

Diagnosis of cholesteatoma by the b1000 value DWI MRI according to the signal intensity

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Abstract

Objective: The cholesteatoma (CL) can be evaluated visually or numerically on an apparent diffusion coefficient (ADC) map, which obtained from at least two different b-valued diffusion-weighted imaging (DWI). In this study, we aimed to evaluate the signal intensity (SI) of the lesion both visually and numerically only on the DWI image without ADC. In case of positive results a second 'b' value is not required, so this method could be shorten the duration of the MRI examination.

Material and Methods: Between January 2017 and May 2018, we included patients with chronic otitis media (COM) with a clinical suspicion of primary CL who underwent DWI. Two radiologists and one ear, nose, throat specialist evaluated the radiological images and the pathology results.

Results: The mean SI measurement was significantly higher in the CL group by both observers (observer LR; CL: 107.94 ± 53.36 , COM: 37.34 ± 14.70 , observer FC; CL: 108.56 ± 50.00 , COM: 37.06 ± 15.44 ; $p < 0.0001$). ROC analysis showed that a mean SI value of 48.6 was the cut-off value in predicting the diagnosis of CL. The mean SI was significantly higher in the CL group ($p < 0.001$).

Conclusion: We demonstrated a significant difference between CL and COM concerning the diagnosis by visual and numerical signal evaluation only via b1000 valuable images. In false-positive cases, ADC is still confirmatory for high diagnostic accuracy.

Keywords: Cholesteatoma, diffusion, signal intensity, quantitative assessment, false positive

Introduction

Cholesteatoma (CL) is a keratin collection filling the squamous epithelium sac. This benign but destructive lesion causes bone erosions in the middle ear and mastoid bone and subsequently causes complications such as loss of conductive hearing, facial paralysis, and labyrinthitis (1). The treatment includes an intact canal wall or canal wall down mastoidectomy based on the extent of the disease and the surgeon's preference (2). Both techniques carry the risk of residual CL in a wide frequency range (3, 4). Second look surgery is often required 6 - 18 months after surgery. However, advances in radiology over the past decade have given reliable non-invasive hope for the diagnosis of primary and residual cholesteatoma (5).

The high resolution computed tomography (CT) is an excellent imaging tool with its high spatial resolution to demonstrate the localization concerning bony neighbors and extension of the lesion (6). However, its specificity is as low as 48%, and the soft tissue cannot differentiate between CL and other middle ear pathologies (7, 8).

The postcontrast T1-weighted magnetic resonance imaging (MRI) is one of the effective techniques for distinguishing soft tissue pathologies from CL. The CL is avascular and does not enhance with contrast material, whereas others such as granulation tissue are vascularized and contrasted (7). Although the sensitivity and specificity of this technique in the diagnosis of postoperative residual or recurring CL were 90% and 100%, respectively (9), 30-45 minutes of post-contrast imaging decreases practice efficiency and irritate the patients that limit the availability of the technique (1).

Today, the highest sensitivity (100%) and specificity (90%) of the radiological modality is diffusion-weighted imaging (DWI) (10). During the past decade, data have been published advocating DWI for primary diagnosis and evaluation of the residual CL following mastoidectomy (11). Many centers have used non-echo-planar imaging (EPI) for the follow-up of patients for a residual lesion in the place of second-look surgery (12, 13).



The lesion can be evaluated both visually and numerically on the ADC map obtained from at least two different b-valued DWI images. The limited molecular diffusion with decreased signal intensity (SI) on the ADC map is caused by the excellent keratin content of CL (1). To date, this technique is considered as state-of-the-art cholesteatoma imaging.

In this study, we aimed to evaluate the signal intensity of the lesion both visually and numerically only on the DWI image without creating an ADC map in diffusion MRI where we shortened the examination time by taking a single b value (b 1000) instead of taking multiple b values.

Material and Methods

Study population: The approval for the retrospective study without patient informed consent was taken from the local institutional review board (12/04/2018-18/287). The patients who had been referred to our radiology unit with a clinical suspicion of primary CL and examined with HASTE DWI MRI between January 2017 and May 2018 were included in the study. The radiological reports, physical examination findings, conductive hearing test, and the pathology results, if operated, were evaluated by two radiologists and one ear, nose, throat specialist. The follow-ups of patients who did not undergo surgery were investigated on the hospital system for up to 18 months after the first imaging. As a result, the CL group of 31 patients was formed based on the pathology report (three of 31 patients with no signal in the DWI were excluded from the statistical evaluation). Thirty patients of chronic otitis media (COM) without CL formed COM group. Out of 30, 12 patients were confirmed by surgery, and 18 patients with chronic otitis media had negative otoscopy and hearing test with a negative DWI MRI during 18 months of the follow-up period.

Imaging technique: MRI was performed on a 1.5-T superconductive unit (MagnetomAvanto; Siemens Medical Solutions, Erlangen, Germany) with the use of the standard Head Matrix coil. Axial 5-mm thick accurate FISP T2-weighted images (TR 4640 ms; TE 103 ms; matrix 245x384; the field of view 150 x200 mm) were performed. In all patients, a 2-mm thick HASTE DWI sequence was acquired in the coronal plane (TR 2000 ms; TE 147 ms; matrix 134 x 192; the field of view 220x 220 mm; b factors 0 and 1000 mm²/s; acquisition time 3 minutes 38 seconds).

MR imaging analysis

The images were evaluated by one head and neck radiologist who has at least five years of experience in temporal bone imaging (F.C.), one radiology resident (L.R.) and one ear, nose, and throat specialist (H.G.) who were blinded to the radiological and clinical data.

In the first step, the b1000 images were evaluated visually and numerically on DWI. Two of the three observers (F.C. and L.R.) were trained for standardization of the SI measurement, and all of the three observers (F.C., L.R., and H.G.) were trained for visual assessment of signal compared to brain parenchyma in five cases who were not included in the study. The qualitative and quantitative evaluation of the lesion signal was analyzed for each test

lesion. In case of any discordance in the assessment of the lesion, a more detailed investigation was performed retrospectively for possible reasons to make a standard evaluation. After the training period was completed, all three observers separately evaluated all of the cases randomly.

Secondly, the ADC maps using b0 and b1000 values were evaluated by both of the observers (F.C. and L.R.).

Determination of the lesions for evaluation

On a standard PACS monitor, axial T2, coronal DWI, and CT images were evaluated for the determination of the middle ear and mastoid lesions. Due to the insufficient spatial resolution of HASTE DWI, CT images were examined to confirm whether the SI was in the mastoid bone and the middle ear or outside both locations. There were no more than two weeks between DWI MRI and CT examinations.

Qualitative analysis by visual inspection

The criteria for the diagnosis of CL at DWI was based on the evidence of a hyperintense middle ear or mastoid lesion, compared with the SI of the brain parenchyma. If the SI of the pathology were hyperintense compared to brain parenchyma on b1000 DWI, it would be diagnosed as CL. During the visual assessment, the SI of the part of the lesion with the highest intensity was taken into account.

To prevent the false-positive results due to some possible hyperintense non-CL lesions, we graded SI in three levels as isointense, mildly hyperintense, and hyperintense compared to the brain parenchyma.

The pathologies were evaluated in two separate groups with different visual signal intensities. In Group 1, the hyperintense lesions were considered as CL, mildly hyperintense, and isointense pathologies as COM. In Group 2, the hyperintense and mildly hyperintense lesions were thought of as CL and isointense lesions as COM.

Quantitative analysis

The SI of the lesions was determined by using a region of interests (ROIs) ranging in size from 3 to 6 mm² on b1000 DWI images. In the same image, the SI of the adjacent temporal lobe parenchyma was also measured by using a similar-sized ROI.

The central SI of the lesion was usually higher than peripheral, and particular attention was paid to achieve a standardized evaluation by localizing the ROI on the highest signal-containing portion of the pathology and in the adjacent temporal lobe parenchyma. To prevent the partial volume effect that might lead to a decrease in the measured SI of the lesion on DWI, the measurement of the SI was attempted on the image seen by the broadest diameter of pathology and the axial T2 and multiplanar CT images were also used to determine the slice passing through the central part of the pathology.

Quantitative characterization of a lesion with the severity of SI may not be accurate due to scanner related and magnetic susceptibility artifacts in MRI. Thus, we rated the SI of

lesion and brain parenchyma and performed lesion signal intensity ratio (SIR) to normalize signal differences.

Statistical analysis: The data were analyzed using SPSS version 22 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics related to discrete data were expressed as numbers (n) and percentages (%). Continuous variables were expressed as a mean±standard deviation. A Kolmogorov-Smirnov test was used to test for the normal distribution of continuous variables, and parametric tests were used to compare the normally distributed data between the groups, while nonparametric tests were used for the comparison of data without normal distribution. A parametric paired sample t-test was used to compare two independent groups, and a nonparametric independent sample t-test was used for the comparison of matched groups. Pearson's correlation coefficient was used to evaluate the correlation between variables. The discriminative power of the numerical signal intensity data was predicted using the area under the curve in the ROC curve analysis, along with sensitivity-specificity parameters. A p-value of <0.001 was considered statistically significant in the comparisons.

Results

The study included 28 patients with primary CL (48.3%) and 30 patients with chronic otitis media (COM) without CL (51.7%). The mean age of the patients was 36.53±15.20 (min-max: 12–72 years). The mean age was 32.68±14.07 years (min-max: 12–58 years) in the CL group and 40.13±15.56 years (min-max: 20–72 years) in the COM group. A comparison of age and gender between the groups showed no statistically significant difference (p=0.061 and p=0.754, respectively).

The mean lesion size was 12.71±7.34 mm (min-max: 5.0–42.0) in the CL group (Figure 1) and 12.64±4.30 mm (min-max: 5.4–24.0) in the COM group. There was no statistically significant difference between the groups (p=0.964).

There was a statistically significant difference in the visual SI evaluation between CL and COM groups (p<0.001) (Table 1). The analysis of the correlation between the numerical and visual signal intensities assessed by physicians showed a significantly positive and robust correlation (Table 2).

When a hyperintense lesion was considered diagnostic for CL, and mildly hyperintense and isointense pathologies for COM (Group 1) according to the analysis of visual signal intensity, the sensitivity was 82.14%, specificity was 90%, PPV was 88.46%, and NPV was 84.37%. When hyperintense and mildly hyperintense lesions were considered diagnostic for CL and an iso-intense pathology for COM (Group 2), the sensitivity was 96.43%, specificity was 73.33%, positive predictive value (PPV) was 77.14%, and negative predictive value (NPV) was 95.65%.

In Group 1, there were five false-negative results in the CL group and three false-positive results in the COM group (Figure 2). In Group 2, there was one false-negative result in the CL group and eight false-positive results in the COM group (Table 3).

The mean SI measurement of the observer (LR) was 107.94 ± 53.36 (min-max: 47.75 ± 263.75) in the CL and 37.34 ± 14.70 (min-max: 21.00 ± 94.67) in the COM. The mean SI was significantly higher in the CL group (p<0.001). The SIR measurement value of observer (LR) was 3.270 ± 1.77 (min-max: 1.32 ± 8.09) in the CL group, while it was 1.15 ± 0.46 (min-max: 0.61 ± 3.04) in the COM group and SIR rates were significantly higher in the CL group (p < 0001). The mean SI of the brain parenchyma did not differ significantly between the CL and COM groups (p=0.159 and p=0.823, respectively). Therefore, we were able to evaluate the SIR between the two groups.

In the measurements of other observer (FC), both SI means (CL: 108.56 ± 50.00, min-max: 40.25 ± 220.96 and COM: 37.06 ± 15.44, min-max: 19.75 ± 100.50) and SIR values (3.34 ± 1.71, min-max: 1.10 ± 7.56 and COM: 1.14 ± 0.50, min-max: 0.59 ± 3.24) were higher in the CL group (p < 0.001, p < 0.001, respectively).

Based on the results of the ROC curve analysis, a mean SI value of 48.625 was considered as the cut-off value in predicting a diagnosis of CL. The reference value was 1.322 when the SIR was taken into account for diagnosis.

The rate of patients diagnosed with CL according to the maximum and mean SI values was 56.9% (n=33). Furthermore, five patients were falsely diagnosed with CL according to the numerical SI value. The sensitivity was 96.43%, and the specificity was 80% based on the mean SI values. The PPV was 81.82%, and the NPV was 96%. The diagnose of CL was also predicted in 34 patients according to the reference value of SIR. Accordingly, sensitivity was 96.43%, specificity was 76.67%, PPV was 79.41%, and NPV was 95.83%.

The mean numerical SI value was 48.58 ± 6.89 (n=5, min-max: 38.67–54.00) in five patients in the COM group who had a mildly hyperintense lesion upon a visual SI evaluation, and 65.56 ± 25.26 (n=3, min-max: 49.50–94.67) in three patients who had a hyperintense pathology (Table 4).

Only one patient was found to have an isointense lesion in a visual SI evaluation in the CL group. The mean numerical SI value of this CL was 47.75.

The mean ADC values were 1.1 ± 0.1 × 10⁻³ mm²/s for the CL group and 1.9 ± 0.6 × 10⁻³ mm²/s for the COM group. If the ADC value of the lesion is ≤ 1.1 × 10⁻³ mm²/s, CL could be diagnosed with 97 % sensitivity, 89% specificity, 91% PPV, and 96% NPV.

Table 1: Comparison of visual signal intensity evaluation among three observers (LR, FC ve HG).

Observers Groups		Isointense n (%)	Mildly hyperintense n (%)	Hyperintense n (%)	Total n (%)	P*
LR	CL	1 (3.6)	4 (14.3)	23 (82.1)	28 (100.0)	<0.001
	COM	22 (73.3)	5 (16.7)	3 (10.0)	30 (100.0)	
	Total	23 (39.7)	9 (15.5)	26 (44.8)	58 (100.0)	
FC	CL	-	5 (17.9)	23 (82.1)	28 (100.0)	<0.001
	COM	24 (80.0)	5 (16.7)	1 (3.3)	30 (100.0)	
	Total	24 (41.4)	10 (17.2)	24 (41.4)	58 (100.0)	
HG	CL	-	5 (17.9)	23 (82.1)	28 (100.0)	<0.001
	COM	20 (66.7)	9 (30.0)	1 (3.3)	30 (100.0)	
	Total	20 (34.5)	14 (24.1)	24 (41.4)	58 (100.0)	

*Pearson chi-square test, CL: Cholesteatoma, COM: Chronic otitis media without cholesteatoma

Table 2: Correlations of observers (LR, FC ve HG) in evaluating the numerical and visual signal intensity

SI evaluation _ Observer		r	p*
Numerical SI_LR	SIR_LR	0.987	<0.001
	Numerical SI_FC	0.981	<0.001
	SIR_FC	0.971	<0.001
	Visual SI_LR	0.711	<0.001
	Visual SI_FC	0.740	<0.001
	Visual SI_HG	0.737	<0.001
SIR_LR	Numerical SI_FC	0.960	<0.001
	SIR_FC	0.976	<0.001
	Visual SI_LR	0.687	<0.001
	Visual SI_FC	0.713	<0.001
	Visual SI_HG	0.709	<0.001
Numerical SI_FC	SIR_FC	0.982	<0.001
	Visual SI_LR	0.755	<0.001
	Visual SI_FC	0.783	<0.001
	Visual SI_HG	0.768	<0.001
SIR_FC	Visual SI_LR	0.732	<0.001
	Visual SI_FC	0.758	<0.001
	Visual SI_HG	0.743	<0.001
Visual SI_LR	Visual SI_FC	0.950	<0.001
	Visual SI_HG	0.904	<0.001
Visual SI_FC	Visual SI_HG	0.917	<0.001

*Pearson Correlation Test (Correlation is significant at the 0,005 level. (2-tailed)), SI: Signal intensity, SIR: Signal intensity ratio

Table 3: Comparison of pathology results with visual signal evaluation. In group 1, a hyperintense lesion was considered diagnostic for cholesteatoma. In group 2, hyperintense and mildly hyperintense lesions were deemed to be symptomatic for cholesteatoma.

Group 1 (Hyperintense=CL)			
Pathology	Visual SI	n	%
COM (n=30)	COM	27	90.0
	CL	3*	10.0
CL (n=28)	COM	5*	17.9
	CL	23	82.1
	Total	28	100.0
Group 2 (Hyperintense ve mildly hyperintense=CL)			
Pathology	Visual SI	n	%
COM (n=30)	COM	22	73.3
	CL	8**	26.7
CL (n=28)	COM	1**	3.6
	CL	27	96.4
	Total	28	100.0

SI: Signal intensity, CL: Cholesteatoma, COM: Chronic otitis media without cholesteatoma. *(If mildly hyperintense and isointense lesions were considered diagnostic for COM (group 1) in visual SI evaluation, there were five false-negative results in the CL group and three false-positive results in the COM group.) ** (If hyperintense and mildly hyperintense lesions were considered diagnostic for CL (group 2) in visual SI evaluation, there was one false-negative result in the CL group and eight false-positive results in the COM group. Of the eight false-positive results, three were hyperintense, and five were mildly hyperintense.)

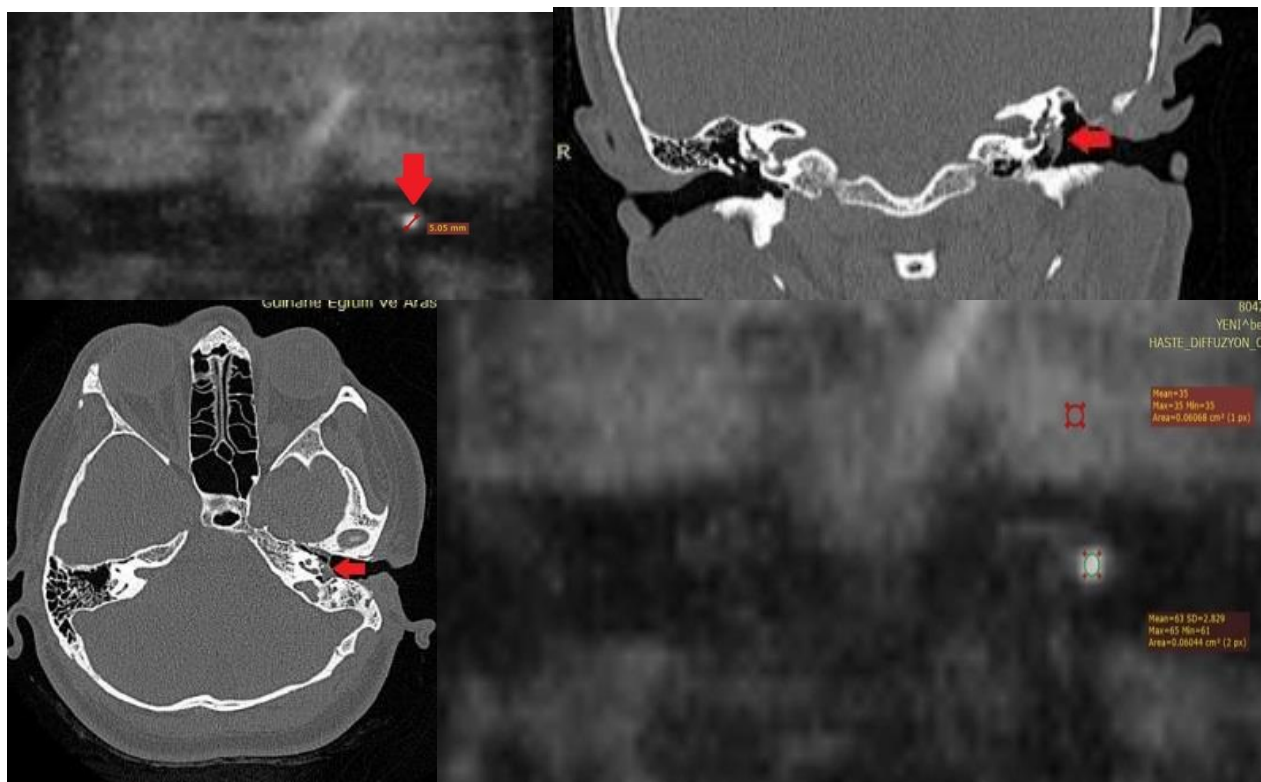


Figure 1. Cholesteatoma (red arrow) in the left middle ear cavity. A. Round shape lesion with 5 mm diameter was hyperintense compared to the brain parenchyma on HASTE DWI at $b=1000 \text{ mm}^2/\text{s}$. B-C. On the temporal bone CT, the cholesteatoma as a nodular soft tissue density localized at mesotympanum. D. The SI ratio (SIR) of cholesteatoma to the brain parenchyma (cholesteatoma SI/Brain parenchyma SI) was 1.8.

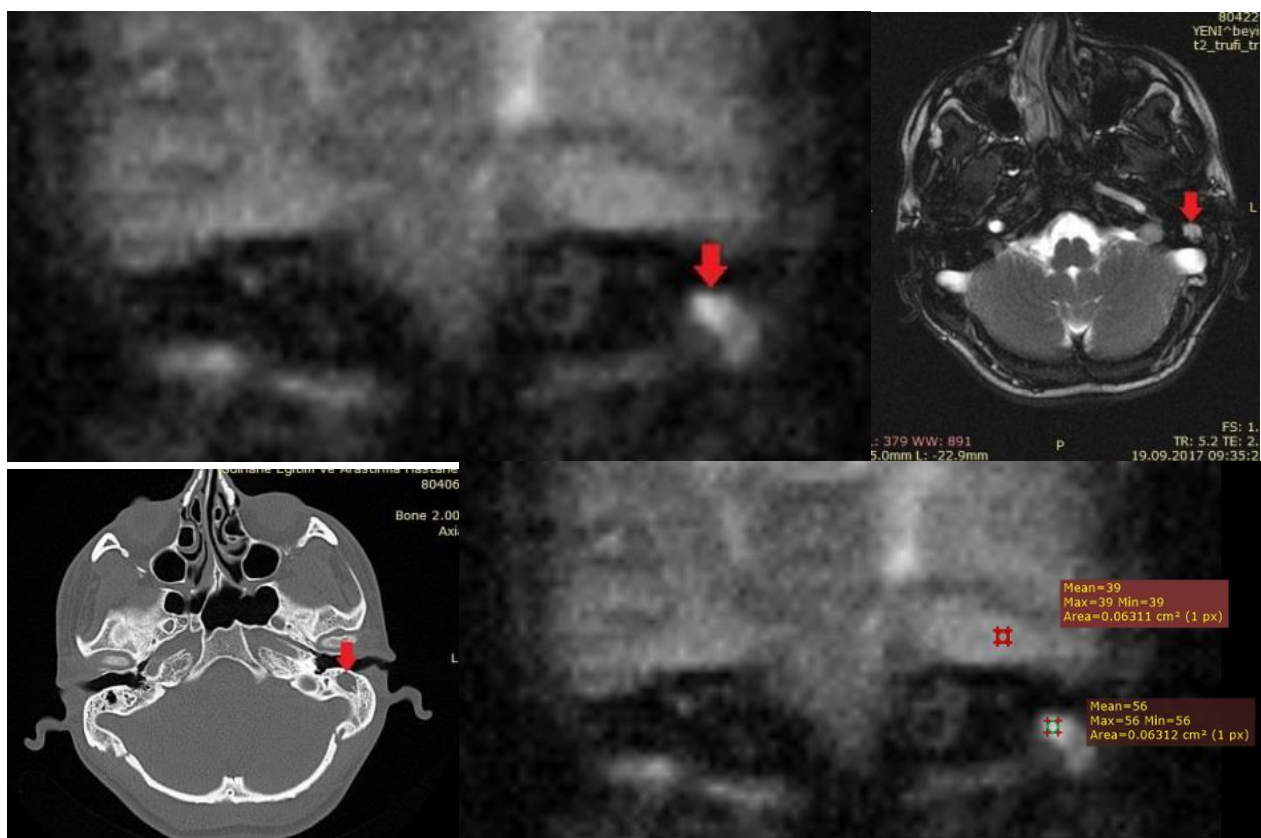


Figure 2. False positive non-cholesteatoma lesion (red arrow) with the histopathologic diagnosis of chronic inflammation. A. Nodular mildly hyperintensity compared to the brain parenchyma on HASTE DWI. B. Axial T2-weighted image showed hyperintense lesion at the mastoid cavity. C. The lesion observed at the mastoid tip within no bone trabeculation on axial CT image. D. The SIR of non-cholesteatoma lesion to brain parenchyma was 1.4.

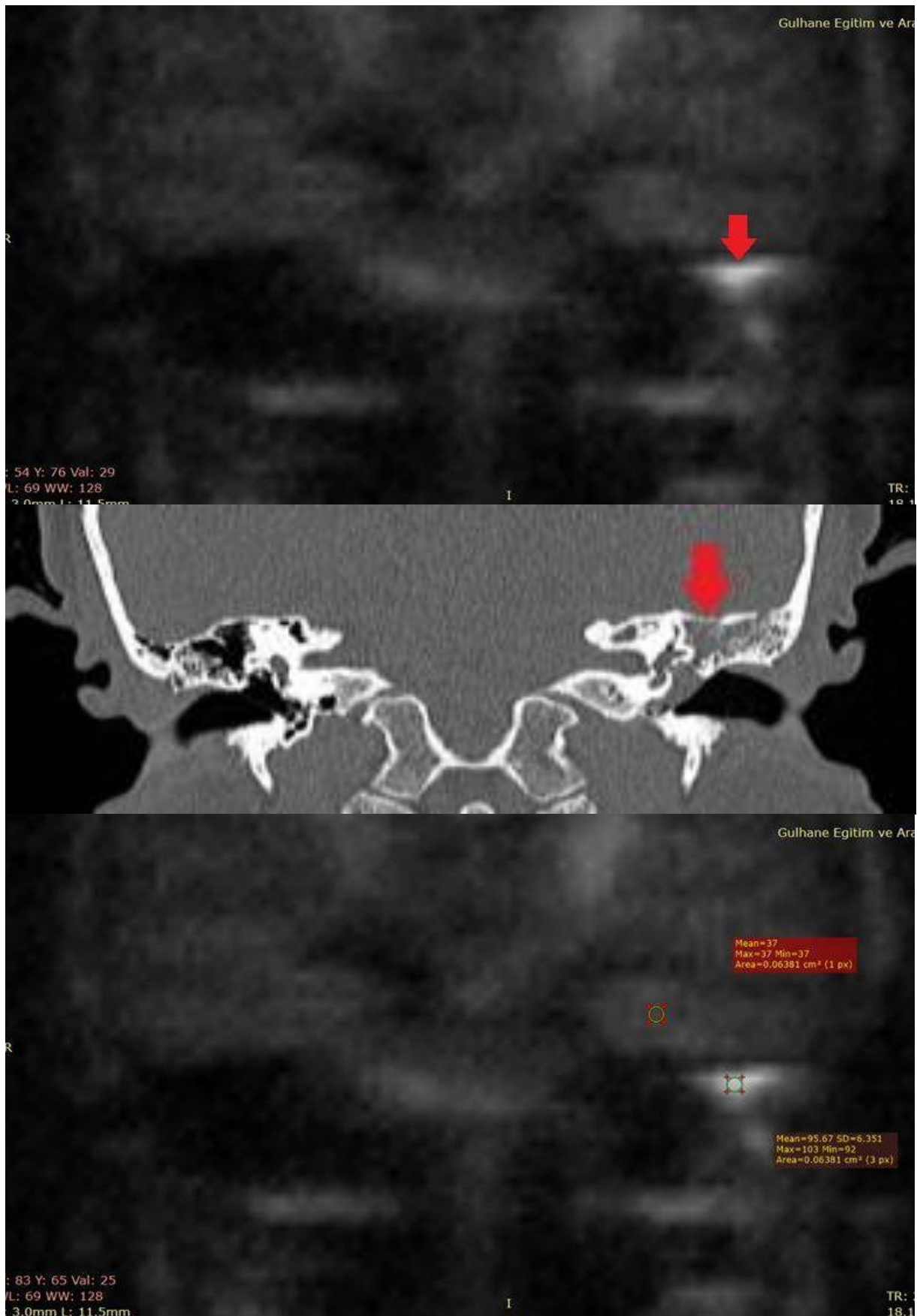


Figure 3. Carcinoid tumor (red arrow) confirmed by surgery. A. The lesion demonstrated very high signal compared with the brain parenchyma on HASTE DWI at $b=1000 \text{ mm}^2/\text{s}$ B. The soft tissue observed at the mastoid antrum on the coronal CT image. The tegmen tympani was intact. C. The SIR was 2.5.

Discussion

The current approach in the diagnosis of CL is the visual and numerical evaluation of the ADC map on diffusion MRI. To create an ADC map, at least two 'b' values of DWI images must be obtained. In our study, we aimed to perform a visual and numerical evaluation on a single 'b' value (b1000) of the DWI image. A significant difference in the visual assessment method was noted between CL and COM by the three observers by using only the b1000 value of DWI with a half short examination time in the present study ($p < 0.001$). According to the sensitivity (82%–92%) and specificity (86%–96%) values reported in the literature with the same assessment method (2, 10, 13–17), the higher sensitivity found in our study was due to the presence of a single patient with a false negative result.

False-negative results, which can affect sensitivity rates, are often due to the technical incapacities of the DWI. Small lesions and retraction pockets, referred to also as dry lesions, can be misdiagnosed on DWI (3). The mean lesion size in the present study was 12.71 mm, with the smallest lesion measuring 5 mm in size. Three of CL lesions measuring less than 3 mm that were removed with surgery were not included in the statistics due to lack of an abnormal signal on DWI. There was only one patient who was diagnosed false negatively due to an isointense sign with surrounding inflammation on DWI, and who was diagnosed with CL after surgery. There was no CL lesion located in the retraction pocket. Dry retraction pockets are lesions in which the keratin has disappeared, and only the surrounding epithelium with persistent aggressive potential is retained, making them undetectable on DWI (12, 18).

The eight patients in the COM group, who were misdiagnosed as CL, thus reduced the specificity of visual SI assessment. In a visual qualitative assessment, a mildly hyperintense signal may not always indicate cholesteatoma and may decrease the uniqueness of the method with false-positive results (3). The most common reason for false positivity is chronic inflammatory lesions occurring at a rate of 88.9%, while other causes include cholesterol granuloma, abscess, fat grafts, and bone cement (7, 10–12, 19–21). Of the eight patients with a false-positive diagnosis of CL, seven had an inflammatory lesion, and one had carcinoid tumor, which was not reported in the literature previously (Figure 3).

To preclude a false-positive diagnosis of COM due to high signal intensity relative to the brain parenchyma, the visual SI was also evaluated in three grades as hyperintense, mildly hyperintense, and isointense. When a hyperintense lesion was considered CL and mildly hyperintense and isointense pathologies were considered COM, the sensitivity, specificity, PPV, and NPV were 82.14%, 90%, 88.46%, and 84.37%, respectively. The number of patients with false-positive results decreased from eight to three, and the specificity increased to 90%, although sensitivity decreased to 82.14% with the five false adverse effects of CL.

Studies have reported good interobserver agreement between experienced neuroradiologists in a visual qualitative SI assessment (12), while there is no data on the

level of cooperation between general radiologists (8,20). A significant and robust positive correlation was identified between the visual assessment results of three physicians from different branches with varying levels of experience (Table 3).

As one of the objectives of the present study, a numerical evaluation was made of the SI and SIR values of the lesions, with the aim being to increase the sensitivity and specificity of DWI, despite those as mentioned above false negative and positive results (10, 11, 22). Özgen et al. reported a sensitivity and specificity of 100% using numerical values (3). In our study, the sensitivity and specificity of statistical SI assessment were 96.43% was 80% and showing no statistically significant difference to the visual SI assessment ($p < 0.001$). The numerical SI values of the lesions that showed false positive or false negative results in the visual qualitative assessment were around the cut-off values considered for the diagnosis of CL (Table 4).

Limitations: The numerical SI results of the present study must be repeated and confirmed for different non-EPI DWI sequences and various magnetic fields, and each clinic must determine its cut-off value. A histopathological examination did not support the absence of CL in some patients who were negative based on clinical and radiological evaluation in the COM group.

Conclusion

There is a significant difference between cholesteatoma and chronic otitis media in the diagnosis made by visual and numerical signal evaluation only via b1000 valuable images. However, in false-positive cases, the ADC map is a problem solver and is required for high diagnostic accuracy.

Acknowledgments: FC conceived the idea and designed the study. FC and HG carried out the data analysis, which was overseen by OS, and interpreted the findings. FC, BS, and MT wrote the first draft of the report, which was critically reviewed and edited by all the authors. All the authors approved the final article. According to local regulation in place during the time of the study, retrospective studies did not require ethical approval. We thank **Lacin Ramazanli** for image analysis. Financial Disclosure: The financial support for this study was provided by the investigators.

Conflict of Interest: The authors declare that they have no competing interests.

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