Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial

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Summary

Background Transoral robotic surgery (TORS) with concurrent neck dissection has supplanted radiotherapy in the USA as the most common treatment for oropharyngeal squamous cell carcinoma (OPSCC), yet no randomised trials have compared these modalities. We aimed to evaluate differences in quality of life (QOL) 1 year after treatment.

Methods The ORATOR trial was an investigator-initiated, multicentre, international, open-label, parallel-group, phase 2, randomised study. Patients were enrolled at six hospitals in Canada and Australia. We randomly assigned (1:1) patients aged 18 years or older, with Eastern Cooperative Oncology Group scores of 0–2, and with T1–T2, N0–2 (≤4 cm) OPSCC tumour types to radiotherapy (70 Gy, with chemotherapy if N1–2) or TORS plus neck dissection (with or without adjuvant chemoradiotherapy, based on pathology). Following stratification by p16 status, patients were randomly assigned using a computer-generated randomisation list with permuted blocks of four. The primary endpoint was swallowing-related QOL at 1 year as established using the MD Anderson Dysphagia Inventory (MDADI) score, powered to detect a 10-point improvement (a clinically meaningful change) in the TORS plus neck dissection group. All analyses were done by intention to treat. This study is registered with ClinicalTrials.gov (NCT01590355) and is active, but not currently recruiting.

Findings 68 patients were randomly assigned (34 per group) between Aug 10, 2012, and June 9, 2017. Median follow-up was 25 months (IQR 20–33) for the radiotherapy group and 29 months (23–43) for the TORS plus neck dissection group. MDADI total scores at 1 year were mean 86·9 (SD 11·4) in the radiotherapy group versus 80·1 (13·0) in the TORS plus neck dissection group (p=0·042). There were more cases of neutropenia (six [18%] of 34 patients *vs* none of 34), hearing loss (13 [38%] *vs* five [15%]), and tinnitus (12 [35%] *vs* two [6%]) reported in the radiotherapy group than in the TORS plus neck dissection group, and more cases of trismus in the TORS plus neck dissection group (nine [26%] *vs* one [3%]). The most common adverse events in the radiotherapy group were dysphagia (n=6), hearing loss (n=6), and mucositis (n=4), all grade 3, and in the TORS plus neck dissection group, dysphagia (n=9, all grade 3) and there was one death caused by bleeding after TORS.

Interpretation Patients treated with radiotherapy showed superior swallowing-related QOL scores 1 year after treatment, although the difference did not represent a clinically meaningful change. Toxicity patterns differed between the groups. Patients with OPSCC should be informed about both treatment options.

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Introduction

There has been a substantial rise in the incidence of oropharyngeal squamous cell carcinoma (OPSCC) worldwide, due to increasing prevalence of oral infection with human papillomavirus (HPV).[1] HPV-related OPSCC arises in a younger and healthier cohort than traditional smoking-related and alcohol-related cancers, and the proportion of patients who are cured of their disease is higher, with 5 year survival exceeding 80%.[2] In light of these changes in incidence, demographics, and treatment outcomes, the importance of quality of life (QOL) after treatment has increased substantially, given that patients might need to live with treatment-related morbidity for decades.[3]

Historically, the management of OPSCC has relied on radiotherapy-based approaches. Older surgical approaches, consisting of techniques that required large incisions, mandibulotomies, and division of the floor-of-mouth musculature, were not favoured at most institutions, because of the high morbidity and mortality shown in

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See Online for appendix

Research in context

Evidence before this study

A previously published systematic review of the literature by Yeh and colleagues (2015) did not identify any randomised trials comparing transoral robotic surgery (TORS) and radiotherapy for the treatment of oropharyngeal cancer. The review concluded that both modalities achieved similar oncological outcomes, but that functional outcomes appeared better with TORS, based on non-randomised studies. This previous systematic review examined English-language MEDLINE studies published before July, 2015, using search words referring to "transoral robotic surgery", "radiation therapy", "oropharyngeal cancers", and synonymous terms. We updated the systematic review to April 1, 2019, based on the previously published detailed search strategy of Yeh and colleagues and did not identify any new randomised trials.

Added value of this study

In this randomised trial, swallowing-related quality of life was improved with radiotherapy compared with TORS, although the difference was not a clinically meaningful change. The two approaches differed in their toxicity profiles, and oncological outcomes were similar. These findings conflict with previous non-randomised comparisons of radiotherapy and TORS, and suggest that the conclusions from such comparisons were subject to selection bias or confounding.

Implications of all the available evidence

These findings suggest that the TORS should not be favoured over radiotherapy, and that the widespread adoption of TORS in some jurisdictions was premature.

observational studies.[4] The addition of concurrent chemotherapy to radiotherapy has improved oncological outcomes and survival,[5] at the cost of markedly increased toxicity, with a treatment-related mortality risk of up to 3%.[2,6]

The development of minimally invasive surgical techniques, including transoral laser microsurgery (TLM) and transoral robotic surgery (TORS), has led to a resurgence of surgery as the primary treatment of OPSCC.[7] In the USA, based on data from the National Cancer Database, the percentage of patients undergoing primary surgery for T1–T2 stage OPSCC increased from 56% (318 of 568) in 2004 to 82% (837 of 1021) in 2013, driven by patient preferences and assumptions of reduced toxicity or improved QOL.[7] This important shift has occurred despite a scarcity of evidence from randomised trials, making the management of OPSCC controversial.[8] Radiotherapy-based approaches have also evolved, with randomised trials showing less toxicity with newer technologies, because of better sparing of important normal structures, including the organs responsible for swallowing and saliva production.[9]

To our knowledge, no prior randomised trial has compared radiotherapy and any type of surgical approach for OPSCC. In this Article, we report the outcomes of a randomised trial comparing primary radiotherapy (with or without chemotherapy) to TORS with neck dissection (with or without adjuvant therapy) in patients with OPSCC, designed to definitively compare QOL between the two approaches.

Methods

Study design and participants

The ORATOR trial was an investigator-initiated, multicentre, international, open-label, parallel-group, phase 2, randomised study. Patients with T1 or T2, N0–N2 (maximum nodal size ≤4 cm) OPSCC were randomly assigned to either radiotherapy, with concurrent chemotherapy in node-positive patients (radiotherapy group), or TORS plus neck dissection, with adjuvant therapy depending on pathological findings (TORS plus neck dissection group). The abridged protocol has been published elsewhere,[10] and the full protocol is available in the appendix. Patients were enrolled at six hospitals in Canada and Australia (appendix p 2). Appropriate regulatory approval, including ethics institutional review-board approval, was obtained in all jurisdictions.

Patients were required to be aged 18 years or older and willing to provide informed consent, with good performance status (Eastern Cooperative Oncology Group [ECOG] score 0–2), and histologically proven OPSCC, with stage T1–2, N0–2, M0 disease (all staging reported herein is as per the 7th edition of the American Joint Committee on Cancer staging manual). All nodes were required to be 4 cm or smaller, without extranodal extension on imaging, and the primary tumour site had to be located in the oropharynx. Patients were required to have adequate bone marrow, hepatic, and renal function for chemotherapy, defined as: haemoglobin higher than 80 g/L; absolute neutrophil count higher than $1·5\times10^9$ cells per L; platelet count higher than 100×10^9 per L; bilirubin concentration lower than 35 µmol/L; aspartate aminotransferase or alanine aminotransferase lower than three times the upper limit of normal; and serum creatinine concentration less than 130 µmol/L or creatinine clearance of at least 50 mL/min. Imaging evaluation included a CT or MRI of the neck, with a CT of the chest. PET CT was optional. We did not centrally review the staging imaging. Assessment at a head-and-neck multidisciplinary clinic (with assessment by a radiation oncologist and surgeon) and presentation at a multidisciplinary tumour board were required before enrolment, for confirmation of trial appropriateness. All patients provided written informed consent.

The exclusion criteria included serious medical comorbidities precluding radiotherapy, chemotherapy,

or surgery, previous history of head-and-neck cancer within 5 years, previous head-and-neck radiation at any time, distant metastatic disease, previous invasive malignancy within 5 years (except non-melanoma skin cancer), inability or unwillingness to complete QOL questionnaires, and pregnancy or lactation.

Randomisation and masking

Patients were randomly assigned (1:1) to groups using a computer-generated randomisation list, prepared by a statistician who was not involved in subsequent trial conduct, using a 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). Patients were allocated after receipt of a completed enrolment form and other regulatory documents (including consent); these documents were received by fax at the coordinating centre. On receipt of these documents, enrolment and assignment were done by a trial coordinator who was not involved in clinical management. The co-ordinator was the only person able to access the locked, concealed randomisation list, and treatment group was communicated by email. Neither patients nor enrolling physicians were masked to treatment allocation.

Procedures

In the radiotherapy group, radiation was delivered using intensity-modulated radiotherapy techniques, including volumetric modulated arc therapy. Full details of the procedures are available in the protocol (appendix p 21); briefly, the prescribed dose was 70 Gy in 35 fractions over 7 weeks to areas of gross disease, and 56 Gy to low-risk nodal areas. An optional 63 Gy volume was allowed for high-risk nodal areas. Peer-review of radiation plans was required. Concurrent chemotherapy was recommended for patients with node-positive disease. High-dose cisplatin (100 mg/m² intravenously) every 3 weeks was preferred, but in patients who were not sufficiently fit, this schedule could be modified to weekly cisplatin, cetuximab, or carboplatin. In patients not receiving chemotherapy, the radiation could be delivered over 6 weeks at the discretion of the radiation oncologist. Radiotherapy response was evaluated 8–12 weeks after radiotherapy using CT with or without PET–CT, as per local institutional standards, with salvage surgery recommended wherever feasible for persistent or recurrent disease. There were no planned neck dissections (ie, salvage surgery was only undertaken if persistent disease was documented on imaging).

In the TORS plus neck dissection group, a surgical robot was used to excise the primary tumour with 1 cm margins, with selective neck dissections done at the time of surgery or within 2 weeks. Full surgical details are available in the protocol (appendix p 26). It was mandated that the lingual and facial branches of the external carotid artery ipsilateral to the tumour be ligated. The protocol was modified after a death due to oropharyngeal bleeding to strongly recommend (but not mandate) a tracheostomy at the time of surgery for all patients, to provide airway protection in case of swelling or bleeding. A detailed analysis of surgical techniques, including margin control, margin status, nodal yield, frequency of contralateral lymph node metastases, local reconstruction techniques used, compliance with ipsilateral external carotid ligation, and discrepancy between clinical and pathological stage, will be reported separately in a future publication. Adjuvant radiotherapy, to a total dose of 60 Gy in 30 fractions and starting within 6 weeks of surgery, was recommended for patients based on intermediate-risk pathological features (pT3 or pT4 disease, close resection margins [<2 mm], nodal disease, or lymphovascular invasion). In situations with high-risk features (positive margins or extra-nodal extension), adjuvant chemoradiotherapy was given, and the radiation dose was increased to 64 Gy in 30 fractions.

Follow-up occurred every 3 months for the first 2 years, and every 6 months thereafter until 5 years and included patient history and physical examination (all visits), adverse event monitoring (all visits), QOL scoring (every 6 months), chest x-ray every 6 months except at 1 year when a CT of the neck and chest was completed, and an audiogram 1 year after treatment (full details described in the protocol (appendix p 32). In the radiotherapy group, an additional scan was done 8–12 weeks after radiotherapy to assess response and need for salvage surgery, as previously described. Patients could voluntarily discontinue parti-cipation in the study at any time.

The primary QOL tool used was the MD Anderson Dysphagia Index (MDADI). The MDADI score ranges between 20 and 100, and a higher score represents better QOL.[11] A 10-point change in scores was considered a clinically meaningful change.[12,13] The MDADI is also subdivided into subscales, including functional (five questions), physical (eight questions), emotional (six questions), and global (one question) domains; the former three domains are also combined into the composite score; all domains are reported as scores from 20 to 100. Other QOL scales we used included the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients general (QLQ-C30) and head & neck (H&N35) scales, the Voice Handicap Index (VHI-10), the Neck Dissection Impairment Index (NDII), the Patient Neurotoxicity Questionnaire (PNQ), and the Functional Oral Intake Scale (FOIS). The EORTC QLQ-C30 and H&N35 include a variety of subscales, including global health status (two questions), physical (five questions), role (two questions), emotional (four questions), cognitive (two questions), and social (two questions) and a variety of symptom-based subscales, each normalised to a scale of 0–100 with higher scores indicative of worse QOL (with the exception of global health status). The VHI-10 has a score range between 0 and 40 and the NDII has a

	All patients (n=68)	RT group (n=34)	TORS + ND group (n=34)
Age, median (IQR)	58·5 (52·9–65·2)	60·0 (53·2–65·2)	58·1 (52·6–64·5)
Sex			
Male	59 (87%)	31 (91%)	28 (82%)
Female	9 (13%)	3 (9%)	6 (18%)
Smoking history	49 (72%)	28 (82%)	21 (62%)
>21 drinks per week	7/40 (18%)	1/18 (6%)	6/22 (27%)
Primary site			
Tonsil or tonsillar foss	50 (74%)	26 (76%)	24 (71%)
Base of tongue	18 (26%)	8 (24%)	10 (29%)
Clinical T stage			
T1	30 (44%)	13 (38%)	17 (50%)
T2	38 (56%)	21 (62%)	17 (50%)
Clinical N stage			
N0	21 (31%)	12 (35%)	9 (26%)
N1	12 (18%)	5 (15%)	7 (21%)
N2	35 (51%)	17 (50%)	18 (53%)
Baseline ECOG			
0	60 (88%)	30 (88%)	30 (88%)
1	8 (12%)	4 (12%)	4 (12%)
Baseline scan			
CT head, neck, and chest	40 (59%)	22 (65%)	18 (53%)
CT chest and MRI head and neck	6 (9%)	2 (6%)	4 (12%)
CT neck and chest	9 (13%)	4 (12%)	5 (15%)
PET and CT neck and chest	13 (19%)	6 (18%)	7 (21%)
p16 positive	60 (88%)	30 (88%)	30 (88%)
Radiotherapy	56 (82%)	32 (94%)	24 (71%)
Chemotherapy	31 (46%)	23 (68%)	8 (24%)
Chemotherapy regimen			
Cisplatin	24/31 (77%)	19/23 (83%)	5/8 (63%)
Carboplatin	6/31 (19%)	3/23 (13%)	3/8 (38%)
Cetuximab	1/31 (3%)	1/23 (4%)	0
Chemotherapy cycles, median (IQR)	3 (3–6)	3 (2–6)	6 (4·5–6)

Data are presented as number (%) unless otherwise stated. RT=radiotherapy. TORS + ND=transoral robotic surgery and neck dissection. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline and treatment characteristics**

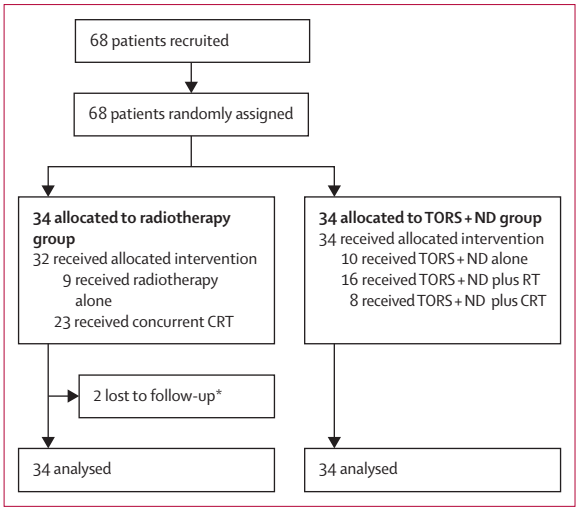

Figure 1: **Trial profile**
RT=radiotherapy. CRT=chemoradiotherapy. TORS + ND=transoral robotic surgery plus neck dissection. *Withdrew consent after randomisation to the radiotherapy group, and did not receive allocated intervention.

score range between 0 and 100, both with higher scores representing worse QOL. The PNQ includes two items to indicate the level of neurotoxicity on the basis of numbness and weakness using a 5-point Likert scale. The FOIS is comprised of seven levels ranging from 1 (nothing by mouth) to 7 (total oral diet with no restrictions), with higher scores indicative of better QOL. All QOL scores were centrally reviewed, but imaging data were not.

Outcomes

The primary endpoint was a definitive comparison of the total score on the MDADI at 1 year. Prespecified secondary endpoints were: overall survival, defined as time from randomisation to death from any cause; progression-free survival, defined as time from randomisation to death or recurrence, whichever occurred first; QOL at other time points using the MDADI, the EORTC QLQ-C30, H&N35 scales, the VHI-10, NDII, and the PNQ; toxicity, as assessed by the Common Toxicity Criteria for Adverse Events (CTC-AE) scale version 4; and swallowing function, as measured by the percutaneous feeding-tube use at 1 year, and the FOIS, in addition to the MDADI and CTC-AE scores.

Statistical analysis

The study was designed to definitively compare MDADI scores between groups at 1 year. We 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 of 0·05 and power of 90%, assuming 10% dropout, to detect a 10-point improvement in QOL in the TORS plus neck dissection group a total of 68 patients were required.

Although all analyses were by intention to treat, and all available data were included, patients who withdrew from the study, died, or were lost to follow-up within 1 year could not be included in the 1 year MDADI analysis. We anticipated this by including a 10% anticipated dropout in our sample-size calculation. We did not attempt to replace missing data using statistical techniques (eg, imputation or a last-observation-carried-forward technique), and therefore QOL analyses are based on the number of completed surveys at each time point, whereas survival analyses use censoring as per the Kaplan-Meier method. Numbers of completed surveys and numbers at risk are provided in the relevant figures.

An independent two-sample t-test was used to compare QOL scores at 1 year. The percentage of patients in each group who had a clinically meaningful QOL decline (ten points) were also calculated and compared using the χ^2 Test or Fisher's Exact test as appropriate. Survival was calculated from the date of randomisation using the

Kaplan-Meier method with differences compared using the log-rank test. A preplanned subgroup analysis was undertaken on the basis of the stratification variable (p16 status). For the secondary endpoints involving QOL scales, linear mixed-effects models were created; for the MDADI, NDII, and VHI-10, the total scores were compared between groups, whereas for the EORTC scales, each of the subscales (eg, pain and swallowing) were compared. Other QOL outcomes were compared using the χ^2 Test or Fisher's Exact test as appropriate. Given the possibility that adjuvant treatments affected the QOL scores in the TORS plus neck dissection group, a post-hoc exploratory analysis was done to examine the MDADI scores on the basis of treatment intensity. A separate, post-hoc sensitivity analysis of the primary endpoint, adjusting for stratification, was also done. All statistical analyses were done using SAS version 9.4 software with two-sided statistical testing at the 0·05 significance level.

The data safety and monitoring committee met quarterly after study initiation to review toxicity outcomes. The trial was placed on hold in June, 2013, after an unexpected death caused by bleeding in the TORS plus neck dissection group, and was reopened to accrual in July, 2013. A prespecified interim analysis was undertaken in January, 2017, after 30 patients accrued and were followed-up for 1 year. The prespecified Haybittle-Peto stopping rule (a difference in overall survival meeting a threshold of $p<0·001$, with no p value penalty in the final analysis) was not met at the interim analysis, and the trial continued to full accrual. The data safety and monitoring committee also had the ability to adjust the sample size calculation if the assumptions, particularly the standard deviations of the MDADI scores, were erroneous, but no changes were required. The dataset was locked for outcomes on Jan 14, 2019. This study is registered with Clinicaltrials.gov (NCT01590355).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The first author (ACN), last author (DAP), and statistician (AW) had full access to the data, vouch for the integrity of the data and the adherence to the study protocol, and are responsible for the final decision to submit for publication.

Results

Between Aug 10, 2012, and June 9, 2017, 68 patients were randomly assigned (34 in each group) to the radiotherapy group or the TORS plus neck dissection group. Baseline characteristics are shown in table 1. The groups were well balanced for baseline factors, including p16 status. Median age was 58·5 years (IQR 52·9–65·2) and 59 (87%) of 68 patients were men. Primary tumour sites were palatine tonsil (26 [76%] of 34 for radiotherapy group and 24 [71%] of 34 for TORS plus neck dissection group) and base of tongue (8 [24%] and 10 [29%], respectively).

The trial profile is shown in figure 1. Two patients that were assigned to the radiotherapy group withdrew from the study after randomisation. Of the remaining 32 patients in the radiotherapy group, nine (28%) received radiotherapy alone while 23 (72%) received concurrent chemotherapy. Four (12%) patients required salvage surgery when imaging after radiotherapy was suspicious for persistent disease (n=1 at the primary site and n=3 in the neck), with surgery completed at a mean of 97 days after radiotherapy. In the TORS plus neck dissection group, ten (29%) of 34 patients received surgery alone, 16 (47%) received postoperative radiotherapy, and eight (24%) received postoperative chemoradiotherapy. Resection margins were negative in 30 patients (ie, an R0 resection) and positive in four patients (R1 resections). There were no patients with macroscopic residual disease (R2 resections). Pathological staging was pT1 in 15 patients, pT2 in 15 patients, pT3 in four patients, pN0 in ten patients, pN1 in seven patients, and pN2 in 17 patients.

Median follow-up was 27 months (IQR 20–48): 25 months (20–33) for the radiotherapy group and 29 months (23–43) for the TORS plus neck dissection group. MDADI scores at 1 year, including subscales, are shown in table 2. Total mean MDADI scores (the primary endpoint) were 86·9 (SD 11·4) in the

	1 year				Clinically meaningful decline*		
	RT group	TORS + ND group	Effect estimate (95% CI)	p value†	RT group	TORS + ND group	p value
Total (primary endpoint)	86·9 (11·4)	80·1 (13·0)	6·7 (0·2 to 13·2)	0·042	7/27 (26%)	11/27 (41%)	0·25
Global	89·6 (15·1)	79·3 (22·6)	10·3 (0·2 to 20·4)	0·046	6/27 (22%)	14/27 (52%)	0·024
Emotional	88·8 (12·0)	81·3 (12·5)	7·4 (0·9 to 14·0)	0·027	5/27 (19%)	13/27 (48%)	0·021
Functional	89·9 (11·5)	86·5 (12·0)	3·4 (−2·9 to 9·6)	0·28	7/27 (26%)	9/26 (35%)	0·49
Physical	83·1 (14·1)	75·3 (16·5)	7·9 (−0·3 to 16·0)	0·058	12/27 (44%)	16/27 (59%)	0·28
Composite (total score excluding global score)	86·7 (11·4)	80·2 (13·1)	6·5 (0·0 to 13·1)	0·049	6/27 (22%)	11/27 (41%)	0·14

Data are presented as mean (SD) unless otherwise stated. RT=radiotherapy. TORS + ND=transoral robotic surgery and neck dissection. *Defined as a decrease of at least 10 points. †p values adjusted for stratification by p16 status (post-hoc analysis): total (p=0·054), global (p=0·071), emotional (p=0·040), functional (p=0·29), physical (p=0·064), and composite (p=0·062).

Table 2: **Quality-of-life scores at 1 year for the MD Anderson Dysphagia Inventory**

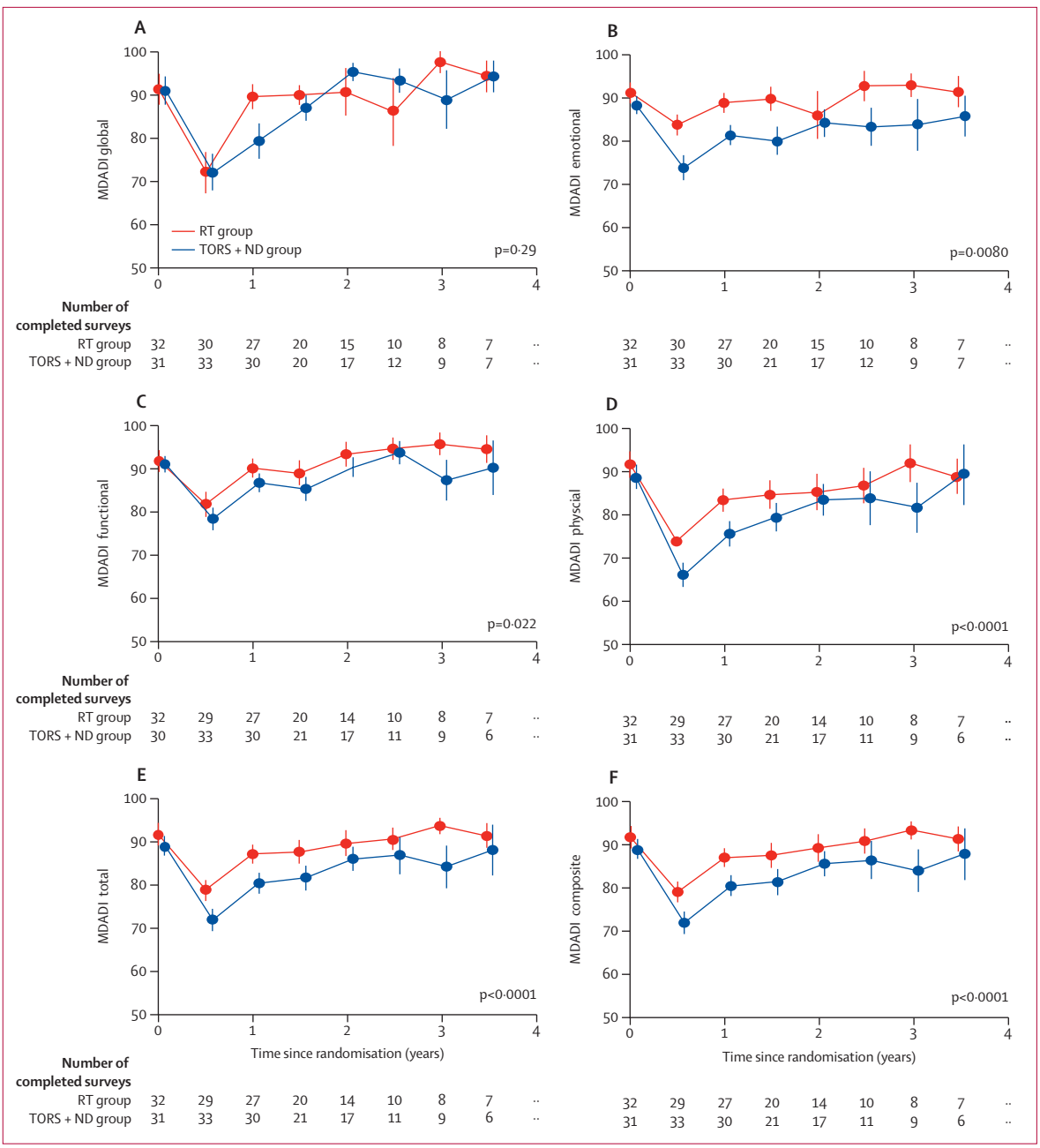

Figure 2: **Changes in MDADI quality-of-life scores over time by domain and by treatment group**
MDADI=MD Anderson Dysphagia Inventory. RT=radiotherapy. TORS + ND=transoral robotic surgery plus neck dissection.

radiotherapy group versus 80·1 (13·0) in the TORS plus neck dissection group (p=0·042), but the difference did not meet the prespecified threshold (10 points) for a clinically meaningful difference. For the 1-year QOL outcomes, data were unavailable for seven patients in the radiotherapy group and four patients in the TORS plus neck dissection group, due to withdrawal from study, deaths, or survey non-completion. Outcomes from other QOL metrics are shown in the appendix (p 3). In general, most QOL scores were similar between the two groups, with the exception of inferior scores regarding EORTC QLQ-C30 pain (p=0·018) and EORTC QLQ-H&N35 teeth scores (p=0·014) in the TORS plus neck dissection group.

Longitudinal MDADI analyses (figure 2) confirmed the statistical superiority of radiotherapy versus TORS plus neck dissection in total MDADI scores overall across all patient visits and most subscales, but with average differences below the threshold of a clinically meaningful change.

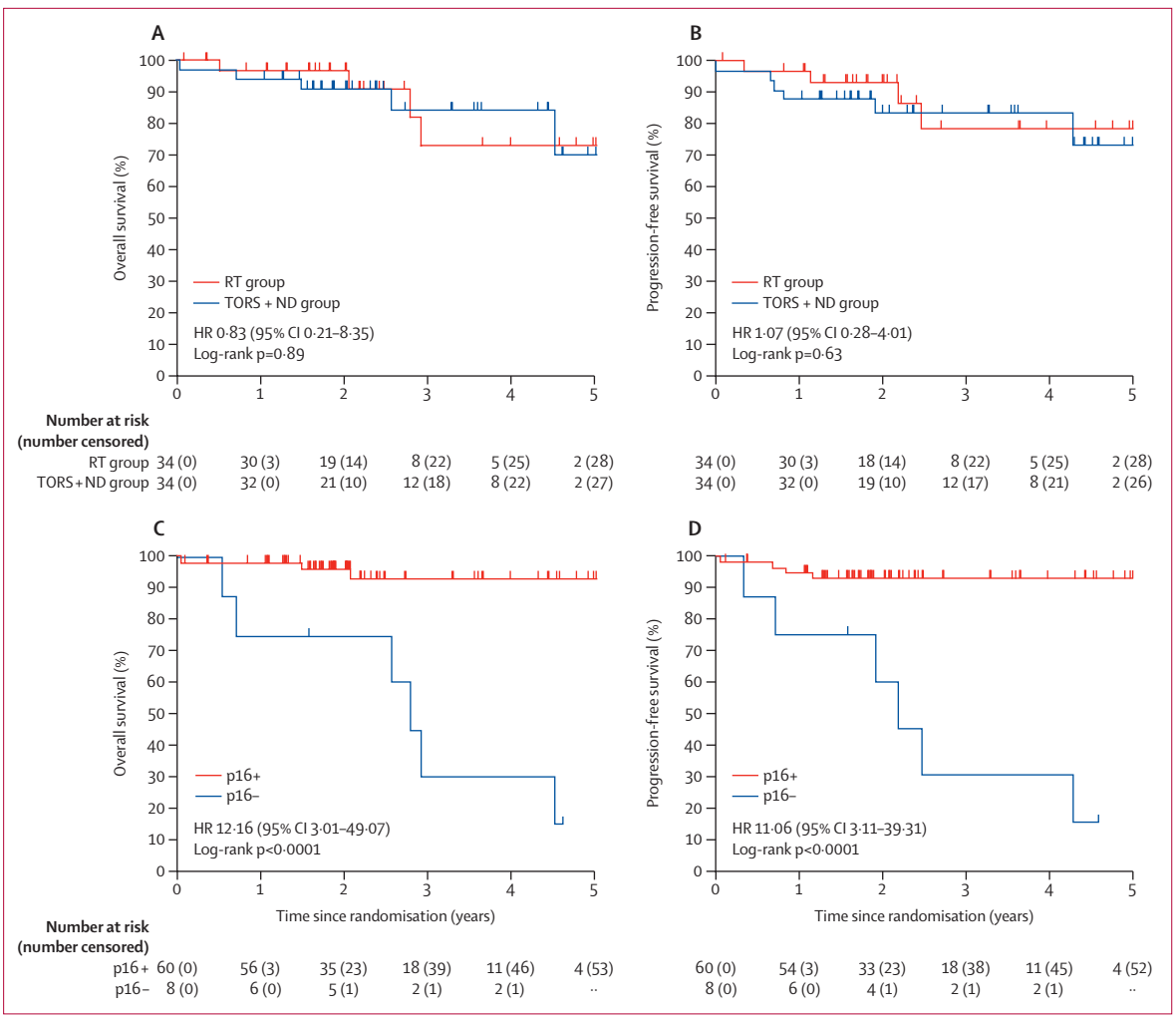

Figure 3: **Overall survival and progression-free survival by treatment group (A and B) and p16 status (C and D)**
HR=hazard ratio. p16+=p16-positive tumour. p16–=p16-negative tumour. RT=radiotherapy. TORS + ND=transoral robotic surgery plus neck dissection.

The proportion of patients with a clinically meaningful decline in QOL scores for each scale other than MDADI is also shown in the appendix (p 5). There was no significant difference in the proportion of patients with a clinically significant decline in the primary endpoint, total MDADI score, or functional, physical, or composite MDADI subscales, but a significantly higher proportion of patients exhibited clinically meaningful declines in global and emotional subscales in the TORS plus neck dissection group (table 2).

The percentage of patients receiving total oral diet with no restrictions (based on the FOIS scale) at 1 year was 27 (100%) of 27 patients in the radiotherapy group and 26 (84%) of 31 in the TORS plus neck dissection group (p=0·055). Of note, the patient in the radiotherapy group with a G-tube at 1 year had a normal FOIS score; tube feeds had been stopped.

The post-hoc analysis of MDADI scores by treatment intensity showed significant differences in the radiotherapy group but not in the TORS plus neck dissection group. In the radiotherapy group, MDADI total scores at 1 year based on treatment intensity were as follows: radiotherapy alone mean 89·5 (SD 6·2); chemoradiotherapy alone 88·0 (11·5); and chemoradiotherapy with subsequent salvage surgery 68·0 (7·1; ANOVA p=0·044). In the TORS plus neck dissection group, MDADI scores by treatment intensity were: TORS plus neck dissection alone 82·8 (10·5); TORS plus neck dissection with radiotherapy 78·5 (11·0); and TORS plus neck dissection with chemoradiotherapy 80·4 (19·6; ANOVA p=0·76). The post-hoc sensitivity analysis re-examining 1 year MDADI comparisons while adjusting for stratification attenuated the strength of the findings, with slightly higher p values for comparisons (table 2).

Overall survival and progression-free survival for both groups are shown in figure 3. Overall survival and progression-free survival were excellent in both groups, and there were no significant differences between groups

	Radiotherapy group (n=34)				TORS + ND group (n=34)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Abscess	0	0	0	0	0	1 (3%)	0	0
Alopecia	11 (32%)	0	0	0	4 (12%)	0	0	0
Anorexia	14 (41%)	2 (6%)	0	0	12 (35%)	0	0	0
Anxiety	3 (9%)	0	0	0	2 (6%)	0	0	0
Appetite	3 (9%)	0	0	0	4 (12%)	0	0	0
Aspiration	0	0	0	0	4 (12%)	0	1 (3%)	0
Aspiration pneumonia	0	1 (3%)	0	0	0	0	0	0
Atrial fibrillation	0	0	0	0	1 (3%)	0	0	0
Bleeding (oral cavity)	1 (3%)	0	0	0	4 (12%)	0	1 (3%)	1 (3%)
Confusion	2 (6%)	0	0	0	0	0	0	0
Constipation*	9 (26%)	0	0	0	2 (6%)	0	0	0
Cough	4 (12%)	0	0	0	11 (32%)	0	0	0
Decrease oxygen	0	0	0	0	1 (3%)	0	0	0
Dehydration	3 (9%)	3 (9%)	0	0	1 (3%)	1 (3%)	0	0
Dermatology (skin)	4 (12%)	2 (6%)	0	0	3 (9%)	0	0	0
Diarrhoea	3 (9%)	0	0	0	2 (6%)	0	0	0
Dry mouth	24 (71%)	1 (3%)	0	0	18 (53%)	0	0	0
Dysgeusia	9 (26%)	0	0	0	3 (9%)	0	0	0
Dysphagia	21 (62%)	6 (18%)	0	0	21 (62%)	9 (26%)	0	0
Esophagitis	1 (3%)	0	0	0	0	0	0	0
Fatigue	20 (59%)	0	0	0	12 (35%)	0	0	0
Febrile neutropenia	0	2 (6%)	0	0	0	0	0	0
Headache	5 (15%)	0	0	0	5 (15%)	0	0	0
Hearing loss (audiogram)*	7 (21%)	6 (18%)	0	0	5 (15%)	0	0	0
Haemoglobin	0	1 (3%)	0	0	0	0	0	0
Hoarseness	0	0	0	0	2 (6%)	0	0	0
Hyperglycaemia	0	0	0	0	0	1 (3%)	0	0
Hypoglycaemia	0	0	0	0	0	1 (3%)	0	0
Hypokalaemia	1 (3%)	1 (3%)	0	0	1 (3%)	0	0	0
Hypomagnesium	1 (3%)	1 (3%)	0	0	1 (3%)	0	0	0
Hyponatremia	0	0	1 (3%)	0	0	0	1 (3%)	0
Infection (normal ANC)	0	0	0	0	1 (3%)	0	0	0
Infection (unknown ANC)	0	0	0	0	1 (3%)	0	0	0
Insomnia	4 (12%)	1 (3%)	0	0	4 (12%)	1 (3%)	0	0
Mood change	1 (3%)	0	0	0	1 (3%)	0	0	0
Mouth sores	6 (18%)	4 (12%)	0	0	5 (15%)	0	0	0
Mucositis (oral)	11 (32%)	4 (12%)	0	0	8 (24%)	0	0	0
Nausea	16 (47%)	3 (9%)	0	0	11 (32%)	1 (3%)	0	0
Neutropenia*	3 (9%)	2 (6%)	1 (3%)	0	0	0	0	0
Night sweats	1 (3%)	0	0	0	0	0	0	0
Odynophagia	9 (26%)	0	0	0	9 (26%)	0	0	0
Oral pain	3 (9%)	1 (3%)	0	0	1 (3%)	1 (3%)	0	0
Other pain	12 (35%)	1 (3%)	0	0	22 (65%)	1 (3%)	0	0
Pancytopaenia	2 (6%)	0	0	0	0	0	0	0
Peripheral motor neuropathy	1 (3%)	0	0	0	1 (3%)	0	0	0
Plethoric face	0	0	0	0	1 (3%)	0	0	0
Pneumonia	0	1 (3%)	0	0	2 (6%)	1 (3%)	0	0
Poor oral intake	0	1 (3%)	0	0	0	0	0	0
Post-operative haemorrhage	0	0	0	0	0	2 (6%)	0	0
High potassium serum	0	0	1 (3%)	0	0	0	0	0

(Table 3 continues on next page)

	Radiotherapy group (n=34)				TORS + ND group (n=34)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Saliva (extra)	3 (9%)	0	0	0	3 (9%)	0	0	0
Sensory neuropathy	3 (9%)	0	0	0	6 (18%)	0	0	0
Shoulder weakness	0	0	0	0	3 (9%)	0	0	0
Skin (dermatitis or rash)	19 (56%)	1 (3%)	0	0	13 (38%)	0	0	0
Sore throat	6 (18%)	1 (3%)	0	0	4 (12%)	0	0	0
Stomatitis or mucositis	1 (3%)	1 (3%)	0	0	0	0	0	0
Taste alteration	19 (56%)	0	0	0	17 (50%)	0	0	0
Thick mucous	4 (12%)	0	0	0	8 (24%)	0	0	0
Thrombocytopaenia	0	1 (3%)	1 (3%)	0	0	0	0	0
Tinnitus*	11 (32%)	1 (3%)	0	0	2 (6%)	0	0	0
Trismus*	1 (3%)	0	0	0	8 (24%)	1 (3%)	0	0
Urinary frequency or urgency	1 (3%)	0	0	0	0	0	0	0
Vomiting	9 (26%)	1 (3%)	0	0	3 (9%)	0	0	0
Low white blood cell counts	1 (3%)	0	0	0	0	0	0	0
Weakness (subjective)*	4 (12%)	0	0	0	11 (32%)	0	0	0
Weight loss	10 (30%)	0	0	0	11 (32%)	0	0	0

TORS + ND=transoral robotic surgery and neck dissection. ANC= absolute neutrophil count. *Statistically significant as follows: constipation (p=0·037); hearing loss (audiogram; p=0·028); neutropenia (p=0·025); tinnitus (p=0·0055); trismus (p=0·020); and weakness (subjective; p=0·030).

Table 3: **Summary of adverse events**

(figure 3A, 3B). Patients with p16-positive tumours had markedly improved overall survival and progression-free survival compared with those with p16-negative disease (figure 3C–D; 3-year progression-free survival 93·0%, 95% CI 82·4–97·3 *vs* 30·0%, 4·4–62·8; p<0·0001; 3-year overall survival 93·1%, 79·4–97·8 *vs* 30·0%, 4·4–62·8; p<0·0001).

The incidence of treatment-related grade 2 or higher adverse events were similar (31 [91%] of 34 patients in the radiotherapy group *vs* 33 [97%] of 34 in the TORS plus neck dissection group; table 3). Patients in the radiotherapy group had more hearing loss, neutropenia, constipation, and tinnitus, whereas oral bleeding and trismus was more common in the TORS plus neck dissection group, with one bleeding-related death (table 3). Apart from this death, no patients discontinued treatment because of toxicity. A description of serious adverse events is available in the appendix (p 7). In the radiotherapy group, the causes of death were metastatic disease (n=3, one of which was from a second cancer), and one deemed to be probably due to a sudden cardiac event at an outside hospital. In the TORS plus neck dissection group, causes of death were metastatic disease (n=3, one of which was from a second cancer), one sudden cardiac arrest after presenting with alcohol overdose and severe hypoglycaemia, and one TORS-related bleeding death. Four recurrences were observed in each treatment group. In the radiotherapy group, one local, two distant, and one locodistant recurrence were observed compared with three distant and one regional-distant recurrences in the TORS plus neck dissection group. Use of percutaneous feeding tubes at 1 year was required in one (3%) of 34 patients in the radiotherapy group and no patients in the TORS plus neck dissection group.

Discussion

Herein we report the first randomised comparison, to our knowledge, of radiotherapy versus TORS plus neck dissection for patients with OPSCC, and found results that conflict with previous retrospective data:[14–17] TORS plus neck dissection was not associated with better QOL. Much of the QOL data in this study favour the radiotherapy group; MDADI scores at 1 year were statistically superior after radiotherapy (although the differences did not meet the definition of a clinically meaningful change), radiotherapy patients had better functional oral intake at 1 year (as measured by the FOIS scores), and longitudinal analyses confirmed the durability of these QOL findings.

A previous systematic review comparing outcomes after radiotherapy versus TORS suggested that although oncological outcomes were similar with both modalities, TORS appeared to achieve better functional outcomes.[17] The review identified no previous randomised comparisons, and conclusions were based only upon observational studies. However, the systematic review identified a strong risk of bias due to the inclusion of radiotherapy cohorts in which some patients had advanced T-stage disease that would not be amenable to TORS, and cohorts from earlier years when intensity-modulated radiotherapy was not available.[17] The conflict

between the conclusions of our trial and the previous retrospective studies comparing radiotherapy and TORS likely reflects these biases, and other limitations inherent to retrospective comparisons.

Our data also show a risk of bleeding after TORS that was not well recognised at the time of trial design, and the trial was paused and amended to mitigate that risk. Bleeding after TORS might be an under-reported risk that probably represents an important decision-making factor for patients. These bleeds can be potentially serious, resulting in cerebral hypoxia and death, since arterial blood might enter the airway directly and lead to airway compromise. A systematic review has reported bleeding incidence of 0·5–7·1% after TORS and TLM,[18] and a survey of TORS surgeons reported an operative mortality incidence of 0·3%.[19] However, there is a concern that bleeding has been under-reported in the retrospective literature and the mortality figure might be higher. We reported four bleeding-related adverse events of grade 2 or higher (all within the TORS plus neck dissection group) including two grade 2 events, one grade 4 event, and one death. This risk of bleeding, and the higher pain scores in the TORS plus neck dissection group, must be weighed against the toxicities that were more common in the radiotherapy group, including hearing loss, neutropenia, constipation, and tinnitus.

Our conclusions should 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, our study was not designed to definitively compare survival outcomes, and larger trials are needed for those endpoints. Our sample size, although modest in absolute numbers, is large in the context of trials of surgery versus radiotherapy in oncology in general, of which 75% do not accrue (including one previous TORS *vs* radiotherapy trial).[20] A second limitation is the absence of a universal consensus regarding the indications for adjuvant treatment (ie, radiotherapy or chemoradiotherapy) after TORS plus neck dissection. The indications for adjuvant treatment have been questioned, particularly in the current era where most oropharyngeal cancers are HPV-related and associated with lower recurrence risks, but no level-1 evidence is yet available to guide these decisions. In theory, the use of adjuvant treatment could have worsened the QOL scores in the TORS plus neck dissection group, but our post-hoc analysis showed no differences in MDADI scores on the basis of whether patients received TORS plus neck dissection alone, TORS plus neck dissection and radiotherapy, or TORS plus neck dissection and chemoradiotherapy. This finding suggests that differences in adjuvant treatment did not affect our primary endpoint. The optimal use of adjuvant treatment will be clarified by the ECOG3311 study (NCT01898494), in which patients are randomly assigned after TORS to differing adjuvant therapy approaches, on the basis of pathological findings. In addition, there might be subsets of patients with OPSCC that are more likely to benefit from one modality over another, perhaps on the basis of subsite (ie, tonsil or base of tongue) or tumour size, and such analyses will require larger sample sizes.

There is a substantial research interest in de-escalating treatment for patients who are HPV positive, given their excellent outcomes, in an effort to decrease treatment toxicity.[21] Ongoing trials are investigating lower doses of radiotherapy, decreasing or omitting chemotherapy, decreasing adjuvant therapy doses after primary surgery, and adding immunotherapy.[21,22] The ORATOR2 trial (NCT03210103) is currently accruing, comparing a de-escalated radiotherapy approach versus a TORS approach with de-escalated adjuvant therapy, and an avoidance of triple-modality therapy in both groups.

In conclusion, the clinically-similar QOL outcomes, and differing spectra of toxicities indicate that clinicians and patients should be involved in shared decision making, in a multidisciplinary context, to individualise treatment for OPSCC.

Contributors

ACN, DAP, and JT contributed to trial conception and design. ACN, DAP, and AW contributed to data analysis and initial draft of the manuscript. The first author (ACN), last author (DAP), and statistician (AW) had full access to the data, vouch for the integrity of the data and the adherence to the study protocol, and are responsible for the decision to submit the manuscript. All authors contributed to data collection, data interpretation, and revision of manuscript for crucially important content.

Declaration of interests

EB has received honoraria and educational grants from Eisai and Genzyme-Sanofi unrelated to this work. All other authors declare no competing interests.

Data sharing

The trial protocol did not include a data sharing plan, and therefore data from the trial will not be shared publicly because sharing was not included in the ethical approvals.

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References

1 Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol* 2013; **31:** 4550–59.

2 Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010; **363:** 24–35.

3 Ringash J. Survivorship and quality oflife in head and neck cancer. *J Clin Oncol* 2015; **33:** 3322–27.

4 Parsons JT, Mendenhall WM, Stringer SP, et al. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. *Cancer* 2002; **94:** 2967–80.

5 Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol* 2011; **100:** 33–40.

6 Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol* 2008; **26:** 3582–89.

7 Cracchiolo JR, Baxi SS, Morris LG, et al. Increase in primary surgical treatment of T1 and T2 oropharyngeal squamous cell carcinoma and rates of adverse pathologic features: National Cancer Data Base. *Cancer* 2016; **122:** 1523–32.

8 Yom SS. The tonsillar fossa battleground. *Int J Radiat Oncol Biol Phys* 2017; **97:** 1–2.

9 Gupta T, Kannan S, Ghosh-Laskar S, Agarwal JP. Systematic review and meta-analyses of intensity-modulated radiation therapy versus conventional two-dimensional and/or or three-dimensional radiotherapy in curative-intent management of head and neck squamous cell carcinoma. *PLoS one* 2018; **13:** e0200137.

10 Nichols AC, Yoo J, Hammond JA, et al. Early-stage squamous cell carcinoma of the oropharynx: radiotherapy vs. trans-oral robotic surgery (ORATOR)–study protocol for a randomized phase II trial. *BMC Cancer* 2013; **13:** 133.

11 Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg* 2001; **127:** 870–76.

12 Hutcheson KA, Barrow MP, Lisec A, Barringer DA, Gries K, Lewin JS. What is a clinically relevant difference in MDADI scores between groups of head and neck cancer patients? *Laryngoscope* 2016; **126:** 1108–13.

13 Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer* 2007; **110:** 196–202.

14 de Almeida JR, Byrd JK, Wu R, et al. A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: a systematic review. *Laryngoscope* 2014; **124:** 2096–102.

15 de Almeida JR, Moskowitz AJ, Miles BA, et al. Cost-effectiveness of transoral robotic surgery versus (chemo)radiotherapy for early T classification oropharyngeal carcinoma: a cost-utility analysis. *Head Neck* 2016; **38:** 589–600.

16 de Almeida JR, Villanueva NL, Moskowitz AJ, et al. Preferences and utilities for health states after treatment for oropharyngeal cancer: transoral robotic surgery versus definitive (chemo)radiotherapy. *Head Neck* 2014; **36:** 923–33.

17 Yeh DH, Tam S, Fung K, et al. Transoral robotic surgery *vs* radiotherapy for management of oropharyngeal squamous cell carcinoma: a systematic review of the literature. *Eur J Surg Oncol* 2015; **41:** 1603–14.

18 Ibrahim AS, Civantos FJ, Leibowitz JM, et al. Meta-analysis comparing outcomes of different transoral surgical modalities in management of oropharyngeal carcinoma. *Head Neck* 2019; **41:** 1656–66.

19 Chia SH, Gross ND, Richmon JD. Surgeon experience and complications with transoral robotic surgery (TORS). *Otolaryngol Head Neck Surg* 2013; **149:** 885–92.

20 Nguyen TK, Nguyen EK, Warner A, Louie AV, Palma DA. Failed randomized clinical trials in radiation oncology: what can we learn? *Int J Radiat Oncol Biol Phys* 2018; **101:** 1018–24.

21 Chera BS, Amdur RJ. Current status and future directions of treatment deintensification in human papilloma virus-associated oropharyngeal squamous cell carcinoma. *Semin Radiat Oncol* 2018; **28:** 27–34.

22 Ling DC, Bakkenist CJ, Ferris RL, Clump DA. Role of immunotherapy in head and neck cancer. *Semin Radiat Oncol* 2018; **28:** 12–16.