



# American Head and Neck Society - Journal Club

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### **[Acupuncture in Shoulder Pain and Functional Impairment After Neck Dissection: A Prospective Randomized Pilot Study](#)**

*Alberto Deganello, MD, PhD; Nir Battat, MD; Enrico Muratori, MD; Glauco Cristofaro, MD; Ana Buongiorno, MD; Giuditta Mannelli, MD; Mario Picconi, MD; Rita Giachetti, MD; Giulia Borsotti, MD; Oreste Gallo, MD*

*from **The Laryngoscope**, August 2016*

**Objectives/Hypothesis:** The efficacy of conventional physiotherapy and antiinflammatory/analgesic drugs in the management of shoulder pain and functional disability following neck dissection is often disappointing. Acupuncture is a safe and well-tolerated method. We report the results regarding our pilot trial of acupuncture versus conventional care in the management of postoperative shoulder pain and dysfunction after neck dissection.

**Study Design:** Pilot study.

**Methods:** Patients at a tertiary university center with chronic pain or dysfunction attributed to neck dissection were randomly assigned to either weekly acupuncture or usual care (eg., physical therapy, analgesia, and/or anti-inflammatory drugs) for 5 consecutive weeks. The Constant-Murley score, a composite measure of pain, function, and activities of daily living, was the primary outcome measure. As secondary end point, The Neck Dissection Impairment Index (NDII) was used to quantify site-specific, self-reported quality of life (QOL).

**Results:** After randomization, 48 patients completed the study (23 and 25 patients on acupuncture and control arms, respectively). Constant-Murley scores improved more in the acupuncture group (gain difference between groups 13.6,  $P < 0.01$ ), a statistically significant improvement in site-specific QOL was also recorded at NDII (gain difference between groups 11.5,  $P < 0.01$ ).

**Conclusion:** Acupuncture is safe and effective; it should be introduced and offered to patients suffering from neck pain and dysfunction related to neck dissection.



Summary:

- Provides early evidence to suggest acupuncture can be used as an additional treatment tool to help patients with pain and dysfunction after neck dissection.
- Provides education on the principles of acupuncture, an area that is often unfamiliar to most surgeon specialists.

Strengths:

- Randomized pilot study
- Statistically significant differences were reported

Weaknesses:

- Short follow up. Does the difference found to be statistically different hold up over time? 13 patients were re reviewed at 4-10 months and the improvement does seem to persist in this small subset of patients.
- Question more than a weakness (and admits my own lack of experience with this modality) can the acupuncture technique be replicated by different providers in different areas?

Suggestions for further study:

- Consider a third arm in the study combining standard physical therapy and acupuncture. Are they synergistic?

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## **Neoadjuvant chemotherapy and transoral surgery as a definitive treatment for oropharyngeal cancer: A feasible novel approach**

*Nader Sadeghi, MD, Ning-Wei Li, MD, M. Reza Taheri, MD, PhD, Samantha Easley, MD, Robert S. Siegel, MD*

*from **Head & Neck**, June 2016*

ABSTRACT:

**Background.** The purpose of this study was to present our evaluation of the outcome of oropharyngeal cancer managed with neo-adjuvant chemotherapy and transoral surgery (TOS) with neck dissection as definitive treatment.

**Methods.** This is a case series of 17 patients with advanced oropharyngeal cancer who were treated with neoadjuvant chemotherapy followed by TOS. The treatment details and oncologic outcome are reported. The volumetric response of the tumor to neoadjuvant chemotherapy is evaluated and validated by histopathology.

**Results.** Seventeen patients with TNM stages III and IV oropharyngeal cancer constitute this series for survival analysis. On a median and mean follow-up of 31 and 40 months, respectively, 16 of the 17 patients were alive without recurrence. Disease-specific survival (DSS) and over-all survival (OS) at 3 years were 94.1%.

**Conclusion.** Adjuvant chemotherapy followed by TOS and neck dissection is a feasible and efficacious novel therapeutic approach for definitive management of moderately advanced oropharyngeal cancer, reserving radiotherapy (RT) for salvage or adverse features



The authors introduce a novel method for treating OPSCC patients by utilizing neoadjuvant chemotherapy followed by transoral resection and neck dissection. They demonstrated an excellent treatment response in advanced oropharyngeal cancer without the use of radiotherapy, thereby deintensifying the treatment and avoiding long-term morbidity.

#### Strengths

- innovative concept with excellent outcomes
- systematically executed study with strong objective data reporting response to neoadjuvant chemo

#### Weaknesses

- small size
- retrospective nature with potential for selection bias
- no patient-reported functional data

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## **Clinical and histopathological staging in oral squamous cell carcinoma - Comparison of the prognostic significance**

*Kreppel M, Nazarli P, Grandoch A, Safi AF, Zirk M, Nickenig HJ, Scheer M, Rothamel D, Hellmich M, Zöller JE.*

*from Oral Oncology, September 2016*

This retrospective study included 392 treatment patients with biopsy proven oral squamous cell carcinoma of advanced stages I–IVb, who were treated with curative intent at the Department for Oral and Craniomaxillo-Facial Plastic Surgery at the University of Cologne between 2003 and 2010. Clinical and histopathologic staging was conducted according to the 7th edition of the Union for International Cancer Control, for carcinoma of the oral cavity. Patients with distant metastases were excluded.

At the time of diagnosis, the patients' age ranged from 25 to 90 years with an average age of 61.8 years. Clinical staging data were obtained using the results from clinical examinations, CT, MRI, ultrasound of the head and neck region, and three-phase bone scintigraphy using <sup>99m</sup>Tc pre-treatment reports from the Department of Radiology. Lymph nodes of a diameter >1.5 cm were considered as positive and uptake of contrast medium with a diameter > 1 cm, round shape and central necrosis. To detect distant metastases chest X-ray and abdominal ultrasound were conducted.

Resection specimens were analyzed macroscopically according to tumor localization and nodal stage. Cross sectioning was performed and tissue was embedded into Paraffin. Paraffin blocks were sliced into 4 μm thick sections and analyzed by senior pathologists.

All patients were treated with radical surgery including neck dissection.

Different teams of surgeons, radiation oncologists, medical oncologists, radiologists and pathologists determined the indications for adjuvant treatment individually so that some patients with stage without the risk factors of stage III and IV, positive or close margins, lymphangiosis carcinomatosa, extracapsular spread and poor histopathologic differentiation received a postoperative radiotherapy or chemo – radiotherapy. Radiotherapy was delivered by 6-MV photons of a linear accelerator in daily fractions of



1.8 Gy, five-times a week with a total dose 60–66 Gy. When chemotherapy was given, it was administered in a concomitant setting during the first and fifth week of radiotherapy. Carboplatin was given as a short-term infusion 1 h before radiation at a dose of 70 mg/m<sup>2</sup>/day.

The average follow-up time for patients alive was 46.1 months. Out of the patients alive, 28 patients had a follow up of less than 12 months. The mean nodal yield was 24.8.

None of our patients died because of treatment related complications. Five year overall survival (OS) was 73%. Univariate analysis revealed that clinical as well as pathological T-stage and N-stage are feasible predictors for OS ( $p < 0.001$ ). The 5-year OS rate decreased from pT1 (96%) to pT4b (28%). Patients with no histological evidence of cervical lymph node metastases had a significantly higher 5-year OS rate (pN0, 85%) in comparison to patients with cervical lymph node metastases. While patients with pN1 status had a 5-year OS rate of 68% the 5-years OS rate dropped to 25% for patients with pN3-status ( $p < 0.001$ ). Out of the patients with histologically confirmed metastases 12% of the patients were staged as cN0 without clinical or radiological signs of the disease spread but had metastases in the neck dissection specimen (cN0pN+). Compared to the patients with cN0pN0-status, they had a significantly poorer 5-year overall survival rate (61% vs. 80%,  $p = 0.004$ ). When comparing cN0pN0 and cN + pN0 no significant differences were observed between both groups for OS (5-year OS 81% vs. 90%,  $p = 0.463$ ). Concordance between clinical and pathological staging of the primary tumor was 62%. In 58% of the discordant cases, discordance was due to overstaging of the size of the primary tumor. In comparison to the T-classification concordance between clinical and pathological staging for the N-classification was smaller (in 59%). In case of discordance, overstaging of the cervical lymph nodes occurred in 86%. The sensitivity for the cT- classification was 78%, for the cN-classification the sensitivity was 91%. The mean delay between three-dimensional and surgery was 16.5 days. There were no statistically significant associations between the delay of surgery and discordance of cT- and pT-classification ( $p = 0.541$ ) or discordance of cN- and pN-classification ( $p = 0.340$ ). They concluded that the despite advances and modern radiologic techniques, pTNM have a higher prognostic quality than cTNM. Also discordance between clinical and histopathologic staging was observed in up to 40%. When discordance was observed overstaging for cT- and cN-stage was more likely than understaging.

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## **Classification of TP53 Mutations and HPV Predict Survival in Advanced Larynx Cancer**

*Scheel A, Bellile E, McHugh JB, Walline HM, Prince ME, Urba S, Wolf GT, Eisbruch A, Worden F, Carey TE, Bradford C.*

*from The Laryngoscope, September 2016*

**Objectives/Hypothesis:** Assess tumor suppressor p53 (TP53) functional mutations in the context of other biomarkers in advanced larynx cancer.

**Study Design:** Prospective analysis of pretreatment tumor TP53, human papillomavirus (HPV), Bcl-xL, and cyclin D1 status in stage III and IV larynx cancer patients in a clinical trial.

**Methods:** TP53 exons 4 through 9 from 58 tumors were sequenced. Mutations were grouped using three classifications based on their expected function. Each functional group was analyzed for response to induction chemotherapy, time to surgery, survival, HPV status, p16INK4a, Bcl-xl, and cyclin D1 expression.



**Results:** TP53 mutations were found in 22 of 58 (37.9%) patients with advanced larynx cancer, including missense mutations in 13 of 58 (22.4%) patients, nonsense mutations in four of 58 (6.9%), and deletions in five of 58 (8.6%). Highrisk HPV was found in 20 of 52 (38.5%) tumors. A classification based on Evolutionary Action score of p53 (EAp53) distinguished missense mutations with high risk for decreased survival from low-risk mutations (P = 0.0315). A model including this TP53 classification, HPV status, cyclin D1, and Bcl-xL staining significantly predicts survival (P = 0.0017).

**Conclusion:** EAp53 functional classification of TP53 mutants and biomarkers predict survival in advanced larynx cancer.

**Key Words:** TP53, p53, larynx cancer, Bcl-xL, cyclin D1, HPV.

**Summary:**

- TP53 mutations were found in 22 of 58 (37.9%) patients with advanced larynx cancer.
- High risk HPV was found in 20 of 52 (38.5%) tumors.
- As a single variable, HPV status was not predictive of DSS.
- 66% of patients responded to induction chemotherapy. No significant predictors of response to induction chemotherapy were found in any of the TP53 classifications.
- A model with Bcl-xL, cyclin D1, EAp53 classification, and hrHPV status was highly significant as a prognostic model for DSS.
- In this clinical trial, patient selection through induction chemotherapy resulted in larynx preservation in 70% of patients and DSS of 87%. Although patient survival was improved, there was still a subset of patients with poor outcome. The EAp53 classification / model has potential to identify this subset of patients that could lead to recommendations for more aggressive treatment.

**Strengths:**

- A detailed review and analysis of TP53 pathways and EAp53 classification.
- Provides further insight and considerations for this difficult subgroup of patients with advanced laryngeal cancer who do not respond favorably to traditional therapy having lower DSS. Giving some clues as to potential targets for further treatment considerations.

**Weaknesses:**

- Details for clinical implementation of the “model” remain to be understood.
- As a single variable, power was lacking to demonstrate any potential difference in survival based on HPV status.

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