



# American Head and Neck Society - Journal Club

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### [Validation of the pathological classification of lymph node metastasis for head and neck tumors according to the 8th edition of the TNM Classification of Malignant Tumors](#)

*Jacinto García, Montserrat López, Laura López, Silvia Bagué, Esther Granell, Miquel Quer, Xavier León*  
*from **Oral Oncology**, July 2017*

One of the main objectives of a staging system, as stated in the introduction of the 8th edition of the TNM Classification of Malignant Tumors is to provide prognostic information and it incorporates modifications that improve the prognostic capacities of the classification and the creation of a specific staging system for p16-positive oropharyngeal carcinomas and the inclusion of extracapsular spread as a criterion for evaluating the regional extension, both clinical (cN) and pathological (pN).

As a general rule, patients with lymph node metastasis with extracapsular spread are upstaged as compared to similar cases without extracapsular spread: it is defined as extension of the tumor outside the lymph node capsule.

The authors performed a retrospective study based on prospectively collected information of patients with HNSCC treated in their center. A total of 1188 patients who had an HNSCC located in the oral cavity, oropharynx, hypopharynx, or larynx diagnosed from 1990 through 2013, and treated with a unilateral or bilateral neck dissection were included in the study. HPV status in oropharyngeal tumors was analyzed retrospectively.

They retrieved information concerning the type of neck dissection, the number of nodes dissected, positive nodes and the number of nodes with extracapsular spread for all patients. They performed 1820 neck dissections on the patients and the patients were included in the study. A total of 683 patients had bilateral neck dissections, and the results were analyzed adding the neck nodes dissected on both sites of the neck. The mean number of lymph nodes studied per patient was 32.6. In 157 cases, they performed



the neck dissections after a previous treatment with radiotherapy or chemoradiotherapy. The interval between the radiotherapy or chemoradiotherapy and the neck dissection was 6 to 10 weeks. A total of 596 patients had postoperative adjuvant treatment with radiotherapy or chemoradiotherapy. Patients with advanced tumor, either locally (pT3-T4) or regionally (pN2-N3), microscopically involved surgical margins, or extracapsular spread was considered candidates to adjuvant treatment. Postoperative radiotherapy was delivered in 2 Gy fractions to a total of 50 Gy in 5 weeks directed to both the primary site and the neck.

The mean follow-up time was 5.6 years. During the follow-up period, 213 patients had local failure, 158 had regional failure, and 172 presented distant metastases. They found lymph node metastases in 50.1% of the patients. In 50.5% of these cases the pathological report revealed extracapsular spread. The new staging system produced the upstaging of 20.9% of the patients classified as pN1 to pN2a, and of 58.4% of the patients classified as pN2 to pN3b.

Five-year cause specific survival for pN2 was very similar to pN3 according to the 7th ed. TNM. The implementation of the changes of the 8th ed. TNM achieves more evenly spread curves. In the new classification, 5-year cause specific survival for pN2 (53.3%) sits in an more intermediate position between pN1 (70.5%) and pN3 (24.0%). Five-year cause-specific survival for patients with extracapsular spread (n = 217) was 22.4%, and for patients without extracapsular spread (n = 157) it was 51.4%. Patients classified as pN1 in the 7th ed. TNM did not show survival differences when stratified by the presence of extracapsular spread, as proposed in the 8th ed. Five-year cause-specific survival for patients with extracapsular spread (n = 33) was 63.5%, and for patients without extra-capsular spread (n = 125) it was 70.5%. All patients classified as pN3 in the 7th ed. TNM presented ECS, and were reclassified as pN3b in the new classification.

According to their results, the inclusion of extracapsular spread in the pathological classification of the 8th ed. TNM improved the prognostic capacity of the classification, as compared with the previous version. The objective comparison of both editions showed better results for the 8th ed. TNM in terms of a more even distribution of the any patient. The new pN3a category is formed by patients with very large nodal metastasis without extracapsular spread. The vast majority of lymph node metastasis this size show extracapsular spread in pathological analysis.

#### **Strengths:**

- Patients with limited nodal disease classified as pN1 in the 7th ed. TNM do not show a significant alteration in survival related to extracapsular spread
- The inclusion of ECS in the pathological classification of the neck nodes improves the prognostic capacity of the 8th edition of the TNM Classification of Malignant Tumors.

#### **Weaknesses:**

- The potential number of patients included in the pN3a category is limited.
- This study is a retrospective evaluation of a series of consecutive patients treated in a single institution.



## Quantitative pretreatment CT volumetry: association with oncologic outcomes in patients with T4a squamous carcinoma of the larynx.

Shiao JC, Mohamed ASR, Messer JA, Hutcheson KA, Johnson JM, Enderling H, Kamal M, Warren BW, Pham B, Morrison WH, Zafereo ME, Hessel AC, Lai SY, Kies MS, Ferrarotto R, Garden AS, Schomer DF, Gunn GB, Phan J, Frank SJ, Beadle BM, Weber RS, Lewin JS, Rosenthal DI, Fuller CD.

From *Head & Neck*. February, 2017

After the first prospective randomized study that started data collection during the 1980's, other studies in North America and Europe confirmed that organ preservation strategies must be the treatment of choice only for selected patients with advanced larynx squamous cell carcinoma. However, objective parameters of clinical evaluation of advanced tumors based on anatomic extension and maximum diameter are clearly not satisfactory and difficult to reproduce. Several studies had shown that imaging-derived volumetry has prognostic significance and can predict response to radiation therapy (Hermans et al., 2001, Doweck et al., 2002, Studer et al., 2007, Chen et al., 2009).

The Shiao et al (2017) study proposes to analyze a cohort of 124 patients with T4a larynx carcinoma treated with curative intent at The University of Texas, MD Anderson Cancer Center from 2000 to 2011. All patients had pretreatment contrast-enhanced CT or PET-CT. Patients with T4b or M1 stage were not included. Images were imported to a commercial image segmentation software, tumors were manually contoured by two radiation oncologists and tumor volume measurements were collected by an independent medical student, possibly with no information regarding outcomes. Most cases were males (83%), smokers (97%), with supraglottic tumors (68%) and cN+ regional lymph nodes metastasis (67%). Only 41 patients (33%) were treated with larynx preservation approaches. A total of 83 patients (67%) underwent total laryngectomy and postoperative radiotherapy.

The mean primary tumor volume of the patients submitted to surgical treatment ( $29.5 \pm 36 \text{cm}^3$ ) was not significantly different from the volume of the tumors of the patients treated with non-surgical strategies ( $27.9 \pm 39.8 \text{cm}^3$ ) ( $p=0.82$ ). Recursive partitioning analysis identified  $21 \text{cm}^3$  as a cutoff point associated with the risk of death in the entire cohort. Patients with tumor  $>21 \text{cm}^3$  had a 5-year OS of 44%, significantly lower than the patients with tumors  $<21 \text{cm}^3$  ( $P=0.003$ ). On multivariate analyses the only significant predictors of the risk of death were tumor volume  $>21 \text{cm}^3$  (HR 2.9; 95% CI 1.6-5.2) and ECOG status  $\geq 2$  (HR 2.08; 95% CI 1.04-3.96). Considering therapy cohorts, 5-year OS of patients of the larynx preservation group were not significantly different of the patients of the laryngectomy group (50% vs 56%,  $p=0.7$ ). Using the tumor volume cutoff of  $21 \text{cm}^3$  there was no differences on metastasis-free survival, local control or loco-regional control. However, there was a significant difference in 5-year OS (42% for higher volume tumors vs 64% for the low volume tumors,  $p=0.003$ ) who underwent non-surgical treatment. Furthermore, the patients with low volume tumors had a better laryngopharyngeal dysfunction-free survival compared with patients with higher volume tumors (38% vs 15%,  $p=0.02$ ). In the total laryngectomy group, this difference was not statistically significant (50% vs 63%,  $p=0.058$ ). The authors concluded that in T4a laryngeal SCC, increased primary tumor site assessed by CT-based volumetry was associated with worse oncologic and survival outcomes in patients treated with larynx preservation.

The strongest point of this article was the uniform data collection from a cohort of patients treated in a single institution. The results encourage further research including tumor volumetry to other known clinical parameters associated with the response to non-surgical treatment of advanced larynx cancer.



The problem of this study is its retrospective nature. Several factors could influence the treatment decision such as comorbidities, tracheostomy and patient's preference. Clearly, tumor volume must be included in future prospective studies on larynx preservation.

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## **Incidence of Contralateral–Bilateral Nodes in the Human Papillomavirus Era**

*Tritter AG, Mehta V, Samuelson M, deGravelle G, Ma X, Medlin-Moore T, Takalkar A, Caldito G, Nathan CO.*

*From **Laryngoscope**. June, 2017*

**Objectives/Hypothesis:** HPV-positive oropharyngeal squamous cell carcinoma has a more favorable prognosis when compared to HPV-negative disease, regardless of the presence of nodal metastases. However, the importance of contralateral neck treatment based on HPV status has not been well studied. Given the historically poor prognostic implications of cervical nodal metastases, this study sought to elucidate the relationship between HPV status and contralateral/bilateral nodal metastasis in patients with oropharyngeal squamous cell carcinoma.

**Study Design:** Retrospective cohort analysis.

**Methods:** Data were collected on patients with oropharyngeal squamous cell carcinoma from 2001 to 2014. Nodal status was determined by contrast-enhanced computed tomography, positron emission tomography, or surgical pathology when available. Survival rates and associations between HPV status and demographic/tumor characteristics were assessed.

**Results:** Of 178 total patients, 46 (26.0%) had contralateral/bilateral metastases. There was no significant difference in incidence of contralateral/bilateral nodal metastases between HPV-positive and HPV-negative patients (24.6% vs. 29.1%,  $P = 5.53$ ). Tonsil primaries had significantly lower incidence of contralateral/bilateral nodal metastases compared to tongue base (20.9% vs. 34.3%,  $P = 5.048$ ). On multivariate regression, tumor size was the only factor associated with contralateral/bilateral nodal metastases (T4 vs. T1–3 odds ratio 5.515, 95% confidence interval: 2.4–11.2). Five-year overall survival among all patients with and without contralateral/bilateral nodal metastases was 45.4% and 65.2%, respectively ( $P = 5.007$ ).

**Conclusions:** Our results did not show a significantly different incidence of contralateral/bilateral nodal metastases between HPV-positive and HPV-negative patients. T4 stage and tongue base location, however, were associated with contralateral disease. These data suggest treatment of bilateral necks might be warranted in these cases, regardless of HPV status.

**Summary:** 178 patients were reviewed in a retrospective fashion. Nodal status was determined by contrast-enhanced computed tomography, positron emission tomography, or surgical pathology when available. There was no significant difference in incidence of contralateral/bilateral nodal metastases (CBNM) between HPV-positive and HPV-negative patients (24.6% vs. 29.1%,  $P = 5.53$ ). Tumor primary site, however, was a significant predictor of CBNM, where the incidence was lower among patients with primary tumors of the tonsil when compared to those with primary tumors of the BOT or other sites within the oropharynx (20.9% vs. 34.3%,  $P = 5.048$ ). The only other factors observed to be significantly associated with incidence of CBNM was T stage. The odds of having CBNM among patients with T4



tumors being 5.15 times the odds among those with T1- T3 tumors. The results of this article would suggest that HPV status in OPSCC does not have an impact on the decision to treat the contralateral neck.

#### **Strengths:**

- Largest cohort to date reporting the incidence of contralateral/bilateral nodal metastases in patients with HPV positive SCCA of the oropharynx.
- Divided patients into subsites BOT and tonsil for further sub analysis.
- Good follow up - average 3.8 years.
- Suggests HPV status does not affect incidence of contralateral/bilateral nodal metastases in patients with SCCA of the oropharynx and thus should not have an impact on decision to treat the contralateral neck.

#### **Weaknesses:**

- Retrospective study
- Patients were staged by various methods, with 118 staged with PET/CT, 35 using CT neck, chest x-ray, and LFT's, and 25 staged using surgical path of the ipsilateral neck and imaging of the contralateral neck yet all patients were analyzed as one cohort. This inconsistency in staging all patients via the same modality creates room for error and bias.
- Micro metastasis in the contralateral neck would largely be undetected by current imaging regimen.

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## **[A Multi-Institutional Comparison of Outcomes of Immunosuppressed and Immunocompetent Patients Treated with Surgery and Radiation Therapy for Cutaneous Squamous Cell Carcinoma of the Head and Neck.](#)**

*Manyam BV, Garsa AA, Chin RI, Reddy CA, Gastman B, Thorstad W, Yom SS, Nussenbaum B, Wang SJ, Vidimos AT, Koyfman SA.*

*From **Cancer**, June 2017*

**BACKGROUND:** Patients who are chronically immunosuppressed have higher rates of cutaneous squamous cell carcinoma of the head and neck (cSCC-HN). This is the largest multi-institutional study to date investigating the effect of immune status on disease outcomes in patients with cSCC-HN who underwent surgery and received postoperative radiation therapy (RT).

**METHODS:** Patients from 3 institutions who underwent surgery and also received postoperative RT for primary or recurrent, stage I through IV cSCC-HN between 1995 and 2015 were included in this institutional review board-approved study. Patients categorized as immunosuppressed had chronic hematologic malignancy, human immunodeficiency/acquired immunodeficiency syndrome, or had received immunosuppressive therapy for organ transplantation 6 months before diagnosis. Overall survival, locoregional recurrence-free survival, and progression-free survival were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using Cox proportional-hazards regression.

**RESULTS:** Of 205 patients, 138 (67.3%) were immunocompetent, and 67 (32.7%) were immunosuppressed. Locoregional recurrence-free survival (47.3% vs 86.1%;  $P < .0001$ ) and progression-



free survival (38.7% vs 71.6%;  $P = .002$ ) were significantly lower in immunosuppressed patients at 2 years. The 2-year OS rate in immunosuppressed patients demonstrated a similar trend (60.9% vs 78.1%;  $P = .135$ ) but did not meet significance. On multivariate analysis, immunosuppressed status (hazard ratio [HR], 3.79;  $P < .0001$ ), recurrent disease (HR, 2.67;  $P < .001$ ), poor differentiation (HR, 2.08;  $P < .006$ ), and perineural invasion (HR, 2.05;  $P < .009$ ) were significantly associated with locoregional recurrence.

**CONCLUSIONS:** Immunosuppressed patients with cSCC-HN had dramatically lower outcomes compared with immunocompetent patients, despite receiving bimodality therapy. Immune status is a strong prognostic factor that should be accounted for in prognostic systems, treatment algorithms, and clinical trial design.

#### Strengths

- Large, multi-institutional cohort
- Significantly higher risk of locoregional recurrence despite the addition of XRT in many immunosuppressed patients
- Also higher distant metastatic rate in the immunosuppressed population, which highlights need for escalation of therapy in these patients. These data suggest the need for a clinical trial to assess the addition of systemic agents to possibly improve outcomes

#### Limitations

- Retrospective data with possible selection bias
- Treatment heterogeneity among centers and practitioners
- Heterogeneity of immunosuppression types
- No statistical difference in overall survival (61 vs 78%,  $p = .135$ ); however data is suggestive

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## **Triple-modality treatment in patients with advanced stage tonsil cancer.**

Roden DF, Schreiber D, Givi B.

From *Cancer*. April 25, 2017

**BACKGROUND:** Concurrent chemoradiation (CCRT) and upfront surgery followed by adjuvant therapy both are recommended treatment options for patients with advanced stage squamous cell carcinoma (SCC) of the tonsil. To the authors' knowledge, the question of whether surgical-based treatments can achieve better survival compared with CCRT has never been compared in a clinical trial. The authors analyzed the National Cancer Data Base to measure the impact of different treatment modalities on overall survival (OS).

**METHODS:** All patients aged  $\leq 70$  years diagnosed with clinical stage III to IVB (excluding T4B) SCC of the tonsil from 1998 through 2011 were selected. Analysis was limited to patients receiving CCRT, surgery plus CCRT, or surgery followed by adjuvant radiotherapy (RT). OS was compared using the Kaplan-Meier method and log-rank test. Univariable and multivariable hazards analyses were performed to identify factors significant for survival. Propensity score matching was performed.

**RESULTS:** There were 16,891 patients who met the inclusion criteria. The most common treatment was CCRT (8123 patients; 48.1%), followed by surgery plus CCRT (5249; 31.1%) and surgery plus RT (3519 patients; 20.8%). Patients treated with surgery plus CCRT were found to have the highest 3-year OS rate (88.5%) followed by those treated with surgery plus RT (84%) and CCRT (74.2%) ( $P < .0001$ ). In a



propensity score-matched subpopulation of 4962 patients, the 3-year OS rate was 90.2% for those treated with surgery plus CCRT, 84.9% for those treated with surgery plus RT, and 82.1% for those treated with definitive CCRT ( $P < .0001$ ).

**CONCLUSIONS:** Patients with advanced stage SCC of the tonsil who underwent surgery followed by CCRT had the greatest OS. Patients undergoing upfront surgery may avoid chemotherapy without jeopardizing survival. Triple-modality therapy may provide a survival benefit for a subset of patients with advanced stage tonsil cancer.

### **Strengths**

- Large dataset, multi-institutional
- Propensity matching may help eliminate inherent biases in the analysis
- Primary surgical treatment was associated with improved mortality in the propensity matched cohort within the multivariable model for both surgery + CCRT and surgery + RT vs primary CCRT.

### **Limitations**

- Retrospective, database study which does not account for selection bias
- Use of overall survival only with no data on disease specific outcomes
- Lack of HPV status
- No functional outcomes data

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