



Original Article

Short-term Effects of Radioiodine Therapy on Auditory Function

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OBJECTIVE: Radioiodine therapy (RIT) is frequently utilized as an adjunctive treatment option for differentiated thyroid carcinoma following surgical intervention. The side effects of RIT are considered to emerge as a result of radioiodine accumulation in non-thyroidal tissues capable of iodine uptake. We aimed to evaluate the effects of RIT on auditory function.

MATERIALS and METHODS: Patients who had undergone total thyroidectomy and diagnosed to have differentiated thyroid carcinoma were analyzed. Those who were given RIT were included. Pure-tone audiometry and distortion product otoacoustic emission (DP-OAE) results were recorded along with patient demographics, RIT dose, and thyroid hormone profiles, both before and 3 months after RIT.

RESULTS: Here, 63 patients were enrolled. Following RIT, audiometric thresholds at 0.25, 0.5, 4, and 8 kHz in addition to pure-tone average increased significantly; however, the change in DP-OAE results was not statistically significant at any frequency. The RIT dose had no effect on auditory function.

CONCLUSION: In this study, we found some deleterious effects of RIT on audiometric thresholds, with no significant effect on DP-OAE results.

KEYWORDS: Radioiodine therapy, inner ear, audiometric thresholds, otoacoustic emission

INTRODUCTION

Radioiodine therapy (RIT) is commonly used for the treatment of well-differentiated thyroid carcinoma ^[1, 2]. It has the advantage of eradicating neoplastic foci and reducing the risk of recurrence ^[1, 3]. Several side effects of RIT were previously reported including salivary gland dysfunction, blood dyscrasias, alopecia, headache, epigastric pain, lacrimal gland dysfunction, conjunctivitis, nausea, vomiting, and secondary malignancies ^[1-5]. Salivary gland dysfunction is considered to be the most common complication of RIT and occurs in 11.5%-86% cases ^[1, 3]. In as many as 15% patients, this side effect may be permanent ^[2, 6]. Toxicity was reported to be associated with repeated RIT administration ^[1, 6]. The Na/K/Cl cotransport system concentrates radioactive iodine in the salivary gland and makes the salivary glands prone to dysfunction ^[3, 7]. The inner ear also harbors this Na/K/Cl cotransport system, located mainly in the stria vascularis, spiral ligament, and endolymphatic sac ^[8-11]. This system helps to maintain the endocochlear potential and the ionic composition of the endolymph ^[12]. Stria vascularis provides electrical drive to the outer hair cells ^[13].

Cochlear function can be monitored by otoacoustic emissions (OAEs). OAE and cochlear status are so closely associated that OAEs are used in many aspects of hearing evaluation including the differential diagnosis of sensorineural hearing loss, monitoring for occupational- and noise-induced hearing loss, and ototoxicity ^[14, 15]. Among the two commonly evoked OAEs, distortion product otoacoustic emissions (DP-OAE) provide a more specific frequency evaluation of the cochlea when compared to transient-evoked otoacoustic emissions (TE-OAE) ^[16]. DP-OAE is generated by the outer hair cells and recorded in response to two stimulating tones. Outer hair cells along with stria vascularis are considered as the primary targets of ototoxicity ^[13].

In this study, we aimed to investigate the effects of RIT on outer hair cell function in patients with the diagnosis of differentiated thyroid carcinoma.

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MATERIALS and METHODS

A prospective study was performed in the departments of otorhinolaryngology and nuclear medicine. Patients with differentiated thyroid carcinoma admitted for RIT between 2014 and 2016 were enrolled. The diagnosis of differentiated thyroid carcinoma was confirmed with histopathological examination following total thyroidectomy. Patients with systemic comorbidities including diabetes mellitus, hypertension, autoimmune diseases, and those using ototoxic drugs, as well as those with a history of ear surgery, hearing loss, and neoplastic disease, were not included. Otorhinolaryngological examination was performed on all the patients, and patients with tympanic membrane perforation, tinnitus, vestibular complaints, and vocal fold paresis/paralysis were excluded. Informed consent was taken from the patients and the study was approved by the Local Ethics Committee (505-25/7/2014).

The age and gender of the patients were recorded along with definitive histopathological results. To obtain a relatively homogenous population, only patients with papillary thyroid carcinoma were investigated. For all the patients, thyroid-stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4), thyroglobulin (Tg), and anti-thyroglobulin (anti-Tg) levels were determined, and conventional pure-tone audiometry and DP-OAE testing were performed both before and at least 3 months after the completion of RIT. Following total thyroidectomy (before RIT), patients were not given any external thyroid hormone supplements to provide a state of iodine starvation.

Pure-tone audiometry (AC 40; Interacoustics, Middelfart, Denmark) and DP-OAE (Otodynamics ILO 292 Echoport, Otodynamics Ltd., London, United Kingdom) were performed in a soundproof chamber by the same personnel. Middle-ear status was evaluated by both physical examination and immittance measurements. Patients with sensorineural or conductive type of hearing loss and those with type-B or type-C tympanograms were not included. Pure-tone thresholds were determined at 0.25, 0.5, 1, 2, 4, and 8 kHz frequencies. The pure-tone average (PTA) was determined by calculating the arithmetic mean of the threshold values at 0.5, 1, 2, and 4 kHz. Patients were instructed to stand still and breathe normally during DP-OAE testing. DP-OAEs were recorded bilaterally. The intensity of the F1 and F2 tones were 65 and 55 dB SPL, respectively, whereas F2/F1 (frequency) was 1.22. The emission at the 2F1-F2 frequency was recorded at 1, 1.4, 2, 2.8, and 4 kHz F2 frequencies. The test was repeated in the presence of a high rejection rate.

Radioiodine therapy was used to ablate any microscopic and/or macroscopic disease 4-6 weeks following total thyroidectomy. The RIT dose was adjusted as 100 or 150 mCi depending on the tumor size. Patients were internalized for at least 2 days in the nuclear medicine inpatient department.

The main outcome measures were the changes in the pure-tone audiometric thresholds and DP-OAE results (signal-to-noise ratio, SNR) following RIT. Secondary outcome measures included the effect of preoperative TSH, Tg, and anti-Tg levels; RIT dose on the change in audiometric thresholds; and DP-OAE results.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA). was used for statistical analysis. Mean, me-

Table 1. Thyrotropin, thyroglobulin, and anti-thyroglobulin levels before and after RIT

	Before RIT	After RIT	
	Mean±SD	Mean±SD	p
TSH	82.1±26.3	2.1±7.6	0.000
Tg	5.9±8.9	0.2±0.5	0.000
Anti-Tg	11.9±55.2	4.6±20.3	0.000

RIT: R-radioiodine therapy; TSH: thyroid-stimulating hormone; Tg: Thyroglobulin; Anti-Tg: anti-thyroglobulin; SD: standard deviation

Table 2. Audiometric thresholds and DP-OAE results before and after RIT

	Before RIT	After RIT	
	Mean±SD	Mean±SD	p
Audiometric thresholds			
0.25 kHz	13.7±7.1	15.0±7.3	0.043
0.5 kHz	12.1±6.9	13.4±7.3	0.035
1 kHz	12.8±6.8	13.5±8.7	0.570
2 kHz	12.8±7.8	13.9±8.3	0.157
4 kHz	17.8±8.7	20.8±14.7	0.012
8 kHz	19.5±9.1	26.4±16.4	0.000
PTA	13.9±6.1	15.4±7.9	0.008
DP-OAE results (SNR)			
1 kHz	2.1±8.6	2.8±9.6	0.344
1.4 kHz	6.1±9.7	6.4±8.8	0.513
2 kHz	4.8±8.7	5.3±8.3	0.242
2.8 kHz	2.4±9.8	2.5±10.3	0.588
4 kHz	3.4±10.9	4.1±10.0	0.391

RIT: radioiodine therapy; SNR: signal-to-noise ratio; SD: standard deviation

dian, standard deviation, minimum and maximum, frequency, and ratio parameters were used in the descriptive statistical investigation. The distribution of the data was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test was utilized for quantitative data analysis, and the Wilcoxon test was used for repeated measure analysis. Correlation was determined by the Spearman test. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 98 patients were investigated with the diagnosis of papillary thyroid carcinoma. Here 35 patients were excluded due to the abovementioned criteria, and 63 patients who received RIT were enrolled. None of the patients exhibited regional metastasis to the neck. The mean age was 45.4±11.6 years (range: 19-66 years) and the female-male ratio was 2:1. The RIT dose was 100 mCi for 44 patients (69.8%) and 150 mCi for 19 patients (30.2%). The mean TSH, Tg, and anti-Tg levels both before and after the completion of RIT are listed in Table 1.

Audiometric thresholds and DP-OAE results before and after RIT are given in Table 2. Although audiometric thresholds at all the frequencies increased following RIT, only the changes at the thresholds of 0.25, 0.5, 4, and 8 kHz and PTA were statistically significant ($p<0.05$), whereas the changes at 1 and 2 kHz frequencies were not ($p>0.05$).

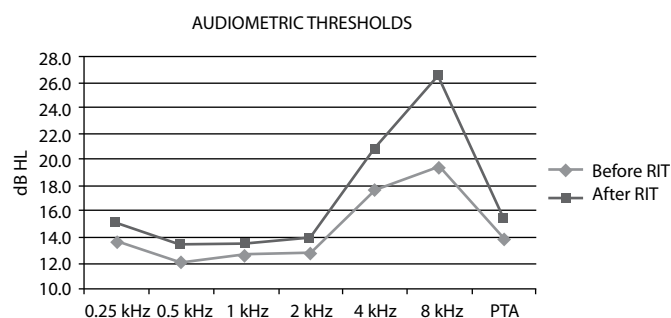


Figure 1. Changes in audiometric thresholds at specific frequencies.
RIT: radioiodine therapy

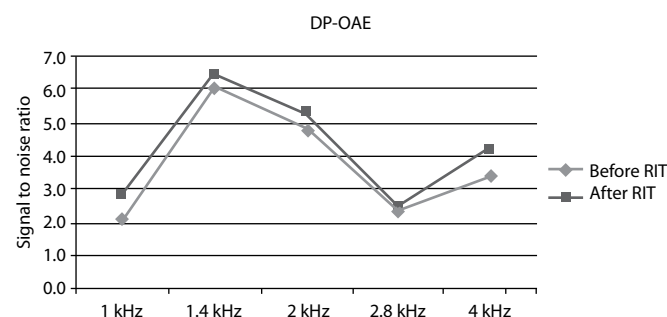


Figure 2. Changes in DP-OAE SNRs at specific frequencies.
RIT: radioiodine therapy; DP-OAE: distortion product otoacoustic emission

Table 3. Effect of RIT dose on audiometric thresholds and DP-OAE results

	RIT / 100 mCi (44 pt)	RIT / 150 mCi (19 pt)	
	Mean±SD	Mean±SD	p
Change in Audiometric Thresholds Following RIT			
0.25 kHz	1.3±7.7	1.4±8.5	0.845
0.5 kHz	1.4±7.1	1.0±7.7	0.401
1 kHz	0.9±8.2	0.3±5.4	0.998
2 kHz	0.7±6.6	2.1±6.5	0.385
4 kHz	2.3±11.4	4.8±10.8	0.113
8 kHz	7.7±13.1	5.0±14.7	0.203
PTA	1.3±6.1	2.0±5.0	0.451
Change in DP-OAE Results (SNR) Following RIT			
1 kHz	0.6±9.6	0.9±9.8	0.544
1.4 kHz	0.4±7.9	0.0±11.1	0.842
2 kHz	0.2±8.4	1.1±6.9	0.786
2.8 kHz	-0.2±8.7	0.9±8.3	0.422
4 kHz	0.9±10.7	0.5±8.7	0.996

RIT: radioiodine therapy; DP-OAE: distortion product otoacoustic emission; SNR: signal-to-noise ratio; SD: standard deviation

Following RIT, DP-OAE results increased at all the frequencies; however, no significant change was detected at any frequency ($p>0.05$). The changes in audiometric thresholds and DP-OAE results are shown in Figures 1 and 2, respectively.

The effect of RIT dose (100 vs. 150 mCi) on the changes in audiometric thresholds and DP-OAE results was not significant at any frequency ($p>0.05$) (Table 3).

The changes in audiometric thresholds were not correlated with the TSH, Tg, and anti-Tg levels at any frequency ($p>0.05$). Age was found to have a positive correlation with the changes in audiometric thresholds only at 4 and 8 kHz frequencies ($p=0.016$ and $p=0.023$, respectively).

The changes in DP-OAE results were not correlated with age and anti-Tg level at any frequency ($p>0.05$). On the other hand, the TSH level before RIT had a negative correlation with the change in DP-OAE result at only 2 kHz ($p=0.027$) and the Tg level before RIT had a positive correlation at only 4 kHz ($p=0.001$).

DISCUSSION

Radioiodine therapy is commonly used as an adjunctive treatment for differentiated thyroid carcinomas following surgical intervention as well as a primary treatment modality in Grave's disease, albeit at lower doses [17]. RIT is administered to ablate residual and/or metastatic disease [18, 19]. Additionally, radioactive iodine (^{131}I) is also used during follow-up scanning and treatment of recurrent disease. The ability of the thyroid tissue to take up ^{131}I depends on a transport mechanism, namely, sodium iodine symporter (NIS). Physiologically, the main function of NIS is to transport iodide from the blood to the thyroid follicular cells along with sodium [20]. $\text{Na}^+/\text{K}^+\text{ATPase}$ pump provides energy for this transport system [21]. Interestingly, NIS was demonstrated to be expressed in various normal non-thyroid tissues including salivary glands, lacrimal glands, breasts, stomach, intestine, lungs, and kidneys [22, 23]. This finding may be associated with both the early/short-term and late/long-term side effects of RIT, including sialadenitis, xerostomia, gastritis, nausea/vomiting, dental caries, taste dysfunction, dry eye, and pulmonary fibrosis.

Normal inner ear function is essential for both hearing and maintaining balance. The inner ear comprises various ion transport mechanisms located in many types of cells. Hair cells rely on ionic gradients for receptor function. Stria vascularis is known to generate the positive potential for providing ionic gradient [20]. Fibrocytes of the stria vascularis contain $\text{Na}^+/\text{K}^+/\text{Cl}^-$ transporter that concentrates K^+ ions in the intracellular compartment. The same transporter is also located in the cell membrane of the marginal cells facing the interstitial fluid [8].

The inner ear shares some similar transport systems with the thyroid gland. Pendrin, the most important example, helps to provide positive endocochlear potential and high-potassium environment in the endolymph. Pendrin mutation leads to goiter and sensorineural hearing loss, known as Pendred syndrome [24]. In the inner ear, pendrin is expressed in the cells of the spiral prominence and outer sulcus. Pendrin is a member of a family of anion transporters and has been shown to transport iodide, chloride, and nitrate [24]. However, NIS, described in the thyroid follicular cells, was never demonstrated in the inner ear cells to date. In this study, we aimed to investigate the effects of RIT on cochlear function, since the inner ear is well known to harbor similar systems that transport iodine.

We utilized pure-tone audiometry and DP-OAE to evaluate the inner ear function. OAEs are closely related to the outer hair cell function. OAEs, also known as Kemp potentials, have widespread clinical applications [19]. The main advantages of OAEs include simplicity,

non-invasiveness, and cost-effectiveness^[25]. DP-OAEs provide strong evidence of normal cochlear function and have the advantage of reflecting the physiological function of the inner ear more closely than the other types of OAEs^[25]. Our results indicated that RIT had no significant effect on the DP-OAE results. However, RIT seemed to significantly increase the audiometric thresholds at some specific frequencies. Audiometric thresholds at intermediate frequencies (1 and 2 kHz) did not change significantly, but those at lower (0.25 and 0.5 kHz) and higher (4 and 8 kHz) frequencies in addition to PTA increased significantly.

Thyroid hormones are essential for the normal development of auditory systems^[26]. Both early-onset congenital hypothyroidism and environmental iodine deficiency may lead to hearing loss in both humans and rats^[27, 28]. Psaltakos et al.^[29] investigated the changes in audiometric thresholds and TE-OAE results in patients who had undergone total thyroidectomy. They reported a significant decrease in TE-OAE SNRs and increase in audiometric thresholds. We investigated the short-term effects of RIT on hearing function in a similar population and determined that audiometric thresholds increased significantly in some (0.25, 0.5, 4, and 8 kHz) frequencies, whereas no significant change was noted in the DP-OAE SNRs. In some previous reports, the decline in cochlear function following hypothyroidism was reported to improve with thyroid replacement therapy^[30, 31]. In our study, despite the addition of thyroid replacement therapy along with RIT, audiometric thresholds increased in some frequencies.

Increased audiometric thresholds in the presence of similar DP-OAE results may suggest a retrocochlear effect. However, we did not support our findings with auditory brainstem response, which is one of the drawbacks of this study. Since OAE is not related to ion transport through the stria vascularis but associated with outer hair cell function, another explanation for the discrepancy between audiometric thresholds and DP-OAE results might involve damage to the ion transport system by RIT.

The use of different RIT doses (100 vs. 150 mCi) had no significant impact on the change in either the DP-OAE results or the audiometric thresholds. The age of the patient did not have a significant correlation with the change in the DP-OAE results, but it seemed to correlate with audiometric thresholds at 4 and 8 kHz frequencies. The TSH level determined before RIT was only correlated with the change at 2-kHz DP-OAE result, with no effect on the change in audiometric thresholds at any frequency. Similarly, the Tg level was only correlated with the change at the 4-kHz DP-OAE results and the anti-Tg level was correlated with neither the DP-OAE nor audiometric thresholds.

In this study, the deleterious effects of RIT were detected on audiometric thresholds at lower and higher frequencies, with no significant effects on the DP-OAE results.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Training and Research Hospital.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.T.E., M.Y.; Design - M.Y., S.B.; Supervision - O.Y., D.T.E.; Resources - S.B., M.Y.; Materials - M.Y., D.T.E., S.B.; Data Collection and/or Processing - D.T.E., M.Y.; Analysis and/or Interpretation - S.B., O.Y., D.T.E., M.Y.; Literature Search - D.T.E., M.Y.; Writing Manuscript - D.T.E., M.Y.; Critical Review - O.Y., S.B.

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