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Research Article

The Effect of Radiation Therapy on Hearing Loss in Patients with Head and Neck Cancer

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Abstract

Background: Radiotherapy is one of the important components of head and neck cancer (HNC) treatment. This treatment method may cause a variety of side effects like oral problems, swelling, and hearing loss.
Objectives: In this study, the effect of radiotherapy on hearing loss in patients with HNC was investigated.
Methods: In this prospective cohort research, patients with head and neck cancer referring to the Shohadaye Tajrish Hospital during 2014 to 2015 were investigated. All of these patients were candidate for radiotherapy as the main treatment. The radiotherapy of patients was done by 3D-computer based treatment planning system, using their CT scan. In order to oncologic assessment, pre- and post-radiotherapy audiologic evaluations were done. The common toxicity criteria for the adverse events (CTCAE V4.02) of the National Cancer Institute (NCI) were used for ototoxicity. A bivariate latent variable model was used to assess the effect of received dose on the severity of hearing loss.
Results: In this study, 66 patients with HNC were investigated. Among them, 46 patients (70%) were male. The mean (SD) age of patients was 45.33 (15.11). The incidence rate of hearing loss in these patients was about 18%. The result of statistical modeling showed a positive relationship between severity of HL and received dose of radiation ($P < 0.001$).
Conclusions: In general, the findings of this study showed a direct relationship between radiation dose received by the ears and severity of hearing loss in patients with HNC. In this context, paying more attention to dose-prescription limits and standards for assessing radiation therapy associated ototoxicity are strictly recommended.

Keywords: Hearing Loss, Radiotherapy, Head and Neck Cancer, Latent Model, Correlated Response

1. Background

Head and neck cancer (HNC) is a term used to describe malignant tumors developed in the airways and upper digestive system (Throat, larynx, nose, sinuses, and mouth) (1). Most of HNCs can be classified as squamous cell carcinoma (2). The epidemiology research studies showed that HNC (As the sixth common cancers throughout the world) had an annual incidence of 690 000 cancer and about 375 000 deaths in 2012 (4.9% of all cancers incidence and 4.6% of all cancers mortality) (3).

Decision about the treatment option of HNC depends on several factors, such as stage of tumor and overall patient conditions. In this context, Radiotherapy (RT) is a common curative or palliative treatment for HNC. It can be used as a main treatment or a complementary treatment after surgery. This therapy can be offered to about 75% of all HNCs (3).

Although in radiation therapy the concentration of the dose is on the tumor area, the normal tissue around the tumor may be affected by the radiotherapy (4, 5). Radiotherapy also may cause a variety of side effects, such as oral problems, redness or skin irritation, swelling, salivary gland damages, etc. Hearing problems are also common side effects of radiotherapy in these patients (6-10). Anteunis et al. reported that more than 50% of patients treated by the radiation suffered from some hearing problems (11).

Bivariate response data sets are frequently observed in the studies related to body paired organs like eyes, ears, kidneys, lungs, etc. In the previous decades, a variety of statistical approaches have been presented for analyzing the different types of bivariate response data. Reviewing the published articles in this field shows that the first focus of data analyst was on the modeling outcomes, which seems to be more straight forward than the other types of bivariate responses (12-14). Afterwards, because of the categorical nature of many medical data, the researchers developed a number of statistical techniques for modeling binary (For instance, the presence of disease) and ordered bivariate categorical outcomes (15-17). In this context, choosing an appropriate method for modeling a bivariate ordered response needs to pay more attention because of the complexity in analyzing these kinds of data sets. When we wish to decide about the statistical method for analyzing these data sets, 2 important properties should be accounted for; firstly, the ordinal nature of the bivariate outcome and secondly, the correlation between the data from the paired organs.

The main aim of this study was to assess the relationship between received dose and hearing loss severity, using the latent variable model with bivariate normal distribution as an underlying distribution to account for the correlation between paired ears.

2. Methods

2.1. Study Sample and Sample Size Determination

In this prospective cohort research, patients with HNC, who were candidate for radiotherapy in the Shohadaye Tajrish Hospital (affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran) during 2014 to 2015, were studied. This study was approved by the Vice Dean of Research of Shahid Beheshti University of Medical Sciences (no.9911). The Ethics Committee of Shahid Beheshti University of Medical Sciences approved this research project. All patients filled out informed consent before participation.

In this study, the auditory toxicity after radiotherapy was evaluated. The procedures were done in accordance with 1975 Helsinki declaration and its version in 2008. Inclusion criteria for patients were as fallow:

1. Auditory apparatus inside the treatment field or near the edge of the treatment field.
2. No discontinued RT before completing treatment
3. Pre-RTaudiologic problems that may cause or contribute to HL have not been reported at the initial consultation
4. Patients received only RT without cisplatin-chemotherapy

To compute the sample size, the NCSS software was used with alpha = 0.05 and power = 0.9. Using the information of a pilot study, the pooled standard deviation was 17.2 and the means of received dose in 3 groups (grade1, 2, and 3) were 18.03, 44.2, and 40.35, respectively. The estimated minimum sample size was about 57.

The study was approved by the Research and Ethics Committee of Shahid Beheshti University of 2.2. Medical Sciences

2.2. Radiotherapy

The radiotherapy of patients was done by 3D-computer based treatment planning system (TPS), using their CT scans. We used a linear accelerator (linac) with 6 MV photon beam. All of the patients were treated in a 5-day per week regime with 1.8 to 2 GY/day daily dose. Among 66 patients, 5 patients had prior treatment with cisplatin-based chemotherapy. A total of 13 out of 66 patients were treated with concurrent chemo radiation with temodal as fallowing regimes:

- 75 mg/m^2 orally daily from the first day of RT until the last day of RT.
- 200 mg/m^2 orally beginning with the second cycle repeat cycle every 4 weeks for up to 6 cycles.
- 120 mg/m^2 orally concurrent with RT up to 42 days.

2.3. Outcome under study

After importing the patients CT scan images to TPS, the primary tumors, post-operative surgical resection bed, lymph node metastases, and lymph nodes as well as the auditory structures were outlined on the CT images by radiation oncologist. Dose calculations were performed, using the collapsed cone convolution algorithm used by the TPS. The TPS was Isogray version 4.1 from Dosis-ft Company with a dose voxel size of $2 \times 2 \times 2$ mm^3.

For otologic assessment, pre- and post-RTaudiologic evaluations were done. Audiometric information included evaluating the air conduction thresholds at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz frequencies. For each patient, the left and right hearing levels were analyzed separately. The common toxicity criteria for adverse events (CTCAE V4.02) of the national cancer institute (NCI) were used for ototoxity.

2.4. Statistical Analysis

In the present study, in addition to descriptive statistics and univariate analysis, a bivariate latent variable probit model for assessing the effect of radiation dose on hearing loss was used. This model allows us to consider deferent values for covariates (Different received dose for each ear) in each organ (ear) under study.

Additionally, because of the ordinal nature of the response data (categorical severity of HL), the cumulative probabilities of HL can be modeled in this approach.

More formally, the applied cumulative bivariate probit model can be written as:

$$\gamma_{hg}\left(\omega, X_i\right) = \phi_\rho\left(\theta_h - \acute{x}_i\ \delta - \acute{x}_{i1}\ \epsilon, \theta_g - \acute{x}_i\ \delta - \acute{x}_{i2}\ \epsilon\right) \quad (1)$$

where γ_{hg} is the cumulative probability of HL of 2 ears (in hth category of right ear and gth category of left ear) and φ is the bivariate standard normal distribution.

The mvtnorm package in R software version 3.2 was used for fitting the described model. In all analysis, P values less than 0.05 were considered statistically significant.

3. Results

In this research, 66 patients with HNC were studied. Among them, 46 cases (70%) were male. The mean (SD) age of the patients was 45.33 (15.11), ranged from 15 to 85 years. The received radiation dose had a mean (SD) of 23.15 (19.15).

Hearing loss after radiotherapy was detected in 25 ears (Grade1 in 14 ears, grade 2 in 5 ears, and grade 3 in 6 ears). In addition, since the severity of HL was not similar in the left and right ears of patients, we presented bivariate distribution of HL (As a main outcome under study) in Table 1.

Table 2 shows the relationship between the severity of HL and some characteristics of the patients. In the next step of the analyses, we fitted the described normal distribution latent model to the bivariate response data (Severity of HL in the left and right ears).

Table 3 shows the obtained estimates from this model. At the first look, one can conclude that there was a significant relation between the severity of HL and received dose ($P < 0.001$). Moreover, it can interpret the estimates in terms of latent variable scale, using the obtained cut of points. The obtained estimate for the dose variable (0.04) shows that each gray increasing in received radiation dose resulted in an increase of 0.04 in latent variable scale. These results may be confusing for some readers with lower knowledge about statistics. To simplify this finding, we present the results in another way. For instance, about 16 GY increase in received dose results in an increase of 16 multiple by 0.04 = 0.64 in the latent variable scale. This can lead to a change in severity of HL from grade 1 ($0.49 < y_i^* < 1.14$) to a worse status of HL (grade 2 and 3).

4. Discussion

In this study, 66 patients with HNC treated by radiotherapy, as their main treatment, were investigated. The threshold hearing of these patients were evaluated before and after radiation. Results from the bivariate latent variable modeling showed a significant relationship between the severity of HL and the received radiation dose. The relationship between received dose and severity of HL was measured with bivariate normal distribution latent variable model. There was a very high significant positive relation between severity of HL and received dose.

Many studies reported that hearing problems is one of the most prevalent adverse events of radiotherapy in head and neck cancers (6-10, 18). Pan et al. reported that hearing system was damaged between 0% to 50% (14). In another study, hearing loss was about 24% to 36% (19). Wang and Bhandare reported that the prevalence of hearing loss was 24% and 15%, respectively in patients with nasopharynx carcinoma (20, 21). In comparison with these studies, a prevalence rate of 18% in HL was observed in the present study. The different prevalence rate of HL in the above-mentioned research studies may be attributed to various sites of tumors, different doses of radiation therapy, and different definitions for HL.

Another reason for different prevalence of HL in different studies can be different population samplings. In this study, patients with variety of HNCs were included (Brain tumor, tongue, nasopharynx, parathyroid, face, jaw, tonsil, and orbital). Although in some studies the effect of radiation on threshold of hearing in patients with different HN tumors were evaluated (14, 22, 23), in most of the studies, only patients with nasopharynx carcinoma were investigated (8, 10, 24-28).

Despite considering different criteria for measuring the outcome (Hearing complications) in the published articles, almost all of them reported significant relationship between HL and received dose of radiation (14, 21, 29, 30). However, the variety in the study designs and the definition of the outcome makes the comparison of the results rather sophisticated. For instance, Bhandare et al. measured the received radiation dose by different parts of auditory system and reported hearing complications (HC) in different parts of external, middle, and inner ear. They considered a binary response variable for HC (present or absent) and used a Chi-square (or fisher exact) test for assessing the association between received dose levels and presence of HC. In this context, paying more attention to dose-prescription limits and standards for assessing radiation therapy associated ototoxicity are strictly recommended. (21). In another study, Chen et al. used the American Speech and Hearing Association guidelines as the definition of HL. They applied both the linear (for continues outcome) and logistic (for binary outcome) for identifying the relationship between received dose and HL. The significant relation between received dose and HL was found, using the both

Table 1. Hearing Loss Condition in Right and Left Ear and Their Relation

	Hearing Loss Grade in Right Ear			
Hearing loss grade in right ear	0	1	2	3
0	44 (66.7)	6 (9.1)	1 (1.5)	2 (3)
1	6 (9.1)	0	1 (1.5)	0
2	1 (1.5)	0	1 (1.5)	0
3	3 (4.5)	1 (1.5)	0	0

Table 2. Relationship Between Severity of HL and Sex, Age, and Received Dose

Factors	**Hearing Loss**					
	Right			**Left**		
	0	**1**	**2/3**	**0**	**1**	**2/3**
Sex						
Male (%)	34 (74)	7 (15.2)	5 (10.8)	36 (78.3)	6 (13)	4 (8.6)
Female (%)	20 (100)	0	0	17 (85)	1 (5)	2 (10)
Age, y	43.35 (14.99)	56.57 (10.41)	51 (16.03)	45.26 (15.63)	39 (11.75)	53.33 (11.41)
Received dose						
Right	18.8 (17.09)	41.43 (16.28)	47.2 (12.24)			
Left				18.09 (17.55)	44.86 (15.57)	40.33 (6.83)
Total	54 (81.8)	7 (10.6)	5 (7.5)	53 (80.3)	7 (10.6)	6 (9.1)

Table 3. Normal Distribution Latent Variable Model Estimates

	Estimated Parameter	**Standard Error**	**P-Value**
Received dose	0.04	0.008	< 0.001
First cut point	0.49	0.31	-
Second cut point	1.14	0.99	-

models. They also reported a strong relation between the reported HL in the right and left ears of the patients (29). Pan et al. studied the relation between received dose and degree of HL in 40 patients with HNC. They considered one ear of each patient as irradiated and the other as contralateral ear. The difference in the threshold levels (dTL) measured at 6 different time points was defined as the hearing loss (outcome variable). dTL was measured in 6 times. They used mixed model to account for correlation between repeated dTL measurements in each patient. They reported a significant relation between received dose and dTL. The estimate of effect of radiation dose on dTL was -5.8 (14). Lisa et al. measured received dose in Cochlea, Middle ear, and Eustachian tube in 251 patients. In this research, HL was investigated by the difference in the threshold level (dTL) of the irradiated ear and contralateral ear for each patient. The patients were divided in 2 groups as healthy or having HL by a protocol based on dTL. The mean received dose was compared in patients with HL and healthy ones by an independent t test. They reported a significant difference between the mean received dose in patients with and without HL. The mean received dose was significantly higher in patients with HL (36.1 vs. 60.5 in cochlea) (30).

Reviewing the applied statistical methods in analyzing HL, the data in the literature show that in most of these studies, the left and right ears of each patient were considered independent from each other. The recently published articles in the field of correlated data analysis reveal that ignoring the correlation between paired organs in the analysis may result in misleading inferences. In the present research, we utilized more complex statistical modelling approach to account for the correlation between left and right ears of a patient in to the analysis. In addition, in our modelling approach, we considered an ordinal scale (Severity of HL) for the outcome variable, including more detailed information compared with the binary scale (The presence of HL).

4.1. Conclusions

In this study, we aimed at determining the effect of received dose on the severity of hearing loss in patients with HNC. In general, the findings of this showed a direct relationship between radiation dose received by the ears and severity of hearing loss in these patients. In this context, paying more attention to dose-prescription limits and standards for assessing radiation therapy associated ototoxicity are strictly recommended.

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Footnotes

Authors' Contributions: None Declared.

Conflict of Interests: The authors declare that they have no conflict of interest.

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References

1. Lee TF, Yeh SA, Chao PJ, Chang L, Chiu CL, Ting HM, et al. Normal tissue complication probability modeling for cochlea constraints to avoid causing tinnitus after head-and-neck intensity-modulated radiation therapy. *Radiat Oncol*. 2015;**10**:194. doi: 10.1186/s13014-015-0501-x. [PubMed: 26377924].
2. Baxi SS, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB. Causes of death in long-term survivors of head and neck cancer. *Cancer*. 2014;**120**(10):1507–13. doi: 10.1002/cncr.28588. [PubMed: 24863390].
3. Simard EP, Torre LA, Jemal A. International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site. *Oral Oncol*. 2014;**50**(5):387–403. doi: 10.1016/j.oraloncology.2014.01.016. [PubMed: 24530208].
4. Khan FM, Gibbons JP. *Khan's the physics of radiation therapy*. Lippincott Williams Wilkins; 2014.
5. Center MS KC. *A practical guide to intensity-modulated radiation therapy: Medical Physics Publishing Corporation*. 2003.
6. Talmi YP, Finkelstein Y, Zohar Y. Postirradiation hearing loss. *Audiology*. 1989;**28**(3):121–6. [PubMed: 2660774].
7. Johannesen TB, Rasmussen K, Winther FO, Halvorsen U, Lote K. Late radiation effects on hearing, vestibular function, and taste in brain tumor patients. *Int J Radiat Oncol Biol Phys*. 2002;**53**(1):86–90. [PubMed: 12007945].
8. Grau C, Overgaard J. Postirradiation sensorineural hearing loss: a common but ignored late radiation complication. *Int J Radiat Oncol Biol Phys*. 1996;**36**(2):515–7.
9. Borsanyi SJ. The effects of radiation therapy on the ear: with particular reference to radiation otitis media. *South Med J*. 1962;**55**:740–3. [PubMed: 13871475].
10. Coplan J, Post EM, Richman RA, Grimes CT. Hearing loss after therapy with radiation. *America J Diseas Child*. 1981;**135**(11):1066–7.
11. Anteunis LJ, Wanders SL, Hendriks JJ, Langendijk JA, Manni JJ, de Jong JM. A prospective longitudinal study on radiation-induced hearing loss. *Am J Surg*. 1994;**168**(5):408–11. [PubMed: 7977961].
12. Adell N, Puig P, Rojas-Olivares A, Caja G, Carne S, Salama AA. A bivariate model for retinal image identification in lambs. *Computer Electronic Agricult*. 2012;**87**:108–12.
13. Lee H, Chung JL, Kim EK, Sgrignoli B, Kim TI. Univariate and bivariate polar value analysis of corneal astigmatism measurements obtained with 6 instruments. *J Cataract Refract Surg*. 2012;**38**(9):1608–15. doi: 10.1016/j.jcrs.2012.04.035. [PubMed: 22795977].
14. Pan CC, Eisbruch A, Lee JS, Snorrason RM, Ten Haken RK, Kileny PR. Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. *Int J Radiat Oncol Biol Phys*. 2005;**61**(5):1393–402. doi: 10.1016/j.ijrobp.2004.08.019. [PubMed: 15817342].
15. Zayeri F, Kazemnejad A. A latent variable regression model for asymmetric bivariate ordered categorical data. *J Appl Statist*. 2006;**33**(7):743–53.
16. Molenberghs G, Lesaffre E. Marginal modeling of correlated ordinal data using a multivariate Plackett distribution. *J America Statist Associat*. 1994;**89**(426):633–44.
17. Kim K. A bivariate cumulative probit regression model for ordered categorical data. *Statist Medicin*. 1995;**14**(12):1341–52.
18. Borsanyi SJ, Blanchard CL. Ionizing radiation and the ear. *JAMA*. 1962;**181**(11):958–61.
19. Merchant TE, Gould CJ, Xiong X, Robbins N, Zhu J, Pritchard DL, et al. Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. *Int J Radiat Oncol Biol Phys*. 2004;**58**(4):1194–207. doi: 10.1016/j.ijrobp.2003.07.008. [PubMed: 15001264].
20. Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. *Otol Neurotol*. 2004;**25**(2):168–73. [PubMed: 15021778].
21. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. *Int J Radiat Oncol Biol Phys*. 2007;**67**(2):469–79. doi: 10.1016/j.ijrobp.2006.09.017. [PubMed: 17236969].
22. Herrmann F, Dorr W, Muller R, Herrmann T. A prospective study on radiation-induced changes in hearing function. *Int J Radiat Oncol Biol Phys*. 2006;**65**(5):1338–44. doi: 10.1016/j.ijrobp.2006.03.032. [PubMed: 16863923].
23. Zuur CL, Simis YJ, Verkaik RS, Schornagel JH, Balm AJ, Dreschler WA, et al. Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. *Radiother Oncol*. 2008;**89**(1):38–43. doi: 10.1016/j.radonc.2008.06.003. [PubMed: 18706728].
24. Honore HB, Bentzen SM, Møller K, Grau C. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. *Radiotherap Oncol*. 2002;**65**(1):9–16.
25. Kwong DL, Wei WI, Sham JS, Ho WK, Yuen PW, Chua DT, et al. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. *Int J Radiat Oncol Biol Phys*. 1996;**36**(2):281–9. [PubMed: 8892450].
26. Petsuksiri J, Sermsree A, Thephamongkhol K, Keskool P, Thongyai K, Chansilpa Y, et al. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. *Radiat Oncol*. 2011;**6**:19. doi: 10.1186/1748-717X-6-19. [PubMed: 21333025].
27. Chan SH, Ng WT, Kam KL, Lee MC, Choi CW, Yau TK, et al. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. *Int J Radiat Oncol Biol Phys*. 2009;**73**(5):1335–42. doi: 10.1016/j.ijrobp.2008.07.034. [PubMed: 18922648].
28. Raaijmakers E, Engelen AM. Is sensorineural hearing loss a possible side effect of nasopharyngeal and parotid irradiation? A systematic review of the literature. *Radiother Oncol*. 2002;**65**(1):1–7. [PubMed: 12413668].
29. Chen WC, Jackson A, Budnick AS, Pfister DG, Kraus DH, Hunt MA, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. *Cancer*. 2006;**106**(4):820–9. doi: 10.1002/cncr.21683. [PubMed: 16421885].
30. van der Putten L, de Bree R, Plukker JT, Langendijk JA, Smits C, Burlage FR, et al. Permanent unilateral hearing loss after radiotherapy for parotid gland tumors. *Head Neck*. 2006;**28**(10):902–8. doi: 10.1002/hed.20426. [PubMed: 16783830].