original reports

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

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abstract

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).

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ASSOCIATED CONTENT

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Data Supplement

Protocol

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

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INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) is one of the fastest rising incident cancers worldwide, largely because of increasing rates of oral infection with human papillomavirus (HPV).[1] HPV-related OPSCC, particularly early T-stage tumors, are highly curable, with long-term survival of more than 85%.[2] On average, patients with HPV-related tumors tend to be younger and healthier, in the midst of their working life, compared to patients with HPV-negative tumors typically associated with tobacco and alcohol use, who are typically older with more comorbidities.[3] Given the high cure rates in this high-functioning population, increased attention has been given to the long-term quality of life (QOL) for these patients.

Options for management of early-stage HPV-positive and -negative OPSCC include a primary radiotherapy (RT) approach with or without chemotherapy versus transoral surgery and neck dissection (ND) followed by pathologically directed adjuvant therapy. Both approaches have their relative risks and benefits. RT, particularly with concurrent chemotherapy, carries the risks of short-term and long-term swallowing dysfunction, xerostomia, hearing loss, neutropenia, and treatment-related death, but avoids surgical risks for the majority of patients.[2] Primary surgery has the risks of

CONTEXT

Key Objective

To compare long-term swallowing outcomes after a primary radiation (radiotherapy [RT]) approach versus a primary transoral robotic surgery approach, in patients with oropharyngeal squamous cell carcinoma.

Knowledge Generated

Longitudinal quality-of-life scores were statistically superior after radiation, although this difference did not meet the predefined threshold of a clinically meaningful change. Overall, transoral robotic surgery and RT had differing toxicity profiles, but similar long-term oncologic outcomes.

Relevance

With the rapid rise in incidence of human papillomavirus–related oropharyngeal cancer, these data allowed better-informed shared decision making in deciding on a primary treatment approach.

serious oral bleeding, nerve injury, stroke, acute and chronic dysphagia, and treatment-related death. Although some patients can be managed with surgery alone, most require adjuvant RT (83%), with approximately half requiring adjuvant chemoradiotherapy (CRT, 54%), which is associated with a significant toxicity burden.[4] With very different spectrums of potential toxicity and strong patient and provider preferences, whether to manage early T-stage OPSCC with transoral surgery or RT is a highly debated issue in head and neck oncology.[5]

The ORATOR study was the first randomized trial comparing a primary RT approach versus a primary transoral robotic surgery plus ND (TORS + ND) approach in patients with OPSCC, designed to definitively compare swallowing QOL at one year between the two modalities.[6] In the initial report, primary RT had statistically superior swallowing QOL at 1 year (as measured by the MD Anderson Dysphagia Inventory [MDADI]), but did not meet the prespecified criteria to qualify as a clinically meaningful change (CMC).

Although 1-year QOL outcomes are of great interest, a late decline in swallowing function after treatment for OPSCC with radiation has been well described.[7] Thus, there has been uncertainty as to whether the superior MDADI scores would persist in the RT arm over time in the ORATOR population. Long-term data on swallowing function, QOL, and oncologic outcomes may better inform risk and benefit decisions for both patients and physicians. Additionally, because of observed bleeding, TORS patients were required to have elective temporary tracheostomies placed, and the impact of these on long-term swallowing function was unknown. Herein, we report the extended outcomes of the ORATOR trial more than 36 months after completion of accrual.

METHODS

Study Design

The ORATOR trial (A Phase II Randomized Trial for Early-Stage Squamous Cell Carcinoma of the Oropharynx: Radiotherapy vs Transoral Robotic Surgery) was an investigator-initiated open-label parallel-group phase II randomized study that enrolled patients from six centers internationally. The trial was registered before activation (ClinicalTrials.gov identifier: NCT01590355), and the Protocol (online only) has been previously published and is available. As the trial details and statistical analyses have been published in detail, only a short summary is provided here.

Participants

Patients were age 18 years or older, with good performance status (Eastern Cooperative Oncology Group score 0-2), and histologically proven OPSCC, with stage T1-2, N0-2, M0 disease, as per the American Joint Committee on Cancer, 7th edition. All nodes were required to be 4 cm or smaller, without extranodal extension on imaging. Patients were required to have sufficient renal, liver, and hematologic function for chemotherapy, as defined in the Protocol. Preenrollment imaging evaluation included a computed tomography (CT) or magnetic resonance imaging of the neck, and a CT of the chest, with positron emission tomography-CT optional. All patients provided written informed consent, and presentation at a head and neck multidisciplinary tumor board was required before random assignment.

Random Assignment and Masking

Patients were assigned to groups using a computer-generated randomization list using permuted block design (block size of four, known only to the statistician until analysis was complete), stratified by p16 status (a surrogate marker of HPV status). Neither patients nor enrolling physicians were blinded to treatment allocation.

Procedures

In the RT arm, radiation was delivered using intensity-modulated radiation therapy of 70 Gy in 35 fractions over 7 weeks to areas of gross disease, and 56 Gy to low-risk nodal areas, with mandated peer review of radiation plans. Concurrent chemotherapy was recommended for patients with node-positive disease. Bolus cisplatin (100 mg/m^2) day 1, 22, and 43 of radiation was preferred, but this could be modified to

weekly cisplatin (40 mg per m^2), cetuximab (400 mg per m^2 loading dose one week prior to radiation then 250 mg per m^2), or carboplatin (area under the curve 1.5) for seven doses with radiation depending on patient fitness. Radiation treatment response was evaluated 8-12 weeks after radiation using CT and/or positron emission tomography-CT, and salvage surgery recommended for persistent or recurrent disease.

In the TORS + ND arm, a surgical robot was used to excise the primary tumor with 1-cm margins. Selective NDs were done at the time of surgery or within two weeks. Ligation of the lingual and facial branches of the external carotid artery ipsilateral to the tumor was mandated. After a death occurred because of oropharyngeal bleeding, the trial was modified to strongly recommend (but not mandate) a tracheostomy at the time of surgery to provide airway protection in case of swelling and/or bleeding. Adjuvant RT (60 Gy in 30 fractions) was recommended for patients on the basis of intermediate-risk pathologic features (lymphovascular invasion, close margins [< 2 mm], and pT3-T4 or node-positive disease). Adjuvant CRT was given with the radiation dose increased to 64 Gy in 30 fractions for high-risk pathologic features (positive margins or extranodal extension). RT was delivered using simultaneous integrated boosts in both arms.

Follow-up visits were scheduled every 3 months for the first 2 years, and every 6 months thereafter until 5 years.

Outcomes

The primary end point was a comparison of the total score on the MDADI at 1 year. The MDADI score ranges between 20 and 100, and a higher score represents better QOL.[8] A 10-point change in scores was considered a CMC.[9,10] Prespecified secondary end points were overall survival (OS), progression-free survival (PFS), QOL at other timepoints using the MDADI, the European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients General and Head & Neck 35 scales, the Voice Handicap Index-10, the Neck Dissection Impairment Index, and the Patient Neurotoxicity Questionnaire; toxicity, assessed by the Common Toxicity Criteria for Adverse Events scale version 4; and swallowing function, measured by the percutaneous feeding-tube rate at 1 year and the functional oral intake scale score, in addition to MDADI scores and Common Toxicity Criteria for Adverse Events data.

Statistical Analysis

The study was designed to definitively compare 1-year MDADI scores between treatment arms, powered for a 10-point improvement in the TORS + ND arm. The sample size calculation assumed that the QOL scores would be normally distributed with a standard deviation of 12. Using an independent two-sample *t*-test with an α level of .05 and power of 90%, assuming a dropout rate of 10%, a total of 68 patients were required.

Descriptive statistics were generated for all patients (N = 68) and stratified by treatment arm for baseline patient, tumor, and treatment characteristics and stratified by treatment arm for QOL end points at baseline, 1, 2, and 3 years using the chi-square test, Fisher's exact test, independent two-sample *t*-test, or Wilcoxon rank sum test as appropriate. Linear mixed-effects models were used to analyze data longitudinally over time, as specified in the Protocol. These models incorporate all follow-up data for a specific QOL outcome, testing for changes in QOL over time as a fixed effect (modeled as continuous), adjusting treatment arm as a fixed effect and adjusting for patient number as a random effect. We carried out a post hoc comparison of each patient relative to their own baseline score using the paired *t*-test and also calculated the percentage of patients that experienced a CMC from baseline at each yearly timepoint, compared using the chi-square or Fisher's exact test as appropriate.

In addition, we carried out exploratory post hoc analyses of MDADI scores to examine the impact of p16 status, primary site, T stage, extent of nodal disease, use of elective tracheostomies, and therapeutic intensity in each treatment arm. For these subgroups, MDADI scores were compared using an independent two-sample *t*-test or analysis of variance, and linear mixed modeling was used to assess outcomes longitudinally over time. Similarly, linear mixed modeling was performed to test for changes in QOL over time adjusting for these same factors as fixed effects. We also carried out an exploratory qualitative comparison of the 1- and 2-year composite MDADI results of the surgical arm of this study stratified by adjuvant therapy versus the presented results of Eastern Cooperative Oncology Group ACRIN 3311 (E3311, 360 of 519 patients enrolled)[11] through generation of boxplots with 95% confidence.

Kaplan-Meier estimates were generated for OS and PFS for all patients (N = 68) and stratified by treatment arm, p16 status, and primary site (tonsil *v* base of tongue), compared using the stratified log-rank test (treatment arm and primary site) or log-rank test (p16 status only). All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC), using two-sided statistical testing at the .05 significance level.

Accrual completed in June 2017, and after 1 year of follow-up and time to resolve data questions, the data set was locked for outcomes on January 14, 2019. Data collection continued thereafter, and the data set was locked for this long-term analysis on November 6, 2020.

RESULTS

Baseline Characteristics and Treatment

Sixty-eight patients were randomly assigned (n = 34 in each arm) between August 10, 2012, and June 9, 2017 at six centers in Canada and Australia. Baseline characteristics are listed in Table 1. The arms were balanced for baseline factors, including p16 status (88% in each arm). Median age at diagnosis was 59 years (interquartile range:

TABLE 1. Baseline and Treatment Characteristics

Characteristic	All Patients (N = 68)	RT Arm (n = 34)	TORS + ND Arm (n = 34)
p16 status, No. (%)			
Positive	60 (88)	30 (88)	30 (88)
Negative	8 (12)	4 (12)	4 (12)
Age, years, median (interquartile range)	58.5 (52.9-65.2)	60.0 (53.2-65.2)	58.1 (52.6-64.5)
Sex, No. (%)			
Male	60 (88)	31 (91)	29 (85)
Female	8 (12)	3 (9)	5 (15)
Smoking history, No. (%)	49 (72)	28 (82)	21 (62)
> 21 drinks per week, No. (%)	7 (18)	1 (6)	6 (27)
Primary site, No. (%)			
Tonsil or tonsillar fossa	50 (74)	26 (76)	24 (71)
Base of tongue	18 (26)	8 (24)	10 (29)
Clinical T stage, No. (%)			
T1	30 (44)	13 (38)	17 (50)
T2	38 (56)	21 (62)	17 (50)
Clinical N stage, No. (%)			
N0	21 (31)	12 (35)	9 (26)
N1	12 (18)	5 (15)	7 (21)
N2	35 (51)	17 (50)	18 (53)
Baseline ECOG, No. (%)			
0	60 (88)	30 (88)	30 (88)
1	8 (12)	4 (12)	4 (12)
Baseline scan, No. (%)			
CT head, neck, and chest	40 (59)	22 (65)	18 (53)
CT chest + MRI head and neck	6 (9)	2 (6)	4 (12)
CT neck and chest	9 (13)	4 (12)	5 (15)
PET-CT neck and chest	13 (19)	6 (18)	7 (21)
RT, No. (%)	56 (82)	32 (94)	24 (71)
Chemotherapy, No. (%)	31 (46)	23 (68)	8 (24)
Chemotherapy regimen, No. (%)			
Cisplatin	24 (77)	19 (83)	5 (63)
Carboplatin	6 (19)	3 (13)	3 (38)
Cetuximab	1 (3)	1 (4)	0 (0)
Chemotherapy cycles, median (interquartile range)	3 (3-6)	3 (2-6)	6 (4.5-6)

Abbreviations: CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; PET, positron emission tomography; RT, radiotherapy; TORS + ND, transoral robotic surgery plus neck dissection.

53-65 years) and 85% were male. Primary tumor sites were palatine tonsil (74%) and base of tongue (26%).

The CONSORT diagram is shown in Figure 1. Two patients who were assigned to the RT arm withdrew from the study after random assignment. Of the remaining 32 patients, in the RT arm, 9 (28%) received RT alone, whereas 23 (72%) received concurrent chemotherapy. Four patients (12%) required salvage surgery for persistent locoregional disease detected on clinical examination and/or imaging within 4 months of treatment. In one of these, residual disease was at the primary site only, and he underwent successful resection but died of unknown cause. The other three had NDs for residual lymphadenopathy, two of which showed cells with squamous atypia but were of uncertain viability, and all remained free of disease thereafter.

In the TORS + ND arm, 10 of 34 (29%) of patients received surgery alone, 16 of 34 patients (47%) received postoperative RT, and 8 of 34 (24%) received postoperative CRT.

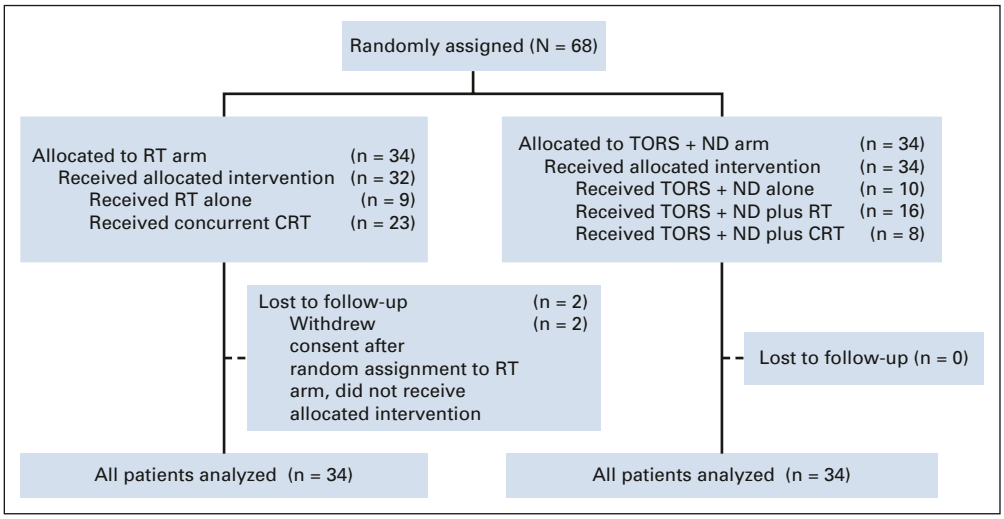

FIG 1. CONSORT diagram. CRT, chemoradiotherapy; RT, radiotherapy; TORS + ND, transoral robotic surgery plus neck dissection.

Swallowing and Dietary Outcomes

Median follow-up was 45 months. The total and composite MDADI scores at 1, 2, and 3 years, including subscales, are shown in Table 2. Mean ± standard deviation total MDADI scores were 86.0 ± 13.5 in the RT arm versus 84.8 ± 12.5 in the TORS + ND arm ($P = .74$) at 2 years and 88.9 ± 11.3 versus 83.3 ± 13.9 ($P = .12$) at 3 years. The differences did not meet the prespecified threshold (10 points) for a CMC at any timepoint (Data Supplement, online only). However, the longitudinal MDADI analyses using linear mixed-effects models (which consider all data at all timepoints) demonstrated statistical superiority of the RT arm ($P = .049$, Fig 2, Table 2). In the post hoc comparison of each patient's MDADI scores relative to baseline, there were no differences between the RT and TORS groups at any timepoint (Table 2).

The percentage of patients receiving total oral diet with no restrictions (on the basis of the functional oral intake scale scores) at 1 year was 100% in the RT arm and 84% in the TORS + ND arm (Data Supplement, $P = .055$). The percutaneous feeding-tube rate at 1 year was 3% in the RT arm (n = 1, removed at 15-month follow-up) and 0% in the TORS + ND arm. In the RT arm, 100% of all patients maintained a total oral diet with no restrictions at 2 and 3 years. The only patient with significantly altered oral intake past 15 months had surgical treatment for a base of tongue tumor and required adjuvant CRT after surgery for both a positive margin and extranodal extension. He was the only TORS patient who required a feeding tube postoperatively and had it removed at month 7. However, his function declined at 30-month follow-up and required replacement of the tube, which remained in place at 54-month follow-up.

Post hoc subgroup analyses by tumor location, T-stage, N-stage, treatment intensity, and use of tracheostomies are shown in the Data Supplement; these subgroup analyses are limited by small sample sizes and considered hypothesis-generating. There was no difference in total MDADI scores between treatment arms for tonsil cancers, but scores were superior for base of tongue tumors treated with RT at 3 years (96.6 ± 3.8 *v* 82.8 ± 16.6, $P = .040$, Data Supplement) and including all data over time using linear mixed-effects models ($P < .001$). The difference qualified as a CMC. Analysis over time demonstrated improved scores for N+ patients treated with RT ($P = .011$, Data Supplement). When stratified by treatment intensity within each arm, there was no difference in total MDADI scores for patients receiving RT versus CRT at any timepoint (Data Supplement). There was no difference in MDADI scores for patients receiving TORS alone, versus TORS + RT and versus TORS + CRT at 1, 2, or 3 years; however, analysis over time was significant for poorer scores with increasing modalities ($P = .0084$, Data Supplement). The use of elective tracheostomies was not associated with significant changes in MDADI scores at any timepoint (Data Supplement). Comparisons of MDADI composite scores of the ORATOR surgical arm with E3311 at 1- and 2-year follow-up are shown in the Data Supplement. MDADI scores in the TORS-only cohort were higher in E3311, whereas outcomes for the TORS + RT and TORS + CRT groups were similar in the two trials.

Survival Outcomes

OS and PFS for both treatment arms are shown in Figure 3. OS and PFS were excellent in both groups, and there were no significant differences between treatment arms (3-year OS: 87.2% [95% CI, 69.4 to 95.0] for RT arm *v* 88.2% [95% CI, 71.6 to 95.4] for TORS + ND arm; 3-year PFS: 87.3% [95% CI, 69.5 to 95.0] *v* 85.3% [95% CI, 68.2 to 93.6], Figs 3A and 3B). Patients with p16-positive tumors experienced markedly improved OS and PFS compared with patients with p16-negative (n = 8) disease (3-year OS:

TABLE 2. Quality-of-Life Scores at 2 and 3 Years for the MD Anderson Dysphagia Inventory

Variable	Baseline, Mean ± SD			Year 2, Mean ± SD Year 3, Mean ± SD			Difference From Baseline at Year 2, Mean ± SD Year 3, Mean ± SD			Percentage of Patients With CMC[a] at Year 2, % Year 3, %			
	RT Arm (n = 32)	TORS + ND Arm (n = 32)	*P*	RT Arm (Y2: n = 24) (Y3: n = 25)	TORS + ND Arm (Y2: n = 29) (Y3: n = 26)	*P*	RT Arm (Y2: n = 24) (Y3: n = 25)	TORS + ND Arm (Y2: n = 29) (Y3: n = 26)	*P*	RT Arm	TORS + ND Arm	*P*	LMM, *P*
Global	91.3 ± 20.3	90.6 ± 18.3	.90	87.5 ± 20.3 93.6 ± 13.8	92.4 ± 13.5 86.9 ± 21.9	.32 .20	–3.3 ± 27.5 1.6 ± 24.4	0.0 ± 20.0 –4.8 ± 27.3	.63 .39	25.0 20.0	18.5 24.0	.57 .73	.18
Emotional	91.1 ± 13.4	87.8 ± 12.0	.30	86.0 ± 13.9 88.8 ± 10.5	83.4 ± 13.3 81.5 ± 13.7	.50 **.039**	–3.5 ± 18.9 –1.2 ± 17.6	–5.8 ± 14.1 –6.8 ± 12.1	.62 .20	37.5 32.0	37.0 40.0	.97 .56	**< .001**
Functional	91.6 ± 14.3	90.5 ± 10.6	.71	90.2 ± 12.0 91.7 ± 11.0	89.2 ± 11.4 87.7 ± 14.0	.78 .26	–0.8 ± 16.3 –0.3 ± 17.5	–1.3 ± 12.4 –3.0 ± 14.3	.90 .56	25.0 28.0	29.6 25.0	.71 .81	.066
Physical	91.4 ± 17.5	87.7 ± 15.9	.38	83.3 ± 15.9 86.6 ± 16.6	82.2 ± 15.9 81.4 ± 16.8	.79 .27	–7.3 ± 22.4 –5.2 ± 25.2	–7.1 ± 17.9 –6.8 ± 14.4	.98 .79	41.7 36.0	40.7 36.0	.95 > .99	**.020**
Total	91.4 ± 14.7	88.3 ± 12.7	.38	86.0 ± 13.5 88.9 ± 11.3	84.8 ± 12.5 83.3 ± 13.9	.74 .12	–4.3 ± 18.9 –2.4 ± 19.3	–4.9 ± 13.4 –5.8 ± 11.7	.90 .47	33.3 32.0	33.3 32.0	> .99 > .99	**.049**
Composite (excl. global)	91.4 ± 14.5	88.2 ± 12.8	.36	86.0 ± 13.4 88.6 ± 11.3	84.4 ± 12.6 83.1 ± 13.7	.67 .12	–4.4 ± 18.6 –2.7 ± 19.1	–5.2 ± 13.7 –5.8 ± 11.6	.86 .48	33.3 28.0	33.3 32.0	> .99 .76	**.033**

NOTE. Defined as decrease of at least 10 points.

Abbreviations: CMC, clinically meaningful change; LMM, linear mixed modeling; RT, radiotherapy; SD, standard deviation; TORS + ND, transoral robotic surgery plus neck dissection; Y, year.

[a]*P* values < .05 shown as bold.

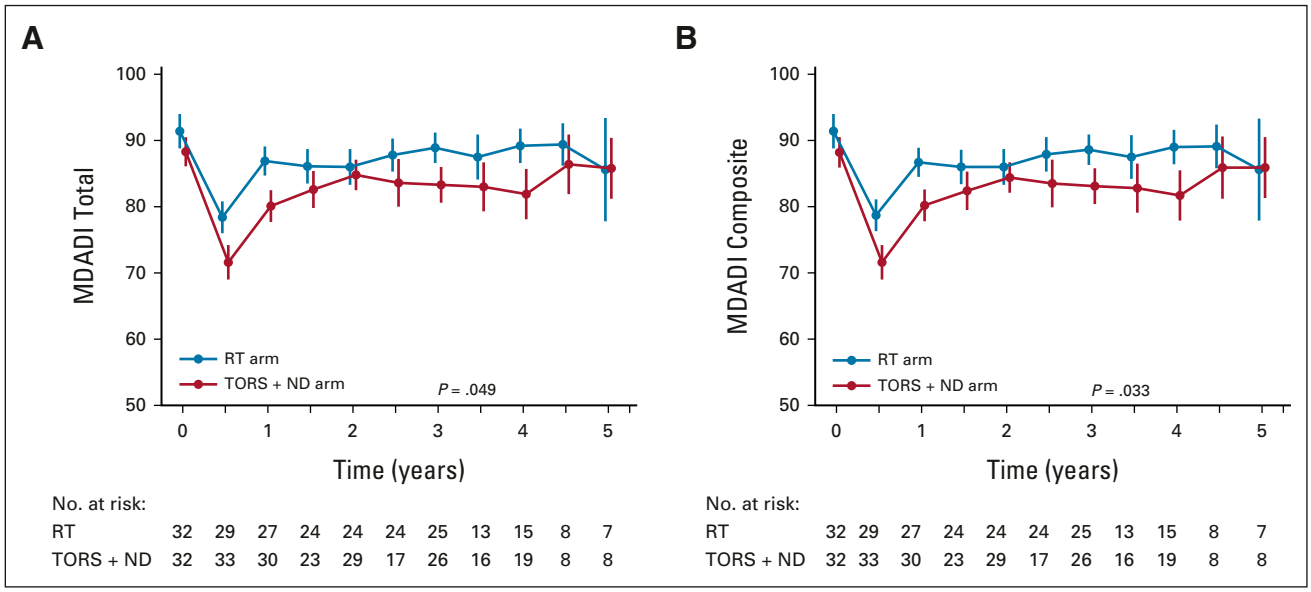

FIG 2. Changes in MDADI (A) total and (B) composite quality-of-life scores over time by treatment arm. Error bars represent standard errors. MDADI, MD Anderson Dysphagia Inventory; RT, radiotherapy; TORS + ND, transoral robotic surgery plus neck dissection.

94.8% [95% CI, 84.8 to 98.3] *v* 37.5% [95% CI, 8.7 to 67.4], $P < .001$; 3-year PFS: 93.1% [95% CI, 82.7 to 97.4] *v* 37.5% [95% CI, 8.7 to 67.4], $P < .001$, Data Supplement). For p16-positive patients, the 3-year OS and PFS for the RT arm were both 96.3% (95% CI, 76.5 to 99.5), and 93.3% (95% CI, 75.9 to 98.3) and 90.0% (95% CI, 72.1 to 96.7), respectively, for the TORS + ND arm (Data Supplement). For p16-negative patients, the 3-year OS and PFS for the RT arm were both 25.0% (95% CI, 0.9 to 66.5), and both 50.0% (95% CI, 5.8 to 84.5) for the TORS + ND arm (Data Supplement).

Additional QOL Metrics

Outcomes from other QOL metrics are shown in the Data Supplement. In general, most QOL scores were similar between the two groups at 2 and 3 years, with few exceptions. On the European Organisation for Research and Treatment of Cancer Head & Neck 35, significant differences on longitudinal analyses were noted for speech, social eating, dry mouth, and coughing. Dry mouth was worse in the RT arm, whereas social eating and coughing were worse in the TORS + ND arm. Differences in speech fluctuated over time. No differences were noted in Neck

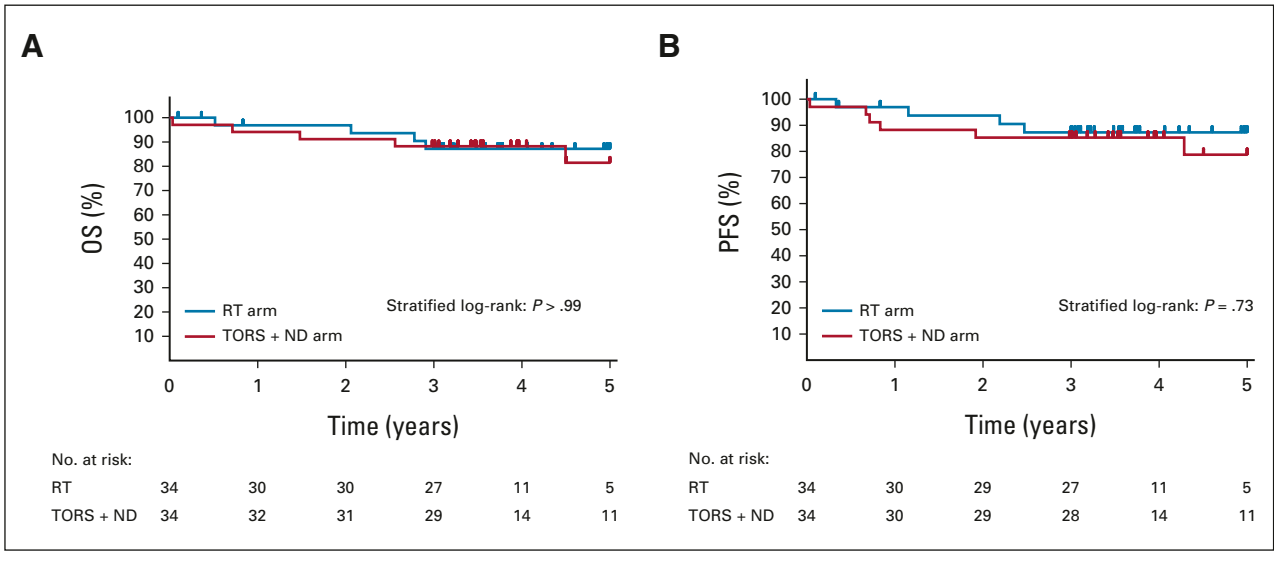

FIG 3. (A) OS and (B) PFS stratified by treatment arm. OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TORS + ND, transoral robotic surgery plus neck dissection.

TABLE 3. Summary of AEs Significantly Different Between Treatment Arms

	RT Arm					TORS + ND Arm					
AE	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5	*P*
Constipation	5	4	—	—	—	2	—	—	—	—	.037
Cough	3	—	—	—	—	9	2	—	—	—	.040
Hearing loss (on the basis of audiogram)	5	2	6	—	—	5	—	—	—	—	.028
Neutropenia	—	3	2	1	—	—	—	—	—	—	.025
Other pain	5	7	1	—	—	8	15	1	—	—	.038
Tinnitus	11	—	1	—	—	2	—	—	—	—	.0055
Trismus	1	—	—	—	—	6	2	1	—	—	.020
Weakness (subjective)	2	2	—	—	—	10	1	—	—	—	.030

NOTE. Complete list of AEs is reported in the Data Supplement.
Abbreviations: AE, adverse event; G, grade; RT, radiotherapy; TORS + ND, transoral robotic surgery plus neck dissection.

Dissection Impairment Index or Voice Handicap Index scores over time.

Adverse Events

Overall rates of treatment-related grade ≥ 2 adverse events were unchanged from those reported previously (31 [91%] of 34 patients in the RT arm *v* 33 [97%] of 34 patients in the TORS + ND arm, $P = .61$, Table 3 and Data Supplement).[6] Similarly, patients in the RT arm experienced more hearing loss (on the basis of audiogram; $P = .028$), neutropenia ($P = .025$), constipation ($P = .037$), and tinnitus ($P = .0055$), whereas patients in the TORS + ND arm experienced more trismus ($P = .020$) and weakness (subjective; $P = .030$), unchanged from those previously reported by grade (Table 3). In addition, patients in the TORS + ND arm experienced more cough ($P = .040$) and pain ($P = .038$), both previously not significant.

DISCUSSION

With extended follow-up in the ORATOR trial, differences in MDADI scores between the RT and TORS + ND arms remain statistically significant on longitudinal analysis, but decrease over time, and do not meet the definition of a CMC. However, aside from strictly swallowing QOL, the different modalities have important trade-offs, including more ototoxicity and neutropenia in the RT arm, and more pain, trismus, and bleeding in the TORS + ND arm. Although important, the ototoxicity and neutropenia in the RT arm were mild. The two treatments have similar oncologic outcomes. Ultimately, the risks and benefits of each treatment approach need to be a joint decision between patients and caregivers, taking into account outcomes and experience at each center.

To provide more robust assessments of QOL compared with the initial report of this trial, we compared each patients' MDADI score with their own baseline score, and we also assessed the number of patients with CMCs at 2 and 3 years, and there were no differences between the RT and TORS + ND arms. Notably, the impact of adjuvant treatment after TORS on long-term MDADI scores was relatively small. Post hoc analyses suggest that some of the differences in swallowing outcomes may be because of base of tongue lesions compared with tonsillar fossa lesions, a finding that will be clarified by the full reporting of other surgical trials including PATHOS and E3311.[11] Caution must be taken when comparing outcomes across clinical trials; however, our qualitative comparison of the composite MDADI scores to E3311 stratified by adjuvant therapy suggests the external validity of our findings.

Our conclusions must be considered in the context of the limitations of this trial. The main limitation is the modest sample size. Although sufficiently powered to compare QOL outcomes at one year, with the attrition in QOL completion over time, our study was not powered to definitively compare long-term QOL outcomes, survival outcomes, or the post hoc analyses that we have carried out on an exploratory basis. Although this study is modest in absolute numbers, it is large in the context of trials of surgery versus RT in oncology in general, of which 75% fail to accrue (including one previous TORS *v* RT trial).[12] A second limitation is the lack of a universal consensus regarding the indications for adjuvant treatment (ie, RT or CRT) after TORS and for use of concurrent chemotherapy for N1 disease. In effect, rather than being a pure comparison of RT alone versus TORS + ND, this trial is a comparison of two treatment packages that include multiple modalities for most patients. Considering the results of the E3311 and HN002 trials,[11,13] in retrospect, our approach was likely aggressive in both arms, although well within the realm of standard practice at the time of study design.

In conclusion, in contrast to prior retrospective comparisons, RT- and TORS-based approaches were associated with clinically similar QOL outcomes, but differing spectra of toxicities, and differences in QOL between arms decreased over time. Clinicians and patients should be involved in shared decision making, in a multidisciplinary context, to individualize treatment for OPSCC.

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DISCLAIMER

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DATA SHARING STATEMENT

The trial Protocol did not have a data-sharing plan, and data sharing was not included in the letter of information and consent; thus, the source data from the trial will not be shared publicly.

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

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