original report

Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma

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abstract

PURPOSE The purpose of this study was to determine if dose de-escalation from 60 to 66 Gy to 30 to 36 Gy of adjuvant radiotherapy (RT) for selected patients with human papillomavirus–associated oropharyngeal squamous cell carcinoma could maintain historical rates for disease control while reducing toxicity and preserving swallow function and quality of life (QOL).

PATIENTS AND METHODS MC1273 was a single-arm phase II trial testing an aggressive course of RT de-escalation after surgery. Eligibility criteria included patients with p16-positive oropharyngeal squamous cell carcinoma, smoking history of 10 pack-years or less, and negative margins. Cohort A (intermediate risk) received 30 Gy delivered in 1.5-Gy fractions twice per day over 2 weeks along with 15 mg/m^2 docetaxel once per week. Cohort B included patients with extranodal extension who received the same treatment plus a simultaneous integrated boost to nodal levels with extranodal extension to 36 Gy in 1.8-Gy fractions twice per day. The primary end point was locoregional tumor control at 2 years. Secondary end points included 2-year progression-free survival, overall survival, toxicity, swallow function, and patient-reported QOL.

RESULTS Accrual was from September 2013 to June 2016 (N = 80; cohort A, n = 37; cohort B, n = 43). Median follow-up was 36 months, with a minimum follow-up of 25 months. The 2-year locoregional tumor control rate was 96.2%, with progression-free survival of 91.1% and overall survival of 98.7%. Rates of grade 3 or worse toxicity at pre-RT and 1 and 2 years post-RT were 2.5%, 0%, and 0%. Swallowing function improved slightly between pre-RT and 12 months post-RT, with one patient requiring temporary feeding tube placement.

CONCLUSION Aggressive RT de-escalation resulted in locoregional tumor control rates comparable to historical controls, low toxicity, and little decrement in swallowing function or QOL.

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ASSOCIATED CONTENT

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Data Supplement

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

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INTRODUCTION

Human papillomavirus (HPV)–associated oropharyngeal squamous cell carcinoma (OPSCC) represents a demographically and biologically distinct disease compared with historical head and neck squamous cell carcinomas.[1,2] Patients are more likely to be younger and nonsmokers and have fewer medical comorbidities.[3] Furthermore, in vitro and in vivo experiments have demonstrated that these tumors are more sensitive to radiotherapy (RT) and chemotherapy compared with historical head and neck squamous cell carcinomas.[4-6] This combination of factors has led to markedly improved clinical outcomes after standard treatments.[7] For patients who are never-smokers, survival rates can be as high as 90% after standard therapy.[8] These high survival rates translate into a growing population of otherwise healthy, younger survivors who will live with treatment sequelae for a long time.

Standard treatment of HPV-associated OPSCC consists of either 7 weeks of RT (70 Gy) combined with concurrent cisplatin or surgery followed by 6 weeks of adjuvant RT (60 to 66 Gy) with or without cisplatin, depending upon risk factors.[9,10] Both approaches incur significant post-treatment sequelae. One third of patients or more will have long-term grade 3 or worse toxicities, such as xerostomia, dysphagia, neuropathy, neck fibrosis, or osteoradionecrosis.[11,12] In the context of a highly curable cancer with prolonged survival, clinical trials examining treatment de-escalation for reducing toxicity while preserving historically high cure rates are urgently needed.

MC1273 was a phase II nonrandomized trial exploring an aggressive course of de-escalated adjuvant RT after curative-intent surgery for patients with HPV-associated OPSCC. Recognizing that a majority of long-term effects of head and neck therapy originate from cumulative RT dose, MC1273 tested whether 30 to 36 Gy delivered with once-per-week docetaxel is sufficient for disease control after margin-negative surgery in never- to seldom-smokers. The motivation for de-escalating the dose to 30 to 36 Gy originated with the Nigro[13] regimen for anal cancer. This regimen achieved a complete response rate of 84% for gross disease with 30 Gy and concurrent fluorouracil and mitomycin.[14,15] Docetaxel was selected as the systemic regimen because of suggestions of improved efficacy and lower toxicity when compared with cisplatin in RTOG 0234.[16,17] Finally, twice-per-day fractionation was selected to reduce RT-induced sequelae, particularly xerostomia.[18]

PATIENTS AND METHODS

Patient Characteristics

This study was approved by the Mayo Clinic Institutional Review Board and Scientific Review Committee. All participants provided written informed consent before registration and treatment. Eligible patients had American Joint Committee on Cancer (AJCC; seventh edition) pathologic stage III to IV HPV-associated OPSCC and had greater than 70% p16 immunoreactivity on immunohistochemistry. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or lower and smoking history of 10 pack-years or less. Screening for distant metastases was performed with either chest computed tomography (CT) or positron emission tomography/CT within 7 weeks of registration. Presurgical evaluation was performed by an experienced surgical team and involved a detailed physical examination, neck CT with contrast, and, when questions concerning tumor invasiveness existed, head and neck magnetic resonance imaging.

Cohorts and Treatment

All patients underwent margin-clearing surgery with real-time pathologic assessment for the primary tumor and neck dissection with curative intent. Eligible patients had either a pathologic high-risk factor (extranodal extension [ENE]) or one or more intermediate-risk factors (lymphovascular space invasion, perineural invasion, involvement of $\geq$ two regional lymph nodes, any lymph node $>$ 3 cm in size, or $\geq$ T3 primary tumor). Exclusion criteria included a history of head and neck RT, another malignancy within 5 years of registration, or connective tissue disorder requiring immunosuppressive medication.

Patients were prospectively stratified according to presence of ENE (Fig 1). Patients without ENE were treated in cohort A and received 30 Gy in 1.5-Gy fractions twice per day over 2 weeks to the primary site and dissected and elective nodal volumes. Fractions were separated by at least 6 hours. Intravenous (IV) docetaxel (15 mg/m^2) was administered on days 1 and 8 of treatment. The 30-Gy clinical target volume included the primary tumor bed, ipsilateral dissected nodal levels (II to IV, $\pm$ IB, V, and retropharyngeal), and, in instances of a tongue base primary or tonsil primary with base of tongue or soft palate involvement greater than 1 cm, contralateral nodal levels (II to IV), all in one continuous volume. Patients with any ENE were treated in cohort B and received a simultaneous integrated boost to 36 Gy in 1.8-Gy fractions twice per day to the nodal level with ENE only. All treatment plans were reviewed by the

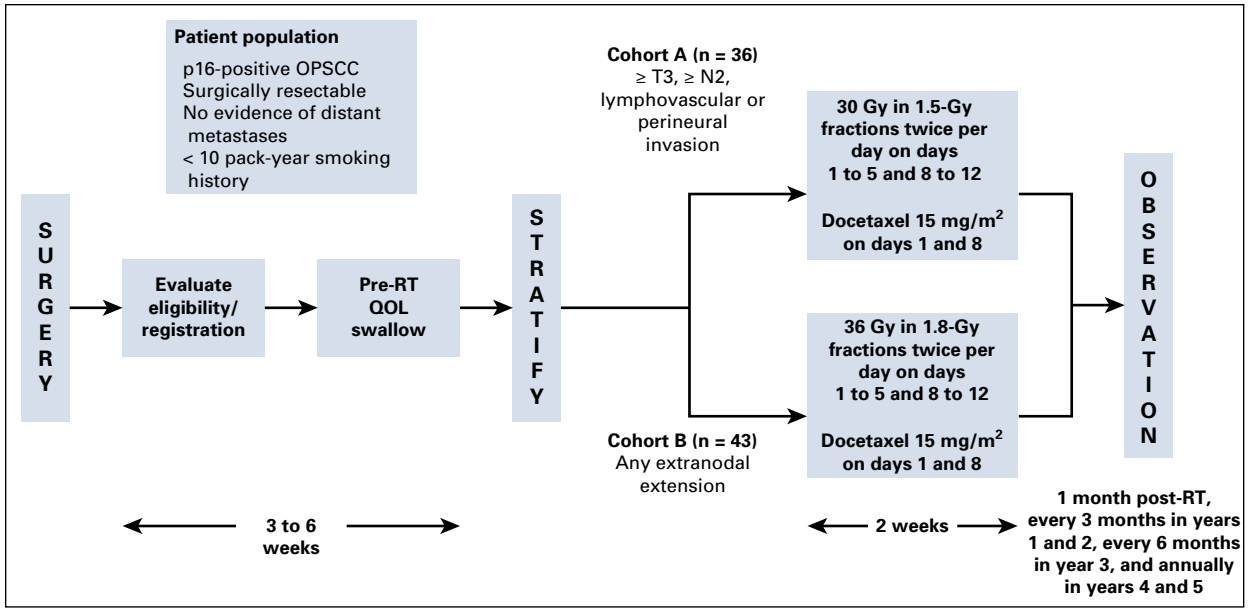

FIG 1. Protocol schema. OPSCC, oropharyngeal squamous cell carcinoma; QOL, quality of life; RT, radiotherapy.

head and neck RT oncology group before treatment, and treatment was delivered using volumetric modulated arc therapy with cone beam CT scans before each fraction for patient positioning. Dose constraints and mean dose for normal structures along with example plans are summarized in Appendix Table A1 (online only) and Appendix Fig A1 (online only). All patients began adjuvant RT within 6 weeks of surgery.

Follow-Up Evaluation

Adverse events were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Patients were assessed at least once every five fractions during RT for performance status, weight, and adverse events. Follow-up evaluations after RT occurred every 3 months for 24 months, with surveillance imaging performed at the 3-, 12-, and 24-month time points and as clinically indicated. Patients were subsequently evaluated every 6 months during year 3 and annually during years 4 and 5.

Patients underwent a modified barium swallow impairment profile evaluation before RT and at 1 and 12 months after completion of treatment. Patients also had quality-of-life (QOL) assessments, consisting of the University of Michigan Xerostomia QOL Scale (XeQoLS), the Functional Assessment of Cancer Therapy–Head and Neck Cancer (FACT-HN; version 4), three-level version of the EuroQol five-dimensional instrument (EQ-5D-3L), and the European Organisation for Research and Treatment of Cancer QOL Questionnaire for Head and Neck Cancer Module 35 (EORTC-QLQ HN35), pre-RT and 1, 3, 12, and 24 months post-treatment.

Patients treated at Mayo Clinic Rochester underwent a financial analysis. Costs for treatment were obtained from the Mayo Clinic Cost Data Warehouse. Professionally billed services based upon Medicare reimbursement rates were compiled. A retrospective control group of patients with HPV-associated OPSCC treated at Mayo Clinic Rochester with either surgery followed by standard RT with or without chemotherapy or definitive chemoradiotherapy from May 2013 to October 2017 was also included for cost comparison.

Statistical Design and Study End Points

MC1273 was a phase II trial design with a safety analysis in the first five patients. The primary end point was locoregional tumor control (LRC) at 2 years. Secondary end points included 2-year progression free survival (PFS), overall survival (OS), toxicity, swallow function, and patient-reported QOL. Given that standard therapy yields a 2-year cumulative incidence of locoregional recurrence (LRR) of approximately 10%, the study regimen would be considered for phase III evaluation if the 2-year cumulative incidence of LRR were 20% or less, with a reduction in the acute grade 3 or worse toxicity rate from 40% as reported in EORTC 22931 to less than 20%.[10] A sample size of 35 evaluable patients for each cohort was sufficient to estimate LRR of 20% or less with a two-sided 85% CI that would contain 10% (nQuery Advisor [version 6.01]; CIs for a single proportion) and had 85% power to detect a decrease in acute grade 3 or worse toxicity from 40% to 20% or less, assuming a one-sided significance level of .06. Five additional patients per cohort were enrolled to account for ineligibilities or cancellations, for a planned total accrual of 80 patients. The 2-year cumulative incidence of LRR was estimated by the competing risk method, where the competing risks were distant failures and deaths resulting from other causes.[19] The distribution of OS, PFS, and other time-to-event data were estimated using the Kaplan-Meier method. Adverse events were summarized descriptively with frequencies and percentages. Mean QOL scores were plotted over time, with 95% CIs around the means. The paired *t* test was used to assess changes in the QOL and swallowing scores from pre-RT over time.

RESULTS

Study Population

A total of 80 patients enrolled between September 2013 and June 2016 in Mayo Clinic Rochester and Mayo Clinic Arizona (cohort A, n = 37; cohort B, n = 43; Table 1.) AJCC (eighth edition) staging is summarized in Appendix Table A2 (online only). One patient (1.2%; cohort A) was excluded from analysis before initiating follow-up after he was found to have falsified his smoking history to allow for study participation. Of the patients in this study, 75 (95%) underwent transoral surgery, two underwent a hybrid transoral procedure with transhyoid pharyngotomy, and two underwent a lip-split mandibulotomy and radial free-flap reconstruction. All patients received their prescribed dose of RT and docetaxel. No patients required treatment delays during RT longer than 2 days

Treatment Outcomes

Median follow-up was 35.7 months (range, 25.2 to 61.8 months). During the entire follow-up period, no patients in cohort A and four in cohort B experienced LRR, with a 2-year overall LRC of 96.2% (cohort A, 100%; cohort B, 93.0%; Fig 2A). One patient in cohort A (2.8%) and nine patients in cohort B (20.9%) experienced any disease recurrence, with a 2-year distant metastasis–free survival rate of 94.9% and PFS of 91.1% (Table 2; Figs 2B and 2C). As of last follow-up, one patient in cohort A (cardiac event) and two in cohort B (cardiac event and pneumonia) had died, with a 2-year OS rate of 98.7% (Fig 2D).

Adverse Effects

Grade 2 and grade 3 or worse toxicity rates at pre-RT and 1 and 2 years post-RT were 11.4% and 2.5%, 1.4% and 0.0%, and 6.7% and 0.0%, respectively. The most frequent grade 2 events were dysphagia, xerostomia, and oral mucositis. Toxicities are summarized in Table 3. All grade 3 or worse toxicities occurred by 3 months (n = 13; 16.5%)

TABLE 1. Pretreatment Demographic and Clinical Characteristics by Cohort

Characteristic	No. (%)		
	Cohort A (n = 36)	Cohort B (n = 43)	Total (N = 79)
Age, years			
Mean	58.4	58.9	58.7
SD	6.7	10.2	8.8
Median	60.0	61.0	61.0
Sex			
Female	3 (8.3)	5 (11.6)	8 (10.1)
Male	33 (91.7)	38 (88.4)	71 (89.9)
ECOG PS			
0	34 (94.4)	41 (95.3)	75 (94.9)
1	2 (5.6)	2 (4.7)	4 (5.1)
Primary tumor site			
Base of tongue	16 (44.4)	21 (48.8)	37 (46.8)
Tonsil	15 (41.7)	18 (41.9)	33 (41.8)
Tonsil and tongue	5 (13.9)	4 (9.3)	9 (11.4)
Pathologic T stage			
pT1	18 (50.0)	19 (44.2)	37 (46.8)
pT2	14 (38.9)	13 (30.2)	27 (34.2)
pT3	4 (11.1)	4 (9.3)	8 (10.1)
pT4a	0 (0.0)	7 (16.3)	7 (8.9)
Pathologic N stage			
pN0	2 (5.6)	0 (0.0)	2 (2.5)
pN1	6 (16.7)	4 (9.3)	10 (12.7)
pN2a	13 (36.1)	9 (20.9)	22 (27.8)
pN2b	12 (33.3)	17 (39.5)	29 (36.7)
pN2c	3 (8.3)	5 (11.6)	8 (10.1)
pN3	0 (0.0)	8 (18.6)	8 (10.1)
Total No. of involved lymph nodes			
0	2 (5.6)	0 (0.0)	2 (2.5)
< 5	32 (88.9)	36 (83.7)	68 (86.1)
≥ 5	2 (5.6)	7 (16.3)	9 (11.4)

NOTE. Pathologic staging based on American Joint Committee on Cancer (seventh edition).

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

and resolved by 6 months. One patient had a transient grade 4 hypotensive event related to docetaxel infusion that responded quickly to IV fluids and diphenhydramine. One patient had a percutaneous endoscopic gastrostomy (PEG) tube placed immediately after RT, which was removed within 1 month post-treatment. No patient had a PEG tube in place after 1 month post-treatment.

Anecdotally, this regimen consistently generated a brief period of brisk acute mucositis that was similar in intensity to the last week of standard treatment. This mucositis began the day after completion of therapy, was often associated with oral thrush, and resolved in approximately 5 days. Supportive care, including pain medication, antifungal medications, and IV fluids, was generally enough to bridge this acute period. This brief but intense period of mucositis was unanticipated when the toxicity evaluation time points were originally designed and therefore was not adequately captured during data collection. The follow-up phase III study includes a 3-day post-treatment time point specifically to document this effect.

QOL

Full details for individual QOL subdomains will be published separately. At 1 year post-treatment, QOL (± standard deviation [SD]) as measured by FACT-HN (116.9 ± 17.2 *v* 127.2 ± 17.7; $P < .001$), EORTC-QLQ HN35 (106.3 ± 10.7 *v* 111.4 ± 9.2; $P < .001$), and EQ-5D-3L (6.3 ± 1.3 *v* 5.5 ± 0.9; $P < .001$) improved slightly compared with pre-RT (Figs 3A to 3C). Swallowing function (± SD) also improved slightly on formal evaluation between pre-RT and 12 months post-RT (pharyngeal total modified barium swallow impairment profile, 5.8 ± 3.8 *v* 4.5 ± 3.6; $P = .01$; diet normalcy as measured by the Functional Oral Intake Scale, 6.0 ± 0.9 *v* 6.3 ± 1.0; $P = .01$). Only xerostomia (± SD) as measured by XeQoLS worsened in the 1-month post-treatment period (0.3 ±0.4 *v* 0.6 ± 0.5; $P < .001$) and returned to baseline by 1 year post-treatment (0.3 ± 0.4; $P = 0.67$; Fig 3D).

Financial Analysis

Total average treatment cost for Mayo Clinic Rochester patients (n = 67) was $45,884, of which $17,791 comprised chemotherapy and RT charges and $28,093 surgical or staging charges. Average total charge for patients receiving standard adjuvant therapy during this same time period (n = 101) was $57,845, of which $26,603 comprised chemotherapy and RT charges and $31,242 surgical or pretreatment evaluation charges. This study had a 33% reduction in RT cost and a 21% reduction in total treatment cost compared with standard adjuvant therapy. Patients receiving definitive chemoradiotherapy treated during the same time period (n = 56) had an average charge of $47,763, of which $39,936 comprised chemotherapy and RT charges and $7,827 pretreatment evaluation charges.

DISCUSSION

MC1273 exists alongside a diverse collection of de-escalation efforts. Other adjuvant de-escalation trials include ECOG 3311, which has randomly assigned patients with intermediate-risk factors after surgery to 50 versus 60 Gy of adjuvant RT, and PATHOS (Postoperative Adjuvant Treatment for HPV-Positive Tumours), which has randomly assigned intermediate-risk patients to 50 versus 60 Gy and patients with ENE to 60 Gy with or without

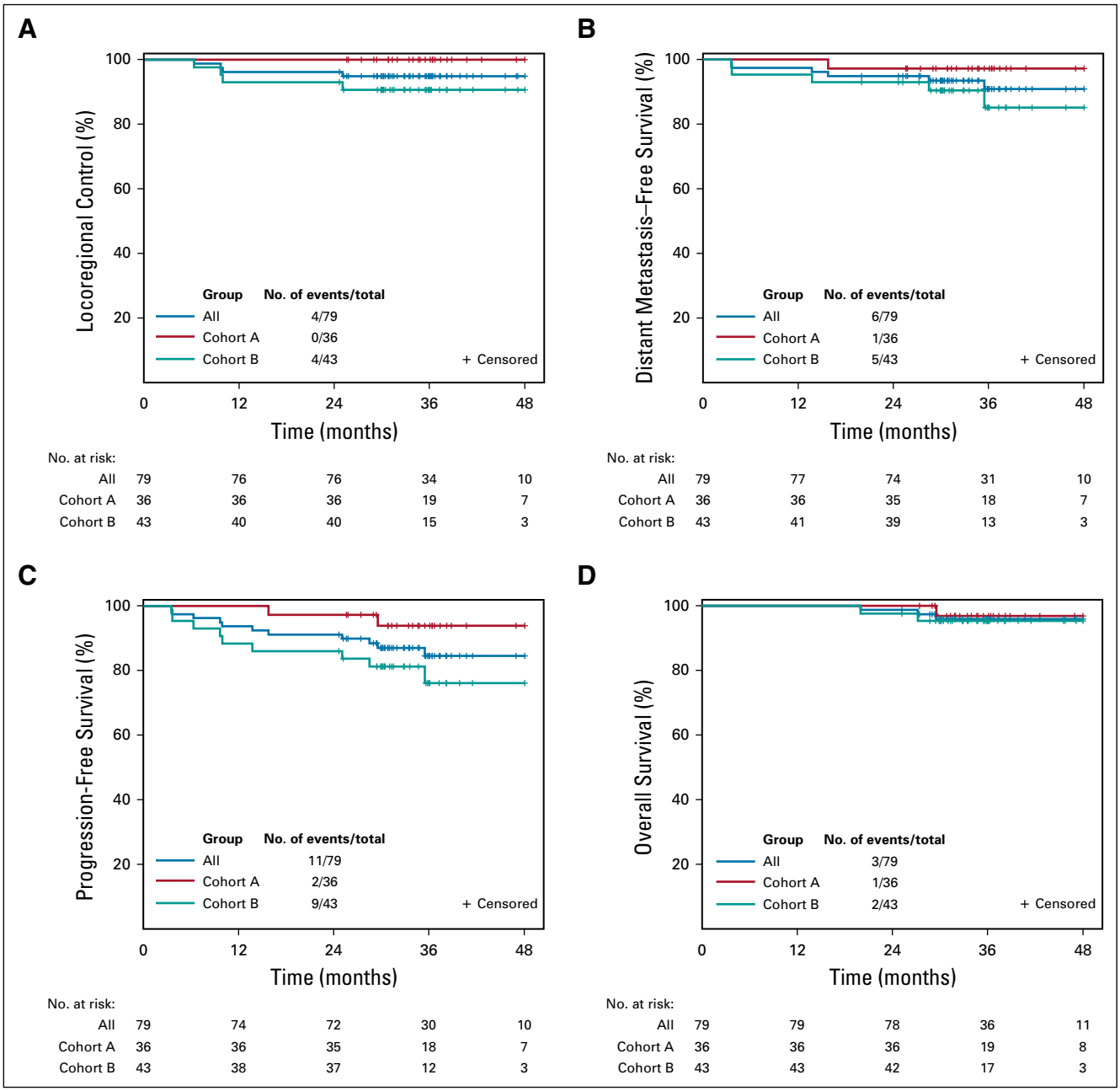

FIG 2. (A) Locoregional control, (B) distant metastasis–free survival, (C) progression-free survival, and (D) overall survival for patients in MC1273. Red line indicates cohort A (extranodal extension [ENE] negative), green line indicates cohort B (ENE positive), and blue line indicates total cohort. Crosses indicate censored observations. Error bars represent 95% CIs for given time points.

cisplatin.[20] In the definitive setting, other efforts include NRG HN002, which has randomly assigned patients to 60 Gy (over 6 weeks) with cisplatin versus 60 Gy (over 5 weeks) alone, and RTOG 1016 and DeESCALaTE (Determination of Cetuximab Versus *Cisplatin* Early and Late Toxicity Events in HPV+ OPSCC), which have randomly assigned patients to 70 Gy plus cisplatin versus cetuximab.[21] Other trials, such as ECOG 1308 and CCRO022, have used induction chemotherapy to de-escalate the radiation dose to 54 Gy.[22] At 30 to 36 Gy, MC1273 represents the most aggressive radiation dose de-escalation effort, although the radiosensitizing effect of docetaxel may make the effective dose somewhat higher. An ongoing trial at Memorial Sloan Kettering is also investigating the use of hypoxia imaging to select patients with HPV-associated OPSCC to 30 Gy with concurrent chemotherapy followed by a post-treatment neck dissection (ClinicalTrials.gov identifier: NCT00606294).

With 2-year LRC, PFS, and OS rates of 96.2%, 91.1%, and 98.7%, respectively, this study demonstrated outcomes comparable to those of contemporary series using standard adjuvant treatment. For comparison, the 2-year PFS for the

TABLE 2. Local, Regional, and Distant Recurrence Patterns by Cohort and Stage

Patient	Cohort	pT	pN	Time to Relapse (months)	Recurrence		
					Local	Regional	Distant
1	B	T4a	N2c	9	+		
2	B	T1	N3	26			Lung
3	B	T2	N2b	31			Lung
4	B	T4a	N3	3			Bone
5	B	T1	N2b	25	+		
6	A	T1	N2a	12			Liver
7	B	T4a	N2b	12			Lung
8	B	T4a	N2b	9	+		
9	B	T2	N2b	6		+	
10	B	T4a	N2c	12			Lung

cisplatin cohort of p16-positive patients in RTOG 0234 was 86.4%.[23] Given the somewhat delayed recurrence pattern that can be seen with HPV-associated OPSCC, we waited to publish these results until all patients had had at least 2 years of follow-up (median, 3 years.) Additional follow-up is required to ensure that this regimen does not simply delay recurrence, but the current trend suggests that these locoregional tumor control rates may be durable. Although the disease outcomes for cohort B were worse than those for cohort A, they remain consistent with expected rates of LRC and distant metastasis for an ENE-positive population of patients with HPV-associated OPSCC.[24-26]

Although the sample size is not large enough to make definitive statements, patients who experienced local recurrence shared similar characteristics. Two of the three patients with local recurrence had pT4a primary tumors and required multiple excisions at the same tumor edge within the same surgery to achieve final negative margins. The third patient had a pT1 primary tumor but also required multiple margin excisions, because the tumor was endophytic. We postulate that these patients had more than the microscopic levels of residual disease that this trial was designed to sterilize. Previous work by our group has shown that more than two attempts to clear frozen section margins in the same surgery is a risk factor for both locoregional and distant recurrences.[27] This recurrence pattern among larger tumors mirrors other de-escalation studies, such as ECOG 1308, which evaluated de-escalated radiation doses after induction chemotherapy.[28] Similarly, RTOG 1016 found cetuximab to be inferior to cisplatin for intact HPV-associated OPSCC.[29] Taking these observations into account, we postulate that radiation dose de-escalation may be most viable in the context of microscopic residual disease. The follow-up phase III trial excludes patients with T4 disease or primary tumors that require more than two excisions to clear a margin edge.

The toxicity profile of this regimen represents a significant improvement in both acute and late toxicity rates when compared with historical adverse event rates seen with standard adjuvant regimens. Of particular note, only one patient required a PEG tube immediately after treatment, and no patients required a PEG tube by 1 month after treatment. In contrast, modern RT series often have PEG dependence rates of 18% or higher.[30] Likewise, QOL improved slightly between pre-RT and 1 year post-treatment. Only xerostomia as measured by XeQoLS worsened in the immediate post-treatment interval. Formal swallow evaluation demonstrated a slight improvement in swallowing function 1 year after completion of treatment compared with pre-RT. We attribute this slight improvement to continued surgical recovery. Because trial registration was dependent upon postsurgical risk factors, we were unable to collect presurgical swallow and QOL data for comparison. We consider this a study limitation and have included a preregistration step in our phase III trial. Nevertheless, our dietary normalcy data demonstrated that most patients had a completely oral diet with only some dietary modifications at the pre-RT time point, congruent with the existing transoral surgery literature.[31-33]

A 2-week treatment course also generated financial savings. Because RT is often reimbursed on a per-fraction basis, the 20 fractions used in this study represent a 33% less expensive treatment compared with standard adjuvant therapy. These savings do not include cost savings from reduced toxicity management, which will be separately reported. For patients who travel for therapy, a 2-week course removes 4 weeks of transportation, food, housing, and caregiver costs. In an era where health care value is being increasingly prioritized, this regimen may provide a cost-effective means to achieve cure.

Some have argued that this regimen may represent overtreatment, because many patients in this study would now be classified as having stage I to II disease under AJCC (eighth edition) and therefore fall into a low-risk category.[34] However, it is worth noting that the classification for low risk only occurs in the setting of adjuvant therapy.[26] In

TABLE 3. Most Common Postbaseline Adverse Events by Grade and Cohort

	Grade							
	1		2		3		4	
Adverse Event by Cohort	No.	%	No.	%	No.	%	No.	%
Dry mouth								
A	27	75	8	22.2				
B	31	72.1	11	25.6				
Fatigue								
A	27	75	5	13.9	1	2.8		
B	30	69.8	8	18.6				
Dysphagia								
A	15	41.7	10	27.8	2	5.6		
B	23	53.5	10	23.3	1	2.3		
Superficial soft tissue fibrosis								
A	20	55.6	3	8.3				
B	28	65.1	2	4.7				
Mucositis oral								
A	14	38.9	4	11.1	3	8.3		
B	18	41.9	8	18.6	2	4.7		
Oral pain								
A	13	36.1	6	16.7	1	2.8		
B	24	55.8	5	11.6				
Lymphedema								
A	15	41.7	2	5.6	1	2.8		
B	23	53.5	3	7				
Nausea								
A	13	36.1	3	8.3				
B	10	23.3	3	7				
Pharyngitis								
A	10	27.8	3	8.3				
B	15	34.9						
Lymphocyte count decreased								
A			2	5.6	1	2.8		
B			1	2.3				
Radiation dermatitis								
A					1	2.8		
Osteonecrosis of jaw								
A			1	2.8				
Vasovagal reaction								
B							1	2.3

multi-institutional analyses, these presumptively low-risk patients still harbor a 26% risk of locoregional disease recurrence without adjuvant RT, a risk that rose to 52% in the population with ENE.[35,36] Patients with intermediate-risk factors are expected to have a 12% risk of LRR with observation alone. Although this would be above the threshold that many oncologists use for treatment, whether this magnitude of disease control is balanced by the toxicities of standard treatment has often been a difficult patient decision. An aggressive de-escalation regimen provides an alternative option that balances disease control with long-term QOL and may provide better clinical equipoise.

Like all phase II studies, this study requires confirmation from a randomized phase III trial before the results can be

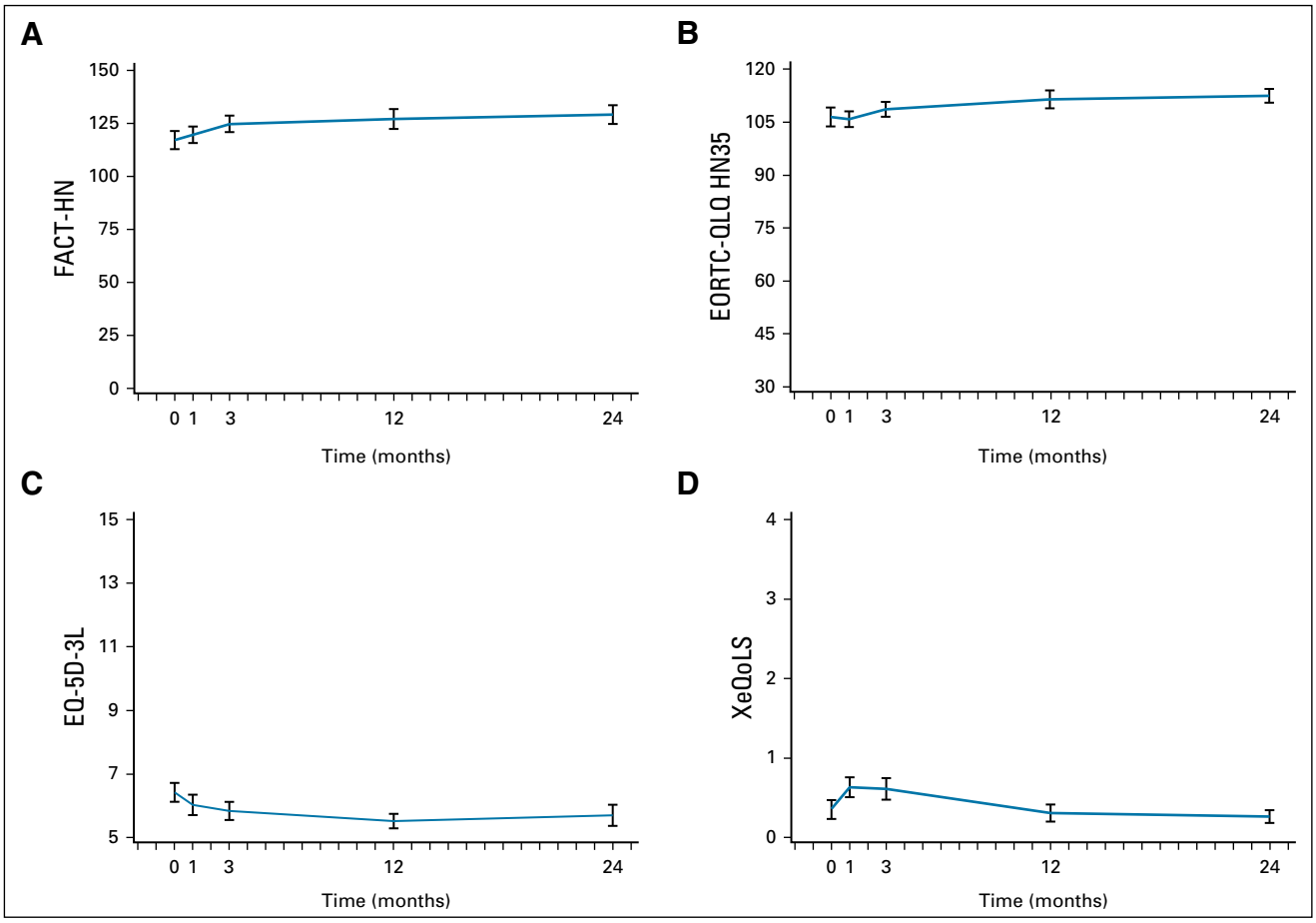

FIG 3. Patient reported outcome for quality of life as measured by (A) Functional Assessment of Cancer Therapy–Head and Neck Cancer (FACT-HN; version 4), (B) European Organisation for Research and Treatment of Cancer QOL Questionnaire for Head and Neck Cancer Module 35 (EORTC-QLQ HN35), (C) three-level version of the EuroQol five-dimensional instrument (EQ-5D-3L), and (D) University of Michigan Xerostomia QOL Scale (XeQoLS). Error bars represent 95% CIs for given time points.

broadly applied. Furthermore, this study was conducted at academic centers with high volumes of transoral surgery and subspecialized head and neck radiation and medical oncologists and used uniform RT techniques. It remains unclear whether these results can be replicated at lower-volume surgical centers or with heterogeneous RT techniques.[37,38] Finally, the applicability of this regimen in heavy smokers is uncertain, because they were excluded from this trial. To address this issue, we are currently running a phase III study that stratifies patients by smoking status and randomly assigns them to either the MC1273 regimen or standard adjuvant treatment (ClinicalTrials.gov identifier: NCT02908477.) Completion of trial accrual is anticipated in 2021.

In conclusion, aggressive radiation dose de-escalation in the adjuvant setting for selected patients with HPV-associated OPSCC achieved LRC rates comparable to historical controls while producing toxicity and QOL outcomes superior to those of standard adjuvant treatment. These results are currently undergoing additional evaluation in a phase III randomized trial.

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma

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APPENDIX

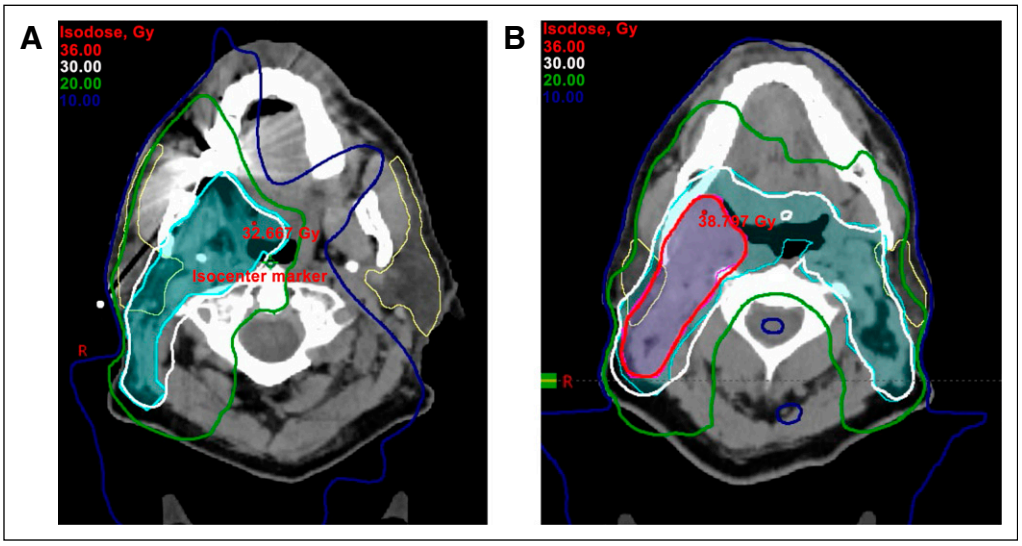

FIG A1. Representative isodose lines for (A) patient in cohort A (well-lateralized tonsil cancer) and (B) patient in cohort B (tongue base cancer). PTV3000 in cyan, and PTV3600 (for cohort B) in pink; parotids in yellow.

TABLE A1. Recommended and Achieved Dose Constraints for Normal Structures

		Dose (Gy)	
Structure	**Recommended Constraint**	**Mean**	**SD**
Constrictors	As low as feasible	24.8	3.7
Cord	< 30 (maximum)	11.8	3.0
Larynx	As low as feasible	17.6	4.3
Oral cavity	< 20 (mean)	19.3	2.8
Parotid left	< 10 (mean)	16.8	7.3
Parotid right	< 10 (mean)	18.8	7.1
Parotid total	< 15 (mean)	17.8	3.3
Submandib left	As low as feasible	26.7	8.5
Submandib right	As low as feasible	28.7	7.6

Abbreviation: SD, standard deviation.

TABLE A2. AJCC Staging (eighth edition)

	No. (%)		
Stage	**Cohort A**	**Cohort B**	**Total**
I	29 (80.6)	28 (65.1)	57 (72.2)
II	7 (19.4)	12 (27.9)	19 (24.1)
III	0 (0.0)	3 (7.0)	3 (3.8)

Abbreviation: AJCC, American Joint Committee on Cancer.