



# American Head and Neck Society - Journal Club

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### [The Role of Adjuvant Treatment in Early-Stage Oral Cavity Squamous Cell Carcinoma: An International Collaborative Study](#)

*Fridman E, Na'ara S, Agarwal J, et al.*

*from Cancer, July 2018*

**Background:** Up to half of patients with oral cavity squamous cell carcinoma (OCSCC) have stage I to II disease. When adequate resection is attained, no further treatment is needed; however, re-resection or radiotherapy may be indicated for patients with positive or close margins. This multicenter study evaluated the outcomes and role of adjuvant treatment in patients with stage I to II OCSCC.

**Methods:** Overall survival (OS), disease-specific survival, local-free survival, and disease-free survival rates were calculated with Kaplan-Meier analysis.

**Results:** Of 1257 patients with T1-2N0M0 disease, 33 (2.6%) had positive margins, and 205 (16.3%) had close margins. The 5-year OS rate was 80% for patients with clear margins, 52% for patients with close margins, and 63% for patients with positive margins ( $P < .0001$ ). In a multivariate analysis, age, depth of invasion, and margins were independent predictors of outcome. Close margins were associated with a >2-fold increase in the risk of recurrence ( $P < .0001$ ). The multivariate analysis revealed that adjuvant treatment significantly improved the outcomes of patients with close/positive margins ( $P = .002$  to  $.03$ ).

**Conclusions:** Patients with stage I to II OCSCC and positive/close margins have poor long-term outcomes. For this population, adjuvant treatment may be associated with improved survival.

#### **Strengths**

- Large, multi-institutional dataset of T1-T2N0 disease only
- Large differences seen in DFS for close/+ vs negative (>5mm) margin, especially at 10 years
- Distinct survival advantage seen in close/positive margins with adjuvant therapy



### Limitations

- Retrospective data
- Could not account for all additional negative prognostic factors i.e. LVI and PNI
- Heterogeneity with regard to subsite and adjuvant treatment given

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## [Association of Tumor Size With Histologic and Clinical Outcomes Among Patients With Cytologically Indeterminate Thyroid Nodules](#)

*Pablo Valderrabano, MD, PhD; Laila Khazai, MD; Zachary J. Thompson, PhD; Kristen J. Otto, MD; Julie E. Hallanger-Johnson, MD; Christine H. Chung, MD; Barbara A. Centeno, MD; Bryan McIver, MD, PhD*

*from JAMA Otolaryngology Head & Neck, September 2018*

**Importance:** Tens of thousands of unnecessary operations are performed each year for diagnostic purposes among patients with cytologically indeterminate thyroid nodules. Whereas a diagnostic lobectomy is recommended for most patients with solitary indeterminate thyroid nodules, a total thyroidectomy is preferred for nodules larger than 4 cm.

**Objective:** To determine whether histologic or clinical outcomes of indeterminate thyroid nodules 4 cm or larger are worse than those for nodules smaller than 4 cm, thus justifying a more aggressive initial surgical approach.

**Design, Setting and Participants:** In this retrospective cohort study, 652 indeterminate thyroid nodules (546 nodules <4 cm and 106 nodules ≥4 cm) with surgical follow-up were consecutively evaluated at an academic cancer center from October 1, 2008, through April 30, 2016.

**Exposure:** Tumor size.

**Main Outcomes and Measures:** Differences in cancer rates, rates of invasive features, cancer aggressiveness, and response to therapy between indeterminate thyroid nodules smaller than 4 cm and 4 cm or larger.

**Results:** A total of 652 indeterminate thyroid nodules (546 nodules <4 cm and 106 nodules ≥4 cm) from 589 patients (mean [SD] age, 53.1 [13.8] years; 453 [76.9%] female) were studied. No differences were found in the baseline characteristics of patients or nodules between the 2 size groups. Tumor size was not associated with the cancer rate as a categorical (140 of 546 [25.6%] for nodules <4 cm and 33 of 106 [31.1%] for nodules ≥4 cm; effect size, 0.05; 95% CI, 0.002-0.12) or continuous (odds ratio [OR], 1.03; 95% CI, 0.92-1.15) variable. No association was found between nodule size and prevalence of extrathyroidal extension, positive margins, lymphovascular invasion, lymph node metastasis, or distant metastasis. Most malignant tumors were low risk in both size groups (70% in the nodules <4 cm and 72% in the nodules ≥4 cm), and tumor size was not associated with tumor aggressiveness as a categorical (effect size, 0.10; 95% CI, 0.03-0.31) or continuous variable (OR for intermediate-risk cancer, 0.91; 95% CI, 0.72-1.14; OR for high-risk cancer, 1.43; 95% CI, 0.96-2.15). At the last follow-up visit, 88 of 105 patients (83.8%) with malignant tumors in the smaller than 4 cm group and 21 of 25 (84.0%) in the 4 cm or greater group had no evidence of disease, and tumor size was not associated with response to therapy (effect size, 0.13; 95% CI, 0.07-0.33).



**Conclusions & Relevance:** Most indeterminate thyroid nodules are benign or low-risk malignant tumors regardless of tumor size. In the absence of other indications for total thyroidectomy, this study suggests that a thyroid lobectomy is sufficient initial treatment for most solitary cytologically indeterminate thyroid nodules independent of the tumor size.

#### Strengths

- Large database which addresses an important issue regarding de-escalation of initial surgical management for large thyroid nodules
- Incorporation of the NIFTP classification and mutational data
- Sound study design and statistical methodology

#### Limitations

- Retrospective data with inherent selection biases
- Single institution data
- Limited number of cancers, and high-risk cancers, in the >4cm group

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## [Primary Surgery vs. Primary Radiation-Based Treatment for Locally Advanced Oropharyngeal Cancer](#)

*Kamran SC, Qureshi MM, Jalisi S, Salama A, Grillone G, Truong MT.*

*From Laryngoscope, June 2018*

**Objectives:** To evaluate practice patterns and compare overall survival between primary surgery and radiation-based treatments for locally advanced oropharyngeal cancer using the National Cancer Database.

**Study Design:** National Cancer Database (NCD) review.

**Methods:** Review of patients whose first primary malignancy was diagnosed as locally advanced SCC of the oropharynx from the NCD. Patients treated with primary chemo radiation (CRT) were matched and compared to those undergoing surgery + radiation (aRT) +/- chemotherapy (CT) between 2004 and 2013. Results: 22,676 patients with complete data were reviewed with mean follow up of 40.7 months. 6,584 deaths were reported during the follow-up period. 3-year actuarial survival rates for CRT versus surgery with aRT +/- CT were 72.6% and 85.4%, respectively ( $P < 0.0001$ ). On the multivariate analysis worse survival outcome was noted for increasing age, black patients, nonprivate insurance, Charlson-Deyo score 1 and  $\geq 1$ , advancing clinical T stage, and N2 or N3 disease. HPV was documented in 6,872 patients. The prevalence of HPV positive OPC was 69.3% for CRT and 78.6% for surgery with aRT +/- CT group ( $P < 0.0001$ ). 3-year survival rates for HPV-positive patients was 92.2% and 86.1% for patients receiving surgery with aRT +/- CT and CRT, respectively,  $P < 0.0001$ , and for HPV negative patients was 79.9% and 64.7%,  $P < 0.0001$ .

**Conclusion:** Superior survival outcomes with primary surgical treatment compared to primary radiation-based treatment in locally advanced OPC. The survival difference attenuated in patients with very advanced disease (cT4N3).

**Summary:**



- Review of 22,676 patients within the NCD demonstrating superior survival outcomes with primary surgical treatment compared to primary radiation-based treatment in locally advanced OPC.

**Strengths:**

- large number of patients
- data addresses survival differences between primary surgery versus primary radiation approaches for OPC

**Weaknesses:**

- HPV data not available prior to 2010.
- Potential bias in staging given patients treated with CRT staged clinically and patients treated surgically were staged pathologically.
- NCDB also lacks data on chemotherapy type
- Radiotherapy technique, dose, number of fractions, or treatment fields were not included in this analysis
- Surgical techniques and extent of surgery not available or reviewed.
- Functional outcomes (including speech and swallowing), local control, toxicities from treatment, and cosmetic outcomes) are not accounted for in these analyses

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**[Neck recurrence in clinically node-negative oral cancer: 27-year experience at a single institution](#)**

Mizrachi A, Migliacci JC, Montero PH, McBride S, Shah JP, Patel SG<sup>6</sup> Ganly I.

from **Oral Oncology**, March 2018

**Objectives:** Neck failure in patients with oral squamous cell carcinoma, carries a poor outcome, yet the management of patients who initially present with clinically node-negative (cN0) neck is not clearly defined.

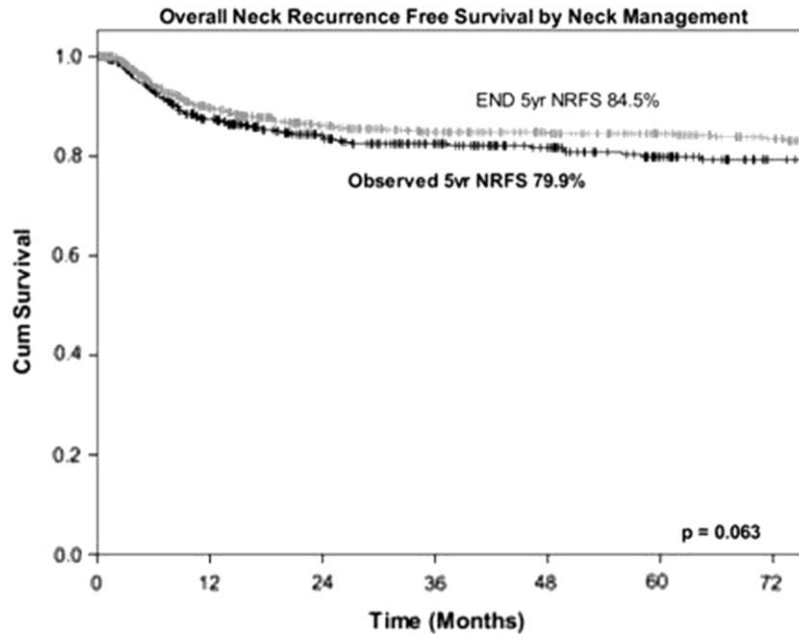
**Patients and methods:** Patients with cN0 oral squamous cell carcinoma treated at Memorial Sloan Kettering Cancer Center from 1985 to 2012, focusing on rate, pattern and predictors of neck failure, salvage treatment, and survival outcomes.

**Study design:** Retrospective review.

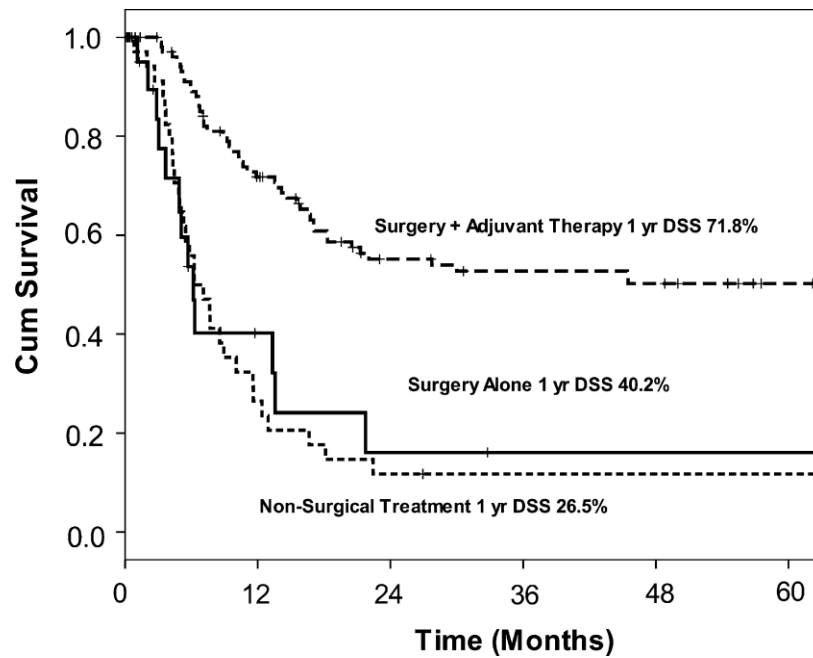
**Results:** Of 1,302 patients, 806 (62%) underwent elective neck dissection and 496 (38%) had observation. 190 patients (15%) developed neck recurrence. Median follow-up was 58.5 months (range 1–343); 5-year neck recurrence-free survival (NRFS) was 85% and 80% for the elective neck dissection and observation group respectively ( $p = .06$ ). Patients with neck failure had poorer outcomes than patients without neck failure (5-year overall survival, 37% vs. 74% [ $p < .001$ ]; disease-specific survival 41% vs. 91% [ $p < .001$ ]). Independent predictors of neck failure were smoking, primary tumor subsite (hard palate and upper gum), and extranodal extension. 87% of patients underwent salvage treatment (elective neck dissection: 81.1%; observation: 94%). Salvage surgery with adjuvant (chemo) radiation had better disease-specific survival than surgery alone or nonsurgical salvage.

**Conclusions:** In this cohort of patients with initially cN0 oral squamous cell carcinoma triaged to elective neck dissection vs. observation using clinical parameters, 15% developed neck failure. Salvage treatment

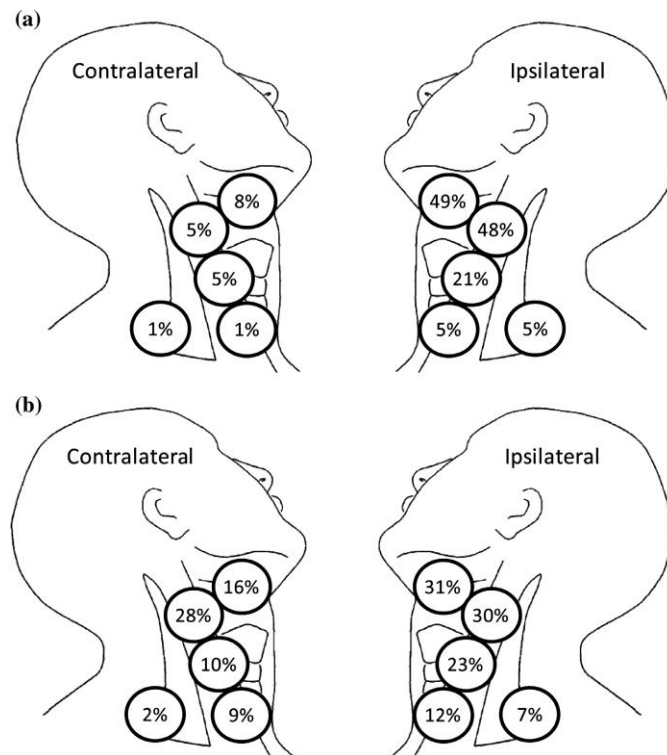
was feasible in most cases but survival was poorer compared to patients without neck failure. Surgery followed by adjuvant (chemo) radiation resulted in the best outcome.



**Neck recurrence-free survival.**



**Kaplan-Meier curves demonstrating disease-specific survival (DSS) by salvage treatment modality**



**(a) Anatomical illustration showing location and pattern of neck recurrence in patients in the observation, and (b) elective neck dissection groups**

### Strengths

- Well designed study
- 1302 patients with cN0 neck, were identified from a cohort of 1866 patients who underwent surgical resection in 27 year experience
- Provides data regarding regional recurrence rates in early stage oral cancers
- Schematic anatomical illustrations showing location, pattern of neck recurrence and each percentage in patients with recurrence, who recurred in specific level of the neck in observation and elective neck dissection groups.

### Weaknesses

- A large single-institution database, retrospective study.
- The decision of when to perform elective neck dissection is strongly influenced by patient and physician bias, as is the decision regarding postoperative adjuvant radiation. Unfortunately, such selection bias cannot be corrected for in retrospective studies and can only be addressed in properly conducted randomized controlled trials.
- The presence of misclassification bias. Before 90`s, they often did not perform CT or ultrasound imaging of the neck. The status of the neck was determined by clinical examination. This would overestimate the recurrence rate in the observation group and is another explanation for why the neck failure rate in their observation group was higher than expected.



## [Increasing Prevalence of Human Papillomavirus–Positive Oropharyngeal Cancers Among Older Adults](#)

Winston MJ, D'Souza G, Rettig EM, Westra WH, van Zante A, Wang SJ, Ryan WR, Mydlarz WK, Ha PK, Miles BA, Koch W, Gourin C, Eisele DW, Fakhry C

From **Cancer**, July 2018

**Background:** The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing among older adults. It is unknown whether these trends can be explained by human papillomavirus (HPV) and whether HPV-related tumors remain associated with an improved prognosis among older patients.

**Methods:** In a retrospective study of OPSCCs diagnosed from 1995 to 2013 at 2 National Comprehensive Cancer Network–designated cancer centers, p16 immunohistochemistry and in situ hybridization (ISH) for HPV-16, high-risk DNA, and/or E6/E7 RNA were performed. The median age at diagnosis was compared by p16 and ISH tumor status. Trends in age were analyzed with nonparametric trends. Survival was analyzed with the Kaplan-Meier method and Cox proportional hazards models.

**Results:** Among 239 patients, 144 (60%) were p16-positive. During 1998-2013, the median age increased among p16-positive patients ( $P_{\text{trend}} = .01$ ) but not among p16-negative patients ( $P_{\text{trend}} = .71$ ). The median age of p16-positive patients increased from 53 years (interquartile range [IQR] in 1995-2000, 45-65 years) to 58 years (IQR for 2001-2013, 53-64 years). Among patients 65 years old, the proportion of OPSCCs that were p16-positive increased from 41% during 1995-2000 to 75% during 2007-2013 ( $P_{\text{trend}} = .04$ ). Among all age groups, including older patients, a p16-positive tumor status conferred improved overall survival in comparison with a p16-negative status.

**Conclusions:** The median age at diagnosis for HPV-related OPSCC is increasing as the proportion of OPSCCs caused by HPV rises among older adults. The favorable survival conferred by an HPV-positive tumor status persists in older adults.

### **Summary:**

- Retrospective study of 2 institutions OP cases over 18 years, with centralized pathology testing in 2015
- Continuation / connected to a prior study published in 2017
- Provides prevalence information and demonstrates improved prognosis with P16 positive tumors among all age groups (young, middle, and older than 65)

### **Strengths:**

- One of the first studies that demonstrates the observed rise in OPSCC among older adults is driven by an increased prevalence of p16-positive tumors
- Highlights that HPV related OP cancer is not just a disease of the young

### **Weakness:**

- Small overall sample sizes per category

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