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Apparent diffusion coefficients for predicting primary cholesteatoma risk of recurrence after surgical clearance

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ABSTRACT

Purpose: Beside the well-known accuracy of non-EPI DWI techniques and relative ADC maps in detecting cholesteatomatous tissue, ADC can also represent a useful tool for stratifying cholesteatoma risk of recurrence. Aim of this study is to test the role of ADC in determining risk of recurrence for primary middle ear cholesteatoma, proposing stratification based on pre-operative mean (mADC) and normalized (nADC) ADC values.
Methods: In this prospective study, 60 patients with primary unilateral middle ear cholesteatoma underwent a three-years-long follow-up to assess the presence of recurrent disease after macroscopically complete excisional surgery. Baseline MRI examination mADC and nADC values in the group with early evidence of recurrent cholesteatoma were compared to the group with no evidence of recurrence by using T statistics.
Results: ADC values on pre-operative MRI examination were lower in cholesteatomas with early evidence of recurrence, and statistical significance was slightly higher for nADC compared to mADC measurements. We also determined a cut-off between the two groups, proposing stratification in high-risk of recurrence cholesteatomas (mADC$\leq$ 1000 or nADC < 1.3) and low-risk cholesteatomas (mADC > 1000 or nADC$\geq$1.3).
Conclusions: ADC values resulted discriminating in identifying cholesteatomas with higher risk of early recurrence, both for mean and normalized ADC, with optimized tissue characterization and outcome prediction.

1. Introduction

Acquired primary middle ear cholesteatoma is a cystic-like pseudoneoplastic lesion of the middle ear cavity, typically arising from Prussak space and epitympanum, formed by an inner core of lamellar keratin desquamating debris lined with multi-layered squamous epithelium and surrounded by mesenchymatous granulation tissue. Although benignant, cholesteatoma shows a locally aggressive behaviour, with tendency to erode and destruct the ossicular chain and the surrounding bony structures [1].

Beside clinical and otoscopic examination, magnetic resonance imaging (MRI) has proved to be the most accurate imaging tool for demonstrating cholesteatoma presence and extension, largely relying on specific techniques such as diffusion weighted imaging (DWI). On DWI cholesteatoma shows pathognomonic restriction of water diffusion related to its high keratin content, allowing for distinction from possible mimickers including granulation tissue, cholesterol granuloma, and other non-specific middle ear cavity filling tissues [2], either before or after middle ear cavity surgery [3].

Among different DWI techniques, the superiority both in terms of interpretability and reproducibility of non-echo-planar imaging (non-EPI) DWI over conventional EPI sequences in identifying primary or recurrent cholesteatoma has been validated by several literature studies [2], [4–7]; the best diagnostic accuracy was obtained with multi-shot (MSH) compared to single-shot (SSH) techniques [8–10]. Many Authors proposed the use of DWI with respective apparent diffusion coefficient (ADC) for detection and differential diagnosis of residual/recurrent cholesteatoma [10–14], but no evidence emerged concerning the use of ADC for pre-operative prediction of primary acquired cholesteatoma recurrence after macroscopically complete excisional surgery.

Abbreviations: MRI, Magnetic Resonance Imaging; DWI, Diffusion Weighted Imaging; EPI, Echo-Planar Imaging; MSH, multi-shot; SSH, single-shot; ADC, Apparent Diffusion Coefficient; nADC, Normalized Apparent Diffusion Coefficient; ROI, Region Of Interest; mADC, Mean Apparent Diffusion Coefficient; NAWM, Normal Appearing White Matter

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Moreover, ADC measurements are at least in part affected by acquisition technique, imaging system and post-processing platform used [15,16]. ADC normalization, defined as the ratio between the ADC of the lesion divided by the one of a normal reference tissue, can help to correct for differences depending on technical factors and to reduce the variation due to individual characteristics [17].

Aim of this study is to assess the role of mean (mADC) and normalized ADC (nADC) in determining risk of recurrence for primary middle ear cholesteatoma, proposing stratification based on pre-operative values.

2. Materials and methods

2.1. Participants

From January 2010 to June 2016, of all patients followed at our University Department, we prospectively recruited 60 subjects (29 males; 31 females; mean age 35.2 ± 20.2y) with clinical suspicion and MRI confirmation of primary acquired unilateral cholesteatoma confined exclusively to middle ear cavity (27 right ear, 45 %; 33 left ear, 55 %), then verified at pathological examination. Neither congenital nor residual/recurrent cholesteatoma were included in the study. All patients underwent a first pre-operative MRI within 15 days before first-look surgery, followed by a second post-operative follow-up within three months from macroscopically complete excisional surgery to assess the presence of residual disease. Surgery consisted of open tympanoplasty (or canal wall down technique - 50/60; 83.4 %) or closed tympanoplasty (or canal wall up technique - 10/60; 16.6 %), depending on lesion location and pre-operative imaging evaluation, uniformly carried out by the same surgical team to minimize procedure-related variability (two otorhinolaryngologists respectively with 20 and 10 years of ENT surgery). Canal wall down technique was generally preferred to canal wall up technique due to the lower risk of disease recurrence and long-term post-operative complications [18–20]. It should be considered that DWI after canal wall down mastoidectomy can be subject to higher risk of false-positive results; in this light we excluded all patients with equivocal DWI restriction at 3 months post-operative follow-up (probably due to wax-related artifacts) [20], as well as patients with patent residual cholesteatoma. Among canal wall down techniques, no case of radical mastoidectomy (in which tympanic membrane and ossicular chain are not reconstructed, exteriorizing middle ear cavity and mastoid) was included. The exclusion criteria applied were: low MRI quality due to motion artifacts and/or presence of hearing implants; no pathological confirmation of middle ear cholesteatoma after first-look surgery; MRI evidence of equivocal DWI restriction or residual disease after first-look surgery; patient loss to longitudinal follow-up examination; MRI evidence of concurrent CNS white matter disease.

Until June 2019, after post-surgical negative follow-up MRI, all patients underwent a 3 years-long post-operative follow-up to clinically and instrumentally assess possible relapses. Clinical follow-up examination was carried out every 6 months to detect potential hearing worsening or emergence of new signs and symptoms of the underlying pathology (with MRI performed in case of suspected recurrent disease); patients with no clinical suspicion of recurrence underwent a routine follow-up MRI after 3 years from surgery, also according to recent evidences suggesting a mean recurrence interval of about 3 years from the initial cholesteatoma surgery [19]. Patients were therefore divided in two groups according to the presence or absence of recurrent middle ear cholesteatoma within 3 years from surgery; no case of recurrent cholesteatoma admixed with infection or abscess formation was pathologically observed.

The protocol was formerly approved by local Ethical Committee and written informed consent was preliminarily obtained from all patients included in the study.

2.2. Imaging data acquisition, processing and analysis

The MRI examination, performed on the same 1.5 T MR unit (Philips Intera, Philips Medical Systems, Netherlands) using an 8-channel head coil, consisted of axial and coronal SE T1w, axial TSE T2w, axial 3D T2w DRIVE, completed with coronal MSH non-EPI DWI sequence (20 slides; TR 3000 ms; TE 80 ms; thickness 3 mm; spacing between slices 2 mm; pixel bandwidth 290; FA 90; phase R > L; view size 2338 × 1228; matrix 128 × 128; b = 0 and b = 800 s/mm2; 2 averages; acquition time 2'40''); during the acquisition, cardiac gating was performed to limit possible patient-related artefacts due to heart pulse and blood flow. ADC maps were automatically obtained on the console software after DWI acquisition. The protocol did not routinely include the intravenous administration of gadolinium-based contrast media.

Baseline pre-operative MRI was examined in consensus by two neuroradiologists with a long experience in the field of head and neck imaging (respectively 15years and 5years). The two readers were asked to place a free-hand polygonal region of interest (ROI) in the area of suspected middle ear cholesteatoma on the most representative DWI slice with higher b-value (b = 800), where abnormally restricted water diffusion was more evident. The ROI was then automatically transferred to the co-registered ADC map, to obtain mean ADC (mADC) values within the lesion. A second circular ROI (diameter = 5 mm; about 20mm^2) was placed in a reference site within the homolateral centrum semiovale normal appearing white matter (NAWM) on the most representative DWI slice, and then automatically transferred to the co-registered ADC map to obtain the corresponding ADC values. Finally, for each patient the nADC ratio was calculated by dividing mADC value of cholesteatoma by mADC value of NAWM (mean 875; min 609; max 1163; DS 140). For statistical purposes, the median of the two observers measurements was then considered; inter-observer agreement in most representative slices choice was 0.98.

2.3. Statistical analysis

Between-groups differences in terms of age, sex, side of the lesion and surgical technique were tested by using the Mann-Whitney U. The Kolmogorov-Smirnov D-Test for normality was used to confirm the normal distribution of the collected ADC data; data were then plotted to assess the intersection of the normal probability density functions. Unpaired two samples Student t-test with a significance level $p < 0.01$ was used to assess the difference between the two groups in terms of mADC values and nADC values. ANCOVA F-test with $p < 0.01$ was further applied to test differences in ADC values including age, sex, and lesions' dimensions (expressed in mm^2, on the same most representative slice where ADC values were calculated) as covariates.

Finally, for recurrent lesions, Pearson's Correlation was used to measure the strength of the linear association of interval surgery-recurrence with dimensions and ADC values of the cholesteatoma respectively. All statistical analyses were performed using XLSTAT software v.2019.1 (Addinsoft).

3. Results

During follow-up examinations 24 patients presented with pathologically confirmed recurrent cholesteatoma (mean time surgery-recurrence: 25.3 ± 8.8 months; range 11–36 months), while 36 patients showed no evidence of recurrence. An example of recurrent cholesteatoma is shown in Fig. 1, whereas an example of primary cholesteatoma with no evidence of recurrent disease at longitudinal follow-up is shown in Fig. 2; a flow-chart with patients selection and drop-out over time is shown in Fig. 3. No difference between groups was found in terms of age (p = 0.53), sex (p = 0.88), side of the lesion (p = 0.92) and surgical technique (p = 0.74).

The between-groups analysis with t-test was significant both for mADC and nADC values ($p < 0.0001$), with statistical significance

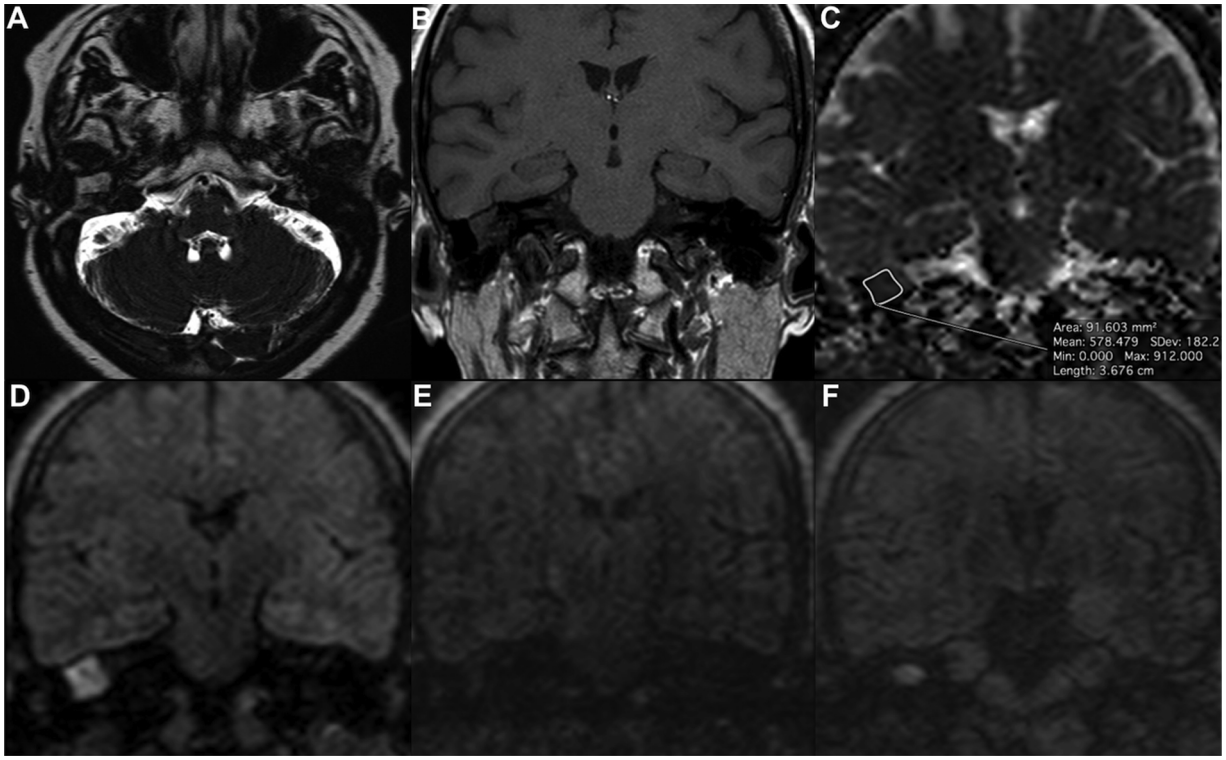

Fig. 1. Right middle ear cholesteatoma in a 63-year-old woman with evidence of recurrence after about 28 months from first-look surgery. (**A–D**) Baseline MRI examination: (**A**) axial T2w 3D TSE; (**B**) coronal T1w SE; (**C**) coronal ADC map showing the co-registered ROI within lesion's margins; (**D**) coronal MSH non-EPI DWI. (**E**) Coronal MSH non-EPI DWI 3 months after first-look surgery, showing absence of residual disease. (**F**) Coronal MSH non-EPI DWI 28 months after first-look surgery, showing recurrent cholesteatoma.

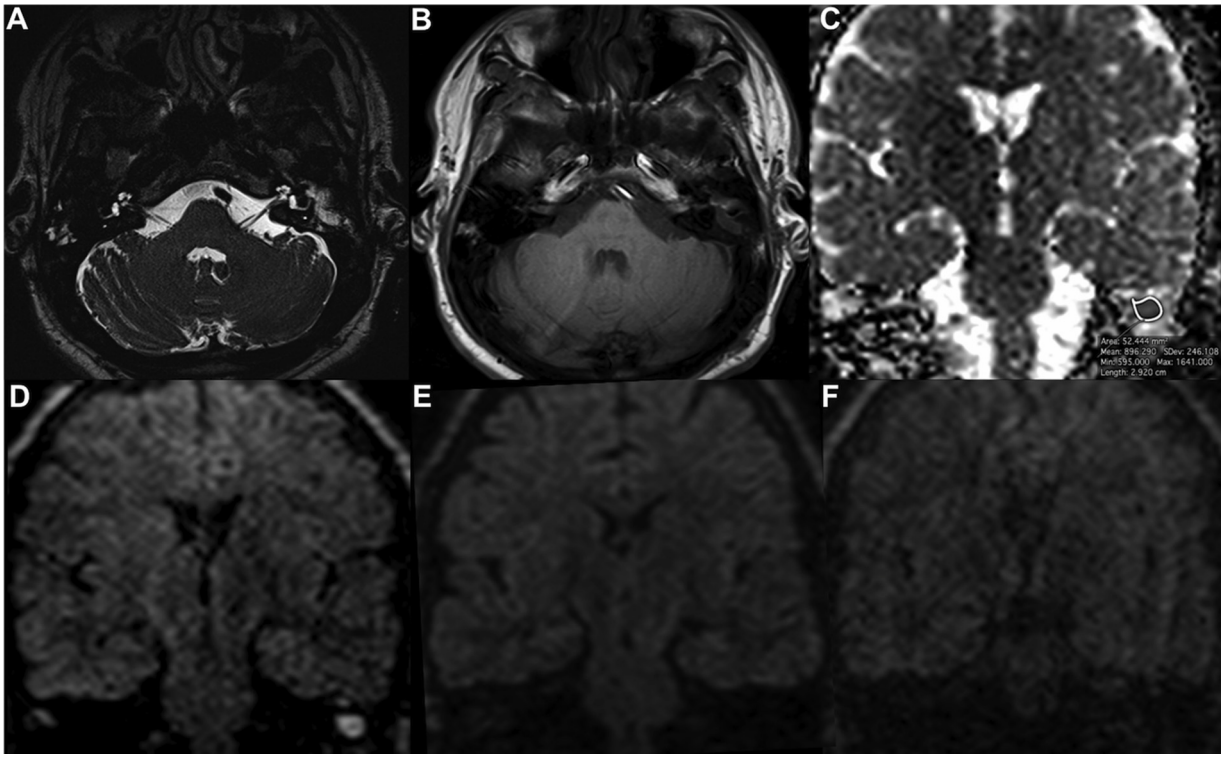

Fig. 2. Left middle ear cholesteatoma in a 55-year-old man with no evidence of recurrence at 3 years-long post-operative follow-up. (**A–D**) Baseline MRI examination: (**A**) axial T2w 3D TSE; (**B**) axial T1w SE; (**C**) coronal ADC map showing the co-registered ROI within lesion's margins; (**D**) coronal MSH non-EPI DWI. (**E**) Coronal MSH non-EPI DWI 3 months after first-look surgery, showing absence of residual cholesteatoma. (**F**) Coronal MSH non-EPI DWI 36 months after first-look surgery, confirming no evidence of recurrence.

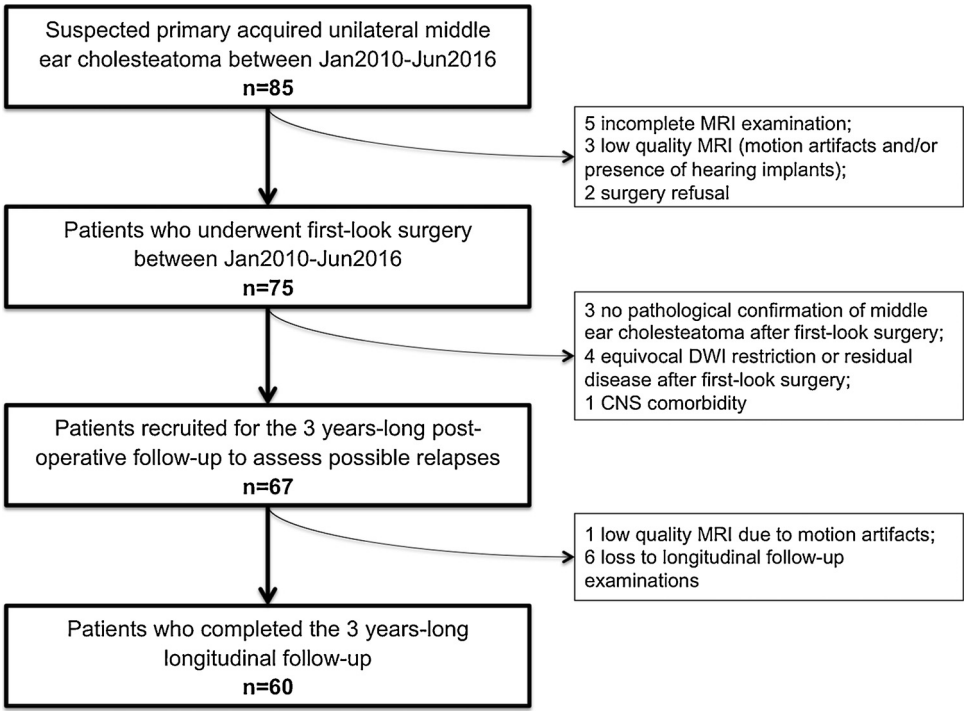

Fig. 3. Flow-chart showing participants selection and drop-out.

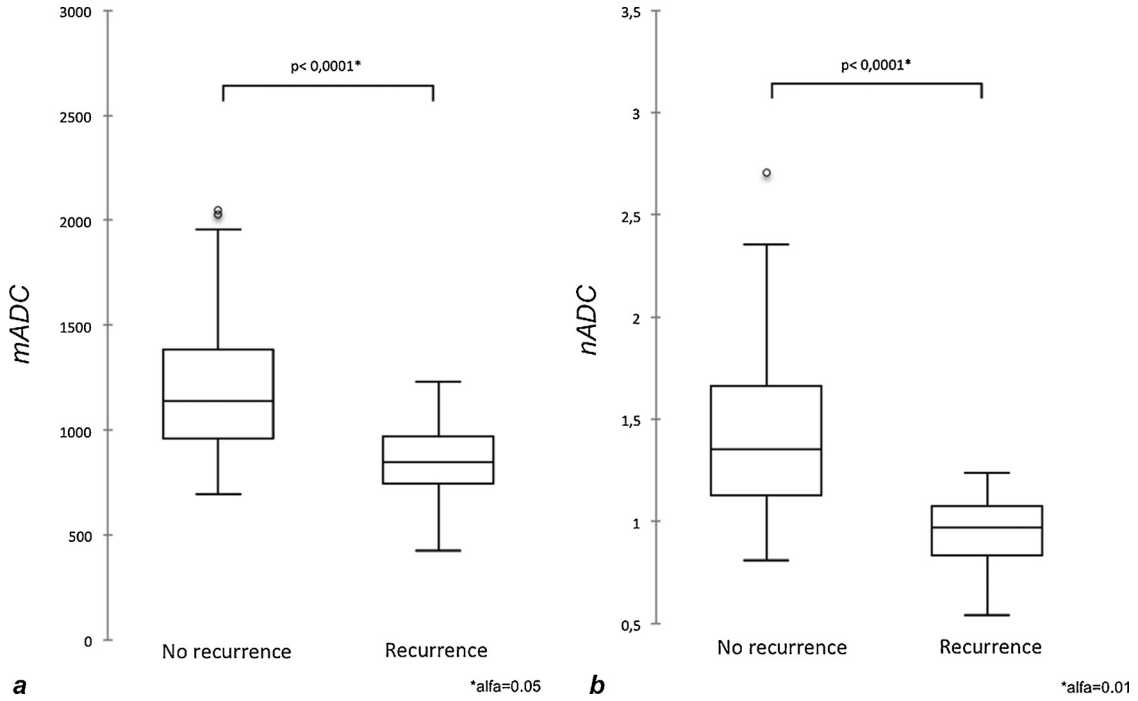

Fig. 4. Boxplot showing mADC (**a**) and nADC (**b**) values distribution in the group with no evidence of recurrent cholesteatoma at 3 years-long post-operative follow-up (*first column*) vs the group with evidence of recurrent disease within 3 years from first-look surgery (*second column*).

slightly higher for nADC (p = 0.000012) compared to mADC (p = 0.000023). Recurrent cholesteatomas showed more restricted water diffusion at baseline MRI examination with lower mADC (mean 861; min 426; max 1229; DS 197) and nADC values (mean 0.952; min 0.542; max 1.238; DS 0.180) compared to cholesteatomas with no evidence of recurrence (mADC: mean 1242; min 695; max 2050; DS 395 - nADC: mean 1.455; min 0.810; max 2.704; DS 0.417). Boxplot graph representing mADC and nADC values distribution in the two groups (no recurrence vs. recurrent cholesteatoma) is shown in Fig. 4. Results were further confirmed with F-statistics including age, sex, and lesions' dimensions as covariates ($p < 0.01$).

According to the Kolmogorov-Smirnov statistics, mADC and nADC values did not significantly differ from a normal distribution, both in recurrence (D_{mADC} = 0.131 and D_{nADC} = 0.123, respectively) and no recurrence (D_{mADC} = 0.148 and D_{nADC} = 0.125, respectively) group. When plotting the two Gaussian distributions on the same graph both for mADC and nADC values, the intersection point of the normal probability density functions of recurrent and non-recurrent disease

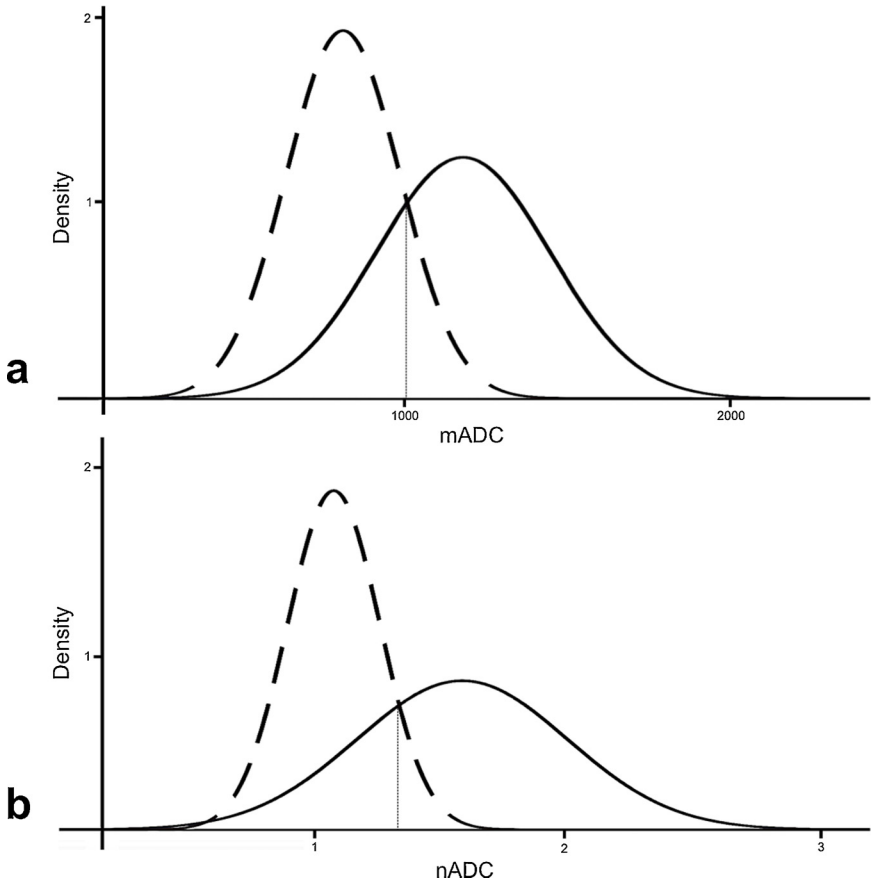

Fig. 5. Probability density functions of group with no evidence of recurrent cholesteatoma at 3 years-long post-operative follow-up (*continuous curves*) and group with evidence of recurrent disease within 3 years from first-look surgery (*dashed curves*), both for mADC (**a**) and nADC (**b**); the intersection point of the curves, representing the optimal cut-point between the two groups, corresponds to about mADC = 1000 and nADC = 1.3 (*dotted lines*).

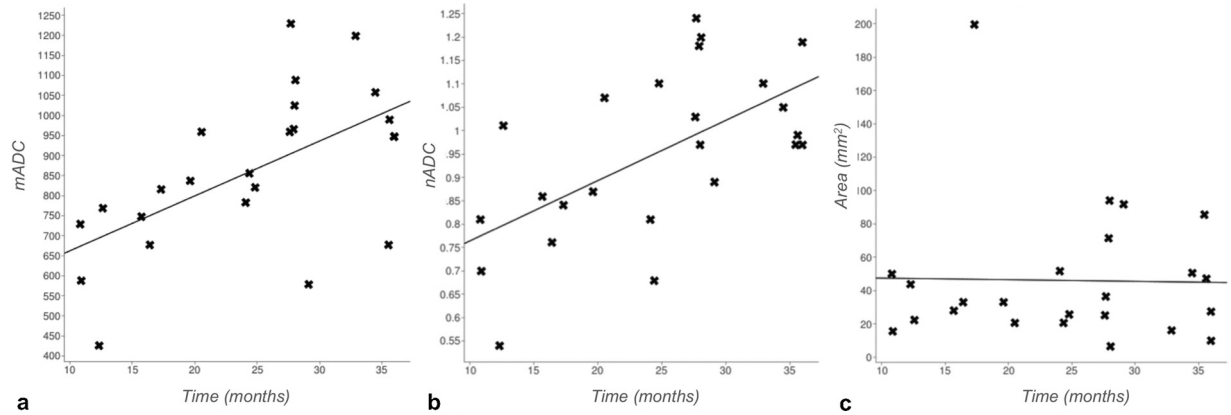

Fig. 6. Pearson's Correlation on the recurrence sub-group: (**a**) moderate positive association between interval surgery-recurrence and mADC values (r = 0.59); (**b**) positive association between interval surgery-recurrence and nADC values (r = 0.61); (**c**) lack of association between interval surgery-recurrence and lesions' area on the most representative slice at baseline MRI examination (r = 0.02), respectively.

(representing the optimal cut-point between the two groups) [21] corresponded to about mADC = 1000 (mADC = 1018) and nADC = 1.3 (nADC = 1.347) (Fig. 5). Finally the ancillary analysis on the recurrence sub-group testing the association with the interval surgery-recurrence showed a trend of positive correlation with ADC values (r_{mADC} = 0.59 and r_{nADC} = 0.61), with earlier evidence of recurrence in case of lower values. Conversely, no significant correlation (r = 0.02) was found with lesion dimensions at baseline MRI examination (mean area on the most representative slice 40mm^2; min 8 mm^2; max 200 mm^2; DS 30 mm^2). Results of Pearson's Correlation are shown in Fig. 6.

4. Discussion

Our results showed a significant difference in ADC values on pre-operative MRI examination between cholesteatomas with early evidence of recurrence within three years from surgery, compared to cholesteatomas with no evidence of recurrence at three years long follow-up. We also determined a cut-off between these two groups based on ADC values, proposing a new stratification in cholesteatoma with high risk of early recurrence (mADC ≤ 1000 or nADC < 1.3) and cholesteatoma with low risk of recurrence (mADC > 1000 or nADC ≥ 1.3).

In recent times many studies highlighted the superiority of non-EPI DWI over conventional EPI sequences in the diagnosis of middle ear

cholesteatoma, mainly because of its ability in combining specificity for keratin-containing tissues and spatial sensitivity even for small lesions [2,3]. Indeed, non-EPI techniques have progressively become crucial for the assessment of suspected cholesteatomas filling the tympanic cavity, especially when detection of residual or recurrent disease after middle ear surgery is required [10,12,13,22–24]. However, no data are currently available on the use of DWI and corresponding ADC values for pre-operative prediction of cholesteatoma recurrence. In this first longitudinal study, we observed more restricted water diffusion and lower ADC values at baseline MRI in recurrent cholesteatomas compared to lesions with no evidence of early recurrence after three years follow-up. Reasons determining such restricted water diffusion signal in cholesteatoma still remain not entirely clear. The most accepted hypothesis is that keratinizing squamous cells in the matrix produce high-density keratin squames mixed with other sebaceous materials within the inner core of the cyst, while inflammatory cells in the perimatrix produce high levels of collagen fibres [25,26]; all these phenomena provide a significant limitation in water diffusivity determining high signal intensity on DWI sequences [22]. Differences among cholesteatomas could therefore be related to variable levels in hyperproliferative/hypersecretive activity of these external layers as well as to different keratin content within the lesion, with hypothesized lower ADC values in lesions with a more aggressive biologic behaviour.

When testing differences between groups, although with no statistical difference, nADC values resulted slightly more discriminating than conventional mADC measurements in distinguish cholesteatomas with higher risk of early recurrence from lesions with lower risk of recurrence. Indeed, it is well known that the generation of ADC maps and the measurements of ADC values within a specific ROI can provide the quantitative counterparty of DWI images. With this knowledge, over time several Authors proposed cut-off values to distinguish cholesteatoma from abscess [11] and non-cholesteatomatous granulation tissue [12,13,27]. However, all these results were strongly affected by vendor, field strength, DWI sequence performed, and post-processing software adopted [15–17]; therefore cut-off values validity and reproducibility among different institutions have never been validated, and their use in daily clinical practice is still limited. ADC normalization represents a possible promising approach to overcome this problem and to make comparable data collected in different conditions. Although still at an immature stage, the use of nADC produced encouraging results and was implemented in different pathological conditions as well as in different anatomical districts [28–33]. In particular ADC normalization has been widely used in abdominal imaging with spleen as reference [29,30], whereas its employment is relatively new in central nervous system and in head and neck imaging [34–39]. For cholesteatoma imaging this type of standardization, although tested on small samples and unrelated to considerations of a prognostic nature, has already been proposed using the pons or the cerebellum as a reference [40,41]. Conversely, we suggest carrying out normalization using as reference the more conventionally adopted NAWM, because easier to sample on a coronal plane and less susceptible to artifacts. However, our study was performed on a same 1.5 T MRI scanner with a specific DWI sequence; therefore the consistency and the reproducibility of normalized values should be further validated in different conditions to ensure that nADC is comparable across vendors and institutions, independently of coil system, sequence, or field strength.

Finally, the supplemental analysis performed on the recurrence subgroup testing the association with the interval surgery-recurrence showed a slightly positive correlation with lower ADC values, but no significant correlation with lesion dimensions at baseline MRI examination. The findings suggest that risk of recurrence is mainly related to cholesteatoma pathological characteristics rather than to lesions' volume and local extension. This evidence further supports the reliability of the proposed stratification in high- and low-risk of recurrence cholesteatoma based on pre-operative nADC values. As an ancillary observation, it should be noted that mean interval between surgery and disease relapse in case of recurrence was about two years (25.3 ± 8.8 months; range 11–36 months). Repeated MR follow-up is therefore crucial to rule out a small growing cholesteatoma despite a negative first post-operative MRI, and some Authors proposed an annual DWI follow-up also in case of apparently complete cholesteatoma surgery [42]. However at present no consensus concerning the optimal follow-up scheme has been reached. According to our findings, we therefore suggest a closer but also prolonged DWI follow-up, especially in patients with ADC values highly suggestive for more aggressive cholesteatoma behaviour.

One of the main limitations of the study is that the accuracy of DWI/ADC in detecting residual disease is partly limited by the size of the lesion, as some very small residual cholesteatomas could have been missed at the first post-operative follow-up MRI examination. Moreover, after histological confirmation, surgical specimens have not been further examined by a pathologist to test the hypothesis that ADC values in the two sub-groups could reflect a different composition of cholesteatomas or a more prominent inflammatory perilesional activity. Therefore future studies are warranted to confirm these initial findings, as well as to implement the use of ADC normalization in routine clinical practice.

5. Conclusions

Beside the well-known accuracy of non-EPI DWI techniques and relative ADC maps in detecting cholesteatomatous tissue, ADC can also represent a useful tool for stratifying primary middle ear cholesteatoma risk of recurrence. Normalized ADC values resulted slightly more discriminating than conventional ADC measurements in distinguish cholesteatomas with higher risk of early recurrence from lesions with lower risk of recurrence, with possible spillover effects on post-operative patients management and outcome prediction.

Disclosures

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Written informed consent was obtained from all subjects (patients) in this study.

Institutional Review Board approval was obtained.

CRediT authorship contribution statement

Camilla Russo: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization. **Andrea Elefante:** Conceptualization, Validation, Investigation, Data curation, Writing - review & editing, Project administration. **Michele Cavaliere:** Validation, Investigation, Data curation, Writing - review & editing. **Antonella M. Di Lullo:** Methodology, Formal analysis, Investigation, Data curation, Visualization. **Gaetano Motta:** Resources, Supervision. **Maurizio Iengo:** Resources, Supervision. **Arturo Brunetti:** Resources, Supervision.

References

[1] Y. Mallet, J. Nouwen, M. Lecomte-Houcke, A. Desaulty, Aggressiveness and quantification of epithelial proliferation of middle ear cholesteatoma by MIB1, Laryngoscope 113 (February (2)) (2003) 328–331, https://doi.org/10.1097/00005537-200302000-00024.

[2] F. Más-estellés, M. Mateos-fernández, B. Carrascosa-Bisquert, F. Facal de Castro, I. Puchades- Román, C. Morera-Pérez, Contemporary non–Echo–planar

diffusion–weighted imaging of middle ear cholesteatomas, RadioGraphics 32 (2012) 1197–1213, https://doi.org/10.1148/rg.324115109.
[3] J.P. Vercruysse, B. De Foer, M. Pouillon, T. Somers, J. Casselman, E. Offeciers, The value of diffusion-weighted MR imaging in the diagnosis of primary acquired and residual cholesteatoma: a surgical verified study of 100 patients, Eur. Radiol. 16 (7) (2006) 1461–1467, https://doi.org/10.1007/s00330-006-0160-2.
[4] B. De Foer, et al., Single-shot, turbo spin-echo, diffusion-weighted imaging versus spin-echo-planar, diffusion-weighted imaging in the detection of acquired middle ear cholesteatoma, Am. J. Neuroradiol. 27 (7) (2006) 1480–1482.
[5] B. De Foer, et al., The value of single-shot turbo spin-echo diffusion-weighted MR imaging in the detection of middle ear cholesteatoma, Neuroradiology 49 (October (10)) (2007) 841–848, https://doi.org/10.1007/s00234-007-0268-3.
[6] M.H.G. Dremmen, P.A.M. Hofman, J.R. Hof, R.J. Stokroos, A.A. Postma, The diagnostic accuracy of non-echo-planar diffusion-weighted imaging in the detection of residual and/or recurrent cholesteatoma of the temporal bone, Am. J. Neuroradiol. 33 (3) (2012) 439–444, https://doi.org/10.3174/ajnr.A2824.
[7] A. Elefante, et al., Diffusion weighted MR imaging of primary and recurrent middle ear cholesteatoma: an assessment by readers with different expertise, Biomed Res. Int. 2015 (2015) 1–8, https://doi.org/10.1155/2015/597896.
[8] N.C. Cimsit, C. Cimsit, B. Baysal, I.C. Ruhi, S. Ozbilgen, E.A. Aksoy, Diffusion-weighted MR imaging in postoperative follow-up: reliability for detection of recurrent cholesteatoma, Eur. J. Radiol. 74 (1) (2010) 121–123, https://doi.org/10.1016/j.ejrad.2009.01.025.
[9] K. Yamashita, et al., Detection of middle ear cholesteatoma by diffusion-weighted MR imaging: multishot echo-planar imaging compared with single-shot echo-planar imaging, Am. J. Neuroradiol. 32 (10) (2011) 1915–1918, https://doi.org/10.3174/ajnr.A2651.
[10] M. Cavaliere, et al., Diffusion-weighted intensity magnetic resonance in the preoperative diagnosis of cholesteatoma, Orl 76 (4) (2014) 212–221, https://doi.org/10.1159/000365931.
[11] S. Thiriat, S. Riehm, S. Kremer, E. Martin, F. Veillon, Apparent diffusion coefficient values of middle ear cholesteatoma differ from abscess and cholesteatoma admixed infection, Am. J. Neuroradiol. 30 (6) (2009) 1123–1126, https://doi.org/10.3174/ajnr.A1473.
[12] R.K. Lingam, P. Khatri, J. Hughes, A. Singh, Apparent diffusion coefficients for detection of postoperative middle ear cholesteatoma on non-echo-planar diffusion-weighted images, Radiology 269 (2) (2013) 504–510, https://doi.org/10.1148/radiol.13130065.
[13] C. Russo, et al., ADC benchmark range for correct diagnosis of primary and recurrent middle ear cholesteatoma, Biomed Res. Int. 2018 (April) (2018) 1–6, https://doi.org/10.1155/2018/7945482.
[14] M. Cavaliere, et al., Cholesteatoma vs granulation tissue: a differential diagnosis by DWI-MRI apparent diffusion coefficient, Eur. Arch. oto-rhino-laryngology 275 (September (9)) (2018) 2237–2243, https://doi.org/10.1007/s00405-018-5082-5.
[15] A.S. Kıvrak, Y. Paksoy, C. Erol, M. Koplay, S. Özbek, F. Kara, Comparison of apparent diffusion coefficient values among different MRI platforms: a multicenter phantom study, Diagn. Interv. Radiol. 19 (1) (2013) 433–437, https://doi.org/10.5152/dir.2013.13034.
[16] A. Ghosh, T. Singh, V. Singla, R. Bagga, N. Khandelwal, Comparison of Absolute Apparent Diffusion Coefficient (ADC) values in ADC maps generated across different postprocessing software: reproducibility in endometrial carcinoma, AJR 209 (May) (2017) 1–8, https://doi.org/10.2214/AJR.17.18002.
[17] A.S. Kolff-Gart, et al., Diffusion-weighted imaging of the head and neck in healthy subjects: reproducibility of ADC values in different MRI systems and repeat sessions, AJNR 36 (February (2)) (2015) 384–390, https://doi.org/10.3174/ajnr.A4114.
[18] M. Ajallouеyan, Experience with surgical management of cholesteatomas, Arch. Otolaryngol. Head Neck Surg. 132 (September) (2006) 931–933.
[19] I. Pai, E. Crossley, H. Lancer, C. Dudau, S. Connor, Growth and late detection of post-operative cholesteatoma on long term follow-up with diffusion weighted magnetic resonance imaging (DWI MRI): a retrospective analysis from a single UK Centre, Otol. Neurotol. 40 (5) (2019) 638–644, https://doi.org/10.1097/MAO.0000000000002188.
[20] R. Nash, A. Kalan, R.K. Lingam, A. Singh, The role of diffusion-weighted magnetic resonance imaging in assessing residual/recurrent cholesteatoma after canal wall down mastoidectomy, Clin. Otolaryngol. 41 (November (2015)) (2016) 305–309.
[21] I. Unal, Defining an optimal cut-point value in ROC analysis: an alternative approach, Comput. Math. Methods Med. 2017 (2017), https://doi.org/10.1155/2017/3762651.
[22] R.K. Lingam, R. Nash, A. Majithia, A. Kalan, A. Singh, Non-echoplanar diffusion weighted imaging in the detection of post-operative middle ear cholesteatoma: navigating beyond the pitfalls to find the pearl, Insights Imaging 7 (2016) 669–678, https://doi.org/10.1007/s13244-016-0516-3.
[23] Ã. Lingam, P. Bassett, A meta-analysis on the diagnostic performance of non-echoplanar diffusion-weighted imaging in detecting middle ear cholesteatoma: 10 years on, Otol. Neurotol. 38 (2017) 521–528, https://doi.org/10.1097/MAO.0000000000001353.
[24] R.K. Lingam, S.E.J. Connor, J.W. Casselman, T. Beale, MRI in otology : applications in cholesteatoma and Ménière's disease, Clin. Radiol. (2017) 1–10, https://doi.org/10.1016/j.crad.2017.09.002.
[25] A. Ferlito, A review of the definition, terminology and pathology of aural cholesteatoma, J. Laryngol. Otol. 107 (June) (1993) 483–488.
[26] C. Kuo, et al., Updates and knowledge gaps in cholesteatoma research, Biomed Res. Int. 2015 (2015), https://doi.org/10.1155/2015/854024.
[27] N.M.M. Osman, A.A. Rahman, M.A.H.A. Talaat, The accuracy and sensitivity of diffusion-weighted magnetic resonance imaging with Apparent Diffusion Coefficients in diagnosis of recurrent cholesteatoma, Eur. J. Radiol. Open 4 (2017) 27–39, https://doi.org/10.1016/j.ejro.2017.03.001.
[28] A.R. Padhani, et al., Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations, Neoplasia 11 (2) (2009) 102–2125, https://doi.org/10.1593/neo.81328.
[29] H. Chandanara, E. Felker, C.H. Hajdu, J.S. Babb, D. Kim, B. Taouli, Diagnosis of liver fibrosis and cirrhosis with diffusion- weighted imaging: value of normalized apparent diffusion coefficient using the spleen as reference organ, AJR 195 (September) (2010) 671–676, https://doi.org/10.2214/AJR.09.3448.
[30] M. Barral, et al., Characterization of focal pancreatic lesions using normalized apparent diffusion coefficient at 1.5-Tesla: preliminary experience, Diagn. Interv. Imaging 94 (6) (2013) 619–627, https://doi.org/10.1016/j.diii.2013.02.011.
[31] E. Jurkiewicz, W. Grajkowska, K. Nowak, P. Kowalczyk, A. Walecka, B. Dembowska-Bagińska, MR imaging, apparent diffusion coefficient and histopathological features of desmoplastic infantile tumors — own experience and review of the literature, Childs Nerv. Syst. 31 (2015) 251–259, https://doi.org/10.1007/s00381-014-2593-2.
[32] E.A. Azab, M.E. Ibrahim, The Egyptian Journal of Radiology and Nuclear Medicine Diffusion weighted (DW) MRI role in characterization of breast lesions using absolute and normalized ADC values, Egypt. J. Radiol. Nucl. Med. 49 (2) (2018) 564–570, https://doi.org/10.1016/j.ejrnm.2018.01.009.
[33] R. Kuwahara, et al., A predictor of tumor recurrence in patients with endometrial carcinoma after complete resection of the tumor the role of pretreatment apparent diffusion coefficient, Int. J. Gynecol. Cancer 28 (5) (2018) 861–868, https://doi.org/10.1097/IGC.0000000000001259.
[34] L. Liu, B. Yin, D. Geng, Y. Li, B. Zhang, W. Peng, Comparison of ADC values of intracranial hemangiopericytomas and angiomatous and anaplastic meningiomas, J. Neuroradiol. 41 (July (3)) (2014) 188–194, https://doi.org/10.1016/j.neurad.2013.07.002.
[35] Lin, et al., Diagnostic accuracy of T1-Weighted dynamic contrast-enhanced–MRI and DWI-ADC for differentiation of glioblastoma and primary CNS lymphoma, AJNR 38 (March (3)) (2017) 485–491.
[36] S. Lee, et al., Application of diffusion-weighted imaging and dynamic susceptibility contrast perfusion-weighted imaging for ganglioglioma in adults: comparison study with oligodendroglioma, J. Neuroradiol. (2016) 1–8, https://doi.org/10.1016/j.neurad.2016.06.001.
[37] J. Wen, W. Huang, W.-X.-Z. Xu, G. Wu, D. Geng, B. Yin, Differentiating primary central nervous system lymphomas from glioblastomas and inflammatory demyelinating pseudotumor using relative minimum apparent diffusion coefficients, JCAT 41 (6) (2017) 904–909, https://doi.org/10.1097/RCT.0000000000000636.
[38] D.T. Ginat, G. Yeaney, S. Ekholm, Diffusion-weighted imaging of skull lesions, J. Neurol. Surg. 75 (2014) 204–213.
[39] L. Qin, et al., Normalization of ADC does not improve correlation with overall survival in patients with high-grade glioma (HGG), J. Neurooncol. 137 (April (2)) (2018) 313–319, https://doi.org/10.1007/s11060-017-2719-y.
[40] H. Suzuki, et al., Numerical assessment of cholesteatoma by signal intensity on non-EP-DWI and ADC maps, Otol. Neurotol. 35 (6) (2014) 1007–1010, https://doi.org/10.1097/MAO.0000000000000360.
[41] M. Sone, et al., Comparison of computed tomography and magnetic resonance imaging for evaluation of cholesteatoma with labyrinthine fistulae, Laryngoscope 122 (May) (2012) 1121–1125, https://doi.org/10.1002/lary.23204.
[42] Ã. Steens, Ã. Venderink, D. Kunst, Ã. Meijer, E. Mylanus, Repeated postoperative follow-up diffusion-weighted magnetic resonance imaging to detect residual or recurrent cholesteatoma, Otol. Neurotol. 37 (2016) 356–361.