A Comparative Study of Sensorineural Hearing Loss in the Treatment of Nasopharyngeal Carcinoma: Conventional Radiation Vs IMRT Technique

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Abstract

Purpose: This prospective study compares the incidence and severity of sensorineural hearing loss (SNHL) in the nasopharyngeal carcinoma patients who received treatment by conventional two-dimensional (2D) radiation to IMRT technique.

Methods and materials: Between November 2009 and August 2010, 18 nasopharyngeal carcinoma patients were treated with chemoradiation (similar to the Intergroup 0099 trial) and randomly assigned to receive radiotherapy by conventional radiation (n=10) and IMRT technique (n=8). Pure-tone audiometries were performed before treatment and on the day that completed radiation to evaluate hearing threshold at low speech (frequencies pure tone average; conversation in normal activities) and high speech frequency (4 kHz). An increase in bone conduction threshold more than 15 dB from baseline was considered as significant SNHL.

Results: The incidences of SNHL at PTA were 10% and 12.5% (p=0.608) and at 4 kHz were 15% and 56.2% (p=0.014) for conventional radiation and IMRT group, respectively. There was no difference in the severities of SNHL between two groups at both PTA and 4 kHz (p>0.05).

Conclusion: No significant difference was seen in the incidence of SNHL at PTA between conventional radiation and IMRT technique. The incidence of SNHL at 4 kHz were significant greater in IMRT group. The severity of SNHL was also not different between two radiation techniques.

Introduction

The standard treatment for nasopharyngeal carcinoma is definitive radiotherapy with or without chemotherapy where chemotherapy is reserved for more advanced lesions [1]. Intensity modulated radiation therapy (IMRT), a type of 3D conformal radiotherapy, has gained its popularity in the treatment of nasopharyngeal carcinoma. With this technique, radiation beams can be modulated such that a high dose can be delivered to the tumor while significantly reducing the dose to the surrounding normal tissue [2-5]. Favorable toxicity profiles were described with IMRT that may be due to the reduced volumes of normal tissue irradiated.

Due to the auditory apparatus especially cochlea lies in close proximity to the nasopharynx and usually receives a significant dose of radiation.

Sensory neural hearing loss (SNHL) is a common toxicity after treatment in patients with nasopharyngeal carcinoma that significantly affects their quality of life. Moreover, the addition of chemotherapy also decrease local, regional and distant recurrence rate while increase some toxicities include SNHL. Because it is well known that Cisplatin is ototoxic with affect high-frequency hearing, the concurrent use of Cisplatin and radiation might act in synergy and result in an increase in the incidence of SNHL [6].

In previous reports, the incidence of hearing loss following radiation treatment (with and without chemotherapy) of nasopharyngeal carcinoma is about 18-49% [7-16]. With IMRT techniques, the incidence of radiation induced SNHL would expect to be decline as a result of fewer dose of radiation to normal tissue causing capability to spare the cochlea. But there is no randomized control trial that comparing about incidence of SNHL from each radiation techniques. This is the first study that prospectively to compare the incidence and severity of SNHL in the nasopharyngeal carcinoma patients who received radiation treatment between conventional two-dimensional (2D) radiation and IMRT technique.

Methods and materials

Patient population

Patients with newly diagnosed stage IIB-III nasopharyngeal carcinoma who were treated between November 2009 and August 2010 at Chiang Mai University were included. Eligible patients were age 18-70 years, histological proven, non-metastatic stage IIB-III nasopharyngeal carcinoma (AJCC staging 2002, 6th edition) receive treatment with combination of radiation and Cisplatin chemotherapy, ECOG (Eastern Cooperative Oncology Group) performance Status 0-1 and adequate haematological, renal, and hepatic function. Patients with history of other malignancies or head and neck radiotherapy or conductive hearing loss in either ear before treatment were excluded.

Study design and procedure

Patients were randomly assigned to receive either conventional two-dimensional (2D) radiation technique or IMRT technique. Data of patients' characteristics, computed tomography scans, AJCC 2002 stage distribution and pure-tone audiogram were collected.

Chemotherapy

Cisplatin at 100 mg/m2 infusion over 3 hr was given on days 1, 22 and 43 concurrently with radiotherapy. Adjuvant chemotherapy consisting of Cisplatin 80 mg/m2 intravenously and 5-FU infusion at 1000 mg/m2/day by 96 hr infusion was given every 4 weeks for a total of 3 cycles, beginning 4 weeks after the end of radiation therapy.

Radiotherapy

Patients were randomized to receive:

Arm 1: Conventional two-dimensional (2D) radiation technique

All patients were treated with 6-MV photon linear accelerator. Parallel opposed portals were used for the primary tumor site and the upper neck with spinal cord and brainstem shielding at the dose of 40 Gy. The lower neck was treated with the anterior split field with central shielding. Radiation therapy was delivered at 2 Gy per fraction, 5 fractions per week with dose 70 Gy to gross tumor and involved lymph nodes with a 2 cm margin, and dose 50 Gy to clivus, skull base, inferior sphenoid sinus, posterior third of nasal cavity, maxillary sinus, pterygoid fossa, cervical nodal regions level I-V and supraclavicular nodal regions.

Arm 2: IMRT technique

A computed tomography (CT) was used for simulation and treatment planning. CT images indexed every 3 mm were obtained. Thermoplastic masks were used for immobilization. Patients were treated with 6-MV photon linear accelerator and a step and shoot IMRT technique. Target and organ at risk were contoured and prescribed radiation dose according to RTOG Guideline, Report No. 0225 [24]

Pure-tone Audiometry

Standard pure tone audiometry was done in a soundproof room. Baseline pre-treatment audiograms were obtained. Post-treatment audiograms were scheduled at completion of concurrent chemoradiation.

The audiograms included assessment of bone conduction thresholds at 0.5, 1, 2, and 4 kHz. As in previous reports by other authors [9,17,21], high and lower frequencies in the speech range were represented by the threshold at 4 kHz and the average of 0.5, 1, and 2 kHz (PTA: pure tone average) thresholds, respectively. For each patient, the left and right hearing levels were analyzed separately.

Hearing threshold change was determined relatively to each patient's baseline. An increase in bone conduction (BC) threshold more than 15 dB from baseline was considered as significant represented SNHL in the present analysis.

Statistical Analysis

The data was analyzed using SPSS version 15 (Chicago IL, USA). Each ear was analyzed independently. Differences in the incidence of SNHL between conventional radiation and IMRT group were analyzed using Fisher's exact test. Differences in hearing level between pre and post-radiotherapy in each technique were analyzed using paired sample t-test. The Mann-Whitney U test was performed to compare the hearing levels between the conventional radiation and IMRT group groups at pre and post-radiotherapy. A p-value of < 0.05 was considered significant.

Results

Between November 2009 and August 2010, 19 nasopharyngeal carcinoma patients were enrolled into the study and randomly assigned to receive radiotherapy by conventional radiation (n=10) and IMRT technique (n=9). One patient in IMRT arm were excluded due to GFR <40 which is not suitable for receiving Cisplatin chemotherapy. Therefore data from 18 patients (36 ears), 10 for conventional radiation and 8 for IMRT arm were analyzed. Patient characteristics are given in Table 1. There were comparability in both arms, including age, gender, tumor staging, and Cisplatin dose.

Baseline pre-treatment audiograms (Table 2) showed that number of ears which had abnormal hearing loss (BC threshold >20 dB without AB gap) before treatment at the pure tone average (PTA) of 0.5, 1, 2 kHz or low speech frequencies were 8 and 5 for conventional and IMRT groups, respectively. At 4 kHz or high speech frequency, they showed abnormal hearing in 13 ears for conventional and 11 ears for IMRT group.

Table 1: Patients' characteristics

Characteristic	2D (n=10)	IMRT (n=8)	P value
• Age (years)			
- Median	45	53	0.504§
- Range	33-57	46-60	
• Gender			
- Male, n (%)	7 (70%)	5 (62.5%)	0.563¶
- Female, n (%)	3 (30%)	3 (37.5%)	
• Stage			
- II, n (%)	4 (40%)	1 (12.5%)	0.225¶
- III, n (%)	6 (60%)	7 (87.5%)	
• Cisplatin dose (mg/m2)			
- Median	200	197.95	0.593§
- Range	100-300	100-295.9	

Test : §Mann-Whitney U test; ¶Fisher's exact test.

Table 2: Baseline hearing abnormality

	Conventional No. of ears (%)	IMRT No. of ears (%)	P value
PTA			
- Normal	12 (60%)	11 (68.7%)	0.731¶
- Abnormal	8 (60%)	5 (31.3%)	
4 kHz			
- Normal	7 (35%)	5 (31.3%)	0.549¶
- Abnormal	13 (65%)	11 (68.7%)	

Test: ¶Fisher's exact test

The incidence of SNHL

The incidence of SNHL (BC threshold increase at least 15 dB from baseline) at PTA was 11.1% and at 4 kHz was 33.3% that were summarized in Tables 3 and 4. At PTA, the incidence of SNHL in the conventional radiation group and IMRT group were 10% and 12.5% respectively (p=0.608). At 4 kHz, the incidence of SNHL in the conventional radiation group was significant lower than in IMRT group (15 Vs 56.2%, p=0.014).

The severity of SNHL

The hearing levels in the conventional radiation and IMRT groups at pre and post-radiotherapy were illustrated in Figures 4 and 5. The box-plots show that the hearing level at post-radiotherapy time point were higher than pre-radiotherapy in both groups, especially for IMRT group which the post-radiotherapy hearing threshold were statistically significant higher (P<0.05).

Table 3: The incidence of SNHL in low speech frequencies (PTA)

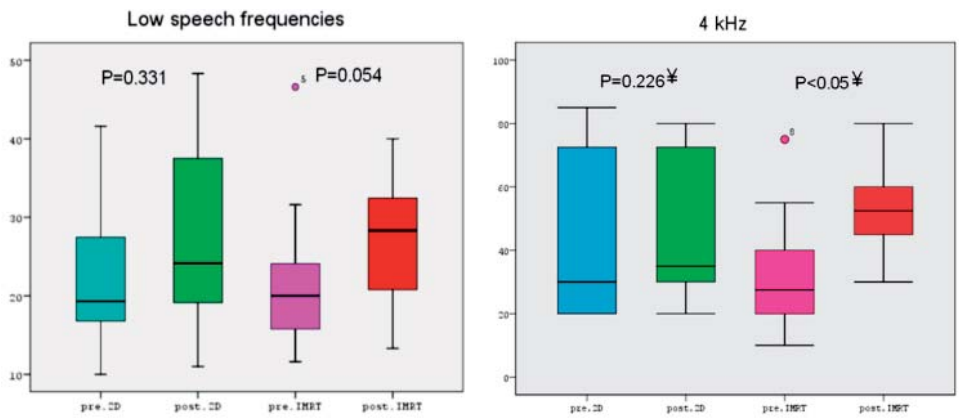
	Normal No. of ears (%)	SNHL at PTA No. of ears (%)	P value
Conventional (20 ears)	18 (90%)	2 (10%)	0.608¶
IMRT (16 ears)	14 (87.5%)	2 (12.5%)	(NS)
Total	32 (88.9%)	4 (11.1%)	

Test: ¶Fisher's exact test.

Table 4: The incidence of SNHL in high speech frequency (4 kHz)

	Normal No. of ears (%)	SNHL at 4 kHz No. of ears (%)	P value
Conventional (20 ears)	17 (85%)	3 (15%)	0.014¶
IMRT (16 ears)	7 (43.8%)	9 (56.2%)	(Sig)
Total	24 (66.7%)	12 (33.3%)	

Test: ¶Fisher's exact test.



Test: ¥Paired sample t-test.

Figure 4 and 5: Box plots to compare pre and post-radiotherapy bone conduction hearing thresholds (dB) at low speech frequencies and 4 kHz.

At baseline pre-radiotherapy, the hearing threshold at PTA and 4 kHz were not different (P>0.05). At post-radiotherapy, there was also no difference in hearing level between two groups at both speech frequencies (Table 5). The changing of median of the hearing threshold at PTA and 4 kHz were 5 dB and 12.5 dB for conventional radiation and were 8.3 dB and 25 dB for IMRT group, respectively. Therefore the magnitude of post-radiotherapy hearing loss was much greater at the high speech frequency than at the lower speech frequencies.

Table 5: Bone conduction thresholds at the low and high (4 kHz) speech frequencies for patients in the conventional radiation (2D) and IMRT groups at pre and post-radiotherapy

Time	Low speech frequencies (PTA)		4 kHz	
	2D	IMRT	2D	IMRT
Pre-radiotherapy				
No. of ears	20	16	20	16
Threshold (dB)				
-Median	20	20	35	27.5
-Statistical sig.	0.378§		0.304§	
-Mean	25	21.1	44.4	32.2
-Range	10-48	11.6-46.6	5-85	10-75
Post-radiotherapy				
No. of ears	20	16	20	16
Threshold (dB)				
-Median	25	28.3	47.5	52.5
-Statistical sig.	0.774§		0.576§	
-Mean	27.3	27.7	49.25	52.5
-Range	11-48.3	13.3-40	20-80	30-80

Test: §Mann-Whitney U test.

Discussion

The feature of SNHL after irradiation on inner ear was documented in many literatures. The main characteristics of radiation induced SNHL are as following:

(1) It usually develops during or after radiation therapy due to the impairment of audition already occurred during radiotherapy [6,14,19,20].

(2) It is radiation dose dependent [12,13, 15,22].

(3) High frequency was more commonly affected than lower frequencies [18].

There is a radiation induced pathophysiologic changes of the auditory system starting from the eustachian tube to the brain stem with clear correlation between missing hair cells on the organ of Corti and radiation dose. In addition, outer hair cells of higher frequency area are more commonly affected and it is closely correlated with clinical findings of high frequency SNHL [18].

The findings that radiation dose may have significant long-term audiologic impact is particularly relevant in nasopharyngeal carcinoma. Ondrey et al. [23] calculated radiation dosimetry to otologic structures from computed tomogram treatment plans on head and neck cancer patients and demonstrated that patients with cancers arising in or involving the nasopharynx were at greatest risk for receiving high radiation doses to otologic structures, and the cochlea always received nearly full tumor doses of radiation. Conventional radiation treatment planning based on lateral opposed fields provides no cochlear sparing. IMRT not only allows superior dose distribution, but also enables the delivery of high fractional doses to the tumor, while delivering a more conformal radiation dose to reduce the dose exposure to surrounding normal structures [2-5].

In previous reports, the incidences of radiation induced SNHL with various radiation techniques are range from 7.9-18% for low speech frequencies (PTA) and 18.5-60% for high speech frequency (4 kHz) [16,17,21]. In our study, the cumulative incidences of SNHL at PTA and 4 kHz were comparable with other studies (11.1% and 33.3%, respectively). The observation in our study that higher frequency (4 kHz) hearing was generally more affected than lower frequency (PTA) hearing is consistent with findings from other clinical studies. Ho WK et al. [21] showed that the incidence of SNHL after radiation by conventional technique at PTA and 4 kHz was 18% and 60%, respectively. For IMRT technique, Chan SH et al. [15] reported that the incidence of SNHL was 7.9% at PTA and 55% at 4 kHz. Such findings are expected because both Cisplatin and radiation are known to cause high-frequency hearing loss more than low frequency hearing loss.

This study is the first prospectively attempt to compare the incidence and severity of SNHL between conventional two-dimensional (2D) radiation and IMRT technique. We found that the incidence and severity of SNHL at PTA or low speech frequencies of two radiation techniques were not different. But at the higher speech frequency (4 kHz), there is unexpected result that the incidence of conventional group was significant lower than IMRT group (15 vs 56.3%, p=0.014). While the hearing threshold at pre and post-radiotherapy between two groups was not different. We reviewed the treatment planning and mean cochlea radiation doses of the patients who had SNHL in IMRT group to explain this finding. They showed that the nasopharyngeal tumor or enlarge lymph nodes of 2 patients (3 ears) were close to their cochlea. It resulted that the CTV 70 were involved or near to the cochlea and recieved a radiation dose higher than 50 Gy (constraint dose) to the cochlea.

Several studies [12-15] found that older age is one of the risk factors for unfavorable post-treatment hearing outcome. In this study, the baseline patients' characteristics were not statistically significant different. Except the age of patient between two groups, there was slightly higher of the median age of patients in IMRT than conventional group (53 vs 45). Therefore, older age of patients in IMRT group may be the one of factor that contributed to higher incidence of high frequency SNHL in this group.

However at this time, it is difficult to conclude firmly whether the hearing loss was greater in conventional or IMRT technique. Beyond a small sample size in our study, we have a low power to detect a significant difference in patients' characteristics and hearing level. Moreover, the short follow-up period of this study is another limitation. While our study evaluated audiogram at the day that patient had completed of concurrent chemoradiation, the post-treatment sensorineural hearing loss is expected to further increase with the onset of delayed radiation-induced hearing loss at 6-24 months after radiation [15]. Furthermore, SNHL can be transient and reversible so the incidence and severity of hearing loss can be change over time. It remains to be seen how the post-treatment sensorineural hearing outcomes between the two groups will differ in the longer term because the rate and degree of deterioration may not necessarily be the same. It is suggested that monitoring of hearing should be continued so that hearing rehabilitation can be administered before significant hearing disability arises. The long term result of this study would help to improve the radiation treatment planning in term of increasing capability to preserve the otologic structures and reducing the incidence of SNHL which could result in a better quality of life of the patients.

Conclusion

After radiation treatment of nasopharyngeal carcinoma, the incidences of SNHL at low speech frequencies between conventional (2D) radiation and IMRT technique were similar. But the incidences of SNHL at high speech frequency were significant greater in IMRT group. The severities of SNHL between two radiation techniques were not different. Due to a small sample size and short follow up period, it is important to replicate the findings presented here for future research.

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