A Systematic Review of Non-Echo Planar Diffusion-Weighted Magnetic Resonance Imaging for Detection of Primary and Postoperative Cholesteatoma

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Abstract

Objective. To investigate the diagnostic value of non–echo planar diffusion-weighted magnetic resonance imaging (DW-MRI) for primary and recurrent/residual (postoperative) cholesteatoma in adults (≥18 years) after canal wall up surgery.

Data Sources. We conducted a systematic search in PubMed, Embase, and Cochrane up to October 22, 2014.

Review methods: All studies investigating non–echo planar DW-MRI for primary and postoperative cholesteatoma were selected and critically appraised for relevance and validity.

Results. In total, 779 unique articles were identified, of which 23 articles were included for critical appraisal. Seven articles met our criteria for relevance and validity for postoperative cholesteatoma. Four studies were additionally included for subgroup analysis of primary cases only. Ranges of sensitivity, specificity, positive predictive value, and negative predictive value yielded 43%-92%, 58%-100%, 50%-100% and 64%-100%, respectively. Results for primary subgroup analysis were 83%-100%, 50%-100%, 85%-100%, and 50%-100%, respectively. Results for subgroup analysis for only postoperative cases yielded 80%-82%, 90%-100%, 96%-100%, 64%-85%, respectively. Despite a higher prevalence of cholesteatoma in the primary cases, there was no clinical difference in added value of DW-MRI between primary and postoperative cases.

Conclusion. We found a high predictive value of non–echo planar DW-MRI for the detection of primary and postoperative cholesteatoma. Given the moderate quality of evidence, we strongly recommend both the use of non-echo planar DW-MRI scans for the follow-up after cholesteatoma surgery, and when the correct diagnosis is questioned in primary preoperative cases.

Keywords

DW-MRI, cholesteatoma, primary, postoperative, residual, recurrent

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Methods

Search Strategy

We conducted a systematic search in PubMed, Embase, and Cochrane up to October 22, 2014. A syntax was designed with synonyms for non-EP DW-MRI (determinant) and cholesteatoma (outcome; Figure 1). Reporting of our data is done according to the PRISMA statement.

Study Selection

Screening of publications was performed by at least 2 authors independently (S.L.E., I.S.). Any difference in opinion was resolved by consensus. Duplicates were removed from the retrieved articles. Title, abstract, and, ultimately, the full text of potentially eligible articles were screened with criteria shown in Figure 2. A thorough analysis of selected articles was made, and their bibliographies were analyzed to identify...
any additional articles that could be relevant for this review. We included patients with primary and postoperative cholesteatoma. Since the diagnostic value of magnetic resonance might differ in these patients, as a result of changed anatomy and the presence of postoperative soft tissue in the tympanic cavity, we performed an additional subgroup analysis.

Concerning postoperative cholesteatoma, our primary objective was to include only patients after canal wall up (CWU) surgery. CWU surgery is associated with a higher incidence of residual or recurrent disease, which may not be evaluated adequately on clinical examination alone. Articles reporting on both techniques were included only when CWU data could be separately analyzed. When the method of primary surgery (CWU or canal wall down [CWD]) was not specifically reported, the authors were contacted for further information. Since non-EP DWI has shown more promising results than EP DWI, we included only studies using non-EP DWI sequences. Concerning outcome, surgery as a reference standard had to be available for all patients.

Critical Appraisal of Included Studies

On the basis of predefined criteria, articles were critically appraised for relevance and validity. Data collected included study design, number of primary and recurrent episodes, and standardization and adequate reporting of non-EP DWI protocol and surgical procedures, including presence or absence of surgical intervention following negative DW-MRI results. The interval between DW-MRI and surgery was reported, as well as blinding of radiologists to the surgical outcome. Missing data were scored as adequate if all consecutive patients underwent both DW-MRI and surgery. Missing data were considered inadequate if patients were excluded a priori on the basis of incomplete data (DW-MRI or surgical data).

Data Extraction and Statistics

To evaluate the diagnostic value of non-EP DW-MRI, positive predictive value (PPV), negative predictive value (NPV), sensitivity (SN), and specificity (SP) were extracted from eligible articles or, when not described, calculated (when possible) from the original data. Subsequently, subgroup analysis of primary and postoperative cholesteatoma was done.

Results

Search Strategy and Study Selection

Our search strategy yielded 779 unique publications (Figure 2). After title and abstract screening, 42 articles were left for full-text assessment, of which 20 were excluded for various reasons. Cross-reference checking yielded 1 additional article. This resulted in a total of 23 eligible studies.4-26

Critical Appraisal

Appraisal of 23 eligible studies is presented in Table 1. All studies were case series or cohort studies; 17 of 23 studies were prospective. The number of episodes varied between 8 (suitable for review) and 120. The mean number of episodes of all 23 studies was 39.

We initially excluded 14 studies on the basis of relevance.13-26 Five studies included CWU and CWD procedures, of which the CWU data could not be extracted.13,17,20,24,26 In another 5 studies, the authors could not be contacted, and operative technique (CWU or CWD) could not be specified with certainty.14,15,16,19,21 Seven studies were excluded because not all patients received surgery as a reference standard, and the radiologic findings could therefore not be confirmed.18,20,25 Of these 14 excluded studies, 5 were eligible for subgroup analysis of primary cholesteatoma only (reported with “p” in Table 1).13-17 Following appraisal of relevance, 9 studies were eligible for quantitative analysis of primary and recurrent cholesteatoma, and 5 were eligible for subgroup analysis of primary cases only. Following assessment for validity, 2 additional articles were excluded for primary and recurrent cases,11,12 and 1 was excluded for primary subgroup analysis.17 The main reason of exclusion was that not all patients with positive and negative DW-MRI results underwent surgical intervention and/or missing data were not mentioned. This resulted in a total of 7 studies included for final quantitative analysis of primary and recurrent cases4-10 and 4 studies for subgroup analysis of primary cases only.13-16

Data Extraction and Statistics

Study characteristics are shown in Table 1. The 7 selected studies included a total of 223 episodes, of which 69 were primary cases and 154 were analyzed for recurrent/residual cholesteatoma. Additionally, 87 episodes (of 4 studies) were included for primary subgroup analysis only. There were differences in technique among studies with regard to timing of MRI relative to surgery and imaging protocols. The calculated diagnostic value of DW-MRI is presented in Table 2.

The ranges for SN, PPV, NPV, and NPV were 43%-92%, 58%-100%, 50%-100%, and 64%-100%, respectively, for the whole patient population respectively (Table 2). Kasbekar et al reported a relatively low diagnostic value of DW-MRI as compared with other studies.8 The PROPELLER sequence used in that study was not able to detect cholesteatoma <4 mm, comparable to EP DWI results.

The PPV and NPV are shown in Figure 3, with wide variation in NPV. Studies by Akkari et al and Khemani et al reported particularly low NPVs.5,9 Two studies could not be plotted because of absence of positive DW-MRI findings and unknown prevalence.8,10 The added value of non-EP DW-MRI for a positive result (PPV minus prevalence) ranged from 20% to 39%. The added value for a negative result (NPV minus [1 minus prevalence]) ranged from 38% to 55%.

In the primary cholesteatoma subgroup analysis, SN, SP, PPV, and NPV were 83%-100%, 50%-100%, 85%-100%, and 50%-100%, respectively (Table 3). The added value for a positive result (PPV minus prevalence) in primary...
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**Table 1.** Critical Appraisal of Relevance and Validity.

Abbreviations/Symbols: *, accurate; o, not accurate; ?, unknown. * CWU or CWD not known with certainty; authors could not be reached; included only for primary subgroup analysis; ***, CWU and CWD results could not be separately analyzed in recurrent/residual group; suitable only for primary subgroup analysis. CO, cohort study; CS, case series; CWD, canal wall down; DW, diffusion weighted; EP, echo planar; FASE, fast advanced spin echo; HASTE, half-Fourier acquisition single-shot turbo spin echo; MRI, magnetic resonance imaging; MSTSE, multishot turbo spin echo; P, prospective; R, retrospective; PROPELLER, periodically rotated overlapping parallel lines with enhanced reconstruction sequence; SE, spin echo; SSTSE, single-shot turbo spin echo.

*Exclusion of 2 patients with CWD after contact with author.

*Exclusion of 5 children.
cases varied between 10% and 44%. The added value for a negative result (NPV minus [1 minus prevalence]) in primary cases varied between 36% and 56%.

In postoperative patients analyzed for residual/recurrent disease, only 2 studies could be plotted. SN, SP, PPV, and NPV in these 2 studies were 80%-82%, 90%-100%, 96%-100%, and 64%-85%, respectively (Table 4). The added value for a positive result (PPV minus prevalence) in recurrent cases was 22% to 55%. The added value for a negative result (NPV minus [1 minus prevalence]) in recurrent cases only was 30% to 38%.

**Discussion**

In this systematic review, we investigated the diagnostic value of non-EP DW-MRI for the detection of primary and recurrent cholesteatoma after previous CWU surgery in adult patients. As stated earlier, non-EPI sequences are less susceptible to magnetic interface artifacts than the previously used EPI sequences, which is of great importance in the temporal bone, where air, bone, tissue, and fluid lie in close proximity to one another. Non-EPI sequences also have a better spatial resolution, providing improved image quality with a short acquisition time.

Our results show overall high PPV and NPV of the non-EP DW-MRI technique for postoperative cholesteatoma; ranges of SN, SP, PPV, and NPV yielded 43%-92%, 58%-100%, 50%-100%, and 64%-100%, respectively. The added value of non-EP DW-MRI for a positive result (PPV minus prevalence) ranged from 20% to 39%. The added value for a negative result (NPV minus [1 minus prevalence]) ranged from 38% to 55%. Despite a higher prevalence of cholesteatoma in the primary cases, there was no clinical difference in added value of DW-MRI between primary and postoperative cases.

The findings in this study are comparable to the high PPV and NPV reported for non-EP DW-MRI in a previous systematic review.27 We included only 2 of 8 previously reviewed non-EP DWI studies by Jindal; the other 6 studies were excluded. Two studies focused on the pediatric population; 2 studies included patients without surgery as a reference standard; and in 2 studies, CWU and CWD could not be separately analyzed. Of 23 eligible studies assessed in our review, 16 were published after the previous systematic review. Jindal reported SN, SP, PPVs, and NPVs of 91%, 96%, 97%, and 85%, respectively. This is in accordance with our results, with the exception of the moderate diagnostic value reported by Kasbekar et al. The overall SN and the SN in the postoperative subgroup analysis were slightly lower than previously reported.

In this review, we included only studies after CWU. Since there are a number of studies reporting on the value of DW-MRI for evaluation of cholesteatoma, we were able to narrow our inclusion criteria. Specifically, 14 studies were excluded for further analysis due to lack of a description of the primary surgery (CWU vs CWD), the inclusion of both adults and pediatric patients, or a lack of a surgical reference standard for confirmation of radiologic findings. A recent meta-analysis of surgical technique demonstrated a 3-times-greater likelihood of recurrence with CWU surgery than CWD surgery.28 After CWU surgery, residual cholesteatoma is reported to be as high as 35%, with recurrence in 8% of cases.29 Following CWD surgery, clinical evaluation becomes more important, and diagnostic impact of DW-MRI may differ.

When our results are interpreted, several limitations need to be considered. First, there was a large difference in methodology and study populations within and between the included studies (eg, different slice thicknesses and imaging techniques, variable parameters and protocols). Therefore, the studies were too heterogeneous to pool. Second, wide variations existed in the time between MRI scanning and second-look surgeries, with a range of 0 to 18 months. A large delay could lead to more false negatives, due to recurrence over time.28 Third, some studies included only patients with a high suspicion for recurrence based on clinical findings. This selection bias could have increased the...
pretest probability, leading to an overestimation of the PPV and underestimation of NPV. We therefore calculated the added value, based on prevalence (Figure 3).

Fourth, most studies showed a high prevalence of cholesteatoma. This was due to the fact that patients with negative MRI findings were excluded from the study, patients were asymptomatic and refused routine reexplorative surgery, or patients were lost to follow-up. This could lead to selection bias. Dhepnorrarat et al, for example, included only 22 of 48 patients from the database, since 26 did not receive second-look surgery or the interval between MRI and surgery exceeded 6 months. Of the 22 study patients, 14 patients already underwent CWD surgery. We therefore excluded these 14 patients, leaving only 8 patients suitable for review. These missing data were often not well described (Table 2).

Furthermore, in 9 studies, not all patients were treated surgically on the basis of positive or negative MRI results. Although this is concordant with clinical practice, it is an important confounding factor. Workup bias cannot be precluded. Asymptomatic patients may have very small residual lesions that are more likely to be missed by MRI, resulting in false-negative MRI results. This could also explain the high percentage of recurrent cholesteatoma in some studies. We therefore excluded these studies in our quantitative analysis.

Accounting for the limitations mentioned above and the number and type of studies included in this review (case series and cohort studies), our results are based on a moderate level of evidence. Despite these limitations, the clinical value of the results remains high. This systematic review supplements available evidence that supports radiologic follow-up with non-EP DW-MRI. When DW-MRI is performed as a primary diagnostic test for follow-up in patients with a history of cholesteatoma and CWU surgery, the risks of unnecessary invasive second-look procedures may be avoided (including hearing loss, vertigo, and surgical trauma to the facial nerve and/or chorda tympani), with potential for cost savings as well. It should, however, again be emphasized that in clinical practice, due to the presence of false-negative results in small cholesteatomas (<2 mm) and the clinical implications of growing cholesteatomas, non-EP DW-MRI has to be repeated within a certain interval.

**Conclusion**

In this study, we found a high predictive and added value of non-EP DW-MRI for primary and postoperative cholesteatoma. However, heterogeneity among studies prevents pooling of data. Also, several limitations of study methodology could affect the interpretation of the results. However the clinical relevance of the included studies is high. Therefore, despite of moderate quality of evidence, we strongly recommend the use of non-EP DW-MRI as a primary diagnostic tool in cases of suspected primary or recurrent (postoperative) cholesteatoma.

**Author Contributions**

Sylvia L. van Egmond, literature search, acquisition and data analysis, writing of article, final approval, accountable for all article contents; Inge Stegeman, literature search, data analysis, article revision, final approval, accountable for all article contents; Wilko Grolman, initiator of concept, revision of article, final approval, accountable for all article contents; Mark C. J. Aarts, references 11, 12, 17, 18, 20, 21, 22, 23, 25

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**Figure 3.** Comparison of pretest probability (prevalence of cholesteatoma) and posttest probability for positive predictive value (PPV) and negative predictive value (NPV) diffusion-weighted magnetic resonance imaging findings: a, primary and postoperative cases (Table 2); b, primary cases (Table 3); c, postoperative cases (Table 4).
contributed to design and analysis of data, revised article, final approval, accountable for all article contents.

Disclosures
Competing interests: None.
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References


