INTRODUCTION
Cholesteatoma can be defined as the presence of a keratinizing squamous epithelium in the temporal bone, which can form macroscopic amounts of keratin [1]. Cholesteatoma is a destructive disease that can aggressively expand and erode the ossicular chain and other surrounding structures. Bone erosion is commonly observed—in the same order—in patients with cholesteatoma: the facial nerve canal, otic capsule (i.e., bony labyrinth), and tegmen [2]. Various complications related to cholesteatoma, such as facial nerve palsy, brain abscess, and meningitis, are known to arise as a consequence of bone defects.

Labyrinthine fistula (LF), a bone defect of the osseous labyrinth, is also a common complication of cholesteatoma. The incidence of LF was reported to be 5-20% in cholesteatoma cases [3-6]. LF results in the direct contact between the cholesteatoma matrix and the internal membrane of the osseous labyrinth or membranous labyrinth [7]. In terms of the LF position, the lateral semicircular canal (LSCC) was the most frequent location, as found in earlier studies [8]. Multiple fistulas have been detected in about 10% cases [3, 8]. The cochlea may also be involved with variable rates of incidences [9]. On rare occasions, cochlear fistulas (CFs) are found alone, without any involvement of the semicircular canals [10].

OBJECTIVES: To analyze the clinical characteristics of cochlear fistulas (CFs) and propose a new fistula classification system with regard to the cochlea.

MATERIALS and METHODS: A retrospective chart review was conducted between January 2008 and December 2015 to identify patients who had undergone surgery for cholesteatoma with an associated CF. The following data were collected: preoperative symptoms, findings of temporal bone computed tomography (TBCT), fistula stage, cholesteatoma classification, surgical technique, and pre- and postoperative pure-tone audiometry.

RESULTS: We analyzed a total of 159 patients, out of which 9 (5.7%) were diagnosed with a CF. The average duration of the chronic otitis media was 19.8 years. Cholesteatomas that induced CF rarely existed in the nonaggressive state; recurrent otorrhea was observed in all but one of our subjects. All the patients with CF had a distinct origin of cholesteatoma that developed from the retraction of posterior pars tensa; further, 88.9% cholesteatomas extended to and filled the sinus tympani. Preoperative audiometry revealed total hearing loss in 4 (44.4%) patients. Further, five patients with residual hearing before surgery had stage I fistulas, and the bone conduction thresholds remained stable after surgery.

CONCLUSION: Cochlear fistulas were often detected in patients with (1) a history of chronic otitis media (exceeding 10 years), (2) frequently recurring otorrhea, and (3) pars tensa cholesteatomas that extended to the posterior mesotympanum and filled the sinus tympani. Such patients can suffer from potentially severe and irreparable sensorineural hearing loss.

KEYWORDS: Cochlea, fistula, classification, cholesteatoma, otitis media
The pathogenesis of LF in cholesteatoma is yet to be completely understood. Although LF has no reliable symptoms, it appears to be present in various locations, which differ in their pathophysiology and their response to specific treatments. In particular, CF has a poorer functional prognosis than fistulas that affect other sites [10]. However, no reliable data exist on the prevalence/incidence of CF in cholesteatoma. Until now, there have been only a few case reports on CF that have included a detailed description of the condition [10-12]. Because of the anatomical difference between the cochlea and semicircular canals, the traditional classification of LF according to the Dornhofffer and Milewski classification has provided limited assistance in our study regarding CFs [13]. Therefore, another approach is needed, one in which fistulas can be classified with respect to the cochlea.

The purpose of this study was to retrospectively analyze the clinical features of CFs, such as disease duration, age distribution, CF location, preoperative symptoms, and preoperative audiometric results in CF patients with middle ear cholesteatoma. Therefore, the appropriate subtyping of CF could facilitate the differential diagnosis and prediction of functional prognosis.

MATERIALS AND METHODS
The present study protocol and a waiver of consent for retrospective chart review were approved by the Institutional Review Board of our center (permit no.: 26-2016-79). All the methods employed in this study were in accordance with the approved guidelines as well as the Declaration of Helsinki. Data were collected from an electronic medical records database and anonymously analyzed.

A retrospective chart review was conducted for the period from January 2008 to December 2015 in order to identify patients who had undergone surgery for cholesteatoma with an associated LF. The surgeries were performed by a single surgeon. Nine cases were diagnosed as having cholesteatoma-induced CF.

The following data were collected: preoperative symptoms; temporal bone computed tomography (TBCT) findings; stage, location, and size of the fistulas; cholesteatoma classification; surgical technique; and pre- and postoperative audiometric results.

The operative video records were used to stage the LF. Although the three-point classification of Dornhofffer is one of the most used LF classification strategies in earlier studies [4, 13-16], we suggested a modified two-point CF classification strategy that emphasized the differences in the cochlea and the inner structure of the semicircular canal (Figure 1). A stage I CF has the same definition as a type I fistula in the Dornhofffer fistula staging system, which was defined as an erosion of the bony labyrinth with an intact endosteum [13]. On the other hand, effecting a reliable differentiation between type II and type III CFs was difficult by means of the Dornhofffer fistula staging system, where a type II fistula was considered to be a true fistula with an opened perilymphatic space and a type III fistula could be characterized by the destruction of the membranous labyrinth [13]. In this study, type II and type III CFs were regrouped into a common “stage II CF,” since they anatomically overlapped in the cochlea. Data collected from the operative records also included the following: operation type, fistula repair technique (including the materials used), and one-/two-stage surgery. Patients were excluded from this study if any of the parameters described above were missing from their data.

The otoendoscopic findings were analyzed, and the cholesteatomas were grouped according to the modified classification system of Tos.
and Lau [17], where the cholesteatomas were divided into the (1) attic, (2) pars tensa, and (3) combined groups [18]. In addition, cholesteatomas were also classified according to the presence of inflammation, such as purulent secretions.

### Statistical Analysis

The data are presented as the median value with range. The disease durations were compared according to the classification of cholesteatoma and were analyzed by means of the Mann-Whitney U test. The U test was also used to compare the baseline data according to type of fistula. Here, p<0.05 was considered to be statistically significant. Statistical analysis was performed using the Statistical Packages for the Social Sciences (SPSS) version 19 software (IBM Corp., Armonk, NY, USA).

### RESULTS

Between 2008 and 2015, 159 surgeries were performed at our hospital toward chronic otitis media with cholesteatoma, 27 cases of which were diagnosed as LF (incidence: 23.3%). Out of these, nine patients (incidence: 5.7%) were identified as having a CF. CF was identified on the left-hand side in seven cases and on the right-hand side in two cases. Three patients were male and six were female. The chief complaint was recurrent otorrhea in 8 (88.9%) patients and hearing loss in 1 (11.1%) patient. The median patient age was 59 years, ranging from 15 to 85 years. The median duration of the chronic otitis media was 15 years, ranging from 3 to 40 years (Table 1).

All the cases underwent a one-stage surgical procedure, including three revision surgeries for the recidivism of cholesteatoma after previous operations at other hospitals. Canal wall down mastoidectomy was performed in eight patients and one patient underwent subtotal petrosectomy. Cholesteatomas over the fistula were completely removed in all the cases, regardless of the size of the fistulas. A blunt dissection around the fistula was performed by means of a Fisch micro-dissector; further, a fine dissection of the matrix from the fistula was performed by using a Rosen pick by the dominant hand under high magnification. The matrix was held by the suction in the nondominant hand and gently retracted. The smallest suction (24 gauge) was used to maintain a blood-free operative field and not applied directly to the perilymphatic space. After the complete removal of the matrix, CFs were generally covered with a cartilage slice taken from either the concha or tragus (n=9). The bone pate (n=2) and temporalis fascia (n=1) were also used to cover the bony defect. In four cases, fibrin glue was used to prevent the movement of the covering materials.

Cochlear fistulas were detected before surgery in the TBCT scans of all the cases and confirmed during surgery. The fistula of six patients (incidence: 3.7%) was found in the cochlea alone without any accompanying fistula at other sites, and three multiple fistulas were combined with the fistulas in the LSCC. During surgery, CFs were classified as stage I (Figure 2) in six patients and stage II (Figure 3) in three patients. Patients with stage II CF were likely to have a longer disease duration (20–10-40 years) as compared to those with stage I CF (12.5; 3-40 years); however, the difference was not significant (p=0.510). The size of the fistulas was also evaluated during the operation. The maximum diameter of the fistula was determined using a measuring rod and categorized as <2.0 mm (two cases) and ≥2.0 mm (seven cases) according to the methods described in earlier studies [19–21].

Cholesteatomas have rarely existed in a nonaggressive or inactive state (retraction pocket with or without the accumulation of debris); recurrent otorrhea and/or granulation tissues were observed in all but one of our cases. According to the otoscopic classification system based on the origin site, cholesteatomas were grouped as follows: attic group, 0% (n=0); pars tensa group, 33.3% (n=3); and combined group, 66.7% (n=6). Although combined cholesteatoma tended to have more
aggressive sac development than that in pars tensa cholesteatoma, we observed that both the groups of cholesteatomas in the mesotympanum commonly extended posteriorly and filled the sinus tympani. The mean disease duration was 17.7 (3-40) years and 20.8 (10-40) years in the pars tensa and combined types of cholesteatomas, respectively; this difference was not statistically significant (p=0.510).

Nearly half (55.6%) of the cases reported vertigo before the operation. One of them was diagnosed as accompanied with benign paroxysmal positional vertigo. The fistula test was routinely performed, and two patients (case nos. 4 and 9) exhibited nystagmus with positive middle ear pressure. Both the patients with a positive fistula sign presented as stage I CF, and one of these two patients
Based on a 4-tone average (hearing levels at 0.5, 1, 2, and 3 kHz), all residual hearing is related to the stage rather than size of the CF. Interestingly, the case with stage II CF with the largest size (3.5 mm) had preoperative residual hearing. These findings seem to indicate that preoperative total deafness before surgery was found in one (50%) out of the two patients with CF size ≥2.0 mm. Based on the size of the CF, total deafness in four patients (44.4%) was detected in 1 (16.7%) out of the six patients with stage I CF and in 3 (42.9%) out of the seven patients with CF <2.0 mm and in 3 (42.9%) out of the seven patients with stage II CF. The relatively higher incidence observed in the present study is possibly due to inclusion of recurrent cholesteatoma cases. Here, three (33%) cases had concomitant multiple fistulas in other locations, and the LSCC was involved in these cases.

Preoperative audiometry showed conductive hearing loss in two patients (22.2%), mixed hearing loss in three patients (33.3%), and total deafness in four patients (44.4%). Preoperative total deafness was detected in 1 (16.7%) out of the six patients with stage I CF and all (100%) the patients with stage II CF. Based on the size of the CF, total deafness before surgery was found in one (50%) out of the two patients with CF <2.0 mm and in 3 (42.9%) out of the seven patients with CF size ≥2.0 mm. Interestingly, the case with stage II CF with the smallest size (1.0 mm) had a dead ear preoperatively, whereas the case with stage I CF with the largest size (3.5 mm) had preoperative residual hearing. These findings seem to indicate that preoperative residual hearing is related to the stage rather than size of the CF. Based on a 4-tone average (hearing levels at 0.5, 1, 2, and 3 kHz), all the five patients with preoperative residual hearing showed a stable bone conduction (BC) threshold after surgery (Figure 4).

DISCUSSION

Labyrinthine fistulas can occur due to cholesteatoma, granulomatous chronic otitis media without cholesteatoma, as well as postoperative infection [22]. Among these disease entities, the most common cause of LF is cholesteatoma [22]. The mechanisms of LF generation from cholesteatoma can be classified into three categories: pressure of the matrix, enzymatic osteolysis, and inflammation [23]. First, the cholesteatoma sac—filled with keratin debris—can initiate osteolysis via the imposition of pressure without liquefaction [24]. Cholesteatoma in a confined space has no outlet for its growth and therefore exerts pressure on the surrounding structures, thereby leading to bone erosion. Second, the matrix of the cholesteatoma sac can instigate osteolysis via the collagenase enzyme along with liquefied debris and granulation tissue [25]. Tumor necrosis factor-α, produced mainly by macrophages, stimulates the matrix metalloproteinases and can induce bone erosion [26]. In addition, inflammation initiated by cholesteatoma-related infections alters the surface pH of the surrounding bone and also leads to osteolysis [20].

The incidence of LF in cholesteatoma patients is somewhere between 4.0% and 12.7% (Table 2) [13, 19, 20, 27, 28]. LF can occur anywhere, with the most frequent location being the LSCC (incidence: 7%) [8]. The anterior semicircular canal, posterior semicircular canal, and vestibule can also be a probable location [29, 30]. However, LF generated on the cochlea is extremely rare: it is assumed that a considerable number of CF cases can be overlooked. In earlier studies, the incidence of CF was estimated to be in the range of 0.1-2.9% (Table 2) [8, 13, 19, 20, 27, 28]. Some authors have insisted that limited bony erosion with an intact endosteal bone layer or endosteum, such as a “blue lining” or type I fistula according to the Dornhoffer classification, cannot be considered as LF [18]. Our study reported that three (1.9%) out of the 159 patients with middle ear cholesteatoma who underwent surgery presented with stage II CFs. The relatively higher incidence observed in the present study is possibly due to inclusion of recurrent cholesteatoma cases. Here, three (33%) cases had concomitant multiple fistulas in other locations, and the LSCC was involved in these cases.

Labyrinthine fistula formation has been known to progress slowly and to be associated with a long history of chronic otitis media. In the present study, CF cases also tended to have a higher stage of fistula over the course of time. The average age in our study was 57.0 years, which was higher than the average age in earlier studies involving LSCC fistulas (between 38 and 56 years) [8]. However, the mean duration of chronic otitis media in CF cases was 19.8 years, which was similar to, but shorter than, those reported in general LF cases with a history of more than 20 years [8, 20]. In the present study, six patients with CF (66.6%) suffered for less than 20 years, although there were certain doubts regarding the reliability because the data were based only on the patients’ recollections. All these patients, except 1 (case no. 6), had a disease duration of more than 10 years. This patient was suffering from otorrhea for only three years and presented with stage I CF. In this patient, the cholesteatoma itself was not located in a confined space. This may support the recently suggested theory according to which middle ear infections stimulate the aggressiveness of the cholesteatoma and enhance the osteolytic effects of the cholesteatoma [31, 32].

Cholesteatoma with an infection may cause bone erosion more quickly than that without infection. Infection can make the squamous epi-
Our results are in agreement with those of several other studies that showed that CF can be caused by cholesteatoma in the posterosuperior part of the tympanic cavity [15, 11]. Our results showed that cholesteatoma developed in the mesotympanum and then extended to the sinus tympani, causing erosion of the bony cochlea: pars tensa type in 33.3% and combined type in 66.7%. We were able to consider the combined type as an advanced stage of the pars tensa type due to the limitation of the Tos classification system. Interestingly, in contrast, attic-type cholesteatoma was not found at all in our study. Black et al. [18] noted that the attic-type cholesteatoma tended to show lesser mesotympanic involvement overall. Considering the anatomical positions, it is expected that a cholesteatoma originating in the posterosuperior quadrant of the pars tensa has more opportunities to form a CF. Therefore, the most frequent CF site is the promontory area [14]. Further, we identified the promontory region as the most common location of CF.

Because of the functional vulnerability of the cochlea as compared to that of the LSCC, Meyer et al. [10] considered that the location of LF has a prognostic value for postoperative hearing. Chao et al. [16] described a worse prognosis for CF as compared to that for the LSCC fistula. Meyer et al. [10] reported better preoperative BC hearing levels for the LSCC fistula, which showed normal hearing in about 57% cases and total hearing loss in only 2% cases. The same authors reported that all the four cases with type III LSCC fistula showed pure-tone averages that were better than 40 decibels hearing level (dB HL). On the other hand, all the patients with stage II CF, and even one patient with stage I CF, presented total hearing loss in this study. However, artificial fistula in a noninfected field, such as stapedotomy, does not always lead to hearing deterioration. It seems likely that the spread of infection into the cochlea rather than just the opening of the perilymphatic space can have a larger impact on hearing. Consequently, an increased correlation to the presence of infection in CF than that in LF in other locations may lead to more serious hearing problems.

In earlier reports, all the CF cases who exhibited some degree of preserved hearing were also considered to be stage I fistula based on the absence of perilymph leakage [12, 20]. Our results also reported five cases of stage I CF with residual hearing (BC pure-tone average: 15-60 dB HL). These patients underwent one-stage canal wall down mastoidectomy with the complete removal of the cholesteatoma over the fistula. As compared to postoperative BC thresholds, all the five cases showed stable hearing. Similar to our study, Moon et al. [26] reported that complete matrix removal did not affect the hearing preservation, regardless of the fistula size. These findings suggest that the residual hearing level is important for a better functional prognosis.

The rate of vertigo and positive fistula tests in CF were similar to the findings in the LSCC fistula study: 55.6% and 22.2% for our series, and 45-100% and 21-65% for the LSCC fistula study, respectively [6, 8, 35]. This may be attributed to the fact that LSCC fistulas were also present in 33.3% cases in our study. Although the positivity of fistula is considered to be a classical sign of bony erosion, earlier studies have reported that the fistula test results were not correlated with the fistula stage and were poor indicators of LF [8]. Jang et al. [21] suggested that the transmission of pressure changes to the fistula can be interrupted by the cholesteatoma.

There are several limitations to consider when interpreting the results of this study. The first one is the limited sample size. This study presents the results obtained from nine subjects, with surgery performed by a single surgeon over eight years. Considering the extremely low incidence of CF, it is difficult to accumulate these data. We believe that this is the largest single institutional series published until now. Another limiting factor of our study is a modified staging system of CF that has not yet been validated. Based on our data, all the CFs were located over the lateral cochlear wall of the promontory. In stage I CF with an intact endosteum—the spiral ligament that provides attachment to the basilar membrane—was observed as a white line (Figure 2b). The basilar membrane bridges the tip of the spiral lamina and the spiral ligament, and it separates the endolympathic space from the perilymphatic space. Fistulization of the lateral cochlear wall over the promontory can result in easy invasion into the endolympathic space through the spiral ligament as well as the perilymphatic space. Our own clinical results have shown that there were no differences among the patients with stage II CF. However, further study is required to prove the prognostic validity of this modification.

CONCLUSION

Labyrinthine fistulas should always be suspected in all the patients undergoing surgery for cholesteatoma. In particular, fistulas in the cochlea can be detected in patients with (1) a history of chronic otitis media >10 years, (2) actively infected cholesteatomas, and (3) pars tensa cholesteatomas that extend to the posterior mesotympanum and fill the sinus tympani. Such patients can suffer from potentially severe and irreparable sensorineural hearing loss. An early detection and treatment of CF when the endosteum is intact may help in preserving the hearing function.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Seoul Metropolitan Governance-Seoul National University Boramae Medical Center (IRB NO: 26-2016-79).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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