



# American Head and Neck Society

## Journal Club

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### **[Oncologic Outcomes After Transoral Robotic Surgery: A Multi-institutional Study](#)**

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*from **[JAMA Otolaryngology Head & Neck Surgery, September, 2015](#)***

This is a retrospective review of 410 patients undergoing TORS for laryngeal and pharyngeal cancers over 5 years from 11 different institutions. This review of a larger more homogenous group of patients aims to better evaluate the oncologic outcomes, patterns of recurrence and mortality associated after TORS. This study was endorsed by the Research Committee of the American Head and Neck Society in 2011.

Treatment specifics for patients were institution dependent. A close margin was defined as less than a negative margin but without tumor at the cut edge of the specimen on final pathology, which was defined as a positive margin. Patients with adverse pathologic features after surgery received either adjuvant treatment with radiation alone or combined chemoradiation as recommended by the local institutional tumor board. Adverse pathologic features included positive or close margins, extra capsular nodal spread (ECS), lymphovascular invasion (LVI), perineural invasion (PNI), multiple positive lymph nodes, or advanced T and/or N classification. Oropharyngeal cancer accounted for a majority of the cases with 364 [88.8%] of which: 45.4% in the tonsil, 31.7% in the tongue base, with T1 & T2 tumors accounting for 83.5% of the patients in this study with a mean follow-up of 20 months

HPV status was known in only 229 (55.9%) of patients, 159 patients (69.4%) were positive via in-situ hybridization techniques. Of the 219 patients with known p16 status, 158 (72.1%) were p16-positive by



immunohistochemical staining. Of the 393 patients (95.9%) who had known margin status, 39 (9.9%) had positive margins. Of those with known adjuvant treatment status, TORS alone was performed in 160 (47.3%) of 338 patients, 106 (31.4%) of 338 underwent adjuvant radiotherapy, and 72 (21.3%) of 338 patients underwent adjuvant chemoradiation.

Forty-three patients (10.5%) experienced recurrences. Thirty-three patients (8.0%) experienced local or regional recurrences. Ten patients (2.4%) experienced distant metastases. The median time to locoregional recurrence was 16.4 months. The greatest difference in locoregional control was seen when comparing patients with positive margins and those with clear margins ( $P = .001$ ). At 2-year follow-up, the locoregional control rate for patients with positive margins during TORS was 78.6% compared with 92.9% when surgical margins were negative. At 3-year follow-up, the locoregional control rate for patients with positive margins during TORS was 63.5% compared with 91.2% when surgical margins were negative. In univariate analysis, older age, smoking status, oropharyngeal wall or faucial arch primary tumor site, and positive margins were risk factors for disease recurrence. Tonsil primary site predicted a lower risk of recurrence compared with all sites. In multivariate analysis, none of these predictors remained a significant predictor of recurrence.

Overall, there were 30 deaths (7.3%) in the cohort. There was a single mortality related to surgery due to postoperative hemorrhage on the night of surgery, 0.2%. Seventeen patients (4.2%) died of their disease, and 13 patients (3.2%) died without any evidence of disease. The 2- and 3-year overall survival rates were 91% (95% CI, 86.5%-94.0%) and 87.1% (95% CI, 81.4%-91.2%), respectively. The 2- and 3-year disease-specific survival rates were 94.5% (95% CI, 90.6%-96.8%) and 92.5% (95% CI, 87.8%-95.5%), respectively. When comparing overall and disease-specific survival rates based on HPV and p16 status, no significant differences were observed. In this subset of patient on univariate analysis, risk factors for death of any cause included age, male sex, tobacco history, and oropharyngeal wall or faucial arch primary site. On multivariate analysis, only tobacco smoking history predicted worse overall survival, whereas tonsil primary site was associated with improved over- all survival

#### Limitations

- Treatment specifics were institution dependent and adjuvant treatment not standardized
- Variability in reporting across the centers and missing data elements
- HPV status known in approximately 55% of patients
- Mean follow up (20 months)

#### Strengths

- Large, multicenter collaborative study of 410 patients
- Providing incidence data regarding mortality related to TORS
- Retrospective data on the percentage of patients receiving single, dual and tri-modality treatment
- Highlights the importance of margin status and TORS, which requires prospective study

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## **The Impact of Diagnostic Changes on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Selected High-Resource Countries.**

Salvatore Vaccarella, Luigino Dal Maso, Mathieu Laversanne, Freddie Bray, Martyn Plummer and Silvia Franceschi

from ***THYROID***, October 2015

This paper seeks to estimate the fraction of thyroid cancer attributable to increased surveillance of the thyroid gland following introduction of the neck ultrasonography in the 1980s. It is a population-based study comparing age-specific incidence rates across high resource countries and time periods.

Using data from the series *Cancer Incidence in Five Continents*, the authors compared new cases and rates of thyroid cancer in Nordic (Denmark, Finland, Norway, Sweden) and European (England, Scotland, France, Italy) countries as well as the US, Australia, Japan and the Republic of Korea. Age-standardized incidence rates (ASR) were calculated and compared in 1988-1992 versus 2003-2007. Expected age-specific thyroid cancer incidence rates were calculated from 1958-1967 historical data from the Nordic countries cohort.

Age-standardized thyroid cancer incidence rate ratios for the period 2003-2007 compared to 1988-1992 (1993-1997 for the Republic of Korea) were calculated. Rate ratios  $>2.0$  were found in France, Italy, Korea, Australia, and the US. Age-specific incidence rates from 2003-2007 demonstrated an elevated observed age curve relative to expected for all countries except Japan (men only). In other words, thyroid cancer incident rates were higher in the observed group and specifically in the middle aged female population. The largest difference between observed and expected ASRs was found in Korea with 49.8 extra cases of thyroid cancer per 100,000. Large discrepancies were also found in Italy (18.6 extra cases per 100,000), the US (13.6), France (10.9) and Australia (9.1). Proportion of cases attributable to diagnostic changes was also determined (O-E/O, %) and found to be 83% (Korea), 68-70% (Italy, US, France, Australia).

### Strengths

- Unique approach to comparing thyroid cancer rates across many different countries and age ranges
- Excellent and thoughtful discussion section addressing limitations

### Limitations

- Population based data with estimates based on assumptions and correlative hypotheticals
- Many of the conclusions rely on Nordic countries data to establish expected rates. Is this a valid comparison?

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## **Effects of Honey on Oral Mucositis in Patients With Head and Neck Cancer: A Meta-Analysis**

*Hye Kyung Cho, MD, PhD; Yeon Min Jeong, MD; Ho Seok Lee, MD; Yeon Ji Lee, MD;  
Se Hwan Hwang, MD, PhD*

*from Laryngoscope, September, 2015*

This is a Meta-analysis coordinated by a two authors at a single institution with the objective of identifying all studies dating up to June 2014 comparing the efficacy of honey in the management of oral mucositis during radiotherapy or chemoradiotherapy in patients with head and neck cancer. Outcomes of interest included the degree and incidence of mucositis, incidence of microbial colonization, and weight loss. Inclusion criteria included: randomized controlled studies published in English comparing the oral administration of honey (honey group) with placebo or no treatment (control group) in patients with head and neck cancer who were undergoing radiotherapy or chemoradiotherapy. Exclusion criteria included: studies that failed to report quantifiable outcome measures regarding oral mucositis. Outcomes of interest included the degree and incidence of mucositis, incidence of microbial colonization, and weight loss.

A total of 476 patients were included (nine studies meeting inclusion criteria). Honey was given before and/or after radiation therapy treatments. No detail was provided as to the type of honey (local or otherwise) nor detailed administration schedules. Mucositis was graded in each study by one of the following; World Health Organization (WHO), the Radiation Therapy Oncology Group, or the Oral Mucositis Assessment Scale. The onset of mucositis was significantly later in the honey group than that of the control group (SMD = 2.64, P=.0036). The incidence of moderate to severe mucositis (log OR = -1.94, P<.0001) and mean mucositis grade during the first 3 weeks of therapy (SMD = -0.93, P = .0114) were also significantly lower in the honey group. Honey administration had a significantly greater effect in preventing moderate to severe mucositis in patients receiving radiotherapy alone than in patients receiving chemoradiotherapy (logOR = -2.87, P<.0001). The authors also demonstrated the incidence of weight loss was significantly lower (logOR = -1.94; P<.0001) in the honey group than control group. There was no significant differences in the incidences of microbial or fungal colonization and pain experienced between the two groups.

This meta-analysis demonstrates oral administration of honey during radiotherapy could prevent moderate to severe mucositis and associated weight loss. If this were validated in future studies it could provide a cheap, readily accessible prevention for an all too common and debilitating complication of radiation often leading to treatment breaks and decreased prognosis.

### Strengths:

- Meta – analysis
- Detailed exclusion and inclusion criteria maintained throughout the study

### Weakness:

- Small study size. 9 papers over the lifetime of the searchable databases limiting bias analysis (i.e. publication bias).
- Types and amounts of honey administered were not discussed. Unclear consistency in administration schedules across the papers reviewed.

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## **Oncologic outcomes of supratracheal laryngectomy: critical analysis**

*Giuseppe Rizzotto, MD, Erika Crosetti, MD, Marco Lucioni, MD, Andy Bettolin, MD, Valentina Monticone, MD, Andrea Elio Sorio, PhD, Giovanni Nicolao Berta, PhD, Giovanni Succo, MD*

*from Head & Neck, October, 2015*

The treatment strategies of Clinical Stage III and IV larynx carcinoma are currently focused on conservative surgical procedures (for selected patients) or chemoradiation (for T3 and low volume T4a tumors in patients who are candidates to total laryngectomy) aiming to achieve long term survival with anatomic and functional preservation of the larynx.

Function-sparing open partial laryngectomy (usually a supracricoid laryngectomy) has been in use in Europe for several decades, but it has not been used worldwide because functional results have not been repeatable. The main limitation of the procedure was subglottic extension. A more extensive procedure designed for transglottic tumors with subglottic tumor extension, supratracheal laryngectomy was described by Serafini on 1972, but only in 2006 Rizzotto et al presented technical modifications and showed encouraging oncologic and functional outcomes. Supratracheal laryngectomy comprises the resection of thyroid cartilage, supraglottis and glottis, sparing both or at least one functioning cricoarytenoid unit. The inferior limit of the resection encompasses the cricoid ring sparing the first tracheal ring. The synthesis is done with hyoid epiglottopexy or trachea-hyoid-pxy.

This retrospective multicentric study included 115 consecutive patients with supraglottic or glottic squamous cell carcinoma who underwent supratracheal partial laryngectomy with trachea-hyoid epiglottopexy or supratracheal partial laryngectomy with trachea-hyoid-pxy over a 10-year period. A total of 36 patients underwent salvage supratracheal laryngectomy (12 chemoradiation failures, 16 recurrences after transoral laser surgery, 8 after other partial laryngectomy). There were 103 glottic and 12 supraglottic tumors. Only 14 glottic tumors were T2. All the others were T3 or T4a tumors. The most frequently performed procedure was supratracheal partial laryngectomy/trachea-hyoid-epiglottopexy with removal of one cricoarytenoid unit (95 cases, 82.6%). Intraoperative frozen section was done to examine resection margins in all patients. Neck dissection was performed in 75 patients. In 55 cases a paratracheal dissection was done. Thirty-one patients with extralaryngeal extension of primary tumor or pN+ were submitted to postoperative radiotherapy.

Laryngeal function preservation was maintained in 78.3% of patients. These results were affected by T4a classification (59.3%) and age >65 years (64.6%). Close margins were reported in 11 cases (9.6%). Acute complications were reported in 7 patients (6.1%). Four patients (3.5%) had postoperative aspiration pneumonia. Seven patients (6.1%) had aspiration pneumonia later. There were no postoperative deaths. There were loco-regional recurrences in 28 patients (20 local, 8 regional). Patients with local recurrences were salvaged with total laryngectomy. The 5-year overall survival, disease free survival and loco-regional control were 78.9%, 68.5% and 69.6%, respectively.

The authors conclude that for selected cases of advanced transglottic or glottic tumors with subglottic extension, supratracheal partial laryngectomy can be an alternative to chemoradiation. It was considered effective in terms of local disease control, survival and functional outcomes.

### Strengths:

- Large case series of consecutive cases treated in different institutions.
- Clear definition of indications and contraindications, as well as accurate description key technical points.



- Detailed description of complications, pathological findings, adjuvant treatment, recurrences, survival and functional outcomes. Although aspiration pneumonia was reported in a small number of patients, the performance of the supratracheal laryngectomy does not seem to entail major complications that render it unfeasible.

**Weakness:**

- Some heterogeneity of the patients included (primary surgery and salvage surgery after surgical or chemoradiation failures).
- The 5-year overall survival and larynx preservation rates are similar to the reported with chemoradiation for T3 and low volume T4a tumors.
- Supratracheal partial laryngectomy produces significant functional deficits and rehabilitation following it may require a motivated patient and long term speech/swallowing therapy.

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## [Human Papillomavirus-related Tumors of the Oropharynx Display a Lower Tumor Hypoxic Signature](#)

*Elodie Hannsa, Sylvie Jobb, Pierre Coliata, Christine Wasylyk, Ludivine Ramolua, Erwan Pencreach, Meggy Suarez-Carmona, Michael Herfs, Sonia Ledrappiera, Christine Macabrea, Joseph Abecassisa, Bohdan Wasylyk, Alain C. Jung*

*from [Oral Oncology](#), September 2015*

This study had two different approaches of looking at HPV status and hypoxia in head and neck cancer: 1) an *in vitro*, cell-line based study looking at HPV positive and negative HNSCC cells and seeing differences in their gene expression after incubation under hypoxic conditions 2) Looking at HNSCC patient tumor samples and analyzing for expression of hypoxia-related genes and neovascularization. Two different HPV negative and two different HPV positive cell lines were cultured under hypoxic conditions (3% oxygen for 24 hours then 1% oxygen) and normoxia (20% oxygen). They were then tested for cell proliferation and expression of known-hypoxia associated cell-response proteins via Western blot and qRT-PCR. Two of the cell lines (HPV + and -) were then xenografted on to nude mice and HIF-1 $\alpha$  and CAIX IHC staining was performed. Tumor samples from 88 patients (54 HPV negative and 34 HPV positive) were analyzed by qRT-PCR and IHC to look for hypoxia gene expression of several genes and by IHC to look at the hypoxia status (CAIX staining) and the relationship between vascular density and the hypoxia status of the tumors (CD105 staining).

In the cell cultures, the HPV negative tumors proliferated in both the normoxia and hypoxia conditions, while the HPV positive tumors grew well in the normoxia environment, but stopped proliferation after about 48hrs and progressively decreased and/or died. The expression profiles of the cell culture, however, showed that both HPV + and - cell lines had functional hypoxia response pathways with minimal difference in expression only in Glut1. In the xenograft models, showed that CAIX and HIF-1 $\alpha$  staining were much more robust in the HPV negative cell line suggesting that HPV positive cell lines are less hypoxic. Within the patient samples, the HPV-related tumors were found to express statistically significant lower levels of several hypoxia-related genes (HIF-1 $\alpha$ , PHD3, Glut1 and Glut 3) and stain less for carbonic anhydrase IX (CAIX). In the CD105 staining/neo-vascularization assessment, HPV-related tumors were shown to have a 3-fold higher mean number of vessels. Overall, the authors conclude that HPV related tumors were less hypoxic, expressed lower levels of hypoxia-responsive genes and had a higher density of neo-blood vessels, all of which may account for the better treatment response seen with treatment and improved prognosis of these tumors

### Strengths

- multiple different methods demonstrating similar results
- results are grounded in observed clinical outcomes and can potentially translate into different therapeutic approaches based on HPV status and response to hypoxia

### Weaknesses

- no major difference seen in the induction patterns of the four cell-line cultures except in glut 1
- exact molecular mechanisms that lead to HPV-related tumor cell death in the hypoxic environment are still unclear

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## **New 2015 ATA Guidelines**

The AHNS Journal Club also wanted to highlight the new ATA 2015 guidelines which were recently published in the journal "Thyroid". Here is the link to the new guidelines for the management of differentiated thyroid cancer, medullary thyroid cancer, and children with thyroid nodules and/or differentiated thyroid cancer.

<http://www.thyroid.org/professionals/ata-professional-guidelines/>

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