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Main Article

Prospective study of sensorineural hearing loss following radiotherapy for nasopharyngeal carcinoma

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Abstract

Objectives: To investigate the severity and incidence of sensorineural hearing loss in patients with nasopharyngeal carcinoma treated with radiotherapy.

Methods: Forty-two patients with nasopharyngeal carcinoma were treated with conventional radiotherapy. Audiological testing was performed to compare patients' hearing before and at varying stages after radiotherapy.

Results: At one month post-radiation, a significant hearing threshold increase was seen only for high frequencies. At 12, 24 and 60 months post-radiation, significant threshold increases were observed at speech frequencies (4.0 and 8.0 kHz), compared with pre-radiation data. The mean values of wave I, III and V latencies and of the I–V interpeak latency intervals were not significantly altered at one month post-radiation, but were significantly prolonged at 12, 24 and 60 months post-radiation, compared with pre-radiation data.

Conclusion: In patients with nasopharyngeal carcinoma treated with radiotherapy, the severity and incidence of radiation-induced sensorineural hearing loss increased with time, especially at high frequencies. This hearing impairment may be due to changes in the cochlea and/or the retrocochlear auditory pathway.

Key words: Nasopharynx; Carcinoma; Radiation Therapy; Hearing Loss

Introduction

Nasopharyngeal carcinoma (NPC) has a high incidence in southern China. Radiotherapy (RT) is an effective treatment for NPC. During RT, the auditory apparatus is inevitably exposed to radiation,[1] receiving a radiation dose approximately equivalent to 80–100 per cent of the therapeutic dose.[2] Radiation damage to the auditory system is one of the major complications of RT in patients with NPC. Bhandare *et al.*[3] undertook a retrospective study on 325 patients who received RT for primary extracranial head and neck tumours with curative intent, between 1964 and 2000 (median follow up, 5.4 years), and found RT-induced morbidity in 41.8 per cent of patients (involving the external ear in 33.2 per cent, the middle ear in 28.6 per cent and the inner ear in 26.8 per cent).

Previous studies have mainly assessed hearing threshold changes in patients sustaining sensorineural hearing loss (SNHL) due to RT for NPC.[4–8] We wanted to gain further understanding of the RT sensitivity of the cochlea and the retrocochlear auditory pathway. Therefore, we undertook a prospective study which aimed to evaluate the severity and incidence of SNHL in NPC patients at differing time points after RT, and to investigate the anatomical sites of radiation damage.

Materials and methods

Patient characteristics

A total of 84 ears in 42 newly diagnosed nasopharyngeal carcinoma patients served as the subjects of this study, which took place in the department of otolaryngology, head and neck surgery and the Institute of Otology at the Second Xiangya Hospital, Central South University of China, from February 1998 to February 2003.

Patients gave their informed consent to involvement in the study, which was approved by the hospital ethics committee.

The 42 patients involved comprised 27 men (54 ears) and 15 women (30 ears), with a median age of 46 years (age range, 28–56 years; Table I). All patients were diagnosed with poorly differentiated squamous cell carcinoma of the nasopharynx, based on histopathological examination. All patients underwent fibre-optic nasopharyngoscopy, chest

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TABLE I

PATIENT CHARACTERISTICS

Characteristic	*n*
Total patients	42
Total ears	84
Secretory otitis media	12
Non-secretory otitis media	72
Gender	
Male	27
Female	15
Age (yr)	
Range	28–56
Median	46
Tumour size	
T_1	30
T_{2a}	12
Lymph node status	
N_0	33
N_+	9

Yr = years

radiography, abdominal B-type ultrasonography and computed tomography (CT) scanning of the nasopharynx, skull base and neck, prior to RT. All 42 patients met the following inclusion criteria: no previous middle-ear pathology (specifically, no otitis media or tumour invasion of the middle or inner ear); no dysfunction of hearing or balance; no history of chemotherapy; tumour confined to the nasopharynx; no invasion of parapharyngeal space and skull base; no cranial nerve involvement; no distant metastases; and no post-RT temporal bone necrosis.

All 84 ears received RT. Twelve ears were excluded from the study as they were confirmed to have secretory otitis media and tympanic effusion following otoscopic examination, pure tone threshold testing, acoustic immittance testing and grommets insertion one to 12 months (average, seven months) post-RT. The remaining 72 ears underwent audiological testing prior to RT and then one, 12, 24 and 60 months after RT (the follow-up period was 24 months for 52 ears and 60 months for 48 ears).

Radiotherapy

A total of 42 patients (84 ears) were treated with three-dimensional, conventional RT. Patients were treated with bilateral anterior aural fields, an anterior facial field and a faciocervical field. All patients underwent a treatment period of six to eight weeks, and received a total radiation dose of 60–65 Gy.

Audiological testing

All audiological testing was performed in a standardised, soundproofed, shielded room.

Bilateral, pure tone hearing threshold testing was undertaken at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz, using a Madsen Midimate 602 pure tone threshold tester (Madsen, Taastrup, Denmark). White noise was presented to the contralateral, untested ear as masking.

Acoustic immittance testing comprised assessment of static compliance, tympanometry and acoustic stapedius reflex, using a Madsen Zodiac 901 middle-ear analyser.

Auditory brainstem response (ABR) audiometry was undertaken using a Madsen ERA 2250 system. Recording electrodes were placed on the patient's head, while reference electrodes were placed on the ipsilateral mastoid and grounded through the nasal root. The click stimulus duration was 100 microseconds, the repetition rate was 20 per second, the click stimulus was superimposed 1024 times, and the stimulus intensity was 90 dB. If there was no reaction at 90 dB, the intensity was increased to 100 dB.

The mean bone conduction threshold was calculated at 0.5, 1 and 2 kHz (representing speech-frequency hearing), at 4 kHz, and at 8 kHz (representing high frequency hearing). Sensorineural hearing loss was defined as an increase in mean bone conduction threshold of more than 15 dB; an increase of more than 30 dB was defined as severe SNHL.[5]

Statistical analysis

Results for bone conduction thresholds, wave I, III and V latencies, and I–V interpeak latency intervals were calculated as mean $\pm$ standard deviation. Continuous variables for audiological testing before RT and one, 12, 24 and 60 months after RT were examined using repeated measures analysis of variance. Statistical analyses were performed using the Statistical Package for the Social Sciences version 13.0 software (SPSS Inc, Chicago, Illinois, USA). A p value of less than 0.05 was considered statistically significant.

Results and analysis

Pure tone hearing threshold

The observed increases in bone conduction hearing thresholds at different time intervals after RT are shown in Figure 1 and Table II. The proportion of ears with a bone conduction threshold increase of more than 15 dB and more than 30 dB at speech-frequency, 4 kHz and high frequency increased with time.

At one month post-RT, mean bone conduction thresholds had increased by 1.9, 3.2 and 8.6 dB at

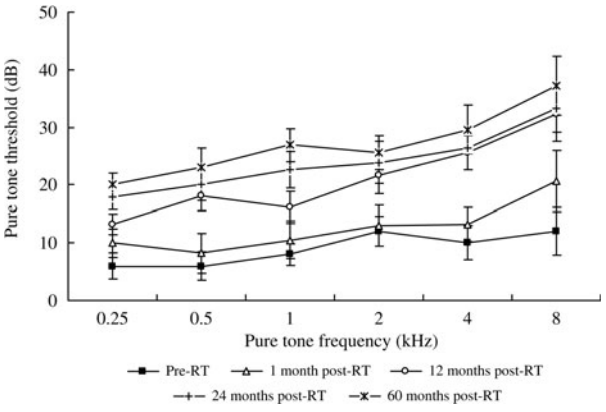

FIG. 1

Graph plotting bone conduction hearing threshold versus pure tone frequency, showing an increase in hearing thresholds as time progressed after radiotherapy (RT).

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TABLE II

SNHL FOLLOWING RADIOTHERAPY

Variable	Time post-RT (months)			
	1	12	24	60
Total ears (*n*)	72	72	52	48
Ears with speech freq SNHL				
≥15 dB (*n*)	6	15	16	20
≥30 dB (*n*)	1	8	6	9
BC threshold increase (mean; dB)	1.9	9.9	13.5	16.5
Ears with 4 kHz SNHL				
≥15 dB (*n*)	9	30	26	28
≥30 dB (*n*)	2	19	12	19
BC threshold increase (mean; dB)	3.2	15.6	16.3	19.6
Ears with high frequency SNHL				
≥15 dB (*n*)	22	32	25	26
≥30 dB (*n*)	7	19	14	20
BC threshold increase (mean; dB)	8.6	20.5	21.2	25.2

SNHL = sensorineural hearing loss; RT = radiotherapy; BC = bone conduction

speech frequency, 4 kHz and high frequency, respectively, compared with pre-RT data. The increase in high frequency bone conduction thresholds was statistically significant ($p < 0.001$), but the increase in speech frequency and 4.0 kHz thresholds was not.

At 12 months post-RT, mean bone conduction thresholds had increased by 9.9, 15.6 and 20.5 dB at speech frequency, 4 kHz and high frequency, respectively, compared with pre-RT data. All these threshold increases were statistically significant, compared with pre-RT data ($p < 0.001$). In addition, all these 12-month post-RT threshold increases were statistically significant when compared with the one-month post-RT threshold increases($p < 0.001$).

At 24 months post-RT, mean bone conduction thresholds had increased by 13.5, 16.3 and 21.2 dB at speech frequency, 4 kHz and high frequency, respectively, compared with pre-RT data. The threshold increase at speech frequency was statistically significant when compared with the speech frequency threshold increase at 12 months post-RT ($p < 0.05$).

At 60 months post-RT, mean bone conduction thresholds had increased by 16.5, 19.6 and 25.2 dB at speech frequency, 4 kHz and high frequency, respectively, compared with pre-RT data. All these threshold increases were statistically significant, compared with pre-RT data and also with corresponding threshold increases at one, 12 and 24 months post-RT ($p < 0.001$).

Auditory brainstem response

The mean value of ABR wave I, III and V latencies and of I–V interpeak latency intervals before and after RT are presented in Table III. These parameters showed no statistically significant difference, comparing one-month post-RT and pre-RT data ($p > 0.05$). At 12, 24 and 60 months post-RT, the wave I, III and V latencies and the I–V interpeak latency intervals were significantly prolonged, compared with pre-RT and one-month post-RT data ($p < 0.05$). There were no statistically significant differences in these parameters, comparing 12-month and 24-month post-RT data ($p > 0.05$). However, the wave I, IIII and V latencies and the I–V interpeak latency intervals at 60 months post-RT were significantly greater compared with both 12-month and 24-month post-RT data ($p > 0.05$).

At 12 months post-RT, wave I disappeared in two ears, waves II to V disappeared in four ears, wave V disappeared in two ears, and the I–V interpeak latency intervals were prolonged to more than 4.5 milliseconds in four ears. At 24 months post-RT, the ABR changes were quite similar to those seen at 12 months post-RT, except that waves II–V disappeared in five ears. At 60 months post-RT, wave I disappeared in two ears, waves II–V disappeared in four ears, waves III–V disappeared in three ears, waves I–V disappeared in two ears, and the I–V interpeak latency intervals were prolonged to more than 4.5 milliseconds in six ears.

Acoustic immittance

At one to 12 months (average, seven months) post-RT, 12 ears were diagnosed as having a tympanic effusion, as a result of a type B or C tympanogram and an absence of acoustic stapedius reflex. At 12, 24 and 60 months post-RT, the acoustic stapedius reflex could not be tested in six, nine and 15 ears, respectively, due to severe SNHL.

Discussion

Radiotherapy is commonly used in the management of nasopharyngeal carcinoma (NPC). Although radiotherapeutic instruments and techniques have greatly improved in recent years, the temporal bone and brainstem still cannot be protected from the radiation field. Radiation damage may thus occur anywhere from the pharyngotympanic tube to the brainstem auditory pathway, and therefore may

TABLE III

ABR WAVE I, III AND V LATENCIES AND I–V INTERPEAK LATENCY INTERVALS, BEFORE AND AFTER RADIOTHERAPY

Variable	Pre-RT	Post-RT (months)			
		1	12	24	60
Total ears (*n*)	72	72	72	52	48
Wave I latency (msec)	1.60 ± 0.13	1.62 ± 0.17	1.78 ± 0.24	1.77 ± 0.19	1.85 ± 0.26
Wave III latency (msec)	3.69 ± 0.17	3.70 ± 0.19	4.07 ± 0.27	4.09 ± 0.31	4.26 ± 0.32
Wave V latency (msec)	5.65 ± 0.20	5.67 ± 0.22	6.03 ± 0.33	6.01 ± 0.16	6.28 ± 0.27
I–V interpeak latency intervals (msec)	3.79 ± 0.21	4.04 ± 0.15	4.24 ± 0.20	4.28 ± 0.23	4.32 ± 0.30

Data represent mean ± standard deviation. ABR = auditory brainstem response; RT = radiotherapy; msec = milliseconds

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cause conductive, sensorineural or mixed hearing loss.[5,8–10] About one-third of NPC patients have been reported to suffer from significant SNHL following RT.[2,11,12]

Ho *et al.*[13] observed deterioration of bone conduction hearing thresholds at 4 kHz and at the pure tone average (averaging 0.5, 1 and 2 kHz) in 31 and 14 per cent of test ears, respectively, at three months post-RT. In the present study, at one month post-RT, there was a statistically significant increase in bone conduction hearing threshold at high frequency (i.e. 8 kHz), compared with pre-RT data; at 12 months post-RT, there were statistically significant threshold increases at speech frequency, 4 kHz and high frequency. Both the incidence and the severity of SNHL increased with time, especially at 4 kHz and high frequency.

We suggest that the hearing loss noted in the early post-RT period may be due to radiation damage to the cochlea.

In a recent study of the cochlear cell line OC-k3,[14] flow cytometry and terminal deoxynucleotidyl transferase(TdT)-mediated dUTP nick-end-labeling (TUNEL) assays were used to document γ radiation induced apoptosis. Apoptosis was found to occur predominantly at 72 hours post-radiation.

Bohne *et al.*[15] investigated radiation damage to the inner ear due to exposure to ionising radiation, and demonstrated (in a chinchilla model) that the most pronounced effect of exposure to high radiation doses was degeneration of the sensory and supporting cells of the organ of Corti and loss of VIIIth nerve fibres; in ears exposed to 40–50 and 60–90 Gy of radiation, the incidence of degeneration of sensory and supporting cells in the organ of Corti and loss of eighth nerve fibers were 31% and 62% in ears exposed to 40–50 Gy and 60–90 Gy of radiation, respectively.

Kim and Shin[16] assessed the effect of fast neutron irradiation on the cochlea of guinea pigs, using transmission electron microscopy. The most significant findings were clumping of chromatin and extension of the heterochromatin in the nuclei of hair cells. Cytoplasmic changes comprised sequestration of cytoplasm, various mitochondrial changes, formation of vacuoles and irregularly arranged stereocilia. The stria vascularis showed intercellular and perivascular fluid accumulation.

Asenov *et al.*[17] conducted a histopathological examination of the temporal bones of a NPC patient who had undergone chemotherapy and RT. The main cochlear changes were stria vascularis degeneration, spiral ligament atrophy and spiral ganglion cell depletion, plus occasional hair cell loss.

Animal studies and histopathological examination of human temporal bones have confirmed the existence of radiation-induced morphological changes in the cochlea, and these changes may be related to the hearing loss observed in the early post-RT stage. The mechanism of radiation-induced hearing loss may proceed as follows. Firstly, the ionising radiation may act on the sensory cells directly, resulting in lipid peroxidation of the cell membrane, mitochondrial membrane and lysosome membrane, and DNA damage in the nucleolus, ultimately leading to disordered metabolism, degeneration, necrosis and dysfunction of hair cells. Secondly, ionising radiation may impair the hearing by causing stria vascularis degeneration, microvascular damage and microcirculatory disturbance.

Auditory brainstem response testing objectively assesses the neural synchrony of the auditory system from the level of the VIIIth nerve to the midbrain. The obtained results can be extrapolated to provide information regarding hearing sensitivity, and can also be used for neurodiagnostic purposes, especially in the diagnosis of retrocochlear hearing loss and other brainstem diseases. It is well known that irradiation of malignant head and neck tumours can lead to brainstem myelopathy and necrosis, but it has been disputed whether radiation would impair the retrocochlear auditory pathway.

A prospective study[18] of ABR changes in NPC patients before and after RT demonstrated that the retrocochlear auditory pathways were functionally intact even in the longer term.

However, Lau *et al.*[19] recorded opposing findings. They undertook ABR testing in 49 NPC patients who had received RT, and found that waves I, II, III and V had prolonged latencies and decreased amplitudes at one month post-RT, while the I–III and I–V interpeak latency intervals were significantly prolonged at one year post-RT. These authors believed the prolongation of interpeak latency intervals to be due to the effect of radiation on the brainstem auditory pathway.

- **Radiation damage to the auditory system is one of the major complications of radiotherapy for patients with nasopharyngeal carcinoma**
- **Although radiotherapeutic techniques have greatly improved in recent years, the temporal bone and brainstem cannot be shielded from the radiation field**
- **The severity and incidence of hearing loss increases with time, especially at high frequencies**
- **Hearing impairment may occur in the cochlea or the retrocochlear auditory pathway, suggesting that sensitivity to radiation damage may vary in different patients and at different anatomical sites within the auditory system**

In the present study, at one month post-RT, the mean latencies of waves I, III and V and the mean I–V interpeak latency interval were not significantly prolonged, and the pure tone threshold test results confirmed high frequency SHNL; these results may be accounted for by cochlear damage. At 12, 24 and 60 months post-RT, the wave I, III and V latencies and the I–V interpeak latency intervals were significantly prolonged, while disappearance of waves I, III and V and prolongation of the I–V interpeak latency intervals to more than 4.5

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milliseconds occurred in some of the test ears. We suggest that the prolongation of wave I latency or the disappearance of wave I arises from damage to the cochlear hair cells and the extracranial segment of the VIIIth nerve. The prolongation of wave III and V latencies may result from radiation-induced damage in the auditory brainstem; however, since these waves originate from multiple sites within the brainstem, we cannot state the exact anatomical site of impairment. The existence of radiation damage to the retrocochlear auditory pathway was also confirmed by significant prolongation of the I–V interpeak latency intervals, especially prolongation to more than 4.5 milliseconds.

In order to determine precisely whether there is radiation-induced impairment of the auditory pathway in such circumstances, studies are needed which involve credible animal models and histopathological examination of the brainstem.

Conclusion

In nasopharyngeal carcinoma patients treated with RT, radiation-induced SNHL starts to develop in the early post-RT period. In our study, the incidence and severity of hearing loss increased over time, especially at high frequencies. This hearing impairment may result from changes in the cochlea and/or the retrocochlear auditory pathway; this suggests that sensitivity to radiation damage may vary in different patients and at different anatomical sites within the auditory system.

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