Population Health & Clinical Research Service

AHNS Population Health & Clinical Research Service Edition

This Issue of the AHNS Journal Club has been compiled and reviewed by members of the AHNS Population Health & Clinical Research Service:
Barry Wenig, Chair MD and Joseph Curry MD, Vice-Chair)

Contributing Members:
Sagar Kansara MD,
Katelyn Stepan MD,
Varun Vendra MD,

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Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG 1008): A Multicenter, Noninferiority Phase II/III Randomized Controlled Trial

Naomi Kiyota, Makoto Tahara, Junki Mizusawa, Takeshi Kodaira, Hirofumi Fujii, Tomoko Yamazaki, Hiroki Mitani, Shigemichi Iwae, Yasushi Fujimoto, Yusuke Onozawa, Nobuhiro Hanai,Takenori Ogawa, Hiroki Hara, Nobuya Monden, Eiji Shimura, Shujiro Minami, Takashi Fujii, Kaoru Tanaka, Akihiro Homma, Seiichi Yoshimoto, Nobuhiko Oridate, Koichi Omori, Tsutomu Ueda, Kenji Okami, Ichiro Ota, Kiyoto Shiga, Masashi Sugasawa, Takahiro Asakage, Yuki Saito, Shigeyuki Murono,Yasumasa Nishimura, Kenichi Nakamura, Ryuichi Hayashi; Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG)

From the ***Journal of Clinical Oncology.*** *June 2022.*

Purpose: The standard treatment for postoperative high-risk locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) is chemoradiotherapy with 3-weekly cisplatin (100 mg/m^2). However, whether chemoradiotherapy with weekly cisplatin (40 mg/m^2) yields comparable efficacy with 3-weekly cisplatin in postoperative high-risk LA-SCCHN is unknown.

Patients and methods*:* In this multi-institutional open-label phase II/III trial, patients with postoperative high-risk LA-SCCHN were randomly assigned to receive either chemoradiotherapy with 3-weekly cisplatin (100 mg/m^2) or with weekly cisplatin (40 mg/m^2) to confirm the noninferiority of weekly cisplatin. The primary end point of phase II was the proportion of treatment completion, and that of phase III was overall survival. A noninferiority margin of hazard ratio was set at 1.32.

Results: Between October 2012 and December 2018, a total of 261 patients were enrolled (3-weekly cisplatin, 132 patients; weekly cisplatin, 129 patients). At the planned third interim analysis in the phase III part, after a median follow-up of 2.2 (interquartile range 1.19-3.56) years, chemoradiotherapy with weekly cisplatin was noninferior to 3-weekly cisplatin in terms of overall survival, with a hazard ratio of 0.69 (99.1% CI, 0.374 to 1.273 [< 1.32], one-sided *P* for noninferiority = .0027 < .0043). Grade 3 or more neutropenia and infection were less frequent in the weekly arm (3-weekly *v* weekly, 49% *v* 35% and 12% *v* 7%, respectively), as were renal impairment and hearing impairment. No treatment-related death was reported in the 3-weekly arm, and two (1.6%) in the weekly arm.

Conclusion: Chemoradiotherapy with weekly cisplatin is noninferior to 3-weekly cisplatin for patients with postoperative high-risk LA-SCCHN. These findings suggest that chemoradiotherapy with weekly cisplatin can be a possible treatment option for these patients.

Summary statements

- Chemoradiotherapy with weekly cisplatin was non inferior to 3-weekly cisplatin in terms of overall survival.
- Grade 3 or more toxicity were less frequent in the weekly arm compared to the 3-weekly arm.

Strengths

- Trial design is robust.

Weaknesses

- No subgroup analysis for p16+ patients; no stratification based on p16 status.
- Higher proportion of pT3/4 patients and pN3 patients in the 3-weekly group. This along with wide noninferiority margin may make the conclusions drawn by the authors difficult to accept unless verified at longer time point or in larger sample size.

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Phase II Clinical Trial of Neoadjuvant and Adjuvant Pembrolizumab in Resectable Local-Regionally Advanced Head and Neck Squamous Cell Carcinoma

Trisha M Wise-Draper, Shuchi Gulati, Sarah Palackdharry, Benjamin H Hinrichs, Francis P Worden, Matthew O Old, Neal E Dunlap, John M Kaczmar, Yash Patil, Muhammed Kashif Riaz, Alice Tang, Jonathan Mark, Chad Zender, Ann M Gillenwater, Diana Bell, Nicky Kurtzweil, Maria Mathews, Casey L Allen, Michelle L Mierzwa, Keith Casper, Roman Jandarov, Mario Medvedovic, J Jack Lee, Nusrat Haru, Vinita Takiar, Maura Gillison

From the ***Clin. Cancer Res.*** *April 2022.*

Purpose: Patients with resected, local–regionally advanced, head and neck squamous cell carcinoma (HNSCC) have a one-year disease-free survival (DFS) rate of 65%–69% despite adjuvant (chemo)radiotherapy. Neoadjuvant PD-1 immune-checkpoint blockade (ICB) has demonstrated clinical activity, but biomarkers of response and effect on survival remain unclear.

Patients and Methods: Eligible patients had resectable squamous cell carcinoma of the oral cavity, larynx, hypopharynx, or oropharynx (p16-negative) and clinical stage T3-T4 and/or two or more nodal metastases or clinical extracapsular nodal extension (ENE). Patients received neoadjuvant pembrolizumab 200 mg 1– 3 weeks prior to surgery, were stratified by absence (intermediate-risk) or presence (high-risk) of positive margins and/or ENE, and received adjuvant radiotherapy (60–66 Gy) and concurrent pembrolizumab (every 3 weeks x 6 doses). Patients with high-risk HNSCC also received weekly, concurrent cisplatin (40 mg/m2). Primary outcome was one-year DFS. Secondary endpoints were one-year overall survival (OS) and pathologic response (PR). Safety was evaluated with CTCAE v5.0.

Results: From February 2016 to October 2020, 92 patients enrolled. The median age was 59 years (range, 27–80), 30% were female, 86% had stage T3–T4, and 69% had ≥N2. At a median follow-up of 28 months, one-year DFS was 97% (95% CI, 71%–90%) in the intermediate-risk group and 66% (95% CI, 55%–84%) in the high-risk group. Patients with a PR had significantly improved one-year DFS relative to patients without response (93% vs. 72%, hazard ratio 0.29; 95% CI, 11%–77%). No new safety signals were identified.

Conclusions: Neoadjuvant and adjuvant pembrolizumab increased one-year DFS rate in intermediate-risk, but not high-risk, HNSCC relative to historical control. PR to neoadjuvant ICB is a promising surrogate for DFS.

Summary Statements:

- Among patients with resectable locoregionally advanced head and neck squamous cell carcinoma, the addition of neoadjuvant and adjuvant pembrolizumab to standard of care adjuvant (chemo)RT resulted in improved disease-free survival among intermediate-risk, but not high-risk, patients compared to historical controls.

- Pathologic response to neoadjuvant pembrolizumab was associated with a significant improvement in disease-free survival relative to patients with no pathologic response, and rates of partial and major pathologic response increase significantly with increased PD-L1 combined positivity score (CPS).

Strengths:

- This is a well-designed appropriately powered multicenter phase II window-of-opportunity clinical trial.
- They also performed analysis of gene expression and tumor microenvironment as they relate to pathologic response, providing interesting insights for further future study.

Weaknesses:

- This study lacks prospective randomization and comparison with placebo control; it compared its findings to historical controls, namely RTOG 9501, which was conducted prior to improvements in standard therapies as used today.
- Median follow-up time and outcomes are relatively short, though this is by design as a signal-seeking phase II trial.

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Unilateral Radiation Therapy for Tonsillar Cancer: Treatment Outcomes in the Era of Human Papillomavirus, Positron-Emission Tomography, and Intensity Modulated Radiation Therapy

Nicolette Taku, Gregory Chronowski, G Brandon Gunn, William H Morrison, Neil D Gross, Amy C Moreno, Renata Ferrarotto, Steven J Frank, C David Fuller, Ryan P Goepfert, Jack Phan, Stephen Y Lai, Jay P Reddy, David I Rosenthal, Adam S Garden

From the ***Int J Radiat Oncol Biol Phys.*** *August 2022.*

Purpose: The goal of this study was to evaluate disease, survival, and toxic effects after unilateral radiation therapy treatment for tonsillar cancer.

Methods and materials: A retrospective study was performed of patients treated at our institution within the period from 2000 to 2018. Summary statistics were used to assess the cohort by patient characteristics and treatments delivered. The Kaplan-Meier method was used to determine survival outcomes.

Results: The cohort comprised 403 patients, including 343 (85%) with clinical and/or radiographic evidence of ipsilateral cervical nodal disease and 181 (45%) with multiple involved nodes. Human papillomavirus was detected in 294 (73%) tumors. Median follow-up time was 5.8 years. Disease relapse was infrequent with local recurrence in 9 (2%) patients, neck recurrence in 13 (3%) patients, and recurrence in the unirradiated contralateral neck in 9 (2%) patients. Five- and 10-year overall survival rates were 94% and 89%, respectively. Gastrostomy tubes were needed in 32 (9%) patients, and no patient had a feeding tube 6 months after therapy.

Conclusions: For patients with well-lateralized tonsillar tumors and no clinically evident adenopathy of the contralateral neck, unilateral radiation therapy offers favorable rates of disease outcomes and a relatively low toxicity profile.

Summary Statements

- Single-institution retrospective (2010-2018) 403 patient cohort receiving unilateral radiation for tonsillar SCC. Majority (85%) treated with IMRT (60-70 Gy to gross disease, 57-66 Gy to postoperative, 54-60 Gy to regions of suspected subclinical disease).
- AJCC 7th edition T1 (60%)/T2 (28%), N0 (15%) / N1 (23%) / N2a (14%) / N2b (45%). 294/301 with available HPV/p16 status were positive. 52% had no gross disease at the primary site and 37% at the nodal basin at the time of radiotherapy. No patients had contralateral neck dissection. 137 patients underwent concurrent chemoradiotherapy.
- Median follow up 5.8 years: local recurrence 9 patients, ipsilateral neck failure in 4 and contralateral in 9, 14 with distant metastatic recurrence. 9/13 neck failures had N2b disease on presentation including 6/9 contralateral failures. 5-year OS was 94% and PFS was 90%. 6/9 contralateral neck failures were salvaged with durable disease-free status.
- 32/377 patients for whom data are available had gastrostomy placed. No patient without recurrence had gastrostomy after 6 months.

Strengths

- Follow up to earlier study in the era of HPV/16 testing and IMRT including over 400 patients with follow up > 5 years.
- Data support unilateral radiation for select patients with excellent locoregional control rates including AJCC 7th edition N2b disease. Data demonstrate that contralateral neck failures can be successfully salvaged.
- Supports volume de-escalation strategies in select patients with lateralized tumors.

Weaknesses

- HPV status was missing for 25% of patients and PET/CT staging was not available in 41%.
- Period of study reflects heterogenous staging and management strategies (introduction of TORS, IMRT/proton, AJCC 8th edition staging) .
- Lack of direct comparison of matched patients treated with elective bilateral neck radiation particularly related to treatment toxicities.

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