original report

Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

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abstract

PURPOSE To report the results of a phase II clinical trial of de-intensified chemoradiotherapy for patients with human papillomavirus–associated oropharyngeal squamous cell carcinoma.

MATERIALS AND METHODS Major inclusion criteria were (1) having American Joint Committee on Cancer (AJCC) 7th edition T0-T3, N0-N2c, M0 (AJCC 8th edition T0-T3, N0-N2, M0), (2) being p16 positive, and (3) reporting minimal or remote smoking history. Treatment was limited to 60 Gy intensity-modulated radiotherapy with concurrent intravenous cisplatin 30 mg/m^2 once per week. Patients with T0-T2 N0-1 (AJCC 7th edition) did not receive chemotherapy. All patients had a 10- to 12-week post-treatment positron emission tomography/computed tomography to assess for neck dissection. The primary end point was 2-year progression-free survival. Secondary end points included 2-year local-regional control, distant metastasis-free survival and overall survival, and patient-reported outcomes (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events).

RESULTS One hundred fourteen patients were enrolled (median follow-up of 31.8 months), with 81% having a minimum follow-up of 2 years. Eighty percent of patients had 10 or fewer tobacco pack-years. Two-year local-regional control, distant metastasis-free survival, progression-free survival, and overall survival were as follows: 95%, 91%, 86%, and 95%, respectively. Mean pre- and 2-year post-treatment European Organisation for Research and Treatment of Cancer quality of life scores were as follows: global, 79/84 (lower worse); swallowing, 8/9 (higher worse); and dry mouth, 14/45 (higher worse). Mean pre- and 2-year post-treatment patient-reported outcomes version of the Common Terminology Criteria for Adverse Events scores (0 to 4 scale, higher worse) were as follows: swallowing, 0.5/0.7, and dry mouth, 0.4/1.3. Thirty-four percent of patients required a feeding tube (median, 10.5 weeks; none permanent). There were no grade 3 or higher late adverse events.

CONCLUSION Clinical outcomes with a de-intensified chemoradiotherapy regimen of 60 Gy intensity-modulated radiotherapy with concurrent low-dose cisplatin are favorable in patients with human papillomavirus–associated oropharyngeal squamous cell carcinoma. Neither neoadjuvant chemotherapy nor routine surgery is needed to obtain favorable results with de-escalation.

J Clin Oncol 37:2661-2669. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 19, 2019 and published at jco.org on August 14, 2019: DOI https://doi.org/10.1200/JCO.19.01007

Clinical trial information: NCT02281955.

INTRODUCTION

Cancer control and survival are excellent in patients with human papillomavirus (HPV)–associated oropharyngeal squamous cell carcinoma (OPSCC),[1] but standard chemoradiotherapy (CRT) regimens produce substantial toxicity.[2] Over the past 10 years, there has been avid interest in evaluating less intensive treatment regimens with the goals of maintaining excellent cancer control and decreasing toxicity. Several different approaches to de-intensify therapy have been or are being studied, with varying degrees of actual de-intensification.[3-9] The most common approaches have been to (1) decrease the radiation dose while increasing the chemotherapy dose (ie, addition of neoadjuvant chemotherapy), (2) decrease the radiation dose by adding transoral surgery, or (3) substituting cetuximab for cisplatin.[4,8,10-12]

In 2011, we initiated a program of de-intensification with a reduction in radiation and chemotherapy dose without adding neoadjuvant chemotherapy or definitive surgery. Our de-intensified CRT regimen consisted of 60 Gy (2 Gy/fx, once per day) intensity-modulated radiotherapy (IMRT) with concurrent cisplatin 30 mg/m^2 (cumulative, 180 mg/m^2) once per week for 6 weeks. In our first phase II study, the primary end point was pathologic complete response (CR).[9] All patients had a planned biopsy of the primary site and selective neck dissection. In 2011, the concept of de-intensification was so new that we designed

our protocol with a pathologic end point so that we would know as quickly as possible if tumor control was being compromised. The results of the first phase II trial were as follows: a pathologic CR rate of 86% and 3-year progression-free survival (PFS) and overall survival (OS) rates of 100%.[9,13] Patients reported favorable long-term quality of life (QOL), with swallowing function returning to baseline and continued improvement in xerostomia symptoms after 1 year.[9,13,14] A major criticism and limitation of this trial was the possibility that the biopsy of the primary site and neck dissection was therapeutic (ie, patients were possibly receiving trimodality therapy).[15]

The next logical step was to conduct a second-generation study that did not mandate post-CRT biopsy and selective neck dissection. We conducted a second phase II study from 2014 to 2017 evaluating the same de-intensified CRT regimen but using the post-treatment (10 to 16 weeks) positron emission tomography (PET)/computed tomography (CT) assessment to guide the biopsy/surgical intervention. We herein report 2-year cancer control, survival, and patient-reported outcomes.

MATERIALS AND METHODS

Study Design and Eligibility

This phase II study was registered with the National Cancer Institute and was approved by the institutional review boards at the participating centers. All patients provided written informed consent. Enrolling institutions included the University of North Carolina Hospitals (Chapel Hill, NC), University of Florida Hospitals (Gainesville, FL), Rex Hospital (Raleigh, NC), High Point Regional Cancer Center (High Point, NC), and Pardee Hospital (Hendersonville, NC).

Eligible patients had untreated, pathologically confirmed p16 positive squamous cell carcinoma of the oropharynx or from an unknown head and neck primary site; were 18 years of age or older; had American Joint Committee on Cancer (AJCC) 7th edition T0-T3, N0-N2c, M0 (AJCC 8th edition T0-T3, N0-N2, M0); reported 10 pack-years or less of smoking history or 30 pack-years or less and abstinence for the past 5 years; had an Eastern Cooperative Oncology Group performance status of 0 to 1; had adequate hematologic, renal, and liver function; and had no history of prior head and neck cancers. Human papilloma virus and p16 were analyzed per institutional standards by florescence in-situ hybridization or immune histochemistry; p16 positivity was defined as more than 70% of carcinoma cells showing nuclear reactivity.

Study Treatment

All patients had standard-of-care pretreatment evaluations and staging procedures, including (1) a complete history and physical examination (including fiber optic nasolaryngopharyngoscopy), (2) panendoscopy with directed biopsies and tonsillectomies if the primary was unknown, (3) at least one diagnostic contrasted neck and chest CT, and (4) standard hematologic, liver, and renal blood studies. No patients had a definitive surgery (ie, transoral resection).

De-Intensified CRT

All patients were treated with IMRT. The total dose to the high-risk regions was 60 Gy at 2 Gy per fraction, 30 fractions, 5 days a week, for 6 weeks. Fifty-four gray was delivered to anatomic regions at risk of subclinical disease as indicated (eg, ipsilateral levels 1B to 5, contralateral cervical levels 2 to 4, and retropharyngeal lymph node basins). Unilateral radiotherapy (RT) was permitted in patients with well-lateralized tonsil primaries.

Cisplatin 30 mg/m^2 once per week was the mandated first-choice chemotherapy; however, alternative regimens once per week were permissible. Typical reasons for a patient not being able to receive cisplatin included renal insufficiency and history of hearing loss and/or tinnitus. The preferred second-, third-, and fourth-choice chemotherapies were (1) cetuximab 250 mg/m^2, (2) carboplatin area under the curve 1.5 and paclitaxel 45 mg/m^2, and (3) carboplatin area under the curve 3. Chemotherapy was given intravenously once per week, preferably on Mondays. Six weekly doses were given concurrently with radiation (ie once per week for 6 weeks). Dose modifications were allowed as needed per the treating medical oncologist's discretion. If a patient could not tolerate cisplatin for more than 1 week, he or she was switched to an alternative regimen. Chemotherapy was not given to patients with T0-2 N0-1 disease (AJCC 7th edition).

Post-CRT Assessment of Clinical Response

Clinical response to CRT was evaluated 10 to 16 weeks after CRT with a PET/CT and clinical examinations by the treating radiation oncologist and head and neck surgeon. Decisions for surgical intervention (ie, biopsy, neck dissection) were based on the PET/CT and clinical evaluations demonstrating suspicion of residual tumor.

Patients were observed clinically every 2 to 3 months for 2 years, then every 6 months for 3 additional years. Chest imaging was performed every 6 months for 2 years and then yearly.

Toxicity and QOL Assessments

Clinician assessments of toxicity (National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE] version 4.03) and patient self-reported symptoms (patient-reported outcomes version of the CTCAE [PRO-CTCAE]) were collected before treatment, weekly during treatment, and during subsequent follow-up visits.[16,17] Thirty head and neck–specific items were selected from the PRO-CTCAE.[18] Patients also completed European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30, EORTC QLQ H&N35, and Eating Assessment Tool 10 questionnaires before treatment, weekly during treatment,

and during subsequent follow-up visits.[19-21] Modified barium swallow studies were performed before treatment, 6 to 8 weeks after treatment, and 6 months after treatment. The Rosenbek Penetration Aspiration Scale was used to quantify dysphagia.[22]

Study End Points and Statistical Analysis

The primary end point of this study was 2-year PFS. The reported PFS for patients with HPV-associated OPSCC treated with standard-intensity 70 Gy and cisplatin in RTOG 0129 was 74% (3 year) and in RTOG 1016 was 78% (5 year).[1] PFS was defined as the time from the beginning of treatment to cancer progression or death. Power calculations were based on the null hypothesis that the true 2-year PFS rate was 87%, with the alternative hypothesis being that the 2-year PFS rate was 0.80 (or less). For a planned total sample size of 90, the null hypothesis would have been rejected if 18 or more patients had a tumor recurrence or death, with a type 1 error of less than 0.05. A pathologically positive lymph node that was found on a neck dissection that was performed because of the results of the 3-month post-treatment PET/CT was not classified as a regional failure. This neck dissection was prespecified in the protocol design, outside of the trial is standard of care, and was considered a planned part of the treatment. Kaplan Meier estimates of local control, regional control, local-regional control (LRC), distant metastasis-free survival (DMFS), PFS, cause-specific survival, and OS were calculated.

RESULTS

Patient Characteristics and Compliance With Study Treatment

One hundred fourteen patients were enrolled between August 22, 2014, and October 6, 2017, because of a higher than expected accrual rate. The median follow-up of all 114 patients was 31.8 months (range, 1.1 to 51.4 months), and 92 patients (81%) had a minimum of 2 years of follow-up. We herein present the analysis for all 114 patients (Table 1). Twenty-seven out of 114 patients (24%) had tonsillectomies as part of their pretreatment work-up. All patients received the intended radiation dose of 60 Gy. The mean radiation doses delivered to relevant organs at risk were as follows: 22 Gy (range, 5 to 45 Gy) to the contralateral parotid (n = 114 patients); 41 Gy (20 to 60 Gy) to the ipsilateral parotid (n = 114); 34 Gy (19 to 52 Gy) to the larynx (n = 114); 39 Gy (30 to 52 Gy) to the oral cavity (n = 90); and 51 Gy (34 to 58 Gy) to the pharyngeal constrictors (n = 97). Eighty-nine of the 114 patients (78%) received chemotherapy. Sixty-four percent (57 of 89) received all six doses of cisplatin, and 80% (71 of 89) received four or more weekly doses of cisplatin. Ten (11%) of the 89 patients received cetuximab upfront starting cycle 1 because of contraindications to cisplatin. One patient died during treatment secondary to neutropenic sepsis.

TABLE 1. Patient Characteristics (N = 114)

Characteristic	Patients
Age, years, mean (range)	62 (37-87)
Sex	
Male	96 (84)
Female	18 (16)
Ethnicity	
African American	7 (6)
White	104 (91)
Other	1 (1)
Unknown	2 (2)
Marital status	
Married	90 (79)
Unmarried	23 (20)
Unknown	1 (1)
Tobacco use	
Never smoked	54 (47)
≤ 10 pack-years	38 (33)
> 10 pack-years	22 (19)
Primary tumor location	
Tonsil	52 (46)
Base of tongue	57 (50)
Unknown primary	5 (4)
T stage*	
T0	5 (4)
T1	35 (31)
T2	61 (54)
T3	13 (11)
N stage (AJCC 7th edition)	
N0	18 (16)
N1	16 (14)
N2a	5 (4)
N2b	57 (50)
N2c	18 (16)
N stage (AJCC 8th edition)	
N0	18 (16)
N1	78 (68)
N2	18 (16)
HPV/p16 status	
HPV+/p16+	46 (40)
HPV−/p16+	12 (11)
HPV unknown/p16+	56 (49)

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviations: AJCC, American Joint Committee on Cancer; HPV, human papillomavirus.
*T stage was the same for AJCC 7th and 8th editions.

TABLE 2. Clinical Characteristics of Patients With Recurrence

Patient Age (years)	T Stage*	N Stage (AJCC 7th ed)	N Stage (AJCC 8th ed)	Tobacco Use (py)	Tumor Genomics (mutations)	Chemotherapy (No. of cycles)	Recurrence Location	Months to Recurrence	Salvage Treatment	Clinical Status
55	T2	N2b	N1	≤ 10	Unknown	6 cisplatin	Distant	18.5	CRT, immuno, chemotherapy	Alive
75	T1	N2b	N1	> 10	Unknown	1 cisplatin, 5 cetuximab	Distant	3.4	None (died before 12-wk PET)	Dead
57	T2	N2b	N1	Never	PIK3CA	6 cetuximab	Regional	25.2	Neck dissection, IORT, chemotherapy	Alive
37	T2	N2b	N1	Never	PIK3CA	6 cetuximab	Regional	16.4	Neck dissection, chemotherapy	Alive
65	T2	N2b	N1	Never	PIK3CA	6 cisplatin	Distant	20.3	Immuno	Alive
74	T1	N2b	N1	> 10	PIK3CA	4 cisplatin	Distant	14.3	Chemotherapy, RT	Alive
68	T2	N2b	N1	Never	Unknown	5 cisplatin	Distant	18.3	Chemotherapy	Alive
63	T3	N2b	N1	≤ 10	Unknown	5 cisplatin	Local and distant	12.0	Chemotherapy	Dead
63	T2	N2b	N1	< 10	Unknown	6 cisplatin	Distant	4.5	Palliative	Dead
87	T2	N0	N0	Never	Unknown	None	Local	12.4	Chemotherapy	Alive
68	T2	N2c	N2	≤ 10	Unknown	6 cisplatin	Local	17.7	Chemotherapy	Alive
65	T1	N2b	N1	> 10	Unknown	6 cisplatin	Distant	21.0	Chemotherapy	Alive
61	T1	N2b	N1	≤ 10	Unknown	2 cisplatin 3 carboplatin	Distant	4.1	RT, chemotherapy	Alive
70	T2	N1	N1	Never	Unknown	None	Local	15.5	Surgery	Alive

Abbreviations: AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; ed, edition; immuno, immunotherapy; IORT, intraoperative radiotherapy; PET, positron emission tomography; py, pack-years; RT, radiotherapy.

*T stage was the same for AJCC 7th and 8th edition.

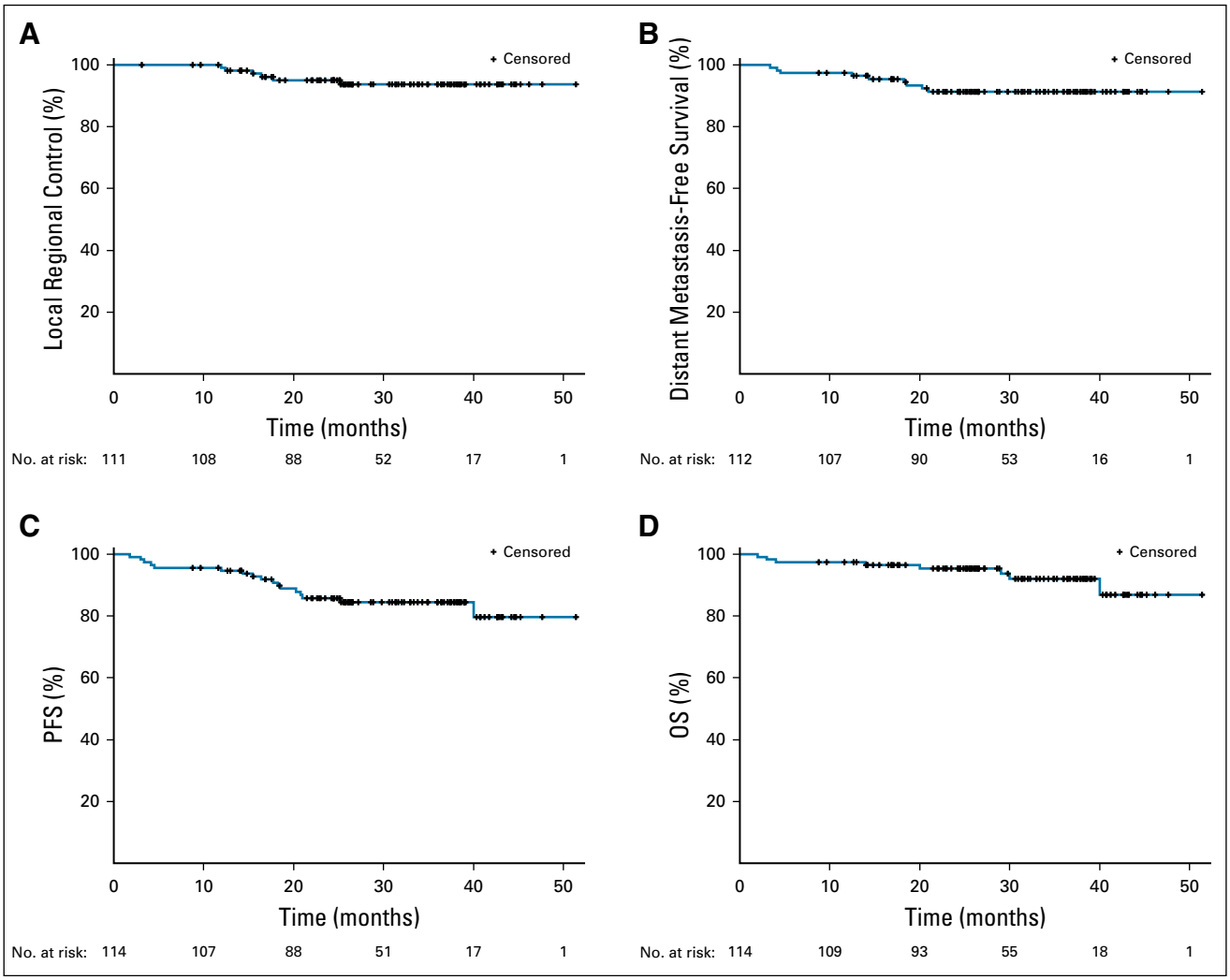

FIG 1. Kaplan-Meier curves for (A) local-regional control (LRC), (B) distant metastasis-free survival (DMFS), (C) progression-free survival (PFS), and (D) overall survival (OS). Two-year LRC, DMFS, PFS, and OS were 95% (95% CI, 88.6% to 97.9%), 91% (95% CI, 83.9% to 95.4%), 86% (95% CI, 77.5% to 91.3%), and 95% (95% CI, 89.3% to 98.1%), respectively. Three-year LRC, DMFS, PFS, and OS were 94% (95% CI, 96.5% to 97.2%), 91% (95% CI, 83.4% to 95.4%), 85% (95% CI, 76.0% to 90.3%), and 95% (95% CI, 89.3% to 98.1%), respectively.

Cancer Control Outcomes

The post-treatment PET/CT CR rate was 93% at the primary site and 80% in the neck. Eleven patients had a neck dissection, with four having pathologic residual disease (all four are alive with no evidence of disease). Eight patients did not have a CR at the primary site: six were observed with no local recurrence and two had biopsy, with one having local persistence and who died. A total of 15 (fewer than 18) patients (out of 114 accrued patients, 92 with at least 2 years of follow-up) had disease recurrence or died, and we thus do not reject the null hypothesis that 2-year PFS is not less than 87%. There were four local failures, two regional failures, and nine distant failures. Table 2 lists the clinical characteristics of the patients who developed failure. Two-year local control, regional control, LRC, DMFS, PFS, cause-specific survival, and OS were as follows: 96% (95% CI, 89.9% to 98.5%), 99% (95% CI, 93.1% to 99.9%), 95% (95% CI, 88.6% to 97.9%), 91% (95% CI, 83.9% to 95.4%), 86% (95% CI, 77.5% to 91.3%), 97% (95% CI, 91.3% to 99.1%), and 95% (95% CI, 89.3% to 98.1%), respectively. Three-year LRC, DMFS, PFS, and OS were as follows: 94% (95% CI, 96.5% to 97.2%), 91% (95% CI, 83.4% to 95.4%), 85% (95% CI, 76.0% to 90.3%), and 95% (95% CI, 89.3% to 98.1%), respectively. Actuarial LRC, DMFS, PFS, and OS are shown in Fig 1. We examined the association between time to disease recurrence and four relevant factors: T stage (AJCC 7th edition), N stage (AJCC 7th edition), tobacco pack-years, and receipt of cetuximab, using both the log-rank test and Cox proportional hazard regression. None of these factors showed statistical significance (minimal *P* value was .18), probably because of the small number of events.

TABLE 3. Clinician- and Patient-Reported Acute Toxicity

Toxicity	CTCAE Version 4.0 Grade 3 or Higher (%)	PRO-CTCAE Severe or Very Severe (%)
Hematologic		
Anemia	1	N/A
Neutropenia	2	N/A
Renal		
Acute kidney injury	1	N/A
Nonhematologic		
Xerostomia	2	60
Dysphagia	21	50
Mucositis (oral and/or pharyngeal)	33	37
Nausea	8	22
Vomiting	2	14
Dermatitis radiation	2	30
Pain	12	45
Hoarseness	0	21
Fatigue	3	39
Anxiety	3	11
Depression	0	10
Appetite	25	59
Tinnitus	0	17

NOTE. There were no clinician-reported grade 3 or higher late toxicities.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N/A, not applicable; PRO-CTCAE, patient-reported outcomes version of the CTCAE.

Clinician-Reported Toxicity

Table 3 lists the incidence of all acute grade 3 or higher clinician-reported toxicities (CTCAE version 4.0). Thirty-four percent of patients (38 of 113) required a feeding tube for a median duration of 10.5 weeks (range, 3 to 66 weeks), and none were permanent (1-year feeding tube dependence rate of 1%). Mean Rosenbek aspiration scores (8-point scale, score of 1 indicates material does not enter the airway) were as follows (pretreatment, 6 to 8 weeks after treatment, and 6 months after treatment): thin substances (1.3, 1.8, 1.8), pureed substances (1.1, 1.1, 1.3), and solid substances (1.0, 1.1, 1.0). There were no grade 3 or higher late adverse events.

Patient-Reported Outcomes

Pertinent patient-reported acute nonhematologic toxicity is listed in Table 3. Complete EORTC QLQ C30 and EORTC QLQ H&N-35 and Eating Assessment Tool 10 results are listed in Appendix Table A1 (online only). Selected domains and symptoms from these QLQs are shown in Fig 2. As expected, we observed declines in global QOL and an increase in symptom scores soon after the completion of treatment. All QOL items, domains, and symptom scores had returned to baseline by 6 months, with the exception of dry mouth and sticky saliva. There was continued improvement in these symptoms beyond 1 year. Notably, patients reported that their swallowing function returned to baseline.

DISCUSSION

In this second-generation phase II evaluation of a de-intensified CRT regimen of 60 Gy of IMRT and weekly low-dose cisplatin (30 mg/m^2), the clinical outcomes were favorable, with an observed 2-year and 3-year PFS of 86% and 85%, respectively, and an OS of 95%. These results compare favorably to the 70 Gy plus cisplatin arm in RTOG 1016 (5-year PFS of 78% and OS of 85%). A second prospective evaluation of 60 Gy plus weekly cisplatin was necessary to verify that a mandated biopsy and selective neck dissection could be safely omitted.

Patients reported favorable long-term QOL and low to moderate symptom burden (Fig 2 and Appendix Table A1). Patient-reported data should be interpreted with caution because patients may modify their conception of QOL and this may introduce measurement error (ie, response shift).[23] This bias is not unique to this study; it is applicable to all patient-reported data.[24] Global QOL returned to baseline (Fig 2A), and long-term swallowing function was favorable, with patients reporting minimal to no worsening of their swallowing function over the long term (Figs 2A and 2B).

The greatest symptom burden was dry mouth, which patients reported to be most symptomatic at 6 to 8 weeks after de-intensified CRT. It continued to improve even after 1 year, although it never returned to baseline. This additional recovery of function after 1 year is longer than that observed after standard-intensity CRT,[25] suggesting that in the long run, the symptomatic burden and bother of dry mouth will be less with de-intensified CRT.

Two phase II trials evaluating paclitaxel-based neoadjuvant chemotherapy followed by de-intensified CRT have been published.[8,10] In both studies, the response to neoadjuvant chemotherapy was used to decide whether to de-intensify the RT dose. In the Eastern Cooperative Oncology Group trial 1308, 70% of patients had a CR at the primary site and 58% had a CR at the nodal sites.[10] Patients received de-intensified CRT (54 Gy plus cetuximab) to either the primary and/or the nodal sites if there was a CR after neoadjuvant chemotherapy. There were several protocol deviations (18 patients) concerning receipt of de-intensified RT, and ultimately, 78% of patients received de-intensified CRT to the primary site. The 2-year PFS was 80%, and all treatment failures occurred in patients who reported more than 10 pack-years. Patients who received 54 Gy compared with those who received 70 Gy reported less difficulty with swallowing solids and less impaired nutrition at 12 months. A single institutional trial conducted by Chen et al[8] at the University of California Davis similarly evaluated neoadjuvant chemotherapy followed by response-based RT de-escalation. Fifty-five percent of

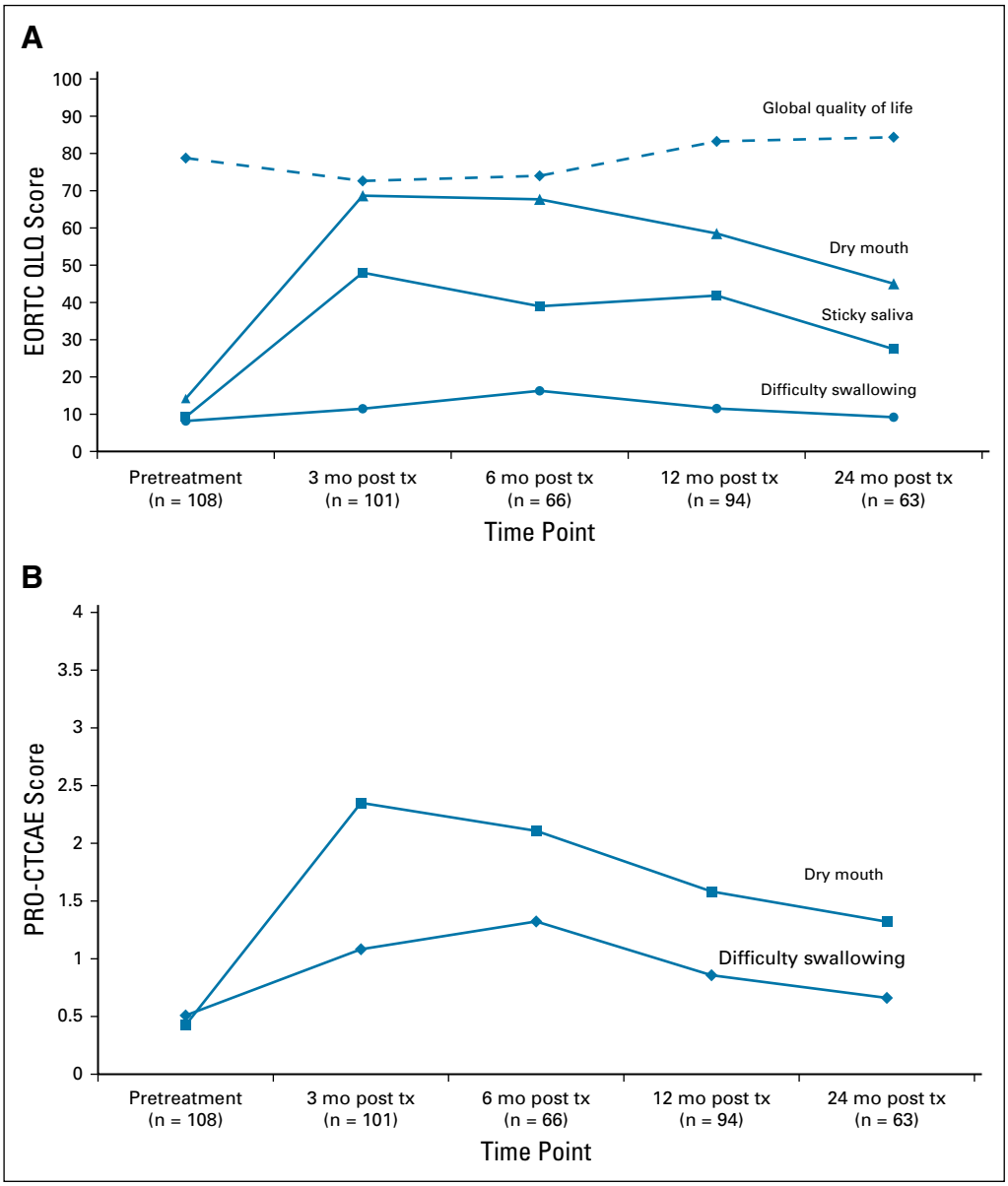

FIG 2. (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 responses (mean scores) for global health status and EORTC QLQ H&N35 responses (mean scores) for selected symptoms. (B) Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE; mean scores) for selected symptoms. tx, treatment.

patients had a CR and received 54 Gy, and the remaining 45% received 60 Gy. The 2-year PFS was 92%. Only 14% required a feeding tube during treatment, and there were no patient-reported outcomes.

In comparison, we evaluated a de-intensified CRT approach that included neither transoral surgery nor neoadjuvant chemotherapy, and all patients received 60 Gy with or without chemotherapy. The data reported herein support the approach of de-intensified CRT without the need of neoadjuvant chemotherapy. Future studies of the neoadjuvant chemotherapy and transoral surgery approach should attempt a more radical reduction in RT dose to further reduce toxicity and improve QOL.

Two randomized phase III trials (RTOG 1016 and De-ESCALaTE) have evaluated the substitution of cetuximab for cisplatin concurrently with 70 Gy.[11,12] The hypothesis was that cetuximab would result in less acute and long-term toxicity and morbidity and similar disease control. The control arm in both studies was 70 Gy with concurrent cisplatin 100 mg/m^2 (two cycles in RTOG 1016 and three cycles in Determination of Epidermal growth factor receptor-inhibitor (cetuximab) versus Standard Chemotherapy (cisplatin) early And Late Toxicity Events [De-ESCALaTE]). Both studies observed significantly inferior OS and PFS and no reduction in acute or late toxicities in the cetuximab experimental arms.

The overall occurrence of late grade 3 to 4 toxicity for both randomized trials was approximately 17% to 30%. Sixty to seventy percent of patients required a feeding tube, and the 1-year feeding tube dependence rate in RTOG 1016 was approximately 9%. In contrast, in the current study, no patient experienced late grade 3 or higher toxicity, 39%

required a feeding tube, and the 1-year feeding tube dependence rate was 1% (none were permanent). Limited QOL data were reported in RTOG 1016 and De-ESCALaTE.

These randomized trials validate cisplatin as the standard-of-care concurrent chemotherapy regimen for patients with HPV-associated OPSCC. In the current study, the 10 Gy reduction in RT resulted in preservation of swallowing function and continued improvement in dry mouth symptoms beyond 1 year after treatment (Fig 2 and Appendix Table A1). The dose-response of normal tissue toxicity rises steeply in the high dose range (50 to 70 Gy), so that modest decreases in total dose (as used in this study) can have a major impact on long-term toxicity.[26] The interpretation of these two randomized trials with the data from our study suggests that radiation dose is the main determinate of long-term toxicity.

The results from the NRG oncology cooperative group HN002 phase II randomized trial of 60 Gy alone accelerated versus 60 Gy with concurrent weekly cisplatin 40 mg/m^2 are pending.[27] It is hoped that this trial will report cancer control and QOL outcomes similar to that which we have observed in this trial and also answer the question of whether the addition of cisplatin to de-intensified 60 Gy RT is necessary. In addition, a randomized NRG phase III trial (HN005) of 60 Gy versus 70 Gy will soon be open for accrual (summer 2019).

Our trial was a single-arm phase II study in carefully selected patients with HPV-associated OPSCC. We did not perform a randomized study to make a direct comparison with standard-intensity therapy, but our results are encouraging. Although our toxicity analysis is robust, with extensive physician- and patient-reported data, we do not have a formal comparison group to prove decreased toxicity. Patients who reported more than 10 pack-years were eligible (limited to those with 30 pack-years or less with 5 years of abstinence), and although some would argue that these patients should not be offered de-intensification, we did not observe a correlation between tobacco pack-years and cancer recurrence. The median follow-up was just short of 3 years. Although most recurrence occurred within the first 2 years after treatment, late distant recurrences (beyond 2 to 3 years) can occur. Thus, our estimation of DMFS and PFS may decline with longer follow-up.

In conclusion, the cancer control and patient-reported outcomes are favorable with a de-intensified CRT regimen of 60 Gy IMRT with concurrent weekly low-dose cisplatin (30 mg/m^2) for patients with HPV-associated OPSCC. Neither neoadjuvant chemotherapy nor surgery is needed to obtain favorable results with de-escalation. Additional efforts are warranted to evaluate novel biomarkers to better optimize the selection of patients for de-intensification.

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SUPPORT

Supported by the University of North Carolina School of Medicine, Department of Radiation Oncology, and by the University of Florida School of Medicine, Department of Radiation Oncology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01007.

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Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank Becky Green, MSW; University of Florida trial coordinator John Lybarger, MPH; Rex trial coordinators Anderson Black, RN, BSN, OCN, and Diane Bracco, RN; High Point coordinator Laura Hayes; and Pardee coordinator Cathy Jenkins, RN, BSN, for their significant roles in ensuring the success of this clinical trial.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Patents, Royalties, Other Intellectual Property: A blood test for detecting circulating viral tumor DNA, patent pending (Inst)

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Patents, Royalties, Other Intellectual Property: In Vitro Microphysiological System For High Throughput 3D Tissue Organization And Biological Function, patent issued 12/06/16–no royalties (I); Microscopy with Lattice Light Sheets and Point Accumulation for Imaging and Nanoscale Topography, patent filed 12/7/15–no royalties (I)
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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Patient-Reported Quality of Life and Symptoms

Measure and Symptoms	Score				
	Baseline (n = 108)	3 Months After Treatment (n = 101)	6 Months After Treatment (n = 66)	1 year After Treatment (n = 94)	2 years After Treatment (n = 63)
EORTC QLQ C30					
Global health status	79 (75-82)	73 (69-76)	74 (69-79)	83 (80-87)	84 (81-88)
Functional scales					
Physical functioning	94 (91-96)	87 (84-90)	90 (86-93)	94 (91-96)	95 (92-97)
Role functioning	90 (86-93)	83 (79-87)	83 (76-89)	93 (90-96)	94 (91-97)
Emotional functioning	78 (75-81)	84 (80-87)	83 (78-88)	88 (85-91)	90 (86-93)
Cognitive functioning	89 (86-92)	87 (84-91)	87 (82-92)	86 (82-90)	90 (86-93)
Social functioning	86 (82-90)	82 (77-86)	87 (81-92)	92 (88-96)	96 (93-98)
Symptom scales/items					
Fatigue	20 (16-24)	31 (26-35)	30 (24-36)	18 (14-22)	15 (10-19)
Nausea and vomiting	3 (1-5)	3 (2-5)	2 (1-4)	1 (0-1)	1 (0-3)
Pain	19 (15-24)	11 (8-15)	16 (10-22)	8 (5-12)	8 (5-12)
Dyspnea	8 (4-11)	9 (6-12)	9 (5-13)	7 (4-10)	6 (2-9)
Insomnia	22 (17-27)	30 (25-36)	25 (18-32)	20 (16-24)	17 (11-23)
Appetite loss	13 (9-17)	32 (26-38)	26 (19-34)	16 (11-21)	9 (4-13)
Constipation	10 (6-15)	13 (8-17)	14 (8-20)	9 (5-13)	6 (2-10)
Diarrhea	3 (1-5)	3 (1-4)	4 (0-8)	3 (1-5)	3 (0-5)
Financial difficulties	16 (11-21)	18 (12-24)	23 (15-31)	13 (8-18)	10 (6-15)
EORTC QLQ H&N35					
Pain	20 (17-24)	17 (13-20)	17 (13-21)	13 (9-17)	7 (4-10)
Swallowing	8 (6-11)	11 (9-14)	16 (12-20)	12 (8-15)	9 (7-12)
Senses problems	7 (4-10)	33 (29-37)	35 (29-41)	26 (22-30)	19 (14-23)
Speech problems	9 (6-12)	14 (11-17)	15 (10-19)	9 (7-11)	7 (4-10)
Trouble with social eating	9 (6-12)	25 (21-29)	23 (18-27)	16 (12-20)	11 (8-15)
Trouble with social contact	5 (3-7)	7 (5-9)	9 (5-13)	3 (1-4)	2 (1-3)
Less sexuality	17 (12-22)	23 (17-28)	26 (18-33)	14 (9-19)	17 (10-24)
Teeth	10 (5-14)	12 (8-17)	19 (12-26)	15 (10-20)	13 (8-18)
Opening mouth	8 (4-12)	10 (7-14)	15 (10-20)	10 (6-14)	10 (6-14)
Dry mouth	14 (10-19)	69 (63-74)	68 (62-74)	59 (54-63)	45 (39-51)
Sticky saliva	9 (6-13)	48 (42-54)	39 (32-46)	42 (36-48)	27 (21-34)
Coughing	21 (18-25)	23 (19-27)	26 (19-32)	21 (16-25)	18 (12-24)
Felt ill	7 (4-11)	8 (4-12)	10 (5-14)	5 (2-9)	6 (3-10)
Pain killers	15 (11-18)	8 (5-11)	7 (4-11)	5 (3-8)	5 (2-8)
Nutritional supplements	11 (8-14)	15 (11-18)	14 (10-18)	12 (9-15)	8 (4-12)
Feeding tube	0 (0-1)	4 (2-7)	3 (1-5)	1 (0-2)	1 (−1-2)
Weight loss	8 (5-10)	12 (9-15)	9 (5-12)	5 (3-8)	2 (0-4)
Weight gain	6 (3-8)	8 (5-11)	9 (6-13)	12 (9-15)	12 (8-16)

(continued on following page)

TABLE A1. Patient-Reported Quality of Life and Symptoms (continued)

Measure and Symptoms	Score				
	Baseline (n = 108)	3 Months After Treatment (n = 101)	6 Months After Treatment (n = 66)	1 year After Treatment (n = 94)	2 years After Treatment (n = 63)
PRO-CTCAE					
Xerostomia, severity	0.4 (0.3-0.6)	2.4 (2.2-2.6)	2.1 (1.9-2.4)	1.6 (1.4-1.8)	1.3 (1.1-1.5)
Dysphagia, severity	0.5 (0.4-0.7)	1.1 (0.9-1.3)	1.3 (1.1-1.6)	0.9 (0.7-1.0)	0.7 (0.5-0.9)
Mucositis, oral and/or pharyngeal, severity	0.5 (0.4-0.7)	0.7 (0.5-0.9)	0.7 (0.4-1.0)	0.3 (0.2-0.4)	0.2 (0.1-0.3)
Nausea, frequency	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.3 (0.1-0.4)	0.1 (0.0-0.2)	0.1 (0.0-0.1)
Vomiting, frequency	0.0 (0.0-0.1)	0.1 (0.0-0.1)	0.1 (0.0-0.2)	0.0 (0.0 to 0.1)	0.0 (0.0-0.1)
Dermatitis radiation, severity	N/A	0.5 (0.3-0.7)	0.3 (0.1-0.5)	0.1 (0.0-0.2)	0.3 (0.1-0.5)
Pain, frequency	1.3 (1.0-1.5)	0.9 (0.7-1.1)	0.7 (0.5-1.0)	0.5 (0.3-0.7)	0.4 (0.2-0.7)
Hoarseness, severity	0.5 (0.4-0.6)	1.0 (0.8-1.2)	0.8 (0.6-1.1)	0.6 (0.5-0.7)	0.5 (0.3-0.6)
Fatigue, severity	0.7 (0.5-0.8)	1.2 (1.0-1.4)	1.1 (0.9-1.4)	0.8 (0.6-1.0)	0.7 (0.5-0.9)
Anxiety, frequency	0.9 (0.8-1.1)	0.7 (0.5-0.9)	0.6 (0.4-0.8)	0.5 (0.4-0.7)	0.4 (0.2-0.6)
Sad or unhappy feelings, frequency	0.9 (0.7-1.0)	0.8 (0.6-1.0)	0.7 (0.5-1.0)	0.6 (0.4-0.7)	0.4 (0.3-0.6)
Nothing could cheer up, frequency	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.1 (0.0-0.2)
Appetite, severity	0.4 (0.3-0.6)	1.1 (0.9-1.3)	1.1 (0.8-1.4)	0.6 (0.4-0.8)	0.4 (0.2-0.5)
Tasting, severity	0.4 (0.2-0.5)	1.8 (1.6-2.0)	1.8 (1.5-2.0)	1.2 (1.0-1.4)	0.8 (0.6-1.0)
Tinnitus, severity	0.4 (0.2-0.5)	0.7 (0.5-0.9)	0.7 (0.5-1.0)	0.6 (0.4-0.8)	0.5 (0.4-0.7)
EAT-10 composite score	4 (2-5)	9 (7-11)	10 (7-12)	7 (5-8)	5 (4-7)

NOTE. Data are presented as mean or mean (95% CI).

Abbreviations: EAT-10, Eating Assessment Tool 10; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; N/A, not applicable; PRO-CTCAE, patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; QOL, quality of life.