



Risk factors of sensory hearing loss in nasopharyngeal carcinoma patients obtaining conventional radiotherapy

Odhi Anggani, Sagung RaiIndrasari, Feri Trihandoko, Anisa Haqul Khoiria, Ashadi Prasetyo*,

Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital Yogyakarta, Indonesia.

ABSTRACT

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Previous studies proven that cochlear hair cells' death plays an important role in sensorineural hearing loss due to radiation exposure. Other studies compared the differences between the impact of conventional radiotherapy (CRT) and intensity modulated radiation therapy (IMRT) on hearing loss in patients with nasopharyngeal carcinoma. Although, few differences found in some clinical manifestation, however no statistical analysis had been carried out. The aim of study was to evaluate the risk of sensory hearing loss in nasopharyngeal carcinoma patients who received CRT compared to IMRT. A case control study was performed on nasopharyngeal carcinoma patients who received radiotherapy at Dr. Sardjito General Hospital, Yogyakarta. The result of DPOAE between NPC patients who received CRT and IMRT was compared in this study. Statistical analysis was performed using chi square test and multivariate analysis. The result showed that patients who received CRT significantly altered the risk for sensory hearing loss in the contralateral ear as much as 11.2 times according to the multivariate analysis (CI 95%: 2.2 – 56.6; p=0.004). In conclusion, the risk of sensory hearing loss in patients with nasopharyngeal carcinoma who received CRT is a greater compared to IMRT.

ABSTRAK

Penelitian sebelumnya membuktikan bahwa kematian sel rambut koklea berperan penting dalam terjadinya gangguan pendengaran sensorineural akibat paparan radiasi. Penelitian yang membandingkan paparan radioterapi konvensional (CRT) dengan intensity modulated radiation therapy (IMRT) terhadap gangguan pendengaran pada pasien karsinoma nasofaring menunjukkan adanya perbedaan pada beberapa manifestasi klinis, walaupun analisis statistiknya tidak dilakukan. Tujuan penelitian ini adalah mengevaluasi risiko gangguan pendengaran sensoris pasien karsinoma nasofaring yang mendapat CRT dibandingkan dengan IMRT. Penelitian dengan rancangan potong lintang ini dilakukan pada pasien karsinoma nasofaring yang mendapatkan radioterapi di RSUP Dr. Sardjito, Yogyakarta. Hasil DPOAE antara pasien KNF yang mendapat CRT dan IMRT dibandingkan dalam penelitian ini. Analisis statistik dilakukan dengan menggunakan uji *chi square* dan analisis multivariat. Hasil penelitian menunjukkan bahwa pasien yang menerima CRT secara signifikan meningkatkan risiko gangguan pendengaran sensoris di telinga kontralateral sebanyak 11,2 kali pada analisis multivariat (CI 95%: 2,2 – 56,6; p=0,004). Dapat disimpulkan bahwa risiko gangguan pendengaran sensoris di telinga kontralateral dari sisi tumor pasien yang menerima CRT lebih tinggi dibandingkan IMRT.

Keywords:
radiotherapy;
CRT;
IMRT;
sensory hearing loss;
risk factors;

INTRODUCTION

Radiotherapy is a notable component in the treatment of cancer, especially in head and neck cancer that can evoke the risk of ototoxicity from the radiation. It has also known as radiation induced sensorineural hearing loss/RISNHL. The induction could be happened when the inner ear was exposed to the radiation field. About one third of head and neck cancer patients who had undergone radiotherapy having a side effect such as ototoxicity.¹ The ototoxicity is defined as a cellular degeneration within cochlear tissue and/or vestibular organ that cause functional changes of the use of some application therapeutic agent.² There were several factors that contributed to the event of hearing problem in post radiation patients including radiation dosage, technique administration of adjuvant chemotherapy, and patient's age.^{3,4}

It was reported that radiation exposure could lead to the demise of cochlear hair cells. It would be impact to sensory hearing loss clinically. The radiation has few side effects on the cell by damaging a chemical bond within cellular basic component of structure such as fat, protein, and the most important genetic component of cells that was a DNA. Generally, cell death is an immensely heterogenic process that could be happened during a pathway of cellular cycle including the process of apoptosis, necrosis, and mitosis.^{1,5}

Nilakhe *et al.*⁶ reported that patients with head and neck cancer who received radiotherapy would encounter a conductive and/or sensory neural hearing loss with the peak incidence was significantly higher at 6th months after radiotherapy. However, only 12% NPC was involved in this study, where laryngeal cancer was 24%. The conclusion of this study became more challenging due to the different dosage of radiation received on the mass of

NPC and the mass of laryngeal cancer. The ear would be more exposed by radiation in NPC's group than Laryngeal cancer's group. In addition, Gabriele *et al.*⁷ demonstrated that the total radiation dose is related to vestibular disorder slightly.

Ondrey *et al.*⁸ studied the amount of radiation dosage received by cochlea in a few cases of head and neck cancer. The result showed that patients who received radiotherapy using external beam radiation therapy (EBRT) with fractionation, only 100 Gray from the total of 7,020 Gray, could seize the cochlea in laryngeal cancer patients. Singh *et al.*⁹ and Chen *et al.*¹⁰ reported that BERA result in post radiation sensorineural hearing lost in head and neck cancer patients showed the representation of cochlear abnormalities without impact in retrocochlear part. Honore *et al.*¹¹ reported a relationship between radiation dosage received by cochlea with the incidence of sensory neural hearing loss in nasopharyngeal cancer's patients after radiotherapy. An uplift of dosage to the cochlea by receiving initial radiotherapy could escalate the risk of sensory neural hearing loss. The aim of the study was to investigate the risk of sensory hearing loss in nasopharyngeal carcinoma patient who received conventional radiotherapy (CRT) compared to intensity-modulated radiation therapy (IMRT).

MATERIALS AND METHODS

Design and subjects

It was a case control study conducted in Dr. Sardjito General Hospital, Yogyakarta involving nasopharyngeal patients who underwent external radiotherapy. The data was collected from March 2nd to March 20th, 2020 at the Department of Radiotherapy, Dr. Sardjito General Hospital, Yogyakarta.

Protocol of study

Protocol of the study has been approved by the Medical and Health Research Ethic Committee, the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital (KE/FK/0200/EC/2020). Distortion product otoacoustic emission (DPOAE) examination was performed to each patient at the ear contralateral to the site of the nasopharyngeal tumor. Otosopic and tympanometry examinations were carried out with the normal results in the outer and middle ear. The diagnose of nasopharyngeal carcinoma was based on histopathologic examination from biopsy of nasopharyngeal mass, and CT scan contributed to determine tumor margins. The function of outer hair cell was examined by DPOAE that the results were that “pass” was referring normal function of outer hair cell and “refer” was referring defect in the outer hair cell. The research sample was defined as all nasopharyngeal cancer patients who underwent radiotherapy at Dr. Sardjito General Hospital, Yogyakarta from one to three years before the DPOAE examination that fulfilled the inclusion and exclusion criteria.

The inclusion criteria of the study were nasopharyngeal carcinoma patients who underwent external radiotherapy with or without chemotherapy between one to three years in advance, normal otoscopic examination, the tympanometry showed type A, and the mass of nasopharyngeal carcinoma was limited to one side of the nasopharynx, not exceeding the midline. The exclusion criteria were patients who had history of radiotherapy or chemotherapy prior to the series of therapy and patients who have previous history of using muscular drugs.

Statistical analysis

A chi squared test was applied for the statistical analysis of this study as

well as Fischer exact test if the data distribution was not compatible for chi square test. The data analyzed was categorized into two groups, case and control based on DPOAE results. The case group consisted of patients with “refer” DPOAE results, and the control group consisted of patients with “pass” DPOAE results. Both intervention of conventional radiotherapy (CRT) and intensity-modulated radiation therapy (IMRT) was classified into case and control group.

The significant value was set at $p \leq 0.05$, the calculation of odds ratio (OR) and confidence interval (CI) of 95% to assess the enormity of the risk factors. Analysis of characteristics of the subjects such as age, gender, history of chemotherapy, and interval between radiotherapy and DPOAE examination (radiotherapy-testing interval) was also performed. If there were some variables that was not homogenous, it would be terminated in the multivariate analysis.

RESULTS

The data obtained from the study was analyzed based on its characteristic and the results of DPOAE. There were 40 subjects that met the inclusion and exclusion criteria, the subjects were divided into case and control groups (TABLE 1). Analysis of radiotherapy techniques on the results of DPOAE in the ear contralateral from the side of the tumor was shown in TABLE 2. There was difference between NPC patients who received CRT compared to IMRT with odd ratio was 9,333 ($p=0.004$).

Multivariate analysis using logistic regression was carried out to demonstrate all variables as shown in TABLE 3. The results showed that only type of radiotherapy was statistically significant to the results of DPOAE ($p=0.004$). Other factors such as age, gender, history of chemotherapy, and radiotherapy-testing interval were not statistically significant ($p > 0.05$).

TABLE 1. Characteristics of subjects

Characteristics	Refer (%)	Pass (%)	Total (%)	p
Age*				
• ≥60 y.o.	5 (12.5)	4 (10)	9 (22.5)	1.000
• <60 y.o.	15 (37.5)	16 (40)	31 (77.5)	
Gender**				
• Male	13 (32.5)	10 (25)	23 (57.5)	0.522
• Female	7 (17.5)	10 (25)	17 (42.5)	
History of chemotherapy*				
• Yes	17 (42.5)	18 (45)	35 (87.5)	1.000
• No	3 (7.5)	2 (5)	5 (12.5)	
Radiotherapy-Testing Interval**				
• 2 to ≤ 3 years	7 (17.5)	7 (17.5)	14 (35)	1.000
• 1 to <2 years	13 (32.5)	13 (32.5)	26 (65)	

*Fisher or **X² test result was considered significant if p<0.05

TABLE 2. Analysis of radiotherapy techniques on the results of DPOAE in the ear contralateral from the side of the tumor

Radiotherapy techniques	Refer (%)	Pass (%)	Total (%)	OR	p
CRT	16 (40.0)	6 (15.0)	22 (55.0)	1	0.004
IMRT	4 (10.0)	14 (35.0)	18 (45.0)	9,333*(2,180-39,962)	

*X²-test result was considered significant if p<0.05

TABLE 3. Analysis of variables related to the results of DPOAE in the ear iscontralateral from the tumor side

Variable	Univariate analysis			Multivariate analysis	
	Total	OR (95% CI)	p	OR (95% CI)	p
Group of Age					
• ≥60 years old	9	1	1.000	1.686 (0.267- 10.636)	0.578
• <60 years old	31	1.333 (0.338-7.725)			
Gender					
• Male	23	1	0.522	3.744 (0.621- 22.569)	0.150
• Female	17	1.857 (0.552- 7.215)			
History of chemotherapy					
• Yes	35	1	1.000	0.248 (0.017- 3.603)	0.307
• No	5	0.629 (0.074- 3.378)			
Radiotherapy-testing interval					
• 2 to ≤ 3 years	14	1	1.000	1.377 (0.269- 7.058)	0.701
• 1 to <2 years	26	1.000 (0.370- 5.028)			
Types of radiotherapy					
• CRT	22	1	0.004*	11.186 (2.211- 56.597)	0.004**
• IMRT	18	9.333 (2,180-39,962)			

*The result was considered significant if p<0.05 in univariate analysis

**The result was considered significant if p<0.05 in multivariate analysis

Age group ≥ 60 y.o., male gender, and radiotherapy-testing interval 2 to ≤ 3 years each increased the risk of sensory hearing loss in the contralateral ears by 1.7 times (CI 95%: 0.27-10.10), 3.7 times (CI 95%: 0.62-22.57), and 1.4 times (CI 95%: 0.27-7.06) respectively. However, they were not significant ($p > 0.05$). History of chemotherapy also was not significantly lowering the risk of sensory hearing loss in the contralateral ear by 0.25 times (CI 95%: 0.02-3.6; $p = 0.307$). It might become a problem, because the number of nasopharyngeal carcinoma patients who did not undergo chemotherapy was very small. The technique of CRT was statistically significant in order to alter the risk of sensory hearing loss in the contralateral ear by 11.2 times (CI 95%: 2.21- 56.6; $p = 0.004$).

DISCUSSION

There were significantly different of DPOAE between case and control group both in CRT and IMRT (OR= 9,333; $p = 0.04$). It indicated that the CRT had higher risk of outer hair cells damage in the ear contralateral to the side of nasopharyngeal carcinoma tumor compared to IMRT. The difference in DPOAE results could be caused by several factors like cochlear dosage to the contralateral side. It had been known that the delineation method in IMRT was better than CRT technique. El-Ghoneimy *et al.*¹² compared the impact of the technique used with the dosage of radiation to the cochlea in the nasopharyngeal carcinoma patients. The results showed that IMRT has lower cochlear dosage significantly than CRT with 7 Gray lower. In addition, the study demonstrated that the total dosage was around 70 Gray divided into 33 fractions. This study correlated with other study in the total dosage given, 70 Gray divided into 30 – 35 fractions, was depending on the therapeutic response from each patient. This dosage distribution by

fractions was known as conventional fractionation method.

This type of fractionation method was not taken into an account as one of the contributing factors in this research because all of external radiation in our institution used conventional fractionation method by dividing three total dosage of 70 Gray into 30-35 fractions within the period of 6 to 7 weeks. It was given 5 fractions per week with every fraction per day. This procedure disclosed that the patient would receive 2.2 Gray each day.

Lannering *et al.*¹³ reported that the use of conventional fractionation method would reduce the cochlear dosage rather than the use of hyper fractionation method in medul loblastoma cases, because the dosage was given 10 Gray greater than conventional. This additional cochlear dosage would increase the risk of cochlear outer hair cell damage that could be observed in DPOAE's results. Chen *et al.*¹⁰ reported that nasopharyngeal patients who received 3D conventional radiotherapy technique would be exposed with higher radiation dosage of 35.5 Gray to the cochlea from the total dosage of 65-70 Gray that was given within the period of 6-8 weeks. The DPOAE results showed significant difference at one year before and after radiotherapy.

Nurmasari *et al.*¹⁴ observed the shorter interval of radiotherapy in the DPOAE examination. It was discovered that there was no statistically significant difference in DPOAE results before and after the administration of 20 Gray dosage. However, after the administered of the total dosage reached 40 Gray, significantly different in statistic began to be obtained before and after therapy. The difference stayed significant even until one month after receiving final total dosage of 66 Gray, but there was no statistically significant difference between shortly after final dosage and one month after latter dosage. Patients

with middle ear abnormality confirmed with tympanometry were excluded from the data calculation. The technique used for the radiotherapy was not mentioned, but considering the timing and date of the data collection, the technique used in the study was probably conventional radiotherapy.

In this study, the interval between radiotherapy and DPOAE examination was appointed at one to three years. This interval was chosen based on two previous studies by Nilakhe *et al.*⁶ and Hwang *et al.*³ who showed that the incidence of sensorineural hearing loss was begun to be detected 6 months after the radiotherapy, and would be altered in the upcoming years, even after 9 years alongside from the patient's age. Another reason was that the modality of radiotherapy in one to three years before the data collection was in the process of transitioning from CRT to IMRT. Therefore it was expected that the retrospective samples hopefully could attain a sufficient proportion.

Petsuksiri *et al.*¹⁵ compared the difference between the technique of radiation therapy specifically CRT and IMRT involving 68 patients with NPC. The incidence of SNHL in 4000 Hz frequency were 48.75% in CRT groups and 37% in IMRT groups. However, it was not statistical analysis performed of the data obtained from research results. Therefore, it was difficult to conclude the different effects of each technique to the incidence of the sensorineural hearing loss. This study was resembling to our study, but the difference was that our study specifically examined the outer hair cell (sensory hearing loss) with DPOAE.

Recently, there are no studies to correlate the damage of outer hair cells in the ear contralateral from the side of the tumor. Most of the previous studies did not separate the side of the tumor with the side of the ear studied. This study will provide a new overview in whether the

contralateral ear can still be maintained if the IMRT radiotherapy techniques was chosen side from to CRT. The use of IMRT provides a protection factor to outer hair cells by 11 times better than those that use CRT, indicating that the application of IMRT can be considered in preserving the hearing function of the contralateral ear.

This study realized the limitations compared to previous studies including the lack of control of the factors that affect the contralateral ear. In addition, the confidence interval of OR value for the type of radiotherapy is still quite wide.

CONCLUSION

There is a greater risk of sensory hearing loss in patients with nasopharyngeal carcinoma who received CRT compared to IMRT. Based on multivariate analysis, the results of DPOAE in the group of contralateral ears who received CRT with "refer" results are 11 times higher than IMRT's group, and 9 times higher based on bivariate analysis.

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