

# Patient-reported Measurements of Oral Mucositis in Head and Neck Cancer Patients Treated With Radiotherapy With or Without Chemotherapy

*Demonstration of Increased Frequency, Severity, Resistance to Palliation, and Impact on Quality of Life*

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**BACKGROUND.** The risk, severity, and patient-reported outcomes of radiation-induced mucositis among head and neck cancer patients were prospectively estimated.

**METHODS.** A validated, patient-reported questionnaire (OMDQ), the FACT quality of life (QOL), and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scales were used to measure mucositis (reported as mouth and throat soreness), daily functioning, and use of analgesics. Patients were studied before radiotherapy (RT), daily during RT, and for 4 weeks after RT.

**RESULTS.** Contrary to previous reports, the risk of mucositis was virtually identical in the 126 patients with oral cavity or oropharynx tumors (99% overall; 85% grade 3-4) compared with 65 patients with tumors of the larynx or hypopharynx (98% overall; 77% grade 3-4). The mean QOL score decreased significantly during RT, from 85.1 at baseline to 69.0 at Week 6, corresponding with the peak of mucositis severity. The mean functional status score decreased by 33% from 18.3 at baseline to 12.3 at Week 6. The impact of mucositis on QOL was proportional to its severity, although even a score of 1 or 2 (mild or moderate) was associated with a significant reduction in QOL (from 93.6 at baseline to 74.7 at Week 6). Despite increases in analgesic use from 34% at baseline to 80% at Week 6, mean mucositis scores exceeded 2.5 at Week 6.

**CONCLUSIONS.** Mucositis occurs among virtually all patients who are undergoing radiation treatment of head and neck cancers. The detrimental effects on QOL and functional status are significant, and opioid analgesia provides inadequate relief. Preventive rather than symptom palliation measures are needed. *Cancer* 2008;113:2704-13. © 2008 American Cancer Society.

**KEYWORDS:** mucositis, radiation therapy, head and neck cancer, patient-reported outcomes, quality of life.

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**M**ucositis is a painful and debilitating side effect of radiation therapy (RT) for head and neck cancers<sup>1</sup> and is exacerbated by concomitant chemotherapy.<sup>2</sup> Mucositis lesions, characterized by ulceration and pseudomembranous formations, occur in the oral cavity, oropharynx, and hypopharynx. Oral mucositis is a consistent finding in patients treated for oral cavity and/or oropharynx tumors, but the reported incidence and severity are less among individuals treated for larynx or hypopharynx cancers.<sup>3,4</sup> However, nonoral mucosal lesions are not easily observed; thus, it is likely that the frequency of mucositis of the hypopharynx is underreported.

In addition to the challenges of observing mucositis lesions, there is no agreement on a method for measuring mucositis' severity, even though numerous scales are in use.<sup>1</sup> Even when the same scale is used, inconsistent scoring by clinicians leads to conflicting estimates of risk and severity.<sup>5</sup> For example, 2 recent reports of similar induction regimens for head and neck cancer had dramatically different estimates of mucositis incidence.<sup>6,7</sup> Reliance on retrospective analysis of mucositis risk and severity also likely leads to major underreporting and a failure to appreciate the severity of the problem.

Finally, there are few estimates of the impact of mucositis on patients' experiences during therapy. Recent reports suggest concordance between clinical assessments of mucositis severity and patient-reported outcomes,<sup>8,9</sup> but, historically, there has been a marked disconnect between the two. This is particularly likely when mucositis involves sites not easily observed by clinicians. Reports of impact on quality of life (QOL) also have been variable.<sup>1,10,11</sup>

Mucositis is a significant clinical challenge and causes a major burden for head and neck cancer patients and their caregivers; its impact on the cost of care may be substantial.<sup>3,12</sup> Accurate characterization of the significance of these burdens is complicated by underreporting of mucositis, inconsistent measurement of severity, retrospective assessments of risk and severity, and failure to examine outcomes from the patient's perspective. To address these issues, we conducted a prospective, multinational study of the burden of illness and patient-reported outcomes of radiation-induced mucositis among patients with head and neck cancers.

## MATERIALS AND METHODS

Risk, clinical outcomes, and patient-reported outcomes of mucositis were prospectively examined among patients with squamous cell carcinomas of the oral cavity, oropharynx, larynx, or hypopharynx (stages I-III) who received a cumulative dose of at least 40 Gy of radiation therapy (RT) in single daily fractions with or without subsequent boost and/or chemotherapy, at 30 centers in the United States, Europe, Australia, and Canada, to ensure that results could be generalized to other populations (grading determined according to the American Joint Committee on Cancer grading system). After patients signed informed consent forms, we evaluated patients at baseline, then followed them prospectively throughout RT for weight loss, placement of gastric tubes (G-tubes), and treatment breaks or dose reductions. By using patient-reported mouth and throat soreness (MTS), we assessed daily mucositis severity and simultaneously

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assessed analgesic use at baseline and daily during RT by using the Oral Mucositis Daily Questionnaire (OMDQ).<sup>8,13</sup> At baseline and each week, patients completed the Functional Assessment of Cancer Therapy (FACT-G), the Esophagus Cancer subscale (ECS) QOL, and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale questionnaires in their preferred language.<sup>14-16</sup> Although esophagitis was not evaluated in this investigation, the ECS questions were relevant to our study population.

### Definitions

Mucositis was measured on the basis of patient-reported MTS, defined as any positive response to Question 2 of the previously validated OMDQ (Fig. 1). MTS was measured on a scale of 0 (no soreness) to 4 (extreme soreness). By using the same tool, Stiff et al found that bone marrow transplant patients' MTS scores were comparable to clinicians' assessments of oral mucositis, a finding which supports our use of this endpoint.<sup>8</sup>

Clinical outcomes (nonprophylactic insertion of G-tubes, weight loss) were collected prospectively. Analgesic use was defined as a positive response to OMDQ Question 7, "During the past 24 hours did you take any medication for pain?" and further characterized by week of RT as none, occasional (use for 1-3 days), or regular (use for 4-7 days). Weight change during RT was calculated as the difference between the baseline weight and the weight recorded at the first follow-up visit 3 weeks after RT was completed.

### Statistical Considerations

Mucositis risk was calculated as the percentage of patients who reported any MTS at any time during RT and further characterized by maximal grade during RT. The mean MTS score during each week of RT was computed for each patient and summarized by week (Fig. 2) for all patients. Analgesic use was categorized as defined previously and described by week of RT (Fig. 3).

The mean FACT-G score and the esophageal cancer, fatigue, physical well-being, and functional well-being subscale scores were also summarized by mean scores and described by week of RT (Fig. 4). Normative reference scores and minimally important differences were based on those previously reported in the literature (Table 1). The percentage change from baseline in FACT-G, and esophagus cancer, fatigue, physical and functional wellbeing subscales was calculated for each week of RT, compared with baseline, and summarized as a mean percentage change by week (Fig. 5).

For analyses of clinical outcomes of mucositis, patients were categorized into 2 groups, by maximum MTS score during RT (0, 1, or 2 vs 3, 4). The percentage of patients with each outcome was computed for each of the 2 MTS groups (Table 2). Patients were further categorized on the basis of baseline MTS score (0 vs >0 MTS score), and outcomes were reported as described above in Table 2. No hypotheses were tested in this descriptive study. However, large differences between the 2 MTS groups were tested for statistical significance by 2-tailed chi-square tests. Differences in mean weight change were tested by 2-tailed Student *t* test.

### RESULTS

Two hundred forty-one patients completed RT, 156 with oral cavity and/or oropharynx cancers and 85 with larynx and/or hypopharynx cancers. Among these, 36 (15%) patients withdrew from the study before 40 Gy had been administered, and they were excluded from the study. Daily diary completion compliance was excellent. Only 14 (6%) patients were ineligible because they failed to complete at least 3 diary entries each week. Thus, 191 (126 oral cavity and/or oropharynx and 65 larynx and/or hypopharynx) patients could be evaluated for analysis. Inevaluable patients were clinically and demographically indistinguishable from evaluable patients except that inevaluable patients were less likely to receive concomitant chemotherapy (0% vs 60%;  $P < .001$ ) and concomitant boost radiation (5% vs 34%;  $P < .001$ ). All patients ultimately received the same median doses of RT (oral cavity and/or oropharynx = 66 and 69 Gy; larynx and/or hypopharynx 66 and 70 Gy). Because most patients who could not be evaluated withdrew before 40 Gy of RT were administered, their maximal MTS score on study was lower than that reported by those patients who could be evaluated (oral cavity and/or oropharynx = 2.6 and 3.3; larynx and/or hypopharynx = 2.4 and 3.2, respectively). However, it is notable that during Weeks 3-4, when most withdrawals took place, patients who could not be evaluated had mean MTS scores virtually identical to the mean MTS scores of patients who could be evaluated (oral cavity and/or oropharynx = 2.6 and 2.3; larynx and/or hypopharynx = 2.4 and 2.3, respectively).

Distributions of mean age, sex, and race of the oral cavity and/or oropharynx and larynx and/or hypopharynx groups were similar (Table 2). There were differences in concomitant chemotherapy (66% vs 48%;  $P = .02$ ) and intensity-modulated radiation therapy rates (71% vs 29%;  $P < .001$ ) between the oral cavity and/or oropharynx and larynx and/or

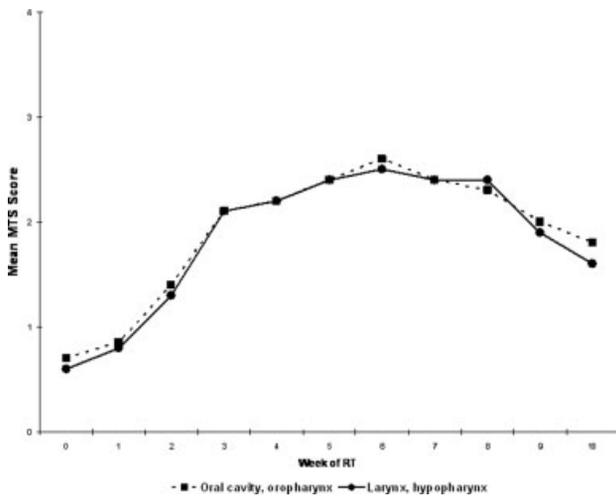
<b>ROMC-TR100</b>	Site No.	Investigator Number	Patient Number	Patient Initials	
<b>DAILY QUESTIONNAIRE</b>				Month	Day
1. How would you rate your <b>OVERALL HEALTH</b> during the PAST 24 HOURS? <i>(Please circle the most appropriate number.)</i> 0    1    2    3    4    5    6    7    8    9    10 Worst Possible ←-----→ Perfect Health					
2. During the PAST 24 HOURS, how much <b>MOUTH AND THROAT SORENESS</b> did you have? <i>(Circle one number)</i> 0                      1                      2                      3                      4 No soreness          A little soreness      Moderate soreness      Quite a lot of soreness      Extreme soreness					
3. During the PAST 24 HOURS, how much did <b>MOUTH AND THROAT SORENESS</b> limit you in each of the following activities?					
	Not limited	Limited a little	Limited some	Limited a lot	Unable to do
a. Swallowing	0	1	2	3	4
b. Drinking	0	1	2	3	4
c. Eating	0	1	2	3	4
d. Talking	0	1	2	3	4
e. Sleeping	0	1	2	3	4
4. On a scale from 0 to 10, how would you rate your <b>OVERALL MOUTH AND THROAT SORENESS</b> during the PAST 24 HOURS? <i>(Please circle the most appropriate number.)</i> 0    1    2    3    4    5    6    7    8    9    10 None ←-----→ Worst Possible					
5. During the PAST 24 HOURS, how much <b>DIARRHEA</b> did you have? <i>(Circle one number)</i> 0                      1                      2                      3                      4 No diarrhea          A little diarrhea      Moderate diarrhea      Quite a lot of diarrhea      Severe diarrhea					
6. On a scale from 0 to 10, how would you rate your <b>OVERALL DIARRHEA</b> during the PAST 24 HOURS? <i>(Please circle the most appropriate number.)</i> 0    1    2    3    4    5    6    7    8    9    10 None ←-----→ Worst Possible					
7. During the PAST 24 HOURS did you take medication for any of the following: <i>(Please check all that apply)</i> <input type="checkbox"/> Pain <input type="checkbox"/> Diarrhea <input type="checkbox"/> Nausea/vomiting <input type="checkbox"/> Did not take medication for pain, diarrhea, or nausea/vomiting					
8. If you checked " <u>Pain</u> " in question 7, please list the medications you took for <i>pain</i> during the PAST 24 HOURS _____ <input type="checkbox"/> Did not take medication for pain.					



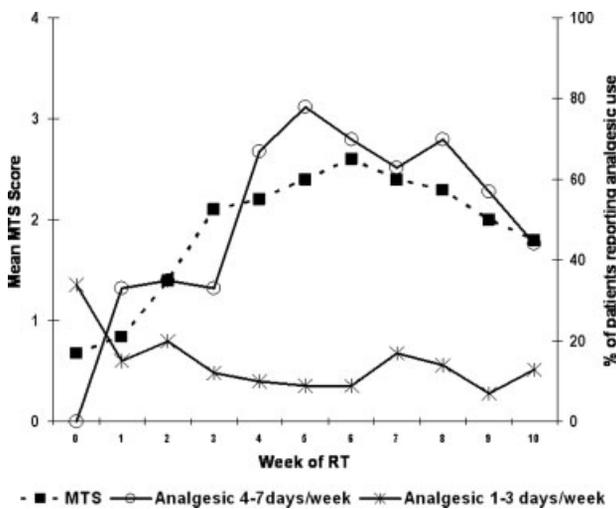
FIGURE 1. Oral Mucositis Daily Questionnaire.

hypopharynx groups, respectively, because of different standards of care. Patients in the larynx and/or hypopharynx group had significantly lower stages of disease than their counterparts with oral cavity and/or oropharynx cancers ( $P < .001$ ; Table 2). Small differences in baseline Eastern Cooperative Oncology Group (ECOG) status reflected the expected clinical presentations of the 2 populations. However, the mean FACT-G, ECS, and FACIT-fatigue scores at baseline were virtually identical and were similar to those previously reported for head and neck cancer

patients (FACT-G head and neck normative reference value = 73.1; standard deviation [SD] = 17.8).<sup>17,18</sup> Fifty-six percent of oral cavity and/or oropharynx and 44% of larynx and/or hypopharynx patients reported MTS >0 at baseline, presumably resulting from either previous surgery or tumor. Mean RT doses (oral cavity and/or oropharynx = 66 Gy; range, 48 Gy to 74 Gy vs larynx and/or hypopharynx = 68 Gy; range, 60 Gy to 72 Gy) and duration (47 days, both groups) were the same for both groups. Median RT doses also were the same (oral cavity and/or



**FIGURE 2.** Mean mouth and throat soreness by week of RT among patients with oral cavity and larynx cancers.

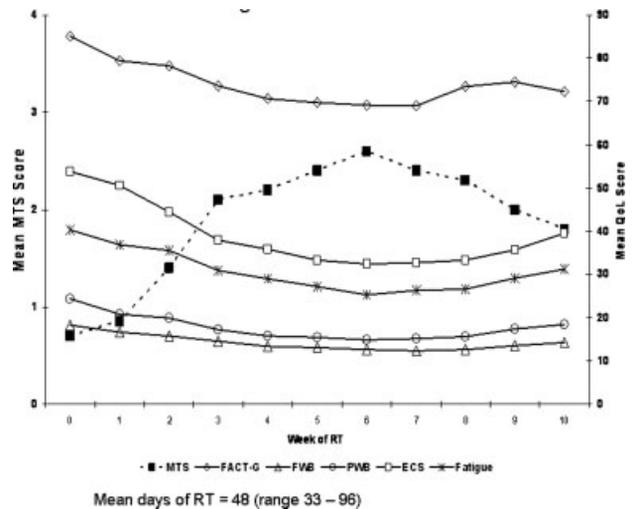


**FIGURE 3.** Relations between mean mouth and throat soreness score (displayed on left vertical axis) and percentage of patients reporting analgesic use during RT (displayed on right vertical axis). Oral cavity and larynx cohorts are combined.

oropharynx = 69 Gy vs larynx and/or hypopharynx = 70 Gy).

**Risk of Mucositis**

The risk of mucositis was the same for patients with oral cavity and/or oropharynx and larynx and/or hypopharynx (99% and 98%, respectively). The maximal MTS score during RT also was the same for the 2 groups (MTS = 0, 2% and 2%; MTS = 1, 3% and 3%; MTS = 2, 10% and 18%; MTS = 3, 48% and 42%; and MTS = 4, 37% and 35%). Furthermore, the pat-



**FIGURE 4.** Relation between mean mouth and throat soreness score (displayed on left vertical axis) and mean quality of life scores (displayed on right vertical axis) during RT. Oral cavity and larynx cohorts are combined.

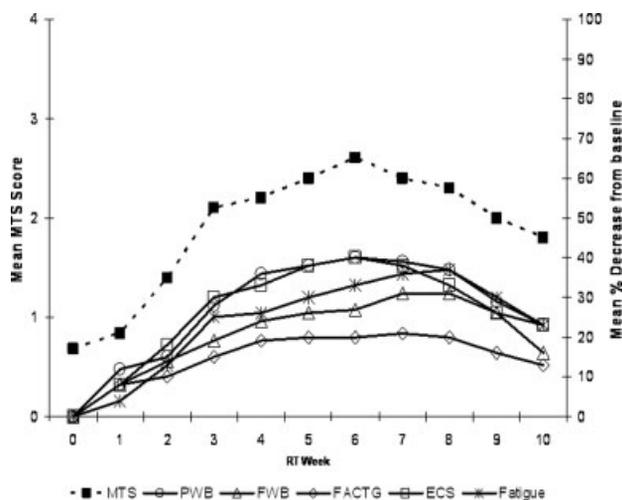
**TABLE 1**  
Reference Values for FACT-G and Fatigue Subscale<sup>17,18,25-29</sup>

Quality of Life Scale	Normative Reference Value		
	All Cancers, Mean Score (SD)	Head & Neck Cancers, Mean Score (SD)	Minimally Important Difference Points on Scale
FACT-G	80.4 (15.9)	73.1 (17.8)	5-7
Physical well being	21.2 (6.2)	19.2 (6.3)	2-3
Emotional well being	18.1 (4.5)	17.7 (5.1)	3
Social well being	22.3 (4.8)	20.2 (5.3)	2
Functional well being	18.8 (6.4)	15.9 (6.8)	2-3
Fatigue subscale	—	—	3-4

FACT-G indicates Functional Assessment of Cancer Therapy-General.

tern of MTS severity over time was identical, peaking at Week 6 and remaining elevated at Week 10 of the study, 3 weeks after completion of RT (Fig. 2). More than 80% of patients reported MTS of 3 or 4 at some time during RT. Of the 98 patients who reported MTS >0 at baseline, none reported decreased MTS during RT, and all but 9 reported an increase in MTS during RT. There were no differences in risk of MTS among study sites ( $P = .79$ ).

Use of chemotherapy did not significantly increase the risk of severe mucositis. Among patients with oral cavity and/or oropharynx tumors, 88% of those who received chemotherapy developed grade 3-4 MTS compared with 85% of those who did not receive chemotherapy ( $P = .93$ ). Only 1 oral cavity



**FIGURE 5.** Relation between mean mouth and throat soreness score (displayed on left vertical axis) and mean percentage decrease in quality of life score (displayed on right vertical axis) during RT. Oral cavity and larynx cohorts are combined.

and/or oropharynx patient escaped mucositis. Similarly, among patients with larynx and/or hypopharynx tumors, 90% of those who received chemotherapy developed grade 3-4 MTS compared with 76% of those who did not receive chemotherapy ( $P = .65$ ). Again, only 1 larynx and/or hypopharynx patient escaped mucositis. The risk of grade 3-4 MTS was not significantly altered by either intensity-modulated radiation therapy (88% with intensity-modulated radiation therapy vs 74% without intensity-modulated radiation therapy;  $P = .41$ ) or concomitant boost (85% with boost vs 79% without boost;  $P = .75$ ).

These results show that the 2 cancer groups were demographically and clinically similar at baseline, received similar RT doses over the same time (although to different locations), and shared the same risk, severity, and duration of mucositis during RT. This observation supports the argument that RT, rather than cancer site, is the major driver of mucositis. On the basis of these similarities, the 2 groups were combined for analysis of outcomes of mucositis.

**Clinical Outcomes**

Only 12% of the MTS 0-2 group compared with 40% of the MTS 3-4 group required nonprophylactic insertion of G-tubes during RT ( $P = .005$ ). Among these, 67% and 78%, respectively, were inserted as a direct result of mucositis ( $P = .56$ ; Table 3). Weight loss among patients with severe MTS was double that observed among patients with MTS 0-2 (5 kg vs 2 kg;  $P = .02$ ).

**TABLE 2**  
Characteristics of Patients at Baseline

Characteristic	Oral or Oropharynx, N=26		Larynx or Hypopharynx, N=65	
	Value	95% CI	Value	95% CI
% Female	23	16-30	23	13-34
% White or Caucasian	87	82-93	89	82-97
% Black	9	4-14	8	1-14
% Hispanic	2	0-5	2	0-5
% Other	2	0-4	2	0-5
Mean age, y	55	53-58	59	56-62
% Tobacco use	74	66-81	91	84-98
% ETOH use	90	84-95	86	78-95
% Candidiasis	3	0-5	0.0	0-5
% Renal failure	1	0-3	2	0-5
% Diabetes	12	6-18	11	3-19
% Inflammatory bowel disease	1	0-3	2	0-5
% Arthritis	3	0-5	2	0-5
% Prior cancer	10	5-16	15	7-24
% Stage I (current cancer)	2	0-4	24	14-35
% Stage 2	10	4-15	17	8-26
% Stage 3	70	63-79	48	36-60
% Unstaged	18	12-25	11	3-18
% RT or chemotherapy for prior cancer	4	1-7	5	0-10
% Pre-RT chemotherapy (conditioning)	21	13-29	12	4-20
% Concomitant chemotherapy	66	58-74	48	36-60
% Intensity-modulated RT	71	63-79	29	18-40
% Concomitant boost	44	35-54	32	20-44
% G-tube	52	44-61	40	28-52
% ECOG performance status=0	8	3-13	39	27-50
% ECOG performance status=1	52	43-60	43	31-55
% ECOG performance status>1	40	32-49	19	9-28
Mean overall health	7.5	7-8	7.6	7-8
% Overall health <7	29	21-37	20	10-30
% WHO mucositis score=0	89	83-94	97	93-100
% WHO mucositis score=1	9	4-14	3	0-7
% WHO mucositis score>1	2	0-5	0	0-5
Mean mouth and throat soreness	0.84	0.7-1.0	0.79	0.5-1.1
% Mouth and throat soreness>0	56	47-65	44	32-57
Mean FACT-G	86.3	84-89	87.6	84-91
Mean ECS subscale	55.3	53-57	54.9	53-57
Mean FACIT-fatigue subscale	41.4	40-43	42.2	39-45
% Analgesics	44	35-52	29	17-39

ETOH indicates ethyl alcohol; RT, radiation therapy; G-tube, gastrostomy feeding tube; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; FACT-G, Functional Assessment of Cancer Therapy; ECS, Esophagus Cancer Subscale; FACIT, Functional Assessment of Chronic Illness Therapy.

At the start of RT, 25% of patients were using analgesics for up to 3 days per week, but no patients were using them for 4 days or more (Fig. 3). After mean MTS scores rose in Week 1, use of analgesics for 4 or more days began and continued to increase until MTS peaked at Week 6, at which time greater than 60% patients were regularly using analgesics. The number using analgesics 1-3 days per week fell in concert, and at Week 6, approxi-

**TABLE 3**  
Relations Between Baseline and Maximum Mouth and Throat Soreness and Clinical Outcomes

Outcome	Maximum MTS			Baseline MTS		
	MTS=0-2 N=34	MTS=3-4 N=157	P	MTS=0 N=87*	MTS>0 N=95*	P
	Value (95% CI)	Value (95% CI)		Value (95% CI)	Value (95% CI)	
% Any nonprophylactic G-tube†	12 (0-25)	40 (30-49)	.005	35 (23-47)	33 (21-45)	.95
% Nonprophylactic G-tube related to mucositis‡	67 (9-99)	78 (61-89)	.56	27 (16-38)	25 (14-35)	.86
Mean weight loss (lbs)	2 (.5-4)	5 (3-6)	.02	4 (2-6)	4 (3-5)	.70
Mean total RT dose	65 (63-66)	67 (66-68)	.01	66 (65-67)	67 (66-68)	.49
Analgesics during RT						
% No use during any week of RT	24 (9-38)	3 (<1-6)	<.001	11 (5-18)	2 (0-5)	.01
% Occasional use during any week of RT	12 (1-23)	10 (5-14)	.69	14 (7-21)	5 (1-10)	.05
% Regular use during any week of RT	65 (49-81)	87 (82-92)	.001	75 (66-84)	93 (87-98)	.001
% Opioid analgesic	44 (27-62)	70 (62-77)	.004	56 (45-67)	75 (65-83)	.009
% Nonsteroidal anti-inflammatory agent	56 (38-73)	38 (30-46)	.058	39 (29-50)	43 (33-54)	.57
% Antifungal agent	12 (3-27)	27 (20-34)	.06	23 (15-33)	25 (17-35)	.72

MTS indicates patient-reported mouth and throat soreness. G-tube, gastrostomy feeding tube; RT, radiation therapy.

Occasional use means a maximum of 1-3 days use during week with highest use during RT. Regular use means 4-7 days using during week with highest use during RT.

\*Baseline MTS not recorded for 9 patients.

†From among patients who did not have G-tube at baseline.

‡From among patients who had G-tube inserted nonprophylactically.

mately 90% of patients reported using analgesia. The increased use of analgesics does not seem to have reduced their MTS scores effectively. At Week 10, >50% of patients still required analgesics. Thirty-four percent of the MTS 0-2 group and only 4% of the MTS 3-4 group reported using no analgesics during the entire study.

Opioid use was significantly more frequent among patients with severe MTS (70%) compared with patients with MTS 0-2 (44%;  $P = .004$ ; Table 3). Furthermore, 87% of patients with severe MTS used analgesics regularly during RT compared with only 65% of patients with MTS 0-2. Patients who reported baseline MTS >0 were more likely to report regular use of analgesics and use of opioids than those with MTS = 0 at baseline. Antifungal agents also were used more commonly by patients with severe MTS (27% vs 12%;  $P = .06$ ). There were no differences in use of other antimicrobials among the MTS groups. (Data not shown.)

### Patient-reported Outcomes

RT and the resulting MTS had a significant and prolonged negative effect on patient-reported QOL. QOL scores began to fall early in the course of RT, before MTS scores rose, and FACT-G (general health), functional well-being, physical well-being, and esophageal subscale scores all fell significantly within 1 week of starting treatment (Figs. 4 and 5). Fatigue scores paralleled the QOL scores. All QOL scores

continued to decline until Week 6, coinciding with the peak of MTS, at which time the mean FACT-G score had fallen from 85.1 at baseline to 69. The mean functional well-being subscale score decreased by 33% from 18.3 at baseline to 12.3 at Week 6. Even among patients whose peak MTS was only mild or moderate, mean FACT-G scores decreased from 93.6 at baseline to 74.7 at Week 6.

After Week 6, all QOL and fatigue scores rose (improved) as MTS severity scores fell. However, at the end of the study at Week 10, despite this being 3 weeks after completion of RT, all QOL scores remained significantly lower (poorer) than baseline, and MTS remained elevated. The ECS score fell significantly in the oral cavity and/or oropharynx cohort. The social and emotional well-being scales did not fall significantly during treatment. Overall, increasing MTS was associated with significant fatigue and reduction in physical and functional well-being.

### DISCUSSION

There is general consensus that mucositis is a common, significant, and costly toxicity of RT for oral cavity and/or oropharynx cancers, but mucositis is less prevalent among patients who are receiving similar treatment for larynx and/or hypopharynx tumors.<sup>3</sup> Disparities exist between perceived risk and severity of mucositis, the burdens these cause

patients, and the burden upon healthcare system. Gaps also exist between clinicians' assessments of severity and patients' experience of severity.<sup>19</sup> We, therefore, undertook a prospective, multinational study of risks and outcomes of mucositis, measured by patient-reported MTS, among patients with head and neck cancers who were receiving RT.

In contrast to most previous reports, we found no differences in risk, severity, or course of mucositis among patients with oral cavity and/or oropharynx cancers compared with patients with larynx and/or hypopharynx cancers. Almost every patient developed mucositis during RT; 80% reported severe MTS. The peak severity, time course, and duration were also identical. It is likely that the limitations of conventional clinical assessment account for the discrepancy between our observations and previous reports. Our measure of mucositis included both mouth and throat soreness. Although the tissues of the mouth are easily observed in a standard clinical examination, the mucosa of the lower oropharynx, the hypopharynx, and the larynx are not. Consequently, in cases in which most damage is not seen and no patient-reported surrogate is captured, incidence may be underestimated. On the basis of our data, risk and severity of RT-induced mucositis are equivalent, no matter where it occurs in the upper digestive tract. A recent report in which MTS data were collected in head and neck cancer patients supports this finding, as no difference in MTS between patients with larynx and/or hypopharynx cancers and other head and neck cancers was seen.<sup>9</sup>

Neither use of intensity-modulated radiation therapy nor concomitant chemotherapy altered mucositis risk or severity. Data suggesting mucositis-sparing among intensity-modulated radiation therapy treated head and neck cancer patients have been inconsistent. Although some investigations propose a benefit,<sup>20,21</sup> results of prospective studies have failed to confirm reduced mucositis risk with intensity-modulated radiation therapy.<sup>22</sup> We found no difference in MTS between patients treated with conventional RT compared with intensity-modulated radiation therapy. Similarly, our results contrast with prior studies<sup>2</sup> that suggest concomitant chemotherapy confers an increased risk of mucositis as measured by clinician assessment and agree with those in which patient-reported endpoints were used.<sup>9</sup> These findings suggest imperfect congruence between the experience of mucositis and its observable manifestations. These findings also underscore the importance of measuring both clinician-reported and patient-reported outcomes.

Our findings are in agreement with earlier reports of strong associations between mucositis and adverse clinical and patient-reported outcomes.<sup>3,9,23,24</sup> The reduction in QOL associated with MTS was significant, and there was a correlation between severity of MTS and drop in QOL. A reduction in score of >4 points is considered significant with the FACT and FACIT scales, and this occurred with an MTS score of only 1 or 2,<sup>25-29</sup> with further drops for each increase in MTS. Again, the drop in QOL persisted until Week 10, in parallel with raised MTS.

As expected, therapeutic G-tube placement was significantly associated with severe mucositis. Whereas 40% of patients with grade 3-4 MTS received nonprophylactic insertion of G-tubes, similar treatment was reported in only 12% of patients with grade 1-2 MTS. Whereas variation in local practice patterns influences G-tube placement, mucositis was cited as the most common cause of G-tube placement in both MTS groups. This rate is consistent with rates reported in previous studies. Vera-Llonch et al<sup>2</sup> reported feeding-tube placement or use of total parenteral nutrition in 34% of head and neck cancer patients with moderate or severe mucositis. In a study reporting resource use at a single center, Elting et al<sup>12</sup> noted that of patients who developed grade 3-4 mucositis, 18% of those who received radiation only and 38% of individuals who received chemoradiation required G-tube placement during RT. Trotti et al<sup>3</sup> noted that 33% of patients who were receiving chemoradiation for treatment of cancers of the head and neck had feeding-tube placement, compared with only 18% who received conventional radiation only.

The use of antifungal agents was twice as common (26.8%) in patients with severe mucositis compared with those with mild mucositis. Given the lack of effective mucositis interventions, clinicians may have prescribed antifungal agents hoping to ameliorate symptoms, despite reports that the incidence of oral candidiasis does not vary with mucositis severity.<sup>12</sup>

Consistent with previous reports, virtually all patients (96%) with grade 3-4 MTS used analgesics during RT. By the time MTS scores peaked at Weeks 5-6, greater than 60% of patients were regularly using analgesics, and almost 90% required analgesics at least 1 day per week. More than half of study subjects were using pain medication at Week 10. The majority of patients with grade 1-2 MTS were treated with nonsteroidal anti-inflammatory agents; however, greater than 70% of patients with MTS scores  $\geq 3$  required opioids. Considering the severity of patient-reported MTS, the frequency of analgesic use was not surprising. However, the persistence of high MTS

scores despite the use of narcotics is a startling finding. Clearly, effective pain control was not achieved.

The poor pain control achieved through appropriate prescription of analgesics underscores the importance of developing management strategies that do more than control the symptoms of mucositis. Prevention of mucositis and reduction of its severity are critical to achieving a true improvement in patient-reported symptoms and outcomes.

### Conclusion and Summary

Our prospective, patient-reported data show that virtually all patients who are undergoing RT with or without chemotherapy for head and neck cancer develop MTS of a sufficient severity to reduce QOL and require analgesics. Even an MTS score of 1 or 2 (mild or moderate) is associated with reduced QOL, and the reduction increases with increasing MTS. Increasing MTS is also associated with increasing weight loss and a need for G-tube feeding. There is no difference in risk, severity, or outcomes between patients with oral cavity and/or oropharynx and larynx and/or hypopharynx tumors, despite previous reports to the contrary. In a large proportion of patients, use of opioid analgesics does not adequately palliate symptoms. We conclude that symptomatic management of mucositis is insufficient to avoid negative clinical and patient-reported outcomes. There is a clear need for agents that reduce the incidence and/or severity of mucositis.

### REFERENCES

1. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100:1995-2025.
2. Vera-Llonch M, Oster G, Hagiwara M, et al. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. *Cancer*. 2006;106:329-336.
3. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol*. 2003;66:253-262.
4. Bentzen SM, Saunders MI, Dische S, et al. Radiotherapy-related early morbidity in head and neck cancer: quantitative clinical radiobiology as deduced from the CHART trial. *Radiother Oncol*. 2001;60:123-135.
5. Stokman MA, Sonis ST, Dijkstra PV, et al. Assessment of oral mucositis in clinical trials: impact of training on evaluations in a multi-centre trial. *Eur J Cancer*. 2005;41:1735-1738.
6. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. 2007;357:1705-1715.
7. Vermorken JB, Remen E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxil in unresectable head and neck cancer. *N Engl J Med*. 2007;357:1695-1704.
8. Stiff PJ, Erder H, Bensinger WI, et al. Reliability and validity of a patient self-administered daily questionnaire to assess impact of oral mucositis (OM) on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). *Bone Marrow Transplant*. 2006;37:393-401.
9. Epstein JB, Beaumont JL, Gwede CK, et al. Longitudinal evaluation of the oral mucositis weekly questionnaire-head and neck cancer, a patient-reported outcomes questionnaire. *Cancer*. 2007;109:1914-1922.
10. Murphy BA, Gilbert J, Cmelak A, et al. Symptom control issues and supportive care of patients with head and neck cancers. *Clin Adv Hematol Oncol*. 2007;5:807-822.
11. Duncan GG, Epstein JB, Tu D, et al; National Cancer Institute of Canada Clinical Trials Group. Quality of life, mucositis, and xerostomia from radiotherapy for head and neck cancers: a report from the NCIC CTG HN2 randomized trial of an antimicrobial lozenge to prevent mucositis. *Head Neck*. 2005;27:421-428.
12. Elting LS, Cooksley CD, Chambers MS, et al. Risk, outcomes, and cost of radiation-induced oral mucositis among patients with head-and-neck malignancies. *Int J Radiat Oncol Biol Phys*. 2007;68:110-120.
13. Stiff PJ, Emmanouilides C, Bensinger WI, et al. Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. *J Clin Oncol*. 2006;24:5186-5193.
14. Cella DE, Tulskey DS, Gary G, et al. The Functional Assessment of Cancer Therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570-579.
15. Bonomi AE, Cella DE, Hahn EA, et al. Multilingual translation of the Functional Assessment of Cancer Therapy (FACT) quality of life measurement system. *Qual Life Res*. 1996;5:309-320.
16. Lai JS, Cella D, Chang CH, et al. Item banking to improve, shorten and computerize self-reported fatigue: an illustration of steps to create and store a core item bank from the FACIT Fatigue Scale. *Qual Life Res*. 2003;12:485-501.
17. Brucker PS, Yost K, Cashy J, et al. General population of cancer patient norms for the Functional Assessment of Cancer Therapy-General (FACT-G). *Eval Health Prof*. 2005;28:192-211.
18. Brucker PS, Yost K, Cash J, et al. Normative reference values for the FACT-G. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System Manual. Chicago, IL: Evanston Northwestern Healthcare. Version 4, 2005.
19. Fromme EK, Eilers KM, Mori M, et al. How accurate is clinician reporting of chemotherapy adverse events? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J Clin Oncol*. 2004;22:3485-3490.
20. Chao KS, Ozyigit G, Blanco AI, et al. Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. *Int J Radiat Oncol Biol Phys*. 2004;59:43-50.
21. Yao M, Karnell LH, Funk GF, et al. Health-related quality-of-life outcomes after IMRT versus conventional radiotherapy for oropharyngeal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2007;69:1354-1360.
22. Lee NY, de Arruda FF, Puri DR, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2006;66:966-974.

23. Rose-Ped AM, Bellm LA, Epstein JB, et al. Complications of radiation therapy for head and neck cancers. The patient's perspective. *Cancer Nurs*. 2002;25:461-467.
24. Peterman A, Cella D, Glandon D, et al. Mucositis in head and neck cancer: economic and quality-of-life outcomes. *J Natl Cancer Inst Monogr*. 2001;29:45-51.
25. Cella D, Hahn EA, Dineen K. Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. *Qual Life Res*. 2002;11:207-221.
26. Yost KJ, Sorensen MV, Hahn EA, Glendenning GA, Gnana-sakthy A, Cella D. Using multiple anchor- and distribution-based estimates to evaluate clinically meaningful change on the Functional Assessment of Cancer Therapy-Biologic Response Modifiers (FACT-BRM) instrument. *Value Health*. 2005;8:117-127.
27. Patrick DL, Gagnon DD, Zagari MJ, et al. Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa. *Eur J Cancer*. 2003;39:335-345.
28. Cella D, Eton DT, Lai JS, et al. Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue scales. *J Pain Symptom Manage*. 2002;24:547-561.
29. Eton D, Yost K. Minimally Important Differences on the Functional Assessment of Chronic Illness Therapy Instruments. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System Manual. Chicago, IL: Evanston Northwestern Healthcare, Version 4, 2005.