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Risk Profiles for Sensorineural Hearing Loss in Patients with Head and Neck Cancer Receiving Cisplatin-based Chemoradiation

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ABSTRACT

Objective: Sensorineural hearing loss (SNHL) is a significant toxicity experienced by some patients undergoing cisplatin-based chemoradiation therapy for head and neck cancer. Therefore, SNHL risk profiles were created based on demographics, hearing thresholds, and treatment parameters.

Methods: Thirty-eight patients with squamous cell carcinoma of the head and neck, treated with postoperative or definitive cisplatin-based chemoradiation at the Princess Alexandra Hospital between 2010 and 2013, were retrospectively reviewed. Patients with pretreatment otologic problems were excluded. Regression models analysed the contributions of collected variables.

Results: All patients (100%) received multiple audiological assessments, with 21 (55.3%) receiving baseline assessment. The mean hearing deterioration at pure-tone average 1–2–4 kHz was mild (range 22.4–27.6 dB). However, clinically significant SNHL was evident in 37 (97.3%), 24 (63.2%), and 14 (36.8%) patients at 8 kHz and pure-tone averages 0.5–1–2 kHz and 1–2–4 kHz, respectively. Principal component analysis indicated two profiles: (1) low or medium frequency SNHL and (2) high-frequency SNHL. Multivariate analysis demonstrated tobacco consumption ($\rho < 0.006$) and alcohol intake ($\rho < 0.08$) predicted high-frequency SNHL ($F(3,33) = 3.59$, $\rho < 0.02$, $R^2 = 0.177$), with cumulative cisplatin dose ($\rho < 0.006$) predicting low and medium frequency SNHL ($F(3,34) = 14.81$, $\rho < 0.001$, $R^2 = 0.528$).

Conclusions: Although hearing loss rates may be under reported without routine audiological assessment, the incidence of cisplatin-based chemoradiation-induced SNHL, in this study, is high. The proposed predictive model can be used as a prognostic tool and potentially mitigate adverse outcomes.

RÉSUMÉ

Objectif : La surdité de perception est un effet secondaire important pour certains patients traités par chimioradiothérapie à base de cisplatine pour un cancer au niveau de la tête et du cou. Par conséquent, des profils de risque de surdité de perception ont été créés, à partir des données démographiques, des seuils d'audition et des paramètres de traitement.

Méthodologie : Les dossiers de trente-huit patients présentant un carcinome squameux de la tête et du cou, traités par chimioradiothérapie postopératoire ou définitive à base de cisplatine à l'Hôpital Princess Alexandra entre 2010 et 2013 ont fait l'objet d'un examen rétrospectif. Les patients présentant des problèmes otologiques avant le traitement ont été exclus. Les variables recueillies ont été analysées à l'aide de modèles de régression.

Résultats : Tous les patients (100%) ont fait l'objet de plusieurs évaluations audiologiques, et 21 (55,3%) ont fait l'objet d'une

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évaluation de référence. La détérioration moyenne de l'audition aux fréquences 1-2-4 kHz (moyennes sons purs) était modérée (plage de 22,4 – 27,6 dB). Cependant, une surdité de perception clinique était évidente chez 37 (97,3%), 24 (63,2%) et 14 (36,8%) patients à 8 kHz et aux moyennes sons purs 0,5-1-2 kHz et 1-2-4 kHz, respectivement. L'analyse des composantes principales indique deux profils: (1) surdité de perception à basse ou moyenne fréquence et (2) surdité de perception à haute fréquence. L'analyse multivariée montre que l'usage du tabac ($\rho < 0{,}006$) et de l'alcool ($\rho < 0{,}08$) sont des prédicteurs de surdité de perception en haute fréquence ($F(3,33) = 3{,}59$, $\rho < 0{,}02$, $R2 = 0{,}177$), tandis que la dose cumulative de cisplatine ($\rho < 0{,}006$) est un prédicteur de surdité de perception en basse et moyenne fréquence ($F(3,34) = 14{,}81$, $\rho < 0{,}001$, $R2 = 0{,}528$).

Conclusion : Bien que les taux de perte d'audition puissent être sous-signalés en l'absence d'évaluation audiologique de routine, l'incidence de surdité de perception induite par la chimioradiothérapie à base de cisplatine, dans cette étude, est élevée. Le modèle prédictif proposé peut être utilisé comme outil de pronostic et pourrait potentiellement atténuer les effets négatifs.

Keywords: sensorineural hearing loss; head and neck cancer; patient quality of life; radiation oncology; medical oncology

Introduction

Radiotherapy with concurrent cisplatin-based chemotherapy is still regarded as the standard of care for locally advanced head and neck cancer (HNC) patients receiving curative (nonoperative) treatment and in the postoperative setting with high-risk features for recurrence. Multiple phase III trials illustrate the survival benefit of this regimen, reporting improved locoregional control and overall survival [1, 2]. Several meta-analyses reported that cisplatin-based chemoradiation therapy (CbCRT) resulted in an absolute improvement in locoregional control of 12.5% and an absolute overall survival benefit of 6.5% at 5 years [1, 3].

Nevertheless, current CbCRT regimes are associated with significant toxicities and potential long-term side effects [3–5]. The addition of cisplatin to radiotherapy, in the Radiation Therapy Oncology Group 9501 study [5], increased the incidence of acute adverse effects from 34% to 77%. The most common grade 3/4 side effects included dysphagia and mucositis, followed by hematologic events, nausea, and vomiting [3].

Treatment-induced ototoxicity is another common and significant complication for patients with HNC, but the degree and incidence remain poorly determined. There are two types of ototoxicity associated with CbCRT; conductive hearing impairment—more specifically Eustachian tube dysfunction—and sensorineural hearing loss (SNHL), caused by damage to the cochlea or the auditory nerve. It is well documented that CbCRT-induced ototoxicity primarily presents as irreversible, high-frequency SNHL [6–8]. The incidence of post-CbCRT SNHL is reported to be as high as 60%–80% at speech frequencies [9, 10]. Factors implicated in the development of SNHL include age, pretherapeutic hearing capability, cisplatin dose (fractional and cumulative), and radiotherapy dose to the inner ear [6, 7, 9]. Nevertheless, the mechanism underlying SNHL, after CbCRT, remains undefined [9].

The demographic of HNC patients receiving CbCRT in developed nations has changed over the last decade, with an increasing number of virally mediated tumours [11]. Given their good prognosis, survivorship issues need to be adequately addressed. Improvements in long-term dysphagia and xerostomia have been seen in modern cohorts receiving intensity-modulated radiotherapy (IMRT) [12]. However, there is limited data on the impact of SNHL and patient reported effects on quality of life because of effects on cognitive function, learning ability, and communication, resulting in isolation and depression [8]. We assessed the development of SNHL in these patients to identify predictive profiles that determine those patients at the highest risk of developing SNHL. We aimed to determine modifiable risk factors that can be manipulated within the radiotherapy process to reduce the development of SNHL, with particular emphasis placed on the impact of treatment parameters.

Materials and Methods

Population

The patient database of the Princess Alexandra Hospital, (Queensland, Australia) was used to identify patients with histologically confirmed, mucosal squamous cell carcinoma treated curatively with definitive or postoperative adjuvant CbCRT, between June 2010 and June 2013. Patients who received at least one cycle of cisplatin and a minimum of two audiological assessments, with one audiogram obtained after the cisplatin infusion, were eligible. Patients with a radiotherapy planning target volume wholly encompassing the auditory system; prior radiotherapy at another facility; palliative, superficial, or incomplete radiotherapy; and pretreatment otologic conditions (Meniere disease and tinnitus) were excluded. This project was approved by Metro South and Queensland University of Technology Human Research Ethics Committees.

Patient data were obtained by review of radiation oncology, otolaryngology, and audiology medical records. Charts were reviewed for patient demographic and tumour characteristics. Prescribed and delivered chemotherapy were analysed including cisplatin dose (mg/m^2), number of cycles and timing of infusions, cumulative cisplatin dose delivered (mg/m^2) and, if applicable, the reason for dose reduction. Patient radiotherapy plans were reviewed to evaluate treatment parameters including prescribed dose, fractionation, and beam energy. The plan dose maximum and position relative to the inner ears were recorded. Both three-dimensional, conformal radiotherapy (3DCRT) and IMRT plans were assessed.