Dynamic Microscopic Optical Coherence Tomography as a New Diagnostic Tool for Otitis Media

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Abstract: Hypothesis: Otitis media (OM) can be successfully visualized and diagnosed by dynamic microscopic optical coherence tomography (dmOCT). Background: OM is one of the most common infectious diseases and, according to the WHO, one of the leading health problems with high mortality in developing countries. Despite intensive research, the only definitive treatment of therapy-refractory OM for decades has been the surgical removal of inflamed tissue. Thereby, the intra-operative diagnosis is limited to the surgeon’s visual impression. Supportive imaging modalities have been little explored and have not found their way into clinical application. Finding imaging techniques capable of identifying inflamed tissue intraoperatively, therefore, is of significant clinical relevance. Methods: This work investigated a modified version of optical coherence tomography (mOCT) regarding its ability to differentiate between healthy and inflamed tissue. Despite its high resolution, the differentiation of single cells with mOCT is often impossible. A new form of mOCT termed dynamic mOCT (dmOCT) achieves cellular contrast using micro-movements within cells based on their metabolism. It was used in this study to establish correlative measurements with histology. Results: Using dmOCT, images with microscopic resolution were acquired on ex vivo tissue samples of chronic otitis media and cholesteatoma. Imaging with dmOCT allowed the visualization of specific and characteristic cellular and subcellular structures in the cross-sectional images, which can be identified only to a limited extent in native mOCT. Conclusion: We demonstrated for the first time a new marker-free visualization in otitis media based on intracellular motion using dmOCT.

Keywords: otitis media; optical coherence tomography; OCT; dynamic OCT; dmOCT; cholesteatoma; optical diagnostic; visualization; inflammation; middle ear

1. Introduction

In industrialized nations, otitis media (OM) is one of the diseases with a significantly high socio-economic burden on the healthcare system [1,2] due to an increased number of medical examinations, antibiotic prescriptions, and surgeries [3]. In developing countries, OM is a considerable health issue with a high infant mortality [1]. Chronic otitis media (COM) significantly affects the patient’s quality of life through ear discharge, hearing loss, and speech development delays and thus can result in complete deafness and dizziness [4,5]. This is even more evident in the course of a particularly aggressive form of COM, which is known as chronic otitis media epitympanalis. Untreated, it leads in most cases to a
cholesteatoma. The cholesteatoma evades antibiotic therapy and behaves like a malignant tumor through progressive inflammatory destructive processes of the middle ear and the surrounding structures [6–8].

Despite intensive research, the only definitive therapy for progressive COM and cholesteatoma for decades has been surgical treatment with a complete removal of the diseased focus [9,10].

So far, successful surgical removal of the diseased tissue is limited to the anatomical localization, extensiveness, and diffusiveness of the cholesteatoma; thereby, it represents a surgical challenge aggravated by the twisted anatomy of the middle ear and the petrous part of the temporal bone. Consequently, at worse-case scenario, it is necessary to create a radical cavity by removing the auditory ossicles, exposing the facial nerve, and sometimes even removing the inner ear and vestibular structures. This approach necessitates a comprehensive surgical procedure to gain the required overview and control in the middle ear and the petrous part of the temporal bone during surgery, entailing increased morbidity and mortality. In addition, a more prominent inflammatory component is a strong negative predictor [6] and becomes lethal when the cholesteatoma spreads to the brain tissue. Furthermore, a high tendency to recurrence of over 30% with an increased number of unreported cases has been estimated [11]. Additionally, more than 70% of patients require another ear operation within ten years, as a “second-look surgery” in order to exclude recurrences and, if necessary, to rebuild the auditory structures for a significant hearing improvement and a significant better quality of life [6]. A post-surgical lifelong state comprises clinical and radiological follow-ups, hospital stays, and potentially further surgeries. Developing new diagnostic and theragnostic surgical concepts is of urgent relevance concerning the high chronification and recurrence rate, the increased antibiotic resistance, further complication risks, and the enormous costs for the health care system. Thereby, a complete and safe resection of the middle ear pathology can only be guaranteed by the reliable in vivo identification of the destructive processes in distinction to the healthy middle ear mucosa and bone tissue. Nowadays, such distinguishing is predominantly based on the surgeons’ visual perception and experience. So far, supportive diagnostic imaging modalities have been little explored and have not found their way into clinical application. Finding imaging techniques that can identify inflamed/cholesteatoma tissue intraoperatively would present an important tool to support surgeons by identifying tissue that must be removed during surgery.

Optical coherence tomography (OCT) is a non-contact, low coherence infrared light-based scanning technique that images optical structures in biological tissue [12,13]. Like ultrasound, OCT measures the echo time delay in tissues but uses light instead of sound. Since light travels significantly faster, interferometers are used to measure the time delays. It is frequently used in ophthalmology [14] and dermatology [15]. With a spatial resolution of around 10 µm to 30 µm, it is well suited for imaging layer structures like the retina and the skin. Unfortunately, it fails to provide a sufficient resolution for visualizing cellular structures. By extending OCT with broader light sources and high numerical aperture objectives, a resolution down to 1 µm can be reached [16]. While this microscopic OCT (mOCT) provides an excellent resolution to visualize cells, the lack of contrast between cells and surrounding connective tissue inhibits cell phenotyping. Therefore, its use as in situ optical histology is limited. While there are no contrast agents available for mOCT, recently remarkable contrast enhancement was achieved by evaluating signal fluctuations based on the intracellular motion [17] induced by ATP consumption. While it was demonstrated first with full-field OCT systems [17], which are quite challenging to translate to in vivo settings, it has since been shown to be feasible with scanning microscopic OCT systems in different tissue types [16,18–20].

Here we demonstrate for the first time the use of marker-free virtual staining by dmOCT to observe multiple middle-ear diseases in their diverse pathologies.
2. Materials and Methods

2.1. Microscopic and Dynamic Microscopic OCT

The dynamic mOCT benchtop setup is shown in Figure 1 and was used previously in a similar configuration [20–22]. Broadband light with a spectral bandwidth of 360 nm centered around 750 nm, emitted from a supercontinuum (SuperK Extreme OCT, NKT Photonics, Birkerod, Denmark), is coupled into a fiber-based Michelson interferometer. The light is split into reference and sample arm by a 50:50 fiber coupler (TTW670R5A2, Thorlabs Inc., Newton, NJ, USA). The reference arm consists of a fiber collimator (60FC-L-4-M25-02, Schäffer + Kirchhoff GmbH, Hamburg, Germany), a glass substrate (Casix Inc., Fuzhou, China) for dispersion pre-compensation, an attenuator (NDC-50C-2M, Thorlabs Inc., USA), a motorized delay line, and a retroreflector, reflecting the light to its origin. In the sample arm, the light is collimated by a fiber collimator (60FC-L-4-M25-02, Schäffer + Kirchhoff GmbH, Hamburg, Germany) before being deflected by a galvanometer scanner (6210 H, Cambridge Technology, Kansas City, KS, USA) configuration consisting of a 4f optic to achieve a single pivot-point scanner and thus avoid field curvature in the OCT image. Then, the beam is enlarged by a telescope (SL50-CLS2 and TL200-CLS2, Thorlabs Inc., USA), before focusing on the sample with a 0.3 numerical aperture microscope objective (HCX APO L 10×/0.3 WUVI, Leica Microsystems, Wetzlar, Germany) providing a lateral resolution of 1.5 µm. The light traveling back from both arms is recombined in the fiber-coupler prior to interference at the high-speed spectrometer. The customized spectrometer with a spectral bandwidth of 360 nm centered around 750 nm can acquire up to 248 k A-scans (depth scans) per second, with an axial resolution of better than 1.5 µm. The average irradiance at the sample is 40 µW.

![Schematic drawing of the mOCT setup showing the various components used for scanning and data acquisition.](image)

**Figure 1.** Schematic drawing of the mOCT setup showing the various components used for scanning and data acquisition. The setup includes a 50/50 fiber coupler (FC), collimators (C1/C2), galvanometer mirror scanners (XY scanner), beam expander lenses (L1, L2), a microscope objective (L3), dispersion compensation (DC), a retroreflector (RR), a data acquisition device (DAQ), and a computer (PC) for scanning control and data processing.

2.2. Data Acquisition and Processing

The dynamic mOCT volumes were acquired and processed as described in Kohlfäerber et al. [20]. A dynamic mOCT volume consisting of $512 \times 512 \times 1024$ pixels covering a lateral FOV (field of view) of $0.5 \times 0.5$ mm$^2$ and an axial depth of 890 µm was recorded with an A-scan rate of 100 kHz. A volume was acquired by taking 150 repetitive B-scans (cross-sectional view) at each cross-sectional scan position with a B-scan acquisition rate of 111 Hz (taking 1.35 s), thus the total volume acquisition time for 512 scan lines accounts for 11.52 min. MATLAB (MATLAB R2019b, The MathWorks, Inc., Natick, MA, USA) was used for the spectral processing and dynamic contrast enhancement of the data. The spectrometer’s raw data were linearized, Hann-windowed, and Fourier-transformed to generate the OCT images. Numerical compensation for residual dispersion was performed.
using a fifth-order polynomial to correct the spectral phase error. The coefficients of the polynomial were determined by optimizing image quality, assessed by the Shannon entropy measurement. Intracellular motion resulting in signal fluctuations was analyzed in a frequency range of up to 55.5 Hz by temporal Fourier transformation and summing up the integral amplitudes in three bands. Each channel was then normalized from 0 to 1. Next, a moving standard deviation image was generated with a window width of 25 images, and the histogram of each channel was matched to this image. The three frequency bands were stacked together into an RGB image where fast fluctuations (4.9–25 Hz) are coded in the red channel, medium motion (0.4–4.9 Hz) in the green channel and slow motion (<0.4 Hz) in the blue channel. The three frequency bands are based on an early work using FF-OCT [23] and matching well-known frequencies of intracellular motion [24]. ImageJ/Fiji (ImageJ-win64) was used for analyzing and visualizing the data.

2.3. Study Design and Experimental Strategy

Diverse physiological and pathological tissue samples of the middle ear were obtained from 12 patients who had undergone otologic surgery at the Otorhinolaryngology department of the University Medical Center Schleswig-Holstein in Lübeck (Germany). Eight patients were diagnosed clinically and radiologically with COM or cholesteatoma. Moreover, tissue of these pathologies was sent and evaluated by our pathologists according to the standard procedure during ear surgery. Healthy middle ear tissue from four patients was collected from a tympanoplasty and three cochlear implantations.

Different human tissue samples from the region of interest were surgically obtained and collected to simulate a situation similar to an optical biopsy during middle ear surgery due to progressive otitis media and cholesteatoma. Ex vivo examinations of tissue probes were carried out employing a prototype of a dynamic mOCT device. The acquired and reconstructed images were correlated with standard histological staining of the examined tissue.

2.4. Human Tissue Sample Collection

The extracted human tissue samples were stored immediately in 0.9% NaCl solution and promptly investigated. The samples were placed in a sample holder and sealed with a cover glass before being placed under the dynamic mOCT. The ethics committee of the University of Lübeck approved all protocols (22-041). All clinical examinations were performed according to the highest ethical standards and principles of the Declaration of Helsinki (1964).

2.5. Histology

Immediately after image acquisition, the middle ear tissue samples were fixed and embedded in 4% paraformaldehyde, washed in PBS, and cryoprotected using 20% sucrose in PBS. Tissue was snap frozen in liquid nitrogen and stored at −20 °C to ensure tissue preservation until further processing. Later, 10 µm thick cryo-sections were cut and mounted on slides. The sections were stained with hematoxylin–eosin (H&E) for microscopical morphological tissue inspection.

3. Results

Using our microscopic optical coherence tomography imaging setup in Figure 2, we gained high-resolution images of living tissues, giving a good impression of the general morphology.
As shown in Figure 2, we can distinguish between the tissue, which was taken out during surgery from a patient suffering from chronic otitis media (Figure 2a) and from a patient suffering from cholesteatoma (Figure 2b). The different cells and tissue types are challenging to differentiate in the traditional mOCT images of otitis media mesotympanalis (a) and cholesteatoma (b). The dynamic mOCT empowers a significant increase in contrast, so that even individual cell types and tissue regions in the otitis media (c) as well as in the cholesteatoma (d) are visible.

Thereby, otitis media is characterized by a largely homogeneous scattering on mOCT images (left part of the panel). In this context, using mOCT, structural differences or individual cells are difficult to observe in chronic otitis media (Figure 2a), even though in cholesteatoma at least some individual cells can be distinguished in the extracellular matrix. However, the specific cells and tissue types between the tissue are challenging to differentiate and often impossible to see in the mOCT images. With the dynamic mOCT (right part of the panel), based on the evaluation of intracellular movements, it is possible to increase the contrast significantly.

Different tissue areas and cells can be identified in both chronic otitis media (Figure 2c), showing different tissue textures by cell movement depicted in green, yellow, and red and in cholesteatoma (Figure 2d), showing decreased intracellular movement depicted in blue-purple.

Imaging via dynamic mOCT allows high-resolution imaging of living tissues to be obtained. This allows the differentiation of various middle ear pathologies that differ morphologically (Figure 3a), like an epitympanic polyp (Figure 3b), a cholesteatoma (Figure 3c), and a normal middle ear mucosa (Figure 3d).
The cholesteatoma with its keratin-accumulated cells appears blue in the dynamic mOCT (5–25 Hz), green—medium movements (0.5–5 Hz), and blue—slow motion frequencies (0–0.5 Hz)).

The volumetric representation enables a more detailed view of a non-inflamed cholesteatoma (Figure 4). The dynamic mOCT empowers the visualization of specific and characteristic cellular and subcellular structures in the 3D cross-sectional images (Figure 4a). The cholesteatoma with its keratin-accumulated cells appears blue in the dynamic mOCT image, indicating that there is no intracellular motion detectable, which is in line with the presence of large amounts of aggregated keratin, absent or sparse organelles, and the absence of a nucleus. The top view (Figure 4b) clearly shows the irregular structure of the flat keratinized cells from above, which appear as bluish areas. Besides the cellular structures, small green spots are visible singularly and accumulated.

While we know that these are particles in the surrounding media and on top of the cholesteatoma, we cannot prove if these are cells, bacteria, or debris due to tissue removal.
The B-Scan with lamellar sheets of keratin (Figure 4c) shows low activity with a high structural similarity to the direct comparison with the histological section (Figure 4d).

Using dynamic mOCT for imaging an epitympanic polyp of a clinically diagnosed cholesteatoma provides a similar level of detail compared to the histological image (Figure 5). From the acquired 3D volume (Figure 5a), four en face planes are presented (Figure 5b–e). The upper cell layer consists of epithelial cells, which, in contrast to the investigated cholesteatoma in Figure 3, still have intracellular motion indicating cell metabolism (Figure 5b). While the peri-matrix area is depicted in the green channel, the matrix is visible in the blue channel showing little scatterer movements. In a direct comparison of the dynamic mOCT scan with histology of the same tissue (Figure 5g), the matrix (upper level including stratified squamous epithelium with keratinization) and the peri-matrix (lower level including connective tissue and immune cells), can be identified, as we know from cholesteatoma.

In Figure 5b, bright green cells are visible. Based on the results of our previous work by Kohlfaerber et al. [20] and the fact that they are present in all layers, we can assume that these are immune cells that have migrated into the epithelium. The following en face plane (Figure 5c) cuts through the epithelium, the lamia propria, as well as the connective tissue.
tissue. The fibrous structure in the lamia propria appears blue, indicating little activity of this tissue.

Taking a closer look at the connective tissue, it appears as a cell-rich layer (Figure 5d). In addition to the immune cells, which appear as green dots, numerous different cell types of the connective tissue, most likely, fibroblasts, macrophages, and mast cells can be seen.

Moving the en face plane further away from the epithelium, we can see that the connective tissue becomes increasingly difficult to discriminate (Figure 5e). However, despite being far from the optical focus, dynamic mOCT still allows us to obtain information such as the presence of inflammatory cells.

This is even more evident in the cross-sectional image of the epitympanic polyp (Figure 5f), showing the epithelium displays stratified squamous epithelium (matrix) in the upper part of the image. Here, the dynamic mOCT B-scan of the epitympanic polyp shows distinct tissue layers of keratin, matrix, and peri-matrix, equally to our corresponding histological image (Figure 5g). Although the polyp looks macroscopically more like inflamed mucosal middle ear tissue (Figure 5b) than a non-inflamed cholesteatoma (Figure 5c), we do see by dynamic mOCT and by histology characteristic images of both inflammation and cholesteatoma, what we know from established histological pictures of inflammatory attached triggered cholesteatomas.

While the histological image provides only static information, such as cell morphology, dynamic mOCT can also visualize long-timescale dynamics like cell migration. To demonstrate this, we acquired cross-sectional images at the same position over 10 min every 10 s (Figure 5f), following a modified imaging protocol of our previous work [20], which allowed the evaluation of the time series to track individual cells over time. In the supplemented video to Figure 5f, when zoomed in, it can be observed that a single cell moves upward and eventually disappears while the surrounding tissue remains unchanged.

4. Discussion

Well known from the microscopic view during surgery, a cholesteatoma may present with white keratin layers surrounded by inflammatory tissue, representing different cells and tissue types of the matrix and peri-matrix. Thereby, the cholesteatoma varies from showing characteristics of minor to high inflammation, which are reflected in the presence or absence of inflammatory cells [25–29].

The identification of the entire cholesteatoma and its complete and residue-free removal poses a significant challenge, as it is crucial to avoid subsequent revision surgeries. So far, there are only a few imaging approaches for the localization of cholesteatoma in situ that go beyond the use of conventional surgical imaging methods.

Early et al., investigated photosensitizer immunoconjugate (PIC) cetuximab benzoporphyrin derivative (Cet-BPD) for intraoperative localization of human cholesteatoma tissue and examined its potential in an animal study [30]. Although the results are promising, the ototoxicity of Cet-BPD in humans is not clear, and side effects such as skin rash are common. Another approach pursued by various research groups is the use of classical OCT. They were able to show that clinically distinct cholesteatomas can be identified based on the appearance of a greater signal intensity of the cholestatoma compared with the lower grayscale values of the mucosa [31]. They could only show that clinically distinct cholesematomas can be identified based on the appearance of a larger signal intensity of the cholestatoma compared with the lower grayscale values of the mucosa. Differentiation of moderately inflamed tissue from normal mucosa was not possible, and the resolution was not high enough to see individual cells. In contrast, dynamic OCT does not require external markers and uses harmless near-infrared light and intracellular motion to provide virtual coloration.

In this study, we could illustrate striking differences in dynamic mOCT images in otitis media mesotympanalis, and otitis media epitympanalis (cholesteatoma), including an epitympanic polyp, regarding tissue structures, subcellular structures, and the appearance of individual cells using temporal fluctuations of the light scattering structures. This is a
main diagnostic advancement in comparison to studies using conventional/commercial OCT imaging systems in otitis media [32–34].

OCT is based on light scattering by subcellular and sub-resolution structures in biological tissues. Whereas layered structures and borders of tissue compartments with different average scattering can be visualized by OCT, even at high resolution it is difficult to discriminate cellular and subcellular structures. However, a greatly increased cellular contrast was achieved by evaluating the intracellular movement of the different scatterers and displaying the fluctuation frequencies in three frequency bands, where slow movements were coded in blue, medium movements in green, and fast movements in red [20]. Active cells, such as epithelium or inflammatory cells were displayed in the green and red channels. In contrast, inactive tissue structures such as keratinized cells in cholesteatoma, the fibrous structures in the connective tissue, or the extracellular matrix were displayed in blue. Although the biological origin of dynamic mOCT is not entirely understood, in this work it is a reasonable assumption that scattering fluctuations are influenced by cellular metabolism.

Using our new dynamic mOCT imaging modality, we demonstrated 3D marker-free images of a characteristic less inflamed cholesteatoma pathology. The images not only showed in the cholesteatoma keratin accumulating cells in white or blue but allowed us to evaluate overlying layers of keratin in an entire texture en face and in B-scan as a mesh, showing little detectable intracellular scatterer movement with less nuclei or organelles. These findings are supported by our histologic studies and by others [25].

In this context, especially the observed difference between the cholesteatoma and the epitympanic polyp is of great interest since we know these polyps are named “signal polyps” of a cholesteatoma, often hidden behind a defect tympanum. In clinical practice, this belongs to one of the otoscopic signs of a possible cholesteatoma, even if the patient presents without perforation, white keratin mass in the epitympanic part, or other symptoms, such as otorrhea, hearing loss, or dizziness [9,35].

Microscopically and macroscopically, the tissue looks like a regular inflamed mucosal polyp of otitis media mesotympanalis. Using 3D imaging with dynamic mOCT, it seems feasible to discriminate the epitympanic polyp from classical inflamed tissue.

Interestingly, the polyp seems to trigger the cholesteatoma growth via inflammation, which can be followed by dmOCT as we can see in the surrounding tissue multiple migrated cells, which most likely are immune cells that have migrated into the epithelium, accordingly to our previous results [20]. We underline this theory since we discovered a live cell movement in the peri-matrix. Furthermore, this was assessed by the clinical histopathological evaluation, revealing stacks of keratin and epithelial cells decomposed with immune and inflammatory cells corresponding to the picture of a medium to high-grade inflammatory cholesteatoma. Several studies associate the interaction of the immune system with the cholesteatoma [6,25–29,36] and even specifically target innate immunoregulatory events [37]. Unfortunately, to date, there are no markers for OCT, which are able to label specific immune cells. For evaluating and detecting specific otitis media and cholesteatoma markers in dynamic mOCT compared to H&E staining, further studies with a higher number of tissue samples and quantitative analysis need to be performed and are under ongoing investigation.

Compared to classical OCT, dynamic mOCT provides a much higher information content, which is essential for a reliable diagnosis. While histology also provides this information, it is laborious and time-consuming because the tissue must be sectioned and stained before being observed under a microscope; dynamic mOCT provides dynamic optical sections within a little more than a second. In addition, the tissue does not need to be stained to achieve sufficient contrast to evaluate tissue morphology. Therefore, dynamic mOCT holds the potential to be used to quickly assess excised tissue in the operating theatre without the need for frozen sections.

In addition, dynamic mOCT can also be used to observe cell migration. In contrast to other imaging techniques able to visualize the cellular movement, such as fluorescence
or multiphoton microscopy, dynamic mOCT does not need extra staining, as is the case for fluorescence microscopy. Furthermore, since dynamic mOCT uses low-intensity near-infrared light, the potential danger of tissue destruction is vastly reduced compared to autofluorescence-based multiphoton microscopy \cite{38,39}, which uses high-energy pulses to achieve the two-photon effect necessary for imaging.

With dynamic mOCT, we so far only measured excised tissue, which is susceptible to potential changes in intracellular motion due to a decrease of the metabolism. However, in both longitudinal measurements and volumetric scans, we did not observe any alterations in coloration despite measurement times of up to 30 min. We therefore expect to be able to achieve similar results in vivo.

Before dynamic mOCT can be used in vivo, technical solutions and advanced image registration methods must be developed to reduce susceptibility to global motion. One promising approach is to perform dynamic mOCT calculations on volumes instead of single B-scans since registration can be carried out in all three dimensions \cite{21}. After solving the current challenges of combining dynamic mOCT with mOCT endoscopy \cite{40}, the technology has a high potential for intra-operative assessment of the middle ear tissue during surgery.

5. Conclusions

We were able to demonstrate a marker-free contrast mechanism in the middle ear based on cellular metabolism by exploiting temporal fluctuations of the interferometric signals of dynamic mOCT. These data demonstrate the usefulness of dynamic mOCT in assessing different pathologies of middle ear diseases. Moreover, it opens up an outstanding possibility to study various processes in the middle ear, such as the movement of immune cells, which goes beyond pure morphology such as 3D real-time histology. The technology is promising, supportive of imaging modality, and can potentially increase intra-operative precision during and after otitis media surgery in the future.


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Data Availability Statement: The data represented in this study are available on request from the corresponding author.

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