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Kole, Suzan Al

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BY
SUZAN AL KOLE

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Suzan Al Kole

AALBORG UNIVERSITY
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PhD supervisor: Clinical Professor, PhD, MD, Michael Gaihede
Department of Otology, Head and Neck Surgery
Aalborg University Hospital
Department of Clinical Medicine Aalborg University, Denmark

Assistant PhD supervisors: Clinical Professor, PhD, MD, Jens Brøndum Frøkjær
Department of Radiology Aalborg University Hospital
Department of Clinical Medicine Aalborg University, Denmark

Clinical Associate Professor, MD, Yousef Yavarian
Department of Radiology Aalborg University Hospital
Department of Clinical Medicine Aalborg University, Denmark

PhD committee: Clinical Professor Henrik Vorum (chair)
Aalborg University, Denmark

Clinical Associate Professor Bjarki Ditlev Djurhuus
University of Copenhagen, Denmark

Clinical Professor Krister Tano
Umeå University Hospital, Sweden

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

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English summary

Middle ear (ME) cholesteatoma is a prevalent inflammatory condition, which involves the abnormal proliferation of keratinized epithelial tissue in the ME and temporal bone, potentially leading to bone erosion. ME cholesteatoma typically arises from the development of abnormal negative pressure in the ME, which creates retraction pockets filled with squamous epithelium and cellular debris. This frequently leads to bacterial infection and recurrent inflammation. Therefore, cholesteatoma can adversely result in ossicle and bone destruction, infection, hearing loss, and potentially life-threatening intracranial issues. This makes early detection crucial, especially given the disease's high rate of recidivism, as the adverse effects have both negative consequences for the patients' physiological and psychological wellbeing and overall quality of life (QoL).

There are significant ongoing concerns in otology with regard to cholesteatoma treatment as the pathogenesis is complex. Diagnostic challenges arise particularly in silent clinical cases, and as the disease tends to recur there are intricacies of complete surgical removal, especially in pediatric patients. Despite these challenges, subjective otomicroscopic evaluations and patient-reported symptoms remain critical in initial diagnosis. This underlines the necessity for thorough understanding and management approaches in this field.

Treatment for ME cholesteatoma typically involves surgical removal and reconstruction of the tympanic membrane and ossicles; an approach especially complex in pediatric cases. Currently, there is an ongoing debate about the most effective surgical approach. Cholesteatoma surgery frequently faces challenges of recidivism of the disease, even when performed by skilled surgeons. However, the choice of surgical technique significantly impacts the outcomes of the procedure. The primary surgical methods commonly employed for ME cholesteatoma treatment involve atticotomy for less extensive cases, involving access and management via the ear canal. In cases of more extensive cholesteatomas, procedures such as canal wall up (CWU) or canal wall down (CWD) techniques, with or without mastoid

obliteration (also known as bony obliteration tympanoplasty or BOT), are utilized. Mastoid obliteration has gained attention as an effective strategy to reduce recidivism, though its full efficacy remains uncertain. This may be caused by the mastoid mucosa's susceptibility to inflammation due to its abundant loose connective tissue and blood vessels with chronic inflammation leading to fibrosis that impairs gas absorption and pressure regulation in the ME. Therefore, mastoid obliteration might be beneficial in mitigating the impacts of diseased mucosa, including decreasing negative pressure and ME complications.

This dissertation compares surgical outcomes of the abovementioned surgical techniques (mastoid obliteration and atticotomy) and the diagnostic value of noninvasive methods with diffusion-weighted magnetic resonance imaging (DW-MRI) scans, specifically the PROPELLER non-echoplanar imaging (non-EPI) sequences for detecting and monitoring ME cholesteatoma. It demonstrates how advanced MRI methods offer a safer and more cost-effective alternative to exploratory surgery. Furthermore, it enhances traditional diagnosis and follow-up practices that include medical history, clinical exams, otomicroscopy, and computed tomography (CT) imaging.

Study I evaluate the preoperative use of PROPELLER diffusion weighted imaging (DWI) before cholesteatoma surgery. The results show high diagnostic sensitivity and specificity of the PROPELLER DWI method. Notably, this approach achieved an 89% accuracy rate in identifying both primary and recurrent ME cholesteatomas, primarily through qualitative analysis. Additionally, the study investigated the role of quantitative metrics, specifically the Apparent Diffusion Coefficient (ADC), in enhancing diagnostic precision and reducing inaccuracies such as false positives and negatives.

Study II examines the clinical long-term effects of the mastoid obliteration technique for cholesteatoma treatment, focusing on recidivism and hearing outcomes. Results of the long-term follow-up showed a recidivism rate of 9%, which was notably higher in children than adults. CWU surgery combined with mastoid obliteration (CWU-BOT) showed a low recidivism rate, possibly due to better ME aeration and pressure dynamics. Moreover, the results revealed that age plays a significant role as children have a 2.6 times higher risk of recidivism than adults. An older age at primary surgery reduces the risk by 6% annually for children below 16 years of age. The study also found that the extent and type of cholesteatoma, particularly sinus cholesteatoma, may contribute to recidivism rates. Importantly, the study revealed that even skilled surgeons cannot eliminate recidivism, which underscores the role of anatomical and physiological factors in these outcomes.

Study III examines the effectiveness of long-term follow-up using non-EPI DWI scans on 86 patients undergoing surgical treatment for cholesteatoma. This method contrasts with the traditional ‘second look’ postoperative approach prevalent in otology. The study finds good efficacy of non-EPI DWI in monitoring potential recidivism of cholesteatoma, demonstrating high accuracy and consistency with surgical outcomes. This development highlights the growing relevance of non-EPI DWI in postoperative assessments, aiding clinicians in evaluating surgical results, especially in children who face a greater risk of recidivism.

Study IV examines the health-related QoL (HRQoL) changes after ME cholesteatoma surgery, as traditional post-surgical evaluations like audiograms and otomicroscopy have limitations in this regard. It specifically investigates post-surgery QoL in cholesteatoma patients undergoing CWU-BOT and atticotomy using the Glasgow Benefit Inventory (GBI) questionnaire, a pioneering approach in Denmark. Cholesteatoma surgery leads to improved QoL for a majority of patients. The study highlights that while objective measures like postoperative air-bone gap (ABG) closure are important, they do not always reflect patients' subjective experiences and QoL. The study reveals a stronger correlation between subjective hearing improvements and QoL than objective measures postoperatively, emphasizing the need to value and incorporate patient-reported outcomes in addition to objective measures. Additionally, a significant correlation between improved QoL and reduced ear discharge in CWU-BOT patients was observed.

In conclusion, this dissertation offers in-depth insights into ME cholesteatoma diagnosis and treatment, emphasizing the complex nature and high recidivism rate of the disease. Our finding of high diagnostic accuracy of the PROPELLER DWI in detecting ME cholesteatoma highlights its important role as a non-invasive and reliable method for both preoperative diagnosis and post-operative monitoring and control of disease. This MRI technique may lead to the avoidance of additional surgical procedures and promote earlier intervention to prevent complications. The research also indicates that surgical approaches, particularly CWU-BOT, can significantly impact recidivism rates and patients' QoL as shown in the substantial postoperative improvements measured by the GBI. Future research should focus on refining surgical methods, enhancing diagnostic precision, and prioritizing patient-reported outcomes for a holistic understanding of cholesteatoma treatment.

Dansk resume

Kolesteatom i mellemøret er en udbredt inflammatorisk tilstand, som involverer unormal spredning af keratiniseret epitelvæv i mellemøret og mastoidet hvilket potentielt kan føre til knogleerosion. Et kolesteatom i mellemøret opstår typisk som følge af en unormal udvikling af undertryk i mellemøret, hvilket skaber retraktionslommer fyldt med pladeepitel og celluar debris. Dette fører ofte til bakteriel infektion og tilbagevendende infektioner. Derfor kan kolesteatom resultere i alvorlige følgevirkninger, herunder destruktion af mellemørets knogler, infektion, høretab og potentielt livstruende intrakranielle problemer. Tidlig diagnostik er derfor afgørende især taget sygdommens høje recidivrate i betragtning, da følgevirkningerne har negative konsekvenser for patienternes fysiske og mentale velbefindende og deres overordnede livskvalitet.

Inden for otologien er der betydelige, vedvarende bekymringer omkring kolesteatom-behandling grundet kolesteatomers komplekse patogenese. Diagnostiske udfordringer opstår særligt i asymptomatiske kliniske tilfælde, og eftersom sygdommen tenderer til tilbagefald, er der vanskeligheder forbundet med fuldstændig kirurgisk fjernelse af kolesteatom særligt hos pædiatriske patienter. På trods af disse udfordringer forbliver subjektive otomikroskopiske evalueringer og patientrapporterede symptomer kritiske i den indledende diagnose. Dette understreger nødvendigheden af grundig forståelse af og behandlingstilgange på dette område.

Behandling af kolesteatom i mellemøret indebærer typisk kirurgisk fjernelse og rekonstruktion af trommehinden og ossikler, hvorfor kirurgisk behandling er kompleks, særligt i pædiatriske tilfælde. I øjeblikket er der en løbende debat om, hvilken kirurgisk tilgang, der er den mest effektive. Recidiv efter kolesteatomkirurgi er almindelig, selv når udført af eksperter. Derudover påvirker den valgte kirurgisk methode betydeligt resultaterne af proceduren. De hyppigst anvendte kirurgiske metoder involverer atticiotomi, til behandling af mindre omfattende tilfælde af Kolesteatom, hvilket indebærer adgang og behandling gennem øregangen. I tilfælde af mere omfattende cholesteatomer anvendes procedurer som ’canal wall up’ (CWU) og ’canal wall down’ (CWD) med eller uden mastoid obliteration, på engelsk kaldet

’bony obliteration tympanoplasty’ (BOT). Mastoid obliteration har fået opmærksomhed som en effektiv metode til at reducere tilbagefald. Den fulde effekt af teknikken er dog stadig usikker. Dette kan være forårsaget af mastoidets slimhindes modtagelighed for betændelse på grund af dens store mængde løse bindevæv og blodkar, hvor kronisk inflammation fører til fibrose, der forringer gasoptagelsen og trykreguleringen i mellemøret. Derfor kan mastoid obliteration være gavnlig til at nedsætte virkningerne af en syg slimhinde, herunder formindske undertryk og komplikationer i mellemøret. Ikke desto mindre er det afgørende at forbedre vores forståelse af både kirurgiske og patientrapporterede resultater for at forbedre effektiviteten af kolesteatombehandling.

Denne afhandling sammenligner de kirurgiske resultater af de ovennævnte teknikker (mastoid obliteration og attikotomi) samt værdien af ikke-invasive diagnostiske metoder med diffusionsvægtede ’magnetic resonance imaging’ (DW-MRI) teknikker, specifikt PROPELLER non-echoplanar imaging (non-EPI) sekvenser til påvisning og monitorering af kolesteatom i mellemøret. Afhandlingen viser, hvordan avancerede MRI-metoder tilbyder et mere sikkert og omkostningseffektivt alternativ til eksplorativ kirurgi. Desuden forbedrer det traditionel diagnostik og opfølgningspraksis, der inkluderer sygehistorie, kliniske undersøgelser, otomikroskopi og ’computed tomography' (CT)-billeddannelse.

Studie I evaluerer præoperativ brug af PROPELLER DWI før operativ fjernelse af kolesteatom. Resultaterne viser høj diagnostisk sensitivitet og specificitet af PROPELLER DWI-metoden. Særligt opnåede denne tilgang en nøjagtighedsrate på 89% ved identifikation af både primære og tilbagevendende kolesteatomer i mellemøret, primært gennem kvalitativ analyse. Derudover undersøgte studiet rollen af kvantitative målinger, specifikt den tilsyneladende diffusionskoefficient, i at forbedre diagnostisk præcision og reducere unøjagtigheder såsom falske positive og negative.

Studie II undersøger de langsigtede kliniske effekter af mastoid obliteration som kirurgisk behandling af kolesteatomer i mellemøret med særligt fokus på forekomsten af recidiv og effekt på hørelse. Resultaterne af langtidsopfølgningen viste en recidivrate på 9% over fem år, hvilket var markant højere hos børn end hos voksne. CWU operation kombineret med mastoid obliteration (CWU-BOT) har en lavere recidivrate, muligvis grundet bedre lufttilsætning i mellemøret og dynamik i trykudligningen. Studiet viste også, at alder spiller en væsentlig rolle, idet børn har en 2,6 gange højere risiko for recidiv end voksne. En højere alder ved primær operation reducerer risikoen med 6 % årligt for børn under 16 år. Studiet fandt også, at omfanget og typen af kolesteatom, især sinus kolesteatom, kan bidrage til recidivforekomsten. Selv dygtige kirurger kan ikke eliminere risikoen for recidiv, hvilket understreger, at anatomiske og fysiologiske faktorer spiller en rolle i disse resultater.

Studie III undersøger effekten af ikke-EPI DWI-scanninger som langtidsopfølgning på 86 patienter behandlet kirurgisk for kolesteatom. Denne metode står i kontrast til den traditionelle 'second look' postoperative tilgang, der er fremherskende i otologien. Undersøgelsen finder god effekt ved brug af ikke-EPI DWI til monitorering af kolesteatomrecidiv, da den demonstrerer høj nøjagtighed og overensstemmelse med kirurgiske resultater. Resultatet understreger relevansen i at anvende ikke-EPI DWI i postoperative vurderinger, hvilket hjælper klinikere med at evaluere kirurgiske resultater, særligt hos børn, der har en større risiko for recidiv.

Studie IV undersøger patienternes sundhedsrelaterede livskvalitet efter kolesteatom-operation, da traditionelle postoperative objektive undersøgelser som audiogrammer og otomikroskopi har vist sig begrænsende i denne henseende. Studiet undersøger og sammenligner den postoperative livskvalitet hos kolesteatompatienter, der gennemgår henholdsvis CWU-BOT og attikotomi; dette gøres ved hjælp af Glasgow Benefit Inventory (GBI) spørgeskema, en banebrydende tilgang i Danmark. Undersøgelsen finder betydelige forbedringer af livskvalitet efter kirurgisk behandling. Undersøgelsen fremhæver, at selvom objektive mål som postoperativ lukning af 'air-bone gap' (ABG) er vigtige, så afspejler de ikke altid patienternes subjektive oplevelse og livskvalitet. Studiet afslører en stærkere sammenhæng mellem subjektive høreforbedringer og livskvalitet end objektive målinger, hvilket understreger behovet for at integrere og tillægge patientrapporterede resultater vægt. Derudover observeredes en signifikant sammenhæng mellem forbedret livskvalitet og reduceret øreflåd hos CWU-BOT-patienter.

Denne afhandling giver en dybdegående indsigt i diagnostik og behandling af kolesteatom i mellemøret samt i sygdommens komplekse karakter og høje recidivrate. Vores fund af høj diagnostisk nøjagtighed af PROPELLER DWI til påvisning af kolesteatom i mellemøret fremhæver metodens vigtige rolle som en ikke-invasiv og pålidelig metode, både til præoperativ diagnostik og postoperativ monitorering og kontrol af sygdommen. MR-teknikken kan medføre færre kirurgiske ingreb for patienterne og fremme tidligere intervention for at forhindre komplikationer. Forskningen indikerer også, at kirurgiske teknikker, især CWU-BOT, kan have en betydelig indvirkning på recidivhyppigheden og patienternes livskvalitet, som vist i de væsentlige forbedringer målt ved hjælp af GBI. Fremtidig forskning bør fokusere på at forbedre kirurgiske metoder og diagnostisk præcision samt prioritere patientrapporterede resultater for en holistisk forståelse af kolesteatombehandlingen.

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"Every day, you may make progress. Every step may be fruitful. Yet there will stretch out before you an ever-lengthening, ever-ascending, ever-improving path. You know you will never get to the end of the journey. But this, so far from discouraging, only adds to the joy and glory of the climb" - Winston Churchill.

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"Never look down to test the ground before taking your next step; only he who keeps his eye fixed on the far horizon will find the right road" – Dag Hjalmar Agne Carl Hammarskjöld.

Abbreviations

ABG - Air-Bone Gap

AC - Air Conduction

ACH - Acquired Cholesteatoma

ADC - Apparent Diffusion Coefficient

ASQ - Anterior Superior Quadrant

CC - Congenital Cholesteatoma

COM - Chronic Otitis Media

CT - Computed Tomography

CWD - Canal Wall Down

CWU - Canal Wall Up

CWU-BOT - Canal Wall Up Bony Obliteration Tympanoplasty

DW-MRI - Diffusion-Weighted Magnetic Resonance Imaging

EAC - External Auditory Canal

EPI - Echo-Planar Imaging

ET - Eustachian Tube

GBI - Glasgow Benefit Inventory

HL - Hearing Level

HR - Hazard Ratio

ME - Middle Ear

MEP - Middle Ear Pressure

MRI - Magnetic Resonance Imaging

MRM - Modified Radical Mastoidectomy

NPV - Negative Predictive Value

Non-EPI - Non-Echo Planar Imaging

OME - Otitis Media with Effusion

PORP - Partial Ossicular Replacement Prosthesis

PPV - Positive Predictive Value

PROMs - Patient-Reported Outcome Measures

PTA - Pure-Tone Average

ROI - Region Of Interest

SRT - Speech Reception Threshold

T - Tesla

List of papers

The present thesis is based on the following publications:

1: The Diagnostic Performance of Non-Echoplanar Diffusion-Weighted MRI in Middle Ear Cholesteatoma. *Submitted to BMC Medical Imaging, November 2023.* Suzan Al Kole, Yousef Yavarian, Jens Brøndum Frøkjær, Michael Gaihede.

2: Long-Term Clinical Follow-Up After Surgery for Primary Middle Ear Cholesteatoma: Recidivism Rates, Prognostic Factors, and Hearing Outcomes. *In preparation*. Suzan Al Kole, Jakob Braun Jepsen, Michael Gaihede.

3: A Long-Term Follow-Up Study with PROPELLER Diffusion-Weighted Magnetic Resonance Imaging in Post-Surgical Monitoring of Middle Ear Cholesteatoma. *Submitted to European Archives of Oto-Rhino-Laryngology and Head & Neck, December 2023*. Suzan Al Kole, Dan Dupont Hougaard, Jens Brøndum Frøkjær, Michael Gaihede, Yousef Yavarian.

4: Post-Surgical Quality of Life in Danish Patients with Middle Ear Cholesteatoma: Analysis Using the Glasgow Benefit Inventory. *Submitted to The Journal of Laryngology & Otology, December 2023*. Suzan Al Kole, Lene Dahl Siggaard, Michael Gaihede.

Contents

1 Background

Middle ear (ME) cholesteatoma, a condition characterized by abnormal keratinized epithelial growth and bone-destructive expansions in the ME and temporal bone, is predominantly caused by abnormal negative ME pressure (MEP). This leads to retraction pockets in the tympanic membrane (TM) filled with squamous epithelium and cellular debris, often resulting in bacterial invasion and recurrent inflammations (Michaels, 1988). Cholesteatomas are typically acquired, linked to Eustachian tube (ET) dysfunction and past otitis media, or less frequently, congenital, appearing as a white mass behind the TM (Louw, 2010). Despite their benign histopathological characteristics, cholesteatomas have the potential to cause destructive lesions within the temporal bone and life-threatening complications such as brain abscesses and meningitis. The exact origins and development of cholesteatomas remain elusive, necessitating a comprehensive understanding of their pathophysiology due to the associated morbidity. This includes chronic otitis media (COM), recurrent infections, dizziness, impaired hearing, and potentially life-threatening consequences, all of which significantly impact the quality of life (QoL) of affected individuals (Rutkowska et al., 2017).

Diagnosing cholesteatomas is challenging due to their often clinically silent nature. Diagnosis relies on clinical suspicion from symptoms like recurrent episodes of otorrhea and conductive hearing loss. Otomicroscopy may reveal keratinized debris, often in relation to a retraction pocket of the TM, which also can include erosion of its bony rim especially in the flaccida region, or erosion in the TM (Levenson et al., 1989). However, deeper cholesteatomas in the ME cavity might not be visible, indicated by dry retraction pockets or granulation tissue near the TM (Sudhoff & Hildmann, 2006). Surgical removal and reconstruction of the TM and ME ossicles is the primary treatment.

Recidivism (referred to as both residual and recurrent), especially in children, remains high due to new cholesteatomas forming from residual epithelial debris or sustained negative MEP. Consequently, mastoid obliteration has become a favored strategy for reducing recidivism, leveraging the mastoid mucosa's inflammation susceptibility, though its full effectiveness is not completely understood (Britze et al., 2017; Tomlin et al., 2013). One plausible explanation pertains to the mastoid mucosa's characteristics: it is rich in loose connective tissue and blood vessels, rendering it more susceptible to inflammation than the ciliated and goblet cell-rich tympanic membrane. Chronic or recurrent infections can precipitate fibrosis, impairing the mucosa's adaptive capacity to modulate its thickness in response to congestion while sustaining gas absorption capabilities. The mastoid's passive anatomical structure plays a pivotal role in both healthy and diseased states, facilitating gas exchange and serving as a pressure buffer owing to its voluminous nature. In scenarios of persistent inflammation, the mastoid mucosa may forfeit its functional attributes, rendering mastoid obliteration a potent strategy to negate the influence of diseased mucosa, potentially enhancing gas absorption and alleviating the development of the ME (Ars et al., 2012; Csakanyi et al., 2014; Gaihede M, 2012).

Accurate diagnosis and assessment of cholesteatomas' size and location are crucial in clinical evaluations. Imaging plays a vital role, with recent advances in non-echo planar diffusion-weighted magnetic resonance imaging (DW-MRI) scans providing a safer, non-invasive alternative to traditional High-Resolution Computer Tomography (HRCT) (Khemani et al., 2011).

This research intends to contribute to the knowledge and understanding of cholesteatoma detection, surgical techniques, patient-reported outcomes, and prognostic factors, ultimately improving the management and outcomes of individuals affected by cholesteatoma. Furthermore, this thesis aims to highlight, explore, and evaluate the patient-reported change in Health-Related QoL (HRQoL) following cholesteatoma surgery using the Glasgow Benefit Inventory (GBI) questionnaire. The thesis aims to improve detection accuracy, surgical outcomes, patient well-being, and prognostic factors related to cholesteatoma recidivism. The following paragraphs offer an overview of the ME anatomy, origin of cholesteatoma, and surgical approaches and advancements in imaging for enhanced cholesteatoma diagnosis.

1.1 Overview of Middle Ear Anatomy

The ME consists of several components, including the TM, epitympanic recess, tympanic cavity, ossicles, aditus ad antrum, and mastoid air cells. The TM, which is a semi-transparent and conically shaped barrier measuring 0.1 mm in thickness, separates the external environment from the ME. The structure of the TM can be divided into two parts: the pars tensa and the pars flaccida (Isaacson, 2018).

The pars tensa, which is mainly attached to the malleus handle, consists of three layers: an outer layer of keratinizing squamous epithelium, a middle layer of vascularized collagen fibers, and an inner layer of low cuboidal epithelium (Lim, 1995).

In contrast, the **pars flaccida**, also known as Shrapnel's membrane, is situated superiorly near the petrous bone. The structure consists of three layers: epidermis, loose collagen fibers, and mucosal tissue. Due to the absence of the fibrous annulus, the structure is more prone to retractions caused by alterations in MEP.

The ME, also known as the tympanic cavity, can be divided into three regions: the hypotympanum, the mesotympanum, and the epitympanum, based on their proximity to the tympanic annulus. The ME is divided into five compartments: epitympanum, mesotympanum, protympanum, hypotympanum, and retrotympanum (Jackler, 1989; Lim, 1995).

The epitympanum, which is connected to the mastoid, contains the ossicular chain and is divided into three sub-compartments: Prussak space, the compartment in front of the malleus, and a posterior compartment that connects to the antrum. Cholesteatoma has the ability to extend beyond the attic and traverse channels in this particular region (Lim 1995; Marchioni, Rubini, and Soloperto 2021).

The mesotympanum is the main section of the ME, located opposite the pars tensa, and it houses the ossicular chain. Cholesteatomas located in the posterosuperior quadrant of the pars tensa have the potential to extend to various adjacent areas, including the hypotympanum, sinus tympani, epitympanum, mastoid, or protympanum.

The tympanic cavity comprises six walls: roof (tegmental wall), floor (jugular wall), anterior (carotid wall), posterior (mastoid wall), medial (labyrinthine wall), and lateral (membranous wall). The labyrinthine wall separates the ME from the inner ear and contains the promontory and tympanic plexus. It also has openings called fenestra vestibuli and fenestra cochleae.

Understanding the complex anatomy of the ME is crucial for surgical procedures, especially those involving cholesteatomas. This knowledge is necessary to perform precise interventions that protect the integrity of both the sound transmission mechanism and the TM.

1.2 Physiology of Pressure Regulation in the Middle Ear

The ME is integral in sound transmission and modulation from the external environment to the inner ear. Within the ME, the mastoid and the ET play active roles in counter-regulating the MEP during short-term pressure changes, as observed in healthy ears (Doyle, 2017; Gaihede et al., 2010). The mastoid primarily regulates minor pressures continuously, while the ET intermittently manages higher pressures. This complementary functioning of both components is crucial for maintaining acoustic impedance and effective sound energy transfer to the inner ear.

The biomechanical properties of the ME are vital for sound energy transmission. These properties influence the ME's response to static pressure loads which, if unregulated, can lead to structural changes in the TM and potentially cause hearing loss. Therefore, keeping the MEP close to atmospheric pressure is essential for the ME's proper functioning (Doyle, 2017). Understanding ME acoustics involves differentiating between dynamic and static pressures. Dynamic pressures relate to sound pressure measurements, whereas static pressures are prone to 'quasi-static' variations, which can be affected by altitude changes or physiological factors. This distinction is key to comprehending the acoustics of the ME and its implications for hearing (Dirckx JJJ, 2013).

1.3 Mechanisms Underlying Middle Ear Pressure

There are two main mechanisms that underlie MEP: 1) Active ET opening through muscular contractions, enabling gas movement (Sadé & Ar, 1997), and 2) passive gas exchange between the ME's air, mastoid air cell and blood compartments, aided by diffusion.

Malfunctions of the ET can result in negative MEP, which may potentially trigger conditions such as otitis media (OM) (Doyle, 2017; Sadé & Ar, 1997). The ME cavity serves as a buffer for pressure changes, and the elasticity of the TM helps regulate pressure (Gaihede et al., 2013; Padurariu et al., 2016). While, the mastoid cell system is regarded as a functional part of the ME, the mastoid process serves as a location for the mastoid air cells, which comprise a network of interconnected cavities that establish communication with the ME cavity and contribute to air pressure management (Ars et al., 2012; Schillinger, 1939), but its physiological role has not been fully elucidated. The mastoid has earlier been regarded to have only a passive role in pressure regulation. However, recent experiments have demonstrated that mastoid may have an active role in overall pressure regulation. These experiments showed gradual pressure changes in the ME due to changes in the thickness or congestion of the mastoid mucosa (Gaihede, 2016b; Gaihede M, 2012).

1.3.1 Clinical Implications of Negative Pressure in the Middle Ear

Negative MEP significantly impacts ME diseases. Broadly, these ailments can be classified into two conditions: 1) Otitis media with effusion (OME), which is prevalent in children. This condition can culminate in hearing impairment. Politzer's foundational theory emphasizes ET dysfunction, leading to continuous net ME gas absorption and subsequent fluid transudation into the ME space as a cause of the disease (Mudry & Young, 2020), and 2) COM, which is characterized by TM retractions, often evolving into acquired cholesteatoma (ACH). This condition can progressively deteriorate the ME components (Sadé & Ar, 1997). Both conditions often require surgical intervention, especially when complications like TM perforations or the progression of cholesteatoma manifests.

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1.4 Cholesteatoma

1.4.1 Cholesteatoma Origin and History

Cholesteatoma, historically documented since the 17th century, is a rare otological condition (Baráth et al., 2011). Its pathogenesis has been a subject of debate since its initial description, with early references dating back to 1683 by the French anatomist Joseph-Guichard Duverney, who described the lesion as 'steatoma' (Benkhadra et al., 2010).

The term 'cholesteatoma' was coined by Muller in 1858 from the Greek 'chole' (bile) and 'stear' (tumor), despite the existence of alternative terms such as 'pearly tumor', 'margaritoma', or 'keratoma' which did not endure (Cruveilhier, 1835; Müller, 1938). Joseph Toynbee's 19th-century work further elucidated ear pathologies, including fatal aural infections that led to intracranial complications associated with a 'soft cheesy mass' in the temporal bone, indicative of cholesteatoma (Mudry, 2012; Toynbee, 1868).

Gray's 1964 definition of cholesteatoma as "skin in the wrong place" (GRAY, 1964) aptly describes the condition as a mass of stratified squamous epithelium that aberrantly proliferates within the temporal bone. This growth results in a conglomerate of keratin, degenerating cells, and chronic inflammation, often accompanied by cholesterol crystals (Cody D.T.R, 1977). Typically, keratinizing stratified squamous epithelium is found on the skin's surface, where it sheds keratin in a regulated manner. However, when this epithelial growth occurs in non-cutaneous sites such as the middle ear or frontal sinus, it is classified as a cholesteatoma leading to the pathological conditions and surgical challenges discussed earlier in this paper (Meyerhoff & Truelson, 1986; PAPARELLA & KIM, 1977) .

1.4.2 Histopathology

Lim and Saunders described the histological characteristics of cholesteatoma in 1972 (Lim & Saunders, 1972). Cholesteatoma consists of three main components: the cystic content, the matrix, and the perimatrix. The cystic content primarily consists of fully differentiated desquamated keratin squamous cells. There may be sebaceous material and purulent and necrotic matter within the cavity. The matrix comprises hyperproliferative keratinized stratified squamous epithelium, closely resembling the normal epidermis with its four layers. The cholesteatoma epithelium includes a basal layer (stratum germinativum), a spinal layer (Malpighian), a granular layer, and a lucid layer. The perimatrix, found at the periphery of the matrix, represents the outermost layer and is characterized by inflamed subepithelial connective tissue containing collagen fibers, fibrocytes, and various inflammatory cells such as lymphocytes, histiocytes, plasma cells, and neutrophil leukocytes. This layer is in direct contact with the bone. The connective tissue, also known as granulation tissue, releases enzymes that contribute to bone destruction (Baráth et al., 2011; Ferlito, 1993; Kuo, 2015).

1.4.3 Epidemiology

The global incidence of cholesteatoma exhibits significant variation, making it difficult to determine an accurate worldwide rate. The incidence rate ranges from 2.8 to 15.6 cases per 100,000 individuals per year, as reported by (Kemppainen et al., 1999; Louw, 2010). Denmark's annual incidence rate is approximately 9 cases per

100,000 (Djurhuus et al., 2015; Kole et al., 2013). A Danish longitudinal study conducted by Djurhuus et al. in 2015 reported a decrease in the incidence rate of ME cholesteatoma from 1977 to 2007 (Djurhuus et al., 2015). Another study by Britze et al. in 2017 reported an annual incidence rate of 6.8 cases per 100,000 individuals (Britze et al., 2017). Previous studies have observed a male predominance in the condition (Djurhuus et al., 2015; Kemppainen et al., 1999). Additionally, Caucasian populations exhibit the highest prevalence, followed by African populations, while non-Indian Asian populations show the lowest prevalence rates (Potsic et al., 2002). In contrast, Inuit Eskimos demonstrate a lower prevalence, likely due to distinct nasopharyngeal anatomical features. The incidence among Greenlanders is comparable to that of Western rates in children, but it appears to be lower in adults (Homøe & Bretlau, 1994). In 2010, Louw reported that developing countries exhibit higher prevalence rates than developed countries (Louw, 2010).

The recidivism rate of cholesteatoma in individuals with a history of the condition is estimated to be between 10-20% during monitoring. This implies that the development of the condition may be influenced by both genetic and environmental factors (Homøe & Rosborg, 2007; Prinsley, 2009). Moreover, cleft palate and similar syndromes are associated with an increased risk of cholesteatoma (Kuo, 2015). Identifying genetic factors can facilitate a better understanding of the disease and the development of more effective strategies for its management.

According to Gilberto et al., the average age for congenital cholesteatoma (CC) in pediatric patients is 4.9 years, while the average age for ACH is 9.7 years (Gilberto et al., 2020). In children, cholesteatoma is present in approximately 10% of cases of COM. COM in childhood increases the likelihood of developing cholesteatoma (Djurhuus et al., 2015). Long-term observations indicate that a small percentage of pediatric cases of COM progress to pars flaccida retraction, and an even smaller percentage escalate to cholesteatoma (Caye-Thomasen et al., 2008; Tos & Poulsen, 1980). The specific factors contributing to the development of cholesteatoma are not fully understood, but it is likely that a combination of environmental, socio-economic, genetic, and random factors play a role (Homøe & Rosborg, 2007; Prinsley, 2009). Animal models and studies have highlighted the significance of chronic mucosal inflammation in the development of cholesteatoma. However, further research is required to clarify the specific pathways involved.

1.4.4 Classification of Cholesteatoma

Cholesteatomas are commonly classified according to their pathogenesis or their location in the ME cavity relative to the TM.

The pathogenesis of cholesteatoma is complex. Most otologists believe there are two types of cholesteatomas: congenital and acquired, unclassifiable (cholesteatoma whose origin cannot be accurately determined) (Baráth et al., 2011).

1.4.4.1 Congenital Cholesteatomas

CC is a rare form of cholesteatoma, accounting for approximately 2-5% of all cases. It is believed to develop from epithelial cells that become trapped in the temporal bone during prenatal development (Gilberto et al., 2020).

CCs are characterized by a white keratinized epithelial mass located behind an intact eardrum, without any previous signs of OM or infection. CCs, which are primarily found in males with a male-to-female ratio of 3:1, are typically diagnosed in children at an average age of 4.9 years, increasing to 6.58 years overall. They account for approximately 16% of pediatric cholesteatoma cases (Gilberto et al., 2020; Kazahaya & Potsic, 2004).

The progression of CC is associated with age, with an annual growth rate of roughly 0.35 mm. Importantly, this correlation remains unaffected by prior ear conditions, surgical interventions, or traumas (Derlacki & Clemis, 1965). Furthermore, it's essential to note that a history of otitis media (OM) does not rule out the possibility of a CC diagnosis (Castle, 2018; Levenson et al., 1988).

CCs are mainly found in the ME, particularly in the anterior mesotympanum or peri-eustachian zone. Excessive growth can obstruct the ET, leading to persistent discharge. Posterior progression can lead to ossicular chain compromise, resulting in conductive hearing loss(Gilberto et al., 2020; Koltai et al., 2002) . In their study, Gilberto et al. classified the spread of CC into three distinct types based on location: Type 1 exclusively affects the ME except for the malleus manubrium, type 2 involves the posterior superior quadrant of the TM, the epitympanum, and the ossicles, and type 3 extends into the mastoid.

1.4.4.2 Acquired Cholesteatoma

Approximately 98% of cholesteatomas are acquired (Kazahaya & Potsic, 2004). ACHs divided into two categories: the primary cholesteatomas, characterized by attic retraction without a previous or little history of otorrhea or TM perforation, and the secondary cholesteatomas, characterized by epithelial migration through the perforated TM due to infection, trauma, or iatrogenesis (The Pathophysiology of Cholesteatoma, 2006).

Otomicroscopic classification system

Understanding the typical anatomy of the tympanic region is essential for accurately identifying the precise positioning of calcified deposits within the tympanic cavity, as well as the ligaments and tendons (Lemmerling et al., 2008).

In 1988, Tos introduced an otoscopic classification system that has since been widely adopted, categorizing cholesteatomas based on their origin (Tos, 1988, 1993). The classification includes three main categories:

***Attic or pars flaccida cholesteatoma**:* These cholesteatomas originate in the region of the Shrapnell membrane (pars flaccida) and extend upwards towards the aditus or antrum. They often extend laterally to the head of the malleus and the body of the incus, resulting in frequent destruction of the scutum and ossicles, particularly the long process of the incus (Kole et al., 2013). Medial displacement of the ossicles is also common. The cholesteatoma can expand further into the attic space, and from there, into the mastoid antrum and other parts of the temporal bone (Jackler, 1989; Jackler et al., 2015). This happens as a result of a retraction or invagination of the pars flaccida occurring due to poor ET function or other factors leading to negative MEP. Over time, if the retraction pocket becomes deeper and is unable to self-clean, keratin debris accumulates, and a cholesteatoma may form (see Figure 1-1 a and Figure 1-2).

Tensa retraction cholesteatoma or pars tensa I, marginal disease: This category involves cholesteatomas originating from the retraction or perforation of the entire pars tensa, affecting the tympanic cavity and the ET. The cholesteatoma typically starts near the annulus, progressing posteriorly and superiorly, wrapping around the ossicles. It can eventually erode the ossicular chain, particularly the long process of the incus and the stapes superstructure (Tos, 1993, 2000) (see Figure 1-1b).

Sinus cholesteatoma, central disease pars tensa II: Cholesteatomas in this category initiate from the posterior superior quadrant of the TM with retraction or perforation of the pars tensa. They predominantly extend into the sinus tympani, along the facial recess, medial to the incus body, the posterior attic, and the mastoid region. The anterior part of the tympanic cavity and the attic are typically not involved. Early ossicle erosion and lateral displacement of the ossicles can occur in pars tensa cholesteatoma (see Figure 1-1c).

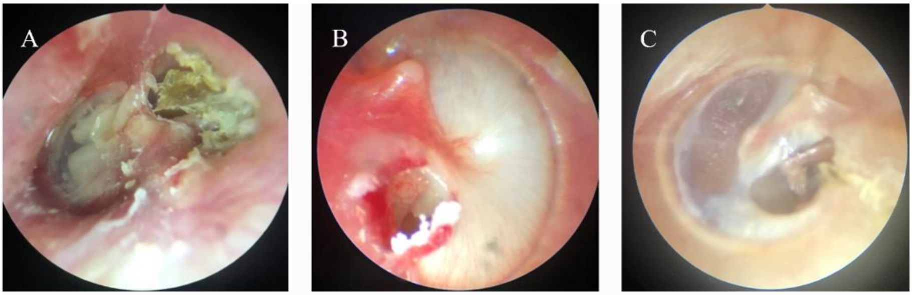


Figure 1-1. Otomicroscopy images of the tympanic membrane. a) left attic/flaccida cholesteatoma dry retraction and erosion, no keration; b) right tensa cholesteatoma, white areas is accumulation of dry keratin debris, pockets margin

inflammed; c) left sinus cholesteatoma. (By courtesy of professor Dr. Michael Gaihede).

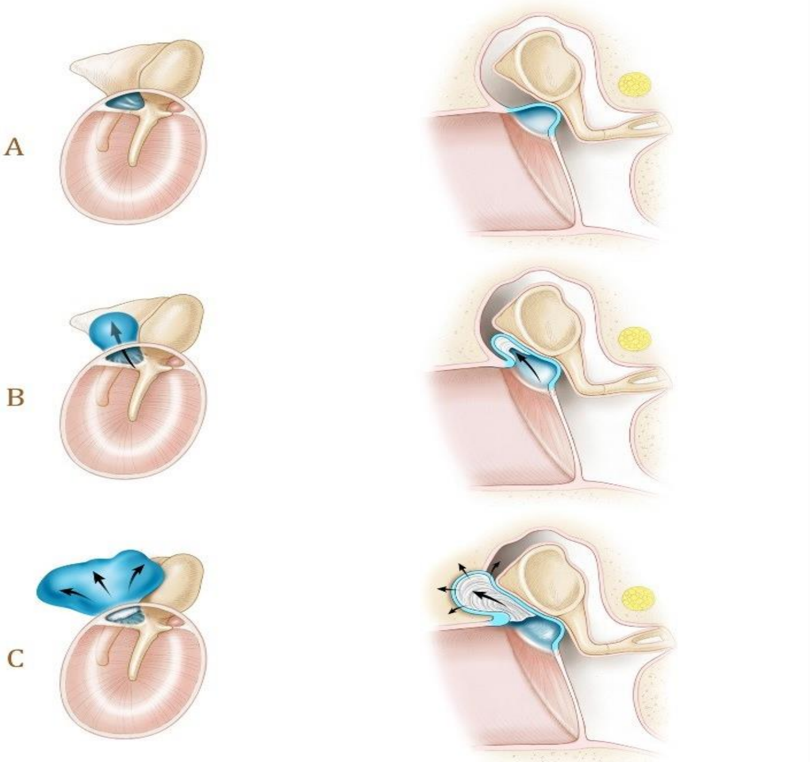


Figure 1-2. Growth pattern of cholesteatoma. Illustration of cholesteatoma progression in the middle ear. The most common type of acquired cholesteatoma is pars flaccida cholesteatoma: (A) Initial attic retraction pocket in the pars flaccida of the tympanic membrane, leading to (B) Cholesteatoma draws into the epitympanum along the incus body and malleus head and begins to accumulate keratin. (C) As it grows, the cholesteatoma becomes filled with keratin debris and expands into the mastoid, passing through the aditus ad antrum. Illustration Chris Gralapp (R. Jackler & Gralapp, 2019).

1.4.4.2.1 Theories on Pathogenesis of Acquired Cholesteatoma

The pathogenesis of ACH is complex and has been a subject of debate for decades, and several attempts have been made to understand the underlying mechanisms of the disease. Cholesteatoma shows diverse pathological findings in various locations in the ME clefts. The pathogenesis of ACH is explained by four primary theories, as illustrated in Figures 1-2: 1) Squamous metaplasia of ME epithelium, 2) epithelial invasion or migration through a perforation (migration theory), 3) hyperplasia theory (papillary ingrowth theory), and 4) invagination (retraction pocket theory) (Louw, 2010; Olszewska et al., 2004; Rutkowska et al., 2017; The Pathophysiology of Cholesteatoma, 2006).

Metaplasia Theory

This theory, introduced by Von Tröltsch in 1864 and later supported by Wendt in 1873, postulated that the metaplastic transformation of the ME mucosa into keratinizing epithelium led to the formation and enlargement of cholesteatomas. According to this theory, the typical appearance of ACH arises as a result of infection and inflammation causing lysis and perforation of the eardrum (Olszewska et al. 200; Semaan and Megerian 2006). This metaplastic theory gained significant acceptance among otologists in the 19th century. Further support for this theory can be found in the works of Sadé, who observed that ME mucosa biopsies taken from pediatric OM patients with effusion occasionally exhibit islands of keratinizing epithelum (Sadé, 1979).

Theory of Epithelial Invasion or Migration (Migration Theory)

Another theory for the etiopathogenesis of ACH is the epithelial invasion or migration, suggesting that the epithelium from the external auditory meatus migrates through a perforation in the TM margin into the ME cavity. In 1888 and 1890, Habermann proposed the migration theory, supported by Bezold’s observations of concave yet intact TMs without perforations, challenging the retraction pocket theory (Bezold, 1889). In 2012, Karmody’s and Northrop’s investigation of temporal bone histologic sections in children found evidence supporting the migration theory, observing cholesteatoma formation through medial migration of stimulated squamous epithelium from the TM. Their findings did not support the retraction pocket theory as a precursor to ACH, suggesting instead that activated squamous epithelium migrates medially from the TM to form cholesteatomas (Karmody & Northrop, 2012).

Hyperplasia (Proliferation) Theory

The basal cell hyperplasia theory, first proposed by Lange in 1925 and later supported by Rüedi in 1958 (Ruedi L, 1958), suggests that cholesteatoma develops as a result of excessive growth of the basal epithelial layer in the pars flaccida. Proliferative activity results in the development of cholesteatoma, characterized by the formation of keratin-filled microcysts and buds that infiltrate the subepithelial tissue of Prussak's space (Kuo, 2015; Ruedi L, 1958). In contrast to the metaplasia theory, this perspective posits that cholesteatoma originates from intrinsic epithelial changes, without requiring a preceding infection.

The Retraction Pocket Theory

Introduced by Wittmaack in 1933, the retraction pocket theory remains the prevailing explanation for cholesteatoma development (Olszewska et al., 2004; Wittmaack k., 1933). Wittmaack differentiated cholesteatomas into pars flaccida and pars tensa types. He postulated that specific prerequisites, including an individual's tendency for hyperplastic mucosa and diminished mastoid cavity aeration, are necessary for cholesteatoma genesis. Initially, squamous epithelia exist in the pars flaccida. For a cholesteatoma to arise, a retraction pocket must form. While Wittmaack observed many such pockets in Prussak's region without full cholesteatoma manifestation, he believed that debris accumulation alone could not account for cholesteatoma progression. He inferred a negative pressure development in the antrum space, noting that sizable cholesteatomas could form without infection, terming them ‘dry cholesteatomas’. Tos et al. substantiated this theory, identifying the retraction pocket as the primary pathology after studying 1100 children over 14 years (Tos, 1988).

These retraction pockets, predominantly in pars flaccida, have the potential to enlarge into Prussack's space. Over time, their growth and exfoliation erode nearby structures, such as the malleus head and incus body. Compromised self-cleaning mechanisms of the external auditory canal (EAC) result in keratin buildup, eventually leading to cholesteatoma. As it enlarges, it can erode structures like the tegmen tympani, the facial nerve's bony canal, and the lateral semicircular canal. In advanced stages, it might affect the membranous labyrinth. Though rarer, pockets can also emerge in the posterosuperior pars tensa, extending around the incus's long process and to the stapes. This cholesteatoma variant, sinus cholesteatoma, typically displaces the ossicular chain laterally as it grows medially and upwards (Jackler et al., 2015) (see Figure 1-3).

Additional insights have been proposed, including Hüttenbrink's self-healing hypothesis in the retraction pocket, suggesting that epidermis migration into the ME cavity is a healing response to inflammation. This overgrowth meets immunologically active tissue, promoting healing and the development of the retraction of the TM and cholesteatoma process (Hüttenbrink, 2019). Similarly, Sudhoff and Tos (Sudhoff & Tos, 2000) and Jackler et al. (Jackler et al., 2015) combined various theories, emphasizing invagination, basal cell hyperplasia, and the dynamic interaction of opposing ME mucosal surfaces.

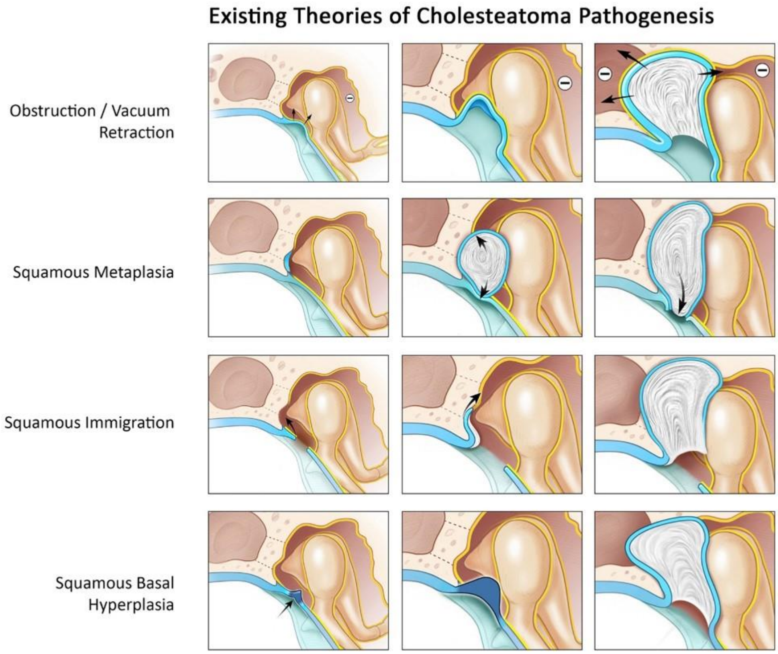


Figure 1-3. Existing theories of cholesteatoma formation. Four prominent theories for the etiopathogenesis of acquired cholesteatoma. A) Invagination Theory (Retraction Pocket Theory). B) Squamous Metaplasia Theory. C) Epithelial Invasion or Migration Theory (Immigration Theory). D) Basal Cell Hyperplasia Theory (Papillary Ingrowth Theory). Illustration by Chris Gralapp (R. Jackler & Gralapp, 2019).

1.4.4.3 Other Types of Cholesteatomas

Mural cholesteatomas are large lesions located in the ME that release cystic contents through the TM into the EAC, while keeping the matrix within the ME. The process of continuous growth, which is facilitated by enzymatic activity, resembles a mastoidectomy cavity, even in the absence of any previous surgical intervention. This phenomenon is referred to as 'automastoidectomy' (Baráth et al., 2011).

External auditory canal cholesteatoma is less common and primarily affects older individuals, in contrast to ME cholesteatomas. EAC cholesteatomas can be categorized into primary (idiopathic) and secondary EAC cholesteatomas.

Primary EAC cholesteatomas typically manifest as a soft tissue mass on the EAC's floor, leading to bone erosion and periostitis due to the invasion of squamous epithelium into the bone. Secondary EAC cholesteatomas, on the other hand, often develop due to previous trauma, surgeries, radiation therapy, or chronic inflammation in the EAC (Rutkowska et al., 2017).

Residual cholesteatoma refers to the presence of keratinizing squamous epithelium that remains after the initial surgical procedure, whereas **recurrence cholesteatoma** can manifest as new formations stemming from the development of new retraction pockets (Vartiainen & Nuutinen, 1993). This phenomenon is commonly referred to as cholesteatoma recidivism.

1.4.5 Complications of Cholesteatoma

Complications associated with cholesteatoma present substantial clinical challenges and can profoundly affect patient health. Among these challenges are:

Infection: Cholesteatoma facilitates bacterial colonization and chronic inflammation, resulting in recurrent or persistent ME infection. This manifests in the clinic as otorrhea, otalgia, and pain.

Destruction of ossicles and bones: Cholesteatoma's progressive erosion of the delicate ossicular chain and adjacent temporal bone structures can lead to functional impairment and anatomical disruption. Conductive hearing loss may be caused by the integrity of the ossicles, including the malleus, incus, and stapes. In addition, erosion of the tegmen tympani, which separates the ME from the intracranial cavity, poses intracranial extension risks.

Hearing loss: Cholesteatoma-related deterioration of ME structures, specifically the ossicles, can result in varying degrees of hearing impairment. Sensorineural hearing loss can occur if the inner ear is affected or if complications extend to the cochlea or cochlear nerve. Conductive hearing loss is more prevalent.

Paresis or paralysis of the facial nerve: In advanced cases of cholesteatoma, the facial nerve may become involved, resulting in facial weakness, paresis, or total paralysis on the affected side. Compression, displacement, or direct injury to the facial nerve can impair its function and profoundly affect facial mobility and expression.

Labyrinthine fistula: Extension of cholesteatoma into the inner ear's labyrinthine structures may result in a communication or fistula between the ME and inner ear compartments. This abnormal connection, a labyrinthine fistula, can result in symptoms such as vertigo, disorientation, incoordination, fluctuating hearing, and perilymphatic fistula syndrome.

Intracranial complications: Although uncommon, the cholesteatoma can penetrate the protective barriers separating the ME from the intracranial space, resulting in potentially life-threatening intracranial complications. Meningitis, brain abscesses, epidural abscesses, and sigmoid sinus thrombosis are infections that necessitate prompt medical intervention to prevent serious morbidity or mortality.

1.4.6 Diagnostics

Traditionally, the diagnosis and follow-up of cholesteatoma relied on medical history, clinical suspicion, otoscopy, and CT scans. However, introducing non-echo planar (non-EPI) DW-MRI sequences has revolutionized cholesteatoma imaging. Clinical suspicion is essential for diagnosing cholesteatoma, with otomicroscopy serving as the primary diagnostic tool. Factors such as a history of OM, habitual sniffing, ventilation tube treatment, and the Valsalva maneuver are important to consider. The clinical presentation of cholesteatoma, ranging from harmless to potentially invasive. Some patients may remain asymptomatic for a significant period, and the cholesteatoma may only become apparent when it has spread extensively (Olszewska et al., 2004; Rutkowska et al., 2017)

Therefore, imaging plays a vital role in cholesteatoma diagnosis (Czerny et al., 2003; Lemmerling et al., 2008). Preoperative imaging assesses cholesteatoma extent, location within the ear (attic, tympanum, antrum, and mastoid), complications (bone lysis, cerebromeningeal issues), and anatomical variations (jugular dehiscence, lateralized sinus). HRCT scans are commonly used for this purpose. In specific cases involving cochlear, labyrinthine, facial nerve, or skull base involvement, specialized techniques like HRCT or MRI scans may be necessary. The choice of imaging method depends on the cholesteatoma type and clinical context. Both CT and MRI scans are valuable, with selection based on specific case requirements, whether it's initial evaluation before first-stage surgery or follow-up to detect residual cholesteatoma.

1.4.6.1 Computed Tomography Imaging

CT imaging, specifically HRCT or cone beam CT, is commonly favored by surgeons as the preferred modality for evaluating the extent of suspected acquired ME or CC prior to surgery. HRCT and cone beam CT provide detailed visualization of the bony destruction caused by the cholesteatoma and typically depicts the cholesteatoma as a soft tissue mass in contrast to the surrounding bone or gas (Lemmerling et al., 2008). HRCT is currently the most common preoperative examination technique for cholesteatoma, providing a clear visualization of the ME's anatomical structures and accurate evaluation of cholesteatoma range and temporal bone invasion, including the tegmen tympani and ossicular chain. However, HRCT alone cannot definitively diagnose or exclude the presence of cholesteatoma in cases of fluid aggregation or myxedema, and its sensitivity and specificity for diagnosing cholesteatoma are limited (Watts et al., 2000; Yigiter et al., 2015).

While CT has excellent spatial resolution, high sensitivity, and precise delineation of anatomical landmarks, it has low specificity for differentiating cholesteatoma from other soft tissues or fluid in the ME or mastoid. Soft tissues such as granulation tissue, inflammation, cholesterol granuloma, or fibrosis can be present even without cholesteatoma in 20% to 30% of previously operated ears. Consequently, CT's sensitivity, specificity, and positive predictive value (PPV) in diagnosing residual and/or recurrent cholesteatoma are relatively low. ‘Second look’ surgical exploration remains the benchmark diagnostic modality in these cases (Ayache et al., 2005; De Foer et al., 2007).

In COM, HRCT is vital for examining the ossicular chain and determining causes of post-inflammatory chain fixation. It accurately reveals the condition of the tympanic and mastoid walls. Erosions in the ossicular chain, especially in the incus long and lenticular processes, are common in both cholesteatomatous and non-cholesteatomatous ME diseases, with the malleus and incus body being more resistant. Modern CT units are capable of visualizing both large and small structures of the ossicular chain, aiding in precise assessments (Lemmerling et al., 2008).

1.4.6.2 Magnetic Resonance Imaging

MRI is crucial in evaluating cholesteatoma, and its diagnostic capabilities have continually improved. The high resolution of soft tissue offered by MRI has contributed to the advancements in diagnosing cholesteatoma (Dietrich et al., 2010; Yigiter et al., 2015). However, standard MRI sequences often have difficulty differentiating cholesteatomas from adjacent tissues. On T1-weighted MRI, cholesteatomas present as hypointense relative to brain gray matter, but this approach has limited accuracy in distinguishing cholesteatomas from inflammatory or fibrous tissues (Kösling & Bootz, 2001; Plouin-Gaudon, Bossard, Ayari-Khalfallah, et al., 2010; Profant et al., 2012). Even with delayed gadolinium-enhanced T1-weighted imaging, cholesteatomas remain challenging to differentiate from inflammatory tissue. As non-vascularized lesions, cholesteatomas do not show enhancement post gadolinium administration. While gadolinium might theoretically highlight a thin, enhanced peripheral rim on T1-weighted images, indicative of the surrounding epithelium or matrix, this is often indistinct and hard to separate from the surrounding inflammatory tissue (De Foer et al., 2010).

Cholesteatoma usually shows up as hyperintense on T2-weighted MRI images, aiding in its identification, although its intensity is typically lower than that of inflammatory tissue or fluid. Its signal intensity on these images is similar to the brain's gray matter (Kösling & Bootz, 2001). In DW-MRI, cholesteatoma shows hyperintensity on b1000 images, while inflammatory or fibrous tissue has low signal intensity. Understanding the T2 shine-through effect is vital for interpreting DW-MRI, as it can affect tissue diffusion appearance.

In the past decade, several studies have demonstrated the role of DW-MRI in cholesteatoma surveillance. DW-MRI was initially used for diagnosing ischemic brain infarction (Forbes et al., 2002). The DW-MRI technique measures the random motion of water molecules in various tissues and is based on the Brownian movement of water molecules to assess tissue microstructure and cellularity. DW-MRI measures the restricted diffusion of water molecules in different tissues, providing information about cellular density and barriers (Dietrich et al., 2010). The Apparent Diffusion Coefficient (ADC) is a key parameter obtained from DW-MRI that quantifies the rate of water molecule diffusion in tissue, providing insights into tissue microstructure. This value is calculated using images taken at different b-values, which adjust the MRI's sensitivity to diffusion. The ADC is determined by calculating the natural logarithm of the ratio of signal intensities from images at two different b-values and dividing by the difference between these b-values. A lower ADC implies restricted diffusion, whereas a higher value suggests more unrestricted diffusion (Bammer, 2003). Cholesteatoma, for example, exhibits restricted diffusion due to the presence of keratin debris, leading to hyperintensity with high signal intensity on DWI (Le Bihan et al., 1988).

Among DW-MRI sequence protocols are echo planer imaging (EPI) DW-MRI and non-EPI DW-MRI (Khemani et al., 2011; Lingam et al., 2013; Más-Estellés et al., 2012). Since the first description of the non-EPI DW-MRI in 2006 in cholesteatoma diagnostic (De Foer et al., 2006; Dubrulle et al., 2006), it has become the method of choice for imaging the ME cholesteatoma. It is believed to be superior to conventional EPI DW-MRI and other MRI variants (Lingam & Bassett, 2017; Más-Estellés et al., 2012; Romano et al., 2020).

EPI DW-MRI is a widely used sequence in DW-MRI. It rapidly acquires images using a single-shot technique, allowing for the quick acquisition of DWI due to its short imaging time of approximately two minutes. However, single-shot EPI has several limitations that can affect the quality of DWI images.

One major issue with single-shot EPI is the presence of severe geometric distortions and T2*-induced blurring. The significant T2* decay and phase error accumulation during the extended readout echo train cause these distortions, especially at high spatial resolution and b-values. Consequently, image quality may be compromised, leading to potentially misleading interpretations. Additionally, patient movement during imaging can further degrade the image quality, making obtaining accurate and reliable DWI results challenging. Moreover, the geometric distortions caused by single-shot EPI can introduce spatial misalignments and affect the accuracy of image registration and analysis (Fitzek et al., 2002; J. P. Vercruysse et al., 2009). EPI DW-MRI produces marked hyperintense artifacts, mainly at the level of the tegmen. These artifacts can hide a small residual cholesteatoma.

Higher magnetic field strengths may be advantageous for anatomical imaging but are not inherently beneficial for DWI using single-shot EPI. Higher spatial resolution and ultra-high magnetic field strengths tend to exacerbate the aforementioned difficulties (Yamashita et al., 2019). Therefore, several reports set the detection threshold of EPI-DWI for cholesteatoma at five mm (Aikele et al., 2003; Venail et al., 2008).

Non-EPI DW-MRI was introduced in 2006 and has become the gold standard for detecting cholesteatoma due to its ability to identify even small lesions, as small as two mm (De Foer et al., 2006; Dubrulle et al., 2006). This technique is less affected by T1 or T2 effects, susceptibility artifacts, and motion distortion compared to other methods. It offers higher spatial resolution, although it may require longer acquisition times but is less susceptible to air-bone distortions.

Variations of non-EPI DW-MRI, such as multi-shot turbo spin-echo techniques with the motion correction (Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (PROPELLER) and BLADE), HASTE or Half-Fourier Acquisition single-shot turbo spin-echo, and others, are available from different MRI vendors (Pipe et al., 2002; Sheng et al., 2020). PROPELLER, for instance, employs a radial k-space-filling pattern, reducing susceptibility artifacts and motion artifacts (F. Mas-Estelles et al., 2010; Lehmann et al., 2009; Pipe et al., 2002). Various MRI vendors offer different variations of MR sequences, each with their own trade names. For example, General Electric uses PROPELLER, Siemens uses BLADE and HASTE, Philips has MultiVane and Multi-shot Turbo Spin Echo, or MSH-TSE, MSHitachi features RADAR, and Canon utilises JET.

Non-EPI DW-MRI demonstrates high sensitivity and specificity for primary cholesteatomas, with positive and negative predictive values (NPV) well above 0.9 (Dubrulle et al., 2006; Van Egmond et al., 2016; J. P. Vercruysse et al., 2006). False-positive cases of cholesteatoma are rare in non-EPI DWI. False-positive reported cases in the literature that affect specificity and the PPV includes Silastic sheets, bone pâté (Muhonen et al., 2020), cartilage (Muhonen et al., 2020), OM (Mateos-Fernández et al., 2012), external canal cerumen, cholesterol granuloma, hemorrhage following a recent surgery, granulation tissue, and abscess (Fan et al., 2019; Lingam et al., 2016). On the other hand, false negatives may occur if cholesteatomas lose their keratin content due to recent procedures, in some cases (Baráth et al., 2011; de Ávila et al., 2013).

Recent studies have integrated quantitative ADC values and qualitative signal intensity in non-EPI DW-MRI for cholesteatoma diagnosis (Kolff-Gart et al., 2015; Russo et al., 2018). The ADC value, calculated using specialized software from Region of Interest (ROI) data, offers objective insights into water diffusion in cholesteatoma lesions, thereby enhancing diagnostic precision (Lingam et al., 2013; Thiriat et al., 2009).

1.4.7 Cholesteatoma Surgery

Surgery of Cholesteatoma

As previously stated, cholesteatoma is associated with bone resorption and bacterial infection. The erosion of ossicular bones, specifically the long process of the incus, results in conductive hearing loss. Treatment primarily involves surgical removal, as no effective nonsurgical options exist.

The surgical process, akin to cancer surgery, requires meticulous removal of the cholesteatoma to prevent recidivism , as even a single residual cell can cause the disease to reoccur (Luers & Hüttenbrink, 2016). This surgery, aiming for complete disease eradication and hearing restoration, has maintained these goals for over seventy years. The complexity and precision required in cholesteatoma surgery have led to the development of advanced techniques, including both open (CWD) and closed (CWU) procedures, utilizing microscopes, endoscopes, or both. The choice between CWD, involving the removal of the posterior ear canal wall, and CWU, preserving the wall, depends on the specific case and surgical objectives. Medical management, such as topical antibiotic eardrops, supports the treatment by addressing superimposed infections (Edelstein and Parisier 1989; Jackler 1989).

Surgical Techniques

Currently, no viable nonsurgical therapies are available. Cholesteatoma surgery is complex, challenging, and time-consuming. The primary surgery goals, which have not changed over the last decades, include total removal of disease with the prevention of recidivism disease, and secondary goals are optimal hearing restoration or preservation of hearing and improvement of discharging ear (Sudhoff & Hildmann, 2006).

Many variables affect the long-term result of surgery. The more widespread the disease and damage at initial presentation, the poorer the outcome. The surgical outcome is also based on the surgeon's personal experience and skills, the choice of the surgical technique, and the material used for the reconstruction (Britze et al., 2017; Ferreira Bento & Carolina de Oliveira Fonseca, n.d.; Mollison, 1930).

It is well-known that recidivism can occur no matter what technique is used. The optimal surgical technique is characterized by its minimal risk of failure. Complete removal is essential to minimize the risk of residual pathology and prevent recurrent disease. Closed cavity procedures include simple (cortical) mastoidectomy and CWU (intact canal wall) mastoidectomy (Milstein, 1980).

Throughout its history, mastoidectomy has tended to preserve or restore hearing. Currently, mastoidectomy is performed to preserve the ear's anatomy, which may require several reoperations because of the tendency of cholesteatomas to recur.

Mastoidectomy and Related Techniques

- Simple mastoidectomy
- CWU mastoidectomy/ intact canal wall
- CWD mastoidectomy
- Radical mastoidectomy
- Modified radical mastoidectomy
- Mastoid obliteration
- Canal reconstruction mastoidectomy
- Retrograde mastoidectomy
- Atticotomy

Simple mastoidectomy consists of opening the mastoid cortex, identifying the aditus ad antrum, and removing the mastoid cortex and varying amounts of the air cell system, depending on the disease process. A simple mastoidectomy or antrostomy was observed to be sufficient in acute mastoiditis cases (Bento & De Oliveira Fonseca, 2013). Indications are mastoiditis and acute otitis.

CWU or intact canal wall is typically performed with the aim of preserving the natural anatomical structure of the mastoid, according to Yasuyuki (Hinohira et al., 2007). Many surgeons consider CWU the preferred surgical technique for most cases.

CWU mastoidectomy is performed when the posterior superior canal wall needs to be preserved. This surgical technique involves the removal of the mastoid air cells, lateral mastoid cortex, and Koerner's septum to establish communication between the surgically created cavity, known as the 'mastoid bowl,' and the attic/antrum. This approach provides access to the epitympanum while maintaining a natural barrier between the EAC and the mastoid cavity.

In most cases, a CWU tympanomastoidectomy is performed to assess the condition of the epitympanum and promote aeration through the development of the facial recess. To preserve sensorineural hearing when working on the ossicles, the division of the incudostapedial joint is a necessary initial step. Additionally, this approach can be combined with a facial recess approach or posterior tympanotomy to address cholesteatoma in the facial recess, enhance exposure of the posterior mesotympanum around the oval and round windows, and improve visualization of the tympanic segment of the facial nerve. If greater exposure is required, the facial recess can be extended either inferiorly or superiorly to gain complete access to the hypotympanum or the epitympanum (Jansen, 1983; Jansen C., 1958; Sheehy & Patterson, 1967a).

CWD mastoidectomy involves the removal of the EAC wall, resulting in a permanent opening or 'down' cavity that communicates with the ME space. This approach allows better visualization and access to the diseased area and facilitates the thorough removal of cholesteatoma and infected tissues. The primary objective of the CWD procedure is to eradicate the disease, ensure that the ear is sterile and free of infection, and prevent recurrence. By removing the canal wall, the surgeon obtains direct access to the ME and mastoid spaces, allowing for more thorough examination, cleaning, and disease management. After removing the canal wall, the ME and mastoid cavities are meticulously cleaned, and any diseased tissue, cholesteatoma, or infected material is removed. If necessary, the surgeon may also perform ossiculoplasty or tympanoplasty.

Radical mastoidectomy is a significant surgical procedure that has been developed for the treatment of COM or acute cases involving intracranial complications. The primary objective of this procedure is to eliminate the disease affecting the ME and mastoid. It involves the removal of the posterior and superior canal walls, performing meatoplasty (reconstruction of the EAC), and exteriorizing the ME. This procedure is commonly indicated for conditions such as cholesteatoma and for removing glomus tumors or carcinomas affecting the ME. It aims to address and eradicate these pathologies to restore normal ear function and prevent further complications.

Modified radical mastoidectomy is a surgical technique that has evolved over time. Described initially by Bondy in 1910, it involved removing portions of the superior or posterior canal wall to address disease limited to the epitympanum. The primary goal of this technique is the removal of mastoid disease. In a modified radical mastoidectomy, the diseased tympanomastoid air cells are completely eradicated and exteriorized through the external meatus. This ensures thorough inspection and regular cleaning of the cavities. However, it is essential to note that this technique does not involve any reconstructive procedures.

The distinguishing feature of this approach is that it does not include the repair of the canal and TM defects, unlike retrograde mastoidectomy. It is typically indicated for cases of limited cholesteatoma confined to the attic and antrum. In contemporary practice, many surgeons use the term ‘modified radical mastoidectomy’ to describe a procedure involving the removal of the EAC wall and subsequent TM reconstruction (Pappas, 1994; Richards, 1911).

Mastoid obliteration is a surgical technique used to address chronic discharge and problematic mastoid cavities or to reduce the recidivism rate in cholesteatoma cases. The procedure involves filling the mastoid cavity with various materials to promote tissue healing and reduce the size of the cavity (Mercke, 1987).

The concept of mastoid obliteration dates back to the late 19th and early 20th centuries. One of the earliest attempts was made by Blake in 1898, who used a blood clot to induce fibrous growth and reduce the size of the mastoid cavity (Blake C, 1898). In 1911, Mosher introduced a post-auricular soft tissue flap to promote the healing of mastoidectomy defects (Mosher, 1911).

Over time, different surgical techniques and materials have been developed for mastoid obliteration. Autologous materials such as fascia (Mollison, 1930), fat (Linthicum, 2002), cartilage (Jalali et al., 2017), and cortical bone chips (Roberson et al., 2003) have been used to fill the mastoid cavity and stimulate tissue growth. These materials are often obtained from the patient's own body, ensuring compatibility, and reducing the risk of rejection. In addition to autologous materials, biocompatible substances have been utilized for mastoid obliteration. These include hydroxyapatite (Yung, 1996), demineralized bone matrix (Skoulakis et al., 2019), ionomeric cements (Mahoney, 1962), and calcium phosphate ceramics (Leatherman & Dornhoffer, 2002). These materials provide structural support and promote bone regeneration.

The specific steps of the mastoid obliteration procedure may vary depending on the surgeon's preference and the patient's individual case. Generally, the procedure involves accessing the mastoid cavity through a surgical incision, removing any unhealthy tissue or debris, and thoroughly cleaning the area. The chosen material, such as autologous bone chips or a biocompatible substance, is then placed within the mastoid cavity to fill the space. The material is carefully positioned to ensure proper coverage and support. The surgical incision is closed, and the patient is monitored for postoperative healing and recovery.

Mastoid obliteration techniques have shown promising results in reducing the size of chronic mastoid cavities, promoting tissue healing, and decreasing the recidivism rate in cholesteatoma cases. However, selecting the specific technique and material depends on factors such as the extent of the disease, individual patient characteristics, and the surgeon's expertise (J. P. Vercruysse et al., 2008; J.-P. Vercruysse et al., 2010).

Canal reconstruction mastoidectomy was first introduced by Mercke in 1987. This technique involves using bone chips and bone pâté to isolate and obliterate the mastoid, attic, and tympanum, thus preventing postoperative retraction pockets. The posterior canal wall is surgically removed using a microsagittal saw to ensure complete removal of the disease.

There are several advantages to canal wall reconstruction with obliteration, including increased intraoperative exposure, removal and obliteration of mastoid epithelium using bone pâté, and reconstruction of the posterior canal wall with mastoid cortical bone at the aditus. The described approach facilitates a comprehensive evaluation of residual disease in ossiculoplasty, as staging is essential to the procedure. Alternative techniques for posterior canal wall reconstruction have also been described. Some authors have proposed the removal of the posterior canal wall, followed by its replacement and fixation using bone cement. This provides stability and support to the reconstructed canal (B. Black, 1998; Gantz et al., 2005). However, it is essential to note that postoperative wound infections are a possible complication of this procedure (B. Black, 1998; Gantz et al., 2005).

The **retrograde mastoidectomy** also called inside-out approach is beneficial in cases with clearly defined disease extent, as it enables a more conservative approach to bone removal and potentially preserves the natural structure of the ear. It begins at the site of the disease and progresses towards the mastoid, then removal of the only portion of the mastoid overlaying the cholesteatoma. The main objective is to eliminate the disease while minimizing the alteration of normal anatomical structures (Jackler, 1989).

The atticotomy procedure is more focused and limited compared to a full mastoidectomy. It is specifically aimed at treating cholesteatomas in the attic region of the ear, typically addressing less extensive cases through access and control via the ear canal.

1.4.7.1 Canal Wall Up or Canal Wall Down Mastoidectomy: Advantages and Disadvantages

Canal wall down

Concept: CWD involves removing a portion of the bony canal wall, creating a larger cavity for enhanced disease visualization and access. The goal is complete eradication of the cholesteatoma, including hidden or residual disease.
Advantages: Provides excellent exposure for ongoing surveillance and cleaning, ensuring thorough disease removal.
Disadvantages: Results in a permanent EAC opening, making the ear more susceptible to infections. Requires regular cleaning and maintenance.
Suitability: Typically chosen for cases with extensive disease involvement and a higher risk of residual cholesteatoma.
Philosophy: Emphasizes disease eradication and extensive exposure.

Canal wall up
Concept: CWU preserves the integrity of the canal wall, maintaining a more natural ear anatomy. It aims to minimize the risk of infections and conserves the EAC.
Advantages: Preserves a more natural anatomical structure and reduces the risk of post-surgical infections.
Disadvantages: Due to limited access, ongoing surveillance may be less effective in identifying and removing residual cholesteatoma.
Suitability: Suitable for cases with limited disease involvement and a lower risk of residual cholesteatoma.
Philosophy: Prioritizes anatomical preservation and function.

Factors influencing the choice of surgical technique
Disease extent: The extent and severity of the cholesteatoma play a significant role in determining the appropriate surgical approach.
Complications: The presence of associated complications, such as ossicular erosion or facial nerve involvement, may influence the choice of surgery.
Patient characteristics: Consideration of patient preferences, medical history, and age is crucial.
Surgeon's expertise: The surgeon's experience and preference may also impact the choice of approach.

Alternative approach - mastoid obliteration
Concept: Mastoid obliteration techniques, like the BOT technique, aim to reduce cholesteatoma recidivism risk by creating a smaller cavity with obliteration of mastoid air cells.
Advantages: Combines elements of both CWD and CWU approaches, offering a compromise between disease eradication and anatomical preservation.

1.4.7.2 General Aspect of Recidivism

Cholesteatoma surgery aims to eradicate the disease, leaving no trace of cholesteatoma behind. Residual cholesteatoma refers to viable clusters of keratinizing squamous epithelial cells that were not completely eradicated during the initial surgery and have regrown into a cholesteatoma. Residual cholesteatoma is a recognized difficulty in cholesteatoma surgery, regardless of the surgical approach or reconstructive technique applied. The rate of residual cholesteatoma reported in the medical literature varies considerably, reflecting differences in surgical procedures. Compared to CWD techniques and the CWU-BOT technique, conventional CWU techniques have a higher rate of residual cholesteatoma. In addition, regardless of the surgical approach, a consistently higher incidence of residual cholesteatoma has been observed in pediatric patients compared to adults. This highlights the importance of diligence and accuracy during pediatric cholesteatoma surgery.

After CWU techniques, exploratory surgical staging has traditionally been deemed essential. As previously stated, advancement in MRI technology, specifically the non-EPI DW-MRI, has transformed postoperative evaluation. Even tiny cholesteatoma pearls as 2 mm can be accurately characterized by MRI, distinguishing them from scar tissue, cholesterol granuloma, granulation tissue, and fluid. This non-invasive and radiation-free imaging method has diminished the need for routine exploratory second-look procedures.

1.4.7.3 Quality of Life Assessment Following Cholesteatoma Surgery

The effect of cholesteatoma surgery is assessed with HRQoL evaluations, specifically those that use Patient-Reported Outcome Measures (PROMs). The significance of the evaluations is widely recognized in the field of chronic conditions and elective procedures (Banks et al., 2013; N. Black, 2013; N. Black & Jenkinson, 2009). In recent years, there has been a growing recognition of the importance of health status assessment, particularly QoL research, in managing chronic conditions and elective interventions. PROMs have been created and validated to assess HRQoL in specific populations, including those with hearing impairment (Banks et al., 2013).

The Glasgow Benefit Inventory (GBI) is a significant PROM in the field of otorhinolaryngology. The GBI, developed by Robinson et al. in 1996, assesses changes in post-interventional HRQoL in otorhinolaryngological treatments (Robinson et al., 1996). The 18-item questionnaire has been validated in multiple languages and provides insights into the factors that contribute to both positive and negative outcomes (Sanchez-Cuadrado et al., 2013). However, the tool has been criticized for its generic nature and emphasis on change rather than current HRQoL (Weiss et al., 2020).

The structure of the GBI encompasses domains that evaluate physical, social, and general health. Questions are assigned numerical values ranging from “1” to “5”. These values are then used to calculate an overall score, which is adjusted using a standard formula. The resulting score can range from “-100” (indicating the worst possible outcome) through “0” (indicating no change) to “+100” (indicating the best possible outcome). To address potential response biases, the survey includes an equal number of questions that assess improvement and deterioration.

On the other hand, certain PROMs, such as the Chronic Ear Survey, concentrate on particular areas such as hearing and limitations related to the ear (Nadol et al., 2000). Quaranta et al. found that the Chronic Ear Survey has shown positive QoL outcomes after surgery for cholesteatoma, regardless of whether the CWU or CWD technique

was applied (Quaranta et al., 2014). However, hearing loss remains a common concern.
In conclusion, the GBI provides a comprehensive view of post-interventional changes in HRQoL, while disease-specific instruments like the Chronic Ear Survey offer specific insights into various aspects of chronic ear diseases. This highlights the significance of using a variety of assessment tools in the field of otolaryngology.

Since your ear operation, do you have more or less self-confidence?				
Much more self-confidence	More self-confidence	No change	Less self-confidence	Much less self-confidence
5	4	3	2	1

Has the result of the ear surgery affected the things you do?				
Much worse	A little or somewhat worse	No change	A little or somewhat better	Much better
5	4	3	2	1

Examples of two questions from the GBI survey

1.4.7.4 Pre- and Postoperative Care

Preoperative counseling is a crucial aspect of the surgical procedure, as it helps manage patient expectations and improves their QoL. During counseling, educating the patient about various aspects related to the disease and the surgical process is important. Firstly, the patient should be informed about the possible pathogenesis of the disease and the importance of ME ventilation, which can be achieved through techniques like the Valsalva maneuver. They should also understand the natural self-cleaning process of the ear canal and the significance of preoperative water protection to prevent complications. Secondly, it is essential to discuss the risks associated with the surgery. The risk of surgical damage to the inner ear leading to sensorineural hearing loss or deafness is estimated to be less than 1%. The risk of accidental injury to the facial nerve is even lower (less than 0.5%). It is also important to mention the possibility of delayed facial dysfunction, which may occur several days after surgery but generally has a good prognosis. Moreover, if the patient presents with a preoperative infection, it is necessary to perform a bacterial culture and appropriately treating the infection with antibiotic eardrops and/or oral antibiotics before surgery.

By providing this comprehensive preoperative counseling, patients can better understand the procedure, potential risks, and necessary precautions, enabling them to make informed decisions and actively participate in their own care.

2 Hypotheses and Aims

2.1 Hypotheses

1. The DWI PROPELLER MRI technique exhibits high accuracy, specificity and sensitivity in early cholesteatoma detection. Moreover, it will enable the definition of an ADC value, which can be used for the demonstration of cholesteatoma.

2. Cholesteatoma surgery with obliteration technique will demonstrate improved clinical and surgical outcomes with lower rates of recidivism compared with non-obliteration technique.

3. Certain prognostic factors such as age, extent of disease, and anatomical considerations can be identified as contributing to higher rates of recidivism, particularly in children.

4. Long-term follow-up examinations with MRI scans may detect cases of disease recidivism, which is not otherwise detected by clinical examinations.

5. Patients undergoing cholesteatoma surgery with obliteration will experience an improvement in their QoL when compared with those undergoing non-obliteration surgery.

2.2 Aims

1. To evaluate the accuracy and sensitivity of DWI PROPELLER MRI as a method for cholesteatoma detection and determine if a reference value can be established for cholesteatoma detection using DW-MRI.

2. To investigate and assess changes in patient-reported HRQoL following cholesteatoma surgery, employing the GBI questionnaire.

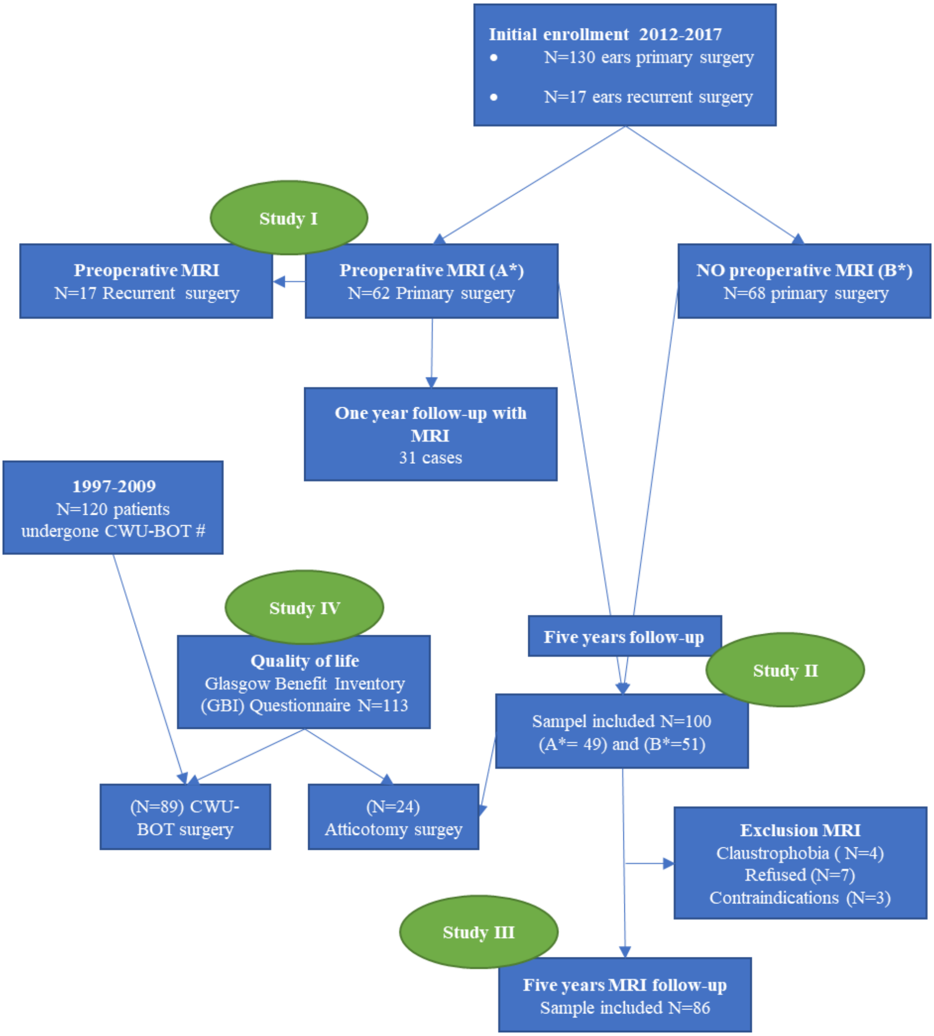
3. To compare the clinical and surgical outcomes of cholesteatoma surgery between obliteration and non-obliteration techniques and evaluate the long-term follow-up results.

4. To identify prognostic factors associated with cholesteatoma recidivism, with a specific focus on children, by considering factors such as age, disease extent, surgical technique, and anatomical considerations.

3 Methods and Materials

The flowchart presented below offers a comprehensive overview of the study's design and the participant cohort. It serves as a visual guide, illustrating the study's framework and sequence.

Flowchart. Overview of the study design and cohort.



All studies in this thesis complied with the Declaration of Helsinki (World Medical Association 2013). The study received approval from the Institutional Review Board prior to conducting the research (Approval No. N-20110054). Data were registered prospectively and organized in a REDCap database hosted by Aalborg University Hospital (2017/73).

Patient inclusion

All patients undergoing surgery for primary ME cholesteatoma were prospectively registered in the database. The patient population was categorized into two groups: adults, defined as those over 16 years of age, and children, defined as those under 16 years of age. Patients with ME cholesteatoma who did not meet the inclusion criteria, and those who required a minimum of five years of follow-up and complete surgical and audiological records both preoperatively and at 1- and 5-years post-surgery, were excluded from the study. Additionally, patients had to be eligible for MRI scans (see Flowchart: overview of the study design and cohort).

Patients with suspected cholesteatoma underwent comprehensive clinical and radiological examinations at the Department of Otolaryngology, Head and Neck Surgery at Aalborg University Hospital. The evaluation process included a detailed medical history review, otomicroscopy, and audiometry. The department follows a standard protocol for the evaluation of cholesteatoma cases. Patients are recommended up to ten years of follow-up after primary surgery, depending on factors such as the patient's age, otomicroscopy findings, and severity of ET dysfunction. The standard follow-up period is one year for adults and five years for children, unless there are specific indications for longer follow-up, such as clinical suspicion of incipient cholesteatoma. In cases of uncertainty, PROPELLER DW-MRI is employed as a screening tool. For the five years follow-up patients, clinical examinations with audiometry and PROPELLER DW-MRI are performed routinely.

In this thesis, the term "recidivism" refers to the residual and recurrent occurrence of cholesteatoma.

Audiometry

Hearing outcomes were assessed in accordance with the guidelines provided by the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium for the treatment of conductive hearing loss (Committee on Hearing and Equilibrium, 1995). The evaluation of hearing outcomes was based on the measurements of air-bone gap (ABG) and pure-tone average (PTA). Successful hearing outcomes were defined as post-surgery ABG values of 20 dB or less and PTA values of 30 dB or less. ABG and PTA measurements were conducted at frequencies of 0.5, 1, 2, and 4 kHz, and the mean value of these frequencies was used to calculate the ABG or PTA value (Committee on Hearing and Equilibrium, 1995).

Surgical Methods (Paper I, II, III and III)

Many surgeons choose the surgical technique based on the individual clinical situation. Surgical decision-making is based on the size and extent of the chole-steatoma. In our department, CWU-BOT is the primary procedure in nearly 60% of cholesteatoma surgeries.

Atticotomy was usually performed in small and limited cholesteatomas. The surgical procedure involved drilling the scutum around the cholesteatoma's epitympanic margins. However, this method was only appropriate for patients with cholesteatoma confined to the central epitympanic region. The surgical procedure included standard vascular strip incisions, a postauricular incision, and an anterior ear reflection. A small diamond burr was used to drill the edge of the scutal defect, and the bone of the superior ear canal was thinned and cupped to facilitate adequate visualization. The edges of the cholesteatoma sac were identified and excised, along with the debris. Typically, the matrix was reflected inferiorly, and a small cartilage graft or bone chip was inserted into the scutal defect. In addition to replacing the vascular strip, an absorbable gelatin sponge was packed into the ear.

When the cholesteatoma extended significantly towards the antrum, the surgeon employed a combined approach technique, drilling from anterior to posterior until the cholesteatoma's limit was reached. If the cholesteatoma extended beyond the posterior limit of the lateral semicircular canal, a CWU mastoidectomy with tympanoplasty and obliteration was needed. This procedure also involved saucerization of the cortex, lowering of the facial ridge, management of the tip, and adequate meatoplasty, especially in poorly pneumatized or sclerotic mastoids.

The bony obliteration technique (BOT) was a surgical approach typically employed in cases involving extensive attic cholesteatomas, particularly when confronted with large cholesteatomas and obscured visualization. This technique was selected for its effectiveness in managing complex and extensive cases, with the primary objective of reducing mastoid size and restoring normal dimensions to the EAC. Our modified approach, known as cortical mastoidectomy with posterior tympanotomy (CWU-BOT), was based on the method initially developed by Mercke (Mercke, 1987), with two notable modifications.

Firstly, instead of removing the posterior canal wall, we adopted the classic combined approach procedure with posterior tympanotomy, which offered improved exposure while preserving the integrity of the canal wall. Secondly, we opted for tympano-ossicular allografts, such as cartilage or perichondrium, as alternatives to the use of fascia and biomaterials. Since 1997, our department has been employing this adapted technique, incorporating the use of bone chips and pâté. This modification had resulted in significantly reduced recidivism rates of cholesteatoma, leading us to discontinue the use of CWD techniques due to their limitations.

All surgeries were conducted under general anesthesia using a retroauricular approach, which included musculo-periosteal incisions. A postauricular incision was made through the superficial layer of the deep temporalis fascia, and a wide musculoperiosteal Palva flap was created to expose the mastoid cortex and temporal squama, facilitating access to cortical bone chips and bone pâté. Cortical bone chips were harvested using a flat chisel and set aside, while bone pâté was collected using a bone pâté collector and cutting burr from the cortex of the mastoid and squamous temporal bone. Both the bone pâté and chips were mixed with an antibiotic solution, typically ciprofloxacin ear drops.

The surgical procedure involved cortical mastoidectomy and posterior tympanotomy using small cutting burrs (1-2 mm) within a combined approach, exposing the mastoid process and ear canal. The descending portion of the facial nerve served as a medial landmark for the posterior tympanotomy, and all mastoid and epitympanic cell tracts were thoroughly cleaned, with unhealthy bone being drilled away. Unlike the original Mercke technique and the procedure described by Gantz, we preserved the posterior canal wall during the surgery (Gantz et al., 2005; Mercke, 1986, 1987).

To preserve sensorineural hearing, the incudostapedial joint was divided as a necessary first step when working along the ossicles. If the cholesteatoma matrix had eroded the incus's short process or the bulge of the semicircular canal, they were removed. Dissection of the canal skin was performed, and if the cholesteatoma extended medially to the incus, the incus was also removed. The remnants of the TM were dissected from the bony annulus and malleus handle, preserving as much healthy canal skin as possible. The diseased portion of the TM was resected, leaving the anterior and inferior rim for graft placement. If the disease extended medially to the malleus head, the malleus or its head was removed. The chorda tympani was usually preserved unless eroded by the cholesteatoma matrix, and if necessary, the chorda tympani was sacrificed. The disease was removed from the anterior attic through the cortical mastoidectomy and the tympanic sinus through the posterior tympanotomy. The facial recess was extended to the floor of the EAC. The incus and malleus heads were removed. To ensure complete sealing of the epitympanum and mastoid from the ME cavity, bone chips were shaped and placed at the tympano-attical barrier and posterior tympanotomy level, with bone pâté carefully inserted in the attic and mastoid to secure the bone chips in place. Subsequently, the TM and ME were reconstructed using the appropriate techniques (see below), with perioperative antibiotics, typically cefuroxime, administered to the patients.

Currently, most cholesteatoma cases are treated using the surgical BOT technique, typically as a single-stage operation without the anticipation of a second procedure. ME reconstruction procedures, such as ossiculoplasty, scutumplasty, and grafting, are commonly performed either as a single-stage procedure or in a relook procedure at a later time. The choice of material for ossicular reconstruction, whether autologous incus, malleus, or cartilage, depends on the specific type of ossicular defect. Paparella and Kim recommended a one-stage tympanomastoidectomy with careful surgical techniques and proper application (Paparella, 1977). They emphasized that planned multiple procedures were generally unnecessary and should be avoided to reduce hospitalization and associated costs.

MRI Protocol (Papers I and III)
The following MRI protocol assessed patients (see Tabel 3-1). Patients with contraindications for MRI scans (such as a pacemaker, metal fragments, unsuitable implants, or claustrophobia) were excluded.

Our current MRI protocol for the preoperative evaluation of primary ACH and the postoperative follow-up of residual and/or recurrent cholesteatoma consists of a combination of T2-weighted images and PROPELLER sequences in only axial section using a 1.5 or 3.0 Tesla (T) (Horizon, GE, Healthcare, Milwaukee, USA) scanner using a circularly polarized transmit and standard head coil). The conventional T2-weighted MRI scan was an anatomical canvas to overlay DW-MRI findings to improve the diagnosis. Since 2012, our department has implemented this technique in clinical practice. A consultant neuroradiologist with extensive experience in ME imaging evaluated all image reports in this study.

MRI 1.5T

- Axial DWI PROPELLER: 16 slices, 3 mm thickness, TR((repetition time) 4982.0 ms, TE (echo time)70 ms.
- Axial T2- PROPELLER: 45 slices, 3 mm thickness, TR 4760 ms, TE 100 ms.
- Coronal T2 Flair: 20 slices, 3 mm thickness, TR 9185.0 ms, TE 120 ms.

MRI 3T

- Axial DWI PROPELLER: 16 slices, 3 mm thickness, TR 3001.0 ms, TE 100 ms.
- Axial T2- PROPELLER: 45 slices, 3 mm thickness, TR 5838.0 ms, TE 100 ms.
- Coronal T2 Flair: 20 slices, 3 mm thickness, TR 9000 ms, TE 120 ms.

Both 1.5T and 3T DW-MRI scans used a b-value of 1000.

MRI Sequence	Cholesteatoma	Fibrous tissue/inflammation	Cholesterol granuloma
b1000 DW-MRI	Hyperintense	Hypointense	Hypointense
ADC Map	Hypointense	Hyperintense	Hyperintense
T2-weighted MRI	Moderate/intermediate intense	Strongly hyperintense	Strongly hyperintense
T1-weighted MRI	Hypointense	Hyperintense	Hyperintense

Table 3-1 Differential Diagnosis and MRI Imaging Features of Cholesteatoma

3.1 Study I

This prospective cohort study aimed to assess the diagnostic value of the non-EPI PROPELLER DWI sequence in detecting primary or recurrent cholesteatoma in a cohort of patients suspected of having ME cholesteatoma and scheduled for surgical procedures. We further aimed to ascertain the accuracy of MRI scans in localizing cholesteatomas in four specific regions, in comparison to surgical findings.

The study was conducted from January 2012 to December 2017. The study adhered to ethical guidelines, including obtaining written informed consent from all participants.

Patient Selection
A total of 79 patients (44 males, and 35 females) were included in the study. These patients, within an age range of 6 to 85 years (mean age: 37.6 years), underwent preoperative PROPELLER DW-MRI examination and subsequently underwent surgery for suspected primary or recurrent cholesteatoma.

The study population was divided into two groups:

- **Primary Acquired Cholesteatoma:** The first group consisted of 62 patients suspected of primary acquired ME cholesteatoma. Among these patients, 42 underwent MRI with a 1.5T scanner, and the remaining 20 underwent MRI with a 3T scanner.
- **Recidivistic Recurrent Cholesteatoma:.** The second group included 17 patients suspected of recidivistic cholesteatoma. Among these patients, 15 underwent MRI with a 1.5T scanner, and the remaining two underwent MRI with a 3T scanner.

Magnetic Resonance Imaging Technique
MRI scans were performed using a 1.5T or 3T scanner (Horizon, GE, Healthcare, USA) with a circularly polarized transmit and standard head coil. The imaging protocol consisted exclusively of PROPELLER sequences in the axial section. PROPELLER DW-MRI with a single b-value of 1000 mm^2/s was employed, and ADC cartography was performed using these acquisition parameters.

Imaging Evaluation
Cholesteatoma detection on PROPELLER was identified by hyperintense signals at b-values of 1000 mm2/s on DWI compared to brain tissue (see Figure 3-1b) and a corresponding low signal on the ADC map (see Figure 3-1c). A consultant neuroradiologist, blind to surgical results, quantitatively assessed these lesions, calculating ADC values per voxel. Lesions were defined by ROI showing low ADC map signals and high DWI signals (see Figure 3-1d). Three ROI measurements were taken for each case to average the ADC value.

Additionally, PROPELLER MRI was combined with T2-weighted imaging and coronal reformatting for a detailed 3D lesion view. Cholesteatoma sizes on DWI were determined using coronal reformatting of axial MRI (see Figure 3-1e).

The surgical findings were considered the authoritative source for determining the cholesteatoma's location. The location was classified into four categories: epitympanum, cavum tympani, antrum, and mastoid. The MRI locations were compared with the surgical findings.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2010. Parametric tests, including Student's t-test, were used for normally distributed data. Sensitivity, specificity, PPV, NPV, and accuracy were calculated using standard equations. The Chi-squared test was used to test relationships between categorical variables. A p-value less than 0.05 was considered statistically significant.

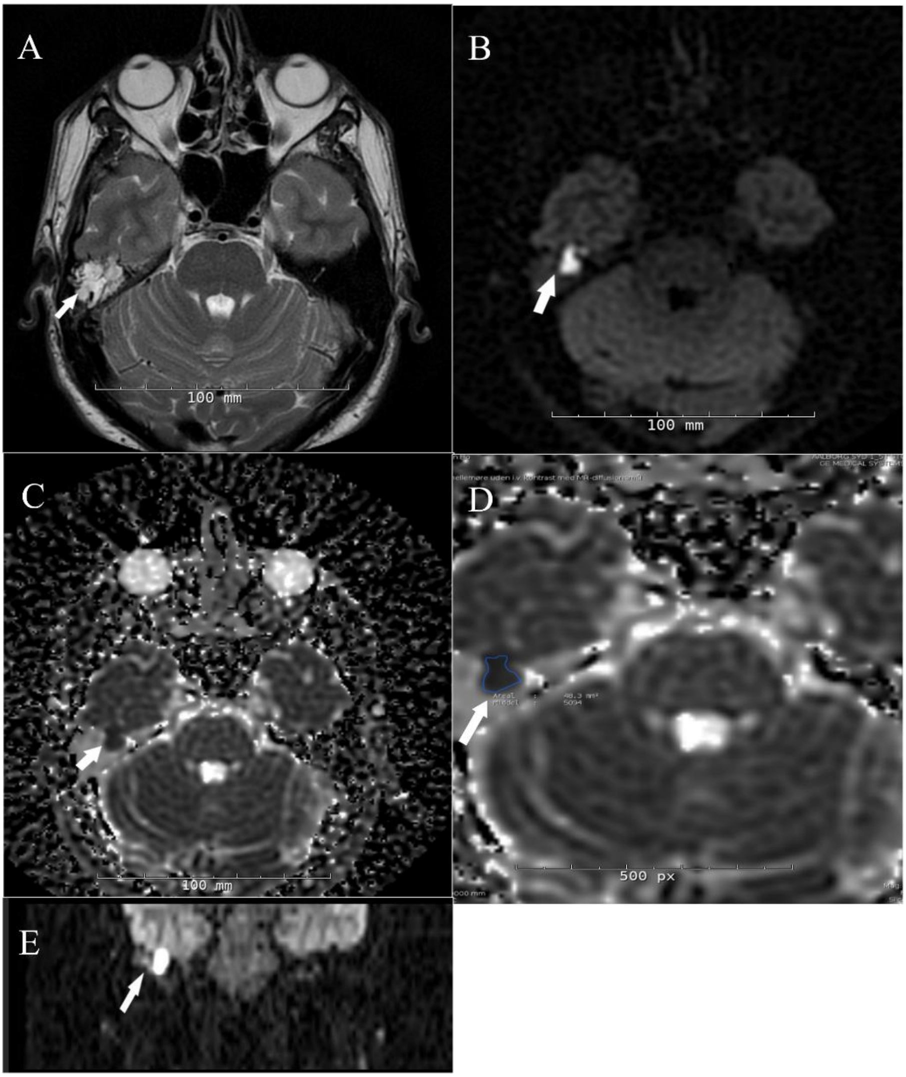
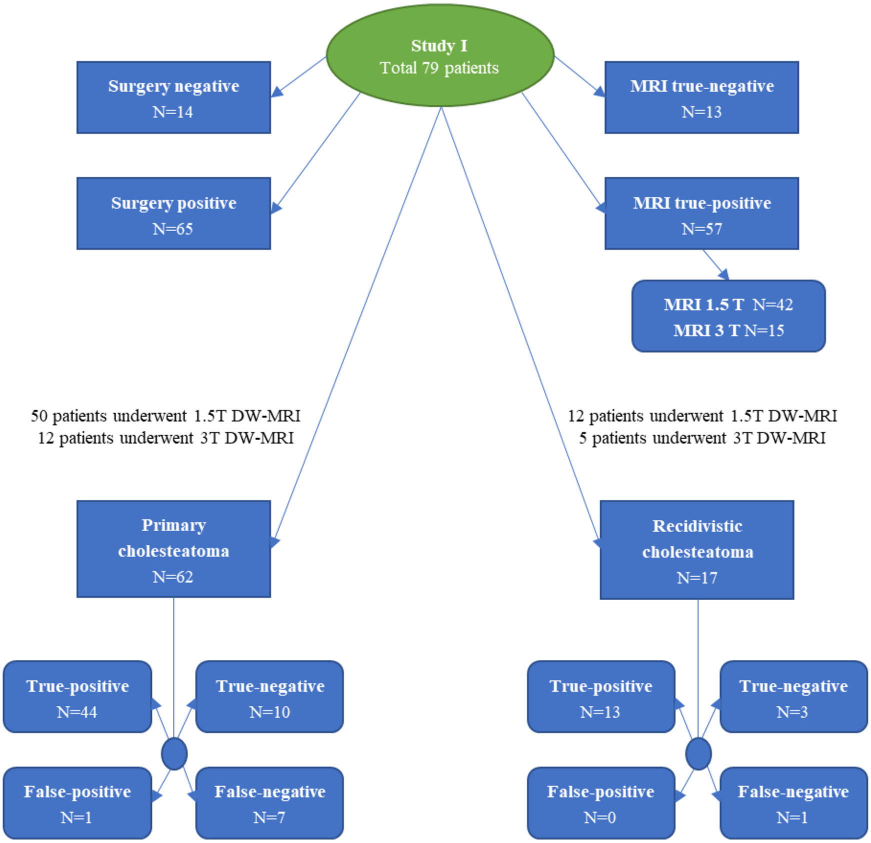


Fig. 3-1. Overview of MRI images in a patient diagnosed with cholesteatoma. A 31-year-old male with right ear primary attic cholesteatoma shows a 16 mm high signal cholesteatoma. The white arrow in all image's points to the cholesteatoma. Inserted scans show a) a hyperintense nonspecific middle ear filling presenting as a focal non-uniform lesion found in the axial T2 image; b) limited diffusion and apparently high signals is seen in the epitympanum on the axial DWI PROPELLER; c) low signal is observed in the ADC image; d) measuring the ADC value included a freehand drawn region of interest (ROI) around the inner border of the lesion (thin blue line); the software then automatically calculated the ADC value 0.5068 x 10^{-3} mm^2/sec on axial ADC map; e) Coronal reformatting of axial PROPELLER images offers enhanced 3D insights into cholesteatoma size and location.

Study I. Flowchart



3.2 Study II

This study is based on clinical and surgical evaluations after five years follow-up, between January 1st, 2012, and December 31st, 2017. The purpose of the research was to examine primary ME cholesteatoma in 100 patients who had not previously undergone ME surgery. During a minimum follow-up period of five years, otomicroscopy and audiometry examinations were conducted on a regular basis. In addition, a non-EPI DW-MRI was performed to evaluate cholesteatoma recurrence at the 5-year follow-up.

Criteria for Participant Selection and Exclusion

Patients were included if they had primary ME cholesteatoma and no prior history of ME surgery. Patients with missing data, a brief duration of follow-up, temporary residency, CC, or cholesteatomas of the EAC were excluded. Two experienced consultants specializing in aural surgery performed the surgical procedures, one with 20 years of experience and the other with over 30 years of experience.

Type and Location Evaluation of Cholesteatoma

During surgery, the type of cholesteatoma (flaccida or attic, sinus, tensa, or combined) as well as the location and extent of the lesion were determined. The ME was divided into four compartments (tympanum, attic, antrum, and mastoid), and the presence and extension of cholesteatoma was documented in each compartment. Various prognostic factors were analyzed, including patient characteristics, and disease-related, and intervention-related factors.

Statistical Analysis

The study utilized various statistical methods to analyze the data. Paired Student's t-tests were employed to compare data pre- and postoperatively. To compare distinct subgroups, unpaired t-tests that consider unequal variances were applied. We assessed the normality assumption using quantile-quantile plots with a significance threshold of p-values below 0.05. The hearing results were analyzed using a two-way analysis of variance. Chi-square tests and Fisher's exact tests were used for analyzing categorical data. The survival analysis employed Kaplan-Meier curves and Cox regression.

The term ‘recidivism’ is used to describe a subsequent cholesteatoma surgery on the same ear, considering the time that has passed since the initial surgery. Excel™ 2010 was utilized for calculating proportions and estimating incidence rates. Statistical analyses were performed using Stata 14 software (StataCorp, College-Station, Texas/USA).

3.3 Study III

Patient Selection

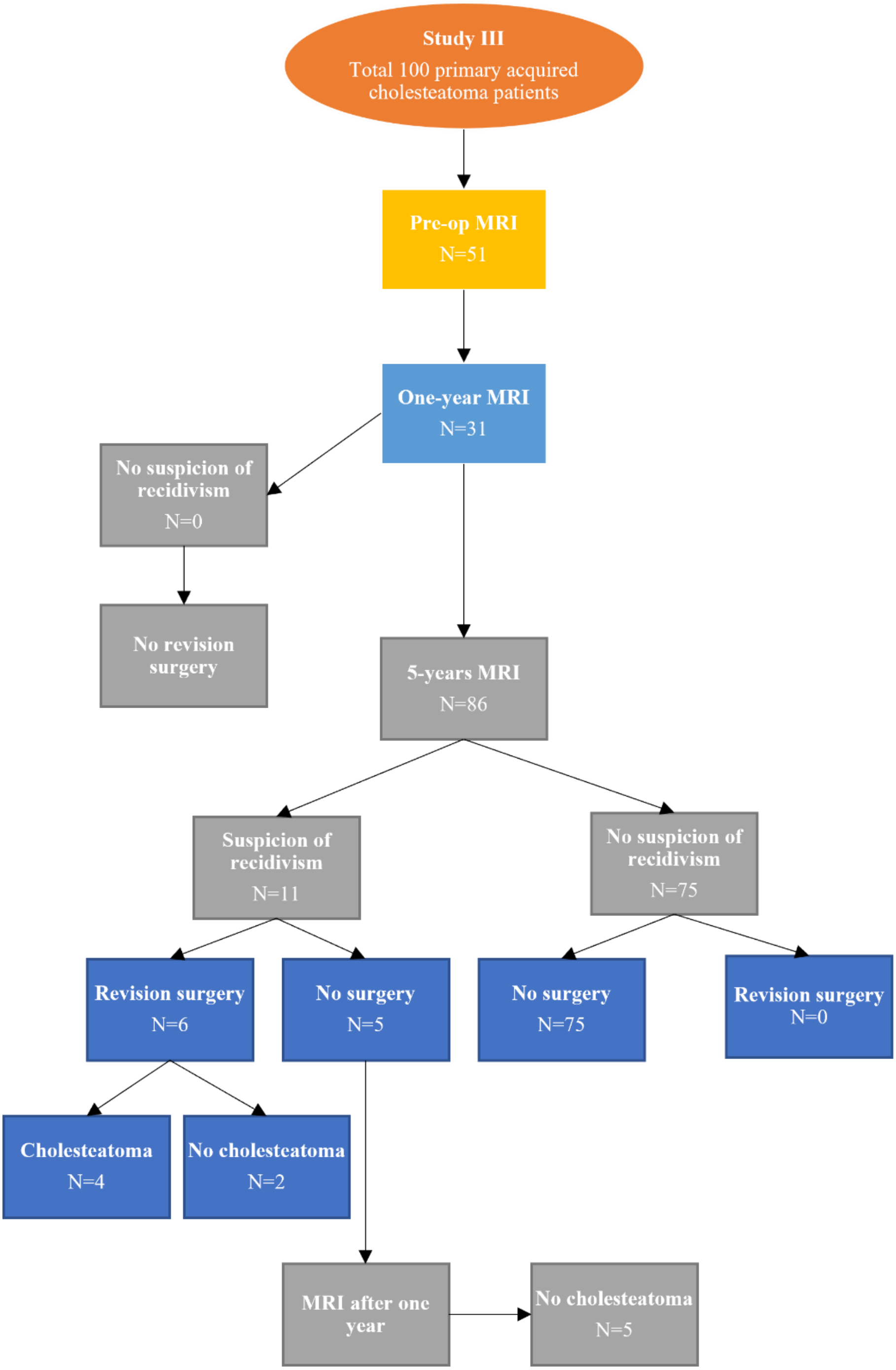
In a prospective observational study from January 2012 to December 2017, we assessed 100 patients diagnosed with primary acquired ME cholesteatoma. Patients underwent either BOT or atticotomy and were followed up at our department until March 2023. DW-MRI conducted at 1- and 5-years post-surgery or based on clinical needs. Of these, 86 underwent a five-year PROPELLER DW-MRI.

Participants were excluded from the study for various reasons: due to non-diagnostic MRI images caused by poor quality or artifacts (n=1), due to claustrophobia (n=4), due to contraindications like dental implants and ICD-pacemakers (n=3), and because some participants refused to undergo MRI (n=6).

DW-MRI images were assessed by a blinded radiologist for radiological evaluation and quantitative analysis. Cholesteatoma lesions were detected using signal intensity and ADC maps in conjunction with conventional sequences serving as anatomical refences. The presence, location, and size of the lesions were recorded. In subsequent assessments, images were categorized as either suggestive or non-suggestive of recidivism, providing guidance for surgical interventions.

Statistical Analysis

The study employed descriptive statistics to summarize the demographics and clinical attributes of the participants. The radiological findings were reported using frequencies and percentages. The study aimed to evaluate the characteristics of cholesteatoma lesions on DW-MRI by correlating clinical and radiological findings. Statistical methods, such as the Chi-square or Fisher's exact test, were employed to establish associations between variables. The analyses were conducted using Excel and Stata, with a significance level of $p < 0.05$.


Study III
Total 100 primary acquired cholesteatoma patients
Pre-op MRI
N=51
One-year MRI
N=31
No suspicion of recidivism
N=0
No revision surgery
5-years MRI
N=86
Suspicion of recidivism
N=11
No suspicion of recidivism
N=75
Revision surgery
N=6
No surgery
N=5
No surgery
N=75
Revision surgery
N=0
Cholesteatoma
N=4
No cholesteatoma
N=2
MRI after one year
No cholesteatoma
N=5

3.4 Study IV

Study Population
The research encompassed two distinct patient groups.

The first group comprised of 121 patients who underwent CWU obliteration of the mastoid and epitympanic space, (CWU-BOT), at the Department of Otolaryngology, Head and Neck Surgery, Aalborg University Hospital, from January 1997 to December 2009. Of these, 89 responded to mailed questionnaires and consent forms, completing the Danish version of the GBI questionnaire in 2013.

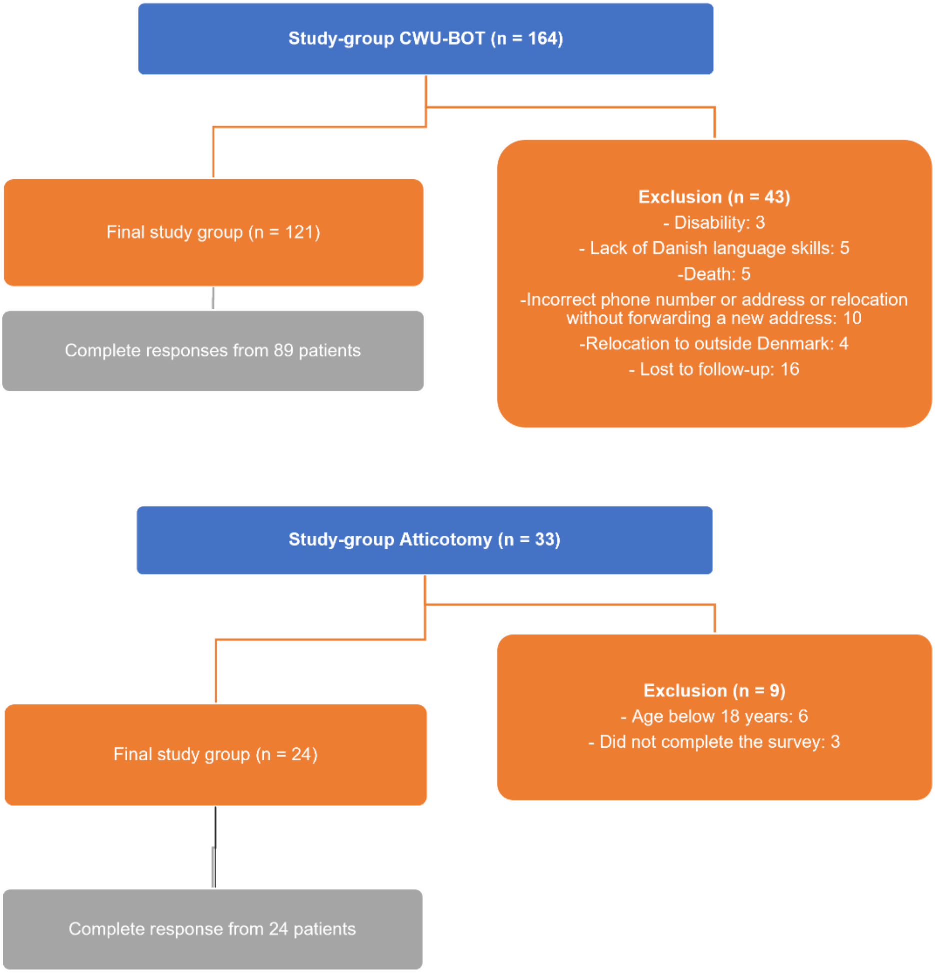
The second group consisted of 24 patients who underwent atticotomy for cholesteatoma between January 2012 and December 2017, completing the Danish GBI questionnaire in 2020.

Inclusion and Exclusion Criteria
Participants were selected based on primary ME cholesteatoma diagnosis, age (18 years or older) and capability to fill out study forms. Exclusions were made for inadequate Danish language proficiency, disability, and death. Additional data collected included age, gender, and PTA.

Assessment Tool
The 18-item GBI questionnaire served as a post-intervention evaluation tool, applied for detecting changes in HRQoL post cholesteatoma surgery.
Questionnaires, dispatched in prepaid pre-addressed envelopes, were accompanied by written informed consent forms. To enhance response rates, two reminders were sent to non-respondents during the study period. The GBI questionnaire usually requires 5-10 minutes for completion and can be either self-administered or conducted as an interview. However, in this study, only a few patients (n=4) opted for the interview-administered questionnaire.

Flowchart Study IV

Flowchart for cholesteatoma patients who undergone CWU-BOT surgery from 1997-2007 and atticotomy from 2012-2017.



4 Results

4.1.1 Study I

The study enrolled 79 patients (44 males, 35 females) with an age range of 6 to 85 years (mean age: 37.6 years). The mean time interval between MRI scans and surgery was 74 days (±SD 56).

MRI identified cholesteatoma in 58 cases, while cholesteatoma was surgically confirmed in 65 cases (82% prevalence), 14 cases exhibited granulation tissue or fibrosis, and one case was diagnosed with granulomatosis with polyangiitis. A total of 8% (14/79) of the patients did not have cholesteatoma despite clinical suspicion. MRI correctly identified cholesteatoma in 57 cases, as true positive, whereas true negatives were observed in 13 cases, resulting in an overall accuracy of 89% (70/79).

These findings, including sensitivity and specificity, are summarized in Table (4-1 and Figure 4-1). It's worth noting that the accuracy of our diagnostic results may vary between primary and recidivistic cases due to alterations in anatomical landmarks or less well-defined features, prompting us to separately evaluate the diagnostic accuracy in these two groups (see Table 4-1).

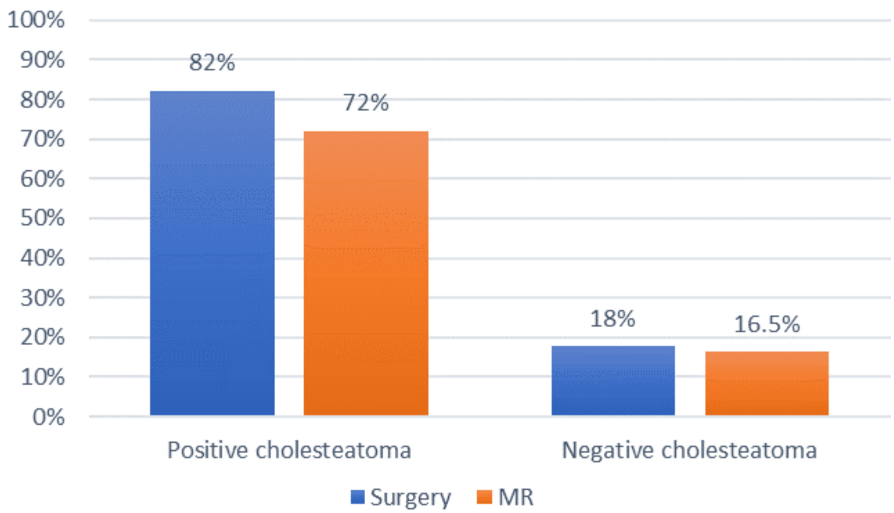
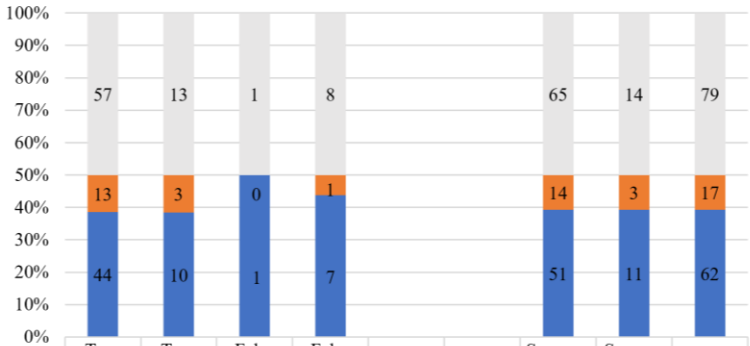


Figure 4-1. Cholesteatoma detection: 79 cases compared between DW-MRI results and surgical outcomes. Seventy-nine cases underwent MRI and surgery. Among these cases, only 57 had cholesteatoma confirmed with MRI, while 65 cases were confirmed during surgery. In 13 cases, MRI was found negative, while in 14 cases surgery was negative.



	True positive	True negative	False positive	False negative		Surgery positive	Surgery negative	Total
Total	57	13	1	8		65	14	79
Recurrent cholesteatoma	13	3	0	1		14	3	17
Primary cholesteatoma	44	10	1	7		51	11	62

Figure 4-2. Comparative Overview: Cholesteatoma Cases through MRI and Surgical Lens. A total of seventy-nine cases underwent surgical procedures. In the MRI section, patients are categorized into two groups: recurrent cholesteatoma and primary cholesteatoma. Meanwhile, the surgery section is divided into cases with positive surgical findings and those with negative findings.

	Total cases cholesteatoma (n = 65)	Primary cholesteatoma (n = 51)	Recidivistic cholesteatoma (n = 14)	P values
Sensitivity (95% CI)	87.7 (77.2 to 94.5)	86.3 (73.7 to 94.3)	92.9 (66.1 to 99.8)	P = 0.92*
Specificity (95% CI)	90.9 (66.1 to 99.8)	90.9 (58.7 to 99.8)	100.0 (29.2 to 100.0)	P = 0.20*
Positive predictive value (95% CI)	98.3 (89.6 to 99.8)	97.8 (87.1 to 99.7)	100.00	P = 0.56*
Negative predictive value (95% CI)	61.9 (45.5 to 76.0)	58.8 (41.2 to 74.5)	75.0 (31.2 to 95.2)	P = 0.23*
Accuracy (95% CI)	88.6 (79.4 to 94.7)	87.1 (76.2 to 4.3)	94.1 (71.3 to 99.9)	P = 0.42*
Mean ADC	0.6213 ± 0.2194 × 10^{-3} mm^2/sec	0.6032 ± 0.1749 × 10^{-3} mm^2/sec	0.6839 ± 0.3331 × 10^{-3} mm^2/sec	P > 0.5#

Table 4-1. Diagnostic performance of DWI in detecting cholesteatoma with surgery as reference
ADC: apparent diffusion coefficient; CI: confidence interval.
P value: probability value.
* Chi-squared of primary versus recidivistic cases.
# T-test primary versus recidivistic cases.

Patients were divided into two groups. The first group consisted of 62 cases with primary ACH, and the second group of 17 cases with recidivistic cholesteatoma. In primary acquired cases, sensitivity, specificity, PPV, and NPV were 86%, 91%, 98%, and 59%, respectively. The mean size was 14.9 mm. Diagnosis accuracy was 87%, with 7 false negatives and 1 false positive (Figure 4-2 and Table 4-1).

For recidivistic cases, sensitivity, specificity, PPV, and NPV were 93%, 100%, 100%, and 75%, respectively. The mean size was 11.9 mm. Diagnosis accuracy was 94%, with one false negative (see Figure 4-2).

Overall sensitivity and specificity for cholesteatoma detection were 87.7% and 91% (see Figure 4-2 and Table 4-1). Mean ADC values for both groups and overall are reported in Table 4-1”

MRI at 1.5T and 3T yielded similar ADC values. A reference range ADC value for cholesteatoma was suggested: 0.1912×10^{-3} mm^2/s to 1.0514×10^{-3} mm^2/s.
Figure 4-3 illustrates the high accuracy of MRI localization for cholesteatoma lesions in various anatomical regions of the ME. The study evaluated the localization accuracy in the four key regions (Figure 4-3):

- **Epitympanum:** The study achieved a localization accuracy rate of 92% (49/53) in identifying cholesteatoma lesions within the epitympanum.
- **Tympanum:** MRI localization accuracy was notably high in the tympanum, with a rate of 96% (47/49), indicating precise detection of cholesteatoma in this region.
- **Antrum:** Cholesteatoma lesions within the antrum were accurately localized with a rate of 84% (32/39), showcasing the capability of MRI in identifying lesions in this challenging area.
- **Mastoid:** The study demonstrated 100% (21/21) accuracy in localizing cholesteatoma lesions within the mastoid, indicating perfect precision in detecting lesions within this region.

Figure 4-3 highlights the effectiveness of MRI in accurately localizing cholesteatoma lesions across different anatomical regions of the ME, providing valuable insights for diagnosis and surgical planning.

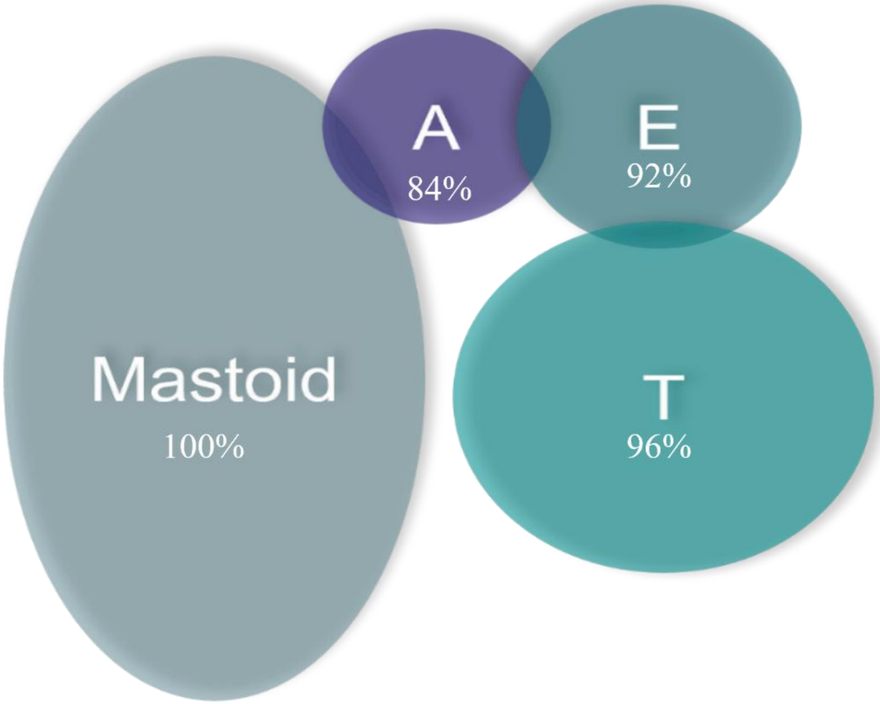


Figure 4-3. Illustration of the anatomical regions of the ME.
Classification of the site of the cholesteatomas (right ear); A = antrum; E = epitympanum; T = tympanum (modified from Yung et al 2017).

Figure 4-4 shows a true-positive MRI scan and Figure 4-5 shows a case with a false-positive MRI scan.

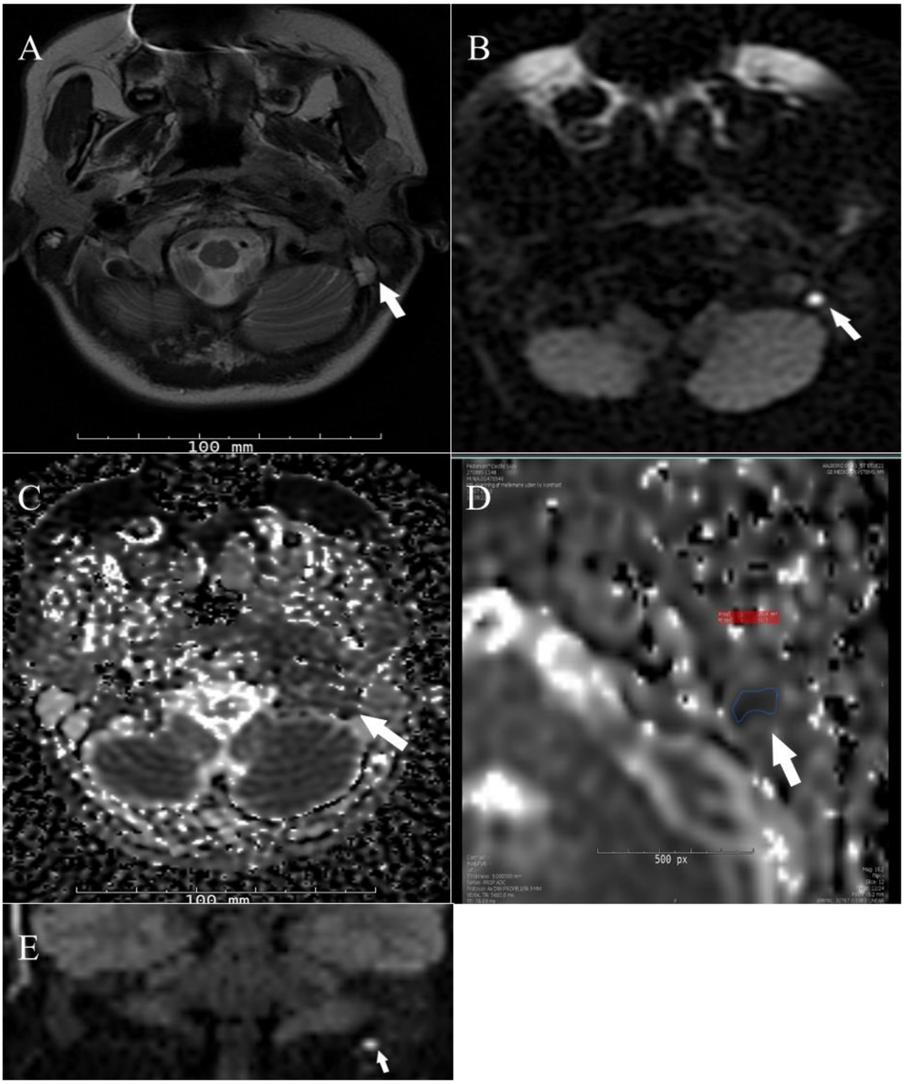


Figure 4-4. True Positive Cholesteatoma: MRI scans effectively pinpoint the cholesteatoma, validated by surgical outcomes. A patient diagnosed with a left ME cholesteatoma. The images display a recurrent cholesteatoma in the epitympanum, measuring 4 mm. In all images, the cholesteatoma is indicated by a white arrow. a) axial T2 image reveals a focal lesion with non-uniform characteristics and indistinct borders presenting with a high signal; b) axial DWI PROPELLER image shows limited diffusion with a pronounced hyperintense signal in the epitympanum; c) low signals are observed in the ADC image; d) the ADC value of the lesion (thin blue line) is measured on the axial ADC map, resulting in a value of 0.4936 x 10^{-3} mm^2/sec; e)

coronal reformatted images from the axial PROPELLER highlight the cholesteatoma's hyperintensity on DWI.

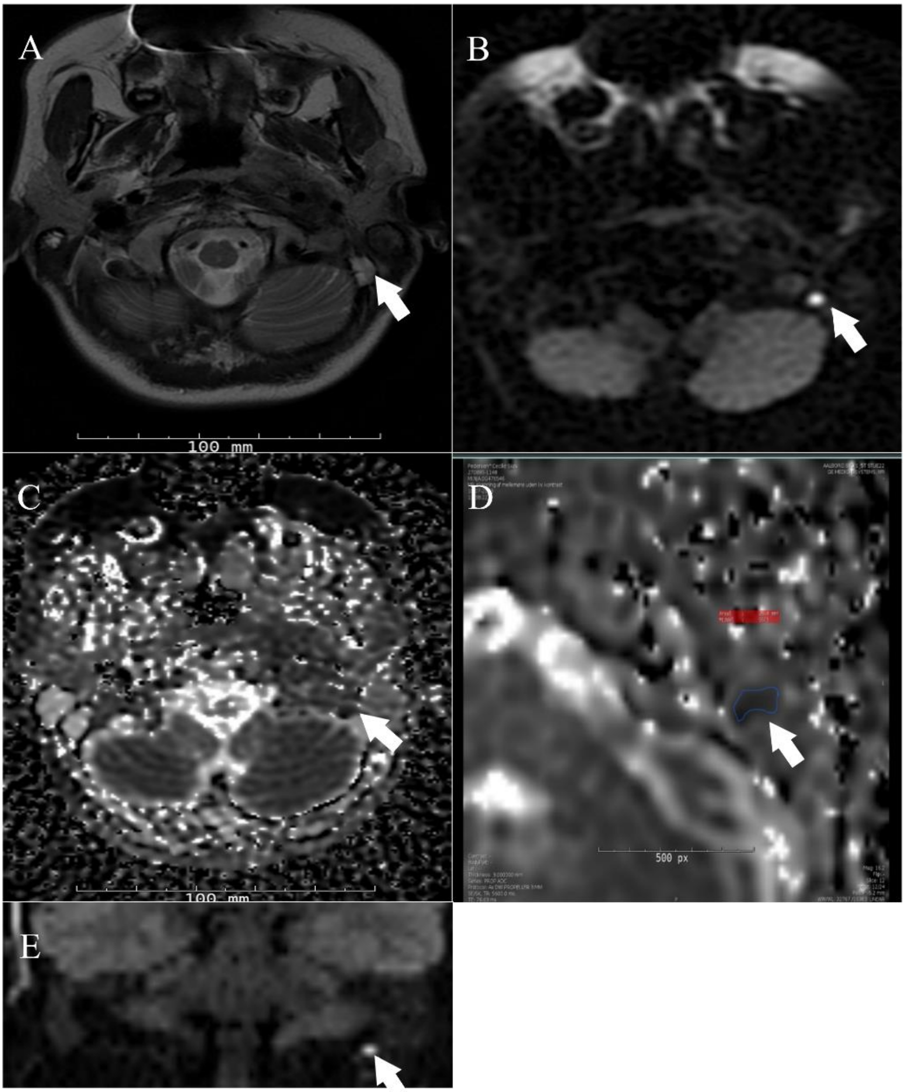


Figure 4-5. False Positive MRI: Wegener's granulomatosis middle ear mimicking cholesteatoma. An 18-year-old female diagnosed with Wegener's granulomatosis (Granulomatosis with polyangiitis) in the left middle ear, confirmed through histopathology. a) Axial T2image displays a focal, non-uniform hyperintense lesion with an indistinct border (*white arrow);* b) Axial DW PROPELLER image reveals a

pronounced high signal in the epitympanum; c) Low signals are observed in the ADC image (*white arrow);* d) The lesion's ADC value is determined on the axial ADC map; e) Coronal images, reformatted from the axial PROPELLER DWI, emphasize the lesion's hyperintensity on DW PROPELLER.

4.1.2 Study II

Demographic Data

The study included 100 patients, with an average age of 39.6 years ± 19.9 (range 6–80 years). Of these, 78 were adults, and 22 were children aged below 16 years. The male-to-female ratio was 60% to 40%. The average follow-up time was 75.4 months (6.3 years) ± 1.95 months.

The overall rate of recidivistic disease requiring surgery was 9.0%. Children had a significantly higher recidivism rate (18.2%) than adults (6.4%). No cases of residual cholesteatoma were found in children, while 2.5% of adults had residual cholesteatoma. Details are depicted in Table 5-1.

Figure 2-1 shows a higher risk of recidivism in children than in adults. After five years, the estimated recidivism rate was 14% for children and 7% for adults. The 10-year cumulative probability of recidivism was 21% for children and 7% for adults. Notably, the age at first surgery showed a 6% risk reduction for each additional year at the time of the procedure (hazard ratio (HR): 0.94, 95% CI: 0.92-0.99, p = 0.04). Age below 16 years emerged as another predictor of higher recidivism HR: 2.67, p = 0.04). Detailed Cox regression analyses are depicted in Table 5-2.

Obliteration Analysis

Figure 5-2 presents the adult recidivis rates over a span of five years: 6% for cases with CWU obliteration and 9% for those without obliteration. The multivariate analysis suggested that CWU obliteration is linked with a slightly diminished recidivism risk (HR: 0.8). However, this wasn't statistically significant.

We further stratified our analysis by age group. In children, the HR for cholesteatoma recidivism in CWU obliteration was 0.9, suggesting a slightly lower recidivism risk compared to non-obliterative cases. In adults, the HR for cholesteatoma recidivism was 0.75, indicating a lower recidivism risk compared to non-obliterative cases. However, it's noteworthy that none of these differences reached statistical significance ($p > 0.05$). This implies that the observed variations in recidivism risk between different cholesteatoma types and age groups may not be statistically robust.

Waiting Times and Times to Recidivism

The average wait time for surgery was 66.3 ± 54.8 days. Children had a slightly shorter waiting period, averaging 51.4 ± 29.8 days. Table 5-3 outlines that there is no discernible correlation between the waiting time for surgery and recidivism rates. Interestingly, a mere 22.22% of recidivism manifested within the first two years of follow-up. In children, all recidivism cases emerged after two years.

When comparing the recidivism rates between the two consultants, no statistically significant difference was observed. The multivariate analysis revealed a slightly higher risk of recidivism with consultant number two than with consultant number one, but it was not statistically significant.

Characteristics, Location, and Type

In this study, the cholesteatoma types included 64 cases of flaccida, 22 cases of sinus, and 9 cases of tensa cholesteatoma. There were also five cases where the cholesteatoma type was unresolved and thus classified as combined (see Figure 5-3). Figure 5-4 illustrates the different cholesteatoma types and their spread within the ME.

Regarding sinus cholesteatomas, in 45% of cases, cholesteatoma predominantly involved the cavum tympani exclusively. In 28% of cases, cholesteatoma originating from the pars flaccida extended into the epitympanum in conjunction with the antrum and cavum tympani, resulting in a more extensive pattern of involvement. Notably, recidivism in sinus cholesteatoma was solely observed when it spanned multiple compartments.

Assessing Recidivism Rates based on Cholesteatoma Types

In total, sinus cholesteatoma was found in 18.2%, combined cholesteatoma in 20.0%, and flaccida cholesteatoma in 6.3%.

However, these disparities were not statistically significant (Chi-square test, $p > 0.05$). The Cox regression analysis showed that sinus and combined cholesteatomas had HRs (HRs 3.2 (95% CI: 0.81-1.3) and 3.9 (95% CI: 0.44-35.6) respectively) for recidivism against flaccida cholesteatoma. Yet, these were not statistically significant, suggesting more extensive research might be essential.
Lastly, Figure 5-3 indicates a disparity in the cholesteatoma types between children and adults. A slightly elevated rate of tensa and sinus cholesteatomas was seen in children compared to adults, but these variances weren't statistically significant.

Audiological Outcomes

This study compared the preoperative hearing outcomes (ABG, PTA, and speech reception threshold (SRT)) with the corresponding 1-year and 5-year hearing outcomes, outlined in Table 5-4. Significant improvements were observed in postoperative hearing at one and five years. The average ABG decreased from 27.5 dB preoperatively to 20.16 dB (one year) and 19.7 dB (five years) postoperatively. The mean average PTA also showed significant improvement, decreasing from 39.1 dB to 30.2 dB (one year) and 29.4 dB (five years).

The percentage of patients with an ABG within 20 dB increased from 41% preoperatively to 62% (one year) and 60% (five years) postoperatively. Moreover, 60% of patients achieved a postoperative PTA of less than 30 dB hearing loss.

Statistical analysis confirmed the significant improvements in ABG, PTA, and SRT at 1-year and 5-year postoperative intervals compared to preoperative measures. The different surgical procedures, CWU obliteration and non-obliteration, both showed significant improvements in hearing outcomes without a significant difference between the two approaches. Also, no statistically significant difference in ABG, PTA, or SRT outcomes were observed between children and adults, neither preoperatively nor postoperatively.

Characteristics (n=100)	**Patients (n)**	**Case of recidivism (%)**
Gender		
Male	60	8 (13.3%)
Female	40	1 (2.5%)
Adults	78	5 (6.4%)
Children<16	22	4 (18.2%)
Surgical Approach		
Total cases of surgery	100	9 (9.0%)
CWU-obliteration	67	6 (9.0%)
Non-obliteration	33	3 (9.1%)
Consultant 1		
CWU-obliteration	25	2 (8.0%)
Non-obliteration	23	2 (8.7%)
Total surgery	48	4 (8.3%)
Consultant 2		
CWU-obliteration	42	4 (9.5%)
Non-obliteration	10	1 (10.0%)
Total surgery	52	6 (9.6%)
Cholesteatoma type		
Flaccida cholesteatoma	64	4 (6.3%)
CWU-obliteration	55	4 (9.1%)
Non-obliteration	9	0
Tensa cholesteatoma	9	0
CWU-obliteration	1	0
Non-obliteration	8	0

Sinus cholesteatoma	22	4 (18.2%)
CWU-obliteration	5	1 (20.0%)
Non-obliteration	17	3 (17.6%)
Combined	5	1 (20.0%)
CWU-obliteration	5	1 (20.0%)
Non-obliteration	-	-
Location		
Epitympanum	85	7 (8.2%)
Cavum tympanum	79	9 (11.4%)
Antrum	61	7 (11.5%)
Mastoid	29	4 (13.8%)

Table 5-1. Patient characteristics and recidivism rates.

Characteristics	HR	95% CI	p-value
Gender			
Female	Ref	-	-
Male	1.3	0.69–2.5	0.279
Age at first surgery(children)	0.94	0.93-0 .99	0.046
Age at surgery			
Adults	Ref	-	-
Children	2.7	1.01-1.34	0.045
Cholesteatoma type			
Flaccida	Ref	-	-
Sinus	3.2	0.81-1.3	0.056
Combined	3.9	0.44-35.6	0.218
Surgical approach			
Non-obliteration	Ref	-	-
CWU-obit	0.8	0.2-3.7	0.932
Children	0.91	0.11-10.7	0.936
Adults	0.75	0.12-4.51	0.075
Time to surgery			
Children	0.99	0.95-1.02	0.536
Adult	1.00	0.99-1.01	.309
Consultant			
Consultant 1	Ref	-	-
Consultant 2	1.2	0.32-4.48	0.786

Table 5-2. Results of the Cox regression analyses with hazard ratio (HR) and95% CIs for recidivism rates based on various prognostic indicators in all cases.

	Pre-op			**1- year post-op**			**5- years post-op**		
	ABG (dB)*	**ACPTA (dB)***	**SRT (dB)**	**ABG (dB)***	**AC-PTA (dB)***	**SRT (dB)**	**ABG (dB)***	**AC-PTA (dB)***	**SRT (dB)**
Type									
Flaccida (67)	25.22±14.45	37.78±22.07	36.41±26.35	19.09±11.50	19.61±11.59	27.11±16.31	19.66±10.55	27.56±15.42	29.30±20.34
Sinus (22)	28.49±11.32	36.78±17.88	33.63±20.84	20.02±11.37	26.26±10.59	22.04±16.26	22.25±12.04	26.58±13.770	28.18±15.63
Tensa (10)	23.01±16.09	36.67±18.99	32.78±11.43	15.14±7.49	25.55±10.91	22.78±17.35	14.86±10.54	26.53±13.75	27.22±16.60
Combined (5)	33.5±7.65	66.85±26.0	48±32.60	26.19±6.02	51.13±14.12	49±13.35	33.2±7.66	49.2±13.24	54±13.66
All cases (100)	27.5±14.6	39.1±22.5	36.1±25.2	20.2±12	30.3±22.6	27.7±19.8	19.7±14.5	29.5±21.9	29.0±19.2
Demografic									
Adults (78)	27.07±14.06	42.44±22.39	36.53±23.38	19.52±11.27	32.68±16.48	29.29±16.77	19.39±10.79	30.05±16.38	31.34±18.97
Children<16	28.11±14.37	26.42±17.81	34.32±30.57	21.08±11.59	25.26±14.44	22.05±17.68	24.34±12.77	22.2±11.48	25.68±21.91
Surgical technique									
CWU-oblit (67)	27,5±14,40	39,12±18,56	36,98±27,78	20,6±13,61	31,12±23,1	29,30±16,59	19,08±12.48	26,31±15.29	28,18±17.01
Non-oblit (33)	28,01±13,66	38,98±22,277	34,5±17.01	19,67±16,1	29,28±22,44	25,01±17,06	21,16±10.82	29,32±15.92	31,04±20.97

Table 5-3. Pre- and postoperative hearing results in 100 patients who underwent cholesteatoma surgery. Bar chart showing mean ABG (air-bone gap). AC-PTA (Air Conduction Pure-Tone Average; dB (decibel); SRT: speech reception threshold.

Waiting time for surgery (days)	Patients (%)	Cases of Recidivism	Recidivism rate (%)	(K–W test) p value
All cases (100)				
≤ 90	83 (83%)	8	9.6%	0.6913
91–180	7 (7%)	0	0.0%	
181–270	10 (10%)	1	10.0%	
Adults (78)				
≤ 90	64 (82%)	4	5.2%	0.4914
91–180	4 (5%)	0	0.0%	
181–270	10 (13%)	1	10.0%	
Children (22)				
≤ 90	19 (86%)	4	21.10%	0.3914
91–180	3 (14%)	0	0.00%	
181–270	0 (0%)	0	0.00%	

Table 5-4. Recidivism of disease by waiting time for surgery.

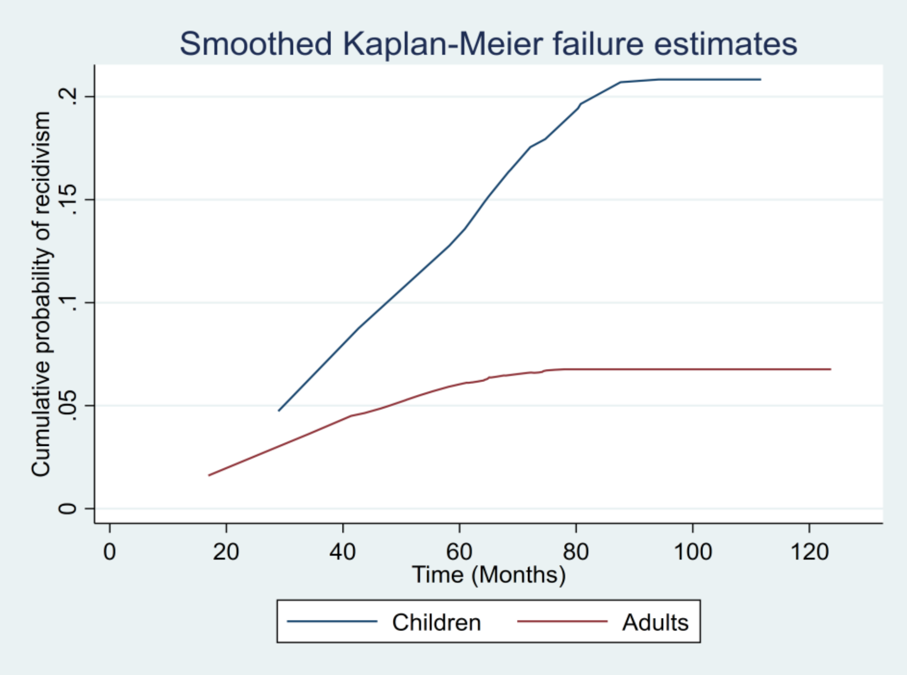


Figure 5-1. Kaplan-Meier Plot: 10-year Cholesteatoma Recidivism Trends. Cumulative probability of cholesteatoma recidivism in children (aged <16 years) and adults. The figure demonstrates a higher risk of recidivism in children compared to adults. After five years, the estimated recidivism rate was 14% (95% CI: 0.05-0.37) for children and 7% (95% CI:0.03-0.16) for adults – a rate that is 2 times higher in children. The 10-year cumulative probability of recidivism was 21% (95% CI: 0.08-0.48) for children and 7% (95% CI: 0.03-0.16) for adults.

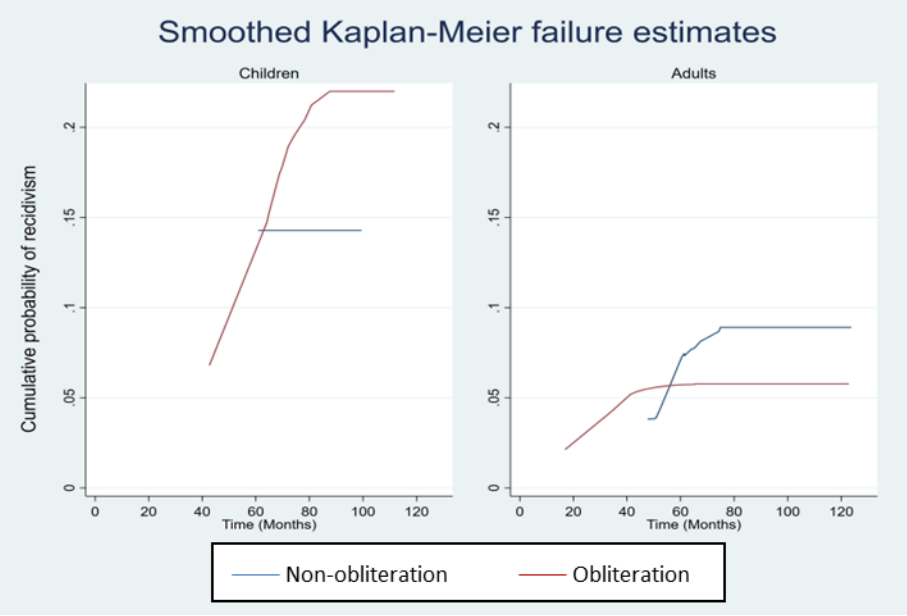


Figure 5-2. Kaplan-Meier Failure Function: Cumulative probability of cholesteatoma recidivism in children aged below 16 years and adults by surgical procedure. Non-obliteration refers to a surgical procedure without obliteration, and Obliteration refers to a surgical procedure with canal wall up mastoid obliteration.

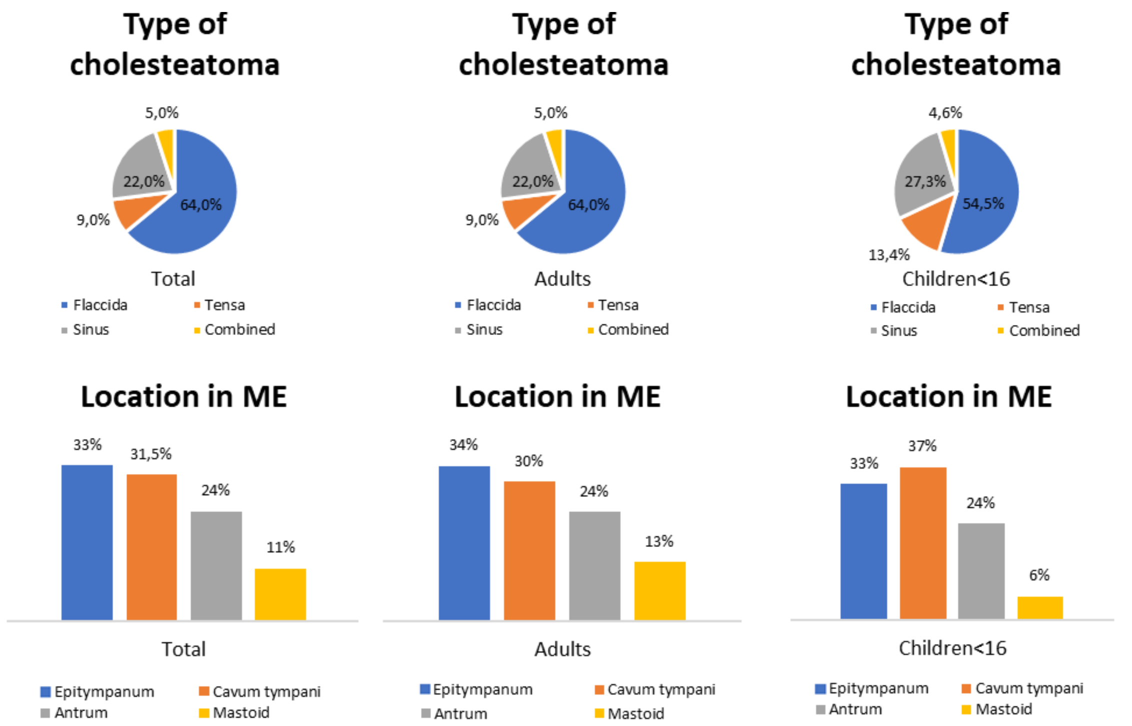


Figure 5-3. Distribution of Cholesteatoma Types and Locations across All Patients, Adults, and Children. This figure provides a comprehensive distribution of cholesteatoma types and locations across three distinct groups: all patients, adults, and children. The data is visually represented to highlight variations and patterns in the occurrence of cholesteatoma based on age categories, aiding in the identification of prevalent types and locations in each group.

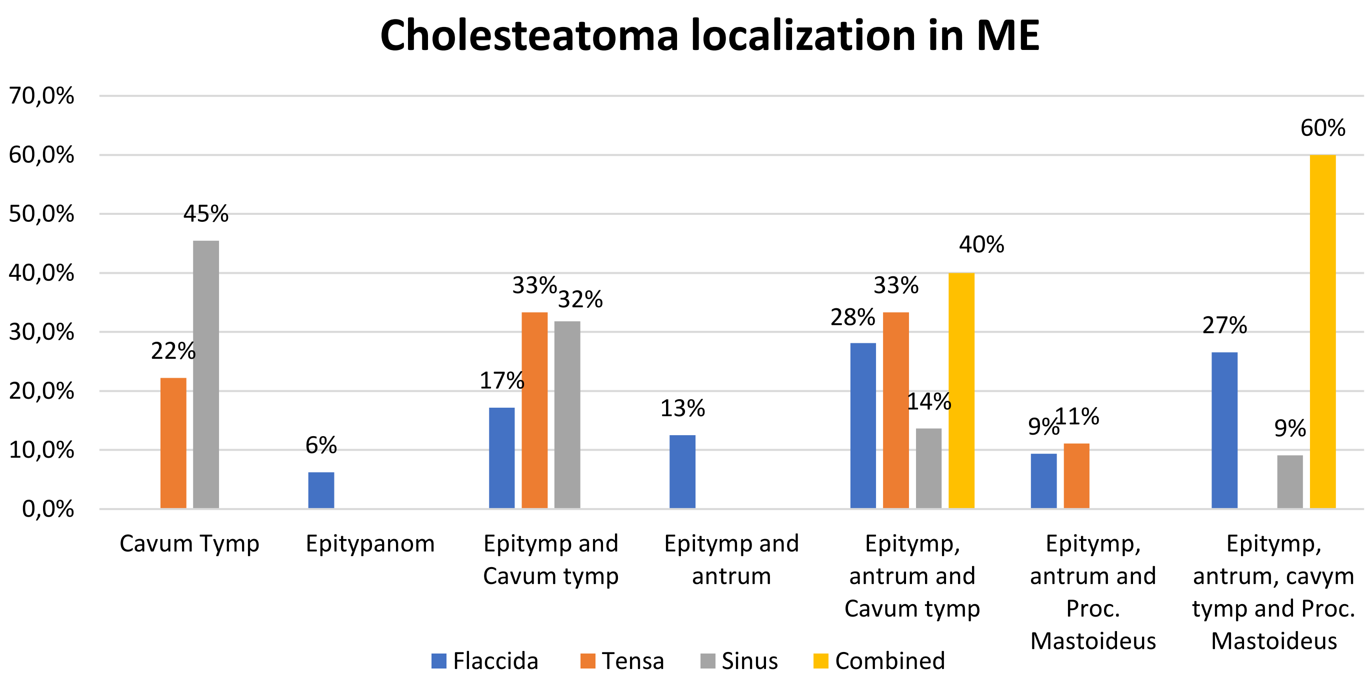


Figure *5*-4. Distribution and extent of cholesteatoma across various compartments of the ME, detailing both the type and location of the cholesteatoma in the ME.

4.1.3 Study III

Throughout the study period, an overall recidivism rate of 9.0% was observed among the patient population. Notably, children exhibited a substantially higher recidivism rate of 18.2% in contrast to the 6.4% recidivism rate observed in adults ($p < 0.05$). None of the pediatric patients displayed residual cholesteatoma, whereas 2.5% of adults exhibited residual cholesteatoma. The average interval between the initial surgery and the recidivism event was 35.8 months ± 18.0, ranging from 16.6 to 68.8 months. Notably, two cases of residual cholesteatoma were identified during the follow-up period, occurring at 16.9 and 35 months after the initial surgical intervention.

Magnetic Resonance Imaging Follow-Up and Revision Surgery Findings
In the one-year MRI follow-up, 31 patients underwent PROPELLER DW-MRI scans. No diffusion restriction was detected, and none required revision surgery during this period.
During the long-term follow 86 (86%) patients underwent PROPELLER DW-MRI scan and 97 MRI scan were performed during the period. Among them, 11 (11/86 =12.8%) cases exhibited uncertain or suspected MRI results, characterized by relatively hyperintense lesions in DW-MRI PROPELLER sequences, as detailed in Table 6-1.

Among these 11 cases, surgical intervention was performed on six individuals, representing 54.5% of the total. Five of these six cases yielded highly suspicious findings, displaying hyperintense signals in DWI alongside low signal intensity in the ADC map. Intriguingly, two of these patients were presented with vague clinical symptoms, and otomicroscopy failed to reveal any indication of cholesteatoma recidivism. The attending otologists did not find clinical suspicion of recidivism. Nevertheless, the DW-MRI scans clearly identified hyperintense regions corresponding to cholesteatoma in two specific compartments, and surgery revealed cholesteatoma in both cases. The location and extension described by the MRI scan were in concordance with surgical findings. Four out of six cases (66.7%) confirmed the diagnosis and location of cholesteatoma as per surgical findings while in one case (9%) surgery confirmed cholesterol granuloma (see Figure 6-1).
The five remaining cases with inconclusive DWI-MRI results underwent follow-up MRI examinations after a period of 6-12 months. Encouragingly, none of these cases exhibited any indications of cholesteatoma recidivism, as observed in both the MRI results and clinical assessments.
There were no false-negative cases on the 86 MRI scans and one false-positive case.
Four of nine recidivism cases were revealed at the 5 years follow-up.
The calculation of ADC values were calculated for these 11 cases. Among patients diagnosed with cholesteatoma during surgery (n=4), the mean ADC value was 0.402 ± 0.2194 × 10^{-3} mm^2/s. In contrast, for patients without cholesteatoma (n=7), the mean ADC value was 0.21 ± 0.2 × 10-^{3} mm^2/s. For in-depth information about each individual case, please see Table 6-1 as well as Figure 6-1 to Figure 6-4.

Table 6-1. Clinical finding on 11 cases in whom the MRI showed a hyperintense signal on DWI. F(female); M(male)

Case nr.	Age	Type	Type of surgery	Time to recidivism	ABG before surgery	ABG one-year after surgery	ABG five years after surgery	Clinical suspicion	MRI suspicion	Mean ADC	Surgery	Cholesteatoma during surgery
1	38 M	Sinus	Atticotomy	58 months	36	20	28	NO	Highly	0.4780×10^{-3}	YES	YES
2	34 F	Sinus	Atticotomy	68 months	35	10	15	NO	Highly	0.2200×10^{-3}	YES	YES
3	64 M	Flaccida	Atticotomy	52 months	30	30	41	Uncertain	Highly	0.7890×10^{-3}	YES	YES
4	12 F	Combined	BOT	43 months	40	35	40	Retraction pocket	Highly	0.1210×10^{-3}	YES	YES
5	15 M	Sinus	Atticotomy		27	35	35	NO	Highly	0.7990×10^{-3}	YES	NO
6	50 F	Flaccida	Atticotomy		15	9	18	YES	Uncertain	0.0866×10^{-3}	NO	
7	30 M	Flaccida	BOT		22	17	30	Small	Uncertain/NO	0.1455×10^{-3}	YES	NO
8	35 M	Flaccida	BOT		35	15	15	NO	NO	0.1112×10^{-3}	NO	
9	46 F	Flaccida	BOT		53	55	60	NO	NO	0.0829×10^{-3}	NO	
10	80 F	Flaccida	BOT		50	55	55	Uncertain	Uncertain	0.1196×10^{-3}	NO	
11	71 F	Flaccida	BOT		45	40	41	NO	Uncertain	0.1820×10^{-3}	NO	

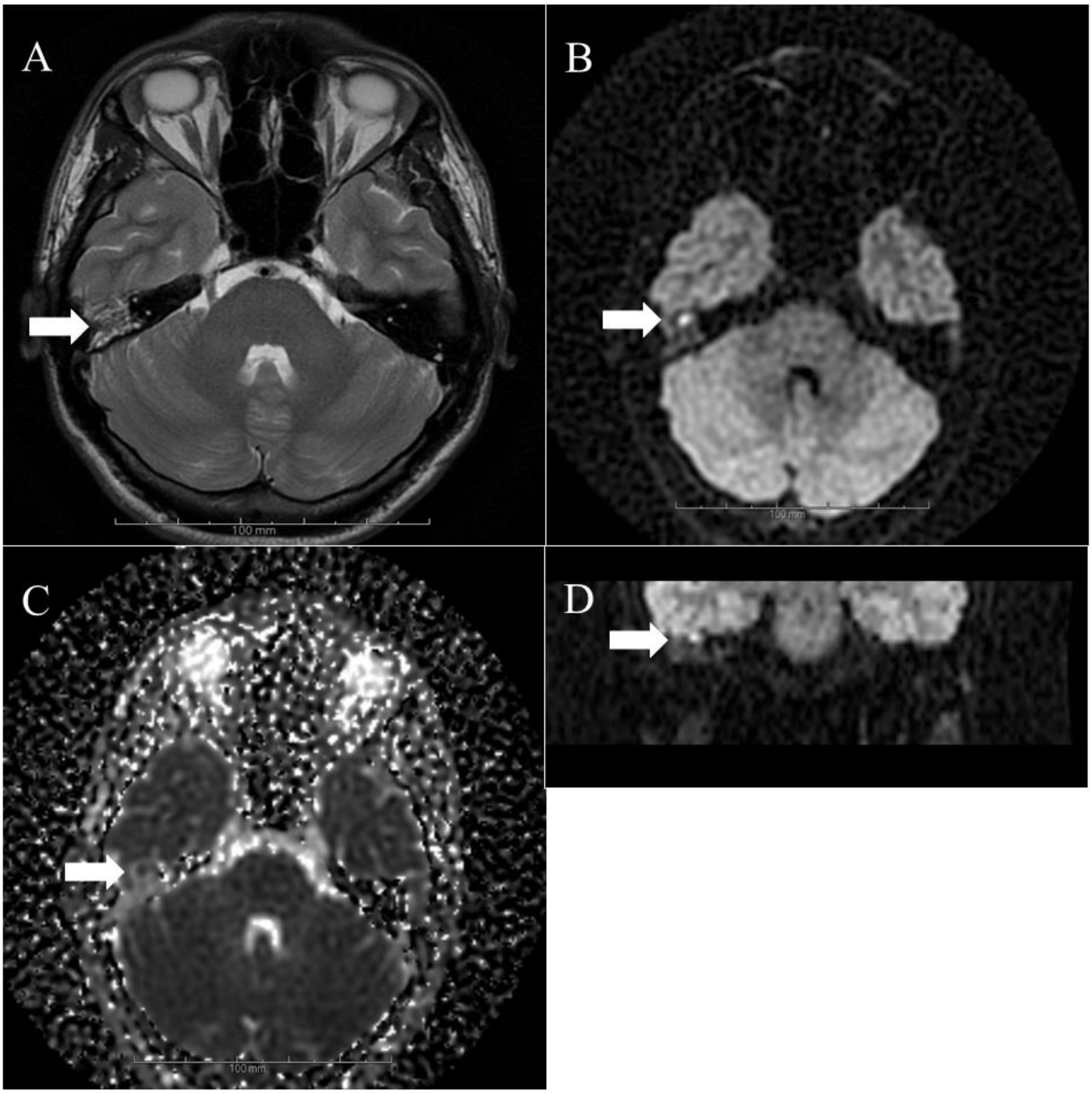


Figure 6-1. MRI Misidentification: A case of cholesterol granuloma in the middle ear inaccurately resembling cholesteatoma. a) In a 15-year-old, an axial T2WI image reveals a focal, non-uniform hyperintense lesion with an indistinct boundary (white arrow); b) A pronounced hyperintense lesion is noticeable in the epitympanum on axial DW PROPELLER; c) The ADC image displays low-intensity signals (white arrow) d) Coronal reformatted visuals from the axial PROPELLER DWI exhibit hyperintensity on DW PROPELLER. Surgery revealed a small cholesterol granuloma.

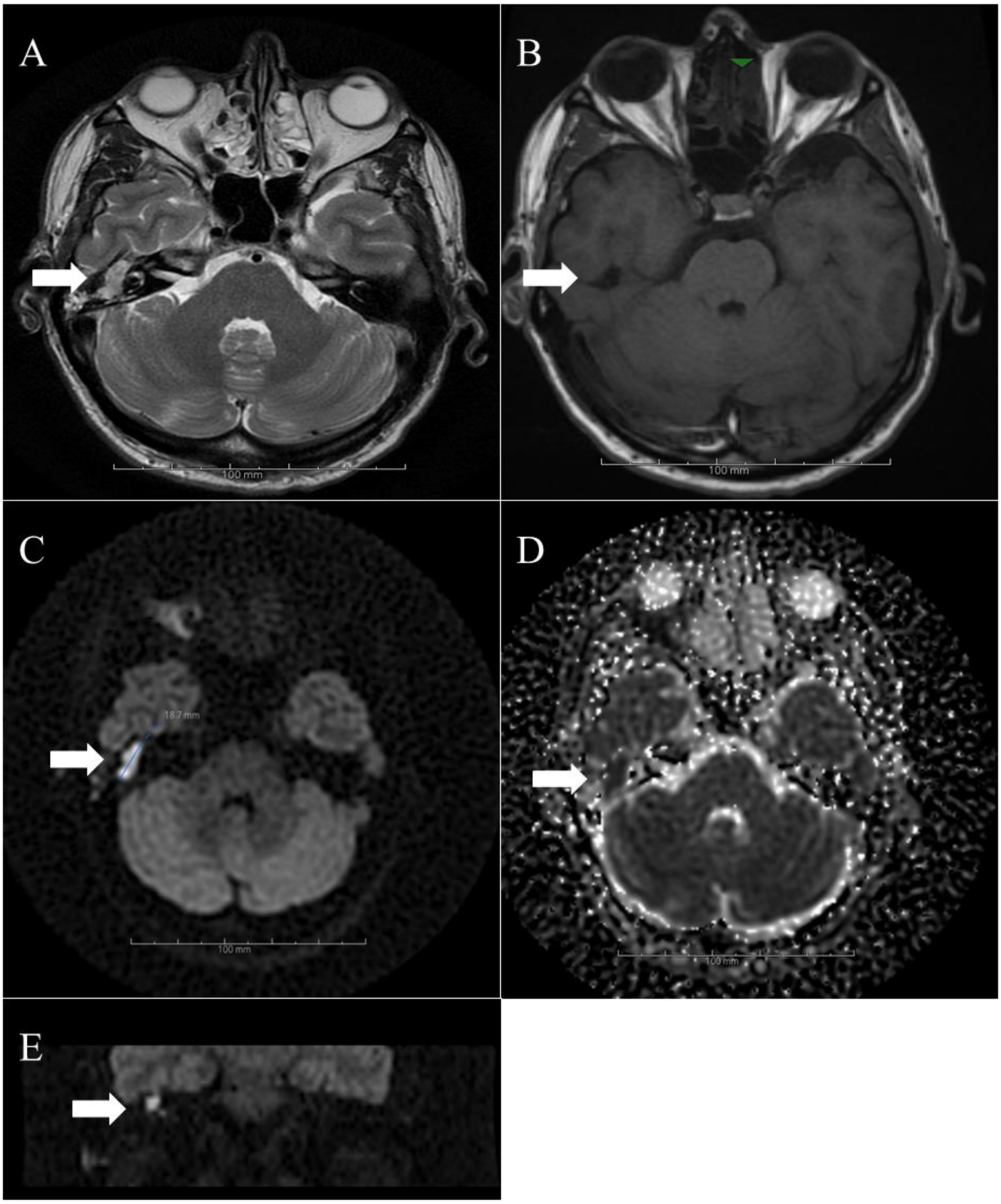


Figure 6-2. MRI confirmation of recurrent cholesteatoma in a case with inconclusive otologic exam results. A 34-year-old female, under a five-year follow-up, presented with mildly progressive decreased hearing. The otologic examination was obscured by cartilage reconstruction and an opaque tympanic membrane. The white arrows in all images point to the cholesteatoma. a) MR imaging shows a slightly hyperintense signal on T2WI and (b) a Hypointense signal on T1WI without clear enhancement; c) ROPELLER DWI shows hyperintensity in this same area, consistent with recurrent cholesteatoma. Surgical findings confirmed the presence of cholesteatoma in this region; d) The ADC map presents with a hypointense signal; e) Coronal image, reformatted from the axial PROPELLER DWI exhibits hyperintensity.

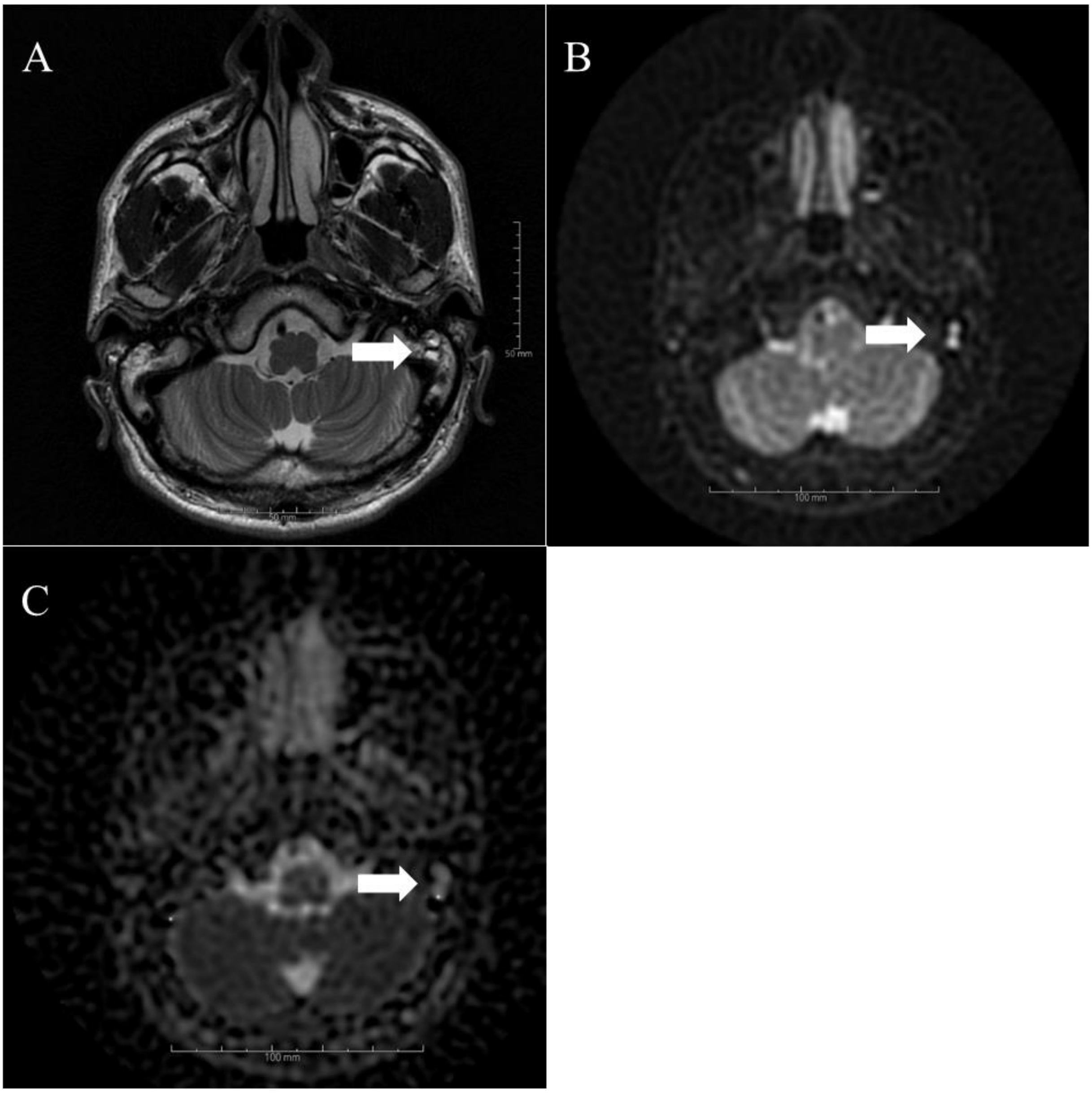


Figure 6-3. MRI visualization of granuloma/inflammation in the left middle ear. A30-year-old male. The otologic examination was obscured by cartilage reconstruction and an opaque tympanic membrane. The white arrows in all images point to the granuloma. a) MR imaging shows a slightly hyperintense signal on T2WI and b) ROPELLER DWI shows hyperintensity in this same area. d) The ADC map presents with hyperintense signal. Surgical findings confirmed the presence of inflammation in this region.

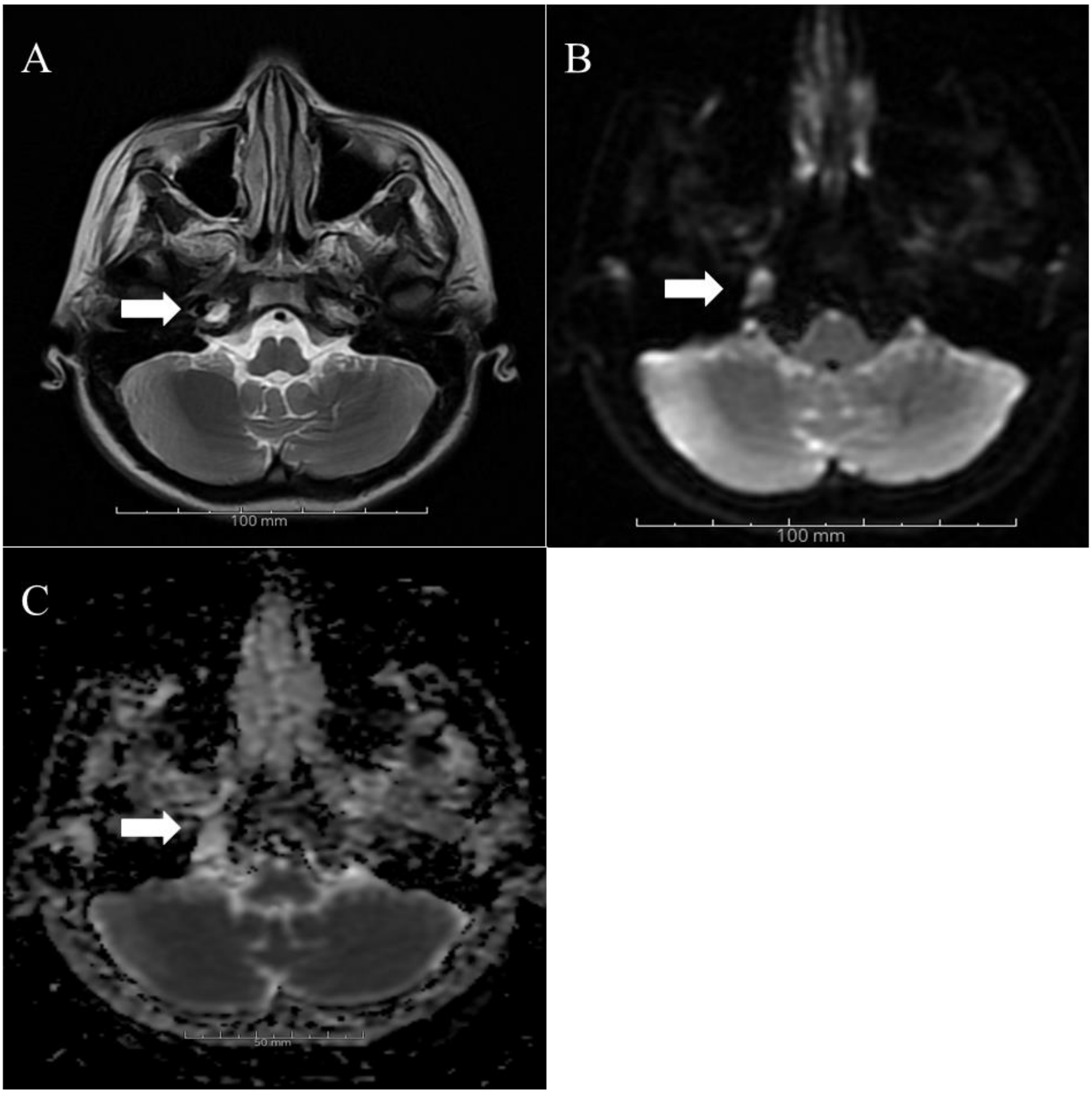
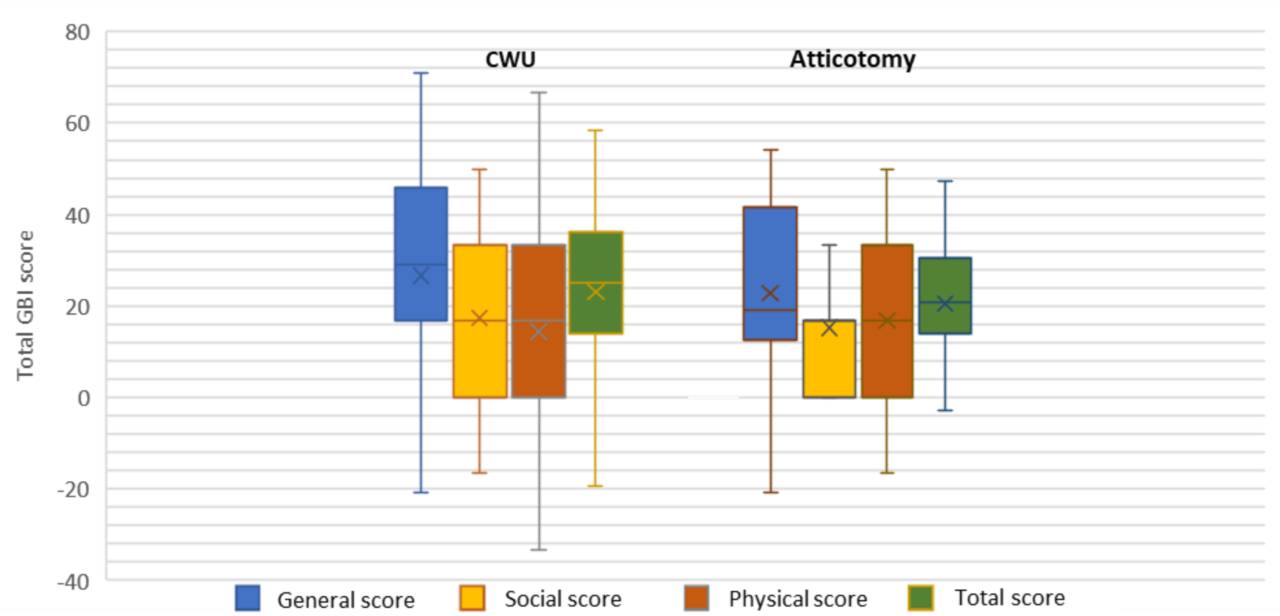


Figure 6-4. MRI case of a cholesterol granuloma located in the petrous apex. A 12-year-old male patient, post-cholesteatoma surgery in the right ear, underwent follow-up MRI. a) The T2-weighted MR image reveals a hyperintense region in the right middle ear extending to the petrous apex (indicated by the white arrow). b) The DW-MRI image shows no restricted diffusion in the area (white arrow). c) The ADC image displays hyperintense signals (white arrow).

4.1.4 Study IV

The study aimed to compare the outcomes of two surgical procedures, CWU-BOT and atticotomy with tympanoplasty, in managing cholesteatoma. A total of 113 patients were included, with 89 undergoing CWU-BOT, and 24 undergoing atticotomy. The patient demographics, specifically age and gender, were comparable across the groups.

Follow-up was conducted with 48 participants from the CWU-BOT group and the mean follow-up times were 8.7 years and 5.4 years for CWU-BOT and atticotomy, respectively. Recidivism rates were 5.6% and 8.3% for CWU-BOT and atticotomy, respectively. GBI questionnaire results for CWU-BOT showed significant improvements in QoL, particularly in the general subscale, while social support and physical health subscore saw less change (see Figure 7-).



	CWU-BOT		Atticotomy	
	Mean	SD	Mean	SD
General score	26.7	23.6	23.1	19.1
Social score	17.4	17.1	15.3	11.7
Physical score	14.4	26.2	16.7	19.8
Total score	23.1	17.8	20.7	15.2

Figure 7-1. Boxplot for GBI score in CWU-BOT and atticotomy patients. The general, social, and total scores are higher for the CWU-BOT group, while the physical score is slightly higher for the Atticotomy group. The standard deviations are relatively large in both groups, indicating variability in the responses.

Canal Wall Up Bony Obliteration Tympanoplasty Patients

In the context of CWU-BOT surgeries, 86% of the participants experienced positive outcomes, 4.5% reported no change, and 10.5% reported deterioration in their condition. Notably, a one-sample t-test revealed a statistically significant improvement in QoL, as indicated by a mean GBI score of 23.1 (SD = 17.8). Details regarding self-reported hearing outcomes are presented in Table 7-1.

Furthermore, positive correlations were observed between improved QoL and ear discharge (correlation coefficient $r = 0.77$, $p > 0.05$), as well as subjective hearing function ($r = 0.68$, $p > 0.05$). Similarly, correlations were found between PTA and total GBI score ($r = 0.70$, $p > 0.05$). However, no significant correlation was detected between postoperative ABG and QoL ($r = 0.1$, $p < 0.05$). Figures 7-2 A-D provide a visual representation of these regression correlation analyses.

Atticotomy Patients

For atticotomy patients, the total GBI score averaged 20.72 (SD = 15), with notable improvements in both overall QoL and its subscores. The self-reported hearing outcomes are detailed in Table 7-1. However, when correlating the total GBI score with discharge and self-reported hearing function, no significant correlations were observed ($r = 0.4$, $p > 0.05$). Similarly, no significant correlation was found between the ABG and total GBI ($r = 0.1$). In contrast, a noteworthy correlation was identified between PTA and the total GBI score ($r = 0.70$, $p > 0.05$). For a graphical representation of these relationships, please see Figures 7-2 E-H.

Comparison of Groups

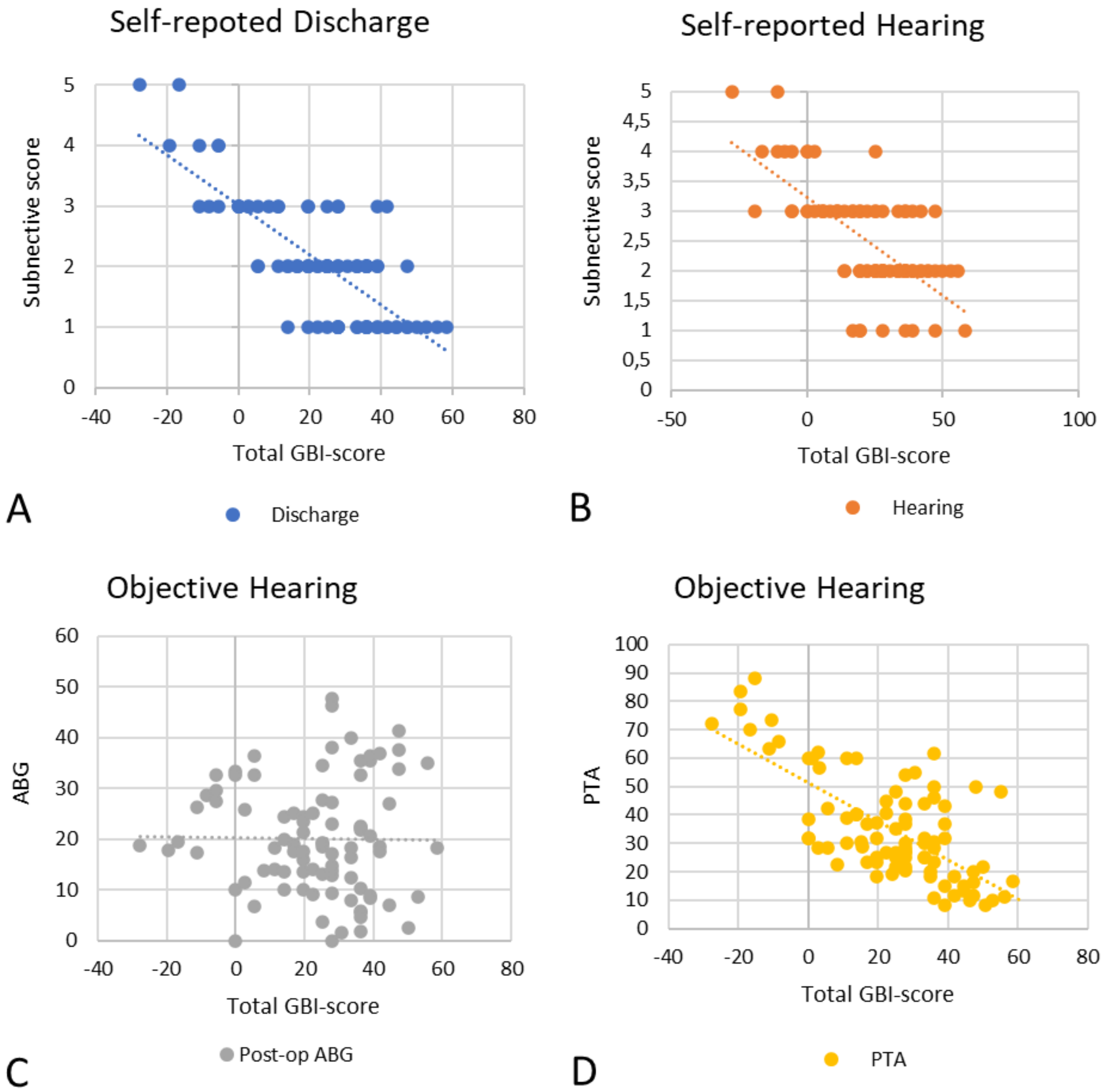
No statistically significant distinction in postoperative GBI scores was found between the study groups, as indicated by the Mann-Whitney U-test results ($z = -0.39$, p-value = 0.699 and $z = 1.13$). Both procedures demonstrated improvements in hearing outcomes with significant alterations observed in PTA.

Audiometric Outcomes

In CWU-BOT patients, preoperative ABG improved from 27 dB (SD = 14) to 18 dB (SD = 12) post-surgery, resulting in a mean ABG closure of 9 dB (SD = 14). Likewise, preoperative air conduction (AC) PTA (AC-PTA) decreased from 41 dB (SD = 20) to 32 dB (SD = 18) post-surgery. We observed a statistically significant difference in both pre-and postoperative ABG ($p < 0.05$) and PTA ($p < 0.05$). The proportion of patients with PTA ≤ 30 dB increased from 44% to 60%, and no total hearing loss cases were reported.

In atticotomy patients, preoperative ABG improved from 22 dB (SD = 12) to 16 dB (SD = 13) post-surgery, resulting in a mean ABG closure of 6 dB (SD = 15). Similarly, preoperative AC-PTA decreased from 35 dB (SD = 21) to 28 dB (SD = 21) post-surgery. However, we did not observe any significant differences ($p > 0.05$) in these hearing outcomes.

Additionally, there were no significant disparities in hearing outcomes between the CWU-BOT and atticotomy procedures.


Self-repoted Discharge
Subnective score
Total GBI-score
A
Discharge
Self-reported Hearing
Subnective score
Total GBI-score
B
Hearing
Objective Hearing
ABG
Total GBI-score
C
Post-op ABG
Objective Hearing
PTA
Total GBI-score
D
PTA

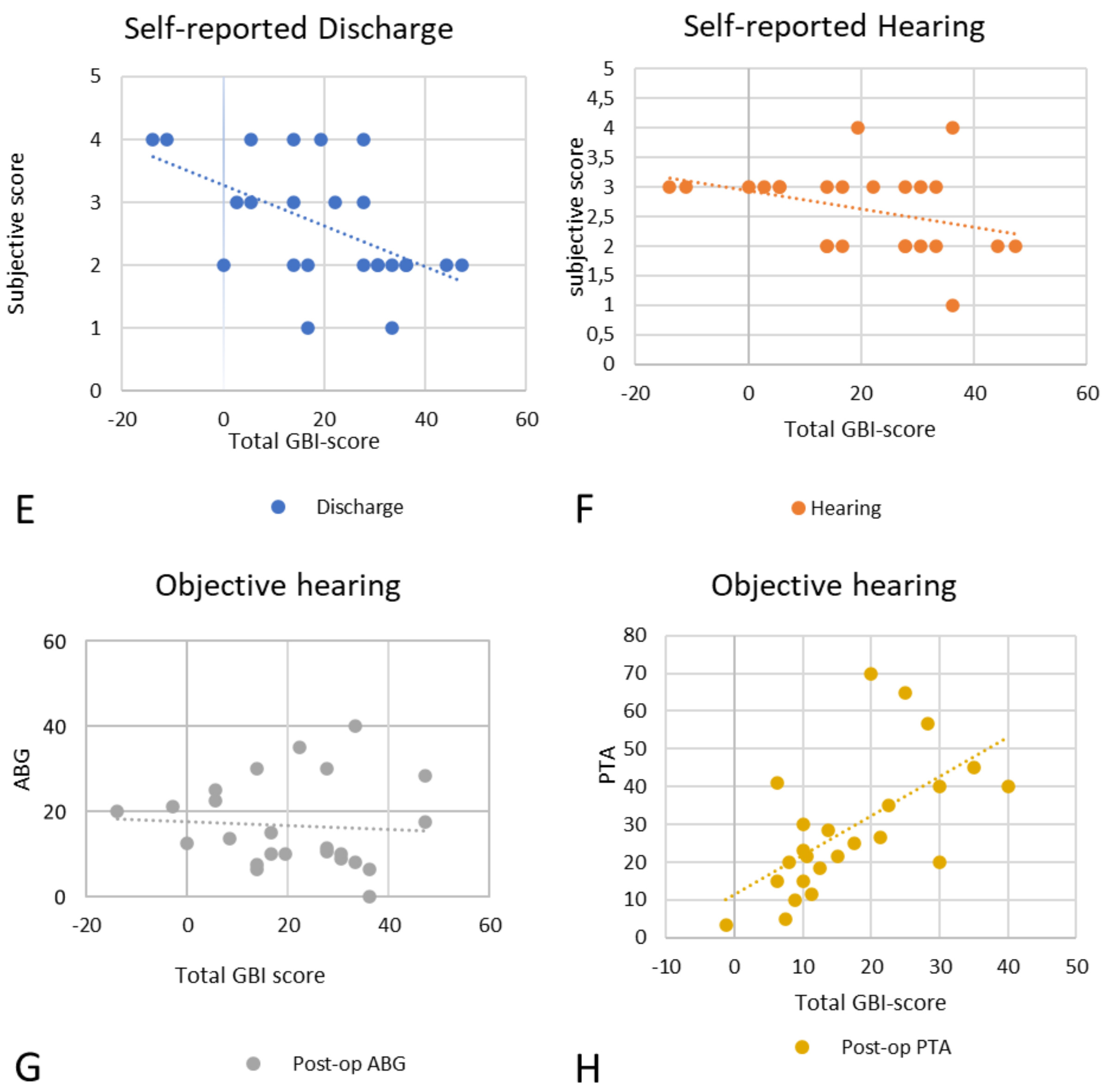


Figure 7-2. The diagram presents an analysis of regression correlation, exploring the connection between QoL, depicted through the Total GBI Score, and various factors for patients with cholesteatoma undergoing CWU-BOT and atticotomy procedures. Figure A-D represent patients group underwent CWU-BOT, and figure E-H represent patients underwent atticotomy.

CWU-BOT= canal wall up boney obliteration.; GBI=Glascow Benefit Inventory; ABG= air-bone-gap; PTA= pure-tone average.

	CWU BOT			ATTICOTOMY		
	Improved	Worse	No change	Improved	Worse	No change
Total GBI	86.5%	9%	4.5%	85.7%	4.8%	9.5%
Surgery-specific questions						
- Drainage	71%	7%	22%	63%	12%	25%
- Self-reported hearing	56%	11%	33%	52%	10%	38%

Table 7-1. Presentation of surgery success rates, surgery-specific questions related to drainage and selfreported hearing, and the percentages of patients with improved, worse, or unchanged outcomes for both CWU-BOT and atticotomy procedures.
CWU-BOT: canal wall up mastoidectomy with boney obliteration; GBI= Glasgow Benefit Inventory.

5 Discussion

"Our imagination is the only limit to what we can hope to have in the future" – Charles F. Kettering.

5.1 Study I

The present study focused on the diagnostic potential of PROPELLER DW-MRI, specifically in the realm of cholesteatoma detection and differentiation, which has gained popularity in cholesteatoma diagnosis due to its speed and suitability, even for pediatric populations (De Foer et al., 2006, 2008; F. Mas-Estelles et al., 2010; Moreno-Ramos MD et al., 2019; J. P. Vercruysse et al., 2006, 2009; Yamashita et al., 2011).

Our research prominently exhibited the diagnostic capacities of the PROPELLER DW-MRI technique for cholesteatoma detection. In the study at hand, PROPELLER DW-MRI demonstrated an accuracy rate of over 89% in diagnosing cholesteatoma, with high sensitivity of 88% (95% CI: 0.71–0.95) and specificity of 92% (95% CI: 0.66–0.99). These results align with previous studies (Jindal et al., 2011; Lingam & Bassett, 2017).

However, despite the high sensitivity and specificity of non-EPI DWI, certain limitations persist. False-negative cases were observed; these are mainly attributed to factors such as empty retraction pockets and small cholesteatoma sizes (Plouin-Gaudon, Bossard, Fuchsmann, et al., 2010). Timing between MRI and surgery is crucial, as delays may lead to false negatives due to disease progression (Tomlin et al., 2013). Factors like micro-suction or emptying cholesteatoma contents before MRI can also contribute to false negatives (Baráth et al., 2011). On the other hand, false positives in non-EPI DWI, though rare, can affect specificity and PPV (Fan et al., 2019; Muhonen et al., 2020). Our study encountered one such case, a 15-year-old female with Wegner's granulomatosis, which has not been previously reported as a false positive in the mastoid cavity.

The optimal magnetic field strength for diagnosing cholesteatoma remains debated. While the 3T scanner's superior signal-to-noise ratio might offer better detection of small lesions, the 1.5T scanner counters with reduced susceptibility to magnetic field irregularities near the temporal bone. Lips et al. (2019) advocate for 1.5T non-EPI (Lips et al., 2019), whereas Fan et al. (2019) (Fan et al., 2019) and Lehmann et al. (2009) (Lehmann et al., 2009) highlight the benefits of 3T non-EPI, emphasizing it's detailed visualization. However, our study, aligning with findings by Kida et al. (2016) and Lincot et al. (2015) (Kida et al., 2016; Lincot et al., 2015), observed minimal ADC value differences between the two strengths. This field strength debate remains pivotal for future research.

Our study underscores the clinical importance of precise diagnostic methodologies. Notably, 8% (14 cases) of participants showed no cholesteatomas during surgery despite having clinical indicators. This emphasizes the need to differentiate cholesteatoma from similar presenting conditions. The combined use of non-EPI PROPELLER and ADC measurements might reduce surgeries, optimizing cost and minimizing surgical complications (D. L. Choi et al., 2019; Kolff-Gart et al., 2015; Russo et al., 2018).

It is important to recognize that our research, like all scientific endeavors, has limitations. The limitations of this study include small sample size and potential biases, particularly when calculating ADC values using observer-defined ROIs. Moreover, the time interval between MRI procedures and subsequent surgeries may complicate the interpretation of false-negative results, suggesting the uncertain progression of cholesteatoma over time. Based on our findings, we recommend conducting more comprehensive investigations. Comprehensive conclusions can be derived from larger-scale studies that include extended monitoring phases and utilize DW-MRI. Future studies should analyze the variability in ADC values across different MRI configurations, techniques, and sequences to establish a standardized approach. Further investigation into the factors contributing to false negatives and examination of other possible false-positive scenarios, such as the unique case of Wegner's granulomatosis in the mastoid cavity, would greatly enhance the scholarly discourse.

5.2 Study II

This study focused on the post-surgical recidivism rates of cholesteatoma, with particular emphasis on the proficiency of the surgeons involved, and the age of the patients. The objective was to identify potential factors associated with recidivism and assess the efficacy of different surgical techniques in reducing these risks.

The primary aim of cholesteatoma surgery is complete pathology eradication. However, the best surgical approach remains debated. Cholesteatoma surgery, despite being performed by skilled surgeons, carries a risk of recidivism due to its complex nature. Recidivism rates exhibit considerable variation, ranging from 0% to 70% across different studies (Edelstein & Parisier, 1989; Rønde Møller et al., 2020; Sheehy & Patterson, 1967b).

Literature indicates variability in recidivism rates, with conventional CWU methods showing consistently higher rate than CWD or CWU BOT techniques (B. Black, 1998; Britze et al., 2017; Gantz et al., 2005; Mercke, 1987; Sheehy & Patterson, 1967b; Shelton & Sheehy, 1990; van der Toom et al., 2022; Van Dinther et al., 2018; J. P. Vercruysse et al., 2008). Newer studies support BOT's effectiveness in reducing recidivism. The rationale behind this obliteration may be based on the etiopathogenesis of mastoid pneumatization of the ME(Gaihede, 2016a). Moreover, irrespective of the surgical method, pediatric cases consistently present higher recidivism than adults (Charachon, 1988; Darrouzet et al., 2000; Edelstein & Parisier, 1989; Nyrop & Bonding, 1997; Tomlin et al., 2013).

This can be attributed to factors like increased keratinocyte proliferation in pediatric cholesteatoma and the expansive pneumatization of the temporal bone in children, facilitating disease spread compared to the sclerotic mastoids in adults (Olszewska et al., 2004). Our study supports this finding. The risk of recidivism decreased by 6% for every additional year in age at the time of the first surgery. Furthermore, age below 16 emerged as a significant predictor of increased recidivism. The study revealed a higher risk of recidivism after five years of primary surgery in children compared to adults, with rates of 14% and 7% respectively based on survival-analyses. This is consistent with prior research (Rønde Møller et al., 2020). Notably, despite an 18.5% recidivism rate, our pediatric cohort showed no residual disease. In a broader context, our study's recidivism rate was 9%, which is relatively lower than other reported studies (Britze et al., 2017; Rønde Møller et al., 2020).

Furthermore, our study explored the effectiveness of CWU BOT as a method for cholesteatoma treatment. Our multivariate analyses indicated a lower risk of recidivism when using the CWU technique with BOT compared to the non-obliteration approach in both children and adult cases, however the difference was not significant.

Although the exact mechanisms behind this effect are not fully understood, a solid understanding of mastoid anatomy and function provides a rationale for cavity obliteration in cholesteatoma surgery. Clinical and animal experiments have provided valuable insights into the underlying mechanisms (Csakanyi et al., 2014; Motegi et al., 2020). Our understanding of mastoid function is currently limited, as it is often considered to be passive and primarily involved in gas exchange and pressure regulation due to its unique structure compared to the tympanum. Recent physiological research has emphasized the role of the mastoid in regulating MEP. This includes its involvement in sudden changes caused by the opening of the ET, as well as gradual shifts resulting from changes in the mastoid mucosa. Further studies confirm this viewpoint, highlighting the importance of the mastoid in maintaining pressure equilibrium (Matanda et al., 2006; Motegi et al., 2020; Padurariu et al., 2016).

The mastoid mucosa, which lacks cilia and goblet cells found in the tympanum, is prone to inflammation. However, it serves a specific function due to its loose connective tissue and abundant blood vessels. Chronic or recurrent infections can cause fibrosis, which restricts the ability to change thickness due to congestion, while gas absorption capacity may remain unaffected, and the mastoid mucosa may lose its functional properties. Obliteration can counteract the effects of compromised mucosa, which may only contribute to gas absorption and the development of MEP (Gaihede, 2016a; Schillinger, 1939).

Csakanyi et al. (2014) (Csakanyi et al., 2014) provide evidence of the benefits of BOT in improving pressure dynamics and optimizing ME function, particularly in cases of insufficient mastoid pneumatization and dysfunctional ET. The study found that smaller ME systems undergo faster pressure changes than larger ones, BOT may be particularly beneficial for smaller ME systems that have limited mastoid pneumatization and impaired ET function.

Our experience indicates that the CWU BOT technique is the preferred method for surgically treating extensive primary and recurrent cholesteatoma, as well as for reconstructing unstable cavities.

One interesting aspect of our study involved investigating the correlation between surgical waiting times and recidivism rates. Contrary to common expectations, prolonged waiting periods did not increase the risk of recidivism or result in significant complications. A significant correlation was observed between the age at the initial surgery and the probability of recidivism. The risk of cholesteatoma recidivism decreases by 6% for each additional year of a child's age at the time of their initial surgery. This finding is consistent with previous studies that have consistently found higher rates of recidivism in younger patients (Hussain et al., 2021; Rønde Møller et al., 2020). Hussain et al. (2021) conducted a parallel study that supported our findings, suggesting that surgical delays, including those caused by external factors such as the COVID-19 pandemic, did not increase the likelihood of recidivism.

Our data indicates that delaying surgery for a year or longer may have potential benefits in reducing the likelihood of recidivism in pediatric patients. It is important to maintain a balance between regular clinical assessments and advanced monitoring techniques, such as DW-MRI, as emphasized by Vercruysse et al. (2010) (J.-P. Vercruysse et al., 2010). Exercising clinical discretion is crucial, particularly in cases involving complications such as cerebral abscesses, meningitis, and facial palsy.

5.3 Study III

In this study, we examined the effectiveness of non-EPI DW imaging for long-term follow-up after primary ME cholesteatoma surgery, addressing the persistent issue of recidivism across different surgical techniques and reconstruction methods (Dornhoffer et al., 2013; Smyth & Patterson, 1985). Ensuring long-term ear safety, particularly in the context of BOT techniques, is of paramount importance due to the risk of concealed residual cholesteatoma (B. Black, 1998), which can lead to delayed symptoms and complications (Nyrop & Bonding, 1997; Palva, 1978; Roberson et al., 2003; J.-P. Vercruysse et al., 2010). To address these concerns and improve post-surgical outcomes, experts like Tomlin et al. (2013) (Tomlin et al., 2013) recommend implementing surgical staging 6-12 months after the primary surgery, despite the associated disadvantages and need for additional procedures (Abeele et al., 1999; D. L. Choi et al., 2019; Crowson et al., 2016; Kimitsuki et al., 2001; Migirov et al., 2009). Consequently, there has been a shift towards imaging-based follow-up, with DW-MRI emerging as an essential tool (J. P. Vercruysse et al., 2006, 2009; J.-P. Vercruysse et al., 2010), especially when otoscopic visibility is limited post-surgery, as it has proven effective in detecting both primary and recurrent cholesteatoma over the last years (Cavaliere et al., 2018; Russo et al., 2020; Van Egmond et al., 2016; J. P. Vercruysse et al., 2006; J.-P. Vercruysse et al., 2010). The introduction of PROPELLER DW-MRI has further improved the accuracy of cholesteatoma detection (Pipe et al., 2002). Our institutional experience corroborates the reliability of PROPELLER DW-MRI sequences in evaluating post-cholesteatoma surgery patients, as detailed in our first study (Study I. Kole et al. 2023).

Additionally, our research explored the differentiation of cholesteatoma from non-cholesteatoma lesions using ADC values, finding a significantly lower mean ADC value for cholesteatoma cases compared to previous studies, albeit with the caveat of small sample size and methodological variations (Cavaliere et al., 2018; Lingam et al., 2013; Russo et al., 2018, 2020).

We encountered 11 cases with ambiguous MRI results, requiring close monitoring and potential repeat scans to ensure accurate diagnosis and optimal clinical management. Based on these 11 cases, we identified four out of nine cases of cholesteatoma recidivism, equating to a 9% recidivism rate, and demonstrated high sensitivity in detecting recidivism even without clear clinical indications. However, this necessitates caution against potential false negatives and rare false positives (Lingam & Bassett, 2017).
In our dataset of 86 patients and over 90 DW-MRI scans, no false-negative cases were reported, but one false-positive case was identified, underscoring the need for careful MRI interpretation, particularly in patients with extensive surgical histories. Pre-existing surgical interventions can induce postoperative changes, such as inflammation and fibrosis, potentially influencing MRI signals and subsequently the ADC value (Kolff-Gart et al., 2015). In the aforementioned false-positive case, the ADC value was 0.7990×10^{-3} mm^2/s, markedly higher than the study's mean for cholesteatomas ($0.402 \times 10^{-3} \pm 0.2194 \times 10^{-3}$ mm^2/s). In contrast, the average ADC value for patients without cholesteatoma was significantly lower, recorded at $0.22 \times 10^{-3} \pm 0.2 \times 10^{-3}$ mm^2/s. This underscores the importance of cautious MRI interpretation in patients with surgical histories. This discrepancy could stem from variations in methodologies, particularly in drawing ROIs, and focusing on the cholesteatoma's center (Kolff-Gart et al., 2015).

These findings emphasize the importance of ADC values as a supplementary diagnostic tool and highlight the need for a specific threshold value to differentiate cholesteatomas from other ME conditions, potentially reducing unnecessary surgeries. Although ADC values are valuable for diagnosis, they should be used as supplementary indicators and not relied upon exclusively for clinical decisions.

Economically, opting for MRI over a second-stage surgery offers cost savings, reduced patient stress, and a more streamlined diagnostic process, although it is essential to acknowledge the limitations of our study, including potential biases, a limited sample size, and variability in imaging techniques (D. L. Choi et al., 2019; Crowson et al., 2016; Keeler & Kaylie, 2016).

In conclusion, our study highlights the significant role of non-EPI DW imaging in the long-term follow-up of cholesteatoma surgery, emphasizing its ability to detect recidivism and the crucial need for cautious interpretation, especially in patients with complex surgical history.

5.4 Study IV

The current healthcare landscape is experiencing a paradigm shift, with an increasing focus on holistic patient well-being rather than solely treating diseases. This study delves into this perspective, aiming to understand the long-term outcomes of patients undergoing cholesteatoma surgery, beyond the standard clinical metrics. While recidivism rates and postoperative ABG closures provide valuable data, these quantitative measures might not fully capture the patient's overall experience and satisfaction (N. Black, 2013).

The study acknowledges that a closed ABG, as seen in previous research by Choi et al. (2012) and Kurien et al. (2013), does not guarantee a patient's comfort or improved QoL (S. Y. Choi et al., 2012; Kurien et al., 2013). This discrepancy between clinical outcomes and patient well-being highlights the necessity of incorporating PROMs into post-surgical assessments. PROMs provide a vital link between objective clinical data and subjective patient satisfaction, ensuring a comprehensive evaluation of the surgical experience (Fayers & Hays, 2005; Muldoon et al., 1998; Peter Fayers and Ron Hays., 2005).

Research has been conducted using various tools to assess the QoL of patients after surgical interventions for conditions like COM and cholesteatoma. Instruments such as the Chronic Ear Survey, COMOT-15, and the recently introduced Chronic Otitis Media Questionnaire (COMQ-12) have proven to be reliable in evaluating postoperative outcomes (Baetens et al., 2019; Baumann et al., 2011; Hwan Jung et al., 2010; Nadol et al., 2000). These studies have revealed a pattern: while some patients report an increase in QoL after surgery, others continue to struggle with decreased QoL, even pre-surgery (Vlastos et al., 2009). This variability not only highlights the diverse implications of the disease but also the different impacts of surgical interventions.

Focusing on the Danish population, our study sheds light on the QoL trajectories of patients following cholesteatoma surgery, specifically when the CWU-BOT and the atticotomy techniques were applied. Utilizing the comprehensive GBI for evaluation, our findings indicate a positive shift in various QoL dimensions, affirming the benefits of the surgical intervention. A significant observation was the strong correlation between enhanced patient-reported QoL and decrease in ear discharge following the CWU-BOT procedure. This is a critical link since ear discharge can significantly affect a patient's daily life and comfort (Chan & Chan, 2012). Our results align with the findings of Dornhoffer et al. (2008) and Mehta & Harris (2006), further validating the efficacy of the CWU obliteration technique (Dornhoffer et al., 2008; Mehta & Harris, 2006).

However, our study also brings to light the complex relationship between perceived hearing improvement and its subsequent impact on HRQoL. While patients often report an improvement in hearing, this is not always reflected in audiometric data, creating a disparity between subjective and objective evaluations of postoperative success (Dutt et al., 2002; Mackenzie & Smith, 2009). This discrepancy emphasizes the need for a holistic approach to assessing post-surgical outcomes, considering both the clinical and personal aspects of recovery (Hallberg et al., 2008). The understated preoperative symptoms in cholesteatoma add another layer of complexity, making it challenging to discern improvements in HRQoL despite favorable surgical outcomes (Smyth & Patterson, 1985).

Despite our study not finding a significant correlation between audiometric outcomes and GBI scores, a strong link was evident between GBI scores and self-reported hearing function. This highlights a discrepancy, as objective audiometric results may not fully reflect a patient's postoperative experience. It also underscores the importance of a holistic approach in assessing post-surgical outcomes, integrating both objective and subjective measures.

In conclusion, this discussion underscores the critical role of PROMs in evaluating post-surgical outcomes, advocating for a balanced approach that considers both quantitative measures and the patient's subjective experience. The positive impact of CWU-BOT on QoL is evident, yet the complexity of the postoperative patient experience necessitates a nuanced understanding and careful interpretation of both objective and subjective outcomes. Future research in this domain should aim to explore these complexities further, contributing to a more comprehensive and patient-centered approach to post-surgical care.

6 Conclusion

In this comprehensive study, we illuminate various facets of cholesteatoma surgery, delving into diagnostic methods, evaluating long-term results, and considering the impact on patient QoL after surgery.

Our investigation underscores the invaluable role of advanced imaging techniques, particularly PROPELLER DW-MRI and ADC mapping, in the accurate diagnosis of cholesteatoma. We have demonstrated that non-EPI DW-MRI, and more specifically PROPELLER DW-MRI, stands out due to its resilience to field inhomogeneities, rapid data acquisition, and reduced image distortion, making it a preferred choice in cholesteatoma monitoring.

The study reaffirms the diagnostic prowess of PROPELLER DW-MRI, achieving a commendable 89% accuracy rate in cholesteatoma detection, and highlights the utility of ADC values in differentiating cholesteatoma from other ME conditions. However, we acknowledge the challenges posed by false negatives and positives, urging the need for continued refinement in diagnostic methodologies.

Economically, the shift towards MRI and ADC values over second-stage surgeries presents a more cost-effective and less stressful diagnostic route, emphasizing the need for a holistic, informed, and cautious approach in integrating these tools into clinical practice.

We have also explored the persistent challenge of post-surgical recidivism, identifying age as a significant factor, and spotlighting the CWU-BOT for its potential in reducing recidivism rates. From a patient-centric perspective, our study delves into the HRQoL post-surgery, using the GBI scores to illustrate the positive impact of CWU mastoid obliteration on patients' experiences.

To sum up, the integration of non-EPI PROPELLER DW-MRI and ADC values emerges as a promising strategy in cholesteatoma diagnosis, contributing significantly to the field and paving the way for optimized patient care, reduced unnecessary interventions, and improved clinical decision-making. While embracing the advantages of these innovations, it is imperative to remain cognizant of the study's limitations and the necessity for a balanced and comprehensive diagnostic approach.

7 Future perspectives

Building on the extensive research conducted in the field of cholesteatoma detection and treatment, our future trajectory is directed toward honing diagnostic accuracy, optimizing surgical interventions, and enhancing patient care post-surgery. The durability of surgical methods applied in cholesteatoma requires validation through extended longitudinal studies. Complementary HRQoL assessments alongside auditory and healing outcomes, incorporating pediatric patients, and potentially qualitative methodologies for a holistic evaluation are pivotal.

Further research encompassing larger patient cohorts and prolonged follow-up periods is imperative for validating the application of DW-MRI, particularly non-EPI DW-MRI, and PROPELLER sequences. These techniques show promise, necessitating optimization and standardization to enhance diagnostic precision and minimize false diagnostic outcomes. The current lack of a standardized approach for ADC calculation in ME cholesteatoma necessitates the establishment of consistent protocols. This includes standardized procedures for delineating ROIs and focusing on the cholesteatoma's core, addressing the observed discrepancies in ADC values between our study and previous literature.

Defining specific ADC-value thresholds is crucial for differentiating cholesteatomas from other ME conditions, requiring future studies with diversified cases and larger sample sizes. This would enable clinicians to make more informed decisions based on imaging, potentially reducing the frequency of unnecessary surgeries. Such a reduction not only alleviates the economic burden on healthcare systems and patients but also minimizes patient exposure to surgical risks.

From an economic standpoint, employing PROPELLER MRI as a diagnostic tool presents substantial implications, highlighting the need for comprehensive cost-benefit analyses to evaluate long-term financial and healthcare outcomes. This includes comparing imaging-based follow-up strategies against second-stage surgeries.

Tailored surgical strategies, particularly for pediatric patients, are necessitated by the variability in rates post-cholesteatoma surgery. Future research should delve into understanding the impacts of surgeon proficiency, patient age, and various surgical techniques on recidivism, aiming for innovative solutions to significantly reduce recidivism rates.

Adopting imaging-based follow-up aligns with a patient-centric approach, enhancing the patient experience and providing an efficient diagnostic process. Future innovations should include PROMs to assess the impact of different follow-up strategies.

The necessity for large-scale, multicenter studies is evident, aiming to fortify the existing evidence base concerning the role of non-EPI DW imaging and ADC-values in cholesteatoma post-surgical follow-up. Holistic assessment models, integrating both quantitative and qualitative measures including PROMs, are crucial for a comprehensive evaluation of post-surgical success, addressing the observed discrepancy between objective and subjective outcomes.

In conclusion, this study sets the stage for a future where cholesteatoma management is patient-centered, characterized by improved diagnostic accuracy, comprehensive post-surgical assessments, and an in-depth understanding of the long-term impacts on patient QoL. The integration of advanced imaging, patient-centered care, and long-term follow-up will be pivotal, aiming to enhance patient outcomes and satisfaction in cholesteatoma management, while also involving patients in the decision-making process and raising awareness.

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