American Head and Neck Society - Journal Club
Volume 41, March 2022

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Prospective Phase II Open-Label Randomized Controlled Trial to Compare Mandibular Preservation in Upfront Surgery with Neoadjuvant Chemotherapy Followed by Surgery in Operable Oral Cavity Cancer

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*From the **Journal Clinical Oncology**. January 2022*

Purpose: The objective of this study was to explore the potential role and safety of neoadjuvant chemotherapy (NACT) in tumor shrinkage and resultant mandibular preservation in oral cancers compared with conventional surgical treatment.

Methods: This study was a single-center, randomized, phase II trial of treatment-naive histologically confirmed squamous cell carcinoma of the oral cavity with cT2-T4 and N0/N+, M0 (American Joint Committee on Cancer, seventh edition) stage, necessitating resection of the mandible for paramandibular disease in the absence of clinicoradiologic evidence of bone erosion. The patients were randomly assigned (1:1) to either upfront surgery (segmental resection) followed by adjuvant treatment (standard arm [SA]) or two cycles of NACT (docetaxel, cisplatin, and fluorouracil) at 3-week intervals (intervention arm [IA]), followed by surgery dictated by postchemotherapy disease extent. All patients in the IA received adjuvant chemoradiotherapy, and patients in the SA were treated as per final histopathology report. The primary end point was mandible preservation rate. The secondary end points were disease-free survival and treatment-related toxicity.

Results: Sixty-eight patients were enrolled over 3 years and randomly assigned to either SA (34 patients) or IA (34 patients). The median follow-up was 3.6 years (interquartile range, 0.95-7.05 years). Mandibular preservation was achieved in 16 of 34 patients (47% [95% CI, 31.49 to 63.24]) in the IA. The disease-free survival (P = .715, hazard ratio 0.911 [95% CI, 0.516 to 1.607]) and overall survival (P = .747, hazard ratio 0.899 [95% CI, 0.510 to 1.587]) were similar in both the arms. Complications were similar in both arms, but chemotherapy-induced toxicity was observed in the majority of patients (grade III: 14, 41.2%; grade IV: 11, 32.4%) in the IA.

Conclusion: NACT plays a potential role in mandibular preservation in oral cancers with acceptable toxicities and no compromise in survival. However, this needs to be validated in a larger phase III randomized trial.

Strengths

- Randomized phase II surgical trial with adequately powered sample size
- Mandible was able to preserve in 47% of the neoadjuvant arm with no discernible different in survival and reported toxicity
- Decreased rates of ORN in neoadjuvant arm

Weaknesses

- Due to inability to adequately assess margins, all patients in the neoadjuvant arm were recommended to receive adjuvant chemoradiation thus potentially escalating therapy. This resulted in 16 in the primary surgical arm receiving CRT vs 26 in the neoadjuvant arm.
- 2 patients stopped treatment completed after receiving neoadjuvant therapy, 10 did not receive all cycles.
- More than 50% of patients (18/34) had either progression or stable disease after receiving neoadjuvant thus suggesting minimal benefit.

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Varied Recurrent Laryngeal Nerve Course Is Associated with Increased Risk of Nerve Dysfunction During Thyroidectomy: Results of the Surgical Anatomy of the Recurrent Laryngeal Nerve in Thyroid Surgery Study, an International Multicenter Prospective Anatomic and Electrophysiologic

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*From the **Thyroid.** November 2021*

Background: The recurrent laryngeal nerve (RLN) can be injured during thyroid surgery, which can negatively affect a patient's quality of life. The impact of intraoperative anatomic variations of the RLN on nerve injury remains unclear.

Objectives: of this study were to (1) better understand the detailed surgical anatomic variability of the RLN with a worldwide perspective, (2) establish potential correlates between intraoperative RLN anatomy and electrophysiologic responses; and (3) use the information to minimize complications and assure accurate and safe intraoperative neuromonitoring (IONM).

Methods: A large international registry database study with prospectively collected data was conducted through the International Neural Monitoring Study Group (INMSG) evaluating 1000 RLNs at risk during thyroid surgery using a specially designed online data repository. Monitored thyroid surgeries following standardized IONM guidelines were included. Cases with bulky lymphadenopathy, IONM failure, and failed RLN visualization were excluded. Systematic evaluation of the surgical anatomy of the RLN was performed using the International RLN Anatomic Classification System. In cases of loss of signal (LOS), the mechanism of neural injury was identified, and functional evaluation of the vocal cord was performed.

Results: A total of 1000 nerves at risk (NARs) were evaluated from 574 patients undergoing thyroid surgery at 17 centers from 12 countries and 5 continents. A higher-than-expected percentage of nerves followed an abnormal intraoperative trajectory (23%). LOS was identified in 3.5% of NARs, with 34% of LOS nerves following an abnormal intraoperative trajectory. LOS was more likely in cases of abnormal nerve trajectory, fixed splayed or entrapped nerves (including at the ligament of Berry), extensive neural dissection, cases of cancer invasion, or when lateral lymph node dissection was needed. Traction injury was found to be the most common form of RLN injury and to be less recoverable than previous reports.

Conclusions: Multicenter international studies enrolling diverse patient populations can help reshape our understanding of surgical anatomy during thyroid surgery. There can be significant variability in the anatomic and intraoperative characteristics of the RLN, which can impact the risk of neural injury.

Summary:

- Data are prospectively collected from 17 centers according to previously determined inclusion and exclusion criteria via a previously designed online system.
- 35 NARs showed LOS. Traction injuries are the most common cause of LOS and are less recoverable.
- 77% of NARs showed expected trajectory. Abnormal course of the RLN was associated with poorer outcome. This finding confirms the previously reported evidence from the literature. The rate of clinically overt VCP was on 38% calling for the need for routine postoperative laryngeal assessment. Risk factors associated with LOS on the left was BMI while lateral ND was associated with LOS on the right neck. Extensive neural dissection was significant risk factor for LOS. RLN on both sides was at risk of invasion by cancer. Total LOS was 3.5%; twice as high on the right than on the left (statistically insignificant).

Strengths:

- This is the first international prospective multicenter study addressing this topic.
- The predetermined inclusion and exclusion criteria, reporting system and previously designed online reporting system adds to the value of this study.
- The sample size is sufficient (n= 1000).

Weaknesses:

- Risk for selection bias as some authors failed to confirm adherence to the inclusion and exclusion criteria. The inhomogeneity of the sample caused by delayed contributions of some centers adds to this risk.
- Some data were subjectively judged by the surgeon like “symptomatic VCP”.
- Time frame for postoperative laryngeal examination was extended for 2 months which might have missed some cases with temporary nerve dysfunction.
- The limited number of nerves with LOS and VCP warrants further larger studies for more comprehensive interpretation of these findings.

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Patterns of Failure After Definitive Treatment of T4a Larynx Cancer

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From ***Otolaryngology Head and Neck Surgery.*** *October 2021*

Objective: Recurrence is known to predict laryngeal squamous cell cancer (LSCC) survival. Recurrence patterns in T4a LSCC are poorly characterized and represent a possible explanation for observed survival discrepancies by treatment rendered.

Methods: Patients with T4a LSCC between 2000 and 2017 were identified and stratified by treatment (chemoradiotherapy [CRT] vs total laryngectomy + neck dissection + adjuvant therapy [surgical]). Primary outcomes were locoregional and distant recurrence. Secondary outcomes of overall mortality, larynx cancer mortality, and noncancer mortality were evaluated in Cox and Fine-Gray models.

Results: A total of 1043 patients had comparable baseline demographics: 438 in the CRT group and 605 in the surgical group. Patients undergoing CRT had higher proportions of node positivity (64.6% vs 53.1%, P \.001). Locoregional and distant recurrence were less common in the surgical group (23.0% vs 37.2%, P \.001; 6.8% vs 13.3%, P \.001, respectively); however, distant metastatic rates did not differ within the N0 subgroup (P = .722). On multivariable regression, surgery demonstrated favorable locoregional recurrence (hazard ratio [HR], 0.49; 95% CI, 0.39-0.62; P \ .001), distant recurrence (HR, 0.47; 95% CI, 0.31-0.71; P \.001), overall mortality (HR, 0.75; 95% CI, 0.64-0.87; P \.001), and larynx cancer mortality (HR, 0.69; 95% CI, 0.56-0.85; P \.001).

Conclusion T4a LSCC survival discrepancies between surgical and nonsurgical treatment are influenced by varying recurrence behaviors. Surgery was associated with superior disease control and improved survival. Beyond the known benefit in locoregional control with surgery, there may be a protective effect on distant recurrence that depends on regional disease burden.

Summary Statements:

- Authors aim to further determine the differences in locoregional and distant recurrence in TL and CRT cohorts and how they may provide explanation on survival differences between two groups, specific to T4 disease as this cohort was underrepresented in the landmark VA larynx and RTOG 91-11 trial which shifted the paradigm for locoregionally advanced LSCC
- Surgery demonstrated significantly longer time to recurrence compared to CRT (47.2 v 30.5, $p < 0.001$)
- Locoregional failure more common in CRT group, regardless of nodal status
- Distant failure more common in CRT group compared to surgical group, with exception of N0 group where they were equivocal

- TL + adjuvant therapy improved overall survival compared to CRT ($P < 0.001$), driven by larynx cancer-specific mortality (no impact on non-cancer mortality)

Strengths:

- Large patient cohort in well-established oncologic database with homogenous treatment arms allowing for subset analysis, univariate,
- and multivariate analysis

Weaknesses:

- Retrospective design subject to selection bias for treatment selection (authors note that this may impact survival, but the limitation should not influence recurrence risk)
- Inaccuracies in medical documentation due to retrospective nature of study

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A Proposal for Risk-Based and Strategy-Adapted De-Escalation in Human Papillomavirus-Positive Oropharyngeal Squamous Cell Carcinoma

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*From **Cancer.** December 2021*

Treatment de-escalation for HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) has become a topic of interest as the current standard of care for treatment in this region was developed for HPV-negative cancers. Patients with HPV-associated OPSCC have a good response to therapy and prognosis in comparison to the negative disease when treated with the same regimen but the morbidity and long-term impacts on quality of life are significant. When assessing de-escalation defining the optimal cohort has been limited due to the variety of trials, and the current focus on an early stage and low risk patient – which inherently only addresses a small fraction of the overall patient population. Multiple approaches to de-escalation have been trialed, including reduction of dose, volume of RT, and omission reduction or substitution of cisplatin after surgery. In this commentary the group describes a schema for surgical and concurrent chemoradiation approaches to compare patients with low-risk disease, or sequential therapy compared to the standard of care for patients with advance/high risk disease.

Summary:

- Clinical prognostication methods: Overall, number of pack-years needs to be considered, but so should other smoking variables such as time from cessation and smoking status at cancer diagnosis. 8th Edition AJCC staging may not appropriately risk stratify and does not include granular staging factors. The role significance of ENE in HPV-positive disease is still yet to be determined and is up to variable determination.
- Based on the above it is difficult to define a optimal trial cohort. As a result, multiple clinical armed trials are needed to expand the trial patient population and allow for meaningfully different patient groups.

(Schema)

TABLE 1. Major Clinical Biomarkers in Human Papillomavirus-Positive Oropharyngeal Squamous Cell Carcinoma and Examples of Associated Controversies

AJCC 7 Tumor Classification	Smoking Pack-Years	Pathologic ENE, 2 mm	Positive Margins
T4 → worse PFS (ECOG 1308; Marur 2017[32]) and DC (O'Sullivan 2013[31])	10 (RTOG 0129; Ang 2010[1]) vs 20 (Princess Margaret; Huang 2015[27])	Worse LRC (MC1273; Ma 201941), DC/PFS (Shevach 2017[34]), and OS (An 2017[33]) vs no effect on RFS (Kharytaniuk 2016[35]) or DSS (Sinha 2015[36])	Worse DSS (Sinha 2015[36]) vs no effect on DSS (Iyer 2015[39])
AJCC 7 Lymph Node Status	**Smoking Status**	**Radiographic ENE**	**Medical Comorbidities**
N2c → worse PFS (ECOG 1308; Marur 2017[32]); N3 → worse DC (O'Sullivan 2013[31])	Active smoking → worse PFS (Broughman 2020[28]) and OS (Mirghani 2018,[29] Xiao 2020[30])	Worse DFS (Billfalk-Kelly 2019[38]) vs no effect on OS/PFS/DC/LRC (Liu 2016[37])	ACE-27 score 2-3 → worse OS (Deschuymer 2018[40])

Abbreviations: ACE-27, Adult Comorbidity Evaluation 27; AJCC 7, American Joint Committee on Cancer AJCC Cancer Staging Manual, 7th edition; DC, distant control; DFS, disease-free survival; DSS, disease-specific survival; ECOG, Eastern Cooperative Oncology Group; ENE, extranodal extension; LRC, locoregional control; OS, overall survival; Princess Margaret, Princess Margaret Cancer Center/Princess Margaret Hospital; PFS, progression-free survival; RFS, recurrence-free survival; RTOG, Radiation Therapy Oncology Group.

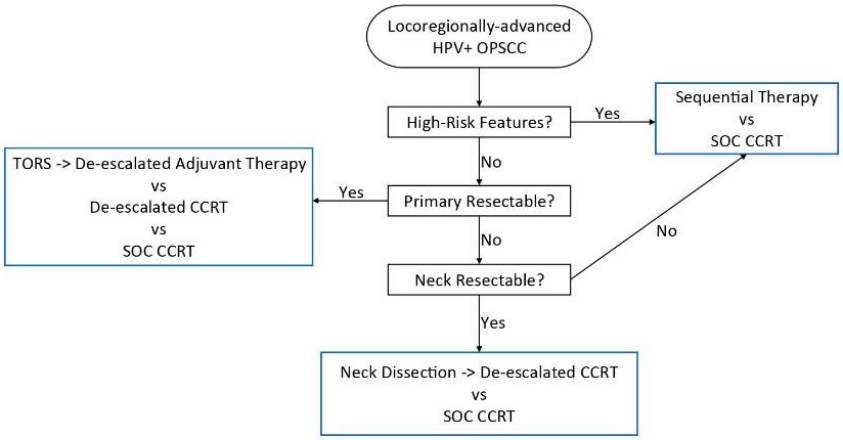

Figure 1. The clinical trial schema is illustrated for risk-based and strategy-adapted de-escalation in human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC). CCRT indicates concurrent chemoradiation; SOC, standard of care; TORS, transoral robotic surgery.

• First arm includes patients with high-risk features (high stage, large nodal burden, former smoking)- enrolled into induction chemotherapy. Experimental arm- induction, assess response, then de-escalated RT with lower RT dose/volume. Control arm- standard CCRT. [De-escalated sequential therapy and current SOC CCRT]
• Second arm involves surgical candidacy. Includes patients with resectable disease without high-risk features. Experimental arm- TORs followed by reduced RT dose/volume based on ENE and margin status. Experimental arm- CCRT with upfront reduction of RT dose/volume. Control arm- standard CCRT.

• Third arm for inoperable primary disease patients without high-risk features. Experimental arm- pretreatment neck dissection followed by CRT with reduced RT dose/volume. Control arm- standard CCRT.

Strengths:
• Strong initial sections discussing some of the nuances of attempts at de-escalation currently for HPV+OPSCC. Salient highlights of the approaches to specific risk factors (smoking, staging, nodal burden, pathologic & radiologic ENE), and the actual meaning of these factors.
• Comprehensive summary of the current trials and the takeaway points of key comparative groups
• Attempts to describe 3 types of trials that can go on to appropriately address the absence of data in specific patient populations and head-to-head comparisons.
• Graphic of schema is straightforward and easy to follow

Weaknesses:
• Ultimately is a pure commentary on the current data, acts like a literature review without the formal analysis of each trial.
• Comments directed to group specific trials that are being run, useful but challenging in context for those not familiar with trials like SIRS.

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Histopathology of Parotid Pleomorphic Adenomas: A "Pleomorphic Approach" to a Demanding Lesion

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*From **Laryngoscope.** July 2021*

Objectives: The aim of this study was to identify potential associations between epidemiologic, morphologic, and histopathologic features in pleomorphic adenomas (PAs) of the parotid gland to extract information about the natural course and biologic behavior of these lesions on the basis of a single-center series of 845 cases within a period of 15 years.

Methods: For this study, an experienced head and neck pathologist critically re-evaluated the histological slides of the pathological specimens of all patients who underwent a parotidectomy for PA of the parotid gland between 2006 and 2020.

Results: A total of 845 cases made up our study sample. Our analysis showed a statistically significant association of the histologic subtype with younger age (P = .001) and maximal diameter (P = .044), with the hypocellular type being encountered more often in younger patients and in smaller lesions. The same subtype was significantly associated with an incomplete capsule (P = .001), pseudopodia (P = .006), and satellite nodules (P = .001). An incomplete capsule was associated with the presence of pseudopodia (P = .001) and satellite nodules (P = .001).

Conclusion: It seems that various histologic subtypes have different capsule-producing properties. Apparently, over the course of time, tumor material builds a finger-like projection still inside the capsule, separates itself from the parenchyma with fibrous tissue still remaining

enclosed within the capsule (pseudopodium), slowly penetrates the capsule (incomplete capsule), and leaves the main lesion taking a part of the capsule with it (satellite nodules).

Summary statements:

- The problem addressed indirectly is of undisputed clinical importance: why pleomorphic adenoma recurs? A second related issue is what is the appropriate surgical margin and thus the procedure for pleomorphic adenoma.
- A re-examination of parotidectomy specimen by a single pathologist of a large number of cases (845) from a single institution was undertaken retrospectively. Statistical correlations were sought among different clinical (tumor size), patient-related (age, gender) and pathological variables (cellular subtype, incomplete tumor capsule, pseudopodia, satellite nodules).
- Hypocellular pleomorphic adenoma are found more often in younger patients with smaller tumors. Hypocellular pleomorphic adenoma are associated with incomplete capsules, pseudopodia, and satellite nodules.

Strengths:

- Large number of parotidectomy specimen.
- Evaluation by a single pathologist.
- Relatively well-defined criteria for pathological variables.
- Definitive confirmation that the subtype of pleomorphic adenoma is associated with other clinical and pathologic factors.

Weaknesses:

- Evaluation by a single pathologist.
- Lack of evaluation of the relationship between clinical and pathologic variables with the important clinical issues (recurrence and type of surgery).

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