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Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002)

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*From the **Clinical Oncology**. March 2021.*

Purpose: Reducing radiation treatment dose could improve the quality of life (QOL) of patients with good-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma (OPSCC). Whether reduced-dose radiation produces disease control and QOL equivalent to standard chemoradiation is not proven.

Patients and methods: In this randomized, phase II trial, patients with p16-positive, T1-T2 N1-N2b M0, or T3 N0-N2b M0 OPSCC (7th edition staging) with ≤ 10 pack-years of smoking received 60 Gy of intensity-modulated radiation therapy (IMRT) over 6 weeks with concurrent weekly cisplatin (C) or 60 Gy IMRT over 5 weeks. To be considered for a phase III study, an arm had to achieve a 2-year progression-free survival (PFS) rate superior to a historical control rate of 85% and a 1-year mean composite score ≥ 60 on the MD Anderson Dysphagia Inventory (MDADI).

Results: Three hundred six patients were randomly assigned and eligible. Two-year PFS for IMRT + C was 90.5% rejecting the null hypothesis of 2-year PFS $\leq 85\%$ ($P = .04$). For IMRT, 2-year PFS was 87.6% ($P = .23$). One-year MDADI mean scores were 85.30 and 81.76 for IMRT + C and IMRT, respectively. Two-year overall survival rates were 96.7% for IMRT + C and 97.3% for IMRT. Acute adverse events (AEs) were defined as those occurring within 180 days from the end of treatment. There were more grade 3-4 acute AEs for IMRT + C (79.6% v 52.4%; $P < .001$). Rates of grade 3-4 late AEs were 21.3% and 18.1% ($P = .56$).

Conclusion

The IMRT + C arm met both prespecified end points justifying advancement to a phase III study. Higher rates of grade ≥ 3 acute AEs were reported in the IMRT + C arm.

SUMMARY STATEMENTS:

- Randomized trial which demonstrates an improved 2-year PFS with a reduced-dose radiation regimen (60 Gy) plus concurrent cisplatin relative to historical disease control rates for traditional treatment regimens (70 Gy plus concurrent platinum-based chemotherapy), justifying advancement to phase III trial for this treatment arm
- Patients who underwent a reduced dose radiation regimen (60 Gy) alone without concurrent chemotherapy notably enjoyed a 2-year PFS of 88%, but this was statistically not significantly better than historical control rates to justify a phase III trial for this treatment arm
- At one year, there was no significant difference between composite swallowing MDADI scores between the IMRT (60 Gy) alone and IMRT (60 Gy) plus cisplatin treatment arms.



Strengths

- Well-designed randomized trial which establishes the efficacy of a de-escalated upfront nonsurgical treatment regimen for low-risk HPV+ SCC of the oropharynx
- Incorporates functional data (composite MDADI swallowing scores) in addition to traditional outcomes data (PFS, OS) to allow comparison of short-term functional outcomes between these de-escalated treatment regimens.

Weaknesses

- No functional MDADI data was provided (and presumably was not available) for traditional treatment regimens (70Gy + chemotherapy) to which to compare the functional outcomes of the presented de-escalated regimens
- 1 year time point for functional swallowing outcomes as assessed by MDADI does not capture important longer-term functional differences between traditionally-dosed and reduced-dosed radiation

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[Phase II Randomized Trial of Transoral Surgery and Low-Dose Intensity Modulated Radiation Therapy in Resectable p16+ Locally Advanced Oropharynx Cancer: An ECOG-ACRIN Cancer Research Group Trial \(E3311\)](#)

Ferris RL, Flamand Y, Weinstein GS, Li S, Quon H, Mehra R, Garcia JJ, Chung CH, Gillison ML, Duvvuri U, O'Malley BW Jr, Ozer E, Thomas GR, Koch WM, Gross ND, Bell RB, Saba NF, Lango M, Méndez E, Burtness B.

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

Purpose: Definitive or postoperative chemoradiation (CRT) is curative for human papillomavirus–associated (HPV+) oropharynx cancer (OPC) but induces significant toxicity. As a deintensification strategy, we studied primary transoral surgery (TOS) and reduced postoperative radiation therapy (RT) in intermediate-risk HPV+ OPC.

Methods: E3311 is a phase II randomized trial of reduced- or standard-dose postoperative RT for resected stage III-IVa (American Joint Committee on Cancer-seventh edition) HPV+ OPC, determined by pathologic parameters. Primary goals were feasibility of prospective multi-institutional study of TOS for HPV+ OPC, and oncologic efficacy (2-year progression-free survival) of TOS and adjuvant therapy in intermediate-risk patients after resection. TOS plus 50 Gy was considered promising if the lower limit of the exact 90% binomial confidence intervals exceeded 85%. Quality of life and swallowing were measured by functional assessment of cancer therapy-head and neck and MD Anderson Dysphagia Index.

Results: Credentialed surgeons performed TOS for 495 patients. Eligible and treated patients were assigned as follows: arm A (low risk, n = 38) enrolled 11%, intermediate risk arms B (50 Gy, n = 100) or C (60 Gy, n = 108) randomly allocated 58%, and arm D (high risk, n = 113)

enrolled 31%. With a median 35.2-month follow-up for 359 evaluable (eligible and treated) patients, 2-year progression-free survival Kaplan-Meier estimate is 96.9% (90% CI, 91.9 to 100) for arm A (observation), 94.9% (90% CI, 91.3 to 98.6) for arm B (50 Gy), 96.0% (90% CI, 92.8 to 99.3) for arm C (60 Gy), and 90.7% (90% CI, 86.2 to 95.4) for arm D (66 Gy plus weekly cisplatin). Treatment arm distribution and oncologic outcome for ineligible or step 2 untreated patients (n = 136) mirrored the 359 evaluable patients. Exploratory comparison of functional assessment of cancer therapy-head and neck total scores between arms B and C is presented.

Conclusion

Primary TOS and reduced postoperative RT result in outstanding oncologic outcome and favorable functional outcomes in intermediate-risk HPV+ OPC.

Summary Statements:

- This multicenter phase II randomized trial sets a benchmark for safety, oncologic outcomes, as well as swallowing and quality of life outcomes for a large cohort of patients across multiple centers.
- Arms B and C of the study, comparing standard adjuvant radiation (60Gy) to a deintensified regimen (50Gy), and demonstrate equivalent survival outcomes in patients with intermediate risk factors that classically require adjuvant radiation alone.

Strengths

- With generalizable results across 87 surgeons and 59 sites, this study demonstrated excellent safety with a post-operative bleed rate of ~6% and only one grade V event due to oropharyngeal bleeding (occurring prior to mandated vessel ligation during neck dissection).
- This study has clear objectives and an appropriate design which allowed for timely patient accrual and straightforward statistical analysis.
- The study has excellent follow-up with over 90% of patients having greater than 30 months follow-up.

Weaknesses

- The 30% of the patient population consisted of patients in arm D. Additional study is needed to determine whether subsets of this population can undergo deintensification of adjuvant radiation (i.e., patients with >1mm extranodal extension) or whether additional systemic therapies can be offered to limit regional and distant metastatic recurrence in this high-risk group.
- Although the majority of patients diagnosed with HPV-associated oropharyngeal cancer are white males, the limited enrollment of patients outside of this demographic prevents additional analysis.
- While the initial study design was limited in terms of its functional assessment and quality of life measures, more robust patient reported outcomes in such a large, multicenter study would have been a welcome addition to the literature.

Randomized Trial of Radiotherapy Versus Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma: Long-Term Results of the ORATOR Trial

Anthony C Nichols, Julie Theurer, Eitan Prisman, Nancy Read, Eric Berthelet, Eric Tran, Kevin Fung, John R de Almeida, Andrew Bayley, David P Goldstein, Michael Hier, Khalil Sultanem, Keith Richardson, Alex Mlynarek, Sureen Krishnan, Hien Le, John Yoo, S Danielle MacNeil, Eric Winquist, J Alex Hammond, Varagur Venkatesan, Sara Kuruvilla, Andrew Warner, Sylvia Mitchell, Jeff Chen, Martin Corsten, Stephanie Johnson-Obaseki, Michael Odell, Christina Parker, Bret Wehrli, Keith Kwan, David A Palma.

*From the **Clinical Oncology**. March 2022.*

Purpose: The incidence of oropharyngeal squamous cell carcinoma (OPSCC) has risen rapidly, because of an epidemic of human papillomavirus infection. The optimal management of early-stage OPSCC with surgery or radiation continues to be a clinical controversy. Long-term randomized data comparing these paradigms are lacking.

Methods: We randomly assigned patients with T1-T2, N0-2 (≤ 4 cm) OPSCC to radiotherapy (RT) (with chemotherapy if N1-2) versus transoral robotic surgery plus neck dissection (TORS + ND) (with or without adjuvant therapy). The primary end point was swallowing quality of life (QOL) at 1-year using the MD Anderson Dysphagia Inventory. Secondary end points included adverse events, other QOL outcomes, overall survival, and progression-free survival. All analyses were intention-to-treat. Herein, we present long-term outcomes from the trial.

Results: Sixty-eight patients were randomly assigned ($n = 34$ per arm) between August 10, 2012, and June 9, 2017. Median follow-up was 45 months. Longitudinal MD Anderson Dysphagia Inventory analyses demonstrated statistical superiority of RT arm over time ($P = .049$), although the differences beyond 1 year were of smaller magnitude than at the 1-year timepoint (year 2: 86.0 ± 13.5 in the RT arm v 84.8 ± 12.5 in the TORS + ND arm, $P = .74$; year 3: 88.9 ± 11.3 v 83.3 ± 13.9 , $P = .12$). These differences did not meet the threshold to qualify as a clinically meaningful change at any timepoint. Certain differences in QOL concerns including more pain and dental concerns in the TORS + ND arm seen at 1 year resolved at 2 and 3 years; however, TORS patients started to use more nutritional supplements at 3 years ($P = .015$). Dry mouth scores were higher in RT patients over time ($P = .041$).

Conclusion

On longitudinal analysis, the swallowing QOL difference between primary RT and TORS + ND approaches persists but decreases over time. Patients with OPSCC should be informed about the pros and cons of both treatment options (ClinicalTrials.gov identifier: [NCT01590355](https://clinicaltrials.gov/ct2/show/study/NCT01590355)).

Summary Statements:

- Long-term analysis of a prospective randomized trial comparing nonsurgical therapy to surgical therapy for oropharynx cancer.
- Swallowing QOL differences between primary RT and Surgery approaches decreased overtime in their cohort.



- Other QOL differences were identified longer term. For example, dry mouth scores were higher in RT patients over time.

Strengths:

- Randomized trial of chemoradiation vs. surgery for oropharynx cancer.
- Long median follow up of 45 months to show long term oncologic outcomes and functional outcomes such as swallowing.

Weaknesses:

- Small sample size of 68 patients (34 in each arm).
- Adjuvant therapy utilized in this study may not be what is currently prescribed at other institutions regarding dose and volume.

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Oncologic outcomes of human papillomavirus-associated oropharynx carcinoma treated with surgery alone: A 12-institution study of 344 patients

William R Ryan, Mary J Xu, Edgar Ochoa, Karolina A Plonowska-Hirschfeld, Aaron L Zebolsky Patrick K Ha, Arnaud F Bewley, Jonathan Mallen-St Clair, Arjun S Joshi, Charles S Coffey, Farhoud Faraji, Bridget V MacDonald, Jeffrey J Houlto, Theodore A Gobillot, Joseph M Curry, Ramez Philips, Trevor G Hackman, Jeremy D Richmon, Andrew J Holcomb, Andrew M Coughlin, Aru Panwar, Russell B Smith, Matthew E Herberg, Carole Fakhry, David M Cognetti

*From the **Cancer**. September 2021.*

Background: The oncologic outcomes of surgery alone for patients with American Joint Committee on Cancer 7th edition (AJCC 7th) pN2a and pN2b human papillomavirus-associated oropharynx squamous cell carcinoma (HPV+OPSCC) are not clear.

Methods: The authors performed a 12-institution retrospective study of 344 consecutive patients with HPV+OPSCC (AJCC 7th pT0-3 N3 M0) treated with surgery alone with 6 months or more of follow-up using univariate and multivariate analyses.

Results: The 2-year outcomes for the entire cohort were 91% (182 of 200) disease-free survival (DFS), 100% (200 of 200) disease-specific survival (DSS), and 98% (200 of 204) overall survival (OS). The 18 recurrences within 2 years were 88.9% (16 of 18) local and/or regional recurrences and 11.1% (2 of 18) distant metastases. Recurrences were not significantly associated with smoking, pT stage, or pN stage. The 16 patients with locoregional recurrences within 2 years all underwent successful salvage treatments (median follow-up after salvage: 13.1 months), 43.8% (7 of 16) of whom underwent salvage surgery alone for a 2-year overall salvage radiation need of 4.5% (9 of 200). The 2-year outcomes for the 59 evaluable patients among the 109 AJCC 7th pT0-2 N2a-N2b patients with 1 to 3 pathologic lymph nodes (LNs) were as follows: local recurrence, 3.4% (2 of 59); regional recurrence, 8.4% (5 of 59); distant metastases, 0%; DFS, 88.1% (52 of 59); DSS, 100% (59 of 59); OS, 96.7% (59 of 61); and salvage radiation, 5.1% (3 of 59).



Conclusions: With careful selection, surgery alone for AJCC 7th pT0-T2N0-N2b HPV+OPSCC with zero to 3 pathologic LNs without perineural invasion, extranodal extension, or positive margins results in high DFS, DSS, OS, and salvage treatment success. Because of the short-term follow-up, these data support further investigation of treatment de-escalation in this population.

Summary Statements:

- This is the largest known multicenter study looking at the outcome of HPV+ Oropharyngeal carcinoma (OCC) treated with surgery alone.
- Low stage HPV+ OCC characterized as T (AJCC 7th pT0-2) and N (AJCC 8th N0-N1, <3 nodes positive and no extranodal extension) have a favorable outcome with surgery alone with roughly 7% recurrence rate.
- Clinicopathologic variables, in particular Lymphovascular invasion (LVSI) and perineural invasion (PNI) were independent risk factors for local and regional recurrence.

Strengths:

- Multicenter trial which involved 12 different institutions and included data from 30 separate surgeons.
- Broad inclusion criteria which is applicable to the vast majority of patients presenting with low-risk HPV+ OCC.

Weakness:

- Retrospective study design with out a comparison to other potential de-escalation treatment strategy.
- Relatively short-term follow up, with on 200 patients (59.3%) with 2-year follow up and only 140 patients (40.7%) with 3 years follow up.
- Authors focused only on oncologic results without assessment of short or long-term functional outcomes.

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[Cell-free human papillomavirus DNA kinetics after surgery for human papillomavirus-associated oropharyngeal cancer](#)

O'Boyle CJ, Siravegna G, Varmeh S, Queenan N, Michel A, Pang KCS, Stein J, Thierauf JC, Sadow PM, Faquin WC, Wang W, Deschler DG, Emerick KS, Varvares MA, Park JC, Clark JR, Chan AW, Busse PM, Corcoran RB, Wirth LJ, Lin DT, Iafrate AJ, Richmon JD, Faden DL.

*From the **Cancer**. March 2022 .*

Background: New ultrasensitive methods for detecting residual disease after surgery are needed in human papillomavirus–associated oropharyngeal squamous cell carcinoma (HPV+OPSCC).

Methods: To determine whether the clearance kinetics of circulating tumor human papillomavirus DNA (ctHPVDNA) is associated with postoperative disease status, a prospective observational study was conducted in 33 patients with HPV+OPSCC undergoing surgery. Blood was collected before surgery, postoperative days 1 (POD 1), 7, and 30 and with follow-up. A

subcohort of 12 patients underwent frequent blood collections in the first 24 hours after surgery to define early clearance kinetics. Plasma was run on custom droplet digital polymerase chain reaction (ddPCR) assays for HPV genotypes 16, 18, 33, 35, and 45.

Results: In patients without pathologic risk factors for recurrence who were observed after surgery, ctHPVDNA rapidly decreased to <1 copy/mL by POD 1 (n = 8/8). In patients with risk factors for macroscopic residual disease, ctHPVDNA was markedly elevated on POD 1 (>350 copies/mL) and remained elevated until adjuvant treatment (n = 3/3). Patients with intermediate POD 1 ctHPVDNA levels (1.2-58.4 copies/mL) all possessed pathologic risk factors for microscopic residual disease (n = 9/9). POD 1 ctHPVDNA levels were higher in patients with known adverse pathologic risk factors such as extranodal extension >1 mm ($P = .0481$) and with increasing lymph nodes involved ($P = .0453$) and were further associated with adjuvant treatment received ($P = .0076$). One of 33 patients had a recurrence that was detected by ctHPVDNA 2 months earlier than clinical detection.

Conclusions: POD 1 ctHPVDNA levels are associated with the risk of residual disease in patients with HPV+OPSCC undergoing curative intent surgery and thus could be used as a personalized biomarker for selecting adjuvant treatment in the future.

Summary Statements

- This report describes results from a study examining the clearance kinetics of circulating tumor HPV DNA (circulating tumor human papillomavirus DNA [ctHPVDNA]) following surgical treatment of HPV+OPSCC.
- The authors found that ctHPVDNA levels 1 day after surgery are associated with the risk of residual disease in patients with HPV+OPSCC and thus could be used as a personalized biomarker for selecting adjuvant treatment in the future.
- These findings are the first to demonstrate the potential utility of ctHPVDNA in patients with HPV+OPSCC undergoing surgery.

Strengths

- Novel study of circulating tumor HPV DNA within a surgical cohort demonstrating the risk of elevated post-operative ctHPVDNA levels stratified by a large and clinically relevant collection of pathologic risk factors.
- This study demonstrates the rapid clearance of ctHPVDNA resulting in stable post-operative levels 24 hours following surgery

Weaknesses

- Small number of patients combined with a heterogenous number of demographic and pathologic risk factors, and a low number of recurrences/distant metastases limits the ability to extrapolate these findings to broader cohort of patients.

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