The Journal of International Advanced Otology

J Int Adv Otol 2023; 19(2): 105–111 • DOI: 10.5152/iao.2023.22758

Original Article

Retrospective Analysis of Postoperative Effect of Supratubal Recess Opened and Bony Obliteration Tympanoplasty

Haiyao Zheng[1,2], Tao Mo[1,2], Huicheng Gong[1,2], Haoliang Zhang[1,2]

[1]The Twelfth People's Hospital Guangzhou, Guangzhou, China
[2]The Twelfth People's Hospital Affiliated to Guangzhou Medical University, Guangzhou, China

ORCID IDs of the authors: H.Z. 0000-0002-0861-0829, T.M. 0000-0001-8610-5409, H.G. 0000-0001-7028-8220, H.Z. 0000-0002-6224-4698.

Cite this article as: Zheng H, Mo T, Gong H, Zhang H. Retrospective analysis of postoperative effect of supratubal recess opened and bony obliteration tympanoplasty. *J Int Adv Otol*. 2023;19(2):105-111.

BACKGROUND: In the surgical development of cholesteatoma, in order to reduce the recurrence of cholesteatoma, 2 kinds of surgeries were carried out: removal of Cog and Korner's septum to ventilate supratubal recess (supratubal recess opened) and obliteration of the mastoid and attic space (bony obliteration tympanoplasty) were invented, respectively. Their purpose is the same but the theoretical basis is different, and the comparison of these 2 methods is not reported in the current literature. This study aims to evaluate the rates of recurrent and residual cholesteatoma with the simple canal wall up and canal wall up-supratubal recess opened and canal wall up-bony obliteration tympanoplasty mastoidectomy in a large cohort of patients. The secondary objectives were to assess the 3 techniques' infection rates and hearing outcomes.

METHODS: Overall, 352 patients with middle ear cholesteatoma preoperatively underwent temporal bone ultrahigh-resolution computed tomography scan. The shape of the Eustachian tube and the supratubal recess were analyzed, and superior and posterior tympanic recesses, including the supratubal recess, were opened in different surgical groups.

RESULTS: After 5 years of follow-up, the results show that the lowest recurrence rate was 6.6% (7/106) for canal wall up-supratubal recess opened, 10.9% (12/101) for canal wall up-bony obliteration tympanoplasty, and canal wall up had the highest recurrence rate of 19.31% (28/145). The postoperative infection rate was 5.7% in the canal wall up-supratubal recess opened group, 10.89% in the canal wall up-bony obliteration tympanoplasty group, and 7.59% in the simple canal wall up group. The postoperative median air conduction was increased 8 dB in the canal wall up-supratubal recess opened group, 1 dB in the canal wall up-bony obliteration tympanoplasty, and 6 dB in the simple canal wall up group.

CONCLUSION: Opening the supratubal recess to ensure the patency of the attic facilitates the gas exchange between the mastoid process and the middle ear and reduces the possibility of cholesteatoma recurrence.

KEYWORDS: Supratubal recess, cholesteatoma, superior tympanic diaphragm, middle ear airflow interaction.

INTRODUCTION

The most common inducement for the formation of middle ear cholesteatoma is the formation of inverted bags in the Shrapnell's membrane, while the formation of inverted bags in the Shrapnell's membrane is caused by negative pressure in the superior tympanic.[1-4] Luntz[5] found that the Shrapnell's membrane contains less collagen fiber, and the shrinkage force of the Shrapnell's membrane is greater than that of the tense part, which is more likely to produce compliance and form a relaxation inverted bag. The mechanism of adjusting the pressure in the middle ear is as follows: (1) the buffer mechanism of the gas reserve of the mastoid cavity to the tympanic cavity, (2) ventilation regulation mechanism of the Eustachian tube, (3) respiratory regulation mechanism of middle ear mucosa, and (4) the neural regulation mechanism of middle ear pressure.[6-9] The first 2 of the above 4 points are particularly important. There are 2 pathways for airflow in the middle ear: (1) Eustachian tube → mesotympanum → supratubal recess → mesotympanum → posterior tympanum; (2) Eustachian tube → supratubal recess → mesotympanum → attic → tympanicantrum → mastoid process. Theoretically, in cholesteatoma patients with normal Eustachian tube function, removing the obstruction on the ventilation path of the middle ear during radical mastoidectomy can help them improve the ventilation and drainage of the middle ear. In this way, the air pressure in the middle ear is stabilized, thereby reducing the recurrence of middle ear cholesteatoma.

Corresponding author: Haoliang Zhang, e-mail: fridge22@163.com

Received: April 7, 2022 • **Accepted:** August 2, 2022 • **Publication Date:** March 24, 2023
Available online at www.advancedotology.org

The attic septum is the barrier between the mesotympanum and attic, preventing the passage of gas from the supratubular recess into the attic. We surgically open the supraductal recess and remove the Cog (anterosuperior tympanic bone plate; the middle portion of the Korner's septum) and Korner's septum. When the attic septum is cleared, airflow from the Eustachian tube can travel more smoothly from the anterior malleus to the attic and then through the middle ear ventilation pathway, thereby reducing the recurrence of cholesteatoma. And this airway is comprised of the Eustachian tube superior recess named the supratubal recess[10] and the posterosuperior tympanic septum.[11] During the operation, we enlarged supratubal recess and removed the Cog and the rest of the Korner's septum to allow the air coming from the Eustachian tube to pass through the malleus anterior and reach the epitympanum to prevent tympanic cholesteatoma recurrence. Using the method of meta-analysis, Tomlin et al[12] analyzed that the recurrence rate of open radical mastoidectomy was 5%-17%, and the recurrence rate of complete radical mastoidectomy was 9%-70%. To reduce the recurrence rate of cholesteatoma in canal wall up (CWU) surgery, many surgeons perform bony obliteration tympanoplasty (BOT) surgery at the same time in the CWU surgery. They believe that BOT fills the attic and mastoid process, and there is no space for the Shrapnell's membrane to retract.[13] This method of preventing recurrent cholesteatoma formation is very different from, or even the opposite of, the theory of improved middle ear ventilation and drainage. The primary aim of this study is to evaluate and compare the recurrent and residual cholesteatoma rates of the CWU-SRO (supratubal recess opened), CWU-BOT, and simple CWU mastectomy. Secondly, we evaluate the infection rate and hearing outcome for all 3 techniques.

METHODS

This study was a retrospective analysis carried out in the Department of Otorhinolaryngology of our hospital between June 2011 and December 2020 from a series of 365 patients surgically treated for middle ear cholesteatoma and was approved by the medical research ethics committee (protocol number: 2022040). All the patients had signed informed consent. We excluded the cases affected by congenital cholesteatoma and included 297 patients (352 ears) in our trial investigation, which are divided into CWU with SRO (106 ears), CWU with BOT (101 ears), and simple CWU (145 ears) (Table 1).

The postoperative anatomical status of the tympanic membrane (TM) was evaluated by semiannual otoscopy, observing for the presence of TM retraction, retraction pockets, canal wall breakdown, transplanted TM, the external auditory canal, and recurrent cholesteatoma. And the postoperative middle ear sinus was evaluated by semiannual high-resolution CT images of the temporal bones to research the cholesteatoma extension and ossicular chain situation. Herein, follow-up for all the patients was performed by semiannual pure tone audiometry (air conduction (AC), bone conduction (BC), and air-bone gap (ABG); calculated at 0.5/1/2/4 kHz) and acoustic immittance (type A, type B, and type C).

Recurrent cholesteatoma was defined as a retraction pocket detected at routine semiannual otoscopy follow-up. Residual cholesteatoma was defined as the presence of keratinized epithelium in the middle ear, especially the area of the Shrapnell's membrane, or the presence of keratinized epithelium in the tympanum and attic on the first CT scan after surgery.

Recurrent and residual cholesteatoma were classified and revised according to the EAONO/JOS classification (pars tensa, pars flaccida, and combination of pars tensa and pars flaccida), staging (I-IV), and the STAMCO system for site involvement (S1, supratubal recess; S2, sinus tympani; T, tympanic cavity; A, attic; M, mastoid; C, complication; O, ossicular).

RESULTS

Statistical Analysis

Independent sample *t*-tests, 2-tailed Fisher's exact tests, Chi-square test, Wilcoxon signed-rank test, Kaplan–Meier method, and Mann–Whitney U tests were used for statistical analysis. $P < .05$ was considered to indicate statistically significant differences and a Bonferroni correction was used when needed. Statistical analysis was conducted using Statistical Package for Social Sciences Version 24.0 (IBM SPSS Corp.; USA).

Cholesteatoma Recurrence Rates and Sites

We defined that the total recurrence was made up with recurrent and residual cholesteatoma, during the 5-year follow-up, the median follow-up time for all patients was 42 (36-50) months. The classification for recurrent cholesteatoma site involvement is based on the STAMCO system. The complete cholesteatoma recurrence rates are shown in Figure 1. In the CWU-SRO group, 99 ears were dry (93.4%), and recurrent cholesteatoma was found in 7 (6.6%) ears, and postoperative infection was seen in 6 cases (5.7%). We observed 1 case of recurrent cholesteatoma with extension into the supratubal recess (14.29%), 2 cases recurrent in the sinus tympani (28.57%), 1 case recurrent in the tympanic cavity (14.29%), and 3 cases recurrent in the attic space (42.86%) (Figure 2A). In the CWU-BOT group, the total recurrence rates were (12/101, 11.88%) and postoperative infection was seen in 11 cases (10.89%). The recurrent sites of cholesteatoma are S1 (5, 41.67%), S2 (2, 16.67%), T (3, 25%), A (1, 8.33%), and M (1, 8.33%) (Figure 2B). For the simple CWU group, the total recurrence rates were 19.31% (28/145) and postoperative infection was seen in 11 cases (7.59%). And the recurrent sites of cholesteatoma are S1 (4, 14.29%), S2 (5, 17.86%), T (3, 10.71%), A (9, 32.14%), and M (7, 25%) (Figure 2C).

Hearing Outcome

Collecting the audiometric testing data from the picture archiving and communication system (PACS) electronic medical record system of about 352 patients during the treatment process was undertaken. And the preoperative hearing outcome revealed a median preoperative AC of 40 (interquartile range [IQR] = 27-51) dBHL with an ABG of 21.38 (IQR = 18.56-25.19) dBHL. There was no statistically significant difference in preoperative ABG between groups as determined by one-way analysis of variance (ANOVA) [F (2, 33) = 0.641, P = .99]. Postoperative hearing levels were measured at least 6 months postoperatively or on the latest evaluation date periodic review (mean follow-up of 43 months), and the final result was shown in Table 2. In the CWU-SRO group, hearing was improved in 83 ears (78.3%). Herein, the median AC hearing threshold and median ABG were 31 (IQR = 22.5-46.25) dB and 13.75 (8.75-28.125) dBHL, respectively. The CWU-BOT group with 63 of them (63/101, 62.4%) experiences hearing improvement postoperatively. And the median AC and the median ABG were 41 (29-53.5) dBHL and 17.5 (8.75-30) dBHL, respectively. For the simple CWU group, 91 ears (62.8%) showed improved hearing postoperatively. Furthermore, the median AC and ABG were 31

Table 1. Features of Patients

		CWU-SRO N (%)	CWU-BOT N (%)	Simple CWU N (%)
Number of cases		106 (30.1%)	101 (28.7%)	145 (41.2%)
Sex	Female	55 (51.9%)	45 (44.6%)	66 (45.5%)
	Male	51 (48.1%)	56 (55.4%)	79 (54.5%)
Side	Left	58 (54.7%)	61 (60.3%)	81 (55.9%)
	Right	48 (45.3%)	40 (39.7%)	64 (44.1%)
Cholesteatoma origin	Pars tensa	25 (23.5%)	29 (28.7%)	36 (24.8%)
	Pars flaccida	53 (50.0%)	53 (52.5%)	49 (33.8%)
	Perforation	15 (14.2%)	10 (9.9%)	38 (26.2%)
	Residual cholesteatoma	NA	NA	NA
	Pars tensa and pars flaccida	13 (12.3%)	9 (8.9%)	22 (15.2%)
	External ear canal cholesteatoma	NA	NA	NA
STAMCO classification	STAM I	5 (4.7%)	13 (12.9%)	2 (1.4%)
	STAM II	22 (20.8%)	32 (31.7%)	45 (31%)
	STAM III	79 (74.5%)	56 (55.4%)	98 (67.6%)
	Cn	96 (90.6%)	89 (88.1%)	127 (87.6%)
	C1	10 (9.4%)	12 (11.9%)	18 (12.4%)
	C2	NA	NA	NA
	On	28 (26.4%)	28 (27.7%)	31 (21.4%)
	O1	40 (37.7%)	35 (34.7%)	41 (28.3%)
	O2	34 (32.1%)	33 (32.7%)	67 (46.2%)
	O3	4 (3.8%)	5 (5.0%)	8 (5.5%)
	Ox	NA	NA	NA
Postoperative ossicular chain reconstruction	No reconstruction, chain intact	28 (26.4%)	28 (27.7%)	30 (21.4%)
	PORP	39 (36.8%)	33 (32.7%)	40 (27.6%)
	TORP	39 (36.8%)	40 (39.6%)	75 (51.7%)
	Missing	NA	NA	NA
Preoperative average air conduction	<25 dB	14 (13.2%)	10 (9.9%)	19 (13.1%)
	25-35 dB	14 (13.2%)	11 (10.9%)	16 (11.0%)
	36-45 dB	39 (36.8%)	39 (38.6%)	50 (34.5%)
	46-55 dB	19 (17.9%)	24 (23.8%)	35 (24.1%)
	56-65 dB	17 (16.0%)	14 (13.9%)	20 (13.8%)
	66-75 dB	3 (2.8%)	3 (2.9%)	4 (2.8%)
	>75 dB	NA	NA	1 (0.7%)
Postoperative infection		6 (5.7%)	11 (10.9%)	11 (7.6%)
Ratio of soft tissue to mastoid cavity in CT		35%	60%	35%
Course of the disease (month)[a]		2-20	2-20	2-20

[a]The unit is months.

BOT, bony obliteration tympanoplast; CT, computed tomography; CWU, canal wall up; PORP, partial ossicular replacement prostheses; SRO, supratubal recess opened; TORP, total ossicular replacement prostheses; the STAMCO system for site involvement, S1, supratubal recess; S2, sinus tympani; T, tympanic cavity; A, attic; M, mastoid; C, complication; O, ossicular (staging (I-III)).

(22-48) dBHL and 12.5 (7.5-26.25) dBHL, respectively. Mann–Whitney *U* test showed a clear significant effect on ABG change (P =.009).

Acoustic Immittance

For all groups, 5 years follow-up was performed. In the CWU-SRO group, the acoustic immittance diagram of 78 (73.6%) ears was A type, 23 (21.7%) ears were B type, and 5 (4.7%) ears were C type, respectively. Because of the intraoperative opening of the passage between the attic and mesotympanum, Eustachian tube dysfunction may be the reason for 5 years being C type. In the CWU-BOT group, the tympanic impedance was type A, type B, and type C in 71 (70.2%)/14 (14%)/16 (15.8%) ears, respectively. For the simple CWU group, the tympanic impedance was type A for 62 (42.8%) ears, type B for 77 (53.1%) ears, and type C for 6 (4.1%) ears.

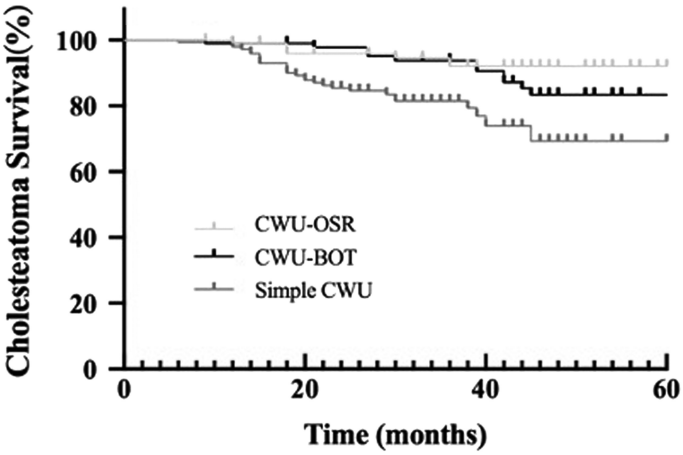

Figure 1. Survival curve for cases with complete recurrent cholesteatoma for all surgical techniques.

Otoendoscopy

For all groups, 5 years follow-up was performed. The status observed in the CWU-SRO group under otoendoscopy, 26 ears wherein the external auditory canal volume were increased. Pars tensa membranae tympani of 7 ears found a perforation at 6 o'clock position. 3 ears had superior semicircular canal fistula and 5 ears had no activity of the TM when making Valsalva maneuver. In the CWU-BOT group, otoendoscopy showed the complete repair of the tension part. The angle between the TM and the external auditory canal was small in the 3 ears, and it was easy to accumulate fluid. The TM of 8 ears had no activity when making the Valsalva maneuver. For the simple CWU group, upon otoendoscopy examination, the loose part of the TM of 8 ears showed invaginated pockets, the temporalis muscle fascia implanted in 9 ears formed a thin area, and the TM of 6 ears had no activity when making Valsalva maneuver.

Complications

In the CWU-SRO group, 1 case of facial nerve canal horizontal segment had incomplete bone and was displaced outward. After 1 year, it had spontaneously recovered and reached house-Blackman grade III. In the CWU-BOT group, 4 patients had mastoid pain and 3 patients developed a facial nerve palsy on the side of the operated ear in the weeks after surgery which was treated with oral steroids where after complete remission was seen. Eleven cases of the chord tympanic nerve were disconnected, resulting in decreased taste, which recovered spontaneously after 2-3 months. In the simple CWU group, 5 of the cases developed a facial nerve palsy on the side of the operated ear in the weeks after surgery, all recovered within 12 weeks. Two cases of cerebrospinal fluid otorrhea occurred after the operation, which disappeared spontaneously without tamponade after 2 weeks. No intracranial infection was found in all 3 groups.

Audile Reconstruction

In the simple CWU group, type I tympanoplasty was performed for 40 ears, type II tympanoplasty and PORP implantation were simultaneously performed for 76 ears, and type III tympanoplasty and total ossicular replacement prostheses (TORP) implantation were simultaneously performed for 29 ears. In the CWU-SRO group, type I was performed for 85 ears and type II was for 21 ears. In the CWU-BOT group, type I was performed for 72 ears and type II was 29.

DISCUSSION

In the Eustachian tube - middle ear - mastoid airflow system, the epitympanum can be relatively easily blocked[3] and the entrance of air from the Eustachian tube into the epitympanum is made difficult by the long and wide tensor tympanic folds. Middle ear cholesteatoma primarily results from hypoventilation in this regard. Healthy individuals can compensate for this mild stenosis of the epitympanum with the air present in the mastoid process, even in the presence of other influencing concerns, such as catarrh, sinusitis, and other nasal aggravating factors. However, considering the poor anatomical condition of the superior tympanum in patients with severe stenosis of the superior tympanic airway, the aforementioned concerns cannot be compensated for by the air present in the mastoid process, thus leading to the gradual formation of middle ear cholesteatoma. In the CWU-SRO group, the airflow from the Eustachian tube enter the middle tympanum first and then into the posterior tympanum. Then it passes through the facial recess and finally enter into the mastoid.[14] Using the CWU-SRO technique can keep a ventilated and hygienic status for postoperative middle ear, thus preventing the recurrence of middle ear cholesteatoma.

The acquired primary cholesteatoma primarily originates from the epidermis[15] wherein invaginated sacs form under local negative pressure conditions. Therefore, the recurrence of middle ear cholesteatoma, except for the secondary cholesteatoma originating in the mastoid process, is inhibited by opening the supratubal recess.[16] The technology of opening the supratubal recess can be applied to epitympanotomy (Figure 3A-I) or CWU mastoidectomy surgery.

The following were the main points of the intraoperative expedition:

1. Pharyngeal orifice of the Eustachian tube was explored, and obstructive factors were removed; then, it was determined if

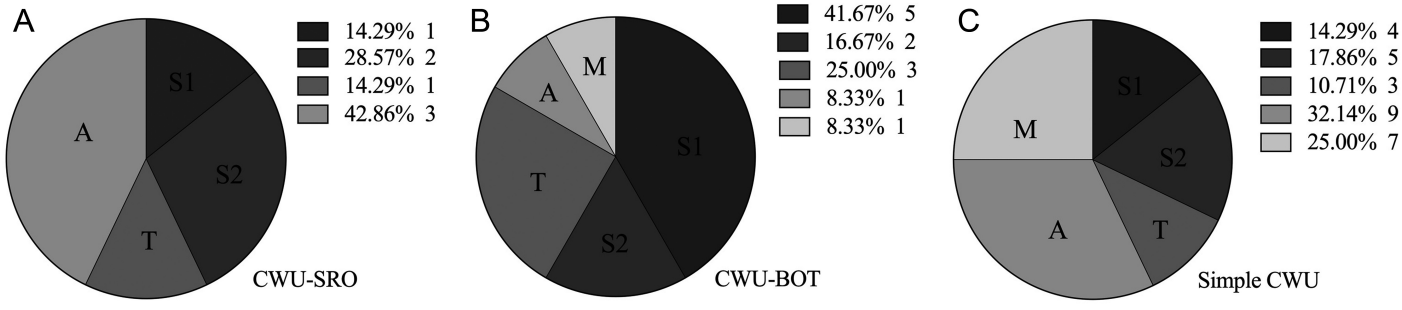

Figure 2. Pie chart of recurrent cholesteatoma and residual sites for all surgical techniques. Pie chart of CWU-SRO (A). Pie chart of CWU-BOT (B). Pie chart of simple CWU (C). CWU-SRO, canal wall up-supratubal recess opened; CWU-BOT, canal wall up-bony obliteration tympanoplasty.

Table 2. Audiological Results

	Air Conduction				Bone Conduction				Air-Bone Gap			
	Preoperative	Postoperative	Change		Preoperative	Postoperative	Change		Preoperative	Postoperative	Change	
	Mean	Mean	Mean		Mean	Mean	Mean		Mean	Mean	Mean	
	Median	Median	Median		Median	Median	Median		Median	Median	Median	
	dB HL (IQR)	dB HL (IQR)	dB (IQR)	*P*	dB HL (IQR)	dB HL (IQR)	dB (IQR)	*P*	dB HL (IQR)	dB HL (IQR)	dB (IQR)	*P*
CWU + SRO	39.70	31.84	7.85	***	17.35	17.21	0.14	.923	22.36	14.63	7.73	***
	40	31	8		13.75	13.75	0		22	14.25	8	
	(27.75-51.25)	(22.5-46.25)	(6-9)		(8.75-30)	(8.75-28.125)	(0-0)		(19-25.5)	(12.5-16.75)	(6-9)	
CWU + BOT	41.99	40.97	1.02	.601	20.28	19.98	0.31	.846	20.75	20.99	0.71	.111
	43	41	1		18.75	17.5	0		22	20.25	1	
	(29.5-54)	(29-53.5)	(0-1)		(10-30)	(8.75-30)	(0-0)		(19.5-24.375)	(18.875-22.875)	(0-1)	
Simple CWU	38.22	32.26	5.97	*	16.76	16.64	0.12	.919	21.46	15.62	5.84	***
	38	31	6		12.5	12.5	0		21	15.75	6	
	(26-50)	(22-48)	(4-7)		(7.5-27.5)	(7.5-26.25)	(0-0)		(17.25-25.5)	(13-19)	(4-7)	

BOT, bony obliteration tympanoplast; CWU, canal wall up; HL, hearing loss; SRO, supratubal recess opened.
$^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

it is the Eustachian tube or the superior tympanum that is not ventilated.

2. In the CWU-BOT group, the obliteration material was dissolved for which a revision procedure was the reason for necrosis and infection. It is expected that recurrent and residual cholesteatoma will occur in the attic and not in the mastoid because of the characteristics of the invagination pouch.
3. In the CWU-SRO group, the gas can simultaneously enter the tympanic isthmus and Prussak's space after passing through the supratubal recess[17]; thereafter, it can enter the mastoid after flowing into the entrance of the tympanicantrum. Air cells of the mastoid process store air within their cavities and the air from the Eustachian tube is supplied to the mastoid process by passing through the complicated attic airway.

In SRO surgery, the following were the bone landmarks that needed to be exposed in the surgical area: ethmoid area, mastoid tip, temporal line, anterosuperior spine, and posterosuperior spine (Figure 3A). To gain intraoperative access to both the mastoid and tympanic views, the skin of the posterior wall of the external auditory canal was incised and stretched forward to expose the TM (Figure 3B). The bone channel was vertically ground into the superior tympanum via the projection on the surface of the superior tympanum, thus exposing Cog. Cog is a horizontal bone hanging from the canopy's left to right. It had to be removed as it occupied most of the anterior recess of the superior tympanum (Figure 3C). A crochet needle was used to identify the recess position on the tube (Figure 3D). The Korner septum, a bone extended by the petroscale fissure, had to be removed since it occupies considerable space in the anterior recess of the superior tympanum (Figure 3E). A coronal ventilation plane was formed in front of the malleus head once the Korner septum and Cog were ground away. The TM was turned up to ensure that the supratubal recess communicates with the anterosuperior tympanic recess and that the superior tympanum communicates with the tympanic sinus (Figure 3F). Auriculoplasty should be done during these operations, the attic lateral wall must be restored by the cartilage of the cavity of the auricular concha, and the outside was covered with fascia (Figure 3G-K). Finally, by using the absorbable material fill the external auditory canal. The pharyngeal orifice of the Eustachian tube can be observed from the view of the external auditory canal (Figure 3I)[18] and leads to the supratubal recess.[19]

After CWU-SRO surgery, the theory of airflow in the middle ear explains that the air entering the middle ear from the Eustachian tube can enter the mastoid through 2 airways by either entering the mastoid from the open crypt or entering the superior tympanum from the supratubal recess and then into the mastoid process through the tympanicantrum.

In addition, SRO also has its own shortcomings. The SRO surgery can provide gas source for the attic, but for the parts far from the supratubal recess, such as the posterior tympanum and mastoid process, the gas supply and influence are relatively insufficient. In this study, there are also some limitations. Considering the interests and prognosis of patients, the surgery selection for patients was according to the initial location of cholesteatoma. Our further study will improve and strictly require random sampling of patients with consistent cholesteatoma invasion location, cholesteatoma grade, and ossicular chain damage, to achieve fewer influencing factors and get more accurate experimental results.

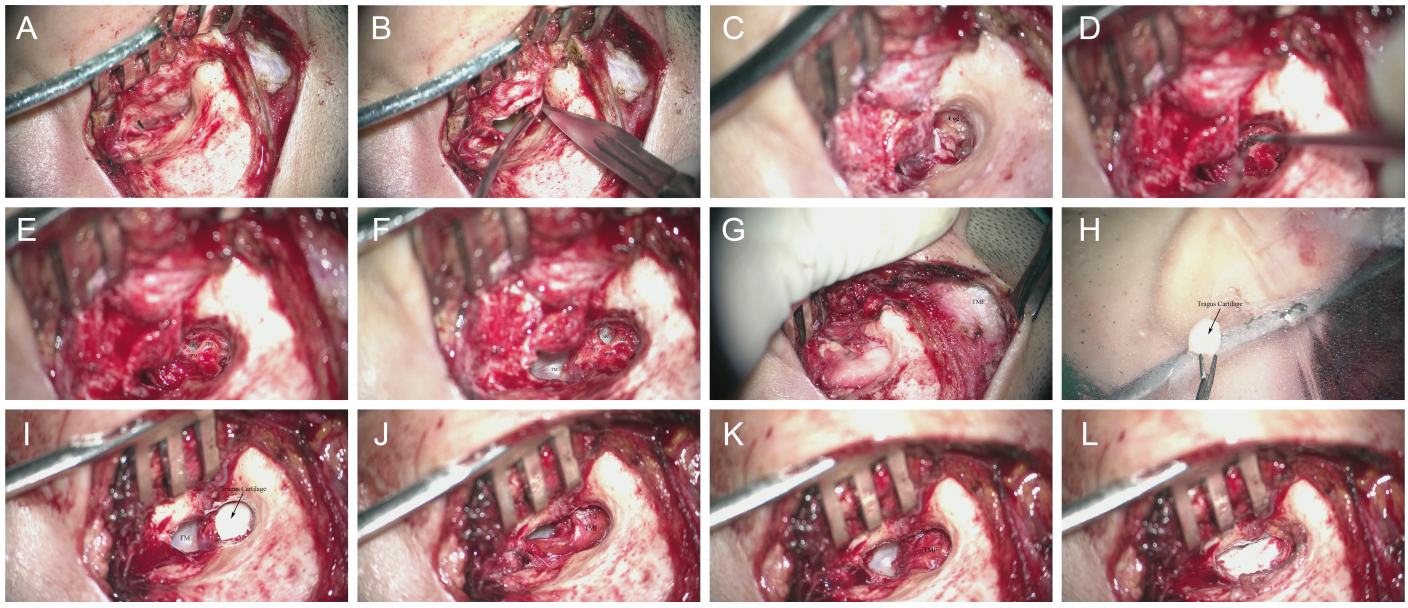

Figure 3. Focus and process of SRO. Make an incision to expose the mastoid process and the external auditory canal (A). The skin of the external auditory canal was cut with a surgical knife (B). Grind the attic using an electric drill (C). Crocheted open supratubal recess (D). The supratubal recess of the ear canal has opened (E-F). The temporal myofascial membrane was taken (G). An appropriately sized cartilage was taken (H). The cartilage replaces the attic lateral wall (I). Temporal muscle fascia is laid out of the cartilage (J). Intrinsic fascia implantation (K). Fill the external auditory canal with absorbable material (L). HM, head of the malleus; SPM, short process of the malleus; SR, supratubal recess; SRO, supratubal recess opened; TM, tympanic membrane; TMF, temporal muscle fascia.

CONCLUSION

By comparing the differences between the 3 surgical methods and analyzing their postoperative results, it is not difficult to conclude that the recurrence rate and infection rate of CWU-SOR is lower than the other 2 surgical methods. Because the CWU-SRO procedure removed the attic diaphragm and opened the supratubular recess, the middle ear ventilation chain (the origin is the nasopharynx and the destination is the mastoid process) was unobstructed. In this way, the airflow in the middle ear is smooth and the air pressure is stable. Moreover, the secretions from the middle ear can also smoothly flow out from the pharyngeal orifice of the Eustachian tube, keeping the middle ear dry and clean. In addition, to achieve the overall curative effect, simultaneous Eustachian tube balloon dilation is a better choice for patients with poor Eustachian tube ventilation function.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Guangzhou Twelfth People's Hospital, (Approval No: 2022040).

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.Z., H.Z.; Design – T.M., H.G.; Supervision – H.Z.; Materials – H.Z., H.G.; Data Collection and/or Processing –T.M., H.G; Analysis and/or Interpretation – H.Z., H.Z.; Literature Review – H.Z., H.G.; Writing – H.Z., H.Z.; Critical Review – T.M., H.G.

Acknowledgments: We thank all the all middle ear cholesteatoma patients for participating in this study, as well as the ancillary examination technicians for their help.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declare that this study had received no financial support.

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