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ORIGINAL ARTICLE

# The Consideration of Diffusion MR Imaging, Dynamic Contrast-Enhanced MR and T2 Relaxation Time Measurements in Distinguishing of Cholesteatoma with Chronic Otitis Media

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**Purpose:** The aim of our study is to investigate the contribution of DWI, DCE-MRI, ADC measurements and T2 relaxometry in diagnosis of distinguishing cholesteatoma and COM

**Materials and Methods:** Our study is created by retrospectively reviewing MR images of a digital archive of totally 41 patients that were clinically or surgically diagnosed as COM and cholesteatoma. DWI, ADC values, T2 relaxation time, and CEP of lesions between the two groups were compared statistically. CEP was qualitatively evaluated. ROC analysis and McNemar statistics test were performed. Level of significance was determined as $p<0.05$.

**Results:** Cholesteatoma detection sensitivity in DWI is determined as 100%, and specificity was determined as 86%. ADC measurements revealed a statistically significant difference in differentiating COM and cholesteatoma ($p<0.05$). When T2 relaxometry were compared between two groups there was no statistically significant difference ($p>0.05$). When the groups were assessed according to the CEP, 13 of the COM cases showed type 1 (progressive heterogeneous enhancement), 2 cases did not show enhancement (type 3) and 6 cases showed type 4 (progressive homogeneous enhancement). Nineteen patients with cholesteatoma showed type 2 (rim-like enhancement), 1 case showed type 4. Statistical analysis of CEP revealed significant differences between types 1 and 2 ($p<0.001$), between types 2 and 3 ($p=0.005$) and between types 2 and 4 ($p<0.001$).

**Conclusion:** DWI, ADC values and DCE-MRI may be beneficial in detecting cases of cholesteatoma of a high percentage.

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## Introduction

Chronic otitis media (COM) is the chronic inflammation of the tympanic cavity and mastoid air cells and is characterized by continuous or recurrent otorrhea and perforation of the tympanic membrane. Otitis media without otorrhea is referred to as inactive or suppurative COM[1]. Cholesteatoma is a histologically benign but locally aggressive and destructive epidermoid tissue within the temporal bone. The most prominent feature of cholesteatoma is its destructive and invasive nature. High morbidity observed in patients with cholesteatoma is the clinical representation of the destructive and invasive nature of cholesteatoma. Even though the ratio varies among different series, Osma and colleagues's study[2] showed that cholesteatoma was present in 78% of COM patients who developed secondary complications. Inactive COM can be treated by topical medications while active COM with cholesteatoma presents with complications and destruction. Differentiation of active and inactive COM is very important clinically and usually requires imaging studies.

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In the present study, we aimed to differentiate inflammation and cholesteatoma using diffusion-weighted Imaging (DWI), apparent diffusion coefficient (ADC), T2 relaxation time and dynamic contrast enhanced MRI (DCE-MRI).

## Materials and Methods

### *Case selection*

Hospital records and digitally stored MR images of patients who had MRI of the internal auditory meatus between March 2008 and January 2011 at the Department of Radiology, Faculty of Medicine University were reviewed retrospectively. Patients was subjected to:

1- Full medical history taking.

2- Clinical examination: All patients are subjected to full Ear Nose Throat (ENT) examination in our ENT department. Otoscopic examination and audiological evaluation.

3- Radiological evaluation: MRİ examination:

4- Operative interference and data correlation: The diagnoses of cholesteatomas were confirmed by pathologic examination.

5- Diagnosis of COM was based on clinical evaluation, including otomicroscopic examination, radiology findings. The diagnosis COM was correlated with those obtained at clinical follow-up (6-12 months).

Patients who underwent middle ear surgery for any reason, patients with any pathology of the middle ear or the temporal bone other than COM or cholesteatoma and patients in whom MRI was contraindicated (pace maker, metallic or cochlear implant, metallic intraocular foreign body, claustrophobia, etc) were excluded from the study. Ethics Board for Medical Research of Faculty of Medicine, University approved the study (Date of approval: 26.05.2009, Reg. no: 2009-9/29).

### *MR Protocol*

A standard MRI protocol was followed for all patients. MR images were acquired on a 1.5T scanner using circular polarized head coil (Magnetom Vision Plus, Siemens, Erlangen, Germany). Following the acquisition of scout images, routine conventional images of the middle ear and mastoid antrum were acquired for anatomical and morphological assessments.

### MRI Techniques

*Axial and coronal T2-weighted* fast spin echo (FSE) [(TR: 3500 ms, TE: 15 ms, flip angle (FA): 180°, slice thickness: 2 mm, interslice gap: 0.20 mm, matrix: 140x256, Field of View (FOV): 230 mm, number of excitations (NEX): 2)], *axial and coronal T1-weighted* SE [(TR: 800 ms, TE: 14 ms, FA: 90°, slice thickness: 2 mm, interslice gap: 0.20 mm, matrix: 192x256, FOV: 230 mm, NEX: 2)], a*xial and coronal DWI [*(TR: 680 ms, TE: 18 ms, FA: 120°, slice thickness: 4 mm, interslice gap: 0.10 mm, matrix: 90x256, FOV: 230 mm, NEX: 2)] were performed. DWI was acquired in the axial and coronal planes using single-shot echo-planar spin echo sequence. For each slice, b value of 0 and 1000 sec/mm² was used and ADC maps were generated.

Axial DCE-MRI was performed using T1-weighted gradient echo (GRE) [(TR: 680 ms, TE: 18 ms, FA: 120°, slice thickness: 2 mm, interslice gap: 0.10 mm, matrix: 90x256, FOV: 230 mm, NEX: 2)]. Contrast-enhanced images were acquired before and 45, 90, 135, 180 seconds and 15 minutes after injection of contrast agent. Gadopentetic acid dimeglumine (Magnevist, Bayer-Schering, Berlin, Germany) or gadobutrol (Gadovist, Bayer-Schering, Berlin, Germany) was used as the contrast agent.

### *Image analysis*

Measurements were made on the ADC maps by drawing a circular region of interest (ROI) not larger than two-thirds of the lesion on an area where partial volume effect was minimal (Figure 1a). Post-processing of the images was carried out on a workstation. Lesions were classified qualitatively based on whether they were hyperintense to or hypointense/isointense with the grey matter on the affected side.

T2 relaxometry was carried out in the axial plane using Carr-Purcell-Meibom-Gill multi SE sequence. Mean T2 relaxation times of the pixels were calculated from 16-echo signal. Quantitative measurements on lesions were also made in ROIs not larger than two-thirds of the lesion (Figure 1b)

DCE-MRI were classified under 4 groups based on enhancement patterns. Type 1: Progressive heterogeneous enhancement; Type 2: More pronounced enhancement towards the periphery of the lesion without central

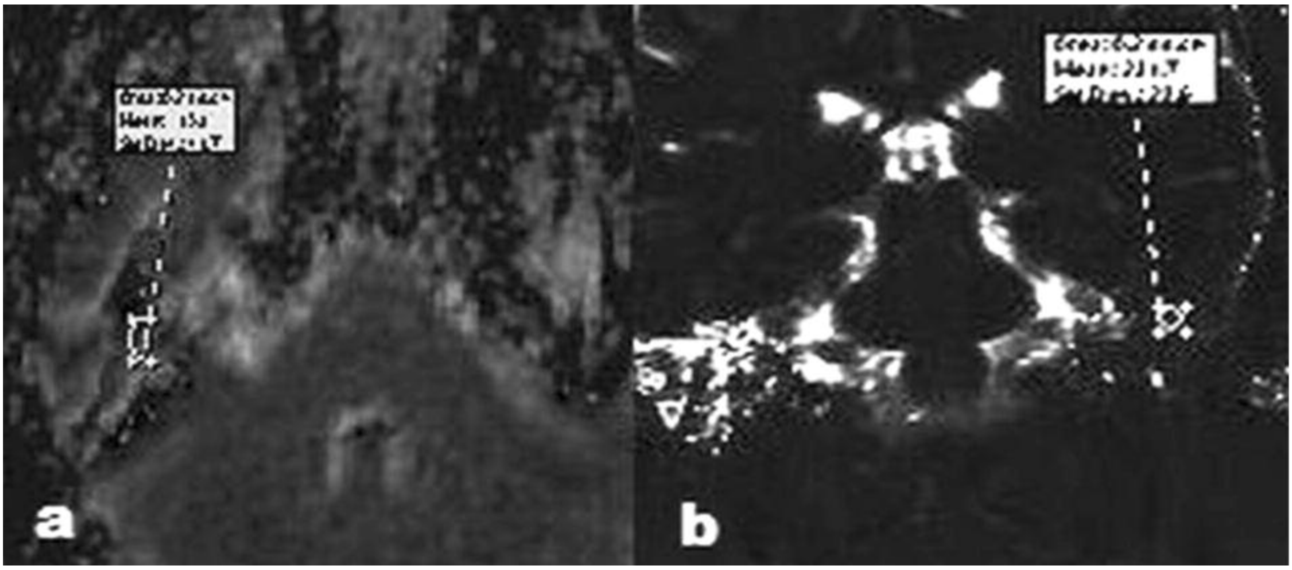


**Figure 1. a.** Measurements made on the ADC map; **b.** Measurements made on T2 relaxometry map

enhancement (Rim enhancement) in the delayed phase; Type 3: Non-enhancement; Type 4: Progressive homogeneous enhancement (Figure 2).

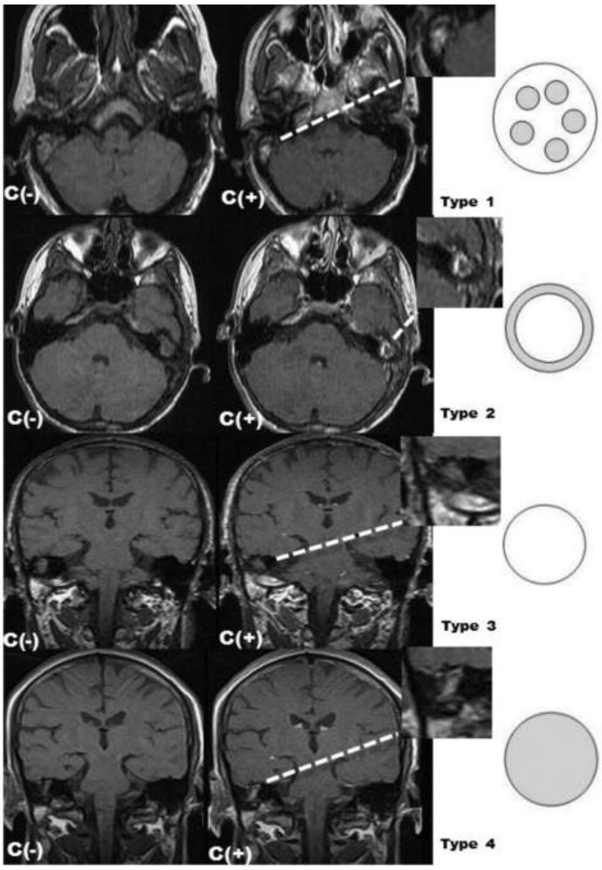


**Figure 2.** Dynamic contrast-enhanced Magnetic resonance imaging (DCE-MRI ) were classified Type 1: Progressive heterogeneous enhancement; Type 2: More pronounced enhancement towards the periphery of the lesion without central enhancement (rim enhancement) in the delayed phase; Type 3: Non-enhancement; Type 4: Progressive homogeneous enhancement

### *Statistical analysis*

Statistical analyses of the data were undertaken using SPSS for Windows v13.0 statistical software (SPSS Inc., Chicago, Illinois, USA). Categorical variables were expressed as frequency and percentage (%). Sensitivity and specificity were calculated for DWI, ADC measurements and T2 relaxometry, taken surgical and audiological examination findings as standard reference. McNemar test was used to determine whether statistically significant differences existed between MR findings and diagnosis. ROC analysis was carried out to examine the general performance of the tests. A p value less than 0.05 was considered significant.

## Results

### *Demographic data;*

Of the 21 COM cases, there were 16 males and 5 females, with a mean (± standard deviation) age of 35.2±14.3 years (range: 14-55 years). Among the 20 cholesteatoma cases, there were 12 males and 8 females with a mean (±standard deviation) age of 29.3±12.4 years (range: 12-50 years). In 19 cases the lesion was localized on the right while in 16 cases it was on the left side and 6 cases bilateral. Diagnosis was established by examination in 16 cases and by surgical operation in 25 cases. The cholesteatomas were measured and the mean of the greatest diameter was 11.2 mm (range: 5-16 mm).

***Diffusion-weight imaging (DWI) and ADC Values;***

In order to compare the cholesteatoma and COM groups, cases were classified qualitatively in terms of signal intensity, i.e. being hyperintense to or hypointense/isointense with the neighboring grey matter. In 18 of the COM cases, hyperintense signal was not observed while 3 cases demonstrated hyperintensity. On the other hand, all cholesteatoma lesions were hyperintense. When only the intensity in DWI were assessed qualitatively, sensitivity, specificity, positive predictive value, negative predictive value and positive probability ratio of the test in differentiating cholesteatoma were found to be 100%, 86%, 0.87, 1.00 and 7.14, respectively.

When two groups were compared, mean ADC in COM patients was $2{,}32\times10^{-3}\pm 0{,}26$ mm²/sec while that in cholesteatoma patients was $1{,}31\times10^{-3}\pm0{,}17$ mm²/sec (Table 1). The difference between groups was highly significant ($p<0.0001$). ROC analysis revealed a cut-off value of 1.50 for ADC. Above this cut-off value, sensitivity was 65% and specificity was 95.2%. Area under ROC curve was 0.815 (Figure 3).

***T2 Relaxometry;***

Mean T2 relaxation time of the patients with cholesteatoma was 262.1 ms while that of the COM patients was 289.3 ms. p value was 0.434, indicating that the difference between two groups was not significant (Table 1)

***Dynamic Contrast-Enhanced MRI (DCE-MRI)***

When the groups were assessed according to the enhancement patterns, 13 of the COM cases showed type 1 (progressive heterogeneous enhancement in delayed phase), 2 cases did not show enhancement (type 3) and 6 cases showed type 4 (progressive homogeneous enhancement). Nineteen patients with cholesteatoma showed type 2 (peripheral, rim-like enhancement), 1 case showed type 4 (progressive enhancement) (Table 2). Statistical analysis of enhancement patterns revealed significant differences between types 1 and 2 ($p<0.001$), between types 2 and 3 ($p=0.005$) and between types 2 and 4 ($p<0.001$). Other differences were not statistically significant.

Radiologic findings of examplary cases with COM and cholesteatoma Figs. 3-5 are presented in.

## Discussion

World Health Organization (WHO) pays importance to COM since it is one of the causes of hearing loss that can be prevented and treated[3]. COM patients with cholesteatoma can progress to active stage in a very short time and intratemporal and intracranial complications can occur if they are treated not surgically. Therefore, numerous studies have been carried out to differentiate cholesteatoma from the neighboring tissues and inflammation.

Even though studies exist in the literature that involved measurement of ADC and assessment of contrast enhancement, number of studies that aimed to differentiate cholesteatoma from inflammation using these methods is limited. Moreover, there are no studies in the literature that investigated T2 relaxation times in such cases.

De Foer *et al*[4]. carried out a DWI study on 21 cases with acquired and congenital cholesteatoma and found that the lesions showed hyperintense signal intensity on DWI in 19 cases. However in 7 of these patients, ADC could not be measured due to size or technical limitations. In the remaining 12 cases, they were compared to the grey matter of the neighboring temporal

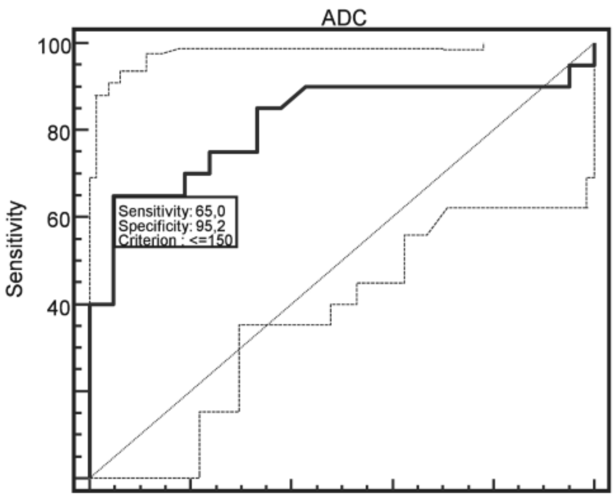


**Figure 3.** ROC curve, specificity, sensitivity and cut off values

**Table 1.** Mean ADC and T2 relaxation time in differentiating cholesteatoma and Chronic otitis media (COM)

| | Chronic Otitis Media Mean ± SD (n=11) | Cholesteatoma Mean±SD (n=21) | p |
|---|---|---|---|
| ADC ( $mm^2$/ sn x 10-3) | 2.32+ 0,26 | 1.31+ 0.17 | <0.0001 |
| T2 relaxation time (msn) | 289.3+ 36 | 262.1+ 32 | >0.05 |

lobe and no significant difference has been found. Further, specificity and sensitivity of echo planar and non-echoplanar DWI studies in detecting different types of cholesteatoma (congenital, acquired, preoperative, postoperative residual-recurrent) varies between 91-100% and 12.5-100%, respectively [4-13] (Table 3). This wide range in specificity and sensitivity can be related to differences in patient selection (residual and/or recurrent, primary, etc), technical parameters (echo planar and non-echo planar sequences, different technical parameters of the scanners) and size of the lesion.

Thiriat *et al.* [14] examined the DWI signal and ADC values in 15 cases with abscess, cholesteatoma or mixed infection and found that these cases were hyperintense and reported that these 3 groups can be differentiated statistically by ADC measurements. Similarly, ADC measurements as well as DWI can differentiate COM from cholesteatoma and this finding is in agreement with the literature.

Difficulty in diagnosis can be encountered in some of the postoperative cases. It could be challenging to differentiate postoperative residual-recurrent cholesteatoma from granulation tissue, cholesterol granuloma, other non-specific tissues filling the mastoid and tympanic cavities[15]. Migirov *et al.*[16] highlighted the

**Table 2.** Enhancement patterns types of COM and cholesteatoma cases

| | Chronic Otitis Media | Cholesteatoma |
|---|---|---|
| Type 1 | 13 (%62) | 0 |
| Type 2 | 0 | 19(%95) |
| Type 3 | 2(%9.5) | 0 |
| Type 4 | 6(%28.5) | 1(%5) |

**Table 3.** Some of the studies that used diffusion MRI for the diagnosis of cholesteatoma.

| Authors | Publication Year | Cholesteatoma type | MRI technique | Patient numbers | Size limit, mm | Sensitivity % | Specificity % | NPV % | PPV % |
|---|---|---|---|---|---|---|---|---|---|
| Fitzek et al.(5) | 2002 | Primary acquired | EPI-DWI | 15 | NDA | NDA | NDA | NDA | NDA |
| Aikele et al.(6) | 2003 | Recurrent | EPI-DWI | 22 | 5 | 77 | 100 | 100 | 75 |
| Ayache et al.(7) | 2005 | Residual | Late post-Gd T1-WI | 41 | 3 | 90 | 100 | 100 | 92 |
| Vercruysse | 2006 | Primary acquired | EPI-DWI | 55 | 5 | 81 | 100 | 100 | 40 |
| et al.(8) | | Residual | EPI-DWI | 45 | 5 | 12,5 | 100 | 100 | 72 |
| Stasolla et al.(9) | 2004 | Residual- Recurrent | EPI-DWI | 18 | 5 | 86 | 100 | 100 | 92 |
| Dubrulle et al.(10) | 2006 | Recurrent | Non-EPI-DWI | 24 | 5 | 100 | 91 | 93 | 100 |
| De Foer et al.(4) | 2007 | Primary acquired | Non-EPI-DWI | 21 | 2 | NDA | NDA | NDA | NDA |
| De Foer et al.(11) | 2010 | Recurrent | Non-EPI-DWI | 120 | NDA | 83 | 87 | 96 | 57 |
| Khemani et al.(12) | 2011 | Recurrent | HASTE | 38 | 2 | 82 | 90 | 64 | 96 |
| Profant et al.(13) | 2011 | Primary and Recurrent | HASTE | 33 | 3 | 96 | 71 | 93 | 83 |

NDA=No data available; EPI-DWI=echo-planar diffusion-weighted imaging; late post-Gd T1-WI=late postgadolinium enhanced T1-weighted imaging; Non EPI-DWI=non echo-planar diffusion-weighted imaging;NPV=negative predictive value PPV= positive predictive value HASTE=half-Fourier acquisition single-shot turbo spin-echo imaging

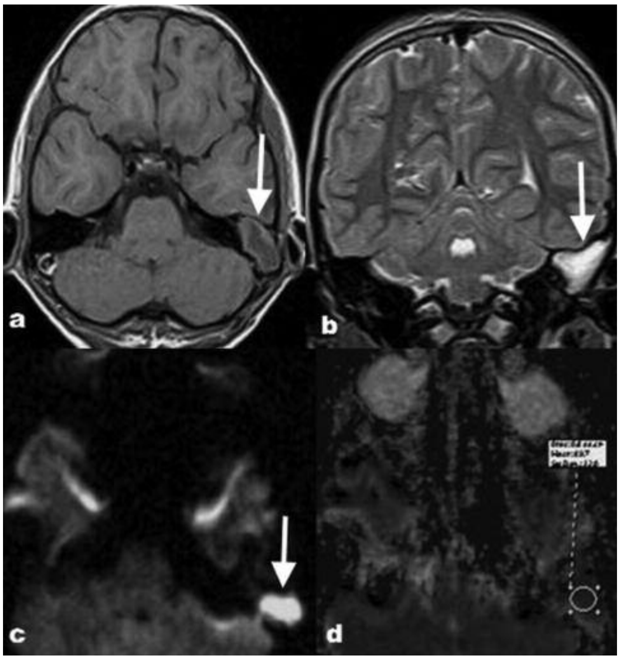

Figure 4. A case of left middle ear cholesteatoma. MRI shows hypointense on T1-weighted image (arrow, a) and hyperintense on T2 (arrow, b). DWI shows hyperintensity in this same area (arrow, c). ADC value was measurement 0,69 x$10^{-3}$ $mm^2$/sec (d).

Figure 5. case of bilateral Chronic Otitis Media. MRI shows T1 hypointense (arrow, a) and T2 hyperintense (arrow, b). DWI shows isointensity in this same area (arrow, c). ADC value was measurement 2,56x$10^{-3}$ $mm^2$/sec(d).

importance of MRI in detection of recurrent cholesteatoma in postoperative cases and prevention of an unnecessary second operation. Aikele *et al.*[6] carried out a study in which they compared DWI and conventional MRI in detecting residual-recurrent cholesteatoma in operated cases. The authors reported that they could diagnose 10 of the 13 cholesteatomas in 22 operated cases (The lesion could not be demonstrated in 3 cases due to the lesion being smaller than 5 mm) while they could diagnose all non-cholesteatoma cases. Ganaha *et al.* [15] argued that DWI was useful even in cases which CT and otoscopic examination failed to detect. However, they reported that sensitivity would be lower if the lesion was 5 mm or smaller. In the present study, the size of the cholesteatoma varied between 5 and 16 mm (mean: 11.2 mm). We chose our cases among preoperative cases and this might explain why there were no cholesteatoma smaller than 5 mm in our study.

Dubrulle *et al.* [10] found the negative predictive value in postoperative recurrent cholesteatoma cases to be 100%. They emphasized that, with this finding, a second operation would be unnecessary if a signal change in DWI was not detected. Meanwhile, Jeunen *et al.* [17] managed to diagnose cholesteatoma in 22 of the 32 cases with postoperative recurrent cholesteatoma by DWI and argued that MRI could not replace a second operation yet.

When we assessed the signal intensity of DW images qualitatively, we found that the sensitivity, specificity, positive predictive value, negative predictive value and positive probability ratio of DWI as 100%, 86%, 0.87, 1.00 and 7.14, respectively. Mean ADCs in the COM and cholesteatoma groups were 2,32 x $10^{-3}$ mm²/sec and 1,31x $10^{-3}$ mm²/sec and the difference was very significant ($p<0.0001$). ROC analysis showed that the cut-off value for ADC was 149.9. These findings are in agreement with the literature.

By T2 relaxometry, changes in the signal intensity of T2-weighted images and hydration ratio of tissues can be quantified. [18] Increase in T2 relaxation time of a tissue indicates increase in free water in the extracellular space. Increase in the amount of proteins, on the other hand, shortens the T2 relaxation time. Numerous researchers carried out studies in the fields of neuroradiology, abdominal imaging and locomotor system by measuring

T2 relaxation times and mapping them to help with the diagnosis. [19-21] Further, it has been argued that T2 relaxation time could be useful in detecting early changes due to decreased collagen content of the patellar cartilage and osteoarthritis. [22] It has been shown that hepatic cysts and hemangiomas can be differentiated from other malignant lesions of the liver while prostatic malignancies can be differentiated from the normal peripheral zone by measuring T2 relaxation time. [20,21] To the best of our knowledge, there are no studies in the literature that employed T2 relaxation time measurements to differentiate cholesteatoma from COM. We found the T2 relaxation time prolonged in COM cases. This finding can be explained by the mechanism explained above. Even though T2 relaxation time was longer in COM cases in comparison to cholesteatoma, the difference was not statistically significant. This can be due to the limited number of subjects in the present study.

DCE-MRI has especially been in use in the imaging of the locomotors system to differentiate residual-recurrent soft tissue lesions from radiation necrosis, in the differential diagnosis of breast pathologies and in the characterization of hepatic lesions. DCE-MRI is capable of narrowing down the differential diagnosis by differentiating benign soft tissue tumors from malignant ones. [18]

There are a multitude of studies in the literature that employed contrast-enhanced MR in cholesteatoma. It has been argued that post-contrast MR images acquired in delayed phase would be very helpful in conjunction with DWI when recurrent cholesteatoma is suspected by CT [17]. Studies in the literature usually compared postoperatively the DWI with delayed contrast-enhanced studies. De Foer *et al*. [11] compared contrast enhanced MRI with non-echo planar DWI and concluded that specificity and sensitivity of DWI study was higher and, therefore, the use of a contrast media unnecessarily increased the cost. However, the need for both studies, especially for smaller lesions has been emphasized in the literature.[19] In the present study, we aimed to differentiate lesions by examining the enhancement patterns in DCE-MRI. In 95% of the cholesteatoma cases, there was a rim-like enhancement in the periphery of the lesion in the delayed phase. Statistical analyses showed that there were significant differences between enhancement patterns in differentiating cholesteatoma (between types 1 and 2: $p<0:001$; between types 2 and 3: $p=0.005$; between types 2 and 4: $p<0.001$). None of the COM cases showed such enhancement. This finding is in agreement with the results of delayed contrast-enhancement examinations. Absence of such enhancement in COM cases indicates the role of DCE-MRI in differentiating two tissues.

There are certain limitations of this study. Firstly, all our cases were preoperative patients. Therefore, the cholesteatomas was larger than the ones reported in the literature. New studies are required to demonstrate the sensitivity of DCE-MRI in postoperative cases, either alone or in conjunction with DWI. We were also unable to generate dynamic curves due to heterogeneous internal structure of the lesions. Therefore, only qualitative assessment could be performed.

In conclusion, the role of radiology in differentiating cholesteatoma cannot be denied since differentiation requires close follow-up and, frequently, surgery. Similar to epidermoid cyst, cholesteatoma contains keratin. Therefore, there were statistically significant differences between cholesteatoma and granulation tissue in signal intensity and ADC that would enable differentiation. Despite existence of differences in T2 relaxation times, the difference was not statistically significant. Rim-type, peripheral enhancement pattern in DCE-MRI was observed in 95% of cholesteatoma cases but none of the COM cases. In the light of these findings, in addition to conventional MR sequences, DWI, ADC mapping and, especially in suspicious cases, DCE-MRI can be utilized to differentiate COM from cholesteatoma.

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