American Head and Neck Society - Journal Club
Volume 29, December 2019

AHNS Mucosal Malignancy Section Edition

This Issue of the AHNS Journal Club has been compiled and reviewed by members of the ***AHNS Mucosal Malignancy Section*** *(Karen Pitman, Chair; Joe Califano, Co-Chair)*

Jeffson Chung
Stephen Lai
Vikas Mehta
Arun Sharma
Meghan Turner

Table of Contents *– **click the page number to go to the summary and full article link.***

Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial

Anthony C Nichols, Julie Theurer, Eitan Prisman, Nancy Read, Eric Berthelet, Eric Tran, Kevin Fung, John R de Almeida, Andrew Bayley, David P Goldstein, Michael Hier, Khalil Sultanem, Keith Richardson, Alex Mlynarek, Suren Krishnan, Hien Le, John Yoo, S Danielle MacNeil, Eric Winquist, J Alex Hammond, Varagur Venkatesan, Sara Kuruvilla, Andrew Warner, Sylvia Mitchell, Jeff Chen, Martin Corsten, Stephanie Johnson-Obaseki, Libni Eapen, Michael Odell, Christina Parker, Bret Wehrli, Keith Kwan, David A Palma

from ***The Lancet****, August 2019*

Background: Transoral robotic surgery (TORS) with concurrent neck dissection has supplanted radiotherapy in the USA as the most common treatment for oropharyngeal squamous cell

carcinoma (OPSCC), yet no randomised trials have compared these modalities. We aimed to evaluate differences in quality of life (QOL) 1 year after treatment.

Methods: The ORATOR trial was an investigator-initiated, multicentre, international, open-label, parallel-group, phase 2, randomised study. Patients were enrolled at six hospitals in Canada and Australia. We randomly assigned (1:1) patients aged 18 years or older, with Eastern Cooperative Oncology Group scores of 0–2, and with T1–T2, N0–2 (≤4 cm) OPSCC tumour types to radiotherapy (70 Gy, with chemotherapy if N1–2) or TORS plus neck dissection (with or without adjuvant chemoradiotherapy, based on pathology). Following stratification by p16 status, patients were randomly assigned using a computer-generated randomisation list with permuted blocks of four. The primary endpoint was swallowing-related QOL at 1 year as established using the MD Anderson Dysphagia Inventory (MDADI) score, powered to detect a 10-point improvement (a clinically meaningful change) in the TORS plus neck dissection group. All analyses were done by intention to treat. This study is registered with ClinicalTrials.gov (NCT01590355) and is active, but not currently recruiting.

Findings: 68 patients were randomly assigned (34 per group) between Aug 10, 2012, and June 9, 2017. Median follow-up was 25 months (IQR 20–33) for the radiotherapy group and 29 months (23–43) for the TORS plus neck dissection group. MDADI total scores at 1 year were mean 86·9 (SD 11·4) in the radiotherapy group versus 80·1 (13·0) in the TORS plus neck dissection group (p=0·042). There were more cases of neutropenia (six [18%] of 34 patients vs none of 34), hearing loss (13 [38%] vs five [15%]), and tinnitus (12 [35%] vs two [6%]) reported in the radiotherapy group than in the TORS plus neck dissection group, and more cases of trismus in the TORS plus neck dissection group (nine [26%] vs one [3%]). The most common adverse events in the radiotherapy group were dysphagia (n=6), hearing loss (n=6), and mucositis (n=4), all grade 3, and in the TORS plus neck dissection group, dysphagia (n=9, all grade 3) and there was one death caused by bleeding after TORS.

Interpretation: Patients treated with radiotherapy showed superior swallowing-related QOL scores 1 year after treatment, although the difference did not represent a clinically meaningful change. Toxicity patterns differed between the groups. Patients with OPSCC should be informed about both treatment options.

Strengths:
- Multi-center randomized trial that managed to accrue subjects successfully despite the previous failure of RTOG 1221
- Sample size calculated and powered to detect a specific endpoint – 10-point improvement on MDADI
- Inclusion of p16- small primary patients reflects real world situation where patient would likely still be offered TORS vs primary CRT

Weaknesses:
- Short median follow-up means that long term side effects of treatment arms are likely under-represented. OS and PFS comparisons also need to be considered with this in mind, along with the fact that the study was not powered to detect this difference

- Tonsil and tongue base cancer treatments have substantially different side effect profiles but sample size is too small to allow for subset analysis
- It is unclear how many patients in each arm had unilateral neck radiation versus bilateral radiation
- Reasoning not given for the requirement that nodes be 4 cm or less, without ENE
- Number of prophylactic tracheotomies was not reported and this is not representative of most surgeon's practices
- Use of adjuvant radiation for any positive nodes is likely considered aggressive by 2019 standards and thus may not be applicable to many practices

Reviewer Comment: This was clearly a very necessary study that was no doubt very difficult to complete. The challenge of having patients consent to be randomized to such immensely different treatment arms cannot be understated. The authors and study participants are to be commended for this landmark trial. I think the results of this study are also very important in that it shows new technology doesn't necessarily imply improved outcomes. This is not to say that robots have no place in surgery. It simply underscores the fact that it needs to be used in carefully selected cases where there are clear advantages like simplified surgical access, and patients need to be properly counseled regarding other treatment options.

back to top

Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

Chera BS, Amdur RJ, Green R, Shen C, Gupta G, Tan X, Knowles M, Fried D, Hayes N, Weiss J, Grilley-Olson J, Patel S, Zanation A, Hackman T, Zevallos J, Blumberg J, Patel S, Kasibhatla M, Sheets N, Weissler M, Yarbrough W, Mendenhall W.

from ***The Journal of Clinical Oncology****, August 2019*

Purpose: To report the results of a phase II clinical trial of de-intensified chemoradiotherapy for patients with human papillomavirus–associated oropharyngeal squamous cell carcinoma.

Materials & Methods: Major inclusion criteria were (1) having American Joint Committee on Cancer (AJCC) 7th edition T0-T3, N0-N2c, M0 (AJCC 8th edition T0-T3, N0-N2, M0), (2) being p16 positive, and (3) reporting minimal or remote smoking history. Treatment was limited to 60 Gy intensity-modulated radiotherapy with concurrent intravenous cisplatin 30 mg/m2 once per week. Patients with T0-T2 N0-1 (AJCC 7th edition) did not receive chemotherapy. All patients had a 10- to 12-week post-treatment positron emission tomography/ computed tomography to assess for neck dissection. The primary end point was 2-year progression-free survival. Secondary end points included 2-year local-regional control, distant metastasis-free survival and overall survival, and patient-reported outcomes (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events).

Results: One hundred fourteen patients were enrolled (median follow-up of 31.8 months), with 81% having a minimum follow-up of 2 years. Eighty percent of patients had 10 or fewer tobacco pack-years. Two-year local regional control, distant metastasis-free survival, progression-free survival, and overall survival were as follows: 95%, 91%, 86%, and 95%, respectively. Mean pre- and 2-year post-treatment European Organization for Research and Treatment of Cancer quality of life scores were as follows: global, 79/84 (lower worse); swallowing, 8/9 (higher worse); and dry mouth, 14/45 (higher worse). Mean pre- and 2-year post-treatment patient-reported outcomes version of the Common Terminology Criteria for Adverse Events scores (0 to 4 scale, higher worse) were as follows: swallowing, 0.5/0.7, and dry mouth, 0.4/1.3. Thirty-four percent of patients required a feeding tube (median, 10.5 weeks; none permanent). There were no grade 3 or higher late adverse events.

Conclusion: Clinical outcomes with a de-intensified chemoradiotherapy regimen of 60 Gy intensity-modulated radiotherapy with concurrent low-dose cisplatin are favorable in patients with human papillomavirus–associated oropharyngeal squamous cell carcinoma. Neither neoadjuvant chemotherapy nor routine surgery is needed to obtain favorable results with de-escalation.

Strengths

- Well-designed, adequately powered phase II trial data with survival, oncologic and quality of life (both subjective and objective) data showing excellent outcomes for proposed de-escalation regimen
- Use of platinum-based chemotherapy in a de-intensified dose (weekly dosing) and the elimination of 10 Gy in XRT which has been shown to be clinically meaningful in other data
- Favorable outcomes when compared to historical data

Limitations

- No comparison group to standard CRT dosing to see outcomes in comparison
- External validity → could these outcomes be replicated in centers with less experience/volume?
- 2 years of follow up in only 92 patients which may underestimate long-term sequelae of CRT
- 34% required g-tube
- Did not count persistent disease requiring neck dissection as regional failure

back to top

Assessment of the Rate of Skip Metastasis to Neck Level IV in Patients With Clinically Node-Negative Neck Oral Cavity Squamous Cell Carcinoma: A Systematic Review and Meta-analysis

Anton Warshavsky, MD; Roni Rosen, BS; Narin Nard-Carmel, MD; Sara Abu-Ghanem, MD; Yael Oestreicher-Kedem, MD; Avraham Abergel, MD; DanM. Fliss, MD; Gilad Horowitz, MD

*From **JAMA Otolaryngology – Head and Neck Surgery**, June 2019*

Importance: The rate of skip metastasis to neck level IV in patients with clinically node-negative neck (cN0) oral cavity squamous cell carcinoma (OCSCC) remains controversial.

Objective: To provide a high level of evidence using a meta-analysis on the rate of skip metastasis to level IV in this subset of patients.

Data Sources: The Embase, PubMed, and Google Scholar databases were searched for articles published during the period of January 1, 1970, through December 31, 2017, using the following key terms: neck dissection, N0 neck, squamous cell carcinoma, skip metastasis, radical neck dissection, lymph node management, neck metastasis, oral cavity cancer, and tongue cancer. Some terms were also used in combination, and the reference section of each article was searched for additional potentially relevant publications. Data were analyzed from January 8 through 11, 2018.

Study Selection: Inclusion criteria were all cohorts, including from any randomized clinical trial, case-control study, case study, and case report; studies of patients with the histopathologic diagnosis of OCSCC; and studies that differentiated data between skip metastasis and sequential metastasis to neck level IV. Of the 115 articles retrieved from the literature, 11 retrospective studies and 2 prospective randomized clinical trials (n = 1359 patients) were included.

Data Extraction and Synthesis: Meta-analysis of Observational Studies in Epidemiology guidelines were followed. Fixed-effects model and 95% CIs were estimated, and data of included studies were pooled using a fixed-effects model.

Main Outcomes and Measures: Overall proportion of neck involvement and the rate of level IV skip metastasis. Subgroup analysis for primary site and tumor staging.

Results: The rate of level IV involvement in patients with cN0 ranged between 0% and 11.40% with a fixed-effects model of 2.53% (95% CI, 1.64%-3.55%). The rate of skip metastasis ranged from 0% to 5.50% with a fixed-effects model of 0.50% (95% CI, 0.09%-1.11%). The rate of level IV skip metastasis did not increase significantly in cases that involved neck levels I through III. Tumor staging and primary site tumor did not significantly affect the rate of skip metastasis.

Conclusions and Relevance: This meta-analysis showed very low rates of skip metastasis to neck level IV in patients diagnosed with cN0 OCSCC. Encountering an allegedly positive lymph node during neck dissection does not portend high rates of level IV involvement. Supraomohyoid neck dissection is therefore adequate for this subset of patients.

Summary statements:

- Risk of level IV involvement was <5% in patients with cN0 oral cavity cancer (overall IV involvement: 2.53%; skip metastases to level IV: 0.50%)
- Rate of level IV involvement for cN0 oral tongue cancer was 3.60%
- Authors conclude it is safe to omit level IV in patients undergoing elective neck dissection for cN0 oral cavity cancer

Strengths:

- Meta-analysis of 13 studies (1,359 patients)
- Although there were variable rates of level IV involvement among the 13 studies included, they did not exceed 12% in any of the studies included

Weaknesses:

- Variable study designs and data reporting by the 13 studies that were included
- Sub-group analyses only included some of the 13 studies (this brings into question the validity of sub-group analyses of rate of level IV involvement based on combinations of other neck levels involved)
- Although omitting level IV can be considered in cN0 oral cavity cancer patients undergoing neck dissection, the (very low) risk of missing an occult node is potentially devastating: pathologic understaging, omission of beneficial adjuvant therapy, nodal recurrence, etc.

back to top

Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer.

Bryant AK, Sojourner EJ, Vitzthum LK, Zakeri K, Shen H, Nguyen C, Murphy JD, Califano JA, Cohen EEW, Mell LK.

from ***Journal of the National Cancer Institute****, December 2018*

Background: Previous studies have reported conflicting information regarding the prognostic role of p16 in nonoropharyngeal head and neck squamous cell carcinoma (HNSCC).

Methods: Using the US Veterans Affairs database, we analyzed 1448 patients with locoregionally advanced HNSCC and known p16 status diagnosed between 2005 and 2015 and treated with surgery, radiotherapy, or chemoradiotherapy. Tumor p16 status was determined through manual review of pathology reports of primary tumor specimens. Oropharyngeal (n = 1061) or nonoropharyngeal (n = 387; hypopharyngeal, laryngeal, or oral cavity) tumor site was determined from tumor registry data and manually reviewed for accuracy. We used multivariable Cox regression to analyze the effect of p16 status on overall survival (OS), cancer-specific survival (CSS), and competing mortality (CM) for oropharyngeal or nonoropharyngeal tumor sites. All statistical tests were two-sided.

Results: In multivariable models adjusting for treatment, stage, age, comorbidity, and body mass index, patients with p16-positive tumors had improved OS, CSS, and CM compared with patients with p16-negative tumors in both oropharyngeal (OS: hazard ratio [HR] = 0.53, 95% confidence interval [CI] = 0.40 to 0.71, P < .001; CSS: HR = 0.50, 95% CI = 0.35 to 0.73, P < .001; CM: HR = 0.59, 95% CI = 0.38 to 0.93, P = .02) and nonoropharyngeal primary sites (OS: HR = 0.41, 95% CI = 0.25 to 0.69, P < .001; CSS: HR = 0.37, 95% CI = 0.18 to 0.77, P = .008; CM: HR = 0.46, 95% CI = 0.23 to 0.95, P = .04). The prognostic impact of p16 status did not statistically significantly differ by primary tumor site for OS, CSS, or CM (Pinteraction > .05).

Conclusions: Our findings support the hypothesis that p16 has a similar prognostic role in both nonoropharyngeal and oropharyngeal cancer. Consideration should be given to increased testing for p16 in laryngeal, hypopharyngeal, and oral cavity primaries.

Summary statements:

- p16 positivity was associated with improved overall and cancer-specific survival (adjusted HR 0.41 and 0.37, respectively) in patients with nonoropharyngeal (i.e. oral, laryngeal, hypopharyngeal) cancer in a national VA database

Strengths:

- Since it was a VA database study, patients were from multiple centers across the country
- VA database contains detailed demographic, tumor-related, and treatment prognostic factors, allowing for robust and reliable multivariable analyses
- VA system generally has long follow-up intervals given the nature of this healthcare system

Weaknesses:

- 92% of nonoropharyngeal cancer patients did not have known p16 status and were excluded (patients for whom p16 testing was not performed had inferior survival)
- Lack of consistent/rigorous definition of p16 positivity (most "p16 positive" nonoropharyngeal cancer patients were "positive NOS", not "strong/diffuse")
- No data on lifetime tobacco exposure was available (although current tobacco status was included in regression analyses)
- Study of VA patients may not be generalizable to non-veteran Americans

back to top

Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma.

Zhang Y, Chen L, Hu GQ, Zhang N, Zhu XD, Yang KY, Jin F, Shi M, Chen YP, Hu WH, Cheng ZB, Wang SY, Tian Y, Wang XC, Sun Y, Li JG, Li WF, Li YH, Tang LL, Mao YP, Zhou GQ, Sun R, Liu X, Guo R, Long GX, Liang SQ, Li L, Huang J, Long JH, Zang J, Liu QD, Zou L, Su QF, Zheng BM, Xiao Y, Guo Y, Han F, Mo HY, Lv JW, Du XJ, Xu C, Liu N, Li YQ, Chua MLK, Xie FY, Sun Y, Ma J

from ***The New England Journal of Medicine****, September 2019*

Background: Platinum-based concurrent chemoradiotherapy is the standard of care for patients with locoregionally advanced nasopharyngeal carcinoma. Additional gemcitabine and cisplatin induction chemotherapy has shown promising efficacy in phase 2 trials.

Methods: In a parallel-group, multicenter, randomized, controlled, phase 3 trial, we compared gemcitabine and cisplatin as induction chemotherapy plus concurrent chemoradiotherapy with concurrent chemoradiotherapy alone. Patients with locoregionally advanced nasopharyngeal

carcinoma were randomly assigned in a 1:1 ratio to receive gemcitabine (at a dose of 1 g per square meter of body-surface area on days 1 and 8) plus cisplatin (80 mg per square meter on day 1), administered every 3 weeks for three cycles, plus chemoradiotherapy (concurrent cisplatin at a dose of 100 mg per square meter every 3 weeks for three cycles plus intensity-modulated radiotherapy) or chemoradiotherapy alone. The primary end point was recurrence-free survival (i.e., freedom from disease recurrence [distant metastasis or locoregional recurrence] or death from any cause) in the intention-to-treat population. Secondary end points included overall survival, treatment adherence, and safety.

Results: A total of 480 patients were included in the trial (242 patients in the induction chemotherapy group and 238 in the standard-therapy group). At a median follow-up of 42.7 months, the 3-year recurrence-free survival was 85.3% in the induction chemotherapy group and 76.5% in the standard-therapy group (stratified hazard ratio for recurrence or death, 0.51; 95% confidence interval [CI], 0.34 to 0.77; P = 0.001). Overall survival at 3 years was 94.6% and 90.3%, respectively (stratified hazard ratio for death, 0.43; 95% CI, 0.24 to 0.77). A total of 96.7% of the patients completed three cycles of induction chemotherapy. The incidence of acute adverse events of grade 3 or 4 was 75.7% in the induction chemotherapy group and 55.7% in the standard-therapy group, with a higher incidence of neutropenia, thrombocytopenia, anemia, nausea, and vomiting in the induction chemotherapy group. The incidence of grade 3 or 4 late toxic effects was 9.2% in the induction chemotherapy group and 11.4% in the standard-therapy group.

Conclusions: Induction chemotherapy added to chemoradiotherapy significantly improved recurrence-free survival and overall survival, as compared with chemoradiotherapy alone, among patients with locoregionally advanced nasopharyngeal carcinoma. (Funded by the Innovation Team Development Plan of the Ministry of Education and others; ClinicalTrials.gov number, NCT01872962.).

Summary statements: Induction chemotherapy with gemcitabine and cisplatin induction in addition to concurrent cisplatin-based chemoradiotherapy for primary treatment of locoregionally advanced nasopharyngeal carcinoma significantly improved 3-year recurrence-free survival (85.3 vs. 76.5%, p=0.001).

The incidence of Grade 3 and 4 complications was 20% higher in the induction group, but the induction regimen was still well tolerated given that 96.7% of patients completed all three induction doses. The incidence of late toxicity was similar, 9.2% vs. 11.4%

Strengths:

- Randomized design assesses the acute and late toxicities of an induction chemotherapy regimen.

Weaknesses:

- Length of follow-up. While recurrence free survival is the ideal endpoint. 3-years is rarely enough time to demonstrate improved recurrence free survival in nasopharyngeal cancer. The average time to recurrence for the gold standard chemoradiotherapy regimen established by the Intergroup 0028 study was X. It is not uncommon for patients to recur

10-20 years after treatment, which for nasopharyngeal carcinoma is not considered a second primary cancer.

This study's 3-year endpoint too short to comment on late toxicities for chemoradiation protocols. As shown by a landmark study by X et al in 2011, late toxicities of chemoradiotherapy can be seen as far as 8-10 years after treatment. The average nasopharynx patient is X years old and enjoys an average survival of X years after treatment. Three years does not provide enough time to make this claim. More follow-up, preferable a ten-year longterm results of this study will provide more accurate assessment of the treatment related toxicities of this new induction regimen.

back to top

Eliminating Postoperative Radiation to the Pathologically Node-Negative Neck: Long-Term Results of a Prospective Phase II Study

Contreras JA, Spencer C, DeWees T, Haughey B, Henke LE, Chin RI, Paniello R, Rich J, Jackson R, Oppelt P, Pipkorn P, Zevallos J, Chernock R, Nussenbaum B, Daly M, Gay H, Adkins D, Thorstad W.

*from the **Journal of Clinical Oncology**, October 2019*

PURPOSE: The volume treated with postoperative radiation therapy (PORT) is a mediator of toxicity, and reduced volumes result in improved quality of life (QOL). In this phase II trial, treatment volumes were reduced by omitting PORT to the pathologically negative (PN0) neck in patients with primary head and neck squamous cell carcinoma.

METHODS: Patients with head and neck squamous cell carcinoma who underwent surgical resection and neck dissection with a PN0 neck and high-risk features mandating PORT to the primary and/or involved neck were eligible. The primary end point was greater than 90% disease control in the unirradiated neck. QOL was evaluated using the MD Anderson Dysphagia Inventory and the University of Michigan patient-reported xerostomia questionnaire.

RESULTS: Seventy-three patients were enrolled, and 72 were evaluable. Median age was 56 years (range, 31 to 81 years); 58 patients were male, and 47 (65%) had a smoking history. Sites included oral cavity (n = 14), oropharynx (n = 37), hypopharynx (n = 4), larynx (n = 16), and unknown primary tumor (n = 1). According to the American Joint Committee on Cancer Staging Manual (7th edition), 67 patients (93%) had stage III/IV disease, and 71% of tumors involved or crossed midline. No patient had contralateral neck PORT. In 17 patients (24%), only the primary site was treated. At a median follow-up of 53 months, two patients experienced treatment failure of the PN0 unirradiated neck; they also experienced treatment failure locally. Unirradiated neck control was 97% (95% CI, 93.4% to 100.0%). Five-year rates of local control, regional control, progression-free survival, and overall survival were 84%, 93%, 60%, and 64%, respectively. QOL measures were not significantly different from baseline at 12 and 24 months post-PORT (P > .05).

CONCLUSION: Eliminating PORT to the PN0 neck resulted in excellent control rates in the unirradiated neck without long-term adverse effects on global QOL.

Summary Statements

1. In postoperative patients with high-risk features in the primary tumor and pathologically node-negative neck, adjuvant radiation therapy was given to the primary tumor and omitted from the neck.
2. The study achieved the primary end point of >90% disease control in the unirradiated neck (97%; 95% CI: 93.4-100%).
3. Quality of life (QOL) measures were not significantly different from baseline at up to 24 months post-PORT.

Strengths

1. This was a single-arm, prospective trial addressing the role of radiation therapy in a pathologically node-negative neck. The findings from this phase II study should motivate a prospective, randomized multi-institutional study with uniform patient cohorts.
2. The study had a relatively long period of patient follow-up (median: 53 months).
3. Eliminating postoperative radiation from larger volumes (e.g., contralateral neck) may improve toxicity profiles more than decreasing dose alone.

Weaknesses

1. Patients enrolled to this study had different disease subsites, including multiple subsites and HPV/p16 status. The prognosis and rates of regional disease involvement and recurrence for these patients is quite different.
2. Radiation fields in the two patients with neck recurrences demonstrated planning treatment volume expansion that included portions of the “unirradiated” neck. Additional clarification regarding the dose-volume to the necks of all patients in the cohort is warranted.
3. Future QOL assessment for these patients should incorporate measures that also assess musculoskeletal effects (e.g., shoulder movement and range of motion).

back to top