



# American Head and Neck Society - Journal Club

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*Table of Contents – [click the page number to go to the summary and full article link.](#)*

***New Feature: Journal Club Recommends:***

***Follicular Carcinoma: A Perspective by Dr. Gil Daniels*** *page 1*

*Meta-Analysis of Induction Chemotherapy as Selection Marker for Chemoradiation in the Head and Neck* *page 1*

*Surgical Management of Normocalcemic Primary Hyperparathyroidism and the Impact of Intraoperative Parathyroid Hormone Testing on Outcome* *page 3*

*Independent Predictors of Prognosis Based on Oral Cavity Squamous Cell Carcinoma Surgical Margins* *page 4*

*Primary Surgery-Versus Primary Radiation-Based Treatment for Locally Advanced Oropharyngeal Cancer* *page 6*

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### **NEW FEATURE: Journal Club Recommends...**

Dear AHNS Journal Club Readers,

During our monthly article selection process we on occasion encounter a “must read” review article by renowned experts in the field. This month’s selection included [Dr. Gil Daniels’ 40 year perspective on follicular carcinoma of the thyroid gland](#). Our understanding of this disease is constantly evolving and a review by one of our most senior endocrinology colleagues is one that every head and neck surgeon should have at their fingertips. We highly recommend that you download this and read it in its entirety as there is no summary that could do it justice!

We will from time to time include similar key reviews by eminent leaders in our field as we continue to do our best to highlight impactful head and neck articles. We hope you enjoy them!

*All the best from your AHNS Journal Club Committee*

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### **[Meta-Analysis of Induction Chemotherapy as Selection Marker for Chemoradiation in the Head and Neck](#)**

*Kiong, K.; Nisa de Souza, N.; Sultana, R; Gopalakrishna Iyer, N.*

*from Laryngoscope, July 2018*

**Objective:** Many trials incorporate induction chemotherapy (IC) in selecting for organ preservation in head and neck squamous cell carcinomas (HNSCC). However, few studies examine IC response in predicting for chemoradiation therapy (CRT) response. This meta-analysis aims to determine the predictive accuracy of IC for subsequent response to CRT and overall survival (OS). Data sources: Medline, EMBASE, Cochrane register.

**Methods:** A systematic search identified studies from database inception to October 2016 that used IC prior to CRT as definitive treatment for advanced HNSCC. The sensitivities and specificities of IC response predicting for complete CRT response were calculated, and the results were pooled in a summary receiver operating curve. One-, 2- and 5-year OS data were extracted.

**Results:** Seven studies (n= 423 patients) were analyzed for response and six (n= 439) for OS. Pooled median sensitivity and specificity of IC response predicting CRT response were 0.95 (95% confidence interval [CI]: 0.72–0.98) and 0.43 (95% CI: 0.00–0.61), respectively. Patients were more likely to respond to CRT given previous response to IC (positive likelihood ratio 5 1.6; 95% CI: 1.21–2.11) and less likely to respond to CRT if they failed to respond to IC (negative likelihood ratio 5 0.16; 95% CI: 0.07–0.38). At 2 years, good response to IC was a statistically significant prognostic marker with a risk ratio of 1.35 (95% CI: 1.12–1.64).

**Conclusion:** Our data suggests that patients with poor IC response will have poorer response to CRT and should be directed to other modalities. In contrast, good IC response does not guarantee a favorable outcome to CRT; however, because these patients are likely to have better prognoses, they should be offered salvage therapies of curative intent despite treatment failure.

### Summary

- Systematic review and meta-analysis methodology using the largest available databases, exploring the use of multiagent induction chemotherapy (IC) as chemoselection to decide to continue with CRT or go to total laryngectomy.
- The IC was analyzed as a diagnostic tool to predict complete response after CRT, exploring operative characteristics (sensitivity, specificity and positive and negative likelihood ratio) with updated and strong statistical tests. Also, a survival analysis was performed.
- 13 studies with 862 patients were included. 10 were rated with moderate to serious risk of bias.
- Median sensitivity and specificity for good response after CRT were 95% and 43%, respectively. Overall positive and negative likelihood ratio were 1.6 and 0.16, respectively.
- The overall survival rate of patients with good response to IC were higher than those without good response. (20% at 12 m and 35% at 24 m)

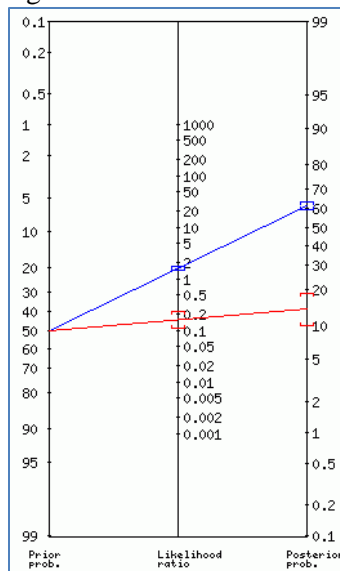
### Strengths

- Strong methodology using Cochrane standards.
- Response evaluated with objective measures as RECIST.
- Quality evaluation with Cochrane tool
- Results support the assumption that with a pretest probability of 50%, in case of poor response to IC, the probability of having a good response if CRT is done, is very low (14%). (Figure)

### Weaknesses

- Information about individual studies is lacking. There is a risk of bias for selecting only studies in English language.
- Nineteen studies were found, but only 13 were included due to incomplete data. Authors didn't get specific information from authors of original articles. The number of studies to evaluate each outcome was small.
- There is no report of the area under the ROC curve. The summary point is far from the left superior corner, which means it is not a good discriminator.
- Heterogeneity was high due to multiple combination of chemotherapy schemes.

Figure



From: <http://araw.mede.uic.edu/cgi-bin/testcalc.pl>

[back to top](#)

## [Surgical Management of Normocalcemic Primary Hyperparathyroidism and the Impact of Intraoperative Parathyroid Hormone Testing on Outcome](#)

*Trinh G, Rettig E, Noureldine SI, Russell JO, Agrawal N, Mathur A, Prescott JD, Zeiger MA, Tufano RP.*

*from Otolaryngology – Head & Neck Surgery, October 2018*

**Objective:** To review our surgical experience and the impact of intraoperative parathyroid hormone (IOPTH) testing among patients with normocalcemic primary hyperparathyroidism. Study Design Case series with chart review. Setting Academic referral hospital. Subject and Methods Normocalcemic hyperparathyroidism (NCHPT) patients were identified with normal-range blood ionized calcium and serum elevated parathyroid hormone. Patient demographics, intraoperative findings, IOPTH dynamics, and biochemical outcomes were compared with those of classic primary hyperparathyroidism (PHPT) patients. Results Of the 2120 patients who underwent parathyroidectomy, 616 patients met the inclusion criteria: 119 (19.5%) patients had NCHPT, and 497 (80.5%) had classic PHPT. NCHPT patients had higher rates of multigland hyperplasia as compared with classic PHPT (12% vs 4%,  $P = .002$ ) and smaller gland size ( $P < .001$ ). Of 119 NCHPT patients, 114 (97%) achieved  $>50\%$  drop in IOPTH intraoperatively, as opposed to 492 (99%) among 497 classic PHPT patients ( $P = .014$ ). IOPTH drop  $>50\%$  had an equivalent positive predictive value for long-term cure in both groups. Conclusions Surgeons treating NCHPT patients should suspect the presence of multigland disease and have a low threshold for converting to bilateral exploration depending on IOPTH decay dynamics.

**Summary:** As compared with classic PHPT patients, NCHPT patients have higher rates of multigland hyperplasia with smaller parathyroid glands resected. NCHPT patients may be treated with a targeted approach with IOPTH, but surgeons should have a low threshold to convert to bilateral exploration if only a small abnormal gland is discovered or if IOPTH does not drop by  $>50\%$  within 10 minutes.



### Strengths:

- Paper provides clear algorithms with risk analyses of operative outcomes and recurrence rates that can be shared with patients.
- Large sample size demonstrating potential pitfalls in surgical management of NCHPT and applicability of classic IOPTH-monitoring criteria to NCHPT patients.

### Weaknesses:

- used iCa to identify NCHPT patients for inclusion but total serum calcium as a secondary outcome.
- retrospective review design. Authors state it was not possible to use iCa as an outcome measure, owing to the clinical practice patterns that favor measuring serum calcium in follow-up for practical reasons.
- selection bias (patients were referred to a tertiary care center, which could include diagnostically equivocal patients or those with negative preoperative imaging)
- limited long-term follow-up.

**Table 2.** Operative Findings and Postoperative Recurrence Rates for All Patients.<sup>a</sup>

Operative Findings	Classic PHPT (n = 497)	NCHPT (n = 119)	P Value
Single adenoma	389 (78)	88 (74)	.34
Double adenoma	87 (18)	17 (14)	.37
Multigland hyperplasia	21 (4)	14 (12)	.002
Gland weight, mg			
Overall	1175 ± 2497	582 ± 887	<.001
Single-gland disease	1277 ± 2142	711 ± 996	<.001
Multigland hyperplasia	264 ± 281	133 ± 86	.02
IOPTH decay rate, pg/min <sup>b</sup>	-3.8 ± 1.9	-2.8 ± 1.5	.69
Single-gland disease	-3.9 ± 2.0	-3.0 ± 1.6	.74
Double adenoma	-3.5 ± 2.0	-2.2 ± 1.2	.60
Multi-gland hyperplasia	-3.3 ± 2.0	-1.6 ± 0.9	.47
IOPTH, %			
At 0 min	45 ± 22	49 ± 21	.04
At 5 min	37 ± 22	44 ± 23	.06
At 10 min	30 ± 19	38 ± 28	.002
At 20 min	24 ± 16	32 ± 22	.005
Recurrence			
Total serum calcium	5 of 356 (1.4)	3 of 90 (3.3)	.22
Serum PTH only	28 of 143 (19.6)	8 of 45 (17.8)	.80
Total serum calcium and PTH	1 of 143 (0.7)	0 of 45	.58

Abbreviations: IOPTH, intraoperative parathyroid hormone; NCHPT, normocalcemic hyperparathyroidism; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

<sup>a</sup>Postoperative recurrence defined as elevated laboratory values at ≥6 months: total serum calcium >10.5 mg/dL, serum PTH >65 pg/mL. Values are presented as n (%) or mean ± SD, unless noted otherwise.

<sup>b</sup>Mean ± SEM.

[back to top](#)

## Independent Predictors of Prognosis Based on Oral Cavity Squamous Cell Carcinoma Surgical Margins

*Buchakjian MR, Ginader T, Tasche KK, Pagedar NA, Smith BJ, Sperry SM.*

*from Otolaryngology – Head & Neck Surgery, October 2018*

**Objective:** To conduct a multivariate analysis of a large cohort of oral cavity squamous cell carcinoma (OCSCC) cases for independent predictors of local recurrence (LR) and overall survival (OS), with emphasis on the relationship between (1) prognosis and (2) main specimen permanent margins and intraoperative tumor bed frozen margins. Study Design Retrospective cohort study. Setting Tertiary academic head and neck cancer program. Subjects and Methods This study included 426 patients treated with OCSCC resection between 2005 and 2014 at University of Iowa Hospitals and Clinics. Patients underwent excision of OCSCC with intraoperative tumor bed frozen margin sampling and main specimen permanent margin assessment. Multivariate analysis of the data set to predict LR and OS was performed. Results Independent predictors of LR included nodal involvement, histologic grade, and main specimen permanent margin status. Specifically, the presence of a positive margin (odds ratio, 6.21; 95% CI, 3.3-11.9) or <1-mm/carcinoma in situ margin (odds ratio, 2.41; 95% CI, 1.19-4.87) on the main specimen was an independent predictor of LR, whereas intraoperative tumor bed margins were not predictive of LR on multivariate analysis. Similarly, independent predictors of OS on multivariate analysis included nodal involvement, extracapsular extension, and a positive main specimen margin. Tumor bed margins did not independently predict OS. Conclusion The main specimen margin is a strong independent predictor of LR and OS on multivariate analysis. Intraoperative tumor bed frozen margins do not independently predict prognosis. We conclude that emphasis should be placed on evaluating the main specimen margins when estimating prognosis after OCSCC resection.

### Summary:

- The results of this study are specifically applicable to a method of intraoperative margin sampling from the patient tumor bed and permanent margin sampling from the main specimen. They conclude that a positive margin on the main specimen predicts LR whereas tumor bed margins do not.
- Definition of margin status includes *positive*, if invasive cancer was present at the inked edge; *very close*, if <1 mm from the edge; *close*, if 1 to 5 mm from the edge; and *negative*, if invasive cancer was >5 mm from the edge. Carcinoma in situ (CIS) or dysplasia at the margin was also noted.

**Table 2.** Independent Predictors of Local Recurrence Based on Multivariate Analysis.<sup>a</sup>

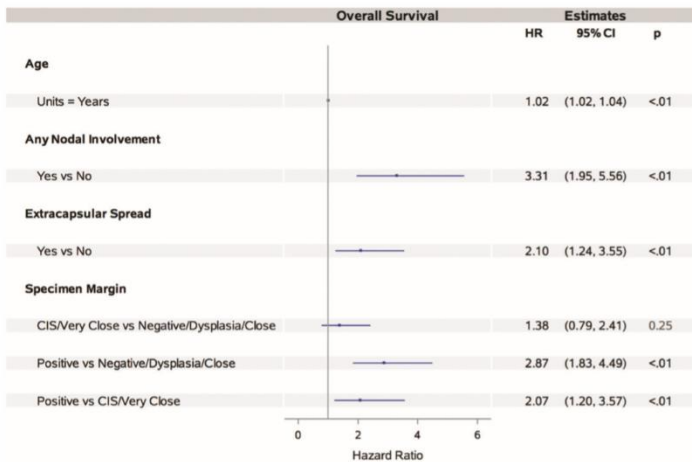
Covariate: Level	n	Local Recurrence		
		Odds Ratio	95% CI	P Value
<b>Any nodal involvement</b>				
Yes	89	2.77	1.50-5.12	<.01
No	269	Reference		
<b>Grade</b>				
Poor	60	3.49	1.76-6.94	<.01
Well	76	1.97	0.94-4.09	.07
Moderate	222	Reference		
<b>Specimen margin</b>				
CIS/very close	69	2.42	1.19-4.87	.01
Positive	80	6.21	3.30-11.93	<.01
Negative/dysplasia/close	209	Reference		

Abbreviation: CIS, carcinoma in situ.  
\*Bold indicates P < .05.

**Table 3.** Independent Predictors of Overall Survival Based on Multivariate Analysis.<sup>a</sup>

Covariate: Level	n	Overall Survival		
		Hazard Ratio	95% CI	P Value
Age	426	1.02	1.01-1.04	<.01
<b>Any nodal involvement</b>				
Yes	126	3.31	1.95-5.65	<.01
No	300	Reference		
<b>Extracapsular spread</b>				
Yes	74	2.10	1.24-3.55	.01
No	352	Reference		
<b>Specimen margin</b>				
CIS/very close	83	1.38	0.79-2.41	.26
Positive	99	2.87	1.83-4.49	<.01
Negative/dysplasia/close	244	Reference		

Abbreviation: CIS, carcinoma in situ.  
\*Bold indicates P < .05.



### Strengths

- This study attempts to include surgical margins in addition to pathological features and clinical variables to develop a prognostic model for LR and OS using a contemporary data set.
- Large data set evaluated from 2005 to 2014 which is more contemporary than previous papers addressing the same question.

### Weaknesses

- “Surgical technique included wide local excision with attempted 3-dimensional 1cm margins as able.” As oncologist, we will try to resect AT LEAST 1cm if not more usually. The generalizability of the data then comes into question.
- Retrospective and limited by inability to evaluate the technique of assessing intraoperative frozen sections directly from the main specimen.



## Primary surgery versus 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

**Objective:** Randomized data comparing surgery to radiation for locally advanced oropharyngeal cancer (OPC) are lacking. This study evaluated practice patterns and overall survival outcomes from the National Cancer Database.

**Methods:** A total of 22,676 patients with stage III to IV, locally advanced OPC were treated between 2004 to 2013 with primary chemoradiation (CRT) or surgery with adjuvant radiotherapy with or without chemotherapy (aRT +/- CT). Survival rates were estimated using the Kaplan-Meier method. Crude and adjusted hazard ratios (HR) were computed using Cox regression modeling.

**Results:** Median follow-up was 40.7 months; 8,555 and 14,121 patients received surgery with aRT +/- CT and CRT, respectively. Corresponding 3-year survival was 85.4% and 72.6% ( $P < 0.0001$ ). On multivariate analysis, adjusting for age, gender, race insurance status, median income, percentage with no high-school degree, Charlson-Deyo score, clinical tumor and node stage, tumor grade, facility type, treatment at  $> 1$  facility, and human papillomavirus (HPV) status, surgery with aRT +/- CT had a reduced hazard of death, HR, 0.79 (95% confidence interval 0.69–0.91),  $P = 0.001$ .

**Conclusion:** Primary surgery with aRT +/- CT for locally advanced OPC has an improved survival compared to primary radiation-based treatment even when stratified by HPV status.

### Summary

- There are no robust studies directly comparing primary surgical management with non-surgical management in locally advanced oropharyngeal carcinoma
- The NCDB provides an opportunity to pool the results of many institutions to indirectly compare similarly staged patients who were treated with surgery + aRT/CRT and definitive CRT.
- Primary surgical treatment was superior to primary radiation based treatment in all patients except those with very advanced disease (cT4N3)
- There are clear socioeconomic variables that affect survival.

### Strengths

- This database driven study attempted to overcome individualized treatment plans that may confound the outcome by performing a number of statistical analyses (propensity score-matching and missing data analysis).
- Over 1,500 hundred institutions contribute data to the NCDB, which aids in generalizing the analyzed survival outcomes.

### Weaknesses

- Nearly 1/3 of eligible patients had to be excluded secondary to missing data
- Retrospective large data set without smoking status, positive margin analysis and functional outcomes of treatment.
- HPV status was only available after 2010 for the cohort studied between 2004 and 2013

