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The RADIO trial: Randomized assessment of cisplatin dosing interval for ototoxicity with curative concurrent chemo-radiation for locally advanced head and neck squamous cell carcinoma.

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The RADIO trial: Randomized assessment of cisplatin dosing interval for ototoxicity with curative concurrent chemo-radiation for locally advanced head and neck squamous cell carcinoma.

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Background: Patients with locally advanced squamous cell carcinoma of the head and neck (LASCCHN) receive curative chemoradiation (CRT) with Cisplatin, as a standard of care. A meta-analysis of 52 randomized trials comparing Low Dose (LD) and High Dose (HD) schedules demonstrated differing toxicity profiles but hearing effects were not rigorously studied. Hearing loss associated with HD Cisplatin can result in survivorship challenges. A local study suggested a protective effect for LD Cisplatin in relation to ototoxicity and pharmacogenomic markers, MATE1 and COMT, to be associated with risk for ototoxicity. We hypothesize that LD cisplatin is associated with reduced frequency of hearing loss when compared to the standard HD cisplatin in LASCCHN patients on CRT and that differences in MATE1/COMT can predict for cisplatin-related ototoxicity and be identified prior to treatment. Our goal is to develop an innovative personalized treatment pathway incorporating predictive pharmacogenomics markers to improve the tolerability and survivorship outcomes of curative CRT for LASCCHN. **Methods:** This is a prospective, open-label, randomized clinical trial. Following informed consent, eligible LASCCHN patients planned for primary CRT will be stratified by tumor p16 status and then randomized in 1:1 fashion to either concurrent LD Cisplatin (40mg/m2 every week) or HD cisplatin (100mg/m2 every 3 weeks). The primary outcome is to measure the change in incidence of CTCAE grade ≥2 hearing loss and hearing-related quality of life (QOL) at 1 year. As part of secondary and exploratory outcomes, differences in survival, loco-regional control, global QOL and other toxicities (e.g. nephrotoxicity, neurotoxicity) will be assessed. The relationship between MATE1 and COMT, as predictors for cisplatin-related ototoxicity will be evaluated. Cost-effectiveness analyses comparing the two regimens will be assessed. *Statistical plan:* Based on rates of CTCAE grade ≥2 hearing loss in an earlier study (Winquist et al., 2016), assuming a conservative rate of hearing loss, amongst treated patients, of 60% with HD cisplatin and 30% with LD cisplatin, a total sample size of 92 patients would achieve > 80% statistical power, (two-sided, alpha = 0.05 test of two proportions) to detect these differences. 100 patients would be targeted to accrual for an assumed 5% noncompliance rate. For hearing related QOL, a two-sided, alpha = 0.05, two-sample t-test with 50 patients per group would achieve > 80% statistical power to detect an effect size of 0.60 and > 95% power to detect an effect size of 0.75. All analyses will be based primarily on the intent-to-treat population. An arms-length data and safety monitoring committee (DSMC) will review safety data bi-annually. *Trial accrual status:* 60 participants have been accrued. Clinical trial information: NCT03649048. Research Sponsor: Academic Medical Organization of Southwestern Ontario, Medical Oncology Research Fund; Juravinski Cancer Center Foundation Grant.