High Frequency Hearing Loss Following Treatment for Nasopharyngeal Carcinoma□

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Objective: *To evaluate the prevalence, severity and differences of high frequency hearing loss in nasopharyngeal carcinoma patients after curative treatment by radiotherapy alone and chemoradiation.*
Material and Method: *Pure tone audiometry was done in nasopharyngeal carcinoma patients who came back to follow-up after curative treatment during the year 2003 and 2004. The patients were divided into three groups, the first group received radiation treatment only, the second group received radiation and cisplatin chemotherapy, and the third group received radiation and carboplatin chemotherapy.*
Results: *Of 192 patients with a mean age 49.9 years, mean radiation dose 6,951.5 cGy, mean follow-up period 3 years and 9 months, 93.8% showed bilateral high frequency hearing loss. There were statistically significant differences in the high frequency hearing threshold between the second group versus the first and the third group.*
Conclusion: *Clinicians should inform patients of the risk of hearing loss, particularly the treatment with cisplatin. Hearing test should be a routine test after treatment completion.*

Keywords: *Nasopharyngeal carcinoma, Radiotherapy, Chemoradiation, Hearing loss*

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Nasopharyngeal carcinoma (NPC) is a common head and neck cancer in Southeast Asia[1]. In Thailand, NPC is the most common head and neck cancer. The age standardized incidence rate in Thailand is 2.8 per 100,000 in males and 1.4 per 100,000 in females. Chiang Mai province has the highest incidence rate, at 3.8 for males and 1.6 for females[2].

Radiation is the primary treatment for NPC. The radiation field for locoregional control of NPC covers the area from the skull base to the lower neck. The temporal bone is inevitably included within the field of external beam radiation treatment and is most at risk for receiving high-radiation doses in NPC patients[3-5]. The incidence of hearing loss following head and neck irradiation is 24-57%[6-8]. The addition of cisplatin-based chemotherapy to radiotherapy has shown improved overall survival[9]. Combination therapy (chemoradiation) is a recommended treatment for NPC stage III or IV[10], which is commonly found in Thai patients.

The rate of hearing loss is expected to increase with more widespread use of combined modality therapy[6]. Audiometry is not a routine test after NPC treatment. Without a hearing test, the hearing-impaired patients themselves may not be aware of their reduced hearing ability, especially at high frequencies.

The present study aimed 1) to evaluate the prevalence and severity of high frequency hearing loss in patients following treatment for NPC; and 2) to determine the differences in high frequency hearing loss for different treatment types.

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Material and Method

The present crossectional study was conducted at the outpatient clinic of the Chiang Mai University Hospital. NPC cases who returned between October 2003 and September 2004 for follow-up of more than 90 days after finishing curative treatment were included in the present study. They received one of three treatments: group I = radiotherapy alone, group II = radiotherapy combined with cisplatin, group III = radiotherapy combined with carboplatin. Patients who had early stage or improper condition for chemotherapy were assigned to receive radiotherapy alone. Patients in groups II and III who could not tolerate the chemotherapy received continuous radiation only. Patients who had recurrent tumors, needed additional radiation, or received palliative treatment were excluded. The protocol was approved by the Ethical Committee, Faculty of Medicine, Chiang Mai University.

Standard pure tone audiometry was done in a soundproof room by an audiologist, who was one of the authors' investigators. The average high frequency hearing threshold was calculated using hearing thresholds at 1, 2, 4 and 8 kHz. Hearing loss was defined as an air conduction hearing threshold of more than 25 dBHL.

Data of age, gender, duration after end of the treatment, AJCC 2002 stage distribution, tumor histology according to the World Health Organization (WHO) classification, modality of the treatment, total radiation dose and hearing test results were collected. The data was analyzed using SPSS (Chicago IL, USA). Differences in high frequency hearing thresholds between ears and genders were analyzed using t-test. Differences of mean age and high frequency hearing threshold between the three treatment groups were analyzed using one-way ANOVA. If there were statistically significant differences between the groups, multiple comparisons (Tukey HSD test) were then used to find differences between each pair in the treatment groups. Pearson correlation was used to analyze correlation between age and high frequency hearing threshold. A p-value of < 0.05 was considered significant.

Results

There were 192 patients (124 males and 68 females), aged 11 to 78 years (49.9 ± 13.5; mean $\pm$ standard deviation (SD)), follow-up duration after treatment 13 to 968 weeks (191.1 ± 180.0) and radiation dose 6,000 to 7,600 cGy (6951.5 ± 171.0). Cisplatin dose was 100 to 1,030 mg (571.8 ± 230.0) and carboplatin dose was 150 to 3,250 mg ($1,870.2 \pm 754.3$).

The number of cases in each stage and group of treatment is shown in Table 1.

Histological classifications of the tumor were undifferentiated carcinoma in 95 cases (49.5%), nonkeratinizing squamous cell carcinoma in 81 cases (42.2%) and keratinizing squamous cell carcinoma in 16 cases (8.3%). There were no statistically significant differences in duration of follow-up (p-value = 0.112) or high frequency hearing threshold (p-value = 0.992, right ear; p-value = 0.678, left ear) among the three histological classifications (one-way ANOVA).

The number of cases in each hearing threshold level for right and left ears is shown in Table 2. Of 192 cases, 180 (93.8%) had bilateral high frequency hearing loss. Of these 110 (57.3%) had bilateral moderately severe loss or worse (56 dBHL or greater).

Means and SD of age in each treatment group are shown in Table 3. There was statistically significant difference by age among the three treatment groups (p-value = 0.002, one-way ANOVA). Multiple comparisons (Tukey HSD method) of age between groups I and II showed statistical difference (p-value = 0.001). There was no statistically significant difference by age between Groups I and III (p-value = 0.084) or between Groups II and III (p-value = 0.278).

Means and SD of high frequency hearing threshold (384 ears) in each treatment group are shown in Table 4. High frequency hearing threshold between ears (p-value = 0.41, t-test) and genders (p-value = 0.261, t-test) showed no statistically significant difference. There was statistically significant difference of high frequency hearing threshold between the three treatment groups (p-value < 0.0001, one-way ANOVA). Multiple comparisons (Tukey HSD method) of high frequency hearing threshold showed statistical difference between groups I and II (p-value = 0.015) and between group II and group III (p-value < 0.0001). There was no statistically significant difference of high frequency hearing threshold between groups I and III (p-value = 0.584).

The number of cases with bilateral high frequency hearing loss in each age group and each treatment group are shown in Table 5. Prevalence of bilateral high frequency hearing loss was 92% (52/56) in group I, 96% (67/70) in group II and 85% (56/66) in group III. Overall prevalence was 91.1%. All patients older than 60 years old had bilateral hearing loss.

Table 1. Number of cases in each stage and group of treatment

Treatment/Stage	Group I	Group II	Group III	Total	
				Cases	%
I	5	0	0	5	2.6
II	7	5	5	17	8.9
III	11	17	11	39	20.3
IV	33	48	50	131	68.2
Total	56	70	66	192	100

Table 2. Number of cases in each hearing threshold level classified by high frequency hearing threshold

Right ear/Left ear	0-25 dBHL	26-40 dBHL	41-55 dBHL	56-70 dBHL	71-90 dBHL	> 90 dBHL	Total (cases)
0-25 dBHL	7	4	0	0	0	1	12
26-40 dBHL	4	4	8	3	1	0	20
41-55 dBHL	0	11	10	6	1	3	31
56-70 dBHL	0	2	8	**29**	**10**	**5**	54
71-90 dBHL	1	3	4	**8**	**15**	**8**	39
> 90 dBHL	0	0	1	**6**	**12**	**17**	36
Total (cases)	12	24	31	52	39	34	192

Bold cells show number of cases with bilateral moderately severe loss or worse (110 cases, 57.3%)

Table 3. Means $\pm$ SD of age in each treatment group

Treatment group	Group I	Group II	Group III	Total
Age (years)	54.8 $\pm$ 13.5	46.2 $\pm$ 13.3	49.6 $\pm$ 12.5	49.9 $\pm$ 13.5
	* p-value = 0.001			

* Statistically significant difference (see text)

Table 4. Means $\pm$ SD of high frequency hearing threshold in each treatment group (384 ears)

Treatment group	Group I	Group II	Group III	Total
Hearing threshold (dBHL)	64.0 $\pm$ 24.1	72.4 $\pm$ 22.5	60.9 $\pm$ 24.7	66.0 $\pm$ 24.8
	* p-value = 0.015		* p-value < 0.0001	
	p-value = 0.584			

* Statistically significant difference (see text)

Discussion

Factors that influence the incidence and severity of hearing loss in combined modality treatment of NPC include cochlear radiation dose, time of audiometric test postradiotherapy, patient age, pretreatment hearing level and number of cisplatin cycles[6]. The severity of RT-induced damage in animal studies varies widely from no observable histopathological change to complete cochlear destruction[11]. Temporal bone histology of patients who underwent

Table 5. Number of cases with bilateral high frequency hearing loss/total of cases within the age group and each treatment group (%)

Treatment/Age group*	Group I	Group II	Group III	Total
≤ 60 years	31/35 (89%)	57/60 (95%)	44/54 (82%)	132/149 (88.6%)
> 60 years	21/21 (100%)	10/10 (100%)	12/12 (100%)	43/43 (100%)
Total	52/56 (92%)	67/70 (96%)	56/66 (85%)	175/192 (91.1%)

* Divided into 2 age groups to compare prevalence of hearing loss in Thai elderly (> 60 years)

chemotherapy and radiotherapy for NPC showed vascular stria degeneration, spiral ligament atrophy and spiral ganglion cell depletion of the cochlea[12].

Prevalence of hearing loss following head and neck irradiation was found at 24-57%[6,8,10]. Overall prevalence of hearing SNHL in Thailand is 3.5-5%[13]. Thai elderly (older than 60 years old) have abnormal hearing level of 52.4%. Bilateral moderate to severe degree hearing loss was found in 9.5% of them[14].

Prevalence of hearing loss in the present study was much higher than of the general Thai population. The authors found the overall prevalence of bilateral high frequency hearing loss after curative treatment for NPC to be 91.1%. Bilateral high frequency hearing loss degree was moderately severe or worse in 57.3%. All patients older than 60 years old had bilateral high frequency hearing loss.

Radiation-induced ototoxicity is typically evident 6-12 months after completion of radiotherapy[7,8]. The median time to develop SNHL was 1.8 years[15]. Risk of hearing loss after treatment for NPC increased significantly with increase in age[4,8]. Pre-irradiation hearing level and patient age did not correlate with post-irradiation SNHL[3,11]. The correlation between age and post-RT SNHL decreased over time. The longer the follow-up, the less the chance of evidence that age contributed significantly to hearing loss[11]. A significant increase in the risk of sensorineural hearing loss (SNHL) was reported among patients who received radiation > 4,800 cGy, a threshold cochlear radiation dose[6]. Mean follow-up in the present study was 191.1 weeks (3 years and 9 months) with the longest follow-up at 968 weeks (18 years and 8 months) after treatment completion. The lowest radiation dose that patients received in the present study was 6,000 cGy, higher than the tolerance threshold of the cochlea.

Patients who received chemoradiation experienced greater sensorineural hearing loss than patients who received radiation alone. The high frequency threshold was more severely affected than the threshold at lower speech frequencies[15,16]. In the present study, the high frequency hearing threshold in group II (cisplatin treatment) was significantly higher than in the other groups, even though the average age was significantly younger. These findings predominantly support the effect of cisplatin on hearing threshold.

Carboplatin, a second-generation platinum complex, has less ototoxicity than does the first-generation platinum drug cisplatin[17]. The authors found that the high frequency hearing threshold of patients who received radiation combined with carboplatin was not different from that in patients who received radiation alone. These findings support that carboplatin has less ototoxicity. A carboplatin treatment regimen should therefore be recommended for patients concerned with hearing deterioration.

Increasing survival rates in patients due to more intense combined modality treatment cause more obvious manifestations of late complications. Cisplatin clearly affects hearing threshold. Hearing loss is an invisible handicap. Patients may not notice their high frequency hearing loss. Unawareness for early detection can cause worsening of hearing threshold, permanent morbidities, and affect quality of life. High frequency hearing impairment can cause unbearable tinnitus. Prompt hearing rehabilitation should improve quality of life. A hearing test should be done routinely after NPC treatment completion.

Conclusion

The prevalence of high frequency hearing loss in treated NPC patients is much higher than that of the general population, particularly in the treatment with cisplatin. Clinicians should be aware when planning treatment and should inform patients of the risk of hearing loss. The aggravation of hearing thresholds before and after the treatment is considered to show ototoxicity induced by treatment. According to medicolegal concern, a routine hearing test has to

be done before starting treatment. Clinicians should inform all patients that hearing loss is an expected side effect.

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การสูญเสียการได้ยินช่วงความถี่สูงหลังการรักษามะเร็งหลังโพรงจมูก

ยุพา สุมิตสวรรค์, วาสนา วะสีนนท์, จารึก หาญประเสริฐพงษ์, กรรณิการ์ รุ่งโรจน์วัฒนศิริ, อิ่มใจ ชิตาพนารักษ์, สุวิชา อิศราดิสัยกุล

วัตถุประสงค์*: เพื่อหาอุบัติการณ์ความรุนแรง และความแตกต่างของการสูญเสียการได้ยินช่วงความถี่สูงในผู้ป่วยมะเร็งหลังโพรงจมูกหลังรับการรักษา ด้วยการฉายรังสีเพียงอย่างเดียวและการฉายรังสีร่วมกับยาเคมีบำบัด*

วัสดุและวิธีการ*: ทำการวัดการได้ยินในผู้ป่วยมะเร็งหลังโพรงจมูกที่มารับการตรวจหลังการรักษาในช่วงเวลา 1 ปี ระหว่างปี พ.ศ. 2546-2547 แบ่งผู้ป่วยออกเป็น กลุ่มที่ 1 ได้รับเฉพาะรังสีรักษา กลุ่มที่ 2 ได้รับรังสีรักษา และยาซิสพลาติน กลุ่มที่ 3 ได้รับรังสีรักษา และยาคาร์โบพลาติน*

ผลการศึกษา*: ผู้ป่วย 192 ราย มีอายุเฉลี่ย 49.9 ปี ได้รับรังสีรักษาปริมาณเฉลี่ย 6951.5 เซนติเกรย์ ร้อยละ 93.8 ของผู้ป่วยทุกกลุ่มมีการสูญเสียการได้ยินช่วงความถี่สูงทั้งสองข้าง ระดับการได้ยินช่วงความถี่สูงในกลุ่มที่ 2 สูงกว่ากลุ่มที่ 1 และ 3 อย่างมีนัยสำคัญ*

สรุป*: แพทย์ควรให้ข้อมูลผู้ป่วยเกี่ยวกับความเสี่ยงในการสูญเสียการได้ยินหลังรับการรักษาโดยเฉพาะในกลุ่มที่ได้รับการฉายรังสีร่วมกับยาเคมีบำบัดซิสพลาติน แนะนำให้ทำการตรวจการได้ยินในผู้ป่วยมะเร็งหลังโพรงจมูกหลังรับการรักษาทุกรายเพื่อเป็นข้อมูลในการอธิบายผู้ป่วยให้เข้าใจ*