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Scientific Article

Preservation of swallowing function with de-intensified chemoradiation therapy for HPV-associated oropharyngeal squamous cell carcinoma

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Abstract

Purpose: This study aimed to compare the swallowing function in patients with human papillomavirus–associated oropharyngeal squamous cell carcinoma treated with de-intensified chemoradiation therapy (6 weeks, 60 Gy) versus those receiving standard-of-care chemoradiation therapy (7 weeks, 70 Gy).

Methods and materials: A retrospective review was conducted of 78 patients with human papillomavirus–associated oropharyngeal squamous cell carcinoma with modified barium swallow studies pretreatment and 6 to 8 weeks posttreatment. The swallowing function was objectively scored for penetration, aspiration, and pharyngeal residue. Forty patients received de-intensified chemoradiation therapy (60 Gy image guided radiation therapy with weekly cisplatin 30 mg/m^2) and 38 patients received standard-of-care chemoradiation therapy (70 Gy image guided radiation therapy with chemotherapy of the medical oncologist's choosing). Univariate and multivariate analyses were performed to detect differences between the cohorts with regard to laryngeal penetration, aspiration, and pharyngeal residue. A multivariate logistic regression was used to determine the overall effect of treatment

Conflicts of interest: There are no known conflicts of interest for any of the authors.

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on the swallowing function. Patient-reported swallowing outcomes in de-intensified cohort were assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Module for Head and Neck Cancer and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events questionnaires.

Results: Patients treated with de-intensified chemoradiation therapy were associated with a suggestion of lower risk of developing overall swallowing dysfunction (odds ratio [OR], 0.62; $P = .07$), laryngeal penetration (OR, 0.63; $P = .12$), and pharyngeal residue (OR, 0.61; $P = .08$). The mean pre- and 2-year post-European Organisation for Research and Treatment of Cancer Quality of Life scores pertaining to swallowing (1-4 scale, higher worse) in the de-intensified cohort were 1.4 and 1.2 for liquids; 1.2 and 1.1 for purees; 1.5 and 1.7 for solids, 1.0 and 1.3 for choked when swallowing; and 9.0 and 10.8 for composite score, respectively. The mean pre- and 2-year post-Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events swallowing difficulty scores (1-5 scale, with higher scores being worse) were 1.5 and 1.8, respectively.

Conclusions: Compared with 7 weeks of 70 Gy, 6 weeks of 60 Gy de-intensified chemoradiation therapy appears to better preserve the baseline swallowing function (per objective modified barium swallow assessment). Patients treated with de-intensified chemoradiation therapy reported minimal changes in swallowing function.

Introduction

Definitive chemoradiation therapy is a standard organ preservation treatment option for patients with human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC). The standard chemoradiation therapy regimen has been a 7-week course of 70 Gy of radiation with concurrent high-dose cisplatin (100 mg/m^2) for 3 cycles. Dysphagia is a common long-term complication of chemoradiation therapy. Patient-reported rates of late (≥3 months) grade ≥2 dysphagia after chemoradiation therapy have been reported to be 12% to 21%, with rates declining with increasing time from completion of therapy.[1,2] Patients are also at risk for potential aspiration, permanent feeding tube dependence, and impairment in their overall quality of life (QoL).[1,3-8]

Improvements in radiation delivery with the use of intensity modulated radiation therapy (IMRT) have been shown to improve sparing of the pharyngeal constrictors and reduce radiation-related dysphagia when compared with conventional radiation therapy in treatment of head and neck cancers.[1,9,10] A dose-response effect has also been seen, with mean dose to the pharyngeal constrictor muscles, glottic, and supraglottic larynx correlating with aspiration, stricture formation, and reduced laryngeal elevation and being predictive of long-term swallow function.[9,11-13] Common dose constraints for pharyngeal constrictor muscles include a mean total dose 58 Gy, V40 85%, V50 76%, V60 61%, and V70 33%. For the larynx, dose constraints include mean total dose 48 Gy, V40 64%, V50 48%, V60 32%, and V70 13%.[9] Additional studies have shown slight variations in these constraints.[12]

In addition to improvements in radiation delivery, de-intensified treatment for HPV-associated OPSCC is currently being studied in an effort to further improve the treatment toxicity profile without a decrement in tumor response. At our institution, the de-intensification paradigm has been to reduce both radiation and chemotherapy.[14] Patients with favorable-risk HPV-associated OPSCC are treated on trial with a 6-week course of 60 Gy of IMRT with 6 concurrent weekly low doses of cisplatin 30 mg/m^2 (without induction chemotherapy or upfront surgery). We have conducted several prospective clinical trials to evaluate this regimen and carefully collected prospective objective (modified barium swallow [MBS] studies) and subjective (patient-reported outcomes [PRO] of symptoms and QoL) assessments of dysphagia from our trial patients. Also, as a standard practice at our institution, all patients with OPSCC regardless of receipt of de-intensified or standard-of-care chemoradiation therapy (ie, on/off protocol) are assessed with pre- and posttreatment MBS studies.

We hypothesize that swallowing function is better preserved in patients who receive de-intensified chemoradiation therapy. The primary aim of the current study is to compare objective swallowing function (using MBS results) in patients with HPV-associated OPSCC treated with de-intensified chemoradiation therapy (6 weeks, 60 Gy) versus those receiving standard-of-care chemoradiation therapy (7 weeks, 70 Gy). The secondary aim was to report on patient-reported swallowing outcomes for patients enrolled on our de-intensified chemoradiation therapy regimen.

Methods and materials

Study design and subjects

This is a single-institution, retrospective analysis that was performed on patients who underwent MBS studies pre- and post-chemoradiation therapy for pathologically confirmed

OPSCC or squamous cell carcinoma of an unknown primary in the head and neck treated at our institution between August 2003 and December 2015. This study was approved by the institutional review board at our institution (16-1830 and 09-2146). Two cohorts of patients were reviewed and compared for this study: Patients who were treated with de-intensified chemoradiation therapy on 2 multi-institutional phase 2 clinical trials (Lineberger Comprehensive Cancer Center (LCCC) 1120 [NCT01530997] and 1413 [NCT02281955]) and those who received standard-of-care chemoradiation therapy. For the de-intensified cohort we selected those patients treated at our institution on the 2 phase 2 de-intensification clinical trials who had both pre- and post-MBS (n = 40).

The inclusion criteria for the de-intensified cohort included pathologically confirmed OPSCC or squamous cell carcinoma of an unknown primary in the head and neck, HPV or p16-positive; T0 to T3, N0 to N2c, M0; age ≥18 years; Eastern Cooperative Oncology Group performance status 0 to 1; and smoking status limited to ≤10 pack-years. Inclusion criteria were similar in the standard-of-care cohort, except for HPV status (any included) and smoking status (not limited) and patients could have received induction chemotherapy.

A posttreatment neck dissection was required for patients in the de-intensified cohort who were selected from LCCC 1120 if they had node positive disease at presentation but was not required in patients from LCCC 1413, and only performed in those patients with residual radiographic disease on posttreatment imaging.

For the standard-of-care cohort, we matched patients across pertinent patient and tumor characteristics to those undergoing de-intensified chemoradiation therapy, including disease site, TNM stage, age, smoking status, HPV status, and performance status. Between August 2003 and December 2015, 400 patients were treated with standard-of-care chemoradiation therapy at our institution, of whom 38 met the inclusion criteria. Of these 38 patients, 25 underwent both a pre- and post-chemoradiation therapy MBS. The other 13 patients only had a post-chemoradiation therapy MBS. A posttreatment neck dissection was not required in the standard-of-care patients and only performed if there was residual or suspicious disease on the 3-month posttreatment imaging.

Chemoradiation therapy

Patients undergoing de-intensified chemoradiation therapy in clinical trials 1120 and 1413 received weekly low-dose cisplatin (30 mg/m^2) intravenously (IV), and 6 doses were administered concurrently with radiation. Radiation was delivered using IMRT to a total dose of 60 Gy at 2 Gy per fraction for a total of 30 fractions, administered once a day, 5 days a week, for 6 weeks. Areas at risk for subclinical disease received a total of 54 Gy. One patient on LCCC 1413 received cetuximab (400 mg/m^2 IV loading dose followed by 250 mg/m^2 IV weekly) concurrent with radiation.

Patients receiving standard-of-care chemoradiation therapy were treated with IMRT to a total dose of 70 Gy at 2 Gy per fraction for a total of 35 fractions, administered once a day, 5 days a week, for 7 weeks. Areas at risk for subclinical disease received a total of 46 to 54 Gy. The chemotherapy regimen was chosen according to medical oncologist preference, with the majority being cisplatin 100 mg/m^2 IV every third Monday with 3 doses administered concurrently with radiation (18 patients). Other chemotherapy regimens used were cetuximab (400 mg/m^2 IV loading dose followed by 250 mg/m^2 IV weekly) concurrently with radiation for a total of 7 doses (10 patients), carboplatin with paclitaxel (300 mg/m^2 IV weekly and 100 mg/m^2 IV weekly, respectively) concurrently with radiation for a total of 7 doses (6 patients), and carboplatin alone (area under the curve 2 = 157 mg weekly for 1 patient; low-dose weekly for second patient) concurrently with radiation for 7 total doses (2 patients). Induction chemotherapy followed by concurrent chemoradiation therapy was administered to 2 patients.

Modified-barium swallow studies

MBS studies were performed by a speech therapist prior to or within the first week after initiating chemoradiation therapy to assess baseline swallowing characteristics and again 6 to 8 weeks after completion of chemoradiation therapy in the de-intensified cohort and in 25 patients in the standard-of-care cohort. The remaining 13 patients in the standard-of-care cohort did not have a baseline MBS documented and thus only had a 6- to 8-week posttreatment MBS study available for review.

The MBS procedure consisted of patients seated and imaged in the lateral plane. A fluoroscopy tube was positioned to view the posterior oral cavity, soft palate, and posterior pharyngeal wall to allow assessment of swallowing. The majority of patients were tested with 3 consistencies of barium (thin liquid, puree, and solid), and several patients were also tested with thick liquid and mixed solid/liquid consistencies. Observations made during each swallow included laryngeal penetration, aspiration, and presence/absence of pharyngeal residue. A speech therapist prospectively assigned an overall severity score of mild, moderate, or severe on the basis of a previously published, standardized severity scale.[15]

Toxicity and quality of life assessments

PRO of symptoms and QoL were prospectively assessed for the de-intensified chemoradiation therapy cohort (ie, per protocol) with the PRO version of the National Cancer Institute Common Terminology Criteria for Adverse

Events (CTCAE) version 4.03, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Module for Head and Neck Cancer (QLQ-H&N35) questionnaire, and the Eating Assessment Tool (EAT-10) questionnaire. Specifically, 1 question from the PRO CTCAE and 4 questions from the QLQ-H&N35 pertained directly to swallowing and were analyzed in the current study. These assessments were collected before treatment and at every subsequent follow-up visit after treatment. PROs were not obtained or not available for the standard-of-care cohort.

Statistical analysis

We examined the homogeneity of the 2 cohorts in terms of baseline variables and outcomes aftertreatment using the χ^2 test to compare categorical variables and Wilcoxon rank sum test to compare numerical variables. We then conducted multivariable analysis of the MBS swallowing function separately for laryngeal penetration, aspiration, and presence/absence of pharyngeal residue. We jointly tested the differences between the 2 treatment cohorts in 3 consistencies of barium (thin liquid, puree, and solid). More specifically, we treated the measurements of the 3 consistencies of barium as clustered binary outcomes and employed the generalized estimating equation approach to examine the overall effect of treatment on swallowing function.

The working model was a logistics regression model for clustered binary data in which treatment (standard-of-care vs de-intensified) was the main covariate and consistencies of barium (thin liquid, puree, and solid) were also included as covariates to reflect the fact that rates vary across side effects. The 2 covariates of tobacco use and T stage), which were not balanced between the cohorts, were also included in the model. We used the unrestricted correlation structure as the working correlation structure and tested the treatment effect using a Wald-type test. We also jointly analyzed all 9 measurements/dependent outcomes (ie, penetration, aspiration, and pharyngeal residue for each consistency [thin, puree, solid]) using the same multivariate approach as described previously. A 1-sided *P*-value of .05 was used for all statistical tests to examine statistical significance because our overall hypothesis was that de-intensified therapy would result in preserved swallowing function posttreatment.

Results

Patient and treatment characteristics

The final analysis included 78 patients with OPSCC who met inclusion criteria. Patient characteristics are shown in Table 1. The cohorts were balanced for age, primary tumor location, N stage, and high-risk clinical target volume (CTV). The majority of patients were married (76%), Caucasian (89%), and male (94%) with tumors located in the tonsils or base of the tongue (91%). Differences between cohorts were observed in smoking status, with the majority of the standard-of-care patients having >10 pack-years of tobacco use (55%) compared with the majority of de-intensified patients who were never smokers (65%), and in HPV status, with 21% of patients in the standard-of-care cohort having HPV/p16 negative tumors.

All patients received the intended treatment, with most patients receiving high-dose cisplatin (47%) or cetuximab (26%) in the standard-of-care cohort. The majority of patients completed chemotherapy (87% and 95% in the standard-of-care and de-intensified cohorts, respectively) and completed treatment without a break (95% in both cohorts). The incidence of needing a percutaneous endoscopic gastrostomy (PEG) tube in both cohorts was similar (63% and 55% in the standard-of-care and de-intensified cohorts, respectively) and none was permanent (mean duration: 16 weeks [standard-of-care cohort]; 14 weeks [intensified cohort]).

With regard to radiation treatment plans, a low number of patients received unilateral neck radiation (4 in the standard-of-care cohort vs 6 in the de-intensified cohort). The high-risk CTV was similar for both cohorts (140 cm^3 in the standard-of-care cohort vs 131 cm^3 in the de-intensified cohort). The instances of sparing the contralateral parotid (95% and 85% in the standard-of-care and de-intensified cohorts, respectively) and submandibular glands (37% and 50%, respectively) were similar between the 2 cohorts.

A posttreatment neck dissection was performed in the majority of patients in the de-intensified cohort (70%, compared with 21% in the standard-of-care cohort), and the mean time interval between treatment completion and neck dissection was 9.5 weeks in the de-intensified cohort (median, 8.8 weeks; range, 6.5-21 weeks) versus 12.1 weeks in the standard-of-care cohort (median, 12 weeks; range, 9-16 weeks).

Objective swallowing outcomes in de-intensified versus standard-of-care cohort

Objective MBS studies occurred at a mean of 7.8 weeks after radiation therapy in the standard-of-care cohort (median, 7 weeks; range, 3.5-15 weeks) compared with a mean of 7.2 weeks in the de-intensified cohort (median, 6 weeks; range, 4-26 weeks).

There were similar numbers of patients with laryngeal penetration, aspiration, and pharyngeal residue with all measured consistencies in the pretreatment MBS study in both cohorts (Table 2). The pretreatment overall severity was slightly worse in the de-intensified cohort prior to treatment ($P = .23$); however, 13 patients in the standard-of-care cohort did not have a baseline MBS study.

Overall, there was a suggestion that patients treated with standard of care had worse posttreatment swallowing

Table 1 Patient characteristics

	Standard of care	De-intensified	Total
Age (y)			
Mean (range)	58.4 (39-79)	58.5 (43-74)	58.4 (39-79)
Standard deviation	9.8	8.2	9.0
Sex (%)			
Male	35 (92.1)	38 (95)	73 (93.6)
Female	3 (7.9)	2 (5)	5 (6.4)
Race (%)			
Caucasian	33 (86.8)	36 (90)	69 (88.5)
African-American	4 (10.5)	4 (10)	8 (10.3)
Hispanic	1 (2.6)	0 (0)	1 (1.3)
Marital status (%)			
Married	28 (73.7)	31 (77.5)	59 (75.6)
Unmarried	10 (26.3)	9 (22.5)	19 (24.4)
Tobacco use (%)			
Never	13 (34.2)	26 (65)	39 (50)
≤10 pack-y	4 (10.5)	13 (32.5)	17 (21.8)
>10 pack-y	21 (55.3)	1 (2.5)	22 (28.2)
Primary tumor location (%)			
Base of tongue	12 (31.6)	20 (50)	32 (41)
Tonsil	23 (60.5)	16 (40)	39 (50)
Posterior pharyngeal wall	1 (2.6)	0 (0)	1 (1.3)
Soft palate	2 (5.3)	0 (0)	2 (2.6)
Unknown primary	0 (0)	4 (10)	4 (5.1)
T stage (%)			
T0	0 (0)	4 (10)	4 (5.1)
T1	4 (10.5)	11 (27.5)	15 (19.2)
T2	24 (63.2)	21 (52.5)	45 (57.7)
T3	10 (26.3)	4 (10)	14 (17.9)
N stage (%)			
N0	3 (7.9)	0 (0)	3 (3.8)
N1	4 (10.5)	2 (5)	6 (7.7)
N2a	3 (7.9)	2 (5)	5 (6.4)
N2b	21 (55.3)	29 (72.5)	50 (64.1)
N2c	7 (18.4)	7 (17.5)	14 (17.9)
HPV/p16 status (%)			
HPV + /p16+	16 (42.1)	24 (60)	40 (51.3)
HPV-/p16+	8 (21.1)	12 (30)	20 (25.6)
HPV-/p16-	8 (21.1)	0 (0)	8 (10.3)
HPV unknown/p16+	0 (0)	3 (7.5)	3 (3.8)
HPV + /p16 unknown	0 (0)	1 (2.5)	1 (1.3)
Unknown	6 (15.7)	0 (0)	6 (7.7)

HPV, human papillomavirus.

function. In the posttreatment MBS studies, the standard-of-care cohort demonstrated more laryngeal penetration with both thin and pureed consistencies (50% vs 45%, $P = .33$ and 18% vs 13%, $P = .23$, respectively). The standard-of-care cohort also had a higher rate of aspiration with thin consistencies (11% vs 8%, $P = .32$). There were no cases of aspiration with pureed or solid consistencies in either cohort.

Pharyngeal residue classified as mild was higher in the standard-of-care cohort with thin and pureed consistencies tested in the posttreatment MBS. Residue classified as moderate/severe was higher in the standard-of-care cohort for all consistencies tested in posttreatment MBS (Table 2).

There were no cases of severe overall severity scores in either cohort; however, the standard-of-care cohort demonstrated a higher moderate overall severity score in posttreatment MBS compared with the de-intensified cohort (42% vs 28%; $P = .2$).

On multivariate analysis, patients treated with de-intensified chemoradiation therapy had a suggestion of a lower risk of developing overall swallowing dysfunction (odds ratio [OR], 0.62; $P = .07$), laryngeal penetration (OR, 0.63; $P = .12$), and pharyngeal residue (OR, 0.61; $P = .08$).

Table 2 Modified barium swallow details

	Univariate analysis							
	Pretreatment				Posttreatment			
	Standard of care (n = 25)[a]	De-intensified (n = 40)	Total (n = 65)[a]	*P*-value	Standard of care (n = 38)	De-intensified (n = 40)	Total (n = 78)	*P*-value
Laryngeal penetration-thin (%)								
Yes	7 (28)	8 (20)	15 (23.1)	.23	19 (50)	18 (45)	37 (47.4)	.33
No	18 (72)	32 (80)	50 (76.9)		19 (50)	22 (55)	41 (52.6)	
Laryngeal penetration-puree (%)								
Yes	2 (8)	2 (5)	4 (6.2)	.31	7 (18.4)	5 (12.5)	12 (15.4)	.23
No	23 (92)	38 (95)	61 (93.8)		31 (81.6)	35 (87.5)	66 (84.6)	
Laryngeal penetration-solid (%)								
Yes	1 (4)	2 (5)	3 (4.6)	.43	3 (7.9)	3 (7.5)	6 (7.7)	.47
No	24 (96)	38 (95)	62 (95.4)		35 (92.1)	37 (92.5)	72 (92.3)	
Laryngeal aspiration-thin (%)								
Yes	0 (0)	1 (2.5)	1 (1.5)	.21	4 (10.5)	3 (7.5)	7 (9)	.32
No	25 (100)	39 (97.5)	64 (98.5)		34 (89.5)	37 (92.5)	71 (91)	
Laryngeal aspiration-puree (%)								
Yes	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
No	25 (100)	40 (100)	65 (100)		38 (100)	40 (100)	78 (100)	
Laryngeal aspiration-solid (%)								
Yes	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
No	25 (100)	40 (100)	65 (100)		38 (100)	40 (100)	78 (100)	
Pharyngeal residue-thin (%)								
None	9 (36)	18 (45)	27 (41.5)	.23	18 (47.4)	24 (60)	42 (53.8)	.27
Mild	15 (60)	18 (45)	33 (50.8)		15 (39.5)	12 (30)	27 (34.6)	
Moderate/severe	1 (4)	4 (10)	5 (7.7)		5 (13.2)	4 (10)	9 (11.5)	
Pharyngeal residue-puree (%)								
None	12 (48)	17 (42.5)	29 (44.6)	.33	16 (42.1)	24 (60)	40 (51.3)	.14
Mild	11 (44)	17 (42.5)	28 (43.1)		14 (36.8)	10 (25)	24 (30.8)	
Moderate/severe	2 (8)	6 (15)	8 (12.3)		8 (21.1)	6 (15)	14 (17.9)	
Pharyngeal residue-solid (%)								
None	8 (32)	13 (32.5)	21 (32.3)	.18	13 (34.2)	15 (37.5)	28 (35.9)	.33
Mild	16 (64)	21 (52.5)	37 (56.9)		14 (36.8)	17 (42.5)	31 (39.7)	
Moderate/severe	1 (4)	6 (15)	7 (10.8)		11 (28.9)	8 (20)	19 (24.4)	
Overall severity (%)								
None	5 (20)	11 (27.5)	16 (24.6)	.23	8 (21.1)	10 (25)	18 (23.1)	.44
Mild	15 (60)	21 (52.5)	36 (55.4)		14 (36.8)	19 (47.5)	33 (42.3)	
Moderate	5 (20)	7 (17.5)	12 (18.5)		16 (42.1)	11 (27.5)	27 (34.6)	
Severe	0 (0)	1 (2.5)	1 (1.5)		0 (0)	0 (0)	0 (0)	

These data were used for the multivariate analysis.

[a] Thirteen patients in the standard-of-care cohort did not have pretreatment modified barium swallow data.

Patient-reported outcomes in de-intensified cohort

PROs for the de-intensified cohort specifically pertaining to swallowing function from the EORTC QLQ-H&N35 and PRO CTCAE are shown in Figures 1 and 2. The mean pre-and 2-year post-EORTC QLQ-H&N35 scores (1-4 scale, higher being worse) were problems swallowing liquids (1.4 and 1.2, respectively), problems swallowing purees (1.2 and 1.1), problems swallowing solids (1.5 and 1.7), choked when swallowing (1.0 and 1.3), and composite swallowing score (0-100 scale, higher being worse: 9.0 and 10.8). The mean pre-and 2-year-post PRO CTCAE scores (1-5 scale, with higher being worse) regarding swallowing difficulty were 1.5 and 1.8, respectively.

The EAT-10 results for the de-intensified cohort are shown in Figure 2. The mean pre-and 2-year post-EAT-10 scores (0-40 scale, higher worse) in the de-intensified cohort were 3.3 and 5.9, respectively.

Discussion

The results of our study suggest that there is preserved baseline swallowing function in patients who receive de-intensified chemoradiation therapy, albeit with limited

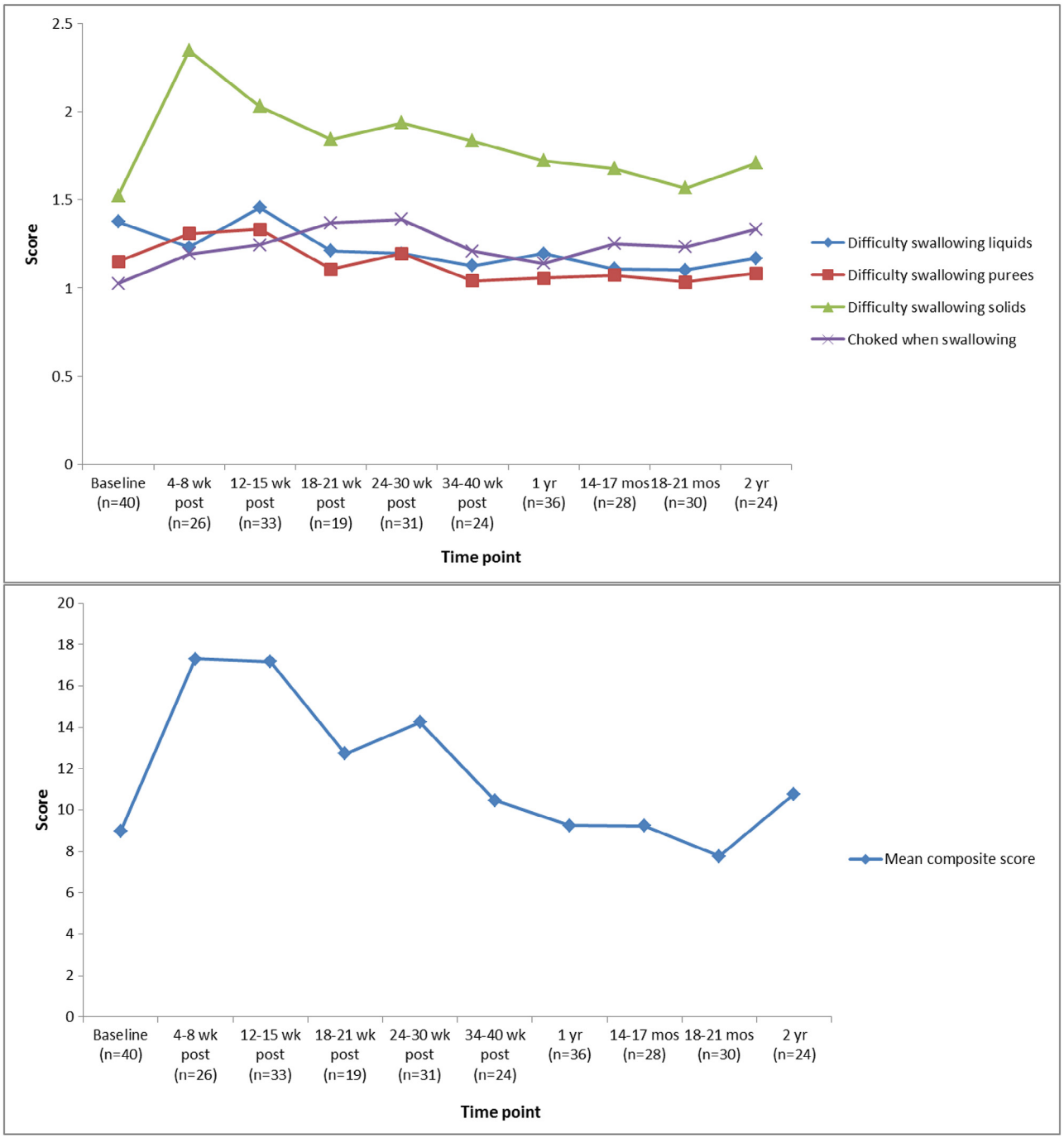

Figure 1 European Organisation for Research and Treatment of Cancer Quality of Life Module for Head and Neck Cancer questionnaire mean individual and mean composite scores for the de-intensified cohort with regard to swallowing dysfunction before treatment and up to 2 years after treatment. Individual score scale (1-4 scale; higher being worse). Composite score calculated from European Organisation for Research and Treatment of Cancer Quality of Life Module for Head and Neck Cancer questionnaire scoring manual (0-100 scale; higher scores being worse). * Scores for the standard-of-care cohort are not shown because patient-reported outcomes were not consistently collected for this cohort during the time period studied.

statistical significance. In addition to objective MBS analysis (Table 2), patients treated with de-intensification reported minimal to no change in their swallowing function (Figs 1 and 2). Although swallowing dysfunction and reduced QoL continue to be troublesome for patients regardless of the treatment modality, our results are in line with the dose response that has been seen previously in swallowing structures where lower dose resulted in less morbidity and loss of function.[9,11-13]

Several studies have looked at dose to specific swallowing structures, such as the pharyngeal constrictor muscles and larynx, with most finding a mean dose >50 Gy

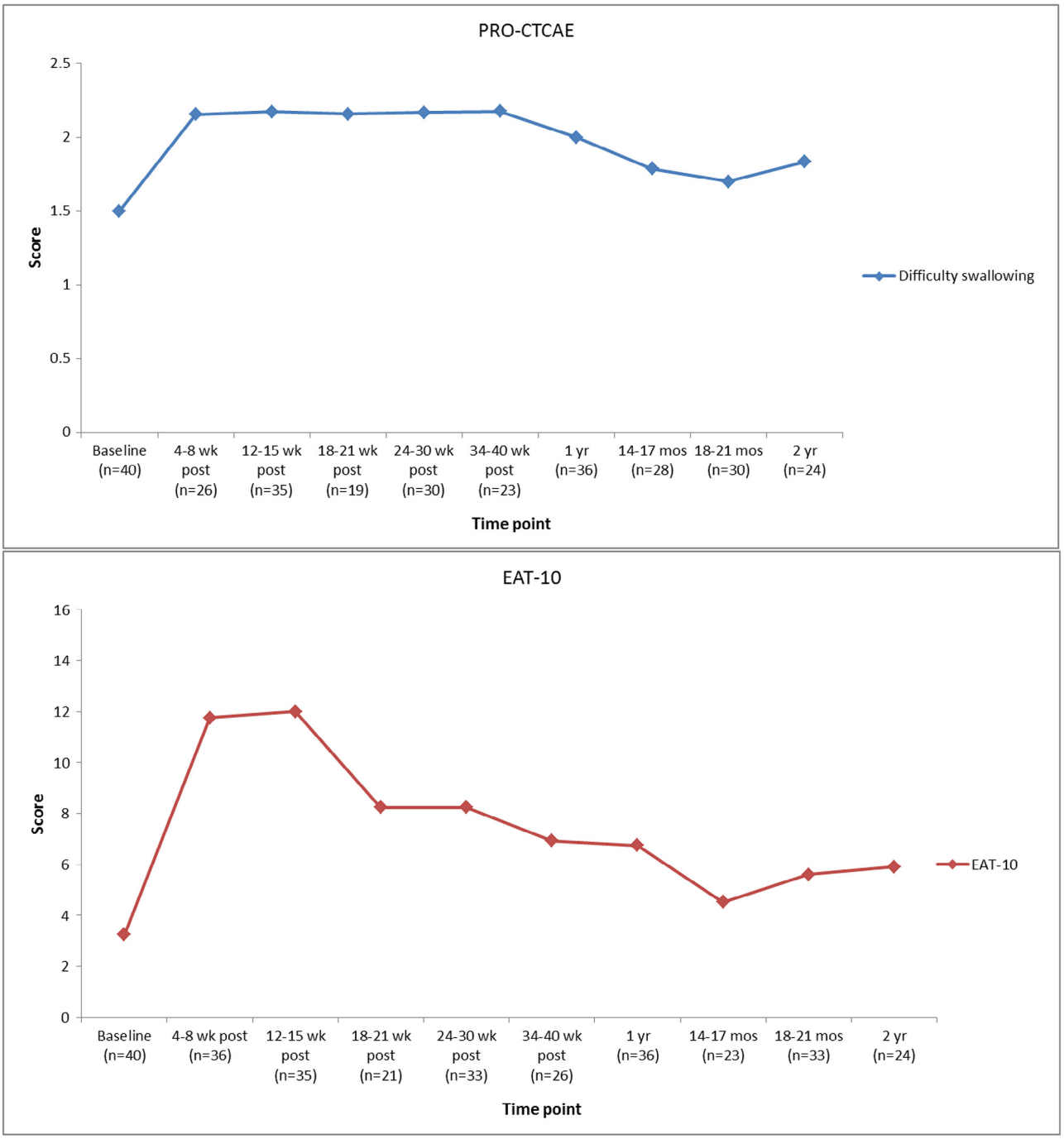

Figure 2 Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events and Eating Assessment Tool questionnaires mean scores for the de-intensifed cohort at baseline and up to 2 years after chemoradiation therapy. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (1-5; higher being worse); Eating Assessment Tool scale (0-40; higher being worse). *Scores for the standard-of-care cohort are not shown because patient-reported outcomes were not consistently collected for this cohort during the time period studied.

significantly correlating to occurrence of aspiration.[9,11,12] Although specific structures such as the pharyngeal constrictors were not specifically contoured or avoided in either of the cohorts presently studied, the dose to the high-risk CTV, which at least partially included the pharyngeal constrictors in most cases, was higher in the standard-of-care cohort (70 Gy) and thus would be hypothesized to more adversely affect swallowing.

In addition to lowering the intensity of therapy, another rationale for why the de-intensified cohort would be expected to have lower toxicity rates is that the vast majority of patients selected for this treatment in our study had a

minimal to no smoking history. Smoking has been associated with higher toxicity during chemoradiation therapy for head and neck tumors,[11,16] but patients with HPV-associated OPSCC generally have minimal tobacco history because the virus drives the carcinogenesis rather than mutations from tobacco. In addition, studies have shown that HPV/p16-positive patients tend to have a better global QoL after treatment,[17,18] with 1 study showing both an improvement in global QoL and swallowing QoL.[19] Thus, this may be one reason why patients with HPV-associated OPSCC have a more favorable prognosis and why their swallowing function was better preserved after treatment in our study.

When evaluating swallowing function posttreatment in patients with OPSCC, it is important to consider aspiration, specifically silent aspiration, because this can be correlated with aspiration pneumonia.[1,20] A reduction in laryngeal sensation posttreatment has been observed after chemoradiation therapy[21] and likely results in silent aspiration because a cough reflex is not elicited in patients. However, in this study, very few patients in either cohort were found to have objective aspiration, including silent aspiration; but patient-reported swallowing outcomes should also be considered because these outcomes can differ from objective assessments. We did not have data regardings PROs for the majority of the standard-of-care cohort; however, for the de-intensified cohort, outcomes seemed to mirror the objective assessments, with an initial minor worsening of the swallowing function shortly after completion of therapy, followed by an improvement over the next 2 years.

With regard to treatment details for this study, the vast majority of patients in each cohort completed the chemotherapy and overall treatment without a break. One interesting observation to point out is that >50% of patients in both cohorts required a PEG tube to maintain nutrition during treatment; however, the duration of use was much lower than in prior studies, with a mean duration of 14 weeks for the de-intensified cohort and 16 weeks for the standard-of-care cohort. Prior studies have shown PEG tube rates for definitive standard-of-care treatment with high-dose cisplatin (100 mg/m^2) to be 50% to 87%[22-24] with up to 30% to 40% of patients requiring durations of ≥12 months posttreatment.[3,25] A possible explanation for the decreased duration in the present study is better supportive care; a speech/swallowing therapist saw patients before, during, and after treatment, and often a nurse practitioner would see patients once a week in addition to the weekly on-treatment visits with the physician.

A posttreatment neck dissection was more common in the de-intensified cohort; however, this was a requirement in LCCC 1120, from which most of the de-intensified cohort was selected. This was our institution's initial de-intensification study, and due to questions on the efficacy of de-intensified therapy, a primary endpoint of pathological response was purposefully designed.[14] Regardless of whether patients in either cohort underwent a neck dissection, all completed the posttreatment MBS within 6 to 8 weeks of completing the chemoradiation therapy. Post-chemoradiation therapy neck dissections have been shown to predict for a greater risk of severe late toxicity, including possible swallowing dysfunction, thought to be due to increased fibrosis and which could limit the mobility of the laryngopharynx.[26] However, given the results of the current study, treating with de-intensified chemoradiation therapy may potentially lessen the dysfunction by reducing the amount of late fibrosis.

There are several limitations to this study, including the retrospective design, low number of patients in the matched standard-of-care cohort, disproportionate number of neck dissections in the de-intensified cohort, lack of PROs in the standard-of-care cohort, missing pretreatment MBS data in the standard-of-care cohort, imbalances in HPV status and tobacco use, heterogeneity of the chemotherapy regimen for the standard-of-care cohort, treatment era bias, and lack of routine contouring of the pharyngeal constrictors. A more generously matched standard-of-care cohort was not performed because the cohort would have included patients with more advanced disease who would not have been eligible for de-intensified treatment and thus would have altered our goal of comparing swallowing function in those eligible for de-intensification therapy but ultimately treated with standard-of-care therapy.

The absence of pretreatment MBS data in 34% of standard-of-care patients likely contributed to the suggestive nature of the MBS analysis rather than significant differences. It is likely that a significant difference will exist with larger samples, with improvements in those undergoing de-intensified therapy.

A higher proportion of neck dissections occurred in the de-intensified cohort; yet, our results suggest improved swallowing function in this cohort despite late fibrosis typically being worse in those undergoing both chemoradiation and neck dissection compared with either alone.

The long time period studied may contribute to treatment era bias because the standard radiation delivery technique changed from static field IMRT to volumetric modulated arc therapy (a type of IMRT in which the machine is continuously moving during treatment, in comparison to static field in which treatment occurs when the machine is stationary). However, treatment plans for static field IMRT and volumetric modulated arc therapy are generally similar.

Finally, the standard-of-care cohort represented patients with a stronger tobacco history and fewer HPV-positive cancers. Smoking and HPV-negative tumors have been shown to have higher toxicity[11,16] and worse global QoL outcomes,[17-19] respectively, and this imbalance between the cohorts may highlight these differences.

Additional data with larger patient numbers are needed to further validate our findings, and a longer follow-up is required to ensure QoL measures continue to improve with time.

Conclusion

Patients undergoing de-intensified chemoradiation therapy appear to better preserve baseline swallowing function per objective MBS clinical assessment compared with patients receiving standard-of-care chemoradiation therapy. Furthermore, patients who receive de-intensified chemoradiation therapy report minimal to no change in swallowing function. Further exploration of objective and subjective swallowing quality and function should be carried out because it is an important QoL aspect for patients posttherapy.

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