Original Article

The Impact of Induction and/or Concurrent Chemoradiotherapy on Acute and Late Patient-Reported Symptoms in Oropharyngeal Cancer: Application of a Mixed-Model Analysis of a Prospective Observational Cohort Registry

Lisanne V. van Dijk, PhD [1,2]; Abdallah S. R. Mohamed, MD [1,3]; Renata Ferrarotto, MD [4]; Lance A. McCoy [1,5]; Christina S. Sharafi [1]; Eva Jones [6]; Kennedy Steele [1,6]; Amy C. Moreno, MD, PhD [1]; Stephen Y. Lai, MD, PhD [1,3,7]; Adam S. Garden, MD [1]; Jeffrey N. Myers, MD, PhD [7]; David I. Rosenthal, MD [1]; Clifton D. Fuller, MD, PhD [1]; and Katherine A. Hutcheson, MD, PhD [1,7]; for the MD Anderson Symptom Working Group

BACKGROUND: The goal of this study was to comprehensively investigate the association of chemotherapy with trajectories of acute symptom development and late symptom recovery in patients with oropharyngeal cancer (OPC) by comparing symptom burden between induction chemotherapy followed by concurrent chemoradiotherapy (ICRT), concurrent chemo-radiotherapy (CRT), or radiotherapy (RT) alone. **METHODS:** Among a registry of 717 patients with OPC, the 28-item patient-reported MD Anderson Symptom Inventory–Head and Neck Module (MDASI-HN) symptoms were collected prospectively at baseline, weekly during RT, and 1.5, 3 to 6, 12, and 18 to 24 months after RT. The effect of the treatment regimen (ICRT, CRT, and RT alone) was examined with mixed-model analyses for the acute and late period. In the CRT cohort, the chemotherapy agent relationship with symptoms was investigated. **RESULTS:** Chemoradiation (ICRT/CRT) compared with RT alone resulted in significantly higher acute symptom scores in the majority of MDASI-HN symptoms (ie, 21 out of 28). No late symptom differences between treatment with or without chemotherapy were observed that were not attributable to ICRT. Nausea was lower for CRT with carboplatin than for CRT with cisplatin; cetuximab was associated with particularly higher scores for acute and late skin, mucositis, and 6 other symptoms. The addition of ICRT compared with CRT or RT alone was associated with a significant increase in numbness and shortness of breath. **CONCLUSION:** The addition of chemotherapy to definitive RT for OPC patients was associated with significantly worse acute symptom outcomes compared with RT alone, which seems to attenuate in the late posttreatment period. Moreover, induction chemotherapy was specifically associated with worse numbness and shortness of breath during and after treatment. ***Cancer* 2021;127:2453-2464**.

LAY SUMMARY:

- Chemotherapy is frequently used in addition to radiotherapy cancer treatment, yet the (added) effect on treatment-induced over time is not comprehensively investigated
- This study shows that chemotherapy adds to the symptom severity reported by patients, especially during treatment

KEYWORDS: chemotherapy, head and neck cancer, mixed models, patient-rated toxicities, radiation oncology, symptoms.

INTRODUCTION

The addition of chemotherapy to radiation for the treatment of head and neck squamous cell carcinoma (HNC) was adopted after showing an improvement in absolute overall survival of 6.55 ± 1.0% at 5 years.[1] In recent years, the overall survival of patients with head and neck cancer—and in particular, those with oropharyngeal cancer (OPC)—has also improved due to the decrease of smoking-related human papillomavirus (HPV)-negative tumors and the increase of HPV-positive OPC. Intrinsically, HPV-associated tumors have a better treatment response[2-5] and are recognized in the 8th edition of the American Joint Committee on Cancer staging system.[6] The increased survival of HPV-positive

Corresponding Authors: Lisanne V. van Dijk, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, FCT6.5000, Houston, TX 77030 (dijkvansanne@gmail.com); Clifton D. Fuller, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, FCT6.5000, Houston, TX 77030 (cdfuller@mdanderson.org); Katherine A. Hutcheson, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, FCT6.5000, Houston, TX 77030 (karnold@mdanderson.org).

[1]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [2]Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [3]Department of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [4]Division of Cancer Medicine, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [5]College of Medicine, University of Houston, Houston, Texas; [6]Texas Undergraduate Medical Academy, Prairie View A&M University, Prairie View, Texas; [7]Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33501, **Received:** October 22, 2020; **Revised:** January 15, 2021; **Accepted:** January 23, 2021, **Published online** March 31, 2021 in Wiley Online Library (wileyonlinelibrary.com)

OPC patients and the focal shift of oncological treatment to spare normal tissue have invoked the demand to better understand symptom development and prevention. Consequently, the relative, as-yet-unquantified potential benefits associated with chemotherapy for HPV-positive OPC patients[7,8] may be offset by the increase in chemotherapy-attributable symptom burden in survivors.

Although level 1 evidence regarding the acute toxicities that can be attributed to the addition of chemotherapy to radiation for HNC has been established via multiple phase 3 prospective trials, a full multisymptom, accurate depiction of longitudinal symptom burden in OPC patients remains undefined,[9,10] especially for mild-to-moderate symptoms.[11-16] Chemo-radiotherapy phase 2/3 clinical trials are designed to investigate treatment effectiveness and feasibility, and routinely only report a limited number of symptoms. These trials have not typically statistically compared toxicity ratings between treatment regimens and have focused mainly on the maximum physician-rated severe adverse effects during the chemotherapy/radiation timeframe or shortly thereafter.[11-16] Therefore, they do not provide robust information about the effects of chemotherapy on treatment-induced symptom development over time, leaving the community challenged in estimating the added effects of chemotherapy on overall symptom burden. For instance, aggregated mild- to moderate-intensity symptoms may alter quality of life, even if no severe toxicity is recorded. The current literature lacks sufficient granularity to quantitate the effect of chemotherapy on quality of life.

Symptom development during HNC treatment and in the recovery period after treatment is a dynamic process that can be reported/observed via a dynamic trajectory of symptoms over time. Mixed-effect models can adequately deal with repeated measures, permitting the investigation of treatment-related adverse effects as trends over time (ie, without reducing this to a single time point or dichotomized endpoint [symptom present/not present]).

We developed and implemented a novel index to measure the overall burden of treatment-induced symptoms over time: the area under the symptom trajectory curve ($AUC_{symptom}$). The major goal of this study was to compare trajectories of acute symptom development and late symptom recovery among OPC patients who received induction plus concurrent chemotherapy (ICRT), concurrent chemotherapy (CRT), or radiotherapy (RT) alone with mixed-model analyses and $AUC_{symptom}$ comparisons.

MATERIALS AND METHODS

Registry Description

Patient symptom, tumor, and clinical data were collected prospectively as part of an active standardized follow-up registry study that was approved by The University of Texas MD Anderson Cancer Center (MDACC)'s Institutional Review Board (PA14-0947 data collection, PA11-0809 analysis). This registry enrolls patients at MDACC who are evaluated for a suspected or confirmed pathologic diagnosis of carcinoma of the oropharynx, including tonsil, base of tongue, or HNC of unknown primary origin.

For this study, sequential OPC patients that received RT with curative intent between February 2015 and January 2020 at MDACC were included. Patients who received radiation in the head and neck region before or during the start of symptom collection were excluded. Additionally, participants needed to have reported symptom scores for at least 2 time points. Surgery was not an exclusion criterion. The inclusion criteria are summarized in Supporting Figure S1.

Patients were classified based on their treatment regimen (ICRT, CRT, or RT alone). Rare cases of patients who received induction chemotherapy followed by RT alone (IRT) (n = 23) were excluded. The addition of chemotherapy, induction and/or concurrent, to RT was recommended after careful consideration by a multidisciplinary team on a per-patient basis as part of standard clinical practice.

Patient-Reported Outcomes: MD Anderson Symptom Inventory–Head and Neck Module

Prospectively surveyed patient-reported outcomes included MD Anderson Symptom Inventory–Head and Neck Module (MDASI-HN) questionnaires collected by the MD Anderson Oropharynx Program Patient Reported Outcomes/Function Core via all available means in the clinic (via Epic or paper surveys) and supplemented with research survey administration via REDCap[17] or paper at baseline, weekly during RT, and at 6 weeks and 3 to 6, 12, and 18 to 24 months after RT.[18] The MDASI-HN is a validated head and neck–specific symptom questionnaire consisting of 28 questions on a scale of 0 to 10, where 0 indicates no complaints and 10 represents the worst imaginable symptom severity. For this study, symptoms were assigned 3 distinct categories: 1) interference, which indicates general health/emotional status (eg, mood, activity, distress, enjoyment); 2) systemic (eg, constipation, fatigue, numbness); and

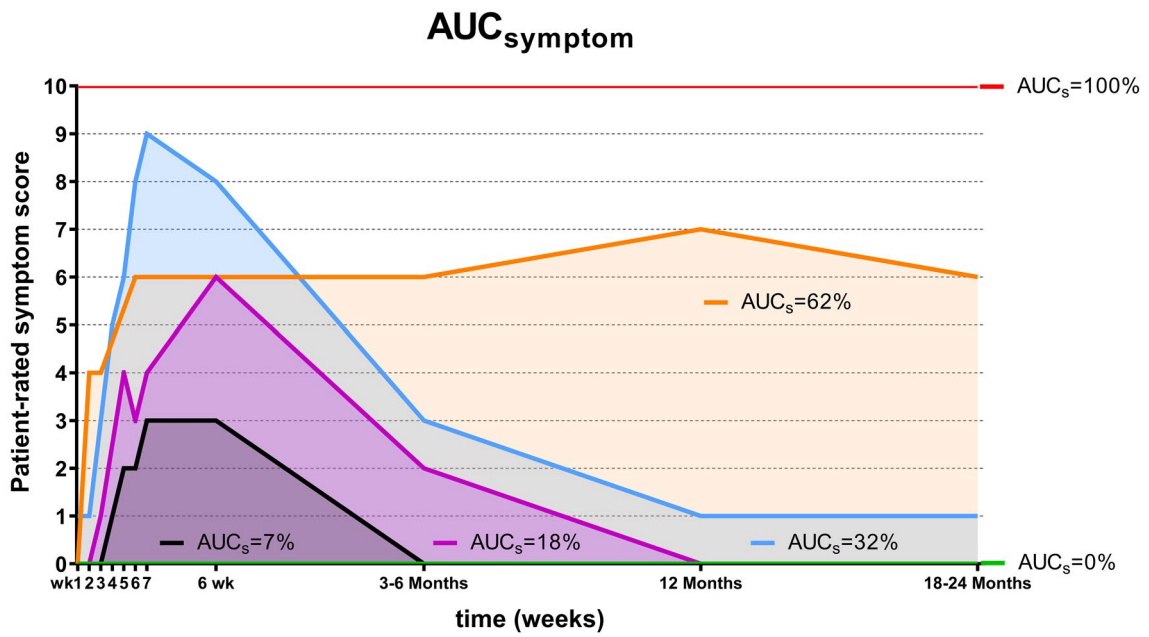

Figure 1. Illustration of the area under the symptom trajectory curve ($AUC_{symptom}$) for different symptom trajectory scenarios. The $AUC_{symptom}$ represents the percentage of area covered by the symptom score over a specific interval divided by the theoretically maximum area, which is a score of 10 for all time points (red line/white area). The orange line (62%) represents a patient who has a moderate symptom score during the final phase of treatment but does not recover, and thus has a much a higher $AUC_{symptom}$ than of a patient who has higher acute symptom scores but recovers after treatment (blue line, 32%).

3) loco-regional symptoms (eg, dry mouth, swallowing dysfunction, taste).

Time points were established as time in weeks from start of RT (ie, week 1 = 0; week 2 = 1… week 6 = 5; 6 weeks post-RT = 12; 3-6 months = 30; 12 months = 54; 18-24 months = 78) for all statistical analysis; Supporting Table S1 details specific time interval constraints. Mixed-model analyses were conducted separately for acute symptoms during the therapeutic phase (ie, RT weeks 1-7), which represent the upward slope of symptom development, and the late symptom period, which represents the downward slope of the recovery phase (including 6 weeks post-RT as the initial start of this symptom recovery phase).

Statistical Analysis: Mixed-Model Analyses

Mixed models were constructed for each individual MDASI-HN symptom using time and treatment regimen (ICRT, CRT, or RT alone) as fixed effects, with the individual patient's categorical identifier as a random effect. Because most of the symptom scores did not exhibit a linear relation over time, a fixed second-order time component was added to the models. In addition, the demographic variables T stage, N stage, and tumor subsite were introduced as fixed terms if identified as significant on multivariable analysis. Mixed-model analysis was performed using restricted maximum likelihood estimation (R package lme4 [v1.1-23]). Differences between treatment cohorts (ie, ICRT-CRT, ICRT-RT, and CRT-RT) were analyzed with simultaneous tests for general linear hypotheses based on least-squares means (R packages multcomp [v1.4-13] and lsmeans [v2.27-2]), which were corrected for multiple testing using the Bonferroni-Holm method.[19]

Time-Weighted Symptom Burden: $AUC_{symptom}$

The $AUC_{symptom}$ is a representation of the overall cumulative time-weighted symptom burden. It reduces the symptom trajectory for a patient to a single measure without discarding temporal information, as it weighs the symptom scores by the duration patients experience them. The $AUC_{symptom}$ is calculated by linearly connecting the available scores, which are plotted over time in weeks, and calculating the area between the x-axis and the symptom curve, and subsequently dividing it by the theoretical maximum area (ie, a score of 10 for all time points). Consequently, late symptom scores were weighted more heavily, as they are more relevant for long-term quality of life.[20,21] A visual representation of $AUC_{symptom}$ is depicted in Figure 1. The $AUC_{symptom}$ analyses were performed for

acute symptoms at an interval between RT weeks 1 to 7 and 6 weeks post-RT and for late symptoms between 3-6 months to 18-24 months post-RT. To ensure reliable calculation of the $AUC_{symptom}$, the time-weighted symptom burden analysis was performed on a subset of patients who had scores at 1) start or week 2; 2) week 5 or 6 or end of treatment; and 3) at least week 2 time points in follow-up after treatment.

A heatmap was created that includes all individual $AUC_{symptom}$ with treatment regimen categorizations while sorting the summed $AUC_{symptom}$ per symptom over patients (columns) and per patient over symptoms (rows). Multivariable linear regression was performed on the average $AUC_{symptom}$ as a dependent variable to test the correlation with treatment regimen (using CRT as a reference) while correcting for clinical variables (ie, T stage = 1, 2, 3, 4; N stage = 1, 2, 3; the reference for tumor site was "BOT"). Individual symptom comparison for $AUC_{symptom}$ was performed with a Mann-Whitney *U* test for ICRT-CRT and CRT-RT.

RESULTS

Demographics

The average trajectories of the 28 symptoms for all 717 patients with OPC who were included in this study are provided in Figure 2. Symptom reporting compliance rates were 88% at baseline, 85% for any score during treatment, and on average 57% (44%-71%) after treatment (Supporting Fig. S2). Demographics are tabulated in Table 1, where tumor subsite and T and N stage distributions were distinct between the ICRT, CRT, or RT alone cohorts (chi-square test; $P < .001$).

The majority of CRT patients (62%) received weekly cisplatin (40 mg/m^2), and the second most common regimen (28%) was weekly cetuximab (400 mg/m^2 loading dose, followed by 250 mg/m^2). The most common induction chemotherapy agent combination was TPF (51%): docetaxel (75 mg/m^2 on D1), cisplatin (75 mg/m^2 on D1) with or without 5-fluouracil (1000 mg/m^2 on D1-D4), administered every 3 weeks for typically 3 cycles; followed by PCC (36%): paclitaxel (135 mg/m^2), carboplatin (AUC 2) and cetuximab (400 mg/m^2, followed by 250 mg/m^2) administered weekly for typically 6 weeks. Carboplatin was used more frequently as a concurrent agent in the ICRT (44%) cohort compared with CRT (9%) (Table 1). The anti-PD1 nivolumab (ICRT, 7%; CRT, <0.5%), other agents such as the PD-L1 inhibitor durvalumab (ICRT, 6%; CRT, 1%), or a second concurrent agent (~5%) were also administered sporadically.

Mixed-Model Analysis

All 28 MDASI-HN symptoms showed a significant increase in symptom scores over time ($P < .001$) during RT; as well as significant recovery over time posttreatment ($P < .03$), except for choking ($P = .93$), numbness ($P = .62$), and memory ($P < .001$; for increase). The model curves over time per treatment regimen are depicted in Supporting Figure S3, illustrating the model fit and to the data per symptom for the acute development and late recovery symptom phase.

T stage was a significant multivariable factor for acute general activity, walking, fatigue, appetite, memory, mucus, mucositis, pain, swallowing, choking, teeth, and voice and late general activity, walking, relations, constipation, appetite, and all late local symptoms, except for shortness of breath, skin, dry mouth, and taste. N stage was a significant factor for acute mood, enjoyment, sadness, and appetite. Tumor site was significant for acute choking and teeth and late choking and skin. Models were corrected for these confounders accordingly.

Addition of Induction to Concurrent Chemoradiotherapy (ICRT vs CRT/RT)

Numbness and shortness of breath increased significantly during and after treatment in patients who were treated with ICRT compared with CRT and RT alone (see *P* values in Fig. 3). The results suggest a specific association with induction chemotherapy, as no significant difference was observed between CRT and RT alone. Additionally, acute taste and late dry mouth were significantly higher in patients who were treated with ICRT compared with those treated with RT alone. Late work was significant in comparisons of both ICRT/CRT and ICRT/RT alone. The model effect sizes demonstrated that for all significant comparisons, ICRT showed worse symptom scores than CRT or RT alone (Supporting Tables S3 and S4). The visualization of the models in Supporting Fig. S3 also show the effect size of the treatment regimen, which shows that for all significant symptoms, the curve is highest (ie, worst symptom severity) for ICRT, followed by CRT and subsequently RT alone.

Addition of Chemotherapy to RT Alone (ICRT/CRT vs RT Alone)

Compared with regimens that included chemotherapy (ICRT or CRT), RT alone showed significantly lower acute interference symptoms (general activity, mood, relations, and work). After correction for T stage and N stage, walking and enjoyment were not significantly different between ICRT/CRT and RT alone.

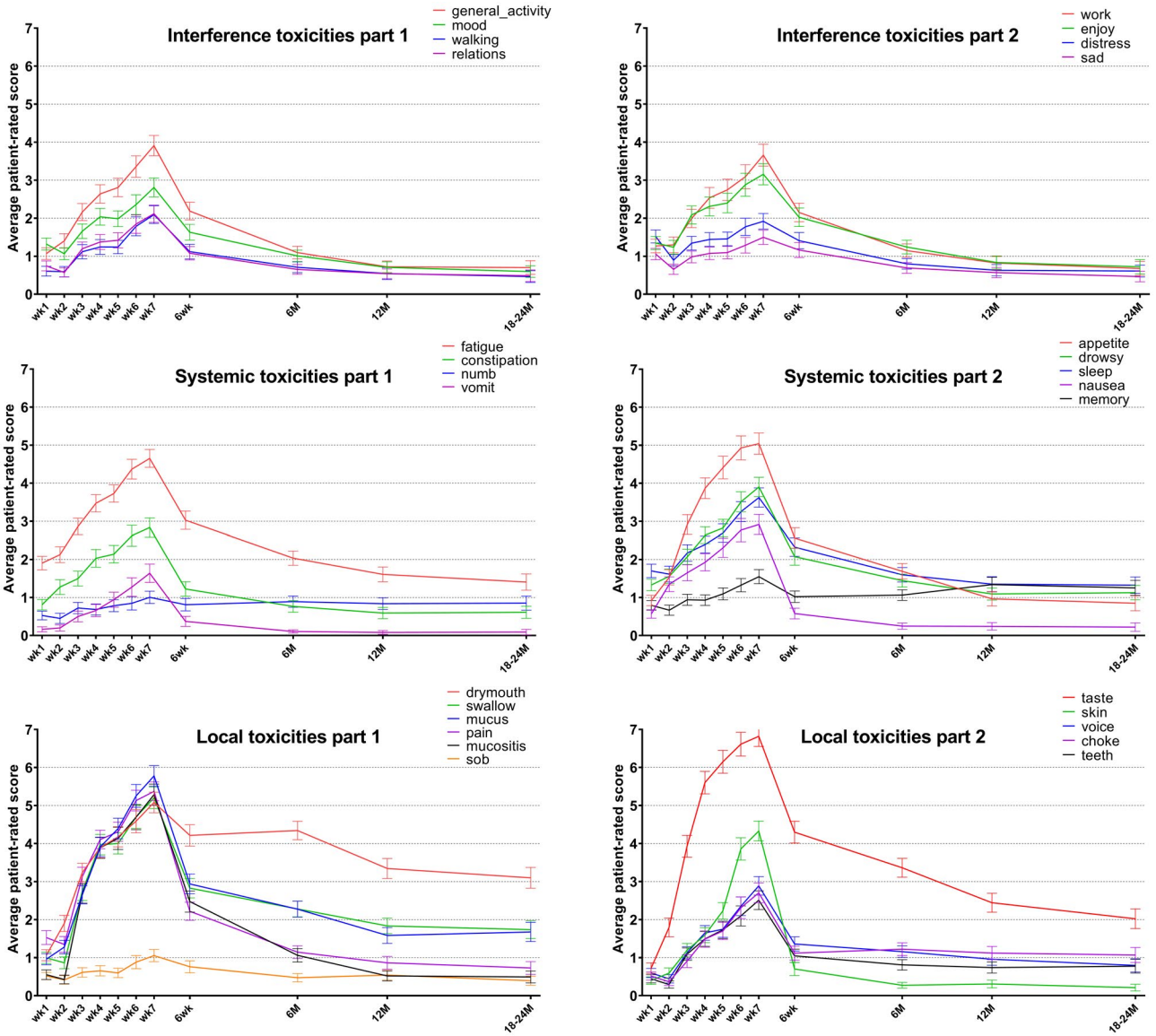

Figure 2. Average patient-reported outcome scores trajectory and 95% CI weekly during treatment and 6 weeks, 3 to 6 months, 12 months, and 18 to 24 months after treatment for all 28 symptoms included in this study among all patients. numb, numbness; sob, shortness of breath.

Chemotherapy significantly increased all acute systemic symptoms, except memory (Fig. 3). The acute local-regional symptoms for which concurrent chemotherapy (CRT) showed significantly higher trajectories for mucus, dry mouth, mucositis, pain, swallowing, skin, voice, but T stage eliminated the significance to treatment regimen for choking in this dataset. No late differences were observed between treatment regimens with and without chemotherapy that could not be attributed to induction chemotherapy specifically. The model effect sizes demonstrated that for all significant comparisons, RT alone showed better symptom scores that ICRT or CRT (Supporting Tables S3 and S4).

To illustrate the severity, the moderate-to-severe incidences, which are defined as MDASI-HN symptom score 5 or higher, are shown for different time points in Figure 4.

Symptom Trajectory Comparison

The trajectory analyses were performed on a subset of 336 patients that had sufficient time points (ie, at the start of RT, the end of RT, and at least 2 follow-up time points) to reliably calculate the $AUC_{symptom}$.

TABLE 1. Characteristics of Patients Included in Mixed-Model Analyses

Characteristic	ICRT (n = 131)	CRT (n = 462)	RT Alone (n = 124)	*P*
Sex				.376
Women	11 (8)	48 (10)	17 (14)	
Men	120 (92)	414 (90)	107 (86)	
Tumor site				<.001
BOT	69 (53)	219 (47)	47 (38)	
NOS	8 (6)	22 (5)	23 (19)	
Pharynx wall	3 (2)	7 (2)	0 (0)	
Soft palate	0 (0)	7 (2)	2 (2)	
Tonsil	51 (39)	207 (45)	52 (42)	
T stage				<.001
T0	7 (5)	21 (5)	23 (19)	
T1	15 (12)	137 (30)	66 (53)	
T2	34 (26)	184 (40)	33 (27)	
T3	28 (21)	75 (16)	1 (1)	
T4	47 (36)	45 (10)	1 (1)	
N stage				<.001
N0	6 (5)	43 (9)	21 (17)	
N1	25 (19)	160 (35)	69 (56)	
N2a	7 (5)	27 (6)	10 (8)	
N2b	39 (30)	182 (39)	24 (19)	
N2c	40 (31)	46 (10)	0 (0)	
N3	14 (11)	4 (1)	0 (0)	
p16 HPV-positive				.702
Positive	93 (71)	351 (76)	95 (77)	
Negative	10 (8)	36 (8)	8 (7)	
Unknown	28 (21)	75 (16)	21 (17)	
Technique				.197
3D CRT	1 (1)	3 (1)	1 (1)	
IMPT	25 (19)	78 (17)	23 (19)	
IMRT	9 (7)	79 (17)	18 (15)	
VMAT	96 (73)	302 (65)	82 (66)	
Surgery primary				<.001
No	127 (97)	436 (94)	89 (72)	
TORS	4 (3)	25 (5)	34 (27)	
Open	0 (0)	1 (0)	1 (1)	
Neck dissection				<.001
No	121 (92)	421 (91)	83 (67)	
Yes	10 (8)	41 (9)	41 (33)	
Age, y				.865
<60	44 (34)	185 (40)	46 (37)	
60-70	58 (44)	175 (38)	50 (40)	
70-80	26 (20)	88 (19)	24 (19)	
>80	3 (2)	14 (3)	4 (3)	
Agents				—
Cisplatin	59 (45)	287 (62)	0 (0)	
Cetuximab	14 (11)	128 (28)	0 (0)	
Carboplatin	58 (44)	40 (9)	0 (0)	
TPF	67 (51)[a]	0 (0)	0 (0)	
PCC	47 (36)[a]	0 (0)	0 (0)	
Nivolumab	9 (7)[a]	2 (0)	0 (0)	
Other	8 (6)[a]	5 (1)	0 (0)	

Abbreviations: 3D, 3-dimensional; BOT, base of tongue; CRT, concurrent chemoradiation; HPV, human papillomavirus; ICRT, induction chemotherapy plus concurrent chemoradiation; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; NOS, not otherwise specified; PCC, paclitaxel, carboplatin and cetuximab; RT, radiotherapy alone; TORS, transoral robotic surgery; TPF, docetaxel, cisplatin with or without 5-fluouracil; VMAT, volumetric-modulated arc therapy.
All data are presented as n (%).
[a]Induction agent.

The heatmaps demonstrate that the overall cumulative time-weighted symptom burden is higher for patients that receive chemotherapy (ICRT/CRT) compared with RT alone (Fig. 5). Multivariable analyses on the average $AUC_{symptom}$ over all symptoms revealed that RT alone yielded a significantly lower acute symptom burden compared with the reference CRT (Table 2). For the late phase, ICRT was correlated with higher symptom burden than the reference CRT (Table 2). For the overall burden, no clinical variables were significant (Table 2).

For individual symptoms, this $AUC_{symptom}$ difference between CRT and RT was significant for 25 of the 28 reported acute symptoms (Fig. 5, bottom). For late symptoms, this seemed less evident, as the results were consistent with those of the mixed-model analysis (before correcting for T stage) in that only mucus was significant. Also in line with the mixed-model analyses, the addition of induction significantly increased the $AUC_{symptom}$ of acute and late numbness, shortness of breath, and choking. In contrast, late teeth, voice, skin, and pain were significantly different for the $AUC_{symptom}$ analyses.

Impact of Chemotherapy Agents

No significant difference was observed in acute and late MDASI-HN scores over time between carboplatin and cisplatin with mixed-model analyses, except for acute nausea, where cisplatin administration resulted in higher symptom scores ($P = .008$). The largest effect of cetuximab compared with either carboplatin or cisplatin was observed for acute and late skin and mucositis. Significant levels are depicted in Supporting Table S2; cetuximab versus cisplatin showed significantly higher symptom scores for acute memory, distress, dry mouth (also cetuximab vs carboplatin), swallow, teeth, and pain, as well as late dry mouth, enjoyment (also cetuximab vs carboplatin), drowsy, and mucus.

DISCUSSION

Given the improved disease prognosis of HPV-associated OPC,[22,23] symptom burden considerations are more pressing now than previously with more aggressive HNC with shorter survivorship.[2,24-26] To our knowledge, this is the first study to comprehensively compare symptom trajectories comparing patients with OPC who were treated with RT with and without chemotherapy using prospectively collected longitudinal scaled multisymptom data, hereby addressing the dearth of knowledge of the (added) effect of chemotherapy in developing symptoms.[9,10] Our results demonstrate that the addition of chemotherapy either as induction and/or concurrently with RT (ICRT/CRT) was associated with significantly worse MDASI-HN symptom

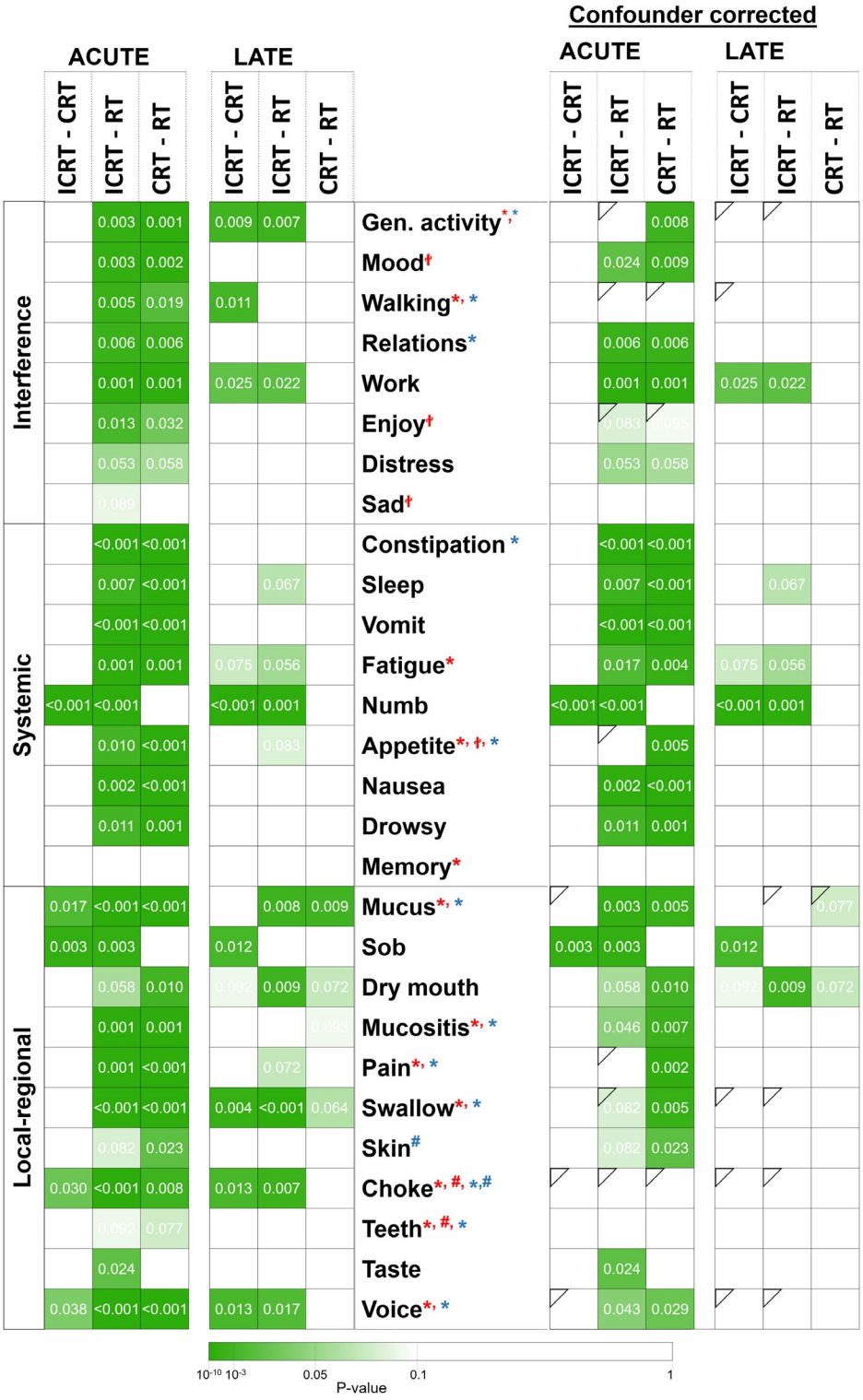

Figure 3. Mixed-model analysis of treatment results without (left columns) and with (right columns) inclusion of confounders. Red symbols indicate acute symptoms; blue symbols indicate late symptoms (*T stage; †N stage; #tumor site). Triangle corners indicate loss of significance after multivariable adjustment. *P* values were corrected for multiple testing. The effect sizes of these model comparisons indicate that for all significant comparisons, the scores were highest for ICRT, followed by CRT and subsequently RT alone (see Supporting Tables S3 and S4 or Supporting Fig. S3). CRT, concurrent chemoradiation; ICRT, induction chemotherapy plus concurrent chemoradiation; RT, radiotherapy alone.

	Start RT			During RT			wk6 post			M3-6			M12			M18-24		
	ICRT	CRT	RT	ICRT	CRT	RT	ICRT	CRT	RT	ICRT	CRT	RT	ICRT	CRT	RT	ICRT	CRT	RT
dry mouth	11	6	5	64	64	56	48	45	33	49	45	39	37	28	32	37	25	30
taste	10	3	4	79	80	79	36	46	41	33	32	28	23	16	19	12	13	17
mucus	11	5	5	75	71	53	20	26	16	20	18	10	15	9	10	17	14	9
swallow	11	5	4	65	70	48	38	23	11	30	14	11	12	8	16	17	9	11
fatigue	18	13	13	63	60	48	39	23	20	20	12	15	12	10	7	15	7	6
appetite	9	6	4	64	71	56	27	23	14	12	12	14	8	7	7	10	5	6
pain	14	13	8	71	72	53	26	18	9	12	7	8	12	4	10	10	4	4
mucositis	5	4	3	65	68	50	24	23	11	5	10	9	3	3	6	4	3	4
sleep	16	14	12	49	50	32	33	17	14	17	13	13	7	8	7	4	10	13
General activity	12	9	7	48	53	36	30	18	14	9	8	7	13	3	5	9	4	5
work	12	10	10	49	50	31	31	17	10	12	7	7	9	4	8	6	5	4
drowsy	10	8	7	50	51	34	25	14	11	8	8	10	5	6	4	8	6	7
enjoy	17	10	11	46	45	30	29	15	9	13	10	6	8	4	10	8	4	6
mood	15	9	7	35	35	20	23	11	10	5	7	9	13	2	3	4	4	4
choke	7	2	3	36	32	16	11	5	4	14	7	2	7	5	7	10	6	7
skin	5	2	2	51	49	39	13	5	3	0	1	1	2	1	1	0	1	0
voice	8	3	2	39	32	16	13	7	3	13	4	5	7	2	10	6	5	6
constipation	13	5	2	30	44	18	11	8	6	11	5	5	2	4	4	6	4	2
teeth	5	3	2	30	31	23	7	5	7	5	4	5	2	3	7	6	6	4
walking	8	5	4	28	26	11	13	8	9	9	4	7	10	3	6	0	2	9
distress	12	10	10	27	23	12	18	10	9	7	4	5	7	3	6	4	2	7
nausea	7	4	3	42	41	23	5	4	3	1	2	2	3	1	3	2	1	4
relations	10	4	4	29	28	12	15	7	6	3	4	3	7	1	4	2	3	7
numb	3	2	5	19	8	7	13	5	4	15	2	6	17	2	4	10	4	4
memory	6	4	6	21	13	12	5	4	4	3	5	3	12	8	7	6	5	6
sad	9	6	7	22	15	11	17	8	6	5	5	6	3	2	4	4	1	6
sob	5	2	2	19	9	5	9	4	7	3	1	3	5	2	3	2	0	4
vomit	1	1	1	24	20	6	7	4	1	0	0	0	0	0	0	0	0	0

Figure 4. Moderate-to-severe symptom (MD Anderson Symptom Inventory–Head and Neck Module score ≥5) prevalence map in percentage (%). The maximum score reported during radiotherapy was used for computing prevalence (see "During RT" column).

trajectories compared with RT alone during radiation treatment. After treatment, these individual symptom differences between treatment regimens seemed to resolve, except for numbness, shortness of breath, and dry mouth. However, overall symptom burden of the late symptoms was higher for ICRT compared with CRT, and in the acute phase RT alone was correlated to lower symptom burden than CRT (Table 2). As expected, the maximum symptom burden was during treatment for all cohorts, with gradual recovery for most symptoms back to baseline levels (Fig. 2), which was most rapid for the RT alone cohort (Fig. 4).

Concurrent cisplatin chemoradiotherapy is the current standard of care for locally advanced HNC, but alternative strategies such as induction chemotherapy for higher-risk disease and RT alone for earlier stage low-risk disease are used in selective cases after careful multidisciplinary consideration. The induction chemotherapy cohort in our study showed higher acute and late overall cumulative symptom burden (Table 2), as well as significantly higher symptom trajectories for numbness and shortness of breath with the mixed-model analyses. At 1 year post-RT, numbness had a higher rate of moderate-to-severe symptom scores in the induction group (17%) compared with CRT (2%) and RT alone (4%) (Fig. 4). Peripheral neuropathy is a well-known dose-limiting toxicity for platinum and taxane chemotherapy agents.[27] However, the majority of induction TPF studies have not emphasized the rates of late neuropathy for patients who tolerate the regimen.[13-15,28] Because of the nature of the survey, other manifestations of neuropathy such as hearing loss, motor, and autonomic toxicities were not investigated. Our findings highlight the importance of careful follow-up of the neurotoxicity signs and symptoms for patients treated with induction chemotherapy regimens.

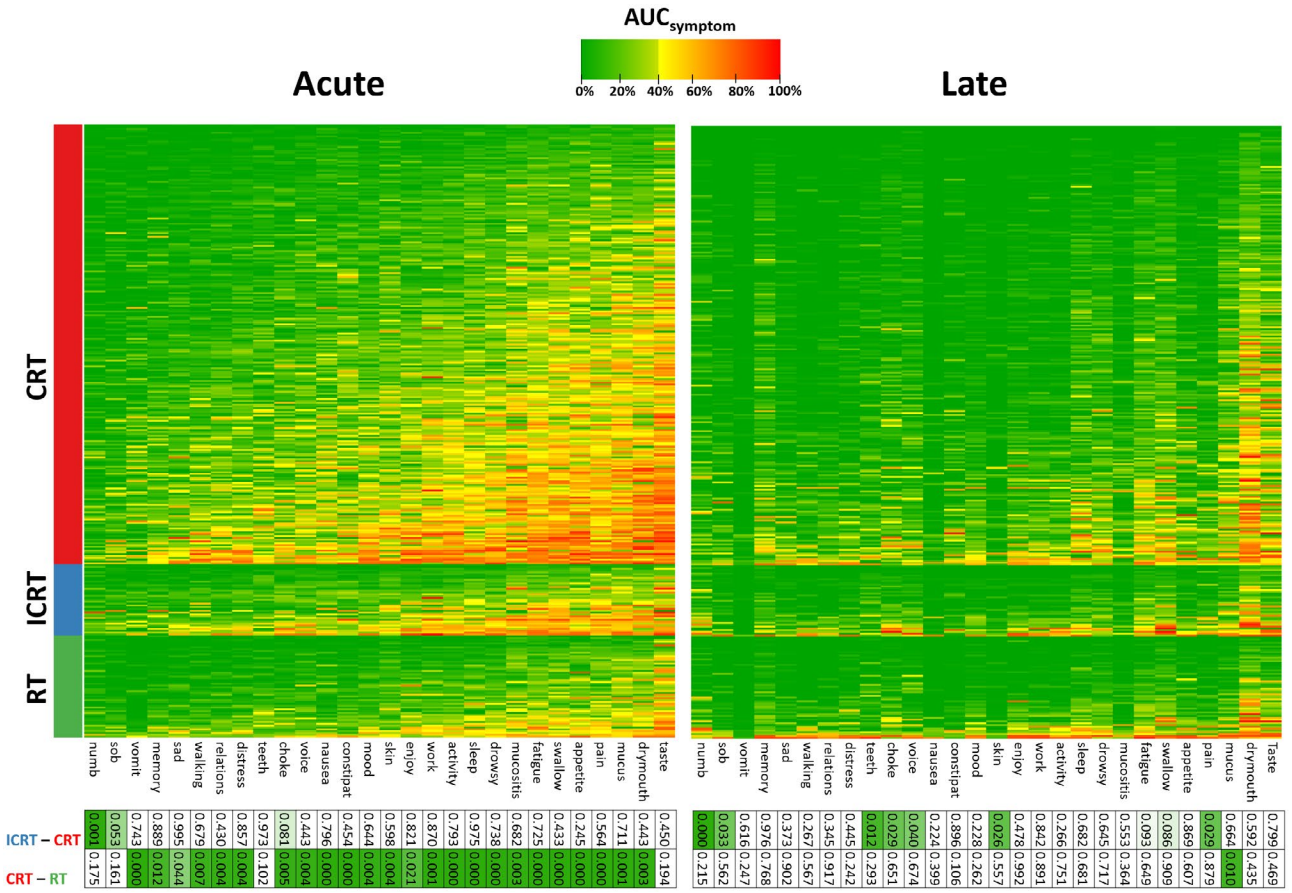

Figure 5. Heat maps representing the area under the PRO-over-time curves for acute and late phase. Toxicities on the x-axis are sorted on overall severity (ie, summed PRO over all patients). The colors represent the percentage of the maximum area under the curve (ie, score of 10 of for all symptoms).

TABLE 2. Multivariable Linear Regression With Overall $AUC_{symptom}$ (Average of All Symptoms) as Dependent Variable

Multivariable Linear Model	Acute Symptoms		Late Symptoms	
	β	*P*	β	*P*
Intercept	0.22	.00	0.05	.02
Treatment (CRT is reference)				
RT alone	−0.08	<.0001*	0.02	.23
ICRT	0.01	.68	0.04	.03*
T stage	0.01	.42	0.01	.36
N stage	0.00	.82	0.01	.17
Tumor site (BOT is reference)				
Tonsil	0.00	.84	0.02	.13
Unknown	0.03	.30	0.03	.17
Soft palate	0.05	.60	0.03	.64
Pharyngeal wall	0.02	.75	0.05	.35

Abbreviations: $AUC_{symptom}$, area under the symptom trajectory curve; ICRT, induction chemotherapy plus concurrent chemoradiation; RT, radiotherapy. The reference for tumor site was the base of the tongue, and the reference for treatment was concurrent chemoradiation.
* significance level *P* value < .05.

As anticipated, systemic symptoms such as nausea, vomiting, and constipation were affected by the addition of chemotherapy; this finding is in line with those of previous studies,[12,29-31] yet these symptoms are frequently not reported.[15,32-34] While local-regional symptoms are attributed to RT, our analysis shows that the majority of these symptoms (eg, dry mouth, mucositis, pain, swallowing) in the acute setting were significantly higher for CRT compared with RT alone. This alludes to the amplified or added damage of chemotherapy combined with RT to the epithelium, as it is likely related to the release of cytokines, which exacerbate tissue response.[35] This is in concert with the significant difference in grade 3/4 mucositis and dermatitis in chemoradiation patients observed in previous trials.[12,31,33,34,36] Finally, interference symptoms are a complex and patient-specific composite of multiple symptoms, providing insight into overall quality of life. General activity, work, mood, and relations showed significantly higher trajectories in the chemotherapy cohorts,

suggesting the impact of chemotherapy on quality of life during treatment and on work after treatment.

The subanalyses of the chemotherapy agents demonstrated that the effect of concurrent systemic therapy was larger for cetuximab compared with both carboplatin and cisplatin for symptoms skin and mucositis. In a phase 3 trial by Mehanna et al[37] comparing severe sequelae between RT combined with cisplatin versus cetuximab regimen, cetuximab did not show reduced toxicity, while showing more unfavorable survival rates for HPV-positive patients who have OPC. Interestingly, similar to our result, much higher skin symptoms were observed for cetuximab (50%) versus cisplatin (4%). Additionally, significantly higher scores for mucositis, dermatitis, fatigue, and hypokalemia were reported in a phase 3 trial comparing cetuximab plus cisplatin (n = 444) CRT compared with cisplatin CRT (n = 447).[38] Subsequent studies have reported conflicting data on whether significantly higher acute gastrointestinal toxicity was associated with cisplatin[39] or cetuximab,[7] while other symptoms were not significantly different, including acute mucositis.

This study predominantly evaluated patients with nonsurgically treated OPC with a large-scale prospective collection of symptom data, and it is inherently biased by the clinical considerations that go into the selection for patients who will receive induction systemic therapy before concurrent chemoradiation. Although this was partly mitigated by correcting for treatment-dictating clinical confounders (eg, T stage, tumor site) in the mixed-model analyses, this was not done for the $AUC_{symptom}$ analyses; therefore, the mixed-model analyses should be considered the leading results in this research. The confounders in the mixed-model analyses eliminated the significant treatment regimen comparisons for some symptoms (triangle corners in Fig. 3), which can indicate that chemotherapy acts as a surrogate for clinical variables, but it may also be that the data are insufficient to demonstrate the treatment regimen effect. Moreover, other unidentified confounders could exist. For example, tumor recurrence could affect the symptom scores. In this cohort, only 23 (3.2%) patients presented with a local-regional recurrence in follow-up, and 11 (1.5%) patients presented with residual disease at ~6 months that resolved. Excluding these patients, showed no change in significance levels for the late confounder-corrected mixed model analyses, except for symptom work, which was significant for comparisons of ICRT/CRT and CRT/RT alone. Another issue that may influence the prevalence/severity of the symptom burden is the proactive supportive care that was also routine in this study interval, including referrals to registered dietitians, speech pathologists, oral/dental oncologists, pain management and other supportive care disciplines that could have influenced the symptom trajectories. Nevertheless, this care was not different between patients who were treated with different regimens.

Another limitation is the disproportionate number of patients in the ICRT (n = 131) and RT alone (n = 124) cohorts compared with the CRT (n = 462) cohort. Consequently, the ICRT/RT alone comparison was statistically less powered than the CRT/RT or ICRT/CRT comparisons. Finally, clinician-rated toxicities, number of chemotherapy cycles (which was not shown significant previously[24]), blood biomarkers, comparison between radiation techniques, and the effect of surgery were beyond the scope of this analysis but would be valuable future work.

In conclusion, our results demonstrate that the addition of chemotherapy to RT for the treatment of patients with OPC is associated with a significantly worse acute symptom burden as demonstrated by higher MDASI-HN symptom trajectories compared with that found for patients who were treated with RT alone. For most symptoms, no significant individual symptom difference between treatment regimens was observed after treatment, except for numbness and shortness of breath, which were more severe in patients receiving induction and concurrent chemotherapy. We developed a new measure of overall cumulative symptom burden, $AUC_{symptom}$, which provides a quantitative composite score that represents a patient's overall symptom burden throughout the duration of treatment and during the posttreatment period, which showed higher rates for both acute and late time points for regimens that included chemotherapy. The negative impact of chemotherapy on the overall symptom burden experienced by patients with OPC must be considered when assessing the overall benefits of chemotherapy.

FUNDING SUPPORT

Direct infrastructure support was provided by the multidisciplinary Stiefel Oropharyngeal Research Fund of the University of Texas MD Anderson Cancer Center Charles and Daneen Stiefel Center for Head and Neck Cancer, and the NIH/NCI Grant (P30CA016672). Lisanne V. van Dijk was supported by NWO ZonMw via the Rubicon Individual career development grant. Abdallah S. R. Mohamed, Stephen Y. Lai, and Clifton D. Fuller were supported by the National Institutes of Health (NIH) National Institute for Dental and Craniofacial Research Establishing Outcome Measures Award (grants R01DE025248, R56DE025248). Abdallah S. R. Mohamed, Stephen Y. Lai, Clifton D. Fuller, and Katherine A. Hutcheson were supported by the NIH National Cancer Institute Early Phase Clinical Trials in Imaging and Image-Guided Interventions Program (grant R01CA218148). Lance A. McCoy

was supported by NIH Research Supplements to Promote Diversity in Health-Related Research (grant R01DE025248-S02). Clifton D. Fuller received funding unrelated to this study from the NIH NCI Cancer Center (grants P30CA016672, P50 CA097007, and R01CA2148250), the NIH National Institute of Biomedical Imaging and Bioengineering (grant R25EB025787-01), the National Science Foundation (grant NSF1557679), the NSF-CMMI (grant NSF1933369), and the Sabin Family Foundation.

CONFLICT OF INTEREST DISCLOSURES

Abdallah S. R. Mohamed has received research support from The University of Texas MD Anderson Cancer Center (Oropharynx Program Discovery Section Award), the NIH National Cancer Institute, and the NIH National Institute for Dental and Craniofacial Research. Renata Ferrarotto has received personal fees from Ayala Pharmaceuticals, Bicara, Klus Pharma, Medscape, Prelude Pharmaceuticals, Regeneron-Sanofi; has received consulting fees from Bicara and Carevive; and has received institutional support from AstraZeneca, Ayala Pharmaceuticals, Genentech, Merck, Pfizer, and Prelude Pharmaceuticals. Clifton D. Fuller has received research support from Elekta AB and the NIH; has received personal fees from the American Association of Physicists in Medicine, American Society of Clinical Oncology, Elekta AB, and the NIH; and has received nonfinancial support from Elekta AB. Katherine A. Hutcheson has received research support from the Charles and Daneen Stiefel Oropharynx Fund, McMaster University, the MD Anderson Institutional Research Grant Program, the NIH, Patient Centered Outcomes Research Institute, THRIVE Foundation, and the University of Illinois–Chicago (sub-award) and has received personal fees from the American Speech–Language–Hearing Association, Atos Medical, and Medbridge. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Lisanne V. van Dijk: Conceptualization, data curation, formal analysis, methodology, software, supervision, validation, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, and project administration; **Abdallah S. R. Mohamed:** Conceptualization, methodology, resources, funding acquisition, writing–review and editing, visualization; **Renata Ferrarotto:** Methodology, resources, writing–review and editing, visualization; **Lance A. McCoy:** Data curation, writing–review and editing; **Christina S. Sharafi:** Data curation, writing-review and editing; **Eva Jones:** Data curation, writing–review and editing; **Kennedy Steele:** Data curation, writing–review and editing; **Amy C. Moreno:** Resources, validation, writing–review and editing, visualization; **Stephen Y. Lai:** Validation, writing–review and editing; **Adam S. Garden:** Validation, writing–review and editing; **Jeffrey N. Myers:** Validation, writing–review and editing, visualization; **David I. Rosenthal:** Validation, writing–review and editing; **Clifton D. Fuller:** Conceptualization, methodology, resources, funding acquisition, supervision, writing-review and editing, visualization; **Katherine A. Hutcheson:** Conceptualization, methodology, project administration, resources, funding acquisition, supervision, writing–review and editing, visualization

REFERENCES

1. Pignon JP, Maître A le, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. 2009;92:4-14.
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. Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. *Oral Oncol*. 2014;50:565-574.
4. Braakhuis BJM, Visser O, René Leemans C. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: increasing incidence, but not in young adults. *Oral Oncol*. 2009;45:e85-e89.
5. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet*. 2008;371:1695-1709.
6. Cramer JD, Hicks KE, Rademaker AW, Patel UA, Samant S. Validation of the eighth edition American Joint Committee on Cancer staging system for human papillomavirus-associated oropharyngeal cancer. *Head Neck*. 2018;40:457-466.
7. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. 2019;393:40-50.
8. 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.
9. Ferrari D, Ghi MG, Franzese C, Codecà C, Gau M, Fayette J. The slippery role of induction chemotherapy in head and neck cancer: myth and reality. *Front Oncol*. 2020;10:1-12.
10. Gau M, Karabajakian A, Reverdy T, Neidhardt EM, Fayette J. Induction chemotherapy in head and neck cancers: results and controversies. *Oral Oncol*. 2019;95:164-169.
11. 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;26:3582-3589.
12. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349:2091-2098.
13. Hitt R, Grau JJ, López-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol*. 2014;25:216-225.
14. Ghi MG, Paccagnella A, Ferrari D, et al. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II-III trial. *Ann Oncol*. 2017;28:2206-2212.
15. Geoffrois L, Martin L, De Raucourt D, et al. Induction chemotherapy followed by cetuximab radiotherapy is not superior to concurrent chemoradiotherapy for head and neck carcinomas: results of the GORTEC 2007-02 phase III randomized trial. *J Clin Oncol*. 2018;36:3077-3083.
16. Giralt JL, Gonzalez J, del Campo JM, et al. Preoperative induction chemotherapy followed by concurrent chemoradiotherapy in advanced carcinoma of the oral cavity and oropharynx: a phase II study. *Cancer*. 2000;89:939-945.
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381.
18. Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M.D. Anderson symptom inventory, head and neck module. *Head Neck*. 2007;29:923-931.
19. Holm S. Board of the Foundation of the Scandinavian Journal of Statistics: a simple sequentially rejective multiple test procedure. *Scand J Stat*. 1978;6:65-70.
20. Hunter KU, Schipper M, Feng FY, et al. Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: prospective study of patient-reported, observer-rated, and objective outcomes. *Int J Radiat Oncol Biol Phys*. 2013;85:935-940.
21. Wijers OB, Levendag PC, Braaksma MM, Boonzaaijer M, Visch LL, Schmitz PI. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. *Head Neck*. 2002;24:737-747.
22. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.
23. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
24. Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 Trial: long-term report of efficacy and toxicity. *J Clin Oncol*. 2014;32:3858-3867.

25. Posner MR, Lorch JH, Goloubeva O, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. *Ann Oncol*. 2011;22:1071-1077.
26. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst*. 2008;100:261-269.
27. Garden AS, Kamal M, Mohamed ASR, et al. Neurologic sequelae following radiation with and without chemotherapy for oropharyngeal cancer: patient reported outcomes study. *Head Neck*. 2020;42:2137-2144.
28. Janoray G, Pointreau Y, Garaud P, et al. Long-term results of a multicenter randomized phase III trial of induction chemotherapy with cisplatin, 5-fluorouracil, ± docetaxel for larynx preservation. *J Natl Cancer Inst*. 2016;108:1-7.
29. Chan A, Shwe M, Gan Y, Yap K, Chew L, Lim W-T. Trajectory and risk factors for chemotherapy-induced nausea and vomiting in Asian patients with head and neck cancer. *Head Neck*. 2015;37:1349-1357.
30. Gibson RJ, Keefe DMK. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. *Support Care Cancer*. 2006;14:890.
31. Adelstein DJ, Saxton JP, Lavertu P, et al. A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. *Head Neck*. 1997;19:567-575.
32. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *JNCI J Natl Cancer Inst*. 1999;91:2081-2086.
33. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy—results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;50:1161-1171.
34. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French head and neck oncology and radiotherapy group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol*. 2004;22:69-76.
35. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol*. 1998;34:39-43.
36. Al-Mamgani A, Van Rooij P, Verduijn GM, Mehilal R, Kerrebijn JD, Levendag PC. The impact of treatment modality and radiation technique on outcomes and toxicity of patients with locally advanced oropharyngeal cancer. *Laryngoscope*. 2013;123:386-393.
37. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet*. 2019;393:51-60.
38. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol*. 2014;32:2940-2950.
39. Magrini SM, Buglione M, Corvo R, et al. Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II trial. *J Clin Oncol*. 2016;34:427-435.