Clinical Predictors of Cisplatin Chemoradiation-Induced Ototoxicity in HPV-Positive Oropharyngeal Squamous Cell Carcinoma

S Alamleh[1], JW Lee[2], L Zhan[2], K Hueniken[2], M Mahler[3], A Billfalk-Kelly[4], J Davies[2], C Brown[2], A Spreafico[2]
S Huang[2], A Hope[2], W Xu[2], D Goldstein[2], G Liu[2]

[1] Temerty Faculty of Medicine, University of Toronto, [2]Princess Margaret Cancer Centre, University of Toronto, [3]Head & Neck Surgery, University College London Hospitals, [4]Sinai Health System, University of Toronto

Background:

- Human papillomavirus (HPV)-oropharyngeal squamous cell carcinoma (OPSCC) is a **distinct head and neck cancer subgroup** with a unique patient profile — typically younger, less exposed to alcohol and tobacco, and improved survivorship, with **increasing incidence** in western countries[1]
- Cisplatin chemoradiation therapy (CRT) is a standard treatment for HPV-positive OPSCC but is associated with **irreversible sensorineural hearing loss** (17% to 88%)[2]
- Sensorineural hearing loss is linked to **decreased mood**, **decreased quality of life**, and **dementia**[3]
- To date, there have been **no studies** examining clinical predictors of hearing loss in HPV-positive OPSCC patients treated with cisplatin CRT[4]

Objective:

To evaluate the **characteristics and clinical risk factors associated with ototoxicity** in HPV-positive OPSCC patients treated with cisplatin chemoradiation therapy

Methods & Statistical Plan:

- A **retrospective case-control** study was conducted on adult patients (>18 years) with histologically confirmed HPV-positive OPSCC between 2001 and 2019 at Princess Margaret Cancer Centre
- **Demographic**, **clinical** and **audiological** (baseline and post-treatment) data were collected on all patients
- Ototoxicity was defined using the **Common Terminology Criteria for Adverse Events v5.0** grading criteria
- **Univariable** and **multivariable** logistic regression models were used to identify predictors that significantly **increased odds of ototoxicity**
- Regression models were controlled for ***a priori* determined confounding variables**, including age at diagnosis, sex, cancer stage, drinking status, smoking status, renal function (eGFR), months of audiometric follow-up, and baseline pure tone audiometry (PTA)
- **Augmented backwards variable elimination** was used to determine the list of confounding variables entered in the final multivariable model

Results:

Table 1. Cohort Demographics & Clinical Characteristics

Clinical Characteristic	Total (n=201)	No Hearing Loss (n=88)	Hearing Loss (n=113)
Age, median years (IQR)	57 (11.0)	56.0 (11.9)	57.6 (9.5)
Sex, Male n (%)	165 (82%)	70 (79.5)	95 (84.1)
Stage, n (%)			
III	9 (4%)	4 (4%)	5 (4%)
IVA	176 (88%)	78 (89%)	98 (87%)
IVB	16 (8%)	6 (7%)	10 (9%)
Drinking Status, n (%)			
Light or Non-drinker	144 (71.6)	65 (73.9)	79 (69.9%)
Moderate to Heavy	47 (23.4)	20 (22.7)	27 (23.9%)
Unknown	10 (5%)	3 (3.4%)	7 (6.2%)
Ever Smoker, n (%)	118 (59%)	40 (45%)	78 (69%)
Pack years among smokers, years (IQR),	20 (25.0)	22.5 (19.5)	20 (25.0)
Cisplatin Cumulative dose, mg/m2 (IQR)	198 (67.7)	198.6 (64.7)	196.8 (71.6)
Cisplatin Dosing, n (%)			
High	194 (87%)	67 (76.1)	107 (94.7)
Weekly	27 (13%)	21 (23.9)	6 (5.3)
Radiation Cochlear Dose, Gy (IQR)	12.3 (12.1)	11.1 (11.2)	13.1 (12.3)
Renal Function, mL/min/1.73 m^2 (IQR)	88 (20.0)	85.8 (19.1)	89.5 (19.0)
Audio follow-up, months (IQR)	8 (6.1)	8.2 (8.0)	7.8 (4.9)
Baseline PTA, dB (IQR)	26.7 (24.2)	28.8 (25.4)	25.8 (18.3)

Table 2. Univariable and Multivariable Analysis Results

Clinical Characteristic	Univariable OR [95% CI], p-value	Multivariable OR [95% CI], p-value
Age, per 10 years	1.25 [0.86-1.83], p=0.25	2.07 [1.25-3.52], **p=0.006**
Sex (Male vs. Female [Reference])	1.36 [0.66-2.81], p=0.41	-
Stage (IV vs. III [Reference])	1.03 [0.25-4.00], p=0.97	-
Smoking Status (Ever vs. Never [Reference])	2.67 [1.51-4.81], **p=0.001**	2.89 [1.51-5.63], **p=0.001**
Drinking Status (Moderate/ Heavy vs. Never/Light [Reference])	1.11 [0.57-2.18], p=0.76	-
Cumulative Cisplatin Dose, per 100 mg/m^2	1.23 [0.72-2.12], p=0.45	1.03 [0.56-1.92], p=0.92
Cisplatin Regimen (High vs. Weekly [Reference])	5.59 [2.27-15.87], **p < 0.001**	4.93 [1.84-14.99], **p=0.003**
Radiation, per 10 Gy	1.61 [1.18-2.27], **p=0.004**	1.58 [1.12-2.30], **p=0.011**
eGFR, per 1 ml/min/1.72m^2	1.01 [0.99-1.03], p=0.22	-
Audiometric follow up, per Month	0.95 [0.92-0.98], **p=0.006**	0.97 [0.94-1.00] p=0.1
Baseline PTA (from 4, 6, and 8 kHz), dB	1.00 [0.98-1.01], p=0.64	0.98 [0.96-1.00], p=0.082

Figure 1.1 – Left Ear Hearing Loss Averaged between Frequencies (kHz)

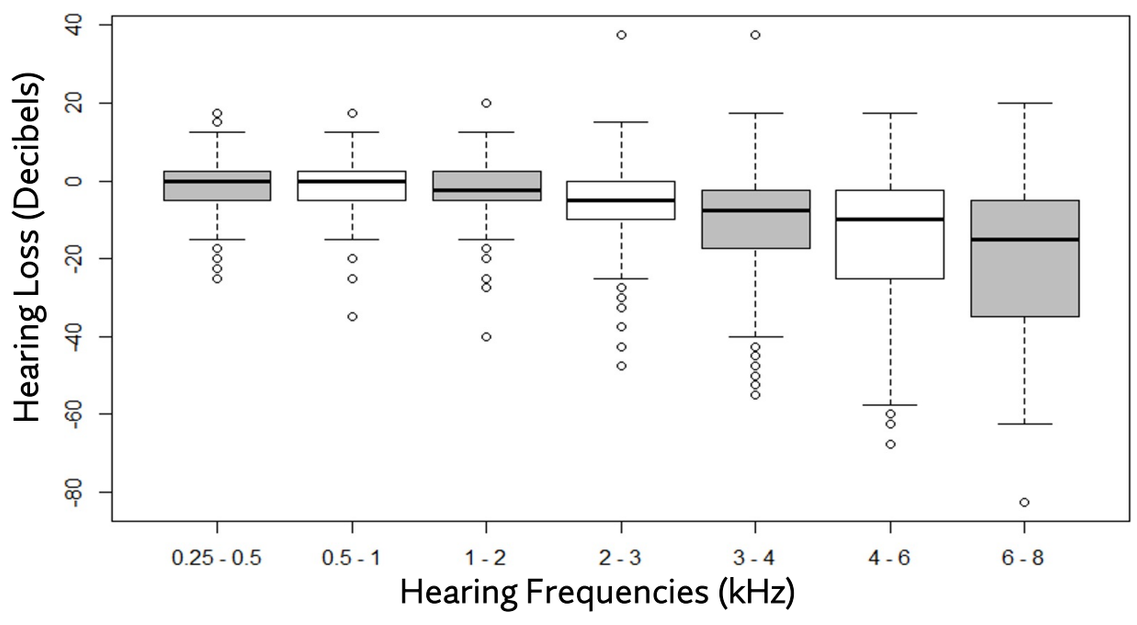
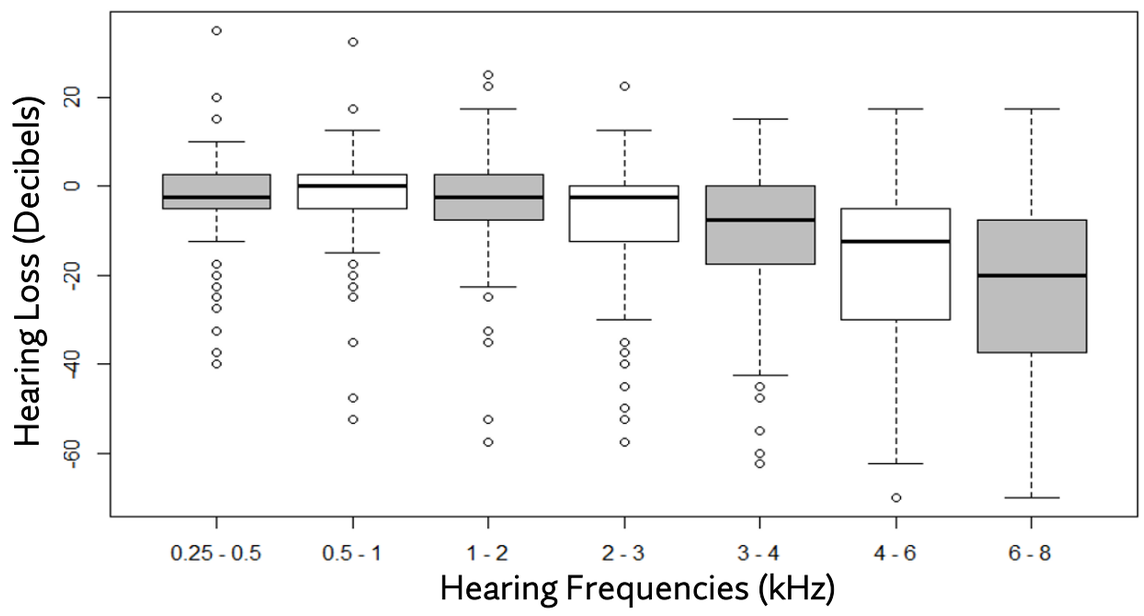


Figure 1.2 – Right Ear Hearing Loss Averaged between Frequencies (kHz)



Discussion:

- Incidence of cisplatin CRT associated ototoxicity was **56%** (n=113). Hearing loss was greatest at **higher frequencies** between 4 and 8 kHz with an average PTA increase of **12.5dB** and **20dB** at 4-6 kHz and 6-8 kHz in the worst ear, respectively
- **High dose cisplatin administration** compared to weekly administration (aOR 4.93), **higher mean cochlear radiation** dose (aOR 1.58), **smoking history** (aOR 2.89), and **every 10-year increase in age** (aOR) were each independently associated with an increased odds of ototoxicity.
- **Cumulative cisplatin dose** was not significantly associated with ototoxicity
- We hope our findings inform **risk stratification** to assess ototoxicity risk and development of intervention such as **otoprotectants** for use during cisplatin CRT for HPV-positive OPSCC patients to reduce the risk of ototoxicity[5]

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