American Head and Neck Society - Journal Club
Volume 34, March 2021

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

Failure Rate in The Untreated Contralateral Node Negative Neck of Small Lateralized Oral Cavity Cancers: A Multi-Institutional Collaborative Study

Howard Yu-Hao Liu, Laura Tam, Neil M Woody, Jimmy Caudell, Chandana A Reddy, Ahmed Ghanem, Matthew Schymick, Nikhil Joshi, Jessica Geiger, Eric Lamarre, Brian Burkey, David Adelstein, Neal Dunlap, Farzan Siddiqui, Shlomo Koyfman, Sandro Virgilio Porceddu

*From the **Oral Oncology**. April 2021.*

Objectives: The importance of treating the bilateral neck in lateralized small oral cavity squamous cell carcinoma (OCC) is unclear. We sought to define the incidence and predictors of contralateral neck failure (CLF) in patients who underwent unilateral treatment.

Materials and methods: We performed a multi-institutional retrospective study of patients with pathologic T1-T2 (AJCC 7th edition) OCC with clinically node negative contralateral neck who underwent unilateral treatment with primary surgical resection ± adjuvant radiotherapy between 2005 and 2015. Incidence of CLF was estimated using the cumulative incidence method. Clinicopathological factors were analyzed by univariate (UVA) and multivariate analysis (MVA) for possible association with CLF. Kaplan-Meier analysis was used to estimate overall survival (OS).

Results: 176 patients were evaluated with a median of 65.9 months of follow-up. Predominant pathologic T-stage was T1 (68%), 8.5% of patients were N1, 2.8% were N2b. Adjuvant radiotherapy was delivered to 17% of patients. 5-year incidence of CLF was 4.3% (95% CI 1.2-7.4%). Depth of invasion (DOI) > 10 mm and positive ipsilateral neck node were significant predictors for CLF on UVA. DOI > 10 mm remained significant on MVA (HR = 6.7, 95% CI 1.4-32.3, p = 0.02). The 2- and 5-year OS was 90.6% (95% CI 86.2-95.0%) and 80.6% (95% CI 74.5-86.8%), respectively.

Conclusion: Observation of the clinically node negative contralateral neck in small lateralized OCC can be a suitable management approach in well selected patients, however caution should be applied when DOI upstages small but deeply invasive tumors to T3 on 8th edition AJCC staging.

Summary Statements:

- This paper evaluated the incidence of contralateral lymph node failure as a first site of regional disease recurrence and to evaluate for clinical and pathological predictors of contralateral neck failure in patients with small (T1-T2, AJCC 7th edition) OCC treated with primary site resection and ipsilateral neck treatment (surgery +/- radiation).
- The overall incidence of contralateral neck failure was 4.3%
- The pathological features associated with contralateral neck failure were depth of invasion >10 mm on multivariate analysis, and ipsilateral positive nodes on univariate analysis.

Strengths

- Largest multi-institutional retrospective review to date addressing the incidence of contralateral neck failures for small, lateralized OCC.
- Provides support that observation of the contralateral neck is adequate for small, thin lateral OCC
- Provides evidence for treatment of the contralateral neck for deeply invasive tumors (DOI > 10 mm), and consideration for treatment in ipsilateral node-positive necks.

Weaknesses

- Retrospective review
- Unable to measure distance of primary tumor from midline to evaluate for proximity of midline as a predictor of contralateral neck failure.
- Unable to compare outcomes of patients with lateralized, early stage OCC that received bilateral neck treatment

back to top

Outcomes in N3 Head and Neck Squamous Cell Carcinoma and Role of Upfront Neck Dissection

Angela Boros, Pierre Blanchard, Arlette Dade, Philippe Gorphe, Ingrid Breuskin, Caroline Even, France Nguyen, Eric Deutsch, François Bidault, François Janot, Stephane Temam, Haitham Mirghani, Yungan Tao

*From the **Laryngoscope.** March 2021.*

Objectives: We investigated the prognostic factor of N3 head and neck squamous cell carcinoma (HNSCC), including the role of upfront neck dissection (UFND) before radiotherapy (RT).

Methods: We retrospectively reviewed the charts of consecutive N3 HNSCC patients treated with curative intent RT.

Results: In the study, 323 N3 HNSCC patients were included. Of those, 125 patients (39%) had UFND. Median follow-up was 3.9 years (0-14.8 years). Overall survival (OS) at 5 years was 31.2%, and progression-free survival (PFS) was 26%. In the multivariate analysis, OS was improved in PS 0, T1-2 tumors, patients receiving concurrent chemotherapy, never or former smokers, and UFND. UFND was strongly associated with increased OS (45.7% vs. 21.2%, $P < .001$), and PFS ($P < .001$). Regardless of neck node size, UFND improved survival ($P = .001$ for ≤ 7 cm and $P = .004$ for > 7 cm).

Conclusion: UFND could improve treatment outcomes in N3 HNSCC, especially for non-oropharyngeal cancer, regardless of neck node size.

Summary Statements:

- A retrospective case series of fit for curative treatment patients with head and neck squamous cell carcinoma (several sites) classified as N3 and who underwent up-front neck dissection or RT/CRT treatment from the Gustav Roussy Center in France for 16 years.
- Interventions were RT dose of 70 Gy (3D or IMRT), concurrent CRT based in platinum or induction chemotherapy for unresectable tumors based in taxane scheme and RND.
- 323 patients included (39% with upfront RND) with a mean age of 58 years, 49% classified T3/4 and 41% located on oropharynx. The median follow-up was 3.9 years.
- 5-year overall survival and locoregional control was 31.2% and 47.4%. Multivariate analysis showed that upfront RND improved overall survival (HR of 0.5 [95% confidence interval 0.38–0.70]) (45.7% vs 21.2%)

Strengths

- Patients selected from a specialized cancer center
- Long-term follow-up

Weaknesses

- Long time study period (16 years) with heterogeneous treatments (RT or CRT or induction CT) and sites (oral cavity, larynx, hypopharynx, oropharynx)
- Surgical patients were selected based in fitness for curative intent, possibilities of resectability and risk of mutilating surgery. By definition, these patients will have a better survival in comparison with those treated with RT/CRT
- Non randomized assessment of the intervention could bias results favoring surgical interventions. Patients allocated in the surgical group had smaller N size (<7 cm 27% vs 44%), smaller tumors (T3/4 41% vs 53%) and more hypopharynx tumors (31% vs 19%)
- The effectiveness of upfront RND in N3 HNC patients must be better explored with randomized controlled trials or with adjusting methods as propensity score.

back to top

Human papillomavirus oropharynx carcinoma: Aggressive de-escalation of adjuvant therapy

Eric J Moore, Kathryn M Van Abel, David M Routman, Christine M Lohse, Katharine A R Price, Michelle Neben-Wittich, Ashish V Chintakuntlawar 4, Daniel L Price 1, Jan L Kasperbauer, Joaquin J Garcia, Michael L Hinni, Samir H Patel, Jeffrey R Janus, Robert L Foote, Dan J Ma

*From the **Head and Neck.** January 2021.*

Background: Aggressive dose de-escalated adjuvant radiation therapy (RT) in patients with human papillomavirus-associated oropharyngeal squamous cell carcinoma (HPV(+)OPSCC).

Methods: Patients with HPV(+)OPSCC on a phase II clinical trial of primary surgery and neck dissection followed by dose de-escalated RT (N = 79) were compared with a cohort of patients who received standard adjuvant therapy (N = 115). Local recurrence-free, regional recurrence-free, distant metastases-free survival, and progression-free survival (PFS) were assessed.

Results: Of 194 patients, 23 experienced progression at a median of 1.1 years following surgery (interquartile range [IQR] 0.7-2.0; range 0.3-5.4); 10 patients in the de-escalated cohort and 13 patients in the standard cohort. The 3-year PFS rate for the de-escalated cohort was 87%, and in the standard cohort was 90% (hazard ratio [HR] 1.18, 95% confidence interval (CI) [0.50-2.75]).

Conclusion: Patients with HPV(+)OPSCC who undergo surgical resection and neck dissection and meet criteria for adjuvant therapy can undergo aggressive dose de-escalation of RT without increasing risk of progression locally, regionally or at distant sites.

Summary Statements:

- Patients with intermediate risk HPV-related OPSCC (classified as negative margins, pN1, and no pENE) had a low risk of recurrence in both the standard adjuvant therapy group and the de-escalated adjuvant therapy group.
- Higher pT stage, pN2 and pENE increased the risk of progression.
- Patients with pN2 and pENE had a higher rate of progression, which was largely distant metastases.

Strengths

- This is a unique study evaluating oncologic outcome differences between patients de-escalated and those treated with standard adjuvant therapy for HPV-related OPSCC. It had a large number of patients from a single institution with the de-escalation arm being studied prospectively.
- Demonstrates that patients can likely safely be de-escalated with low loco-regional recurrence events. This manuscript also discusses that most of the failures were distant. This makes the argument toward de-escalation valid even in patients with factors they considered higher risk (pENE and pN2) as most of their failures were not locoregional.

Weaknesses

- This was not a randomized trial evaluating two different adjuvant therapy regimens. Instead, it compared outcomes from a prospective cohort (de-escalated adjuvant therapy) to a retrospective cohort (standard adjuvant therapy). Although it was not randomized, it does provide important data to demonstrate that de-escalation of locoregional treatment is likely safe.
- Functional outcomes were extremely limited and only mentioned G-tube rates in two separate populations. Randomized data and longer term subjective and objective outcomes measures are necessary to understand if any differences in swallow function exist between the two cohorts.
- Data are from a single institution and thus could have limited external validity. While this is true, many institutions have shown excellent locoregional control utilizing TORS and adjuvant therapy. Thus, the outcomes from this study are likely generalizable to institutions with skilled TORS surgeons and radiation oncologists.

back to top

Induction Chemotherapy Response as a Guide for Treatment Optimization in Sinonasal Undifferentiated Carcinoma

Moran Amit, Ahmed S Abdelmeguid, Teemaranawich Watcherporn, Hideaki Takahashi, Samantha Tam, Diana Bell, Renata Ferrarotto, Bonnie Glisson, Michael E Kupferman, Dianna B Roberts, Shirley Y Su, Shaan M Raza, Franco DeMonte, Ehab Y Hanna

*From the **Clinical Oncology.** February 2019.*

Purpose: Multimodal therapy is a well-established approach for the treatment of sinonasal undifferentiated carcinoma (SNUC); however, the optimal sequence of the various treatments modalities is yet to be determined. This study aimed to assess the role of induction chemotherapy (IC) in guiding definitive therapy in patients with SNUC.

Methods: Ninety-five previously untreated patients diagnosed with SNUC and treated between 2001 and 2018 at The University of Texas MD Anderson Cancer Center were included in the analysis. Patients were treated with curative intent and received IC before definitive locoregional therapy. The primary end point was disease specific survival (DSS). Secondary end points included overall and disease-free survival, disease recurrence, and organ preservation.

Results: A total of 95 treatment-naive patients were included in the analysis. For the entire cohort, the 5-years DSS probability was 59% (95% CI, 53% to 66%). In patients who had partial or complete response to IC, the 5-year DSS probabilities were 81% (95% CI, 69% to 88%) after treatment with definitive concurrent chemoradiotherapy (CRT) after IC and 54% (95% CI, 44% to 61%) after definitive surgery and postoperative radiotherapy or CRT after IC (log-rank P = .001). In patients who did not experience at least a partial response to IC, the 5-year DSS probabilities were 0% (95% CI, 0% to 4%) in patients who were treated with concurrent CRT after IC and 39% (95% CI, 30% to 46%) in patients who were treated with surgery plus

radiotherapy or CRT (adjusted hazard ratio of 5.68 [95% CI, 2.89 to 9.36]).

Conclusion: In patients who achieve a favorable response to IC, definitive CRT results in improved survival compared with those who undergo definitive surgery. In patients who do not achieve a favorable response to IC, surgery when feasible seems to provide a better chance of disease control and improved survival.

Summary Statements:

- Single institution study involving 95 treatment naïve patients of SNUC who were given IC followed by locoregional treatment. Primary end point was DSS, secondary end points were DFS, recurrence and organ preservation.
- Most important factors affecting DSS were response to IC and definitive treatment, orbit invasion, and neural invasion.
- In patients who had partial or complete response to IC, the 5-year DSS probabilities were 81% (95% CI, 69% to 88%) after treatment with definitive concurrent chemoradiotherapy (CRT) after IC and 54% (95% CI, 44% to 61%) after definitive surgery and postoperative radiotherapy or CRT after IC (log-rank P = .001).
- In patients who did not experience at least a partial response to IC, the 5-year DSS probabilities were 0% (95% CI, 0% to 4%) in patients who were treated with concurrent CRT after IC and 39% (95% CI, 30% to 46%) in patients who were treated with surgery plus radiotherapy or CRT (adjusted hazard ratio of 5.68 [95% CI, 2.89 to 9.36]).

Strengths

- Represents the largest cohort of patients with SNUC treated with a uniform and consistent treatment strategy using IC.
- There have been multiple studies highlighting the need for multimodality treatment for this rare disease, this study gives a clearer picture regarding the sequence in which these modalities may be used.
- The results of this study will help design a multi-institutional RCT comparing IC vs upfront surgery for treatment of SNUC.

Weaknesses

- Out of the 95 patients included in the study, 29 were T2/T3 the authors have not mentioned how many of them were upfront operable, even the early stage lesions were given IC.
- Out of 64 patients who had favourable response to IC, 25% underwent surgery, the criteria for selecting these candidates has not been mentioned clearly by the authors.
- Single institution study with retrospective design and 7th Edition of AJCC used.

back to top

Long-Term Follow-Up Results of Ultrasound-Guided Radiofrequency Ablation for Low-Risk Papillary Thyroid Microcarcinoma: More Than 5-Year Follow-Up for 84 Tumors

Se Jin Cho, Sun Mi Baek, Hyun Kyung Lim, Kang Dae Lee, Jung Min Son, Jung Hwan Baek

*From the **Thyroid.** December 2020.*

Background: Despite reports describing favorable short-term results for thermal ablation of thyroid cancer, there remains a need to evaluate long-term results because of its indolent characteristics. The purpose of this study was to evaluate the long-term efficacy and safety of ultrasound (US)-guided radiofrequency ablation (RFA) for low-risk papillary thyroid microcarcinoma (PTMC) over a follow-up period of more than five years.

Methods: From a cohort of patients under surveillance after US-guided RFA for primary low-risk PTMC, those with a record of follow-up data of more than five years were selected for this study. Before RFA, all patients underwent US and computed tomography to evaluate the PTMC and the presence of neck metastasis. RFA was performed using thyroid-dedicated electrodes. Follow-up US was performed 6 and 12 months after initial RFA, and then every 12 months. The status of ablated tumors was evaluated according to volume reduction, local tumor progression, newly developed cancers, lymph node (LN) or distant metastasis, and delayed surgery during follow-up. Complications during the procedure and follow-up period were evaluated.

Results: A total of 84 nodules from 74 patients were included in this study. All patients tolerated RFA, and the mean follow-up duration was 72 months. After RFA, complete disappearance rates of 98.8% and 100% were achieved at 24 and 60-month follow-up, respectively. Additional ablations were performed in 13 of 84 tumors. The mean number of RFA sessions was 1.2. There were four newly developed cancers in three patients, and these were also treated with RFA and completely disappeared. During the follow-up period, there was no local tumor progression, no LN or distant metastasis, and no patients underwent delayed surgery. The major complication rate was 1.4% (1/74), and there was no delayed complication or procedure-related death.

Conclusions: RFA is effective for treating low-risk PTMC patients, without occurrence of local tumor progression, LN or distant metastasis, delayed complications, procedure-related death, or delayed surgery over more than five years of follow-up.

Summary Statements:

- RFA resulted in complete disappearance of all 84 ablated tumors with no lymph node metastases or distant metastases for the cohort and no patients undergoing delayed surgery.
- RFA was overall safe with only 4 complications (two hematomas, one first-degree skin burn, one temporary voice change)
- RFA may alleviate patient anxiety by treating the primary tumor.

Strengths

- Longest follow-up of any RFA study with all patients with at least 5 years follow-up after RFA and mean follow-up duration of 6 years.
- Complete disappearance of all papillary thyroid microcarcinomas with no LN or distant metastases for the entire cohort.
- No patients underwent delayed surgery which is often not the case with an active surveillance approach (cancer progression, patient anxiety).

Weaknesses

- All RFA procedures performed at single institution by one expert radiologist with greater than 10 years of experience with thyroid RFA using hydrodissection technique limits the applicability to institutions with less experience.
- Median tumor diameter was 0.4 cm with only 32 of 84 tumors ≥0.5 cm, therefore the vast majority of these nodules would not meet guidelines for FNA within the United States in the first place.
- Study subject to selection bias due to retrospective study design.