Middle Ear Cholesteatoma

Surgical Treatment, Follow-up and Hearing Restoration

LENNART EDFELDT
Although middle-ear cholesteatoma is a major topic in otological research, its etiology and pathogenesis remain unclear. Pediatric cholesteatoma is considered more aggressive than adult cholesteatoma, as it has a higher rate of growth, is more often infected and exhibits wider extension. Higher incidence of residual and recurrent disease after surgical treatment of pediatric cholesteatoma has been observed in most studies. In this study, the results are presented from a canal wall down (CWD) obliteration technique used in 330 adult patients (Paper I) with cholesteatoma, evaluated at 1, 3 and 6 years following surgery. Additionally, results are offered from 57 pediatric patients (Paper II) using identical surgical technique and compared with adults. The surgical and hearing outcomes in both groups showed a low incidence of residual and recurrent disease and a high rate of ear water resistance without infection. The results were unrelated to the severity and extension of disease, as well as to age and previous surgery. No differences were found in outcomes between adult and pediatric cholesteatoma patients.

The thesis also describes the use of diffusion-weighted magnetic resonance imaging (DW-MRI) (Paper III) in follow-up examinations of adult cholesteatoma patients undergoing surgical treatment. Non-echo planar diffusion-weighted imaging (Non-EPI DW-MRI) increased the accuracy of clinical examinations. It is concluded that the use of non-EPI DW-MRI should be mandatory in clinical follow-ups after cholesteatoma surgery. In Paper IV a relatively new mode of hearing rehabilitation was investigated, with an active middle ear implant (AMEI), in patients with chronically disabled ears. Functional hearing results were compared with the previous use of conventional hearing aids before and after AMEI implantation. Moreover, the consequences of positioning of the implant in the middle ear were evaluated using cone beam computed tomography (CBCT), a modification of conventional computed tomography. The hearing results, assessed with AMEI, were found to be less dependent on the precise positioning of the floating mass transducer (FMT) against the round window membrane (RWM) than was anticipated. Further, the hearing results were noted to be comparable with those with conventional hearing aids and even superior at high frequencies.
“sine ira et studio” - (without anger or fondness.)

(Tacitus 55-120 BC)

To Karin,

Kristin, Harriet, Sebastian and Johanna
This dissertation is based on following papers.


IV. "Round window vibroplasty in chronic ear surgery - comparison with conventional hearing rehabilitation". Edfeldt L and Rask-Andersen H. Accepted for publication in Acta Otolaryngologica 2013
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## Abbreviations

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<th>Description</th>
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<tbody>
<tr>
<td>ABG</td>
<td>air/bone gap</td>
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<tr>
<td>AC</td>
<td>air conduction</td>
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<td>ACH</td>
<td>acquired cholesteatoma</td>
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<tr>
<td>AMEI</td>
<td>active middle ear implant</td>
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<tr>
<td>BAHD</td>
<td>bone-anchored hearing device</td>
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<tr>
<td>BC</td>
<td>bone conduction</td>
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<tr>
<td>CBCT</td>
<td>cone-beam computed tomography</td>
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<td>CCH</td>
<td>congenital cholesteatoma</td>
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<tr>
<td>CHA</td>
<td>conventional hearing aid</td>
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<tr>
<td>COM</td>
<td>chronic otitis media</td>
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<td>CPA</td>
<td>cerebello-pontine angle</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CWD</td>
<td>canal-wall down</td>
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<tr>
<td>CWU</td>
<td>canal-wall up</td>
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<tr>
<td>DW-MRI</td>
<td>diffusion weighted magnetic resonance imaging</td>
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<tr>
<td>EPI</td>
<td>echo-planar imaging</td>
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<tr>
<td>ET</td>
<td>Eustachian tube</td>
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<tr>
<td>FMT</td>
<td>floating mass transducer</td>
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<tr>
<td>GBI</td>
<td>Glasgow Benefit Inventory</td>
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<tr>
<td>HL</td>
<td>hearing level</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>Non-EPI</td>
<td>non-echo planar imaging</td>
</tr>
<tr>
<td>PORP</td>
<td>partial ossicular replacement prosthesis</td>
</tr>
<tr>
<td>PTA</td>
<td>pure-tone average</td>
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<tr>
<td>RWM</td>
<td>round window membrane</td>
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<tr>
<td>RWN</td>
<td>round window niche</td>
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<tr>
<td>TM</td>
<td>tympanic membrane</td>
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<tr>
<td>TORP</td>
<td>total ossicular replacement prosthesis</td>
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1. Introduction

Cholesteatoma of the middle ear was first described as “steatoma” by Du Verney in 1683. The term “cholesteatoma” was introduced by Müller in 1838. The French pathologist Cruveilhier named it “tumeur perlee”, which was adopted by Virchow as “Perlgeschwulst” (“pearly tumor”). Although it is a tumor (-oma), it contains neither cholesterin (chole-) nor fat (-stea)-. The prevalence of cholesteatoma varies between populations, and its incidence is difficult to appraise. For congenital cholesteatoma (CCH), the prevalence was recently estimated to be 2-5 %. An assessment of incidence based on the number of reported surgical procedures is unreliable because a considerable number of surgical revisions have been performed. The annual incidence of cholesteatoma was reported in two studies from the Nordic countries. In a Danish study, it was found to be 3 per 100,000 in children and 12.6 in adults. In a Finnish study, it was estimated to be 9.2 per 100,000 inhabitants in adults. No difference in prevalence was found between different social groups.

Although cholesteatoma is one of the major topics in otological practice and research, its pathogenesis and surgical treatment remain in dispute. Controversy also persists over whether pediatric and adult cholesteatoma differ regarding growth, extension and cellular aggressiveness. Universally accepted guidelines for its classification and follow-up and for a description of the outcomes are still lacking.

The clinical course is often highly variable and unpredictable. It can vary from a harmless lesion to almost malignant invasion, with massive and even intracranial extension. Such extension can strongly influence treatment and outcome. Despite progress in the application of molecular biology in clinical science leading to improvement in understanding of the pathogenesis and nature of several diseases, cholesteatoma remains a largely unexplained pathologic condition. As cholesteatoma is frequently associated with several complications, such as recurrent infection and impaired hearing function, the quality of life of cholesteatoma patients can be seriously affected. In rare cases, life-threatening complications can also occur.

Cholesteatoma surgery is complicated, challenging and time-consuming. The motto of Fisch to “take your time and be precise” is worth remembering.

Hearing is a prerequisite for our ability to communicate and, in childhood, for the development of speech and language. Hearing restoration is therefore essential and should not be considered secondary. Corresponding to the numerous surgical techniques and modifications described in the literature, the
long-term surgical and hearing outcomes remain highly variable. The reported number of cases in many materials of residual and recurrent disease and/or persisting hearing loss requiring revision surgery is still unsatisfactory. When choosing a surgical technique, restoration of anatomical structures and hearing function should be given priority. It is also important to select thoroughly inserted, implanted materials into the middle ear. They must be well tolerated, and the extrusion rate should be low.

The diagnosis and postoperative follow-up are generally based on clinical features and can be adequately supplemented by imaging. High-resolution computed tomography (CT) is one of the most frequently used preoperative imaging techniques. Magnetic resonance imaging (MRI) is more reliable in the detection of postoperative cholesteatoma because it can differentiate between cholesteatoma and other soft tissue changes with high sensitivity and specificity. MRI has been increasingly used in the postoperative follow-up, and it is considered mandatory by many clinicians for the correct interpretation of surgical outcomes.

For a majority of patients undergoing surgical treatment for cholesteatoma, the anatomical structures and hearing function can be restored. Patients with remaining hearing impairment can, in most cases, be rehabilitated with the fitting of a conventional hearing aid. In rare cases with dysfunctional middle ears and severe mixed hearing loss in which, despite multiple surgeries, ossicular reconstruction has failed, the implantation of active middle ear implants can be a valuable alternative.

Furthermore, the importance of a comprehensive, long-term follow-up and a computer-based registry of surgical and hearing results should be emphasized. The present studies that form the basis of this dissertation are founded on the evaluation of a clinical follow-up register in which all patients undergoing surgery were prospectively included. Internationally accepted criteria for the classification of disease, surgical procedures and follow-up could allow in the future for comprehensive comparative assessments of diverse treatment philosophies and modalities.

1.1. Definition

Cholesteatoma is frequently associated with chronic otitis media (COM), but it should be understood as a separate entity. Cholesteatomas are classified as congenital (CCH) or acquired (ACH). CCH is regarded as less common than ACH, and it is defined as embryonic remnants of epithelial inclusions behind an intact tympanic membrane (TM) in patients without a history of otitis media. The classic presentation is in the anterior-superior quadrant of the middle ear. CCH is more common in children. A classification system has been proposed according to the sequence of spread, involving three distinct anatomical
sites. Another staging system for CCH was developed on the basis of clinical experience.

ACH affects both children and adults, and it is characterized by the migration of keratinized hyperproliferative squamous epithelium, positioned in a fibrous stroma, into the middle ear and mastoid cavity. It can be defined as an accumulation of squamous epithelium medial to the normal level of the tympanic membrane (TM) or more simply as “skin in the wrong place”.

“Primary acquired cholesteatoma” originates from the pars flaccida without a history of otorrhea. “Secondary acquired cholesteatoma” is characterized by posterosuperior retractions or perforations, with granulations and often foul-smelling ear discharge. Based on the site of appearance, Tos classified cholesteatoma as attic-, sinus- or tensa-cholesteatoma.

Cholesteatoma can also occur after surgery for non-cholesteatomous middle-ear disease (inclusion cholesteatoma) and posttraumatically (traumatic cholesteatoma).

1.1.1 Pathogenic theories of congenital cholesteatoma

CCH can be located in the middle ear cavity and mastoid, petrous apex, cerebellopontine angle (CPA) and jugular foramen. Forty to 50 percent of cases are located in the CPA. Several theories have been proposed regarding the origin of congenital cholesteatoma. The first description of congenital cholesteatoma was published by Lucae. Teed, in 1936, and Michaels, fifty years later, identified an epithelial rest in the middle ear of the temporal bone of human fetuses. This epidermoid formation was shown to regress by 33 weeks of gestation. If it persists for unknown reasons, it can form a congenital cholesteatoma.

Karmody et al. presented in 1998 the first clear histologic documentation of postpartum congenital cholesteatoma. Tos offered in 2000 a report on the acquired inclusion theory. He concluded that the place of origin of mesotympanic cholesteatoma does not fit with the location of epithelial formation described by Michaels. Based on the places of origin of mesotympanic (congenital) cholesteatoma being commonly connected to the malleus handle, the malleus neck or the long process of the incus, Tos proposed that keratinized squamous epithelium of the retracted eardrum might be implanted into the tympanic cavity. Retraction can occur due to tubal dysfunction with retraction and adhesion of the eardrum, chronic secretory otitis media and acute suppurative otitis media, all of which are very common during childhood. Retractions of the eardrum can be fixated and then loosened again. In this mode, the inclusion of keratin can occur, leading to the formation of cholesteatoma.
1.1.2 Pathogenic theories of acquired cholesteatoma

The pathogenesis of acquired cholesteatoma remains an enigma. Virchow\textsuperscript{23} declared in the middle of the 19\textsuperscript{th} century, “I cannot with accuracy explain how the pearly tumor is formed”, a statement which still seems valid.

Four physiopathological theories or a combination of them has primarily been deliberated.

1. Von Tröltsch introduced the “metaplasia theory” in 1864. Because Virchow\textsuperscript{24} reported cholesteatoma in small cavities in bone and in the dura, in close vicinity to the temporal bone, he rejected the association with the epidermis of the ear canal, as proposed by Toynbee. He classified cholesteatoma either as a separate entity of tumor or as an atheroma or dermoid tumor. Von Tröltsch was the first to consider an epidermal origin and supposed that differentiated respiratory and bony cells were capable, under the influence of chronic inflammation, to dedifferentiate and redifferentiate themselves into squamous epithelial cells\textsuperscript{25}. The theory of metaplasia became well accepted among otologists in the 19\textsuperscript{th} century.

2. The “migration theory” was independently proposed by Habermann in 1888\textsuperscript{26} and Bezold in 1890\textsuperscript{23}. Bezold also described “frequent concave but structural intact tympanic membranes without perforations, characteristic for an occlusion of the Eustachian tube”,\textsuperscript{23} which supports the retraction pocket theory. Michaels\textsuperscript{21} studied the squamous epithelial layer of the adult tympanic membrane and described 3 zones characterized by differences in their thicknesses. It was concluded that cholesteatoma might develop from the most active of these zones, which is situated on the pars flaccida. Karmody and Northrop in 2011\textsuperscript{15} examined histologic sections of the temporal bones of 60 children and concluded that cholesteatomas are formed by medial migration of the stimulated squamous epithelium of the tympanic membrane. They found no evidence for a retraction pocket being the precursor of acquired cholesteatoma.

3. Lange in 1925\textsuperscript{27} questioned the theory of metaplasia. He never saw evidence for “true cholesteatoma”, interpreted as a tumor without a history of previous infection, and he demonstrated the existence of basal cell hyperplasia, known as the “proliferation” theory. Ruedi\textsuperscript{28} provided experimental and clinical evidence for this theory.

4. The “retraction pocket theory” was introduced by Wittmack in 1933,\textsuperscript{29} and is most likely the most widely accepted pathogenetic mechanism of acquired cholesteatoma. Wittmack classified cholesteatoma as genuine, or attic, and secondary, or tensa. The prerequisites for the pathogenesis of cholesteatoma were the patient’s predisposition to develop a hyperplastic mucosa, together with strongly reduced aeration of the mastoid cavity. The starting point was squamous epithelia in the pars flaccida. Wittmack concluded that without the formation of a retraction, the development of cholesteatoma was impossible. In contrast, he frequently observed this forma-
tion of retraction pockets limited to Prussak’s space, without formation of a manifest cholesteatoma. He further postulated that the accumulation of debris in the retraction pocket alone could not be responsible for further development into a genuine cholesteatoma. Wittmack observed mucosal bridges causing a demarcation between the antrum and protympanon, and he assumed, in accordance to Bezold, development of under-pressure in the space of antrum. He also observed that large cholesteatomas could expand without the presence of infection, which he called “dry cholesteatoma”.

Several similar theories have been described. Politzer introduced the “hydrops-ex-vacuo” theory in 1867. It was believed that the tube was blocked by edema or by an adenoid mass. Due to tubal obstruction, negative pressure in the middle ear developed. The middle ear gas was absorbed and replaced by effusion. Opposed to this widespread theory, Hergils et al. demonstrated that despite a closed Eustachian tube (ET), reduction of the negative pressure occurred. The “Toynbee effect” was explained by biphasic pressure, which occurs when swallowing with the nose clogged. That the nose is rarely completely sealed disproves this theory of the induction of negative middle ear pressure.

Magnuson presented a theory that chronic adhesive middle ear lesions and retraction type cholesteatomas could develop as reactions to tubal closing failures. He concluded that the induction of lower pressure could be responsible for retraction and atrophy of the TM, effusion of fluid and progressive atelectasis, with involution and sclerosis of the mastoid. He emphasized that the malfunction of interest in chronic middle ear disease is a failure not of opening but of closing – “tubal closing failure”. The patulous tube is not a static condition, and the malfunction varies over time. This negative pressure can be induced and supported by habitual sniffing. During sniffing, the ET is forced open by the sudden pressure difference between the middle ear and the nasopharynx. The middle ear is evacuated, and the developed negative middle-ear pressure closes the tube. If equalization on swallowing does not occur, this negative intratympanic pressure persists, and as a consequence, the TM retracts, and effusion can arise. Lindeman et al. evaluated three groups of patients with TM perforations due to trauma, COM and ACH, respectively. ET function and aeration of the mastoid cavity were evaluated and compared. The cholesteatomatous ears were associated with poor ET function and small mastoid volumes. A combination of thinning of parts of the tympanic membrane and exposure to negative pressure contribute to the development of retractions. The lack of self-cleaning of debris in the retraction pocket, combined with altered epithelial migration supported by recurrent infection, is considered a prerequisite for developing a manifest cholesteatoma. Additionally, a combination of the retraction theory and proliferation theory has been suggested.
1.2. Molecular biology

According to Albino et al.\(^9\) cholesteatoma can arise as the result of: a) induction of a neoplastic transformation; b) a defective wound-healing process; and c) a pathologic collision of the host inflammatory response.

As in wound healing, cholesteatomas consist of activated keratinocytes, which have been migratory and proliferative\(^{14}\). These cells are activated in response to growth factors, chemokines and local cytokines. Cholesteatoma cells express proliferation cell nuclear antigens across all layers, as opposed to the normal skin of the ear canal from the same patient\(^{37}\). Importantly, the increase in proliferation is not uncontrolled, as in malignant tumors. Several intracellular signaling pathways associated with proliferation have been identified in cholesteatoma. Preciado et al.\(^{14}\) showed that a pathologically relevant agent in cholesteatoma, *Pseudomonas aeruginosa* lipopolysaccharide, can activate keratinocyte hyperproliferation in vitro, indicating that middle ear infections can lead to intracellular conditions that stimulate the aggressiveness of cholesteatoma. We might conclude that the research to date indicates that cholesteatoma is a wound-healing process, rather than a neoplasm\(^{38}\).

1.3. Pediatric cholesteatoma

Pediatric cholesteatoma is considered to diverge from adult cholesteatoma. The pronounced higher incidence of residual and recurrent cases, with an increasing need for revision surgery, has been commonly reported\(^{39-41}\). Pediatric cholesteatoma is also characterized by frequent infections, high proliferation rates and large and well aerated mastoids,\(^{42}\) which influence the surgeon to choose less extensive canal wall up (CWU) approaches. This choice might explain the poorer outcomes obtained in cholesteatoma treatment in children, compared to adults.

1.4. Complications

Complications can be divided into extra- and intracranial complications. Because the treatment of cholesteatoma remains surgical, it is also important to be aware of the risks for surgical complications.

1.4.1 Extracranial complications

Mastoiditis is the most common complication. The equivalent is subperiosteal abscess. It is caused by the spread of infection from the mastoid into the periosteal space, and it is very common in young children. Bezold’s abscess is a cer-
vical abscess, which is identical to a subperiosteal abscess. Apicitis, or petrois-
tis, is a rare infection of the pneumatized petrous apex.

Labyrinthine and cochlear fistulas are also rather frequent. Labyrinthine fist-
tulas are estimated in approximately 7% of all cholesteatoma cases. The
lateral semicircular canal is the most frequently involved part of the canal, in
roughly 90% of cases.

Facial palsy is rare in cholesteatoma. It is perhaps more frequent after surgi-
cal treatment. Accidental injury to the facial nerve, especially in cases in which
the bony canal is defective, can result in facial nerve dysfunction. One out of
ten surgical cases could develop dehiscence of the facial nerve canal.

1.4.2 Intracranial complications

Brain abscess is the most frequent and most dangerous intracranial complica-
tion, followed by meningitis. Sigmoid sinus thrombosis represents approxi-
mately 20% of all intracranial complications. Subdural abscess or empyema
can be induced by bony dehiscence.

1.5. Diagnostics

In most cases, cholesteatoma is diagnosed clinically. The clinical examination
should be performed with a microscope at selective magnification of 6-10x.
The use of Siegel’s pneumatic speculum can facilitate the evaluation of TM
mobility. A history of otitis media, habitual sniffing, previous treatment with
grommets and the patient’s ability to ventilate the ear through the Valsalva
maneuver are important to consider.

Imaging often supports the diagnosis. High-resolution computed tomogra-
phy (CT) can provide useful information about the ossicular chain, facial
nerve, semicircular canals and the size and aeration of the tympanomastoid
spaces. CT possesses a high negative predictive value in excluding cholestea-
toma if there is a complete absence of opacification in a well-aerated tym-
panomastoid cavity. It can also provide useful indirect signs of the presence
of cholesteatoma, such as destruction of the ossicular chain or scutum. How-
ever, CT cannot differentiate between cholesteatoma and other soft tissues,
such as granulation tissue, scar tissue, cholesterol granulomas or inflammatory
mucosa. In cases of opacification, the use of magnetic resonance imaging is
valuable, both pre- and postoperatively. Diffusion-weighted magnetic reso-
nance imaging (DW-MRI) was shown to be a valuable technique in the preop-
erative detection of suspected cholesteatoma. Cone-beam computed tomo-
graphy (CBCT), initially used in dental and maxillofacial imaging, can also
provide accurate diagnostic information about the middle ear structures with
minimal radiation exposure. Due to the low radiation dose and because the
examination can be performed with the patient in a sitting position, CBCT can
be an alternative to conventional CT, especially in children. Audiometric tests are essential for diagnosis and for evaluation during follow-up. Air and bone conduction hearing thresholds (HL), using calibrated audiometers, should always be determined preoperatively. The regular use of a tuning fork (Weber’s and Rinne’s tests) is indispensable.

1.6. Pre-and postoperative care

Careful collection of preoperative information, both oral and written, is of great significance. The preoperative counseling is regarded as a part of the surgical procedure. In conformity with the surgery, it should be careful and complete. It is important to educate the patient about the possible pathogenesis of the disease, the importance of middle ear ventilation (Valsalva maneuver), the self-cleaning of the ear canal, preoperative water protection and the risks for surgical complications. The risk for surgical damage to the inner ear, with ensuing sensorineural hearing loss or deafness, is estimated at <1%, while the risk for accidental injury to the facial nerve is <0.5%. It is also important to mention the risk for delayed facial dysfunction, which usually occurs several days after surgery but with a good prognosis. If a preoperative infection is present, a bacterial culture should be performed and the infection treated with antibiotic eardrops and/or oral antibiotics. On the day before surgery, audiometric test are performed.

The dressing is removed after 7-10 days, depending on whether split skin has been transplanted into the ear canal. Postoperative prescription of antibiotic eardrops for 7-10 days and water protection are recommended until epithelialization of the ear canal is completed, which usually takes 6-10 weeks.
2. TREATMENT

2.1. Historical remarks

Morgagni (1682-1771) was the first surgeon to operate on an otogenic brain abscess. Riolan and Jean-Petit performed the first mastoid trepanation in the middle of the seventeenth century, and Jasser performed it in 1776\textsuperscript{48}. The beginning of modern ear surgery was facilitated by the introduction of the operating microscope. Different scientists have been associated with the first use of a microscope in otology and ear surgery, including Kessel in 1872, Weber-Liel in 1876 and Czapski in 1888\textsuperscript{49}. The first to recognize the need for greater magnification in ear surgery was Nylén in 1921\textsuperscript{50}. Gunnar Holmgren, a Swedish colleague of Nylén’s, was the first surgeon to use the binocular operating microscope: “Together with asepsis the use of the binocular microscope was one of the most important developments in the history of ear surgery”\textsuperscript{51}.

Modern tympanoplasty was introduced after the Second World War and was enabled by the introduction of antibiotic treatment.

2.2. Surgical techniques

The primary goals of surgical treatment are eradication of disease, preservation or restoration of hearing and achievement of a water-resistant and non-infectious ear. Among the numerous surgical techniques described, there are two main techniques that have primarily been represented: canal wall down (CWD); and canal wall up (CWU) with infinite modifications. Generally, CWD is used preferably to obtain an adequate anatomical overview and safe eradication, while CWU is applied when preservation of anatomical structures and restoration of hearing are prioritized. One advantage of CWD procedures is the greater likelihood for a total purge, which in many studies has been reflected in a lower incidence of residual and recurrent disease, compared to CWU procedures. The major disadvantages with this technique include the lack of water-resistance, a general need for regular cleaning and poorer hearing outcomes. These disadvantages, however, can be minimized or eliminated by reducing the area of the mastoid cavity via obliteration with different materials, such as autologous bone chips or bone-paté and muscle, as well as artificial materials, such as hydroxyapatite. Obliteration can also be supported by meatooplasty.
The major advantages with CWU procedures include preservation of the anatomy, rapid postoperative epithelialization, generally better postoperative hearing and superior water resistance. Due to a more limited anatomical overview, the incidence of residual and recurrent disease requiring revision surgery is considered higher.

Ossicular reconstruction can be performed during the primary surgery. Because safe eradication of cholesteatoma is more difficult to obtain with CWU techniques, many clinicians prefer to stage the surgeries. During a “second-look” operation, the surgeon can control eventual residuals or recurrences and can also perform ossiculoplasty.

Different materials have been used for ossicular reconstruction over the last few decades. Ossicular reconstruction, with autologous incus or cortical bone, is increasingly being replaced by alloplastic prostheses. The reasons for using alloplastic materials include the risk for fixation or resorption with autologous bone. The risk of extrusion is certainly greater with alloplastic materials, which is reflected in the mandatory use of cartilage in alloplastic ossiculoplasty.

The advantages of using silastic sheeting in middle-ear surgery include prevention of adhesions, supported regeneration of the middle ear mucosa and improvement of ET functioning. One disadvantage is a certain risk for perforation and rejection. If perforation occurs, the silastic sheet can be removed easily through the perforation, which usually heals within a few weeks.

2.3. Hearing restoration

A prerequisite for obtaining the primary goals in cholesteatoma surgery is eradication of disease. Reconstruction of the ossicular chain is secondary, but it is not irrelevant for the patient. The cholesteatoma patient’s chief complaint is ear discharge, followed by impaired hearing function. Long-term hearing results after ossicular reconstruction in cholesteatoma surgery can also be interpreted as a relevant indicator of the sufficiency of the surgical technique used. In most cases, stable hearing results can be obtained. A requirement for satisfactory hearing outcomes after surgery is aeration of the middle ear, which can be supported by the Valsalva maneuver. In patients with reduced aeration of the middle ear due to ET dysfunction, silastic sheeting can be a valuable adjunct. In cases of remaining conductive hearing losses, ossicular revision should be considered.

Patients with remaining conductive or mixed hearing losses might also benefit from being rehabilitated with the fitting of a conventional hearing aid (CHA). In some cases, the fitting might be complicated or precluded due to anatomical alterations of the ear canal or due to otitis externa. In such cases, the implantation of a bone-anchored hearing device (BAHD) or an active middle ear implant (AMEI) might be advantageous.
Postoperative inner ear function can be examined with a tuning fork (Weber’s test). The first postoperative audiometric test is performed 6-8 weeks after surgery. It is important to follow up hearing function regularly, especially in children.

2.4. Follow-up

Due to the chronic course of cholesteatoma, with the risk of persisting ET dysfunction, increased hearing loss and residual and recurrent disease, close follow-up is recommended. If the ear is stable and well aerated, an annual examination appears to be sufficient. In children with more variable ET function and reduced capability to ventilate the ear through the Valsalva maneuver, more frequent clinical examinations are recommended.

DW-MRI can detect very small cholesteatomas with high sensitivity and specificity52.

Clinical examinations should be supplemented with non-EPI DW-MRI, which is considered the most valuable MRI sequence in the postoperative detection of cholesteatoma. Non-EPI DW-MRI can be used as a screening tool for at least 5 and 10 years after surgery and always before the determination of follow-up.

How long the follow-up should be continued is ambiguous. A general recommendation is up to 10 years after the primary surgery, depending on patient’s age, the status of the middle ear and the grade of ET dysfunction.
The primary aim of this study was to assess the long-term surgical and hearing outcomes of adult cholesteatoma surgery, performed with a well-defined one-step CWD-obliteration surgical technique. As almost half of treated cholesteatoma patients have had previous surgeries, indicating a higher severity of disease, the second aim was to determine whether this technique was suitable for all patients. The third aim of the study was to evaluate whether this surgical technique was also suitable for treating pediatric cholesteatoma. To ensure the difference between adults and children, pediatric cholesteatoma was defined as cholesteatoma in patients younger than 12 years old. The fourth aim was to investigate whether a clinical examination alone is sufficient to determine the correct number of residual and recurrent cholesteatomas after obliteration surgery or whether modern imaging can contribute to more accurate evaluation of long-term follow-up. The fifth aim was to evaluate whether the use of modern active middle ear implants can enable hearing rehabilitation in patients undergoing cholesteatoma surgery but in which, despite multiple surgeries, ossicular restoration has failed, and conventional rehabilitation is difficult or impossible.
4. MATERIALS AND METHODS

4.1. Patients

Our clinical database included a total of 693 operated patients, with ages ranging from 2 to 83 years old. All patients undergoing surgery for cholesteatoma were prospectively registered in the database (Microsoft Access). Adult patients were defined as patients ≥ 12 years of age (Paper I) and pediatric patient as patients < 12 years of age (Paper II). Cholesteatoma patients were not included in the study who did not fulfill the criteria of 6 years of follow-up and complete surgical and audiological records preoperatively and at 1, 3 and 6 years after surgery. Because many patients were referred from other clinics, the obtaining of complete audiological records with air and bone conduction hearing threshold levels corresponding to our criteria was challenging. For this reason, a relative large number of patients could not be included. Three patients had poor hearing preoperatively and developed complete deafness (bone-conduction thresholds > 100 dB) during the study period. After a comprehensive survey, 301 adult patients (330 ears) and 57 pediatric patients were selected and included for Papers I and II, respectively. The concordance between the registry and the casebook of the hospital was randomly controlled.

Paper III was a prospective and blinded study in which 38 adult patients (41 ears), planned for annual clinical follow-up examinations after cholesteatoma surgery using the TRP technique, were included into the study. The patients’ ages varied between 12 and 76 years old, with a mean of 43.3 years.

Paper IV included seven patients with a mean age of 64.7 years old. Due to cholesteatoma or COM induced by osteoradionecrosis (ORN) of the temporal bone, all of the patients except for one had undergone previous surgeries. All of the patients had been previously fitted with a CHA or BAHD on the implanted side and had also previously been aided in the contralateral ear.

4.2. Methods

The study methods included evaluation of surgical and audiological outcomes after cholesteatoma surgery, using an identical technique for adult and pediatric patients, as defined above (Papers I and II). In Paper II, surgical and hearing outcomes were also compared between adult and pediatric patients.
In Paper III, the included patients underwent radiological examinations with diffusion-weighted magnetic resonance imaging with two different sequences (non-EPI and EPI DW-MRI) 1 to 9 months after clinical examinations and evaluations. The results of imaging were evaluated by two independent neuroradiologists blinded to the results of the clinical examination. Patients in whom non-EPI DW-MRI indicated suspected cholesteatoma underwent revision surgery, with one exception. The outcomes of revision surgery were used as references. The results of the agreement between the reviewers’ evaluations and results of the agreement between the two sequences were calculated. Finally, the results, as assessed by clinical and radiological examinations, were compared.

Paper IV included seven patients with dysfunctional middle ears and mixed hearing losses due to cholesteatoma and osteoradionecrosis-induced COM. All of the patients were implanted with the active middle ear implant Vibrant Soundbridge®, (VSB) manufactured by Vibrant-MedEl, Innsbruck, Austria. Three of these patients were simultaneously or previously treated with subtotal petrosectomy and permanent closure of the external ear canal. Six to 63 months after implantation with Vibrant Soundbridge® into the round window niche (RWN), the patients underwent radiological examinations with cone beam computed tomography (CBCT). The position of the FMT in the RWN was determined from coronal projections of CBCT imaging. A half-tone schematic drawing was created, and the location of the RWM was estimated and traced into the drawing, guided by an appropriate radiological projection of the positioning of the FMT in the RWN. The distance between the FMT and the RWM was measured on the radiological image in coronal projection. The angle of the FMT to the RWM was estimated based on the radiological images and graphic reconstruction. Finally, the position of the FMT was compared with the aided postoperative hearing outcomes. In addition, preoperative aided and unaided hearing with conventional hearing aids was compared to aided and unaided hearing after implantation. Thereafter, the patients completed the Swedish version of the Glasgow Benefit Inventory (GBI), which consists of an 18-item post intervention questionnaire, established for otorhinolaryngological interventions.

4.2.1 Audiometry
Psycho-acoustic air (AC) and bone-conduction (BC) hearing thresholds levels (HL) were determined using audiometers, calibrated according to the relevant European standards used in all papers. In Paper II, specially trained pediatric audiologists performed audiometry. In Paper IV, two specially trained CI audiologists performed audiometry.

In papers I and II, the pure tone averages (PTAs) used in the statistical analyses were based on threshold levels at frequencies of 0.5, 1, 2 and 3 kHz. BC thresholds were assessed at 0.5–4 kHz. The PTA air-bone gap (PTA-ABG)
was assessed at 0.5–3 kHz. Audiometric data were reported according to the guidelines published by the Committee on Hearing and Equilibrium of the American Academy of ORL-Head and Neck Surgery.53

In Paper IV, the pure-tone-average (PTA) values were based on thresholds at frequencies of 0.5, 1, 2 and 4 kHz. The high-frequency HL thresholds were assessed at 2-8 kHz. The pre- and postoperative audiometric protocols included air and bone conduction thresholds, along with aided and unaided free-field speech audiometry using warble tones and phonetically balanced words (PB). Standardized test levels of 65 dB were used for free-field speech audiometry. During the pre- and postoperative assessment of aided free-field hearing, 65 and 80 dB levels were used (comfort level).

4.2.2 DW-MRI (Paper III)

Imaging was performed using a 1.5 T scanner (Siemens Avanto, Siemens Medical Systems, Erlangen, Germany). A coronal non-echo planar (non-EPI) diffusion weighted sequence (HASTE type) and an axial echo-planar (EPI) diffusion weighted sequence covering the temporal bone were acquired. Slice thicknesses were two mm for the non-EPI and four mm for the EPI sequences. A b-value of 1000 mm$^2$/s was used in both DWI sequences.

4.2.3 CBCT (Paper IV)

CBCT images were obtained with a 3D Accuitomo 170 (J. Morita MFG. Corp., Japan). After exposure of 85 kV and 5 mA, 1-mm-thick pictures at 0.5 mm increments were created in 3 projections. The field of view was 6 cm in diameter. The effective dose was approximately 0.083 mSv. The position of the FMT in the round window niche was assessed using coro-nal projections.

4.2.4 Surgical techniques

In Papers I, II and III, all of the patients underwent surgery with identical tech-niques. The surgical steps of the total reconstruction procedure (TRP) are illustrated in Figure 1a-e and are also described in detail in Paper I and II.
Figure 1a-e: Surgical steps in Total reconstruction procedure TRP. a) Cholesteatoma extension in middle ear and mastoid process before eradication. ET= Eustachian tube, ME= middle ear, Ch= cholesteatoma, SS= sigmoid sinus b) Wide exposure of middle ear, facial nerve canal (FN) and mastoid cavity after total removal of posterior bony wall and eradication of Ch. RW=round window, SF=stapes footplate, LSSC=lateral semicircular canal, PSSC=posterior semicircular canal c) Silastic sheet (S) with projection into ET is inserted into ME and an autologous cortical columella (TORP) placed on SF d) Bony wall reconstructed with a large piece of cartilage (Ca) harvested from meatoplasty. Mastoid cavity and epitymanic spaces obliterated with bone paté. Large piece of temporal fascia is covering middle ear, reconstructed canal wall and a part of obliterated area. F= fascia, Co=columella glimpsing through F e) Large vascularised muscle flap covers bone paté.
In all cases, autologous material (cortical bone or incus) was used for ossicular reconstruction. In selected cases, a silastic sheet was inserted into the middle ear - Figure 2.

**Figure 2:** Dissected left human ear. Left image shows the localization of cholesteatoma. PF; pars flaccida. PT; pars tensa. Right image shows the silastic sheet in the middle ear as well as the outline of the bony drilling to expose the cholesteatoma disease.

In Paper IV, implantation of an active middle ear implant into the RWN was performed. In Figure 3 a graphic picture of an AMEI implanted into the RWN is shown. The technique of middle ear implantation is fully described in Paper IV.

**Figure 3:** Round window applied middle ear implantation (Source: MED-EL)
4.2.5 Statistics

The STATISTICA® software package was used for the statistical analysis (Papers I and II). A paired t test and ANOVA were used to investigate the differences between groups.

In Paper III, Cohen’s kappa (κ) was calculated between the two radiological reviewers.
5. RESULTS

5.1. Surgical outcomes (Papers I and II)

Three percent of the patients in the adult group and five percent in the pediatric group had residual disease during the study period. The recurrence rates were 12% and 10%, respectively. In 19% of the adults and 14% of the pediatric group, ossicular revision surgery was performed. A majority of the patients in both groups had recurrent ear discharge preoperatively (82-83%). Six years after surgery, 3% of the adult group and none of the pediatric group had discharge. Preoperatively, 5% of the adults and 7% of the children had water-resistant ears. Six years after surgery, 89% of the adult ears and all of the ears in the pediatric group were evaluated as water-resistant. A comparison of intraoperative findings and results between the adult and the pediatric group is shown in Table 1a-b.

5.2. Hearing outcomes (Papers I and II)

AC and BC improved significantly one year after surgery in the adult group. BC levels decreased 6 years after surgery in the adult group to preoperative levels, while AC remained stable over six years. In the pediatric group, BC remained unaffected in all cases.

In the adult group, three cases developed deafness during the study period, while no deaf ears were confirmed in the pediatric group. AC thresholds improved significantly (p<0.001) after surgery and were maintained after six years in the pediatric group. A comparison was undertaken between patients reconstructed with total ossicular replacement prostheses (TORP) and partial ossicular replacement prostheses (PORP) in the pediatric group. In the TORP group, which had stapes erosion and more severe disease, the increase in air bone gap (ABG) closure of < 20 dB increased from 19% to 33%, while patients with less severe disease and intact stapes improved from 33% to 67%.
Table 1a

<table>
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<th>ME Adhesive</th>
<th>ME Path.Mucosa</th>
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Table 1b

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<td>38%*</td>
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<td>12%</td>
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<td>10%</td>
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<td>5%</td>
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</table>

* out of 55 cases. 2 cases had an intact ossicular chain.
5.3. DW-MRI (Paper III)

Six cases were clinically evaluated as having suspected cholesteatoma. Of these cases, five were non-EPI-positive. Because one patient refused revision surgery, four of the six clinically suspected cases underwent revision and were confirmed with disease.

Additionally, another two patients were evaluated as positive on non-EPI sequences but were clinically negative; they underwent revision and were confirmed. Thus, six out of seven non-EPI-positive cases were surgically revised and confirmed.

In only two cases out of six surgically confirmed cholesteatomas, the EPI technique showed suspected cholesteatoma. The inter-rater agreement between the reviewers was 0.91 (p<0.001) for the non-EPI technique and 0.062 (p=0.43) for the EPI technique.

In one case, two portions of residual cholesteatoma, one extracranial and one intracranial, were revealed with non-EPI DW-MRI and are shown in Figure 4a-b.

![Figure 4 a, b](image)

Figure 4 a, b; 30 years old female operated for an extended attic cholesteatoma involving the mastoid in the right ear. Follow-up at 215 months. Normal findings at clinical examination. Non-EPI DW-MRI showed two 18 /22 mm large extra/intracranial high intensity signal lesions in the right ear (arrows) assessed as cholesteatoma by both reviewers. EPI DW-MRI was assessed as positive for cholesteatoma by reviewer 1 but negative by reviewer 2, who interpreted the right-sided signal changes as susceptibility artefacts. At revision surgery both an extracranial and an intracranial cholesteatoma were found.

5.4. Functional hearing results (Paper IV)

Residual hearing remained unchanged in all of the cases after implantation. In two cases changes in aided speech perception in quiet were more pronounced with the VSB®. In all of the other cases, pre-and postoperative aided speech
perception was fairly comparable. In four out of seven cases (1, 3, 6, and 7), the patients were capable of VSB-aided, measurable high-frequency hearing at 6 and 8 kHz, whereas these frequencies were not measurable preoperatively. Functional hearing results were not correlated to the position of the FMT in the RWN.

5.5. Positioning of the FMT (Paper IV)

The angle of the FMT to the RWM varied between 4 and 43°. The distance between the FMT and the RWM varied between 0.0 and 1.0 mm. The positioning of the FMT in one case is shown on CBCT imaging and on a schematic drawing in Figure 5A-B.

![Figure 5A: CBCT imaging: FMT adequate connected with soft tissue to the RWM at a distance of 0.7 mm. B: Schematic drawing of CBCT imaging: Angle (7°) of FMT to RWM indicated](image)

In only two cases, the floating mass transducer (FMT) was completely connected with the soft tissue of the round window membrane (RWM). In five cases, the FMT was partially connected to the RWM. In four cases, the FMT was also partially connected to bone.

5.6. GBI

Six out of seven patients responded to the Glasgow Benefit Inventory (GBI) questionnaire. The results varied between +3 and +64, where 0 represented unchanged conditions.
6. DISCUSSION

6.1. Inclusion and representation of the patient population

At the beginning of the evaluation, the computer-based “Cholesteatoma Register”, established in 1982, consisted of 698 patients treated between 1982 and 2010. Because part of this patient population had shorter follow-up lengths than the required 6 years, and another part had incomplete or missing data, 311 patients could not be included in the study. This failure might implicate the selection criteria for study patients. However, patients with serious complications, such as erosion of the bony labyrinth, cholesteatoma in the only hearing ear and cochlear fistula, were represented among the included patients. Additionally, 47% of all of the included patients in the adult group had undergone 1-6 previous operations, which also indicates a more advanced degree of disease. In total, 387 ears (57 pediatric) were evaluated in Papers I and II, of which ears of 160 patients had undergone previous surgeries.

In Paper III, 41 adult patients from the “Cholesteatoma Register” were randomly included in follow-up examinations. This adult patient group corresponded well with the distributions of the mean age, sex ratio, mean follow-up time and rates of residual and recurrent disease of the adult group in Paper I.

Three out of seven patients in Paper IV were referred having undergone previous surgeries performed by other surgeons, whereas 4 patients had been treated in our clinic but with different and more extensive surgeries, including permanent blind sac closure.

We therefore conclude that the 432 patients in Papers I-IV represent an unselected patient population at a tertiary referral center.

6.2. Evaluation and presentation of results

Surgical and hearing results were evaluated preoperatively and 1, 3 and 6 years after surgery in both the adults and children. To demonstrate possible changes in hearing over time, the hearing results for both groups were presented in this mode. Evaluations of water resistance, mode of infection and middle ear status were only presented preoperatively and at six years after surgery. An adequate concern is that the reported results only reflect the status at one particular follow-up examination, while ear status can fluctuate over time. However, results
six years after surgery must be interpreted as more reliable than results 1 and 3 years after treatment. This fact is also underlined by the experience that most residual effects and recurrences are often combined with hearing impairment, which emerges during the early stages of follow-up.

6.3. Surgical techniques

In numerous studies, the accuracy has been investigated of different surgical techniques applied in different manifestations of cholesteatoma disease. Ideally, such studies should have been prospective and randomized, comparing unselected but comparable groups, which seldom was fulfilled. Because recurrence rates increase with increasing follow-up durations, long-term follow-up is essential to results being reliable and comparable. Modern imaging techniques, such as non-EPI DW-MRI, also contribute to more accurate estimation of results, as shown in Paper III. Depending on the preoperative estimation of cholesteatoma size, site and extension, an appropriate surgical technique is chosen. Other factors, such as the size of the mastoid cavity, the patient’s age, and the surgeon’s level of experience and preference, can also influence the choice of technique. Surgeons’ experience is detectible in few studies. Nyrop et al. compared the long-term results with three different techniques but found that, during most of the study period, the surgeons hesitated to remove the posterior canal wall in children. True, prospective randomization is also difficult to achieve due to differences in pre- and intraoperative findings. An apparently small lesion planned for CWU surgery might be revealed to be a cholesteatoma with large extension, necessitating a CWD procedure. Tos et al. concluded that no single method is optimal in all cases of cholesteatoma and that cholesteatoma surgery should be individualized. In sharp contrast to this opinion, the present study analyzed only one surgical technique, applied in all cholesteatoma cases, independent of disease extension and patient age. This strategy might appear rigid and too extensive for small and less extensive lesions. Most important in cholesteatoma surgery, however, is the achieving of a sufficient overview, allowing for eradication of the disease. This goal was accomplished by complete or partial removal of the bony canal wall and, in almost all cases, also the lateral ossicles. The malleus was regularly extirpated to support contact between the reconstructed tympanic membrane and ossicle (TORP, PORP). Incessant individualization of treatment can also lead to a plethora of different surgical modifications, which can obstruct proper evaluation and comparison. Because the incidence of acquired cholesteatoma is decreasing, surgeons’ individual experience with different techniques will diminish. Staging is commonly used in cholesteatoma surgery, especially in children. The use of staging is also dependent on the surgical technique used. After CWU procedures, which imply a more limited overview of the surgical field than CWD surgery, staging seems more frequent. Advocates for second-
look procedures state that this strategy increases the safety of treatment and that ossicular reconstruction is easier to perform when the middle ear anatomy is restored. Because cholesteatoma surgery is demanding and time-consuming, this philosophy runs the risk of being less meticulous, especially when the surgeon is less experienced, leaving the completion of removal to the next operation. Supplementary weaknesses with second-look strategy are additional and unnecessary operations, which are disabling for patients and expensive for society. In the present study, chain revisions were performed in 19 % of the adult cases and 14 % of the pediatric cases, which is definitely less than 100 % “second-look ossiculoplasties”. One long operation can, in the end, be shorter than several short procedures. Vartiainen⁵⁹ required that an ideal treatment be based on a one-stage procedure that can completely eradicate the disease and prevent its recurrence. A first step in this direction would be internationally accepted and clearly defined criteria for the definition of disease, surgical techniques and reliable guidelines for long-term follow-up.

6.4. Pediatric group

The surgical results of pediatric patients are considered poorer than those of adults⁴⁰. The definition of pediatric patients varies across different studies. In the present study (1), children were defined as patients <12 years of age to demarcate a clear division based on the size of the mastoid cavity, the alleged aggressiveness of the disease, the rate of infection and ET dysfunction. In two other comparable studies, Sun et al.⁴¹(2) included children aged 5-12 years old, and Silvola et al.⁴⁰ (3) included children < 16 years old. The mean ages were 8.2 in (1), 10 in (2) and 9.7 years old in (3), respectively. In (1), (2) and partly in (3), a one stage CWD- obliteration technique was used. The mean follow-up times were 3.1 years in study (2) and 4.8 years in study (3). The residual and recurrence rates were 5% and 12% in (1) and 0% and 4% in (2) respectively, and in (3), the total “recholesteatoma rate” was 29 %. Silvola et al. concluded that pediatric cholesteatoma is more aggressive than adult cholesteatoma. However, the higher recurrence rate was not correlated with incomplete surgical removal, as no cholesteatomas originated from the obliterated area.

The high rate of retraction pockets (25%) in the study by Silvola et al. differed from the present study (14%), whereas this figure was not reported in the study by Sun. In the present study, silastic sheeting was used in 47 % of the pediatric cases, which might explain the difference. Preoperatively, 83 % of our pediatric patients had ear discharge due to recurrent infections. The corresponding rates in studies (2) and (3) were 100% and 55 %, respectively. At the study end, all of the ears in study (1) were dry, while study (2) reported 96 %, and study (3) reported 87%. Other authors have reported analogous results⁶⁰,⁶¹. Bony obliteration of the mastoid cavity is undoubtedly the explanation for these figures. A plausible reason for the different residual/recurrent rates could
be the number of surgeons. The results of three very experienced surgeons in study 1 were compared with the surgical outcomes of 15 young specialists in study (3). The number and experience of the surgeons were not mentioned in study (2). Another observation is the use of a transcana! approach for smaller cholesteatomas in study (3), which might have limited the surgical field. Furthermore, a retroauricular incision is preferable, and such an incision was used regularly in studies (1) and (2). Another key step in providing for dry ears is the creation of a wide meatoplasty, which was reported in studies (1) and (2) but was not mentioned in study (3).

6.5. Adult and pediatric groups

As both groups were treated with identical techniques by the same surgeons and with equal lengths of follow-up, the comparison can be considered conclusive. In contrast to other authors, we found no categorical dissimilarities. The residual and recurrence rates were similar. The number of cases of stapes erosion and chain revisions and the rates of water-resistance and infection were surprisingly less in the pediatric group. The incidence of silastic sheeting, which might reflect the severity of ET dysfunction, was unexpectedly lower in the pediatric group (47% versus 57%). This finding could also be explained by the surgeon’s decision from case to case. The use of silastic sheeting varied among the surgeons in the adult group, between 34% and 62%. The long-term evaluation of hearing displayed similar results in both groups. Pre-and postoperative hearing was certainly better in children, but it improved significantly in both groups and remained stable 1, 3 and 6 years after surgery. These results distinctly support the statement62 that the common attitude that the biology of cholesteatoma in children differs from that in adults should be reconsidered. The results also suggest that surgical technique and performance appear more important than patient age.

6.6. Influences on bone conduction

AC and BC thresholds improved after surgery and were stable 1, 3 and 6 years after surgery. The mean PTA BC hearing level was 16 dB postoperatively in the adult group. One year after treatment, it increased to 14 dB. COM and cholesteatoma are generally associated with some degree of hearing loss.63 Elevation of BC in COM is understood by some researchers to be inflammation of the inner ear.64 Walby et al.65 investigated 12 pairs of temporal bones with unilateral COM and found no evidence that COM caused destruction of hair cells or cochlear neurons. It was concluded that alteration in the mechanics of sound transmission was a more plausible explanation for the hearing losses. Lee et al.63 studied the contribution of the middle-ear mechanism to the bone
conduction response. The bone conduction response employs three different modes: the compressional mode, which leads to basilar membrane vibration; the inertial mode, in which skull vibration causes movement of the ossicular chain; and the osseotympanic mode, in which skull vibration is transmitted to the ear canal, surrounding soft tissues and tympanic membrane. The ossicular chain is not involved in the compressional mode. If the ossicular chain is ankylosed or disrupted, the inertial and osseotympanic motion contributing to the BC response is hindered. In the study of Lee et al., BC thresholds were elevated in patients with COM, similar to patients with otosclerosis. The BC threshold difference was greatest at 2 kHz (the Carhart notch). No relationship was found between an increase in BC and disease duration or the presence of cholesteatoma. The mean postoperative BC thresholds improved after ossicular reconstruction, especially after successful outcomes. This positive influence of ossiculoplasty on bone conduction provides additional support for surgical techniques involving immediate ossicular reconstruction.

The unavoidable use of drills and suction during surgery can have a negative influence on bone conduction threshold hearing levels. Surgery using TRP is characterized by extensive drilling of the mastoid. Yin et al. measured noise levels sufficient to cause sensorineural hearing loss when suction and drills were used during surgery. Noise levels ranging between 117 and 122 dB were measured during the drilling of cortical bone and the mastoid cavity. No differences were detected between cutting and diamond burrs. These levels exceeded 130 dB in the round window when the endosteal membrane was touched by the burr. Kylén et al. measured 5-10 dB lower levels on the contralateral side. The clinical relevance is still unclear, but soft surgery was generally advocated. To reduce the noise levels during surgery, the use of suction with appropriate diameters is recommended. The use of small Skeeter burrs in round window surgery, which are increasingly used for the implantation of cochlear and middle ear implants, could contribute to a lowering of injurious drill-induced noise.

6.7. Follow-up

Because cholesteatoma is a chronic disease influenced by variable ET dysfunction, close and long-term follow-up is generally advocated. The optimal length, intensity and time for the determination of long-term follow-up are unknown. Surgical techniques involving obliteration of the mastoid cavity, which provides for dry ears and which prevents recurrence, have been criticized for incurring the risk of hiding disease inside the obliterated area, rendering it impossible to uncover at the clinical examination. Based on our own experience and the experiences of other researchers, we never detected residual cholesteatoma inside the obliterated space during revision surgeries. A plethora of publications have described the beneficial application of diffusion-weighted
MRI in postoperative ears $^{52,69-71}$, mainly after CWU surgery. The experience with DW-MRI used in CWD-obliterated ears is limited due to the uncommon use of this surgical technique.

DW-MRI is a variation of conventional MRI. The underlying principles of DW-MRI are based on restriction of the Brownian motion of water molecules in pathologic tissues, such as cholesteatoma$^{72}$. This restriction provides a hyper-intense signal, which exceeds any other part of the image and which can be interpreted as a cholesteatoma or an artifact. Due to higher sensitivity and superior positive and negative predictive value, the non-EPI technique is considered more reliable than the EPI technique$^{44}$ and was therefore chosen for selecting patients for revision surgery in our study. Additionally, it is less prone to artifacts, which facilitates interpretation for less experienced radiologists, and it can detect very small lesions 1-2 mm of size. These advantages were also supported by the excellent and highly significant inter-rater agreement for the non-EPI technique, as assessed in the present study. Two clinically unsuspected cholesteatoma were detected with the non-EPI technique, one inside the obliterated space, with intracranial extension 18 years after surgery. Due to these surprising findings, we strongly recommend the use of the non-EPI technique as a screening tool during follow-up.

6.8. Active middle ear implants

Several authors have shown the benefits of AMEIs implanted into the RWN$^{73-77}$. In the present study, seven patients with chronically disabled middle ears were implanted with the Vibrant Soundbridge® into the RWN. In three of the patients, the severity of disease necessitated more extensive surgery, including blind sac closure. The positioning of the vibrating part of the implant – FMT – was assessed with CBCT, which provides for excellent imaging of the small structures of the middle ear, with a minimal radiation dose. CBCT can also be used for preoperative diagnostics in cholesteatoma surgery. Evaluation of functional outcomes is difficult after middle ear implantation in patients with no or few other options for hearing rehabilitation. Even if the fitting of CHA is difficult or impossible, functional outcomes after implantation with AMEI must be evaluated with extended follow-up durations and in comparison with conventional hearing rehabilitation. For this comparison, we used audiometric testing, including air- and bone-conduction thresholds and aided and unaided free-field speech audiometry in quiet. Because the standardized level of 65 dB was not routinely used in all cases pre- and postoperatively, the comparison might be inappropriate. Another limitation was the problematic fitting of the ear mold of the hearing aid, due to discharge in one cases and previous meatoplasty in two other cases. As mentioned earlier, a wide external meatus supports the achievement of a dry ear, but it is problematic when tight fitting of the ear mold is required. This difficult might partly explain the low speech perception
in quiet preoperatively. In addition, an aberration of results was observed by repeated free field measurements, giving rise to the question of whether the use of speech perception tests in quiet is appropriate in cases of severe hearing loss.

VSB-aided hearing was comparable to the outcomes of previous conventional rehabilitation. Functional hearing results with VSB were excellent at the highest frequencies, even in some cases in which these frequencies were immeasurable preoperatively. The lack of feedback is another advantage of this treatment. All of the study patients are daily users of the implant. For accurate evaluation of hearing rehabilitation with active middle ear implants, further studies are necessary, with larger series of patients, extended follow-ups and cost-benefit evaluations of middle ear implantation.
7. CONCLUSIONS

Based on the main findings of this study, the following conclusions were drawn.

1. The evaluated one-step canal-wall down obliteration surgical technique (TRP), using autologous materials and silastic sheeting in selected cases, is suitable for the treatment of adult patients with cholesteatoma, independent of the severity, extent and duration of disease and independent of previous surgeries.

2. Total or partial removal of the bony canal wall is a prerequisite for adequate eradication of disease. Bony obliteration of the mastoid cavity, in combination with meatoplasty, is advantageous for creating dry ears that are free of infection.

3. Immediate ossicular reconstruction improves long-term bone- and air-conducted hearing.

4. The surgical technique and surgeon’s experience seem more important than the severity and extension of the disease.

5. The evaluated surgical technique is particularly appropriate for the treatment of pediatric cholesteatoma, which is considered more aggressive and which has higher rates of residual and recurrent disease than adult cases. The long-term results were superior compared to those in adults.

6. For a correct interpretation of residual and recurrent disease and always before the determination of long-term follow-up after cholesteatoma surgery, the clinical examination should be supplemented with the use of non-EPIDW-MRI.

7. Functional outcomes with round-window vibroplasty in chronically disabled ears are comparable, and at high frequencies, the outcomes are superior to those with conventional hearing aids, even after extended and repeated surgeries.
8. FUTURE STUDIES

Further studies, based on standardized definitions of cholesteatoma classification, surgical techniques and follow-up parameters, are needed that will enable comparisons.

Further studies of the pathogenesis and biology of cholesteatoma are needed.

Further studies with larger series of patients and with extended follow-up durations are needed for the application of diffusion-weighted magnetic resonance imaging after surgery.

Further studies, with larger series of patients and with extended follow-up durations, are also necessary to evaluate and compare results after implantation with active middle ear implants and with conventional hearing aids.

Cost-utility studies should substantiate the benefits of middle ear implantation compared to both conventional hearing aids and CI.
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10. REFERENCES


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11. SVENSK SAMMANFATTNING

11.1. Bakgrund

11.2. Metodik
I denna avhandling utvärderades kirurgiska resultat och hörselresultat hos patienter med kolesteatom behandlade med en kirurgisk teknik benämnd Totalrekonstruktion, där rekonstruktion av anatomi och hörsel med patientens egen vävnad utfördes i en seans (delarbete I och II). Totalt 698 patienter opererade för kolesteatom var registrerade i ett databaserat uppföljningsprogram. Ur detta register extraherades 358 patienter med kompletta data 1, 3 och 6 år efter kirurgisk behandling för vidare utvärdering. 301 patienter (330 öron) definierades som vuxna (>12 år), 57 patienter under 12 år som barn.

I delarbete III undersökt vuxna patienter opererade för kolesteatom med Totalrekonstruktion med två olika diffusionsviktade magnetkameratekniker, ”non-EPI”- och ”EPI” teknik. Resultaten, som utvärderades av två oberoende radiologer, jämfördes sedan med resultaten av den kliniska undersökningen, som utfördes av kirurger. Patienter som upphörde positiva fynd med ”non-EPI” teknik genomgick förnyad operation för att få diagnosn verifierad.

I delarbete IV utvärderades nyttan av ett relativt nytt mellanöronimplantat, som implanteras på patienter med kronisk öronsjukdom, och som inte kunde hörsemblabiliaras med vanliga hörapparater. Hörselstörningen med mellanöronimplantat jämfördes med tidigare förstärkning av hörapparat, som patienterna burit innan implantationen. Även implantatets anatomiska läge i mel-
11.3. Resultat

Frekvensen av kvarlämnad respektive återkommande sjukdom var 3% respektive 10% hos de vuxna och 5% respektive 12% hos barnen. Före operationen besvärades en majoritet av de vuxna och barnen av infektioner och bristande vattentålighet. Sex år efter operationen var 97% av de vuxna öronen och 100% av barnens öron fria från infektion och vattentåliga. Hörseln förbättrades i båda grupperna efter operation och förblev stabil under uppföljningstiden.

Fem av sex patienter, som bedömdes som misstänkta för kolesteatom vid den kliniska undersökningen, befanns också vara positiva med ”non-EPI”-magnetkamerateknik. Ytterligare 2 patienter bedömdes som positiva med ”non-EPI-teknik” men var kliniskt negativa. Alla patienter utom en, som vägrade genomgå förnyad operation, och var positiva med ”non-EPI”- teknik var också positiva för kolesteatom vid förnyad operation. Endast 2 av de 6 patienter, som genomgick revisionsoperation, var bedömda som positiva med ”EPI-teknik”. Överensstämmelsen mellan de två radiologiska bedömnarna var mycket god för ”non-EPI-teknik” men inte för ”EPI-teknik”.

Hörselförstärkningen med mellanöronimplantat var jämförbar och i högre frekvensområden bättre än med konventionell hörapparat och oberoende av implantatets läge i runda fönstret.

11.4. Slutsatser

Kirurgisk teknik med samtidig rekonstruktion av anatomi och hörsel med patientens egen vävnad är en säker teknik som ger goda och stabila resultat oberoende av patientens ålder och om patienten är opererad tidigare. Tekniken förefaller speciellt lämpad för barn med kolesteatom. Den kliniska bedömningen av vuxna patienter opererade för kolesteatom kan förbättras med användning av diffusionsviktad ”non-EPI”-magnetkamerateknik. De patienter, som opererats för kolesteatom eller kronisk otit och inte kan bära eller har tillräcklig hjälp av vanliga hörapparater kan på ett effektivt sätt hörselrehabiliteras med mellanöronimplantat.
A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine.