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

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Abstract: *Background.* The National Cancer Institute of Canada Clinical Trials Group undertook a multicenter, randomized, double-blind controlled trial of an oral antimicrobial versus placebo to prevent and treat mucositis. We present the quality of life (QOL) analysis for this trial.

Methods. One hundred thirty-eight patients were randomly assigned. QOL data were collected every 2 weeks before, during, and after radiotherapy. The European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and a Trial Specific Checklist (TSC) were used.

Results. The antimicrobial lozenge did not impact QOL. The principal acute side effect of radiotherapy is oral pain, affecting more than 90% of patients. Role function is impacted during treatment, and patients experience fatigue. Appetite was reported to markedly increase during radiotherapy. There was a dramatic and persistent increase in dry mouth.

Conclusions. This study highlights the benefits of combining the EORTC QLQ-30 with an ''oral'' TSC in a randomized controlled trial and provides valuable baseline data for their use with an objective mucositis scoring system. © 2005 Wiley Periodicals, Inc. *Head Neck* **27:** 421–428, 2005

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Oral complications after radiotherapy for head and neck cancer substantially affect patients' quality of life (QOL). Pain from mucositis can be severe, requiring opioids, and can reduce oral intake. Mucositis is usually the treatment-limiting acute toxicity in oropharyngeal radiotherapy. Efforts are being made to improve the treatment of oral complications of cancer therapy.[1–3]

Although there are conflicting findings of the impact of an antibacterial/antifungal lozenge on radiation-induced oral mucositis,[4–8] a meta-analysis of 15 studies showed that they are beneficial.[9] A multicenter, randomized, double-blind,

placebo-controlled clinical study of an oral antimicrobial lozenge (BCoG, bacitracin, 6 mg; clotrimazole, 10 mg; and gentamicin, 4 mg) to reduce acute radiation toxicity was carried out by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG).[8] These antimicrobials are active against gram-positive cocci, gram-negative bacilli, and yeast microorganisms.[10] The antimicrobial lozenge BCoG resulted in no significant benefit as measured by physician-rated grade of mucositis. The QOL outcomes of the study are reported in this article.

There is a need for studies to define QOL changes with time.[1,11] In this study, patients were assessed before and during radiation therapy and after treatment. The analysis compares the QOL and symptoms between the trial arms. We describe the acute effects on QOL and oral function seen in these patients and compare this with other reports.

MATERIALS AND METHODS

This NCIC CTG multicenter study treated patients for squamous cell cancer of the head and neck. Patients with nonmetastatic disease (T1–4, N1–3, M0) were eligible. They were all treated to a significant part of the oral and/or pharyngeal mucosa (two or more anatomic sites) with conventional radical or postoperative radiotherapy to a dose of 50 Gy or greater delivered in once-daily fractions (1.8–2.4 Gy). Enrollment in the study was September 1997 to September 1999. Informed consent was obtained. Patients were able and willing to complete QOL questionnaires in English or French. Patients were randomly assigned to treatment with the antimicrobial lozenge (BCoG) or placebo. Standard supportive care measures were allowed.

The primary endpoint of the study was the time to the development of severe mucositis using the oral mucositis assessment scale (OMAS).[12] QOL was one of the secondary endpoints. To assess QOL, the following two tools were used: (1) the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and (2) a Trial Specific Checklist (TSC). The QLQ-C30 is a well-validated instrument providing a broad view of the patients' QOL. For the purpose of this trial, a TSC was developed from a reliable and validated oral assessment scale.[13–15] This checklist was required to capture the main intent of the trial—to assess specific oral symptoms and function during and after treatment.[16–19] The TSC is seen in Table 1 and consists of 15 items.

The QLQ-C30 and TSC were administered at randomization, 2, 4, and 6 weeks during radiotherapy followed by 2 to 3, 6 to 8, and 12 weeks posttreatment. QOL forms were self-administered and completed before physician visits. Patients completed a symptom diary. NCIC CTG Expanded Common Toxicity Criteria (ECTC) were used to assess physician-rated complications.

Statistical Analysis. The EORTC QLQ-C30 was scored using standard algorithms. The TSC was analyzed as single items. For the comparison of a given QOL domain or item between two treatment groups, the patients' QOL responses were calculated as follows. A change score of at least

Table 1. Trial Specific Checklist.

Question	Answers			
During the past week:	Not at all	A little	Quite a bit	Very much
1. Have you had a painful throat?	1	2	3	4
2. Did you have pain in your face?	1	2	3	4
3. Did you have pain in your mouth?	1	2	3	4
4. Did you have any soreness or burning in the mouth?	1	2	3	4
5. Did you have soreness or burning in the mouth while eating?	1	2	3	4
6. Did you have pain in your teeth?	1	2	3	4
7. Did you have pain in your teeth with hot or cold foods or drinks?	1	2	3	4
8. Did you have pain in your teeth with biting?	1	2	3	4
9. Did you have difficulty opening your jaw normally?	1	2	3	4
10. Did you have burning, shooting, or short-lived pains in your mouth or face?	1	2	3	4
11. Did you have numbness in your face?	1	2	3	4
12. Did you have dryness in your mouth?	1	2	3	4
13. Did you have any difficulty with chewing?	1	2	3	4
After completion of radiotherapy:				
14. Did you have increased tooth decay?	1	2	3	4
15. Did you have more difficulty with your dentures than before your cancer treatment?	1	2	3	4

Table 2. National Cancer Institute of Canada Clinical Trials Group expanded common toxicity criteria.

Toxicity	Criteria for grading toxicity				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Taste, sense of smell altered	None	Mild	Moderate	Severe	—
Esophagitis/ dysphagia/odynophagia	None	No treatment required	Requires treatment	Lasting >14 days despite treatment	With ≥10% weight loss, dehydration, in hospital
Cancer pain	None	Pain, no treatment required	Pain controlled, nonopioids	Pain controlled, opioids	Uncontrollable pain
Mouth, nose dryness	None	Mild	Moderate	Severe	—

10 points from baseline was defined as clinically relevant.[20,21] A chi-square test was used to test whether the two study arms had the same underlying multinomial distribution of the QOL responses.[20] The data from both treatment groups were also combined to explore the pattern of the change of QOL and symptom scores over time on study. For each domain and single item, a mixed model with the time of QOL assessment (including baseline) as the only fixed effect covariate was used to test whether there was a significant change of QOL scores over the time course of the study.

RESULTS

One hundred thirty-eight patients (69 on each treatment arm) were randomly assigned—one patient randomly assigned to the placebo arm was later found to not be eligible and excluded from any analysis. The median time to development of oral mucositis (using OMAS) was 3.6 weeks for patients on BCoG and 4.0 for patients on placebo (ie, no significant difference between arms for this primary endpoint).[8] One hundred twenty-two patients (89%) had significant mucositis, and 65 (almost 50%) had ulceration/pseudomembrane. The worst-ever scores on the symptom diary show that more than 75% of patients had "quite a bit—very much" pain in the mouth and soreness or burning in the mouth, and 66% had difficulty chewing and difficulty swallowing. More than half the patients had "very much" problems with their diet. There were no significant differences between the arms for toxicities measured by the NCIC ECTC (physician rated; Table 2). Sixteen patients required opioids for pain control. Note is made that narcotics can exacerbate dry mouth. Only 14 patients had grade 3 dry mouth acutely and eight delayed by ECTC.

Four patients (two on each arm) had baseline QOL forms filled out after they were randomly assigned and were excluded from the analysis. Compliance with QOL forms was 97.1% at baseline, and overall compliance was 93.3%, with no difference in compliance between the treatment arms. The basic demographic and tumor characteristics for 133 patients included in the QOL analysis are balanced (Table 3).

Baseline QOL Scores and Comparison of Treatment Arms. The mean and standard deviation of the baseline score for each QOL domain and item are

Table 3. Demographic and tumor characteristics of patients in quality of life analysis.

Characteristic	No. patients (%) by treatment		Total no. patients (%) (N = 133)
	Placebo (n = 67)	BCoG (n = 66)	
Median age, y	57.3	59.7	58.6
Sex			
Male	52 (78)	48 (73)	100 (75)
Female	15 (22)	18 (27)	33 (25)
ECOG performance status			
0	48 (72)	51 (77)	99 (74)
1	13 (19)	11 (17)	24 (18)
2	5 (7)	4 (6)	9 (7)
3	1 (1)	0 (0)	1 (1)
T and N classification			
T1	14 (20)	13 (18)	26 (20)
T2	28 (42)	29 (42)	56 (42)
T3	17 (25)	13 (20)	30 (23)
T4	6 (9)	11 (17)	17 (18)
Tx	2 (3)	2 (3)	4 (3)
N0	26 (39)	21 (32)	47 (35)
N1	21 (31)	17 (26)	38 (29)
N2	19 (29)	27 (40)	46 (35)
N3	1 (1)	1 (2)	2 (2)
Site of disease			
Oral cavity	27 (40)	22 (32)	49 (36)
Oropharynx	27 (40)	37 (54)	64 (47)
Hypopharynx	6 (9)	6 (9)	12 (9)
Nasopharynx	4 (6)	7 (10)	11 (8)
Larynx	12 (17)	6 (8)	18 (13)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

given in Table 4 for each treatment group and in Table 5 for two groups combined. Patients reported mild problems with emotional and social functions before randomization. Pain, sleep disorder, and fatigue were also evident. Global QOL was impaired (mean score, 68) at baseline. The TSC showed that throat and mouth pain, xerostomia, and difficulty chewing were evident at this time, as well as soreness/burning in the mouth, likely because of the primary tumor.

The QOL responses by treatment arm are given in Table 4 for each domain and item. There are no statistically significant differences between treatment arms.

Change of Quality of Life Scores over Time. The mean and standard deviation of the QOL scores at each assessment time are given in Table 5. By 9 weeks on study, patients experienced a moderate, significant fall in role scores. Patients had a moderate increase in fatigue but began to recover after 8 weeks. Appetite was seen to markedly increase, but declined after several weeks after radiation therapy.

TSC questions showed clinically significant worsening from radiotherapy but improvement by the 12th week of the study. Patients experienced moderate worsening (10–15 points) with chewing and marked worsening (>15 points) with painful throat, pain in the mouth, soreness/burning in the mouth, and soreness/burning in the mouth *while eating*. The most dramatic change was dryness in the mouth, which showed a rapid worsening on radiotherapy and did not recover. These results

Table 4. Comparison of quality of life responses between two treatment arms.

	BCoG				Placebo				
		No. patients (%)				No. patients (%)			
Item	Baseline score, mean (SD)	Improved	Stable	Worse	Baseline score, mean (SD)	Improved	Stable	Worse	*p* value
Global	67 (22)	27 (41)	13 (20)	26 (39)	69 (22)	24 (37)	15 (23)	26 (40)	.77
Physical	91 (16)	10 (15)	31 (47)	25 (38)	89 (18)	12 (19)	36 (57)	15 (24)	.13
Role	85 (20)	20 (30)	20 (30)	26 (39)	84 (27)	13 (21)	26 (41)	24 (38)	.55
Emotional	74 (22)	31 (47)	25 (38)	10 (15)	72 (26)	29 (45)	29 (45)	7 (11)	.87
Cognitive	87 (19)	22 (33)	30 (45)	14 (21)	87 (22)	22 (34)	28 (43)	15 (23)	.92
Social	83 (22)	21 (32)	24 (37)	20 (31)	84 (22)	22 (34)	22 (34)	21 (32)	1.00
Pain	24 (26)	34 (52)	8 (12)	24 (36)	27 (29)	30 (46)	8 (12)	27 (42)	.52
Appetite	12 (21)	11 (17)	18 (27)	37 (56)	18 (36)	16 (25)	18 (28)	30 (47)	.21
Constipation	16 (25)	19 (29)	23 (35)	24 (36)	15 (26)	16 (25)	23 (35)	26 (40)	.58
Financial	17 (28)	12 (18)	40 (61)	14 (21)	17 (28)	14 (22)	36 (57)	13 (21)	.68
Fatigue	24 (23)	27 (41)	11 (17)	28 (42)	22 (24)	25 (39)	7 (11)	32 (50)	.56
Nausea	6 (13)	14 (21)	25 (38)	27 (41)	5 (13)	11 (17)	40 (61)	14 (22)	.22
Sleeping	26 (29)	27 (41)	22 (33)	17 (26)	24 (29)	25 (39)	22 (34)	17 (27)	.85
Diarrhea	9 (31)	9 (14)	51 (77)	6 (9)	7 (20)	10 (15)	52 (80)	3 (5)	.44
Dyspnea	12 (22)	16 (24)	39 (59)	11 (17)	13 (23)	17 (26)	42 (65)	6 (9)	.38
Throat pain	35 (41)	28 (42)	9 (14)	29 (44)	29 (32)	20 (31)	9 (14)	36 (55)	.15
Face pain	18 (25)	22 (34)	22 (34)	21 (32)	12 (22)	15 (23)	23 (35)	27 (41)	.16
Mouth pain	23 (30)	21 (32)	13 (20)	32 (48)	28 (31)	24 (37)	12 (18)	29 (45)	.57
Sore/burning mouth	18 (26)	13 (20)	20 (31)	32 (49)	21 (29)	18 (29)	12 (19)	32 (52)	.65
Sore/burning mouth while eating	17 (25)	14 (23)	15 (25)	31 (52)	21 (30)	20 (33)	11 (18)	30 (49)	.45
Teeth pain	10 (21)	11 (20)	36 (67)	7 (13)	8 (20)	9 (17)	37 (71)	6 (12)	.88
Teeth pain with food/drinks	7 (15)	8 (15)	31 (60)	13 (25)	8 (20)	7 (15)	27 (59)	12 (26)	.92
Teeth pain with biting	7 (18)	6 (11)	34 (65)	12 (23)	9 (23)	7 (16)	24 (55)	13 (29)	.87
Difficulty opening jaw	21 (36)	20 (30)	27 (41)	19 (29)	13 (22)	15 (23)	30 (46)	20 (31)	.48
Burning/shooting pain in mouth/face	19 (26)	23 (35)	18 (27)	25 (38)	15 (22)	20 (31)	23 (35)	22 (34)	1.00
Numbness in face	12 (24)	13 (20)	37 (56)	16 (34)	10 (20)	10 (15)	39 (60)	16 (25)	.68
Dryness in mouth	21 (28)	7 (11)	4 (6)	55 (83)	24 (28)	7 (11)	12 (18)	46 (71)	.27
Difficulty chewing	28 (35)	18 (28)	23 (35)	24 (37)	23 (37)	13 (20)	22 (34)	30 (46)	.22
Increased tooth decay	0 (0)	0 (0)	1 (50)	1 (50)	0 (NA)	0 (0)	1 (50)	1 (50)	NA
Difficulty with dentures	33 (47)	0 (0)	3 (75)	1 (25)	0 (NA)	0 (0)	1 (100)	0 (0)	NA

p values are comparisons between arms (chi-square test).

Table 5. Profile of quality of life scores over time.

		Mean score (SD)						
		Week on study (radiotherapy phase)			Week on study (follow-up)			
Item	Baseline score	Week 2	Week 4	Week 6	Week 8–9	Week 12–14	Week 24	*p* value*
Global	68.1 (21.5)	64.3 (23.5)	61.0 (21.6)	57.3 (22.4)	58.0 (22.4)	62.7 (20.7)	62.4 (23.7)	<.0001
Physical	90.0 (16.9)	88.6 (16.5)	85.7 (20.0)	83.2 (20.3)	80.2 (19.8)	83.7 (20.9)	83.1 (20.5)	<.0001
Role	84.6 (23.6)	81.8 (25.0)	75.1 (28.6)	71.1 (31.2)	67.1 (30.7)	74.6 (28.1)	72.7 (27.7)	<.0001
Emotional	73.2 (24.1)	77.5 (24.1)	77.3 (24.6)	77.3 (24.0)	73.6 (26.3)	76.3 (24.6)	76.9 (23.7)	.16
Cognitive	87.0 (20.3)	86.9 (19.6)	85.1 (21.4)	85.3 (21.6)	84.3 (22.4)	85.9 (22.1)	83.6 (24.1)	.53
Social	83.1 (21.9)	78.1 (26.6)	73.9 (27.2)	69.7 (31.0)	71.7 (26.5)	76.2 (25.3)	75.0 (28.4)	<.0001
Pain	25.4 (27.2)	27.9 (26.7)	33.3 (28.7)	39.3 (30.7)	32.6 (28.3)	24.7 (27.4)	26.3 (29.0)	<.0001
Appetite	15.3 (29.3)	32.8 (35.6)	39.7 (32.9)	44.9 (36.4)	40.2 (32.2)	25.0 (29.1)	29.9 (36.6)	<.0001
Constipation	15.4 (25.2)	18.1 (27.2)	26.4 (29.8)	32.7 (34.8)	33.0 (32.1)	16.4 (23.5)	16.1 (30.3)	<.0001
Financial	17.4 (27.9)	17.8 (28.4)	17.9 (27.6)	21.9 (31.6)	22.7 (31.6)	20.1 (32.3)	24.4 (41.5)	.0053
Fatigue	23.2 (23.7)	30.5 (26.7)	33.7 (27.5)	39.4 (28.2)	39.8 (26.0)	34.2 (27.2)	33.7 (25.1)	<.0001
Nausea	5.4 (12.8)	13.7 (20.1)	13.2 (20.7)	14.1 (20.3)	9.6 (19.7)	6.0 (12.9)	5.7 (12.6)	<.0001
Sleeping	24.7 (28.7)	24.1 (33.7)	22.3 (26.0)	29.0 (31.8)	30.2 (32.3)	22.6 (29.1)	21.8 (26.0)	.043
Diarrhea	7.8 (26.0)	7.4 (26.6)	4.1 (12.6)	4.0 (13.5)	7.2 (16.3)	6.3 (18.1)	6.3 (19.1)	.54
Dyspnea	12.4 (22.7)	11.7 (21.4)	9.6 (18.5)	12.5 (20.2)	15.2 (22.6)	14.5 (21.7)	42 (65)	.085
Throat pain	32.1 (36.7)	38.7 (32.2)	56.1 (29.6)	58.4 (33.7)	46.0 (32.8)	33.0 (32.7)	31.9 (34.7)	<.0001
Face pain	15.0 (23.8)	16.9 (26.0)	27.4 (30.0)	28.1 (31.2)	16.1 (30.9)	14.5 (26.9)	14.5 (28.0)	<.0001
Mouth pain	25.5 (30.5)	32.3 (31.0)	42.8 (32.1)	46.2 (35.4)	39.1 (33.1)	27.8 (29.9)	24.3 (29.7)	<.0001
Sore/burning mouth	19.5 (27.6)	31.2 (30.6)	44.6 (32.4)	46.4 (35.1)	40.2 (33.8)	29.8 (29.1)	23.8 (26.6)	<.0001
Sore/burning mouth while eating	18.8 (27.4)	32.0 (31.9)	45.9 (40.7)	45.3 (36.9)	41.4 (35.7)	30.5 (31.4)	27.0 (29.4)	<.0001
Teeth pain	9.2 (20.6)	10.6 (21.8)	11.6 (24.4)	9.8 (21.7)	16.2 (39.1)	11.2 (23.0)	15.5 (39.8)	.37
Teeth pain with food/drinks	7.4 (17.9)	13.5 (23.5)	12.3 (22.5)	14.1 (25.9)	15.1 (27.6)	14.8 (24.2)	14.2 (22.4)	.095
Teeth pain with biting	7.7 (20.2)	11.6 (24.7)	13.7 (28.2)	14.0 (25.7)	14.2 (26.2)	10.5 (21.7)	11.2 (22.6)	.23
Difficulty opening jaw	16.7 (29.8)	20.9 (26.3)	22.8 (41)	26.3 (31.8)	25.2 (26.3)	19.1 (26.1)	19.4 (30.3)	.0062
Burning/shooting pain in mouth/face	16.9 (24.2)	18.7 (26.3)	44.6 (32.4)	33.6 (33.8)	24.1 (32.8)	19.9 (29.7)	16.2 (30.7)	<.0001
Numbness in face	10.9 (22.4)	12.1 (21.2)	17.2 (23.7)	14.1 (22.8)	13.9 (22.5)	11.9 (25.8)	15.1 (24.3)	.063
Dryness in mouth	22.5 (27.8)	52.7 (30.6)	62.8 (31.5)	66.0 (34.1)	60.1 (33.8)	60.9 (31.0)	64.1 (28.3)	<.0001
Difficulty chewing	25.7 (35.9)	33.3 (36.5)	38.3 (36.6)	37.1 (38.6)	38.7 (36.1)	34.5 (35.9)	32.7 (39.8)	<.0001
Increased tooth decay	0 (0)	NA (NA)	NA (NA)	14.3 (17.8)	2.9 (9.5)	2.9 (12.2)	3.7 (13.9)	.48
Difficulty with dentures (n = 5)	26.7 (43.5)	NA (NA)	NA (NA)	33.3 (44.1)	21.2 (33.6)	26.4 (36.0)	18.8 (32.3)	.54

Abbreviation: NA, Not available (no patients had answered the question).
= Problems evident at baseline – see text.
**p value from the mixed model.*

are generally consistent with the symptom diary and toxicity assessments, except for a marked difference between dryness in the mouth reported by patients (TSC) and lesser change in dry mouth as assessed by physicians (ECTC).

DISCUSSION

The EORTC QLQ-C30 questionnaire revealed no benefit (or detriment) to the BCoG antimicrobial treatment in this trial. Clinically important and notable worsening is seen in role function and fatigue, but these are time limited. The QLQ-C30, therefore, shows the broad impact of oral radiotherapy on the functional domains and symptom scales.

In this trial, we focused on the oral impact of radiation treatment and mucositis in particular. A TSC was developed to capture the experience of patients. Other questionnaires existed at the time of the trial design, and these were reviewed. Bjordal et al[18] studied the use of a 19-item head and neck module in 245 survivors, and after extensive pretesting in Europe, a 37-item module concerning disease and treatment-related symptoms, social function, and sexuality was developed.[22] This has evolved into the EORTC H&N35 module—a lengthy, but well-validated questionnaire—general to all head and neck cancers and all modalities of treatment.[23] The University of Washington has also worked on a Head and Neck

Disease–Specific questionnaire (UW-QOL),[16,17] and a more recent report demonstrates the difficulties of any one questionnaire to adequately evaluate QOL.[24] Like the H&N35, the UW-QOL is a broad tool. In 1999, they published a review of 65 oral QOL studies from 1980 to 1997, identifying 27 commonly used questions.[25] At the time of this trial development, there was the initial report of the Functional Assessment of Cancer Therapy–Head and Neck (FACT-H&N) and Performance Status Scale for Head and Neck Cancer,[26] with subsequent research on the effects of chemoradiotherapy using these instruments.[27–29] A more recent review of head and neck QOL instruments suggests future efforts to evaluate existing tools.[30]

Bansal et al[31] reported on the QOL of 45 patients who received parallel opposed pairs to the primary tumor and neck with a dose of 70 Gy in 35 fractions. The EORTC QLQ-C30 was used, and all symptoms and domains were better at baseline than in the HN2 trial, possibly because of patient selection. During radiotherapy (week 4), Bansal observed a much more pronounced drop in global scores (82 to 30) than we found (68 to 61). Physical, emotional, and social functions; pain; poor appetite; and fatigue are clearly worse. These may, in part, be related to the dose-volume used. It is also interesting to note that 1 month after radiotherapy, scores in the Bansal series are similar to those seen in our study.

One of the authors (JE) developed a specific oral symptom and function checklist that was used to study patients during radiation therapy[14] and to assess chronic complications of radiation therapy more than 6 months after treatment.[13] The results of these and the current study show that the questionnaire is responsive to changes throughout the course of radiation therapy for head and neck cancer and sensitive to long-term changes experienced by patients.

Although there were no apparent differences between the BCoG and placebo arms of this trial, the HN2 study, nonetheless, gives a detailed description of what patients undergoing oral radiotherapy experience. Nearly 90% of patients have significant objective mucositis, with almost half developing ulceration/pseudomembrane. Three of four prior trials of polymyxin E, tobramycin, and amphotericin B lozenges showed clinical benefit,[4–7,32] but this multicenter, controlled study was in an effort to find a more cost-effective agent, and no benefit was seen. It is speculated that differences in radiation protocols, basic oral hygiene, study endpoints, and sample size may explain why some studies were positive. Another difference is in the use of health-care personnel ratings versus patient reports.

Patients are symptomatic from oropharyngeal pain before their radiotherapy, likely because of the cancer and dry mouth, and difficulties chewing are also present (Table 3). Fisher et al[33] also found that pain and chewing were problems even before cancer treatment but saw very little problem with saliva, perhaps because this was not a sample of oral cancers. During and after radiotherapy, we found clinically significant worsening in chewing, pain, and xerostomia observed from the TSC.

Epstein et al[13] found that more than 90% of patients are troubled by xerostomia long term after radiotherapy. The most dramatic change of all the QOL scores in this study is in xerostomia secondary to parotid radiotherapy. Physicians rated xerostomia as grade 3 ("severe") in 14 of 137 patients during or shortly after radiotherapy. The TSC more accurately reflect patients' experience. This has also been shown in the RTOG 97-09 study QOL results.[33] This study shows how pilocarpine may improve salivary function but does not improve patients' perception of salivary function or their QOL. Warde et al[34] found no benefit from pilocarpine in a phase III trial; the French cooperative study found 75% compliance with pilocarpine and an important improvement in QOL for 77%.[35]

Xerostomia is *the* major complication of combined chemoradiotherapy.[36,37] In general, patients with nasopharyngeal cancer have the highest morbidity because of bilateral radiotherapy to all major salivary glands.[38] Xerostomia is associated with increased caries, chewing, swallowing, and speaking problems, as well as a higher incidence of candidiasis.[39] Diet is impaired by xerostomia, and all EORTC QLQ-C30 functional scales are reduced by up to 25%, especially when xerostomia is present.[40]

Radiotherapy salivary-sparing techniques show promise,[41–45] and the mean parotid dose correlates with QOL outcome at 3 months but not later, perhaps representing coping mechanisms.[43] Xerostomia questionnaires have been developed and validated[41–44] and are an important consideration in trials to assess subjective benefit for patients. Xerostomia improves after radiotherapy but does not return to baseline at 1 year.[42,43]

The finding that 66% of patients had substantial problems acutely with swallowing is

similar to the 63% found in an earlier study[13] of late effects, suggesting this may be a clinically important persistent toxicity, perhaps etiologically related to the xerostomia.

This study shows that mucositis clearly has an adverse impact on patients because of pain; difficulty in eating, swallowing, and talking; and sleep disturbances and may impact patient reports of fatigue during radiotherapy. It can lead to disruptions to the planned radiotherapy and is a major limitation to more aggressive radiotherapy and chemoradiotherapy protocols.[1,46–48] Increased acute mucositis of new radiotherapy and chemoradiotherapy protocols suggests that more than 60% of patients will experience grade 3 to 4 mucositis.[47,49–51] Improved understanding of the pathophysiology, frequency, severity, and duration of symptomatic toxicities will allow the rational development of interventions.

QOL and symptoms are an important outcome of therapy and assist in choosing the best approach to therapy. This may lead to not only improved patient care but also ultimately better disease control. As seen in this study, both general and head and neck or oral outcome measures are a crucial component in studying novel approaches to advance the treatment of head and neck malignancy. This study adds to the prior experience with the use of this combined approach to assessing QOL and symptoms in patients with head and neck cancer,[13–15] and it provides a model for future QOL studies.

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