Radio-Tympano-Sinu-Orthesis with ^{186}Re-Colloid: A New Treatment Modality for Chronic Otitis Media and Paranasal Mucositis

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This preliminary treatment trial was performed to evaluate the safety and clinical efficacy of intracavitary therapy with ^{186}Re-colloid in patients with recurrent otitis media and paranasal sinusitis, resistant to pharmacotherapy and surgical treatment. **Methods:** Thirty-nine applications of 5–35 MBq ^{186}Re-colloid into the tympanon and the paranasal sinuses were performed in 6 patients. Biodistribution and biokinetics were studied by gamma-camera imaging. Clinical success was documented 6–20 mo after therapy by each patient's self-evaluation and by rhinootologic follow-up, using a 4-step score. **Results:** No harmful side effects were seen. There was good-to-excellent clinical improvement with a score of $+1.44 \pm 0.5$ by each patient's self-evaluation and by physicians scoring of $+0.81 \pm 0.9$ with only negligible extracranial tracer deposition. **Conclusion:** This novel treatment option using intracavitary application of ^{186}Re-colloid in chronic otitis media and sinusitis is safe and effective. The term "radio-tympano-sinu-orthesis" might be proposed analogously to the well-known radiosynoviorthesis.

Key Words: intracavitary radionuclide therapy; ^{186}Re-sulfide; chronic otitis; eustachian tube dysfunction; paranasal sinusitis

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Radiation therapy of chronic otitis media and paranasal sinusitis is a treatment modality initially established nearly 100 y ago (*1*). In the following decades, tubal irradiation seemed to become an important treatment before tympanoplastic surgery or a monotherapy for therapy-resistant, chronic otitis media (*2*). High rates of recurrent tubal obstructions led to increasing invasiveness with an immediate approach to the pharyngeal tubal ostium using a flexible applicator (*3*) with β-emitting radionuclides for the first time. Because of a limited dosage distribution from outside the tubal ostium, a ^{32}P-filled applicator tube, placed inside the eustachian tube was developed in 1951 (*4*).

During the last 3 decades, irradiation treatment of otitis media became less common because of the increasing use of myringotomy drain tubes and evolution of endoscopic surgery. However, chronic tube dysfunction is still the most important reason for recurrent disease (*5*). Currently, no studies relating to radiotherapy of chronic inflammation of the paranasal sinuses exist.

The intracavitary instillation of unsealed β-emitting radionuclides, leading to a local high-energy irradiation, is a well-known therapeutic principle. Its most frequent application is the intraarticular injection in patients suffering from rheumatoid arthritis. This method is known as radiosynoviorthesis (RSO) and its clinical efficacy is well documented in many studies (*6*). The colloidal radionuclides are phagocytized by the superficial synoviocytes. The local irradiation leads to a reduction of volume of the synovial folds and finally to their dense fibrosis with a decreased secretion (*7*). Because of the resemblance of chronic mucosal inflammation with an enhanced secretory activity and swelling of the intracavitary tissue, the principle of RSO should be transferable to patients with therapy-resistant otitis media and sinusitis.

^{186}Re was chosen in our study because of its favorable biophysical characteristics with a physical half-life ($t_{1/2}$) of 90.6 h, β-emission with a maximum energy of 1,071 keV, and a mean energy of 330 keV, resulting in a mean tissue penetration depth of only 1.2 mm. An additional 8.5% γ-radiation with energy of 137 keV could be used for scintigraphic documentation of radionuclide distribution and dosimetry.

In this pilot study, the intracavitary application of ^{186}Re-colloid was to be investigated as a preliminary treatment trial in patients with therapy-resistant chronic otitis media, eustachian tube dysfunction or paranasal sinusitis. Analogously to RSO, the term "radio-tympano-sinu-orthesis" (RTSO) is proposed for this new treatment modality.

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MATERIALS AND METHODS

Altogether, 39 applications of ^{186}Re-colloid were performed in 6 patients (2 women, 4 men; age, 27–74 y; mean, of 52 y) who suffered from chronic mucositis of the tympanum, the eustachian tube, or the paranasal sinuses. Multiple previous treatment attempts, including surgery, antibiotics, and antiallergic pharmacotherapy, had been performed in all patients for several years but yielded insufficient results. Four of the 6 patients had repeated radionuclide applications with a minimal time interval of 2 wk for the respective localization as shown in Table 1.

All patients gave their informed consent after extensive explanation concerning radiation load and possible side effects such as temporary hearing impairment, tympanophonia, or even transient aggravation of symptoms caused by a radiogenic inflammation, known already from RSO.

To review the feasibility of this novel treatment approach, an initial estimation of the time of persistence of a colloidal radionuclide at the application site was performed using ^{99m}Tc-colloid scintigraphy of both tympanic cavities and the maxillary sinuses in the first patient. One and 24 h after injection of 200 MBq ^{99m}Tc-nanocolloid (Nanocoll; Nycomed Amersham, Buchler, Germany; particle diameter, <80 nm) through tympanostomy and endoscopic tubes, static images of the head were acquired using a double-head gamma-camera system (BodyScan; Siemens, Erlangen, Germany). Time–activity plots of the application sites were obtained using the regions-of-interest (ROI) technique. The biologic $t_{1/2}$ of the radionuclide was calculated by exponential curve fitting.

Commercially available ^{186}Re-colloid (CIS Bio Schering, Berlin, Germany; particle size, 5–10 nm) approved for intracavitary

TABLE 1
Patient Data, Surgical Interventions Before RTSO, and Application Protocol

Patient no.	Sex	Age (y)	Surgery	Localization	Date of application	Activity (MBq)
1	F	56	MT(lr), 3 × EE, 9 × EP, SP, ME(r)	TYR	9/24/99	5
					11/5/99	10
					1/20/00	20
					6/23/00	20
					1/19/01	35
				TYL	9/24/99	5
					1/20/00	20
					6/23/00	20
					1/19/01	35
				FSR	10/21/99	10
					11/5/99	10
					7/14/00	20
				FSL	10/21/99	10
					11/5/99	10
					7/14/00	20
				MSR	10/21/99	10
					11/5/99	10
					1/19/00	35
				MSL	10/21/99	10
					11/5/99	10
					1/19/00	35
2	M	27	4 × EP, SP, FMS(lr)	FSR	3/2/01	20
				FSL	3/2/01	20
				MSR	3/2/01	20
				MSL	3/2/01	20
3	M	62	6 × EP, SP, EE, MT(lr)	TYR	11/11/99	10
					1/20/00	20
					12/1/00	20
				TYL	11/11/99	10
					1/20/00	20
					12/1/00	20
				MSR	12/1/00	20
				MSL	12/1/00	20
4	M	38	MT(r), TP(r), FMS(lr)	TYR	9/15/00	20
5	F	55	MT(lr), TP(lr), ME(r)	TYR	1/20/00	20
					7/14/00	20
				TYL	1/20/00	20
					7/14/00	20
6	M	74	MT(r), TP(r), ME(r)	TYR	1/20/00	20

TYR or TYL = right or left tympanic cavity; FSR or FSL = right or left frontal sinus; MSR or MSL = right or left maxillary sinus; MT = myringotomy tube; (lr) = left/right; EE = ethmoidectomy; EP = (pan)endoscopic polypectomy; SP = septoplasty; ME = mastoidectomy; FMS = fenestration of maxillary sinus; TP = tympanoplasty.

application was used for RTSO. Because of the lack of any preexisting experience, a very small activity of 5 MBq was chosen for the first application cycles, which is known from RSO to exert no serious side effects. Increasing activities, reaching a maximum of 35 MBq, were used for repeated applications under regular follow-up if no hearing impairment, pain, or worsening of audiometric data were seen and the clinical success was poor. A minimum time interval of 2 wk was kept between 2 successive applications at the same region.

Application of the radionuclide was performed either through myringotomy tubes in the case of otitis media or through endoscopic tubes for the paranasal sinuses. For this purpose, winged infusion sets were used after cutting off the needle top. The small activity volumes of approximately 50 μL were preloaded into the transparent tube, seen as a small bolus. Local anesthesia was performed using lidocaine spray. The positioning of the tube was done by the otorhinolaryngologist, with the top of the tube kept strictly in sight during application of the radionuclide.

Biokinetics as well as whole-body distribution studies were accomplished by static images of the head 1, 24, and 72 h after application, shown in Figure 1, with ROI analysis as described above. Planar whole-body images were acquired to evaluate unwanted tracer deposition outside the region of application, especially in cervical lymph nodes or the gastrointestinal tract, demonstrated in Figure 2.

The effects of RTSO were evaluated 6–20 mo after the last radionuclide application both by otorhinolaryngologic follow-up and by each patient's self-evaluation. In the meantime, further local therapeutic interferences were excluded. A scoring regimen was set up concerning the changes of both objective findings and subjective symptoms. All patients were evaluated using a standardized questionnaire concerning secretion of ear and nose, intensity of nostril obstruction and breathing impairment, pain, or degree of deafness in case of middle ear affection.

Objective reevaluation was performed by standard otorhinolaryngologic examination, including otoscopy and endoscopy of the endonasal cavities, audiometry, standard radiographs or CT scans, and sampling of tissue specimens in some cases. The results were summarized in a cumulative score with −1 for impairment in comparison with the state before RTSO, 0 for no changes, +1 for slight improvement, and +2 for excellent improvement.

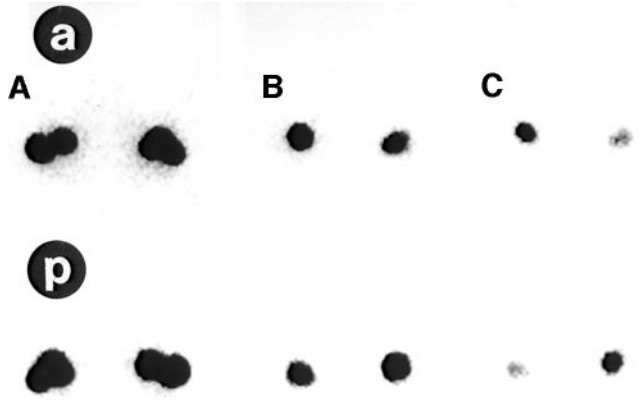

FIGURE 1. Static gamma-camera images of head from anterior (upper row) and posterior view (lower row) after application of 20 MBq ^{186}Re-colloid in each tympanum through myringotomy tube in patient 1. Images were acquired 1 h (A), 24 h (B), and 72 h (C) after radionuclide instillation and were analyzed for persistence of radiopharmaceutical by simple ROI technique. a = anterior; p = posterior.

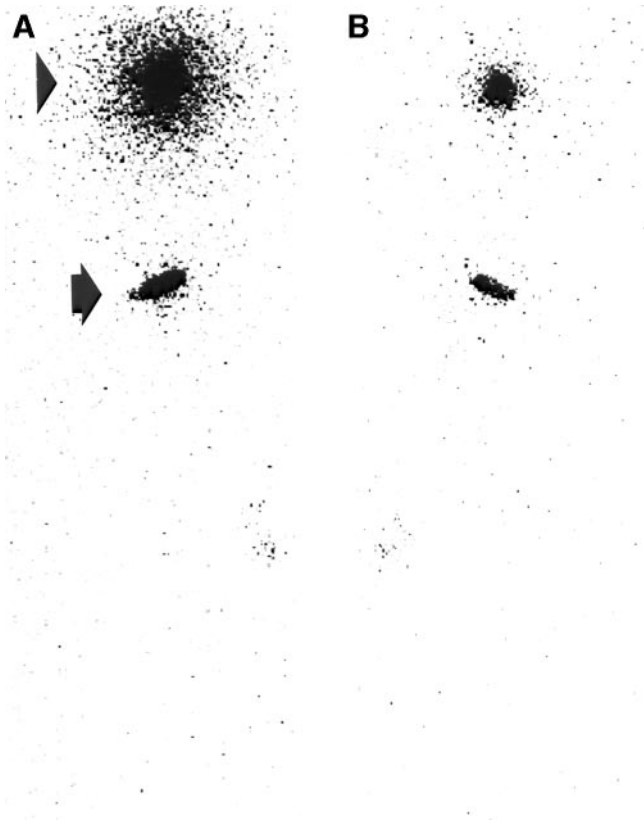

FIGURE 2. Whole-body images from ventral (A) and dorsal (B) view, 30 min after application of 20 MBq ^{186}Re-colloid (each) in both frontal sinuses (arrowhead) in patient 2. Extracranial tracer accumulation is seen in stomach (arrow), which was estimated to be approximately 6% of instilled activity. No activity was seen in cervical lymph nodes.

RESULTS

No serious side effects were observed in any patient. Only 1 patient complained of a slight hearing impairment the day after therapy but recovered completely after 1 wk. This was due to a disorder of sound conduction because of a transient, radiogenic mucositis, proven by endoscopy.

The mean biologic $t_{1/2}$ of the diagnostic ^{99m}Tc-nanocolloid was 29.6 h for the maxillary sinuses. In the case of middle-ear involvement, 36.1 h was calculated for the right and 30.6 h for the left tympanon.

For ^{186}Re-colloid, a mean biologic $t_{1/2}$ of 27.5 ± 13.2 h was demonstrated in the frontal and 25.6 ± 10.9 h in the maxillary sinuses, respectively. Radionuclide retention was always of longer duration in the tympanic cavities with a $t_{1/2}$ of 47.8 ± 15.9 h on the right and 47.6 ± 10.7 h on the left side as shown in Table 2.

Whole-body images showed extracranial tracer deposition only in 3 of 39 applications. A slight radionuclide deposition was seen in the gastrointestinal tract because of

TABLE 2
Mean Biologic Half-Life Values in Different Application Sites

Application site	Radiopharmaceutical	Biologic $t_{1/2}$ (h)
MSR or MSL	^{99m}Tc-Nanocolloid	29.6*
TYR	^{99m}Tc-Nanocolloid	36.1*
TYL	^{91m}Tc-Nanocolloid	30.6*
TYR	^{186}Re-Colloid	47.8 ± 15.9
TYL	^{186}Re-Colloid	47.6 ± 10.7
FSR or FSL	^{186}Re-Colloid	27.5 ± 13.2
MSR or MSL	^{186}Re-Colloid	25.6 ± 10.9

*Only 1 pretherapeutic application procedure.
MSR or MSL = right or left maxillary sinus; TYR or TYL = right or left tympanic cavity; FSR or FSL = right or left frontal sinus.

swallowing after drainage out of the application sites into the nasopharynx as shown in Figure 2. ROI estimation in a whole-body scan 30 min after RTSO revealed this portion to be of a maximum of approximately 6% of the applied activity. Measurable tracer accumulation in regional cervical lymph nodes was never detected.

Overall subjective success was proven by a cumulative mean self-evaluation score in all application sites of +1.44 ± 0.5, thus representing slight (+1) to excellent (+2) improvement. No significant differences in clinical improvement were detected between the mean score values of the tympanic cavity (+1.6 ± 0.5), the frontal sinuses (+1.5 ± 0.7), and the maxillary sinuses (+1.3 ± 0.6). Objective score estimates showed an overall improvement of + 0.81 ± 0.9 as summarized in Table 3. Follow-up examinations demonstrated the therapeutic success in some cases by measurement of audiometric data. A reduction of the mucosal swelling was proven by endoscopy, CT scans (Figs. 3 and 4), and, in 1 patient, by histologic examination. Discordant score data with a better subjective therapy response compared with the objective score were obtained in 3 of 6 patients, shown in Table 3.

No persistent aggravation of complaints was detected either by self-evaluation or by objective examination.

DISCUSSION

In this pilot study, feasibility and clinical efficacy of intracavitary application of ^{186}Re-colloid into the tympanic cavity and the paranasal sinuses in patients with chronic recurrent otitis media, eustachian tube dysfunction, and sinusitis were examined as a novel therapeutic approach. Our preliminary data of 39 applications in 6 patients, oth-

TABLE 3
Therapy Response Scores with Respect to Different Sites of Application, Different Cumulative Activities of ^{186}Re-Colloid, and Mean Biologic Half-Life Values

Patient no.	Application site	Cumulative activity (MBq)	Biologic $t_{1/2}$ (h)	Score		Evaluation (mo after last RTSO)
				Subj.	Obj.* (methods)	
1	TYR	90	37.8 ± 13.3	+1	+1 (A, E, CT)	8
	TYL	80	39.0 ± 9.9	+1	+1 (A, E, CT)	8
	FSR	40	29.0 ± 15.7	+2	+2 (A, E, CT)	14
	FSL	40	29.0 ± 15.7	+2	+2 (A, E, CT)	14
	MSR	55	19.7 ± 6.0	+2	0† (A, E, CT)	20
	MSL	55	19.7 ± 6.0	+2	+2 (A, E, CT)	20
2	FSR	20	23	+1	0 (E, CT, H)	6
	FSL	20	23	+1	0 (E, CT)	6
	MSR	20	26	+1	0 (E, CT, H)	6
	MSL	20	26	+1	0 (E, CT)	6
3	TYR	50	66.3 ± 14.2	+2	0 (A, E, CT)	7
	TYL	50	54.7 ± 3.0	+2	+2 (A, E, CT)	7
	MSR	20	43	+1	0 (A, E, CT)	7
	MSL	20	43	+1	0 (A, E, CT)	7
4	TYR	20	44	+2	+1 (A, E, CT)	6
5	TYR	40	51.0 ± 4.2	+1	—‡	14
	TYL	40	54.0 ± 8.5	+1	—‡	14
6	TYR	20	39	+2	+2 (A, E, CT)	20
	Mean ± SD			+1.44 ± 0.5	+0.81 ± 0.9	

*Estimation of objective score: A = audiometry; CT = CT scan; E = endoscopy with rigid and flexible endoscope and microscope; H = histologic findings.
†Obliteration of right maxillary sinus after surgery.
‡Evaluation only by telephone call.
Subj. = subjective; Obj. = objective; TYR or TYL = right or left tympanic cavity; FSR or FSL = right or left frontal sinus; MSR or MSL = right or left maxillary sinus.
Only 1 radionuclide application was performed in patients 2, 4, and 6 as well as in maxillary sinuses of patient 3.

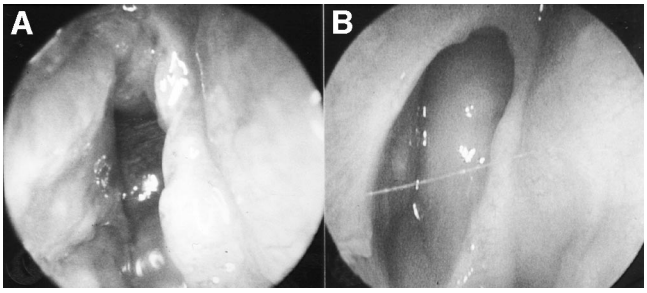

FIGURE 3. (A) Endoscopic view of ostium of left frontal sinus in patient 1, heavily constricted by swollen mucosa, resulting from chronic sinusitis. Fourteen months after treatment with cumulative dose of 40 MBq ^{186}Re-colloid, marked reduction in thickness of mucosal layer is seen (B), accompanied by significant clinical improvement.

erwise resistant to treatment, showed promising results by a subjective self-evaluation scoring system. Otorhinolaryngologic follow-up yielded slightly poorer results but still showed a positive therapeutic effect 6–20 mo after the last radionuclide application.

The most frequent reason for chronic otitis and eustachian tube dysfunction is a metaplastic mucositis and hyperplasia of the mucosa-associated lymphoid tissue in all parts of the tube. This tissue cannot be removed by any of the historical techniques of radiotherapy. Even β-radiation at the tubal ostium had no sufficient effects because of a limited tissue penetration with only 2% of the dosage in 10-mm depth (*8*). Using an applicator tube with 37 MBq of the pure β-emitter ^{32}P, placed directly intratubal under anesthesia for 30 min, a radiation dose of 12 Gy in 1-mm depth and decreasing to 0.7Gy in 3–4 mm was reached (*4*). Further studies referred to the use of other radionuclides such as ^{90}Sr, ^{90}Y, or ^{192}Ir (*5*) but did not change the treatment principle. Clinical success rates ranged from 59% to 76% (*2*). Regarding possible side effects, a slight buzzing in the ear or a temporary impairment of hearing was sometimes reported, but hearing was completely restored 3 wk after therapy (*2*,*9*). Verduijn (*10*) compared >2,500 patients after nasopharyngeal radium irradiation between 1945 and 1965 with an unexposed control group and did not find an overall significant increase in cancer mortality.

Thus, nasopharyngeal radiotherapy suffers either from an insufficient dosage distribution with a high risk of recurrence (*2*,*8*) or from high invasiveness (*4*,*5*). RTSO overcomes both restrictions and thus seems to be a potent new therapeutic approach.

^{99m}Tc-nanocolloid scintigraphy (diameter, <80 nm) revealed a rational retention time in both tympanic cavities and maxillary sinuses of about 30 h. With ^{186}Re-colloid, which has a smaller particle size of 5–10 nm, a longer biologic $t_{1/2}$ of approximately 48 h was seen in the middle ear, possibly due to a larger amount of radionuclide phagocytized by the mucosal cells. Probably because of a faster drainage, the retention times of both colloids are comparable in the paranasal sinuses.

Application of unsealed radioisotopes to the tympanum and the paranasal sinuses is to date restricted mainly to diagnostic procedures. Ventilation studies with ^{133}Xe were performed to noninvasively measure middle ear aeration (*11*). Intratubal application of ^{99m}Tc-albumin was used to evaluate tubal drainage function in transmission deafness (*12*). Moreover, the mucociliary clearance of maxillary sinus mucosa was examined using ^{99m}Tc-sulfocolloid (*13*).

In neurosurgery, a total regression of suprasellar arachnoid cysts was seen after stereotactic injection of ^{32}P, even without preceding surgical intervention (*14*). ^{90}Y-Colloid was used for treatment of recurrent cystic craniopharyngeomas and yielded regression in 88% (*15*). A local dose of approximately 200 Gy to the cyst wall was tolerated without any harmful side effects (*16*).

An exact calculation of total-body radiation load and the local dose at the application site is very difficult to perform in intracavitary therapy. Because of the lack of preexisting data on the application of ^{186}Re-colloid in patients with otitis and sinusitis, an estimation based on the data known from RSO seems reasonable. Manil et al. (*17*) found an effective whole-body dose of 380 μSv/MBq for ^{186}Re-sulfide. Assuming a comparable degree of leakage from the site of application, the maximum applied activity of 35 MBq ^{186}Re in RTSO would lead to an effective total-body dose of 13.3 mSv. However, this seems to be overestimated because of a maximum gastrointestinal leakage of only 6% of the applied activity. This is somewhat lower than drainage values in RSO, ranging from 2% to 12% (*17*).

The local radiation dose to the gastrointestinal tract is difficult to calculate because of the lack of data on ^{186}Re in this therapeutic setting. However, it is negligible compared with radioiodine therapy. Following International Commission on Radiological Protection data, an absorbed dose of 0.46 mGy/MBq ^{131}I for the stomach mucosa is assumed with 25% uptake of the thyroid. The maximum activity of ^{186}Re-colloid from RTSO inside the stomach was 2.1 MBq in our study. Because of a shorter physical $t_{1/2}$ and roughly comparable β-energy, the radiation dose to the stomach

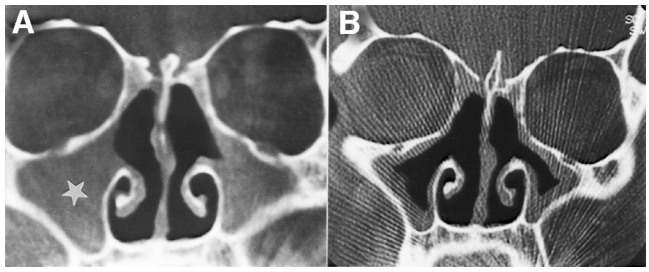

FIGURE 4. (A) On CT image, both maxillary sinuses of patient 1 are filled with swollen mucosa and inflammatory secretion (☆) as result of chronic mucositis. (B) Six months after RTSO of both sinuses with cumulative activity of 55 MBq ^{186}Re-colloid (each), CT follow-up showed significantly decreased mucous layer. However, follow-up another 14 mo later showed recurrent mucositis in right maxillary sinus, although patient still felt better than before RTSO (artifacts caused by dental implants).

should be far less with ^{186}Re than with ^{131}I, which would be approximately 1 mGy from 2.1 MBq activity.

Relating to the local dose at the site of radionuclide instillation, Johnson and Yanch (*18*) found a maximum dose of approximately 0.45Gy/MBq ^{186}Re in a computer simulation of RSO. The highest activity given for RTSO was 35 MBq, leading to a presumed maximum dose of 15.75 Gy on the mucosal surface. However, the depth at which the absorbed dose is equal to 10% of the maximum is only 1.0 mm for ^{186}Re (*18*). Thus, radiogenic damage to surrounding tissues was not expected. Comparable local doses of 12–15 Gy are reported for tubal irradiation with applicator tubes filled with 740 MBq ^{90}Sr or 37 MBq ^{32}P (*4*) and no enhanced rate of malignancies or other complications was reported in a meta-analysis covering 30 y and >28,000 patients (*19*). Thus, comparable clinical efficacy and similar radiation doses to the mucosa are achieved with RTSO, but far less invasively and without anesthesia. Moreover, the risk of a sensorineural deafness as a result of radiogenic cochlea destruction is negligible. A significant hearing loss resulting from percutaneous radiotherapy was reported only in patients with a cochlear dose of ≥60 Gy (*20*). This dose as well as the doses up to 200 Gy in neurosurgical settings (*16*) are far from the values expected in RTSO.

CONCLUSION

Intracavitary treatment of patients with chronic otitis media or sinusitis by application of ^{186}Re-colloid into the middle ear or the paranasal sinuses, called RTSO, was effective and well tolerated in our preliminary study. Clinical improvement is supported by objective data from audiometry, endoscopy, and CT.

The method of local irradiation of an inflamed mucosa by β-emitting radionuclides can thus be extended from RSO to otherwise therapy-resistant patients with chronic otitis media and paranasal sinusitis. Compared with other intracavitary treatments such as irradiation of intracranial cystic tumors, RTSO exerts much less radiation load and did not show any side effects in our first treatment trial. RTSO may overcome the disadvantages of insufficient radiation dose and high invasiveness seen in former treatment methods using simple x-ray therapy or different applicator tubes.

Further studies will be necessary to evaluate the clinical efficacy in a larger number of patients compared with other treatment modalities in chronic otitis media, eustachian tube dysfunction, and paranasal sinusitis.

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