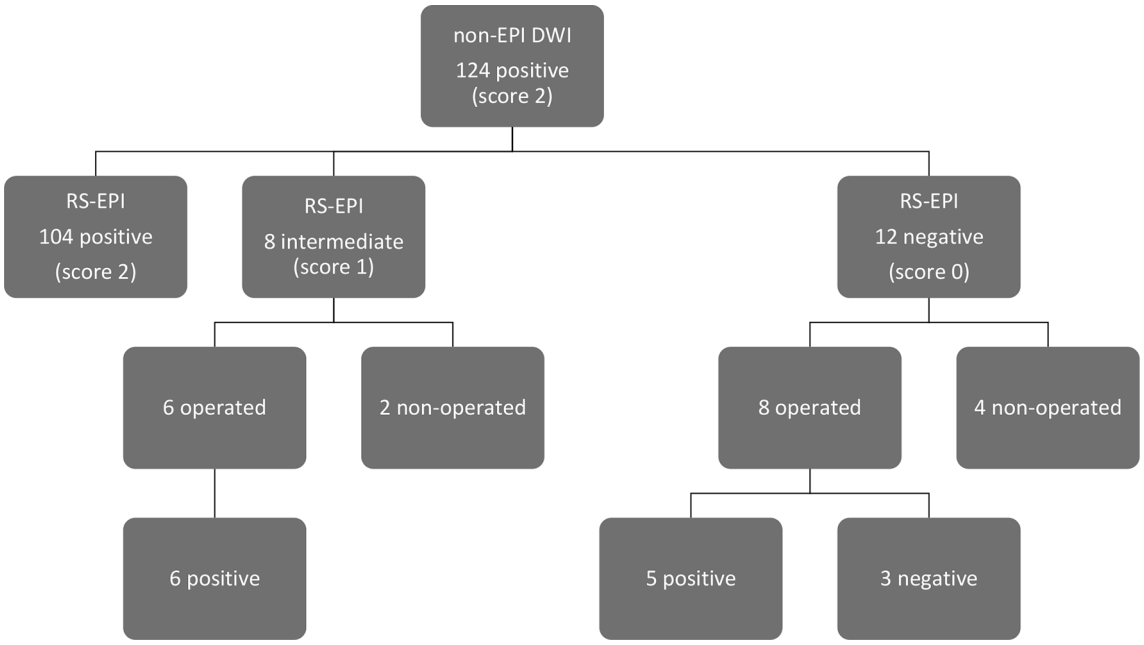
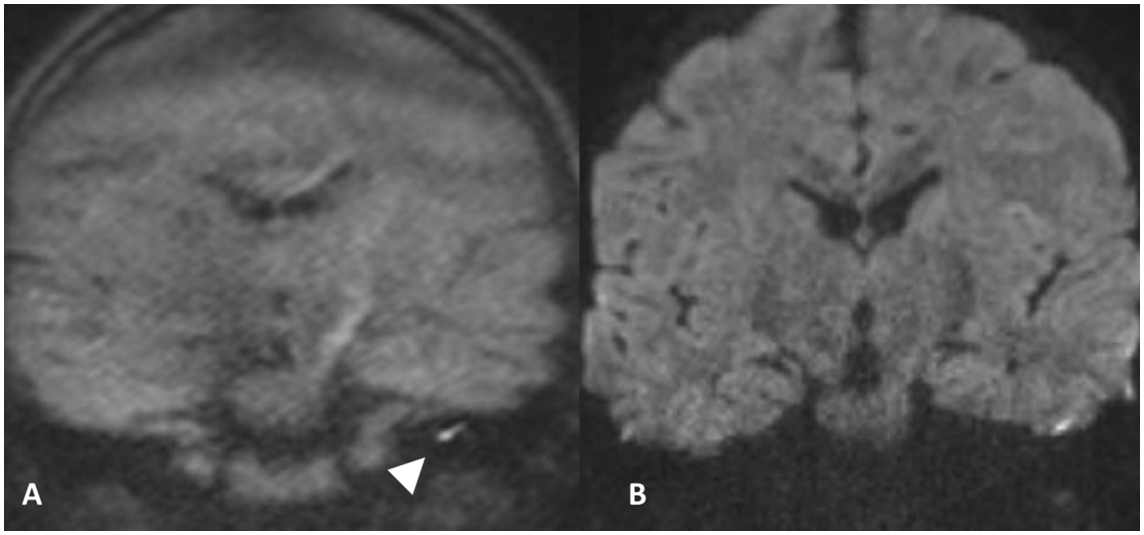


Figure 7. Mismatch cases in which the non-EPI DWI sequence was positive (A, arrowhead) but RS-EPI was negative (B). DWI, diffusion-weighted imaging; RS-EPI, readout-segmented echo planar imaging.



by T1w on the two DWI sequences for CECT/PM lesions ($p < 0.001$).

For the 426 scored entries, the statistical agreement of final scoring by the two DWI techniques was good, $k = 0.75$. 10.8% of lesions differed by one score point and 4.2% by two score points.

The average artefact score for RS-EPI (0–3) was 0.73, when considering all the 426 scored entries. The average non-EPI DWI artefact score was 0; there were three braces distortion. For the 239 MECM lesions, the average measurement difference between the two sequences was 0.53 mm (0.15–0.91).

DISCUSSION

DW MRI imaging has become instrumental in the detection of both primary and post-operative cholesteatoma, with preferential use of non-EPI DWI techniques over standard EPI DWI as the current recommendation. To our knowledge, this is the first direct comparison of a multishot EPI (in this case RS-EPI) with a widely used non-EPI DWI (SS-TSE) in cholesteatoma evaluation. As RS-EPI sequence can be achieved with a significantly shorter TE, there is resultant higher SNR than with non-EPI DWI (Figure 1), which could be potentially traded for shorter acquisition time or thinner slices. The shorter TE also accounts for reduced imaging distortion in comparison with SS-EPI,[16,17,19] hence we felt this new technique merits evaluation against the established non-EPI DWI.

When examining 273 lesions in which both RS-EPI and non-EPI DWI sequences were performed, 102 of which had subsequent surgical correlation, we found very similar PPV's for the two techniques of 93/92.5% respectively, results comparable with the generally accepted PPV values for non-EPI DWI.[13,14,20] Both techniques had better PPV in post-operative cholesteatoma when compared to primary disease, similarly to the systematic review by Van Egmond[15] which found superior PPV's for non-EPI DWI, of 96–100% in post-operative cases compared to 85–100% in primary cholesteatoma. This is presumed due to incipient disease and small retraction pockets in primary cholesteatomas,[21] however a significant difference in primary *vs* post-operative lesion size has not been found in our lesion sample.

Although the lack of comprehensive surgical validation precluded calculation of an encompassing NPV, a comparison was made between imaging findings and the available surgical and clinical outcomes. The NPV for RS-EPI was slightly lower at 70% *vs* non-EPI DWI which had an NPV of 80%, however only a limited number of operations were performed (40 and 30 respectively) and so NPV was largely based on a stable

Table 2. Initial lesion scores by RS-EPI and non-EPI DWI and role of T_1 sequence in resolving them

	RS-EPI	RS-EPI mastoid	Non-EPI	Non-EPI mastoid
Indeterminate lesions, first reading	75	14	88	18
After T_1 assessment, downgraded to negative	44	11	55	12
Definite lesions, first reading	143	16	152	10
After T_1 assessment, downgraded to negative	11	9	5	3

DWI, diffusion-weighted imaging; RS-EPI, readout-segmented echoplanar imaging.

clinical follow-up period without surgical validation. A similar percentage of studies showed no clinical suspicion of residual or recurrent disease over the clinical follow-up period, 94.8% of RS-EPI (n = 163) and 96.7% of non-EPI DWI (n = 147) studies. There appears to be only a small proportion of additional false negative studies in the RS-EPI lesion group, the calculation is, however, limited by the large number of studies with no clinical data available.

There was a modest increase in the NPV value when looking at the operated studies that were negative on both DWI techniques, to 84%, this may be used to increase the confidence of a true-negative study in selected cases such as before discharging a patient from clinical follow-up or to avoid imaging follow-up in difficult settings such as children requiring general anaesthesia.

When looking at our mismatched lesions (scored definite by one technique and intermediate/negative by the other), we validated them against surgery, clinical and imaging follow-up. Although based on very small numbers, the small series of 17 operated mismatched studies reveal a greater proportion of false-negative studies in the RS-EPI group, 11 *vs* 2 in the non-EPI DWI group. We found that non-EPI DWI positive but RS-EPI negative scores were more likely to demonstrate cholesteatoma on surgical and clinical follow-up than RS-EPI positive but non-EPI DWI negative scores, by a ratio of 3:1.

There is little literature available looking at the additional role of T_1W sequences in cholesteatoma diagnosis and although their impact has been recognised, it has not formally been quantified. To objectively assess this, we performed two sets of readings, before and after T_1 sequence assessment, the second reading more in keeping with a clinical setting reading. We found similar considerable proportions of indeterminate scored lesions on initial assessment with either sequence, 27.5% by RS-EPI and 32.2% by non-EPI respectively. Over half of intermediate MECMT lesions were dismissed after T_1W signal assessment on both techniques. The T_1W sequence had an even greater role in downgrading over two-thirds of PM lesions, which appear to be mostly not cholesteatomas. In addition, there was no statistical difference in the likelihood of downgrading by T_1W sequence on the two DWI sequences for CECT and PM lesions.

A similar lesion scoring approach and rationale was used by Yamashita,[18] however, at a single time point, so that the impact of the T_1W sequence in lesion solving was not separately quantified.

Several authors reported false-positive studies corresponding to hyperintense signal on the conventional T_1 weighted images and attributed them to fat in the mastoidectomy cavity or blood.[22,23] We presume that these appearances may also be due to inspissated secretions, and our findings are further supported by the lack of lesion progression on follow-up imaging. Our findings emphasise the major contributory role of conventional T_1 weighted sequences in correlation with DWI in cholesteatoma assessment.

It is well established that non-EPI techniques are associated with decreased susceptibility artefacts at the skull base by comparison with EPI techniques.[10] Not entirely surprisingly, when calculating average artefacts scores for each technique we found our average non-EPI DWI artefact score was 0. The average artefact for RS-EPI (0–3) was 0.73 in the 426 scored entries, overall less than the usual artefact expected at the skull base, implying a significant proportion of studies with no artefact. Although non-EPI DWI is less susceptible to skull base artefacts, RS-EPI artefact was mild and not interfering with diagnosis.

Severe distortion caused by dental devices was recorded in three cases, precluding imaging interpretation on both sequences. To further quantify distortion, we calculated the mean lesion measurement difference by the two techniques, while excluding the smaller mastoid lesions from the calculation in order to avoid skewing the data. There was only 0.53 mm difference in the 239 MECM lesions inferring little difference in distortion. The positive confidence interval suggests the lesions measured larger on RS-EPI compared to non-EPI DWI.

We also found a good final score agreement between the two DWI sequences, k = 0.75, with only 18/426 lesions disagreeing by two score points.

Our study has several limitations. There was a difference in slice thickness between the two techniques, with thinner RS-EPI sections at 2 *vs* 3mm for non-EPI DWI sections, potentially increasing the lesion detection by RS-EPI DWI. Our scoring was performed by two different observers, with possible bias from interobserver variability. Furthermore, not all the patients had available clinical follow up data. Only 102 cases had surgical correlation, limiting our calculation of NPV. There was also a time gap from scan acquisition to surgery of 250.3 days, during which time a lesion could have potentially developed or self-evacuated, confounding the predictive values calculations.

RS-EPI appears to be an improved EPI DWI sequence with reduced susceptibility artefacts whilst having similar PPV and good agreement with the established non-EPI DWI. Our results suggest that if RS-EPI was to replace non-EPI DWI, there is a potential risk of failure to detect some cholesteatomas. As a solution, there is scope to increase the number of segments to reduce distortion at the expense of acquisition time and if further validated, RS-EPI could eventually provide the advantage of shorter acquisition time and better SNR. As it stands, RS-EPI could be introduced in addition to non-EPI DWI in selected cases, to increase the confidence of a true-negative study.

CONCLUSIONS

RS-EPI has comparable PPV with non-EPI DWI in both primary and post-operative cholesteatoma but slightly lower NPV. When there is a mismatch, non-EPI DWI better predicts the presence of cholesteatoma and has slightly higher PPV than RS-EPI. There is good agreement between the sequences

for cholesteatoma diagnosis. The T1W sequence is equally important to both sequences in downgrading indeterminate DWI signal lesions to a negative score, particularly in the PM region. Non-EPI is less susceptible to skull base artefacts, but there is <1 mm difference in lesion measurement as a result of differential distortion.

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