ORIGINAL ARTICLE

Is the risk of idiopathic sudden sensorineural hearing loss higher in nasopharyngeal carcinoma than in hypopharyngeal cancer? A population-based study

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Abstract

Background: The aim of this study was to compare the risk of developing sudden sensorineural hearing loss (SSHL) in patients with hypopharyngeal cancer with that in patients with nasopharyngeal carcinoma (NPC).

Methods: A population-based, retrospective cohort study was performed using the Taiwan National Health Research Database databank. Patients selected for this study were diagnosed with hypopharyngeal cancer or NPC and treated with radiotherapy in the period from 2001 to 2004. Routine follow-up was conducted for 8 years (2004–2012), and the incidence of SSHL was calculated at the final follow-up.

Results: There was no significant difference in the risk of developing SSHL between the hypopharyngeal cancer group and its control group ($p = 1.000$). In hypopharyngeal cancer and NPC groups, the rates of SSHL were 0.12% and 1.00%, respectively ($p < 0.001$). The cumulative hazard of SSHL during the follow-up period was significantly higher in the NPC group than in the control group ($p < 0.001$).

Conclusion: Radiotherapy in patients with hypopharyngeal cancer did not increase the risk of developing SSHL, but postirradiation NPC was significantly associated with an increased incidence of SSHL.

Keywords: Hypopharynx cancer; Incidence; Nasopharyngeal carcinoma

1. INTRODUCTION

The global incidence of sudden sensorineural hearing loss (SSHL) is estimated to be 5–20 cases per 100,000 people per year.[1] SSHL is defined as hearing loss of 30 dB or greater over three contiguous audiometric frequencies within 3 days.[2] Idiopathic SSHL is associated with several diseases or conditions, including autoimmune diseases, ototoxicity, trauma, vascular compromise, tumors, viral infections, and intracochlear membrane rupture.[3] A study revealed that nasopharyngeal carcinoma (NPC) might be associated with an increased risk of developing SSHL and that the risk increased over time.[4] Survivors of NPC who underwent intensity-modulated radiotherapy (IMRT) had a lower prevalence of postirradiation sudden deafness compared with patients who underwent 2-dimensional radiotherapy (2DRT).[5] The study inferred that SSHL might have a correlation with the cochlear radiation dose. Ondrey et al[6] reported that cochlear radiation dosage was around 12–35 Gy in hypopharyngeal cancer and 51–73 Gy in NPC. However, it is unclear whether radiotherapy in patients with hypopharyngeal cancer increases the risk of developing SSHL or not. The purpose of this study was to identify the risk of developing SSHL in patients with hypopharyngeal cancer. A population-based cohort study was performed with a large dataset available from the National Health Insurance Research Database (NHIRD). To the best of our knowledge, this is the first study comparing the rate of postirradiation SSHL between patients with hypopharyngeal cancer and those with NPC.

2. METHODS

2.1. Data (subjects) for analysis

Data from our NHIRD databank were used for analysis. NHIRD has existed as a universal health care data system since 1995. The data were released under a deidentification and encrypted procedure and included all the medical records based on nearly the entire population of Taiwan, which totaled approximately 23 million people at the time the data request was made. Each record contains its related diagnosis codes (International

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Classification of Diseases, Ninth revision [ICD-9]) and treatment codes for all of the procedures.

2.2. Design

A retrospective cohort study was performed in two study groups: (1) an NPC group and (2) a matched non-NPC control group. The data were sorted by the subject's date of NPC diagnosis between the years 2001 and 2004 and was screened with NPC diagnosis codes (ICD-9: 147). A diagnosis of SSHL (ICD-9: 388.2) was made from referring teaching hospitals and referring tertiary medical centers using a consensus definition of a sensorineural hearing loss of 30 dB or more over a period of a few hours to 3 days. Patients without NPC (case: control = 1:5), matched for sex, age, and defined comorbidities, were randomly selected for the control group. Furthermore, two additional study groups, hypopharynx cancer (ICD-9: 148) and matched nonhypopharynx cancer controls (case:control = 1:5), were selected using the same selection process. Defined comorbidities in the study included the following: coronary artery disease (CAD, ICD-9: 410, 411, 413, 414), hypertension (HTN, ICD-9: 401–405), diabetes mellitus (DM, ICD-9: 250), and chronic renal disease (CRD, ICD-9: 581–583, 585–588). Treatment code (36012B) as designated in the NHIRD was used to select patients who received radiotherapy. The index date for the patients in the NPC or hypopharynx cancer group was the date of their first diagnosis, from 2001 to 2004. Follow-up contact with patients were to be continued for 8 years (2004–2012). Cases in the NPC, non-NPC, hypopharynx, and nonhypopharynx cancer groups were accessed to determine the incidence of SSHL during the period 2004–2012. The institution review board approved this study.

2.3. Statistics analysis

Descriptive statistical analysis using Pearson's chi-squared tests was conducted to compare the differences in terms of basic characteristics, comorbidities, and the incidence of SSHL between NPC and the control group. A Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) between the NPC and control group. Propensity score matching was used to reduce selection bias, and it identified the predicted probability of obtaining 1 NPC versus 5 control cases from the logistic regression model based on baseline covariates (age and sex) and comorbidities (CAD, HTN, CRD, and DM). The risk of developing SSHL-related comorbidities, such as HTN, CAD, DM, and CRD, was estimated using Cox proportional hazards models. A Kaplan-Meier analysis was used to calculate the cumulative incidence of SSHL in the NPC and non-NPC groups, and the Log-rank test was used to analyze the differences in the incidence curves between two groups. The same statistics analysis was applied on hypopharynx cancer and its control group. All of the analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC). The statistical significance level was set at p <0.05 (2-tailed).

3. RESULTS

3.1. Incidence of SSHL in NPC, hypopharyngeal cancer, and control groups

The inclusion criteria for NPC were fulfilled by 7506 patients from the NHIRD in the period from 2001 to 2004. After excluding eight patients with NPC based on the exclusion criteria, 7498 patients were recruited in the NPC group. Another 37490 patients without NPC were recruited in the control group (case:control = 1:5). The incidence of SSHL was higher in the NPC group (0.99%) than in the control group (0.15%, $p < 0.001$, Table 1).

Table 1

Profiles of patients in the nasopharyngeal carcinoma group and its control group

	NPC	Non-NPC	
	n = 7498	n = 37490	*p*
Sex			
Male	5477 (73.05)	27385 (73.05)	1.000
Female	2021 (26.95)	10105 (26.95)	
Age	53.41 (SD = 14.02)	53.12 (SD = 14.02)	
<45 y	2220 (29.61)	11140 (29.71)	0.998
45–64 y	3639 (48.53)	18162 (48.44)	
65–74 y	1117 (14.90)	5588 (14.91)	
≥75 y	522 (6.96)	2600 (6.94)	
Cormobidities			
DM			
Yes	911 (12.15)	7700 (20.54)	<0.001*
No	6587 (87.85)	29790 (79.46)	
Hypertension			
Yes	1667 (22.23)	11532 (30.76)	<0.001*
No	5831 (77.77)	25958 (69.24)	
CAD			
Yes	513 (6.84)	5846 (15.59)	<0.001*
No	6985 (93.16)	31644 (84.41)	
Chronic renal disease			
Yes	368 (4.91)	3055 (8.15)	<0.001*
No	7130 (95.09)	34434 (0.15)	
SSHL	74 (0.99)	58 (0.15)	<0.001*

CAD = coronary artery disease; DM = diabetes mellitus; NPC = nasopharyngeal carcinoma; SSHL = sudden sensorineural hearing loss.
*$p < 0.001$.

The inclusion criteria for hypopharyngeal cancer were fulfilled by 2435 patients from the NHIRD in the period from 2001 to 2004. Another 12175 patients without hypopharyngeal cancer were recruited in the control group (case:control = 1:5). The incidence of SSHL was 0.12% in the hypopharyngeal cancer group and 0.15% in the control group ($p = 1.000$, Table 2).

After excluding 110 patients with both NPC and hypopharyngeal cancer among the 7506 patients with NPC, we compared 7396 patients with NPC to the 2435 patients with hypopharyngeal cancer. The incidence of SSHL was significantly higher in the NPC group (1%) than in the hypopharyngeal cancer group (0.12%, $p < 0.001$, Table 3).

3.2. Hazard ratio of SSHL in NPC, hypopharyngeal cancer, and control groups

The HR of SSHL was increased in the NPC group (HR: 6.405, $p < 0.05$), and the HR was increased in patients aged 45–64 years (HR: 1.159, $p < 0.05$, Table 4). A higher adjusted hazard ratio (AHR) was found in patients with NPC (AHR: 7.252, $p < 0.05$) and CAD (AHR: 2.025, $p < 0.05$). Furthermore, a lower AHR was found in patients aged 65–74 years (AHR: 0.473, $p < 0.05$) and those aged ≥75 years (AHR: 0.171, $p < 0.05$).

The rate of SSHL showed no significant difference between the hypopharyngeal cancer group and its control group ($p = 1.00$, Table 5). There was no significant change in HR or AHR of SSHL in the hypopharyngeal cancer group (HR: 0.833, $p = 0.77$; AHR: 1.035, $p = 0.95$), but both were elevated in patients with DM (HR: 3.698, $p < 0.05$; AHR: 4.702, $p < 0.05$).

3.3. Cumulative hazard of SSHL in NPC, hypopharyngeal cancer, and control groups

The cumulative hazard of SSHL (Fig. 1) in the 8-year follow-up period from 2004 to 2012 was significantly higher in the NPC

Table 2

Profiles of patients in the hypopharynx cancer group and its control group

	Cancer of hypopharynx (+)	Cancer of hypopharynx (–)	
	n = 2435	n = 12175	*p*
Sex			
Male	2344 (96.26)	11720 (96.26)	1.000
Female	91 (3.74)	455 (3.74)	
Age	58.14 (SD = 12.419)	58.13 (SD = 12.416)	
<45 y	374 (15.36)	1879 (15.43)	0.999
45–64 y	1308 (53.72)	6544 (53.75)	
65–74 y	485 (19.92)	2415 (19.84)	
≥75 y	268 (11.01)	1337 (10.98)	
Cormobidities			
DM			
Yes	336 (13.08)	3017 (24.78)	<0.001*
No	2099 (86.02)	9158 (75.22)	
Hypertension			
Yes	486 (19.96)	4711 (38.69)	<0.001*
No	1949 (80.04)	7464 (61.31)	
CAD			
Yes	168 (6.90)	2465 (20.25)	<0.001*
No	2267 (93.10)	9710 (79.75)	
Chronic renal disease			
Yes	155 (6.37)	1245 (10.23)	<0.001*
No	2280 (93.63)	10930 (89.77)	
SSHL	3 (0.12)	18 (0.15)	1.000

CAD = coronary artery disease; DM = diabetes mellitus; SSHL = sudden sensorineural hearing loss.
*$p < 0.001$.

Table 3

Sudden sensorineural hearing loss in malignant neoplasm of the nasopharynx and hypopharynx

	Nasopharyngeal carcinoma	Hypopharyngeal cancer	
	n (%)	n (%)	*P*
Total subjects	7396 (100)	2435 (100)	<0.001*
SSHL	74 (1.00)	3 (0.12)	

SSHL = sudden sensorineural hearing loss.
*$p < 0.001$.

group ($p < 0.001$) than in its control group. The cumulative hazard of SSHL (Fig. 2) in the 8-year follow-up period from 2004 to 2012 showed no significant difference between the hypopharyngeal group and the control group ($p = 0.77$).

4. DISCUSSION

In this study, NPC significantly correlated with an elevated risk of SSHL, similar to a previous study.[4] However, the previous study did not mention how the dose or field of radiotherapy would affect the risk of developing SSHL. Therefore, we conducted this study and found that patients with hypopharyngeal cancer, although treated with radiotherapy, did not have an increased risk of developing SSHL. Therefore, the radiation dose and field may play important roles. Another retrospective study[5] performed in a single hospital with a limited sample size focused on the cochlear dose in radiotherapy for NPC and revealed that survivors of NPC who underwent IMRT had a lower prevalence of SSHL than those who underwent 2DRT. For a general perspective, we performed this population-based cohort study comparing postirradiation SSHL between patients with NPC and those with hypopharyngeal cancer and found that the cochlear radiation dose might be correlated with the development of SSHL.

A significantly higher HR in patients aged 45–64 years (HR: 1.159, $p < 0.05$) was found, which might be attributed to the

Table 4

Hazard ratio of sudden sensorineural hearing loss and the hazard ratio adjusted for sex, age, and cormobidities in the nasopharyngeal carcinoma group

	HR (95% CI)	Adjusted HR (95% CI)
Nasopharyngeal carcinoma		
Negative	1.000	1.000
Positive	6.405* (2.542–9.032)	7.252* (5.095–10.320)
Age		
<45 y	1.000	1.000
45–64 y	1.159* (1.070–2.388)	1.355 (0.894–2.055)
65–74 y	0.664 (0.336–1.314)	0.473* (0.232–0.967)
≥75 y	0.259 (0.062–1.080)	0.171* (0.040–0.728)
Cormobidities		
DM		
Yes	1.138 (0.750–1.727)	1.298 (0.818–2.058)
No	1.000	1.000
Hypertension		
Yes	1.204 (0.839–1.729)	1.362 (0.892–2.079)
No	1.000	1.000
CAD		
Yes	1.351 (0.868–2.102)	2.025* (1.229–3.337)
No	1.000	1.000
Chronic renal disease		
Yes	0.679 (0.317–1.454)	0.677 (0.307–1.496)
No	1.000	1.000

CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; SSHL = sudden sensorineural hearing loss.
*$p < 0.05$.

Table 5

Hazard ratio of sudden sensorineural hearing loss and the hazard ratio adjusted for sex, age, and cormobidities in the hypopharyngeal cancer group

	HR (95% CI)	Adjusted HR (95%CI)
Hypopharynx cancer		
Negative	1.000	1.000
Positive	0.833 (2.542–2.829)	1.035 (0.297–3.608)
Age		
<45 y	1.000	1.000
45–64 y	1.076 (0.357–3.242)	0.0834 (0.269–0.590)
65–74 y	0.194 (0.022–1.737)	0.132 (0.014–1.243)
≥75 y	0.351 (0.039–3.138)	0.268 (0.028–2.529)
Cormobidities		
DM		
Yes	3.698* (1.570–8.706)	4.702* (1.851–11.946)
No	1.000	1.000
Hypertension		
Yes	0.906 (0.336–2.244)	0.593 (0.208–1.693)
No	1.000	1.000
CAD		
Yes	1.821 (0.707–4.693)	2.145 (0.743–6.196)
No	1.000	1.000
Chronic renal disease		
Yes	0.994 (0.231–4.266)	0.707 (0.154–3.243)
No	1.000	1.000

CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; SSHL = sudden sensorineural hearing loss.
*$p < 0.05$.

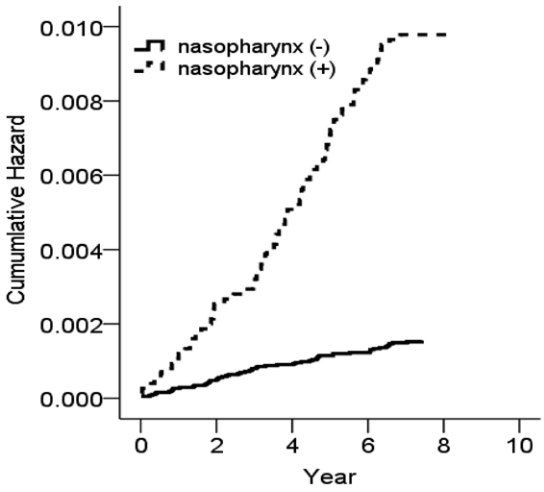

Fig. 1 The cumulative hazard of sudden sensorineural hearing loss in patients with nasopharyngeal carcinoma (+) and its controls (–) in Taiwan from 2004 to 2012.

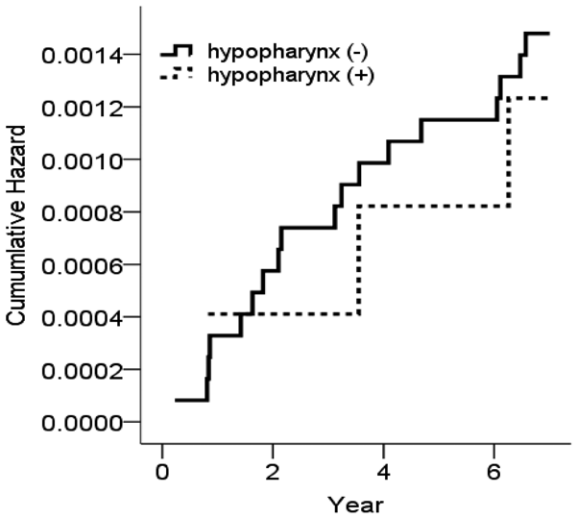

Fig. 2 The cumulative hazard of sudden sensorineural hearing loss in patients with hypopharyngeal cancer (+) and its controls (–) in Taiwan from 2004 to 2012.

median age presentation of NPC of 57.7 years.[7] Additionally, lower AHRs in patients aged 65–74 years and those aged over 75 years were noted. These might be attributed to the fewer cases of NPC in patients aged above 65 years. CAD was significantly associated with SSHL (AHR: 2.025), consistent with a previous study.[8] Furthermore, SSHL in the hypopharyngeal cancer group and its control group was significantly elevated in patients with DM (HR: 3.698; AHR: 4.702), consistent with previous studies.[9–11]

4.1. Effect of radiation on SSHL

SSHL can be caused by radiation therapy. In the etiology of SSHL, apoptosis of the cochlear hair cells occurs during the possibility of the upstream activation of p53 after cisplatin and radiation therapy, and synergistic ototoxicity is seen clinically.[12,13] Radiation-induced changes, including degeneration, epithelial atrophy, and progressive fibrosis of the perilymphatic spaces within the cochlea, were found in pathological studies and on high-resolution computed tomography.[14,15] High-frequency SSHL is significantly associated with the concurrent dose of cisplatin and the mean cochlear radiation dose in NPC.[16] However, the actual mechanisms underlying the development of SSHL in NPC remains unclear. Survivors of NPC who underwent IMRT with an estimated radiation dose of 35 Gy had a 10-fold lower prevalence of postirradiation sudden deafness compared with patients who underwent 2DRT with a radiation dose of around 50 Gy.[5,17] Based on this finding, we speculated that the cochlear radiation dose might be associated with the risk of developing SSHL. In our study, patients with NPC had a 6.6-fold higher risk of developing postradiation SSHL compared with patients with hypopharyngeal cancer. Ondrey et al[6] reported that the cochlear radiation dosage was around 12–35 Gy in hypopharyngeal cancer and 51–73 Gy in NPC, similar to the difference between 2DRT and IMRT. Exposure of the cochlea to the cisplatin chemotherapy and mean radiotherapy dose of 15Gy is associated with hearing loss in patients with head and neck cancer.[18] A cochlear threshold of 35 Gy may lead to hearing preservation after radiotherapy.[19] To the best of our knowledge, the threshold and mechanism underlying the cochlear radiation dose that affects the risk of developing SSHL are unknown. This study showed a significant correlation between the cochlear radiation dose and SSHL. Therefore, further research is required on the mechanism underlying the cochlear radiation dose increasing the development of SSHL.

4.2. Postirradiation vascular effect on SSHL

A consistent association between SSHL and microangiopathy has been reported.[20,21] Increased cardiovascular events and the hazard of stroke were found in patients with SSHL compared with subjects without such a history.[21,22] Percentages of CRD, diabetes, and stroke were higher in the NPC group than in the non-NPC group in a large cohort study.[4] The rate of our baseline comorbidities, such as DM, HTN, CAD, and CRD, was higher in the non-NPC group than in the NPC group. However, the rate of SSHL was higher in the NPC group. This result suggests that these comorbidities should not be considered a major contributing factor in the development of SSHL in patients with NPC.

Chronic cerebral spinal insufficiency is involved in the pathogenesis of SSHL.[23] The mechanism of radiation-induced SSHL is considered an aseptic inflammation of the vascular endothelium. Moreover, the smooth muscles and collagen in the blood vessels swell and degenerate. This process may narrow the lumen of vessel and reduce the blood supply, causing severe thrombosis and atherosclerosis.[24–26] In our findings, patients with NPC had a 6.6-fold higher risk of developing postradiation SSHL compared with patients with hypopharyngeal cancer. We further inferred that when the radiation is much closer to the blood supply of the inner ear, more events of SSHL occur. If vascular injury is far from the cochlea, such as in postirradiation patients with hypopharyngeal cancer, there might be a collateral blood supply to compromise it. Thus, radiotherapy in hypopharyngeal cancer did not increase the risk of developing SSHL.

4.3. Strengths and limitations of this study

This long-term follow-up and large population-based data enhanced the statistical power in this study and provided the risk factors of SSHL in Taiwan with minimal tendency for selection bias. Furthermore, patients with NPC in Taiwan were allowed to visit an otolaryngologist immediately without referral, thus the rate of misdiagnosis from chronic sensorineural hearing to SSHL was minimized. In Taiwan, patients with cancer apply for a catastrophic illness identification card after a routine peer review of their pathology report; hence, the miscoding rate is extremely low.

Due to the limitations of our database, there were no details of the stage of cancer, dose of radiotherapy, usage of cisplatin, or the side of ear with hearing loss. However, radiotherapy for

head and neck cancer was usually bilateral, regardless of the side of ear with the cancer.

Cisplatin, widely utilized as an effective antineoplastic medication for head and neck cancers, is known to cause ototoxicity. However, features of ototoxicity are progressive, symmetric, bilateral, and high-tone SSHL, which is much different from the characteristics of SSHL. Reports of SSHL after cisplatin are few.[27–29] The rate was similar between the hypopharyngeal cancer group and its control group in our cumulative hazard rate of SSHL for head and neck cancers. Thus, cisplatin is less likely to be a cause of SSHL.

Although the details of medical records were unavailable in the databank we used as the basis of our study, our observation has provided an alternative viewpoint to the existing literature through a well-designed screening protocol with definite inclusion criteria for the diagnosis and treatment.

In conclusion, this population-based study demonstrates that postirradiated NPC is associated with an increased risk of SSHL, which, however, is a rare condition. Furthermore, radiotherapy in patients with hypopharyngeal cancer did not increase risk of developing SSHL. It is easy to ignore SSHL in patients with NPC because of similar symptoms as middle ear effusion. Our study emphasizes on the early diagnosis and treatment in high-risk patients and the importance of cochlear protection during radiotherapy.

REFERENCES

1. Olzowy B, Osterkorn D, Suckfüll M. The incidence of sudden hearing loss is greater than previously assumed. *MMW Fortschr Med* 2005;**147**:37–8.
2. Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM, et al; American Academy of Otolaryngology-Head and Neck Surgery. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg* 2012;**146**(Suppl 3):S1–35.
3. Hashisaki GT. Sudden sensory hearing loss. In: Bailey BJ, Johnson JT, Newlands SD, editors. *Head and Neck Surgery-Otolaryngology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006, p. 2231–3.
4. Lin C, Lin SW, Weng SF, Lin YS. Risk of developing sudden sensorineural hearing loss in patients with nasopharyngeal carcinoma: a population-based cohort study. *Head Neck* 2014;**36**:203–8.
5. Cho TY, Cheng PW, Young YH. Evolution of postirradiated sudden deafness in nasopharyngeal carcinoma survivors during the past two decades. *Laryngoscope* 2016;**126**:2016–21.
6. Ondrey FG, Greig JR, Herscher L. Radiation dose to otologic structures during head and neck cancer radiation therapy. *Laryngoscope* 2000;**110**(2 Pt 1):217–21.
7. Colaco RJ, Betts G, Donne A, Swindell R, Yap BK, Sykes AJ, et al. Nasopharyngeal carcinoma: a retrospective review of demographics, treatment and patient outcome in a single centre. *Clin Oncol (R Coll Radiol)* 2013;**25**:171–7.
8. Chang SL, Hsieh CC, Tseng KS, Weng SF, Lin YS. Hypercholesterolemia is correlated with an increased risk of idiopathic sudden sensorineural hearing loss: a historical prospective cohort study. *Ear Hear* 2014;**35**:256–61.
9. Wang IK, Wang CY, Muo CH, Yen TH, Sung FC. Risk of sudden sensorineural hearing loss in patients with end-stage renal disease undergoing dialysis. *Nephrology (Carlton)* 2017;**22**:397–402.
10. Lin SW, Lin YS, Weng SF, Chou CW. Risk of developing sudden sensorineural hearing loss in diabetic patients: a population-based cohort study. *Otol Neurotol* 2012;**33**:1482–8.
11. Lin RJ, Krall R, Westerberg BD, Chadha NK, Chau JK. Systematic review and meta-analysis of the risk factors for sudden sensorineural hearing loss in adults. *Laryngoscope* 2012;**122**:624–35.
12. Low WK, Kong SW, Tan MG. Ototoxicity from combined cisplatin and radiation treatment: an in vitro study. *Int J Otolaryngol* 2010;**2010**:523976.
13. Zhang M, Liu W, Ding D, Salvi R. Pifithrin-alpha suppresses p53 and protects cochlear and vestibular hair cells from cisplatin-induced apoptosis. *Neuroscience* 2003;**120**:191–205.
14. Hoistad DL, Ondrey FG, Mutlu C, Schachern PA, Paparella MM, Adams GL. Histopathology of human temporal bone after cis-platinum, radiation, or both. *Otolaryngol Head Neck Surg* 1998;**118**:825–32.
15. Lambert EM, Gunn GB, Gidley PW. Effects of radiation on the temporal bone in patients with head and neck cancer. *Head Neck* 2016;**38**:1428–35.
16. 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**:1335–42.
17. Chi FH, Young YH. Inner ear deficits in irradiated nasopharyngeal carcinoma survivors. *Laryngoscope* 2015;**125**:2565–71.
18. Schuette A, Lander DP, Kalloqieri D, Collopy C, Goddu S,Wildes TM, et al. Predicting hearing loss after radiotherapy and cisplatin chemotherapy in patients with head and neck cancer. *JAMA Otolaryngol Head Neck Surg* 2020;**146**:106–12.
19. Patel KS, Ng E, Kaur T, Miao T, Kaprealian T, Lee P, et al. Increased cochlear radiation dose predicts delayed hearing loss following both stereotactic radiosurgery and fractionated stereotactic radiotherapy for vestibular schwannoma. *J Neurooncol* 2019;**145**:329–37.
20. Aimoni C, Bianchini C, Borin M, Ciorba A, Fellin R, Martini A, et al. Diabetes, cardiovascular risk factors and idiopathic sudden sensorineural hearing loss: a case-control study. *Audiol Neurootol* 2010;**15**:111–5.
21. Mosnier I, Stepanian A, Baron G, Bodenez C, Robier A, Meyer B, et al. Cardiovascular and thromboembolic risk factors in idiopathic sudden sensorineural hearing loss: a case-control study. *Audiol Neurootol* 2011;**16**:55–66.
22. Lin HC, Chao PZ, Lee HC. Sudden sensorineural hearing loss increases the risk of stroke: a 5-year follow-up study. *Stroke* 2008;**39**:2744–8.
23. Ciorba A, Tessari M, Mazzoli M, Tavoni V, Sisini F, Aimoni C, et al. Cerebral inflow and outflow discrepancies in severe sudden sensorineural hearing loss. *Curr Neurovasc Res* 2018;**15**:220–5.
24. Young YH. Irradiated ears in nasopharyngeal carcinoma survivors: a review. *Laryngoscope* 2019;**129**:637–42.
25. Borsanyi SJ, Blanchard CL. Ionizing radiation and the ear. *JAMA* 1962;**181**:958–61.
26. Young YH, Lou PJ. Post-irradiation sudden deafness. *J Laryngol Otol* 1999;**113**:815–7.
27. Doménech J, Santabarbara P, Carulla M, Traserra J. Sudden hearing loss in an adolescent following a single dose of cisplatin. *ORL J Otorhinolaryngol Relat Spec* 1988;**50**:405–8.
28. Guthrie TH Jr, Gynther L. Acute deafness. A complication of high-dose cisplatin. *Arch Otolaryngol* 1985;**111**:344–5.
29. Chapman P. Rapid onset hearing loss after Cisplatinum therapy: case reports and literature review. *J Laryngol Otol* 1982;**96**:159–62.