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CLINICAL INVESTIGATION **Head and Neck**

OTOTOXICITY AFTER RADIOTHERAPY FOR HEAD AND NECK TUMORS

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Purpose: To investigate the incidence of radiation-induced ototoxicity according to the total dose delivered to specific parts of the auditory system, fractionation, and chemotherapy.

Methods and Materials: Records of 325 patients treated for primary extracranial head and neck tumors with curative intent who received radiotherapy between 1964 and 2000 (median follow-up, 5.4 years) were retrospectively reviewed. Reconstructions of the treatment plans were generated to estimate the doses received by components of the auditory system.

Results: Radiotherapy-induced morbidity developed in 41.8% of patients (external ear, 33.2%; middle ear, 28.6%; and inner ear, 26.8%). Univariate/multivariate analyses indicate that total dose received by parts of the auditory system seem to be significant, though fractionation and chemoradiation may contribute to the incidence of ototoxicities. Sensorineural hearing loss (SNHL) was observed in 49 patients (15.1%). Univariate and multivariate analyses indicated that age ($p = 0.0177$ and $p = 0.005$) and dose to cochlea ($p < 0.0001$ and $p < 0.0001$) were significant, and chemoradiation ($p = 0.0281$ and $p = 0.006$) may increase the incidence of SNHL. Five-year and 10-year actuarial risk of clinically overt SNHL increased to 37% ($p > 0.0001$) above doses of 60.5 Gy compared to 3% at doses below 60.5 Gy. For patients treated with adjuvant chemotherapy, clinically overt SNHL increased to 30% compared to 18% in the no-chemotherapy group at 10 years ($p = 0.0281$).

Conclusion: Radiotherapy toxicity was observed in all parts of the auditory system with median doses for incidence varying between 60 Gy to 66 Gy. Total dose to organ seems to be a significant factor though fractionation and chemo-radiation may contribute to ototoxicities.

Ototoxicity, Radiotherapy, Head and neck tumors.

INTRODUCTION

Often in the course of high-dose radiation therapy (RT) for head and neck cancers, the entire hearing apparatus or parts of the auditory system receive high doses of RT and exhibit various RT-induced injuries to the external, middle, and inner ear (1). Morbidities pertaining to the external ear include reactions involving the preauricular region, the auricle, and the external auditory canal (EAC) (1, 2). Both acute and delayed events with varying degrees of morbidity may occur. Among the middle ear complications, eustachian tube dysfunction, consequential otitis media with effusion (OME), and transient conductive hearing loss remain the most common complications. Thickening of the tympanic membrane (TM) with sclerosis and perforation has also been reported. Higher doses of RT may cause middle ear fibrosis and/or ossicular atrophy. Morbidities associated with the inner ear include a wide variety of manifestations such as tinnitus, labyrinthitis, canal paresis, vertigo/balance problems, and sensorineural hearing loss (SNHL). Hearing loss and neurologic deficits remain the most significant RT-induced ototoxicities.

Depending where the RT-induced lesion is located, the underlying physiologic processes causing hearing loss may differ. If the cause of the hearing loss is damage to components of the middle ear, including the eustachian tube or the osseous chain, it is classified as conductive. Conversely, SNHL is caused by a lesion in the cochlea or retro-cochlear component of the auditory system.

Despite the diversity, complexity, and extent of its functional consequences, post-RT ototoxicity is sparsely reported in the radiation oncology literature. The association of dose received by individual components of the auditory system and subsequent morbidity have been rarely documented. The purpose of this study is to evaluate the inci-

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Table 1. Primary site

Site	Number of patients	Percent
Nasal cavity	60	18
Nasal cavity/nasal vestibule	1	<1
Nasopharynx	124	38
Sinus: frontal	2	1
Sinus: ethmoid	33	10
Sinus: sphenoid	5	2
Sinus: maxillary	58	18
Others	42	13

dence of toxicities associated with individual components of the auditory system and the corresponding RT dose received by those components.

METHODS AND MATERIALS

For this retrospective study, medical records from the Departments of Otolaryngology, Audiology, Radiation Oncology, and Neurology as well as extra-institutional otolaryngologists and audiologists were reviewed for patients treated with RT between 1965 and 2000 for extracranial head and neck malignancies including the nasopharynx, paranasal sinuses, and nasal cavity (Table 1). Patients with primary tumors of any part of the auditory system and those with an extension of primary tumor to any part of the auditory system were excluded.

Additional exclusion criteria were: (*1*) auditory apparatus outside the treatment field or near the edge of the treatment field making the dose calculation difficult; (*2*) less than 6 months of follow-up; (*3*) prior RT at another facility; (*4*) palliative RT; (*5*) discontinued RT before completing treatment; and (*6*) pre-RT audiologic problems or otologic conditions reported at the initial consultation that may cause or contribute to hearing loss. Patients with pre-RT OME secondary to nasopharyngeal disease were included.

Three-hundred-25 patients met the selection criteria, including 214 males and 111 females. Two-hundred-76 patients were White, 40 were African-American, 4 were Asian, and 5 were Latin American.

Treatment considerations

Treatment considerations, beam energies, portal arrangements, fraction size, and total dose varied because of heterogeneity of tumor histologies and due to a time period of 35 years. Two-hundred-3 patients were treated with once-daily fractionation with the fraction size varying from 136 to 200 cGy, and 122 received twice-daily treatment with the fraction size varying between 1.1 and 1.2 Gy. All patients were treated 5 days per week. Among the 42 patients with chemotherapy, 23 patients received neoadjuvant, 6 concurrent, and 11 adjuvant chemotherapy alone, 2 received a combination of the two types. For every patient, by using their original planning computed tomographic (CT) scan, a composite 3-dimensional reconstruction of the treatment plan was generated to estimate doses to the external ear, tympanic membrane, the middle ear, the vestibule, and the cochlea by delineating each structure on the CT scan (Fig. 1). The mean doses to each of the organs at risk (OAR) were utilized for dosimetric analysis.

For patients treated earlier in the series, before the routine use of CT-based treatment planning, Rando Phantom® CT scans (2.0 mm slice in auditory apparatus) scaled to match patient dimensions, were used as a proxy patient. Uncertainties due to anatomic variations between the Rando-CT and actual patient anatomies were reduced by a standard procedure established by superimposing the actual patient contours on the corresponding CT slice of the proxy phantom to determine an averaged scaling factor. The scaled CT slices of the standard proxy phantom were used for treatment planning.

Otologic/audiometric assessment

Pre- and post-RT audiologic evaluations were obtained by reviewing records from intra- and extra-institutional otolaryngology and audiology departments. The median clinical follow-up was 5.4 years (range, 0.5–30.5 years).

The criteria for diagnosing toxicities after radiation included specific morbidity as a documented diagnosis from otologic or audiometric follow-up examinations. Patients receiving either i.v. antibiotic treatment or mastoidectomy for a stated diagnosis of acute mastoiditis were considered to have true acute mastoiditis. Isolated radiographic reports of mastoiditis were excluded. Canal stenosis was identified by otologic examination and/or radiographic reports, but the diagnosis was not based upon rigorous clinical or radiographic criteria such as narrowing of >50% of the bony lumen. Chronic otitis externa included pruritus, otorrhea, scaling, edema, and erythema of the EAC or auricle. Acute otitis externa was defined as acute onset of pain, drainage, and swelling of the ear canal with extreme tenderness to traction on the pinna. Acute OM was diagnosed by the abrupt onset of symptoms due to middle ear inflammation (*i.e.*, otalgia and hearing loss) accompanied by signs of middle ear inflammation, such as effusion, conductive hearing loss and bulging, opacification, or erythema of the tympanic membrane. In the presence of a tympanostomy tube, criteria were similar, albeit with acute otorrhea from the tube. Chronic otitis media was divided into 2 categories: chronic otitis media with effusion (COME) and chronic suppurative otitis media (CSOM). The criteria for COME included documented presence of middle ear effusion without overt signs of acute inflammation. CSOM was diagnosed when the suppurative process persisted through a perforation or a tympanostomy tube. Acute onset of vertigo reported as lasting more than a day accompanied by SNHL was diagnosed as labyrinthitis. Chorda tympani dysfunction was considered as taste disturbance in the absence of mucositis or xerostomia. Semicircular canal paresis was identified by caloric weakness. Osteonecrosis was defined by the exposure of bone in the ear canal or radiographic evidence of bony sequestra.

The criterion for persistent, clinically relevant hearing loss was defined as an increase in the hearing threshold by ≥15 db that persisted for at least 2 consecutive evaluations separated by at least 6 months (3). Transient SNHL was defined as an increase in the bone conduction threshold, indicating clinically relevant SNHL of >15 db as observed on 1 audiogram, but a recovery of the bone conduction threshold of <10 db from the base line in any subsequent audiograms. Audiometric information included evaluating the bone conduction thresholds at 0.5 kHz, 1.0 kHz, 2.0 kHz, and 4.0 kHz, frequencies that cover the range of human speech. The results of these evaluations were reported in terms of the hearing loss (dB) averaged over these frequencies. In some cases, air and bone conduction were not distinguished in separate measurements and no further analysis was performed in those cases.

Of the 49 patients with persistent hearing loss, 27 had pre-RT audiometric evaluations, mostly in response to OM secondary to their disease. Among the remaining 22 patients, no pre-RT audio-

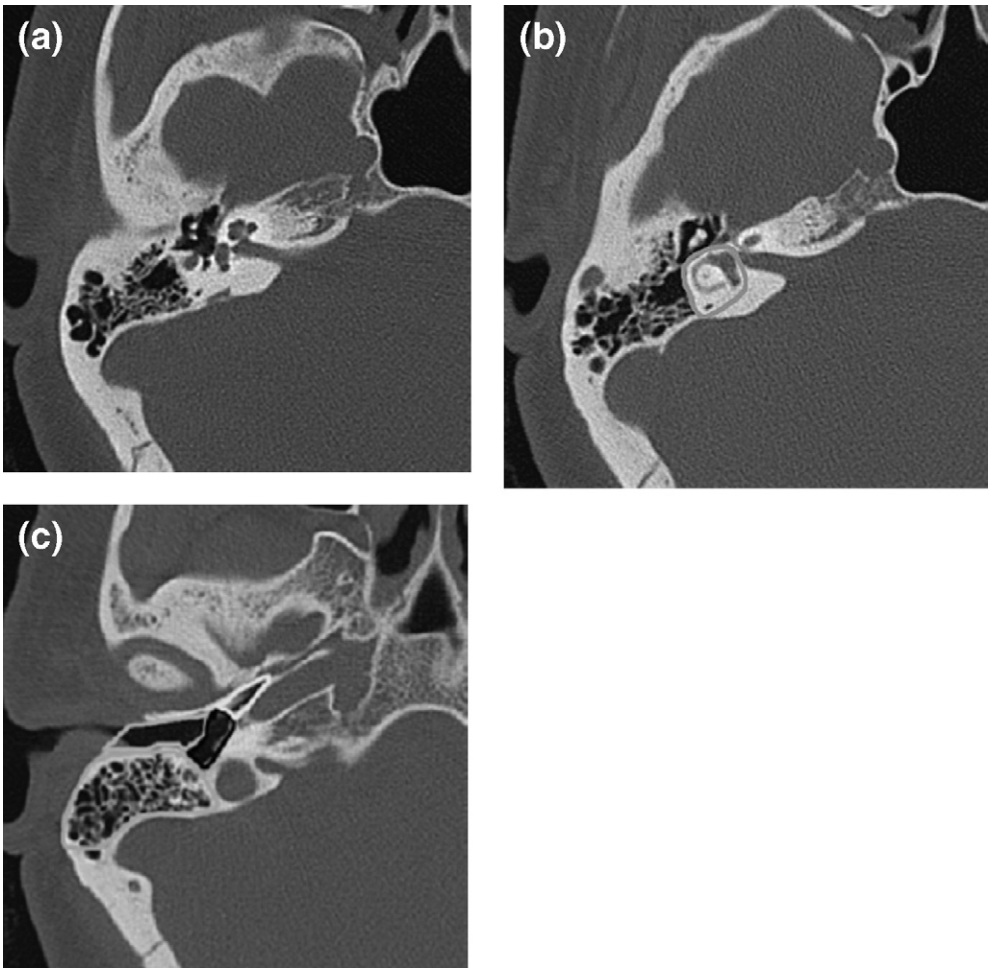

Fig. 1. Computed tomography sections used for dose calculations. (a) Midmodiolar cross-section. (b) Lateral semicircular canal. (c) Through the mastoid and tympanic ring.

metric evaluation was available and the audiologists based the diagnosis by comparing the affected ear to the normal ear or a standard baseline. Twelve patients whose follow-up notes indicated complaints of hearing deterioration were lost to follow-up. Either no audiometric records or no consecutive audiometric records of their evaluation were found to substantiate the diagnosis of persistent hearing loss and were not counted as an event. In addition, 24 patients demonstrated hearing loss greater than 15 db in their first audiogram, but significant recovery in their second audiogram (with an improvement in the hearing threshold of more than 10 db), indicating transient SNHL. These patients were not counted as an event in the analysis for persistent hearing loss.

In the patients for whom the pre-RT audiometric testing was available, the time duration between the testing and RT varied by up to 3 to 4 months. Both intra- and extra-institutional post-RT audiometric testing usually corresponded initially with patient complaints of significant hearing deterioration and, thereafter, at an average duration of 6 months. Due to the retrospective nature of this study, the intervals between post-RT tests and treatment varied from patient to patient; pre-audiometric and post-audiometric tests were also performed by various audiologists. The subject of this study is restricted to the reported incidence of ototoxicity to all parts of the auditory system and the corresponding relevant RT dosimetry, but not the audiometric analysis pertaining to post-RT hearing loss per frequency or loss of discrimination.

Statistical analysis

SAS software (SAS Institute Inc., Cary, NC) was used for all statistical analyses (4). The Kaplan-Meier product-limit method was used to estimate freedom from SNHL (5). The impact on this endpoint by total dose and fractionation was assessed with the log-rank test statistic. Cox regression was implemented to test the impact of selected explanatory variables on freedom from SNHL; the variables were total dose received by the cochlea, fractionation, dose per fraction, gender, age of the patient at the time of treatment, and chemo-radiation (6). Fisher's Exact Test was implemented to assess the correlations among all toxicities.

Time to event data were not reliably available for other recorded toxicities; only the presence or absence of each was recorded. Therefore, Fisher's Exact Test was used to analyze the effect of dose, fractionation and chemo-radiation on each. Further, nominal logistic multiple regression was used to assess the impact of these same 3 explanatory variables on each endpoint. Correlations among these endpoints was also assessed by Fisher's Exact Test.

RESULTS

Radiation therapy-induced morbidity was observed in all parts, often involving multiple parts of the auditory system.

Table 2. Univariate analysis

	TOT-DOSE	FX	CHE-RT
External ear			
Otitis externa acute	0.01	0.020	0.046
Otitis externa chronic	<0.01	<0.01	0.021
Atrophy	<0.01	0.015	0.040
Canal stenosis	<0.01	0.017	0.040
Middle ear			
Tympanic membrane perforation	<0.01	0.11	<0.01
Otitis media with effusion (chronic)	<0.01	0.10	<0.042
Chorda tympani dysfunction	<0.01	0.26	0.51
Middle ear fibrosis	0.02	0.14	0.66
Mastoiditis	0.02	0.12	0.14
Inner ear			
Tinnitis	0.20	0.32	0.81
Vertigo/balance problem	0.032	0.99	0.65
Caloric deficiency (canal paresis)	<0.01	0.040	0.99
Labrynthitis	0.04	0.030	<0.01

Abbreviations: TOT-DOSE = Total dose received by the corresponding part of otologic system; FX = fractionation (once-a-day versus twice-a-day); CHE-RT = chemotherapy and radiation

Among the 325 patients in this study, 136 patients (41.8%) exhibited some ototoxicity pertaining to one or more parts of the auditory system. One-hundred-8 patients (33.2%) had external ear complications, 98 patients (28.6%) had middle ear toxicity, and 87 patients (26.8%) had inner ear morbidity. The results of univariate (Table 2) and multivariate (Table 3) analyses and the percentage incidence of specific toxicity in 5 Gy dose bins is presented in the tables (Table 4). Correlations among patients with simultaneous toxicity are presented (Table 5).

External ear

Among the observed reactions, early external ear morbidity during the course of RT included skin reactions involving the auricle, external auditory canal, and periauricular region. Late reactions included acute otitis externa, chronic otitis externa, atrophy, deep ulceration, osteo/cartilaginous necrosis of the EAC, and/or EAC stenosis.

The percentage incidence of the external ear toxicities and corresponding doses are reported in Table 6. Uninvariate analysis indicated significance of fractionation, chemoradiation, and total dose to the external ear for acute and chronic otitis externa, atrophy, and canal stenosis. Multivariate analysis indicated significance of fractionation for atrophy and canal stenosis, whereas chemoradiation and total dose to the external ear were significant for acute and chronic otitis externa. A Chi-square test indicated a co-relationship among patients with otitis externa and those with atrophy and canal stenosis.

Middle ear

Timpanic membrane complications included sclerosis and persistent perforation without or after removal of myringotomy tubes. Middle ear toxicities included acute OM during or immediately after RT, COME, CSOM, mastoiditis, post-RT transient CHL, long-term CHL in the absence of OME, or Eustachian tube dysfunction considered to be due to ossicular chain dysfunction (either necrosis or fixation). The percentage incidence of the middle ear toxicities, median doses, and median time interval of incidence are reported in Table 7.

Patients with long-term conductive hearing loss also had persistent SNHL, indicating a mixed hearing loss (Table 8). Univariate analysis indicates the significance of total dose to the middle ear for TM-perforation, OME, chorda tympani dysfunction, middle ear fibrosis, and mastoiditis; chemoradiation is significant for TM-perforation and OME. Multivariate analysis indicates the significance of chemo-radiation for OME and TM-perforation and total dose to the middle ear for TM-perforation, OME, and mastoiditis. A Chi-square test indicated a co-relationship among patients with OME and those with chorda tympani dysfunction, middle ear fibrosis, mastoiditis, labyrinthitis and SNHL.

Inner ear

Complications associated with the inner ear included tinnitus and vertigo/imbalance. Caloric weakness of greater than 20% was recorded in 22 of the 61 patients who underwent electronystagmography (ENG). The percentage incidence of the inner ear toxicities, median doses, and median time interval of incidence are reported in Table 8. Univariate analysis indicates the significance of total inner ear dose to vertigo/balance problems, caloric deficiency, and labyrinthitis; chemoradiation is significant for labyrinthitis, and fractionation is significant

Table 3. Multivariate analysis

	TOT-DOSE	FX	CHE-RT
External ear			
Otitis externa acute	0.025	0.290	0.045
Otitis externa chronic	<0.01	0.140	0.039
Atrophy	0.930	<0.01	0.220
Canal stenosis	0.940	<0.01	0.260
Middle ear			
Tympanic membrane perforation	<0.01	0.180	<0.01
Otitis media with effusion (chronic)	<0.01	0.670	0.048
Chorda tympani dysfunction	0.950	0.220	0.730
Middle ear fibrosis	0.940	0.140	0.930
Mastoiditis	0.008	0.200	0.411
Inner ear			
Tinnitis	0.190	0.200	0.590
Vertigo/balance problem	0.038	0.870	0.44
Caloric deficiency (canal paresis)	0.020	0.350	0.526
Labrynthitis	<0.01	0.07	<0.010

Abbreviations: TOT-DOSE = total dose received by the corresponding part of otologic system; FX = fractionation (once-a-day versus twice-a-day); CHE-RT = chemotherapy and radiation

Table 4. Percentage incidence of ototoxicities in relation to total dose received by the organ per dose bin of 5 Gy

Dose in Gy	<50	50-54.99	55.-59.99	60-64.99	65-69.99	≥70
External ear						
Otitis externa acute	1.4	6.6	8.8	9.8	16.6	25
Otitis externa chronic	5.4	11.4	14.0	25.8	33.3	41.6
Atrophy			24.6	38.7	38.8	41.6
Canal stenosis			8.9	32.3	44.4	50
Middle ear						
Tympanic membrane perforation		6.3	6.0	13.5	26.9	35
Otitis media with effusion (chronic)	1.4	11.4	45.6	61.3	61.1	66.7
Chorda tympani dysfunction				7.3	20.5	32.1
Middle ear fibrosis				2.4	9.1	21.4
Mastoiditis		2.8	3.8	3.7	11.4	17.8
Inner ear						
Vertigo/balance problem		21.8	16.6	15.4	17.3	30.3
Caloric deficiency (canal paresis)				7.0	12.0	24.2
Tinnitis		25.7	20.5	13.2	16.2	16.1
Labyrinthitis			2.2	2.6	7.4	19.4
Sensory neural hearing loss			6.8	13.2	33.8	35.5

for caloric weakness and labyrinthitis. Multivariate analysis indicates that total inner ear dose is significant for vertigo/balance problems and caloric weakness; chemoradiation is significant for labyrinthitis. A Chi-square test indicates a co-relationship among the patients with caloric weakness and vertigo balance problems and among the patients with labyrinthitis and SNHL.

The overall incidence of SNHL was 15.1%, whereas SNHL among the patients treated with more than 55 Gy was 22.2% (Table 8). Actuarial analysis showed that the 5- and 10-year freedom from clinically overt SNHL and CHL in the absence of COME or Eustachian tube dysfunction (possible ossicular chain damage) among all the patients was 80% (Fig. 2).

Table 5. Chi-square test indicating co-relationship between patients with simultaneous toxicities

	External ear						
	Atrophy	Canal stenosis					
Otitis externa (chronic)	<0.01	<0.01					
	Middle ear						
	Chorda tympani dysfunction	Middle ear fibrosis	Mastoiditis	Vertigo/balance problem	Caloric weakness	Labyrinthitis	Sensory neural hearing loss
Otitis media with effusion (chronic)	0.01	0.73	<0.01	0.26	0.12	0.01	<0.001
	Inner ear						
	Vertigo/balance problem						
Caloric weakness (canal paresis)	<0.01						
	Tinnitis	Caloric weakness	Vertigo/balance problem	Labyrinthitis			
Sensory neural hearing loss	0.82	0.55	0.83	<0.001			
	Tinnitis						
Labyrinthitis	0.71						

Table 6. External ear complications

Complication	Number of patients (%)	Median dose (Gy) (range)
Early reaction (during the course of radiation therapy treatment)		
Otitis externa (acute): Erythema, dry/moist desquamation, ulceration of skin	93 (28.6%)	60.5 (45 – 84)
Late reactions (after completing radiation therapy treatment)		
Otitis externa (acute)	20 (6.5%)	58 (45 – 82)
Otitis externa (chronic)	42 (12.6%)	
Atrophy (deep ulceration, osteo/cartilaginous necrosis of EAC)	38 (11.6%)	65 (59 – 80)
Canal stenosis	29 (8.9%)	65.5 (59 – 79.5)

SNHL and total dose to cochlea

Both univariate and multivariate analyses indicate the dependence of SNHL on total dose to cochlea (Table 9). Starting at 55 Gy the incidence of SNHL increased consistently with dose to cochlea (Table 4). Five-year and 10-year actuarial risk of clinically overt SNHL increased to 37% ($p > 0.0001$) above doses of 60.5 Gy compared to 3% at doses below 60.5 Gy (Fig. 3a).

SNHL and latency

The median interval between RT and the development of persistent SNHL was 1.8 years (range, 0.5–5.9 years). For patients who received doses greater than or less than 60 Gy, the latency time was similar, indicating that the latency is not affected by the total dose received by the cochlear apparatus. When stratified by fractionation schedule, the median time interval for SNHL was 2.1 years for patients treated with once-daily fractionation compared to 1.45 years for those treated with twice-daily fractionation. The median latency for persistent SNHL among 11 patients who received adjuvant chemotherapy combined with RT was 0.8 years, compared to 2.0 years for 38 patients who received RT alone.

Total dose and age

Eleven percent of the patients below the age of 50 years had SNHL, whereas for those above the age of 50 it was 18%. The median dose received by the cochlea for patients below 50 years with an incidence of SNHL remained comparable to those above 50 with SNHL, indicating a lack of dose-age dependence.

SNHL and hyperfractionation

Of the 49 patients with clinically overt SNHL, 30 were treated with once-daily fractionation and 19 were treated with twice-daily fractionation with an overall incidence of 14.7% for the former and 15.7% for the latter. The 5-year and 10-year actuarial estimates for freedom from clinically overt SNHL and CHL were 81% and 80%, respectively (Fig. 2). When fractionation and total dose were further separated to test the interaction among them, it appears that the impact on SNHL is still due primarily to total dose alone. The 5- and 10-year estimates of freedom from clinically overt SNHL for doses less than 60.5 Gy were 98% for those treated with once-daily and 95% for those treated with twice-daily fractionation (Fig. 3b). When doses greater than 60.5 Gy were delivered with twice-a-day fractionation, the freedom from clinically overt SNHL was 59% at 5 years and 57% at 10 years compared to 71% at 5 years and 67% at 10 years for those irradiated once-daily ($p < 0.0001$).

SNHL after chemotherapy combined with RT

Of the 42 patients who received chemotherapy, 11 patients (26.1%) had SNHL compared with 38 of 282 patients (13.4%) treated with RT alone. Among these patients, 18% were treated with once-daily fractionation and 82% were treated with twice-daily fractionation. Freedom from clinically overt SHNL at 5 and 10 years for patients treated with

Table 7. Tympanic membrane and middle ear complications

Complication	Number of patients (%)	Median dose (Gy) (range)	Median time (years)
Tympanic membrane			
TM sclerosis	67 (20.6%)	60 (50 – 79.5)	
TM perforation (persistent) w/o tympanostomy	29 (9.0%)	63.5 (50 – 82)	0.5 years
TM perforation (persistent) post-tympanostomy	20 (6.1%)	63.5 (50 – 82)	0.5 years
Middle ear			
Acute otitis media	36 (11.5%)	64.7 (45 – 78)	
Chronic otitis media with effusion (OME)	73 (22.5%)	63.5 (45 – 80)	
Chronic suppurative otitis media (CSOM)	28 (8.0%)	65.5 (45–80)	
Chorda tympani dysfunction	23 (7.1%)	67.5 (60 – 76.5)	
Middle ear fibrosis	12 (3.7%)	68.5 (60 – 81)	
Mastoiditis	16 (4.9%)	65.0 (50 – 76.5)	

Table 8. Inner ear complications

Complication	Number of patients (%)	Median dose (Gy) (range)	Median time (years)
Tinnitus	44 (13.5%)	63.0 (50 – 74.5)	
Vertigo/imbalance	49 (15.1%)	64.0 (50 – 78)	
Labyrinthitis	15 (4.6%)	66.0 (55 – 80)	
Canal paresis (caloric weakness)	22 (6.8%)	66.0 (60 – 80)	
Sensorineural hearing loss (persistent)	Among all patients: 49 (15.1%) Among the patients who received dose > 55 Gy to inner ear: 49 (22.2%)	66.5 (55 – 81)	1.8 years (0.5-5.9)
Conductive hearing loss (without OME) (mixed hearing loss)	5 (1.5%)	67.5(65.0 – 74.2)	4.7 years (0.75-6.2)

adjuvant chemotherapy was 70% compared to 82% after RT alone ($p = 0.0281$) (Fig. 4).

Univariate and multivariate analysis

Univariate and multivariate analyses indicate that the patient's age and the total dose received by the cochlea are significant; also, combined chemotherapy with RT may be significant for SNHL, but fractionation schedule and gender are not (Table 9).

DISCUSSION

This study and dataset offer a range of RT-induced ototoxicities on a cohort of patients treated at one institution with megavoltage X-rays. The retrospective nature of this study, reconstruction of treatment plans, lack of consistency, frequency of otologic evaluations, and loss to follow-up may contribute to an underestimation of the results and may affect the interdependence of variables. Due to the availability of limited information on this topic, this study provides a broad basis for understanding ototoxicities and the various factors that may contribute in their incidence. Total dose received by parts of the auditory system seem to be more significant than either fractionation or chemo-radiation, though further studies are needed to verify that both may contribute to the incidence of ototoxicity. While most ototoxicities show a gradual increase in incidence with total dose received by the specific organ, reaching significant levels at or beyond 60 Gy, a specific tolerance level cannot be determined. The only conclusion regarding the correlation between different toxicities in the same patients (Table 3) is that a higher total dose to a specific part of the otologic system, chemo-radiation, or fractionation may result in multiple toxicities, possibly due to a similar pattern of tolerance exhibited by these parts among the individuals. This conclusion may also lead to belief that individuals experiencing one toxicity may be more susceptible to other toxicities, but interdependence of these toxicities cannot be inferred without further patho-physiologic evidence.

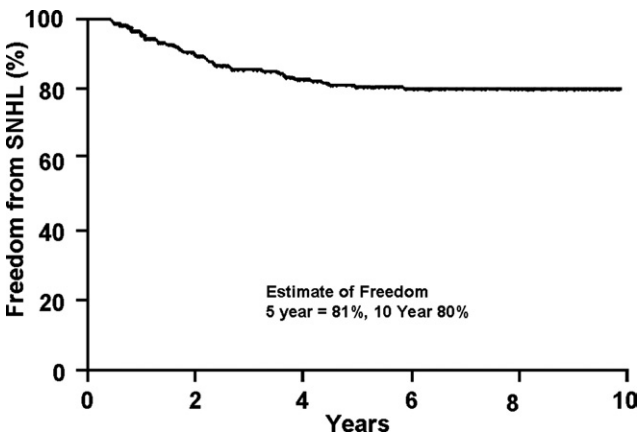

Fig. 2. Freedom from clinically overt sensorineural hearing loss and conductive hearing loss.

External ear

Both acute and late reactions to RT involving components of the external ear have been reported (7). Acute reactions that commonly occur during RT may include otitis externa, erythema, dry and moist desquamation, and ulceration of the skin of the pinna and the EAC resulting in mild to severe pain and otorhea. Radiation may induce osteitis and vasculitis of the surrounding soft tissue of the EAC, deep ulceration of the EAC, and osteonecrosis. Osteonecrosis of the temporal bone may produce persistent symptoms of refractory otitis externa. Damage from osteoradionecrosis to nearby structures may be due to the patients' predisposition to aggressive or chronic infectious processes or tissue destruction by the necrosis (8). Localized but progressive infections may result from bone necrosis with persistent suppuration. Leonetti *et al.* (9) reported on the incidence of life-threatening complications such as multiple brain abscesses, internal carotid artery aneurysm, aggressive EAC cholesteatoma, sigmoid sinus thrombosis, and otitic meningitis associated with temporal bone osteonecrosis.

Table 9. Sensorineural hearing loss

Univariate analysis		Multivariate analysis	
Age	0.0177	Age	0.005
Dose to cochlea	<0.0001	Dose to cochlea	<0.0001
Chemoradiation	0.0281	Chemoradiation	0.006
Fractionation	0.7947	Fractionation	0.4
Gender	0.7959	Gender	0.9

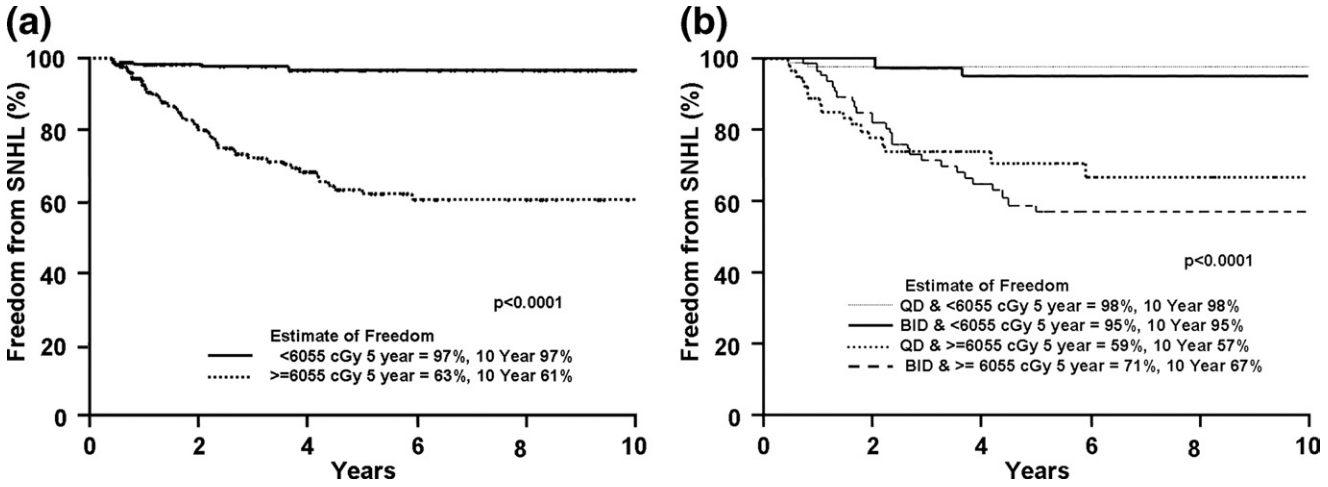

Fig. 3. (a) Freedom from clinically overt sensorineural hearing loss at doses $<$ and $>$ = 6050 cGy. (b) Freedom from clinically overt sensorineural hearing loss at doses $<$ and $>$ = 6050 cGy separated by fractionation.

Middle ear

TM perforation and persistent otorhea can follow fibrovascular granulation tissue proliferation, sometimes with inflammatory polyps formation (7). Radiation therapy-induced changes in the mesotympanic middle ear mucosa result from marked changes in the epithelium, connective tissue, and endothelial cells of blood capillaries. Some studies have reported that a thickened drum may be observed several months after RT; permanent changes in the TM membrane are rarely observed (10). Contrary to those studies, Carls *et al.* (2) reported the observations of TM perforation 8 years post-RT after high-dose RT. Among the patients with TM perforation after radiation (excluding those with myringotomy), median time to the first observed TM perforation post-RT was 0.5 years in our series.

Up to 40% of patients are reported to have acute middle ear side effects during or after RT (7). Radiation therapy-induced OME has been reported as the most common middle ear complication in patients treated for nasopharyngeal malignancies (7). It has also been suggested that the primary cause of RT-induced OM might be injury to the eustachian tube's ciliated epithelium, tubal swelling, and fibrosis that blocks the lumen (7). Eustachian dysfunction following RT for head and neck carcinomas have been reported (7). Widening of the eustachian tube lumen with the atrophy of Ostmann's fat pad may lead to pathologically patent-patulous-eustachian tubes 5 to 10 years after RT (11).

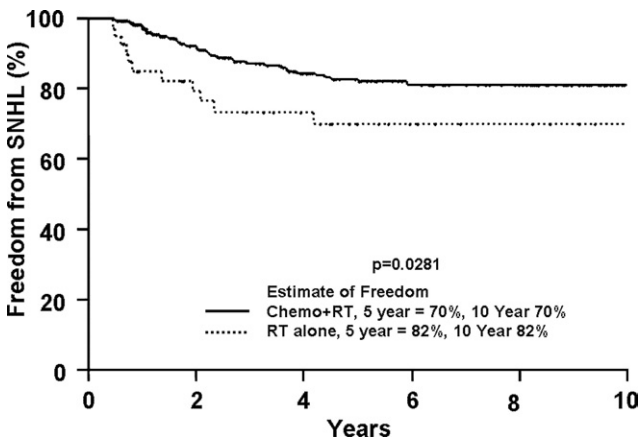

Fig. 4. Freedom from sensorineural hearing loss and the use of adjuvant chemotherapy. Chemo/RT at 5 and 10 years is 70%; RT alone at 5 and 10 years is 82%; p = 0.0281. RT = radiation therapy.

Acute OM usually occurs within a few weeks after RT. Its associated hearing loss is transient. Of the patients in our series, 11.5% were reported to have acute OM. No association was observed between occurence of acute OM and persistent SNHL. Chronic OME after RT has been associated with persistent SNHL (3). We observed a strong relationship ($p < 0.001$) between post-RT chronic OME and the likelihood of persistent SNHL. Kwong *et al.* (3) have suggested that post-RT OME can manifest from RT damage and may indicate individual sensitivity to RT and an increased risk of damage to the inner ear and persistent SNHL. Young *et al.* (12) reported that the prevalence of middle ear complications is low at 10 years after RT due to resolved inflammatory reaction and improved eustachian tube function. An adverse impact on the chorda tympani was observed by Johannesen *et al.* (13) in 3 of 33 patients treated with conventional RT to a mean dose of 53.1 Gy. Persistent conductive hearing loss may occur when atelectactasis or necrosis of the ossicular chain results in persistent conductive hearing loss (14).

Inner ear

Although the exact patho-physiologic processes involved in post-RT tinnitus are not known, hypoxia/ischemia may play an important role in the pathogenesis of tinnitus secondary to SNHL (15). Peripheral labyrinthine dysfunction results in canal paresis, which can dramatically affect quality of life. Post-RT labyrinthitis and neuritis of the acoustic nerve have been attributed to SNHL (16). In this series, a chi-square test indicated correlation between labyrinthitis

and SNHL ($p < 0.001$). Among those treated for chemodectomas of the skull base by fractionated stereotactic RT to a median total dose of 57.6 Gy reported by Zabel *et al.* (17), 16 of 22 patients had tinnitus, and 14 of 22 patients had balance problems. Young *et al.* (18) have attributed post-RT vertigo mainly to peripheral labyrinthine disorder, followed by central vestibular lesions, suggesting that post-RT vertigo may be caused mainly by the sequelae of OM. In the current study, univariate and multivariate analysis showed that the incidence of post-RT vertigo increased with the dose received by the vestibule, and the significance of total dose to the vestibule also increased. However, a Chi-square test did not exhibit a co-relationship between OME and vertigo/balance problems ($p = 0.26$).

Persistent SNHL

The incidence of SNHL after RT for head and neck cancers has been documented (1, 19, 20). In the present literature on this topic, there is a significant variation in the incidence of SNHL after RT. The reported incidence of post-RT SNHL varies from 0% to 54% (3). The significant variation in SNHL after RT may be attributed to factors including the study design, patient selection, total dose, fraction size, length of follow-up, and variation in the evaluations and their interpretations. In a prospective controlled study of patients treated for nasopharyngeal carcinoma with megavoltage X-rays ranging from 59.5 Gy to 76.5 Gy reported by Kwong *et al.* (3), the incidence of persistent SNHL was 24%. Jereczek-Fossa *et al.* (7) reviewed data from several studies and observed that post-RT SNHL occurred in about one-third of patients treated with definitive RT with fields including the inner ear. In another review, Raaijmaker and Engelen (21) suggested that, when averaged over all measured frequencies, the incidence of SNHL was 18% ± 2%, and that at least 1 of 3 patients receiving a dose of 70 Gy at 2 Gy per fraction to the inner ear will likely develop hearing impairment of 10 dB or more in the 4kHz region. In our series, the incidence of persistent SNHL was 15% for all patients and increased to 22% for those who received doses to the cochlea above 55 Gy and 35.5% for doses above 70 Gy. Due to the retrospective nature of this study, and because audiometry was not routinely performed before and after treatment, these observations may well underestimate the rate of SNHL with RT.

No relationship was observed between the fractionation schedule (once-daily vs. twice-daily) and the incidence of persistent SNHL in our series through univariate ($p = 0.7947$) and multivariate ($p = 0.4$) analyses. Thus, fractionation may not impact the likelihood of developing persistent SNHL.

Patho-physiologic evidence for SNHL

A definitive pattern of damage to specific components of the inner ear and its consequential clinical manifestations has not been established despite studies of animals and postmortem patients. The severity of RT-induced damage in animal studies varies widely from no observable histopathological change to complete cochlea destruction (7). It has been suggested that histologic changes of vascular and connective tissue may result in cochlear anoxia that may be manifested as delayed SNHL (1). In terms of histologic studies in humans, Leach (22) reported a histologic study of the inner ear after RT for treating nasopharyngeal carcinoma. The loss of the inner and outer hair cells in the cochlea, spiral ganglion cells in the basal turn, and atrophy of the stria vascularis were reported after high doses to temporal bone (23). Damage to various sites (including the organ of corti and atrophy of the basilar membrane, spiral ligaments, stria vascularis, and hair cells) have been reported (24). In the absence of consistent supporting histologic evidence, caution is recommended when attributing damage to the peripheral auditory system to RT (25).

Transient SNHL

Kwong *et al.* (3) first reported transient and reversible SNHL observed after RT. Among their patients with transient SNHL, the degree of SNHL was less severe (most commonly between 10 to 15 db, and <20 db in all cases). These patients experienced recovery between the first and second audiogram (the hearing threshold improved more than 10 db in all the cases in the second audiogram). Additionally, post-RT OME was much less commonly observed among these patients. The reasons for transient SNHL are unknown.

SNHL and age

In a prospective study of 22 patients treated for nasopharyngeal carcinoma, Grau *et al.* (26) reported that, although the raw data seemed to indicate a significant correlation between patient age and post-RT SNHL, the correlation disappeared when correction for the RT dose was taken into account. Kwong *et al.* (3) reported that older patients were more prone to develop persistent SNHL. In our series, the probability of SNHL increased from 11.6% for patients below the age of 50 years to 18.1% for older patients supporting Kwong's observations. Univariate ($p = 0.018$) and multivariate analyses ($p = 0.005$) indicated a significant correlation between patient age and the incidence of persistent SNHL.

SNHL and gender

Kwong *et al.* (3) observed that the rates of post-RT SNHL were 29.4% for males and 15.5% for females ($p = 0.0132$), suggesting males may be more likely to develop this complication. Other investigators have not reported this. In our series, gender had no impact on the likelihood of developing this complication; the 5-year actuarial rate of freedom from post-RT clinically overt SNHL was 81% for males and 82% for females. Both univariate ($p = 0.7959$) and multivariate ($p = 0.9$) analyses confirmed this observation.

SNHL and latency

The onset of hearing deterioration may begin as early as 3 months after completing RT (20). Kwong *et al.* (3) re-

ported that patients developed SNHL either immediately or up to 48 months after RT (mean, 4 months) which usually progressed to severe SNHL and plateaued within 2 years of treatment (27, 28). We observed that the median time to developing SNHL was 1.8 years (range, 0.5 to 5.9 years).

SNHL and chemotherapy

Although both cisplatin and RT may cause ototoxicity (29), the combined effects of the two are unclear. Severe post-RT hearing loss in pediatric patients has been attributed to the synergistic effects of these 2 modalities (30). Atrophy of stria vascularis and loss of inner and outer hair cells with reduced spiral ganglion cells have been reported in patients receiving cisplatin, RT, or the two combined (23). Cisplatin ototoxicity may be dose dependent (31) and sequence dependent, with increased ototoxicity if given after RT compared to pre-RT administration (30). In their prospective study, Kwong *et al.* (3) concluded that pre-RT low-dose cisplatin did not appear to enhance RT-induced SNHL. Our series included patients treated with cisplatin-based chemotherapy; the incidence of SNHL increased after RT and chemotherapy compared with RT alone. Both univariate ($p = 0.028$) and multivariate (0.006) analyses indicated that adding chemotherapy may increase the likelihood of developing SNHL. Thus, the RT dose to the inner ear should be minimal, particularly for patients who receive cisplatin-based chemotherapy (32). Some have suggested substituting a less ototoxic chemotherapeutic agent, such as carboplatin (33).

Dose limitation

Application of complex treatment modalities such as intensity-modulated RT or proton beam therapy may have an advantage over conventional 3-dimensional conformal RT in optimization of dose to the auditory apparatus. Accurate delineation and identification of the components of the auditory system in CT-based treatment planning are necessary to exclude the auditory apparatus from high doses of RT, particularly when dose escalation is desired.

CONCLUSION

Ototoxicity after RT is a significant complication in a subset of patients who receive high doses to the auditory apparatus. The incidence of ototoxicity in all parts of the auditory system increases with total dose significantly above 60 to 66 Gy, but may be observed at doses as low as 50 Gy. Chemoradiation and fractionation may contribute to incidence of ototoxicities.

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