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OTOLOGY

Diagnostic value of cone-beam CT in histologically confirmed otosclerosis

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Abstract This retrospective case review was performed with the aim to asses the value of cone-beam computed tomography (CBCT) in the preoperative diagnosis of otosclerosis. A total of 32 patients with histologically confirmed stapedial otosclerosis, who underwent unilateral stapedectomies were analyzed. Preoperative temporal bone CBCT scans were performed in all cases. CBCT imaging was characterized by a slice thickness of 0.3 mm and multiplanar image reconstruction. Histopathologic examination of the removed stapes footplates was performed in all cases. Findings of CBCT were categorized according to Marshall's grading system (from grade 0 to grade 3). Histopathologic results were correlated to multiplanar reconstructed CBCT scans, respectively. Histologically active foci of otosclerosis ($n = 21$) were identified by CBCT in all cases with a sensitivity of 100 %. However, CBCT was unable to detect histologically inactive otosclerosis ($n = 11$, sensitivity = 0 %). According to CBCT scans, no retrofenestral lesions were found and all positive cases were recruited into the grade 1 group indicating solely fenestral lesions at the anterior pole of stapes footplates. In conclusion, CBCT is a reliable imaging method with considerably lower radiation dose than high-resolution CT (HRCT) in the preoperative diagnosis of otosclerosis. These results indicate that CBCT has high sensitivity and specificity in the detection of hypodense lesions due to histologically active otosclerosis.

Keywords Cone-beam computed tomography · Hearing loss · Histopathology · Otosclerosis

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Introduction

Otosclerosis is a unique bone dyscrasia of the human otic capsule that is characterized by pathologically increased new bone formation [1]. Aberrant bone apposition in otosclerosis can result in conductive and sensorineural hearing loss due to stapes footplate fixation and pericochlear bone resorption [1, 2]. Hearing loss due to otosclerosis is usually bilateral, which has profound effects on quality of life. Fenestral otosclerosis is caused by otosclerotic foci located at the fissula ante fenestram, which is a small connective tissue island in the enchondral layer of the otic capsule between the oval window and the cochleariform process [3]. Retrofenestral otosclerosis usually leads to sensorineural hearing loss due to morphological changes in the modiolus and in the pericochlear bone resulting in decreased elasticity of the spiral ligament [1, 4]. Several proinflammatory cytokines (TNF-alpha, TGF-beta, RANK, RANKL, BMP) may play a potential role in the pathogenesis of otosclerosis-associated sensorineural hearing loss [4].

In the Caucasian white population, the prevalence of clinical otosclerosis is approximately 0.3–0.4 % of the general population [1]. Histologic otosclerosis without clinical symptoms is much more common that has been reported as 8–11 % in large unselected autopsy series [5]. Otosclerosis makes up approximatley two-third of stapes fixation cases that result in conductive hearing loss [6]. Clinical diagnosis of stapes fixation is based on progressive hearing loss, normal otoscopic findings, negative Rinne's test, conductive or mixed hearing loss, As-type tympanograms and increased resonance frequency (>1,100 Hz) confirmed by multifrequency tympanometry [1, 4, 5]. At this time, exact diagnosis of otosclerosis is still based on postoperative histopathologic analysis of the removed stapes footplates [6, 7].

Modern imaging techniques introduced new insights into the preoperative evaluation of various osseous disorders of the human temporal bone, which have been confirmed by several studies in stapes fixation [8–11]. Preoperative detection of otosclerosis-like hypodense foci has great clinical significance, since it might correspond to the severity and progression of hearing loss [12–14]. Positive imaging findings might serve as real prognostic factors in the assessment of surgical success rates according to the extension and location of hypodense lesions [16–18]. At this time, high-resolution computed tomography (HRCT) is the first imaging method of choice in the evaluation of structural disorders in the human temporal bone in cases of conductive and mixed hearing loss with normal tympanic membranes [11, 18, 19]. Since conventional HRCT has 0.3–0.5 mm power of resolution, it could detect very fine architectural changes in the otic capsule and can serve as an important tool in the differential diagnosis of various middle and inner ear diseases [19]. HRCT has 70.5 up to 84.2 % sensitivity levels in the detection of otosclerosis-like hypodense lesions in the otic capsule [11, 14, 18]. HRCT has been reported to have 100 % specificity values in case of histologically confirmed stapedial otosclerosis that was independent from the histopathologic activity of otosclerotic foci [18].

Cone-beam computed tomography (CBCT) is a relatively new imaging method that is widely used in the fields of endodontics and orthodontics, respectively [20, 21]. The diagnostic capability of CBCT is continuously developing due to the advent of more precise and higher resolution CT techniques and new analyzer softwares [20, 21]. During a CBCT scan, the single scanner and the detector rotate around the patient's head working with a cone-shaped X-ray source that result in up to 1,200 distinct images [21]. The specialized scanning software collects data and produces a digital volume that can be reconstructed as three-dimensional voxels containing axial, coronal and sagittal dimensions [21]. The emitted X-ray dose of CBCT is about 1 % of the conventional temporal bone HRCT scans [9, 10, 21]. The scanning procedure (20–40 s) and the reconstruction time (2 min) are significantly shorter than those in HRCT [10, 21]. There is only one paper in the literature that assessed the use of CBCT in the diagnosis of otosclerosis [22]. In their prospective study, Redfors et al. [22] have compared the diagnostic values of CBCT and HRCT in patients with otosclerosis, who underwent stapedectomy 30 years ago. Authors have reported that CBCT is a valuable and robust imaging method for the detection of otosclerosis-like hypodense lesions in the otic capsule, which is equivalent to HRCT in many ways [22].

There is no widely accepted grading system in the assessment of severity and extension of otosclerosis in the otic capsule [8, 18]. Furthermore, all grading systems were optimized for HRCT findings [23–25]. Valvassori [15] proposed a grading system for cochlear otosclerosis based on the size and location of hypodense foci. Shin et al. [13] reported a location-based classification for otosclerosis distinguishing fenestral and retrofenestral groups. Kiyomizu et al. [17] classified the lesions into five groups that concentrate to the severity of fenestral involvement. Rotteveel et al. [23] introduced the terms of 'double ring effect', 'narrowed cochlear turns' and 'aberrant channels'. Marshall et al. and Lee et al. [24, 25] proposed a clinically valuable grading system for cochlear implantation in otosclerosis, which rates fenestral and cochlear lesions together.

Present study investigates the correlations between CBCT scans and postoperative histopathologic findings in patients with stapes ankylosis to assess the role of CBCT in the preoperative diagnosis of otosclerosis.

Materials and methods

Patients

From March 2012 until April 2013, 102 temporal bone CBCT scans were performed. The indications for CT examination were conductive or mixed hearing loss with normal tympanic membranes in all cases. Finally, 32 patients (64 ears) with stapes ankylosis were included in the study, who underwent stapedectomy with postoperative histopathologic analysis of the removed stapes footplates. The study group consisted of 24 females and 8 males (female/male ratio 3.0). The mean age of patients was 32.57 years (range 26–53 years). The diagnosis of stapes fixation was based on clinical, audiometric, tympanometric and CBCT findings. Indication for stapes surgery was based on 30 dB air-bone gap at 1,000 Hz on pure-tone audiometry and negative Rinne's test on the affected ear. Preoperative tympanometry revealed type-As

tympanograms in 41 ears (64.06 %) and type-A tympanograms in 23 ears (35.94 %). In the operated ear group ($n = 32$), 27 ears (84.37 %) had type-As tympanograms, while in the contralateral ear group ($n = 32$), 14 ears were characterized by type-As tympanograms (43.75 %). Multifrequency tympanometry (MFT) was performed in all ears that revealed 1,100 Hz or higher resonance frequency in 27 ears (84.37 %) in the stapedectomy group and in 15 ears (46.87 %) in the contralateral ear group. Stapes fixation was clinically bilateral in fifteen patients ($n = 15$, 46.87 %); however, only one stapes obtained from each patient was analyzed, because over this period, only unilateral stapes surgeries have been performed. Partially removed stapes footplates were not included in the study, because of the anterior or posterior poles containing the bone lesions fixing the stapes were retained in the oval window niche. Fragmented and reconstructed footplates that could be fully reconstructed during the histologic embedding, however, were not excluded. Stapes footplates were collected from April 2012 until May 2013 (University of Debrecen, Medical and Health Science Center, Department of Otolaryngology and Head and Neck Surgery, Debrecen, Hungary). All patients gave their informed and written consents for our study. The Hungarian Scientific Research Ethical Committee (ETT-TUKEB 84-227/2008-1018EKU) approved this study. The study was carried out according to the Declaration of Helsinki.

Cone-beam computed tomography (CBCT) scans and image review

Cone-beam computed tomography scans of the temporal bone were performed by a multi-slice CBCT scanner (Iluma, GE Healthcare, Milwaukee, WI, USA) with 0.4 mm section thickness by axial, sagittal and coronal imaging. All examinations were performed without contrast material and imaging included the entire temporal bone. The neuroradiologist involved in this study was certified by the Hungarian Board of Radiology (HBR) in diagnostic radiology and had completed a 6-year neuroradiology fellowship and was eligible for a HBR neuroradiology certificate of advanced qualification. All images were reviewed by the last author (T.K.) with 64 agreements (100 %) of the 64 scans. CBCT scans were evaluated by the grading system of Marshall et al.: grade 0, is no manifest sign for hypodense lesion in the otic capsule; grade 1, is solely fenestral lesion and/or thickened stapes footplate; grade 2a, is manifest or missing fenestral involvement with hypodense lesion in the basal cochlear turn; grade 2b, is manifest or missing fenestral involvement with hypodense lesion in the apical cochlear turn; grade 2c, is manifest or missing fenestral involvement with both apical and basal cochlear turn lesions; grade 3, is diffuse or confluent involvement of the entire otic capsule [24].

Histopathologic analysis

A total of 32 ankylotic stapes footplates were fixed in 10 % (w/v) buffered formaldehyde and decalcified in 0.5 M Na-EDTA (sodium ethylene-diamino-tetraacetate, 72 h, 4 °C) containing 0.02 % (w/v) sodium azide. Specimens were embedded in 15 % (w/v) purified gelatin (24 h, 56 °C) and refixed in 4 % (w/v) paraformaldehyde (24 h, 20 °C). Gelatin blocks were cryoprotected in 20 % (w/v) sucrose solution (2 h, 4 °C) and sectioned into 10 µm slides at −25 °C (MNT-200, Slee, Mainz, Germany). Slides were stored in 0.1 M PBS (phosphate-buffered saline) containing 0.03 % (w/v) sodium azide at 4 °C. Sections were processed to conventional hematoxylin and eosin (H.E.) staining. It should be noted that otosclerosis is a multifocal disease; therefore, histopathologic activity of a stapedial otosclerotic focus is not in full correspondence with the clinical activity of otosclerosis. We used the following histopathologic criteria for the diagnosis of otosclerosis: (1) active otosclerosis is displayed by wide pseudovascular spaces filled with increased numbers of large, misshapen and multinucleated osteoclasts. Cement lines show a woven pattern; (2) inactive otosclerosis is marked by obliterated or empty vascular spaces and resorption lacunae with decreased numbers of osteoclasts (empty halo cells). Cement lines show a lamellar pattern. P.Cs., who was blinded for the results of CBCT scans of the temporal bones, reviewed the histopathologic sections. Statistical assessments were performed by Mann–Whitney's U probe with a 95 % confidence interval (SPSS 9.0 for Windows).

Results

Ankylotic stapes footplates ($n = 32$) removed by stapedectomy were analyzed through conventional H.E. staining, respectively. Histopathologic results were correlated to the preoperative CBCT scans and the audiometric findings (Tables 1, 2). Histologic diagnosis of otosclerosis was established in all ankylotic stapes footplates (Figs. 1, 2). Otosclerotic stapes footplates were affected by single otosclerotic foci. Among these specimens, foci of otosclerosis were considered to be active in 21 stapes footplates and inactive in 11 cases (Figs. 1, 2). The localization of otosclerotic foci differed among the 32 ears with manifest involvement of the stapes footplate by otosclerosis at the anterior pole ($n = 28$) or obliteration ($n = 4$) of the oval window niche. During the further analysis, ears were divided into three groups: (1) active otosclerosis ($n = 21$);

Table 1 Preoperative cone-beam computed tomography findings in otosclerosis correlated to audiologic data

Histology of the ankylotic stapes ($n = 32$)	Temporal bone CBCT[a] ($n = 32$)				Sensitivity[b] (%)	Specificity[c] (%)	ABG[d] (0.5–1–2 kHz) (dB)	BC[e] (0.5–1–2 kHz) (dB)
	Positive findings[f]			Negative findings[g]				
	Oval window niche	Round window	Pericochlear					
Otosclerosis ($n = 32$, 100 %)	21	0	0	11	65.62	100	22.4	7.3
Active ($n = 21$, 65.6 %)	21	0	0	0	100	100	17.9	6.8
Inactive ($n = 11$, 34.4 %)	0	0	0	11	0	0	36.1	8.5

[a] Cone-beam computed tomography

[b] Sensitivity of CBCT correlated to histopathologic confirmation of otosclerosis

[c] Specificity of CBCT correlated to histopathologic confirmation of otosclerosis

[d] Air-bone gap average at 0.5–1–2 kHz frequencies

[e] Bone conduction average at 0.5–1–2 kHz frequencies

[f] Hypodensity detected in the otic capsule

[g] No hypodensity detected in the otic capsule

Table 2 Preoperative cone-beam computed tomography grades in otosclerosis and in contralateral ears correlated to audiologic data

CBCT grades[a]						
	0	1	2a	2b	2c	3
Active otosclerosis ($n = 21$)	0	21	0	0	0	0
ABG (0.5–1–2 kHz)[b]	n.a	17.9 dB	n.a.	n.a	n.a	n.a.
BC (0.5–1–2 kHz)[c]	n.a.	6.8 dB	n.a.	n.a.	n.a.	n.a.
Inactive otosclerosis ($n = 11$)	11	0	0	0	0	0
ABG (0.5–1–2 kHz)	36.1 dB	n.a	n.a	n.a	n.a	n.a.
BC (0.5–1–2 kHz)	8.5 dB	n.a.	n.a.	n.a.	n.a.	n.a.
Contralateral ears ($n = 32$)	14	18	0	0	0	0
ABG (0.5–1–2 kHz)	12.4 dB	15.8 dB	n.a	n.a	n.a	n.a
BC (0.5–1–2 kHz)	5.1 dB	5.7 dB	n.a.	n.a.	n.a.	n.a.

n.a. not available

[a] Marshall's HRCT grading system: grade 0, no sign for focal hypodensity; grade 1, solely fenestral lesion or thickened stapes footplate; grade 2a, hypodense focus in the basal cochlear turn; grade 2b, hypodense focus in the middle/apical cochlear turn; grade 2c, hypodense focus in both basal and apical turns; grade 3, diffuse involvement of the cochlea

[b] Air-bone gap average at 0.5–1–2 kHz frequencies

[c] Bone conduction average at 0.5–1–2 kHz frequencies

(2) inactive otosclerosis ($n = 11$); and (3) contralateral ears ($n = 32$) without histopathologic findings.

Preoperative audiometric findings revealed 22.4 dB ABG and 7.3 dB BC levels at the averages of 0.5–1–2 kHz frequencies in all otosclerotic ears (Table 1). Histologically active otosclerosis was characterized by 17.9 dB ABG and 6.8 dB BC levels at the averages of 0.5–1–2 kHz frequencies (Table 1). In contrast, inactive otosclerosis was characterized by 36.1 dB ABG and 8.5 dB BC levels at the averages of the previous frequencies (Table 1). According to these results, both histologically active and inactive cases of otosclerosis displayed pure conductive hearing loss (Table 1). In the contralateral ear group ($n = 32$) of patients with histologically confirmed otosclerosis, audiologic examinations revealed 15 positive findings for conductive hearing loss (Table 2). In this group of ears, ABG at 1,000 Hz frequency was larger than 20 dB in 13 cases (Table 2). According to the audiometric findings, otosclerosis was bilateral in 15 patients (46.87 %). There was a statistically significant association between the histopathologic activity of otosclerosis and ABG averages at 0.5–1–2 kHz frequencies ($p < 0.05$, Mann–Whitney's U probe). In contrast, no statistically significant association was found with BC averages in the two histopathologic groups of otosclerosis.

Among the ears with otosclerosis ($n = 32$), CBCT revealed 21 positive findings indicating a sensitivity for otosclerosis as 65.62 % (Table 1). In the active otosclerosis group ($n = 21$), the sensitivity of CBCT for otosclerosis increased to 100 %, while in case of inactive otosclerosis ($n = 11$), sensitivity levels decreased to 0 % (Table 1). In the contralateral ear group of otosclerotic patients ($n = 32$), CBCT was positive in 18 ears (56.25 %) with unknown sensitivity levels due to the lack of histologic analysis (Table 2). According to CBCT findings, otosclerosis was bilateral in 18 patients (56.25 %), which was higher than those that revealed by preoperative audiometric estimation findings (46.87 %). According to the Marshall's grading system for otosclerosis, the non-operated ears of patients with otosclerosis varied between grades 0 and 1, where 43.7 % of ears belonged to the grade 0 group (Table 2). In active otosclerosis, 100 % of ears were classified as grade 1 indicating solely fenestral otosclerosis (Fig. 1; Table 2). In case of inactive otosclerosis, all ears

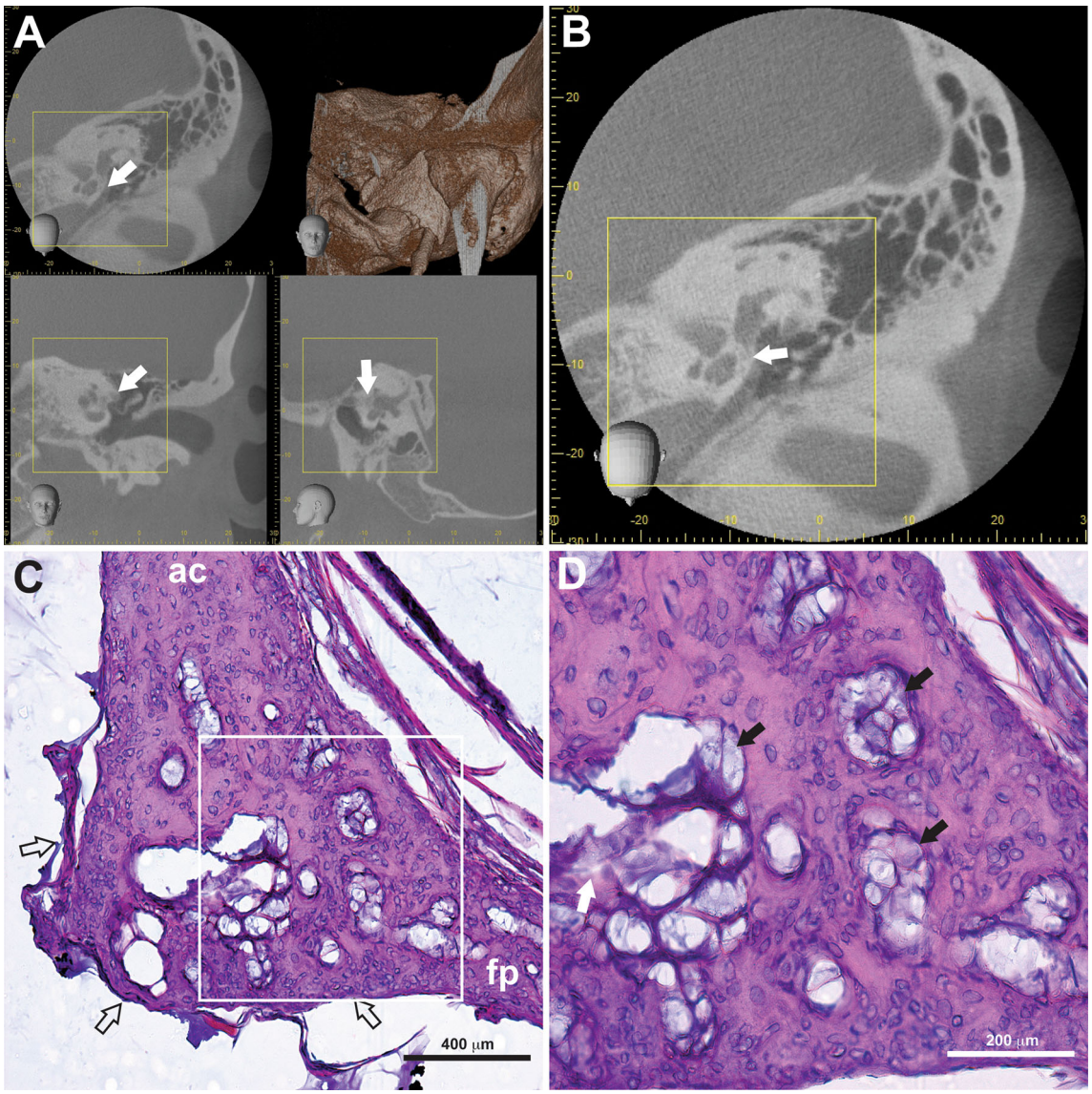

Fig. 1 CBCT scans in histologically active otosclerosis (*left* ear). **a** Axial, coronal and sagittal reconstructions of CBCT images. *White arrows* indicate a hypodense lesion at the anterior part of the oval window niche. *Yellow rectangles* show the region of interest (ROI). The *upper right insert* represents a three-dimensional reconstruction of volume rendering. **b** A single grade 1 otosclerotic focus at the anterior pole of the stapes footplate (axial reconstruction, *white arrow*). **c** Active otosclerotic lesion at the anterior pole of the stapes footplate (H.E.). *White arrows* indicate destructed hyaline cartilage layer at the vestibular surface of the stapes footplate. *ac* anterior crus, *fp* stapes footplate. **d** Higher magnification view of the previous section. Active otosclerosis is characterized by hypercellular osteoid substance and large pseudovascular spaces filled with hyaline content (*black arrows*). A multinucleated osteoclast is also present (*white arrow*)

(100 %) were presented as grade 0 otosclerosis (Fig. 2; Table 2). We have found a statistically significant and inverse association between the CBCT grades and ABG averages in ears with active or inactive otosclerosis ($p < 0.001$, Mann–Whitney's U probe) (Table 2). However, it could not be confirmed in the contralateral ear group (Table 2). On the contrary, CBCT grades did not present statistically significant association with BC averages in the group of ears with different histopathologic activities of otosclerosis (Table 2).

Discussion

In the present study, we demonstrated associations between CBCT scans and audiometric findings in patients with histologically confirmed otosclerosis. The weakness of our study is the relatively low number of subjects, which should be increased in the future to obtain more precise statistical correlations. This project is a comprehensive imaging and histologic study that is able to approximate the sensitivity values of CBCT scans in otosclerosis. Sensitivity levels of

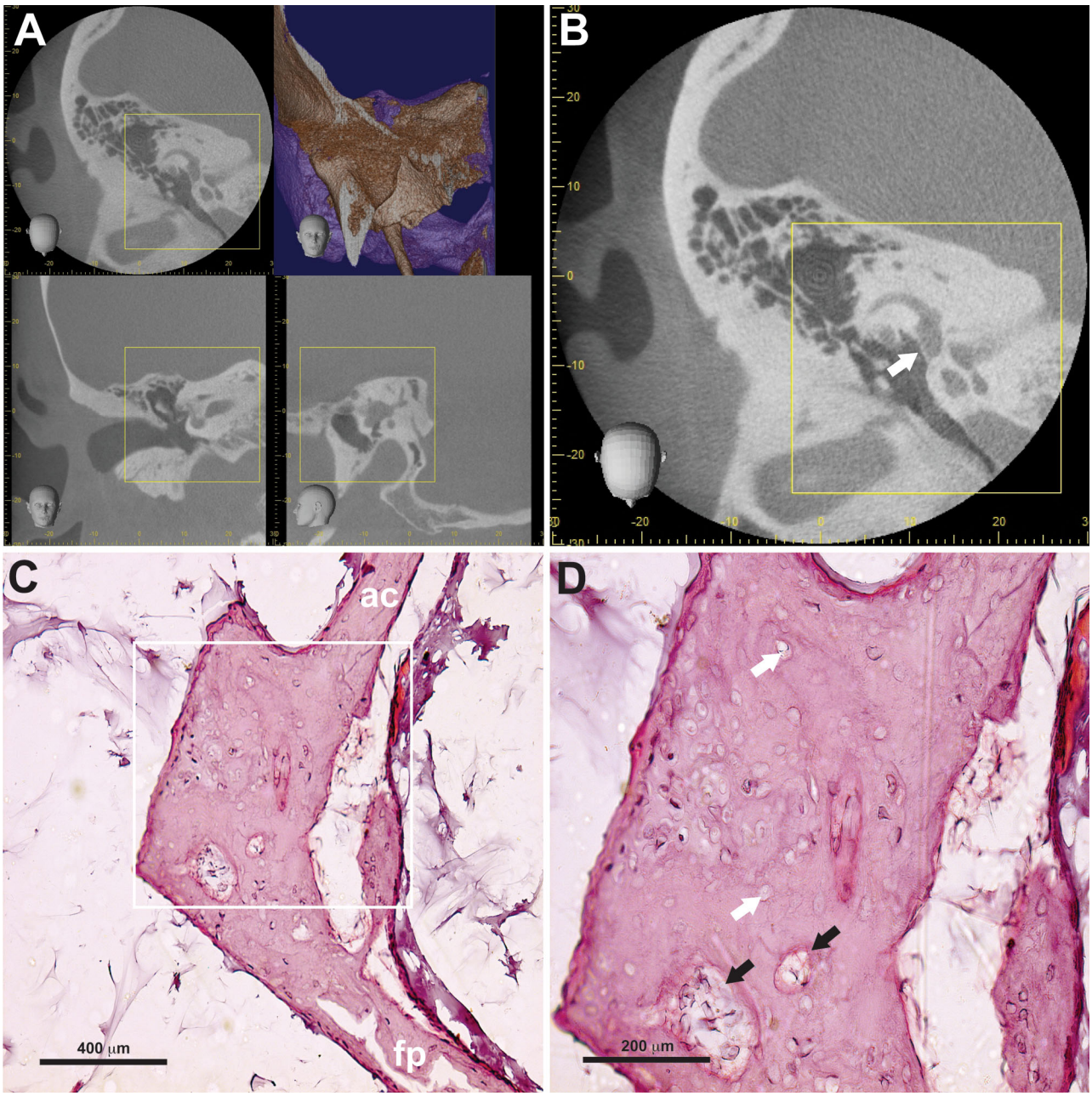

Fig. 2 CBCT scans in histologically inactive otosclerosis (*right* ear). **a** Axial, coronal and sagittal reconstructions of CBCT images. **b** Grade 0 otosclerosis with no signs for hypodense lesions at the oval window niche (axial reconstruction, *white arrow*). **c** Inactive otosclerotic focus at the anterior pole of the stapes footplate (fp) (H.E.). A sharp border can be seen between the inactive otosclerotic lesion and the anterior crus (ac) of the stapes. **d** Higher magnification view of the previous section. Inactive otosclerosis is displayed by obliterated pseudovascular spaces (*black arrows*). The eosinophilic osteoid substance is filled by several empty apoptotic cells (*white arrows*)

HRCT scans have been reported as 70.5–84.5 % in patients with stapes fixation [14, 18]. Specificity levels, however, are not available due to the lack of histopathologic examinations [14, 18]. Redfors et al. [22] have reported 85 % sensitivity of CBCT scans in patients with clinical otosclerosis. According to our observations, in case of histologically confirmed otosclerosis, CBCT showed 65.62 % overall sensitivity, which was lower than that of previous reports [18]. In our series, however, CBCT seemed to be highly sensitive for non-symptomatic otosclerotic foci overestimate revealing bilateral otosclerosis as 56.25 %, in contrast to 46.87 % prevalence revealed by pure-tone audiometry. A non-negligible difference with our study is that diagnosis of otosclerosis was made without histopathologic analysis of

surgically removed stapes footplates, since stapedotomy is not a suitable method to obtain stapes footplate fragments for histopathology.

We have found statistically significant associations between the ABG averages and CBCT grades including the location of hypodense lesions in patients with histologically confirmed otosclerosis. This association followed an inverse function: histologically active otosclerosis with less ABG averages was characterized by positive CBCT findings; however, histologically inactive cases with larger ABG averages displayed negative CBCT scans. These observations were not confirmed in the contralateral ear group. Several studies correlated the HRCT grades of otosclerosis with the severity of preoperative ABG, significantly [12, 14, 16]. Several authors have also shown that the severity of cochlear otosclerosis on HRCT scans correlates with the degree of sensorineural hearing loss [13, 18]. The patients with advanced cochlear otosclerosis may have benefit from cochlear implantation [24]. Nevertheless, the risk of facial nerve stimulation is significantly increased in this group of patients [24, 25]. The location and size of otosclerotic foci seemed to be poorer predictors of sensorineural hearing loss than the endosteal involvement and cochlear wall disruption [18, 24, 25]. The existence of the term of histologic otosclerosis without hearing disorder can be explained by this phenomenon [5, 7]. Regarding to our results, CBCT grades did not present statistically significant association with BC averages in the group of ears with different histopathologic activity of otosclerosis.

In case of inactive otosclerosis, CBCT displayed 0 % sensitivity level, which significantly differs from that of active otosclerosis and from previously published data [18, 22]. Inactive otosclerosis is characterized by hypocellularity, obliterated pseudovascular spaces and dense lamellar osteoid substance [2, 7]. Since CBCT has significantly higher sensitivity for spongiotic osseous lesions, the prevalence of sclerotic foci may be underestimated [20–22]. Hypothetically, this underestimation does not seriously affect the diagnosis of otosclerosis itself due to multifocal characteristics of the disease with coexisting active and inactive foci [1, 8, 9]. However, in case of a solely histologically inactive fenestral otosclerotic lesion, this feature of CBCT might cause a serious differential diagnostic problem [18, 19, 21, 22]. In the lack of histologic findings, inactive otosclerosis and non-otosclerotic stapes fixations may occur as differential diagnostic difficulties during imaging [6, 7, 18]. Audiometry may be helpful in differentiation, since non-otosclerotic stapes fixations usually do not associate with sensorineural hearing loss [8]. Lagleyre et al. [11] have reported that floating or fractured footplate occurred significantly more frequently when an HRCT scan was negative or doubtful. According to our findings, CBCT scans have low sensitivity for pericochlear involvement by otosclerotic lesions. However, we do think that these are distorted findings, since our patients were not characterized by significant sensorineural hearing loss. These audiologic findings might reveal that our patients were not affected by cochlear otosclerosis. This uncertainty should be resolved by larger subject sizes in the future.

As we have previously concluded, preoperative HRCT scan may serve as a valuable imaging method in the planning of stapes surgery [18]. It helps to avoid serious complications and unnecessary stapes surgeries by the detection of several abnormalities in the middle or inner ear, such as large vestibular aqueduct, dehiscent facial canal, superior semicircular canal dehiscence, round window obliteration, persisting stapedial artery and malleus head fixation [9, 19]. Redfors et al. [22] have reported that selected anatomic structures ($n = 16$) of the middle and inner ear were clearly reconstructed by CBCT and no discrepancies were found compared to HRCT findings. These results indicate that CBCT may also serve as the first choice of temporal bone imaging in case of conductive hearing loss with normal tympanic membranes [22]. Furthermore, CBCT is a cheap, easy, robust and a rapid imaging method that is characterized by considerably lower radiation dose than HRCT [20–22].

In conclusion, temporal bone CBCT is a useful imaging method in the preoperative evaluation of histologically active fenestral otosclerosis. Its overall sensitivity falls away from that of histologic analysis; however, it is continuously evolving due to the introduction of higher resolution CT techniques and more powerful analyzer softwares. CBCT has a doubtful correlation with hearing thresholds that depends on the histopathologic activity, the grading system and the size of subject group. In critical interpretation, CBCT seems to be reliable tool in the preoperative diagnosis of otosclerosis; however, further studies are necessary to assess the precise diagnostic values of this imaging technique.

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Conflict of interest None.

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