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RISK, OUTCOMES, AND COSTS OF RADIATION-INDUCED ORAL MUCOSITIS AMONG PATIENTS WITH HEAD-AND-NECK MALIGNANCIES

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Purpose: To study the risk, outcomes, and costs of radiation-induced oral mucositis (OM) among patients receiving radiotherapy (RT) to head and neck primary cancers.

Methods and Materials: A retrospective cohort consisting of 204 consecutive head-and-neck cancer patients who received RT with or without chemotherapy during 2002 was formed; their records were reviewed for clinical and resource use information. Patients who had received prior therapy, had second primary cancers, or received palliative radiation therapy were excluded. The risk of OM was analyzed by multiple variable logistic regression. The cost of care was computed from the provider's perspective in 2006 U.S. dollars and compared among patients with and without OM.

Results: Oral mucositis occurred in 91% of patients; in 66% it was severe (Grade 3–4). Oral mucositis was more common among patients with oral cavity or oropharynx primaries (odds ratio [OR], 44.5; 95% confidence interval [CI], 5.2 to >100; $p < 0.001$), those who received chemotherapy (OR = 7.8; 95% CI, 1.5–41.6; $p = 0.02$), and those who were treated with altered fractionation schedules (OR = 6.3; 95% CI, 1.1–35.1; $p = 0.03$). Patients with OM were significantly more likely to have severe pain (54% vs. 6%; $p < 0.001$) and a weight loss of ≥5% (60% vs. 17%; $p < 0.001$). Oral mucositis was associated with an incremental cost of $1700–$6000, depending on the grade.

Conclusions: Head-and-neck RT causes OM in virtually all patients. Oral mucositis is associated with severe pain, significant weight loss, increased resource use, and excess cost. Preventive strategies are needed. © 2007 Elsevier Inc.

Oral mucositis, Head-and-neck cancer, Radiotherapy, Cost, Outcomes.

INTRODUCTION

Oral mucositis (OM) is a common and dose-limiting toxicity of radiotherapy (RT) among patients with head and neck primary cancers (1). In recent years, altered fractionation and the addition of chemotherapy have improved local control and survival in this population at the expense of an increased incidence of OM (2). This trend is clinically significant because OM leads to a reduction of quality of life through its association with increased pain, declining performance status, inability to eat, and need for feeding tubes (1, 3, 4). However, our knowledge about the incidence of OM and its clinical and economic outcomes is incomplete (1, 5). For example, we know that the incidence exceeds 30% historically and 90% with modern regimens, but we know relatively little about the severity and duration of OM with newer regimens. Clinical trials of RT regimens provide information about dose reductions and delays, but only occasionally about increases in hospitalizations, clinic visits, and usage of antibiotics and pain medications among patients with OM. To our knowledge, there are no recently published reports describing the incremental cost of OM with

modern regimens. Accordingly, we examined the risk of OM in a retrospective cohort of patients who received RT to head-and-neck primaries. We also compared the clinical and economic outcomes among patients with and without OM.

METHODS AND MATERIALS

All newly diagnosed patients with nonmelanotic cancers of the oral cavity, oropharynx, hypopharynx, and larynx who received all their RT treatment and completed all follow-up visits during the 6 weeks after RT at The University of Texas M. D. Anderson Cancer Center during 2002 were identified through the Tumor Registry. From this group of 433 patients, we excluded 113 patients who had second primary cancers, 74 patients who did not receive RT, and 42 patients who received only palliative RT, leaving 204 patients for analysis. The eligible patients' paper and electronic medical records were reviewed for patient, treatment, outcome, and resource use information by trained research nurses using a standardized data abstraction form. Outcomes of RT, total RT doses, and fractionation were validated by a radiation oncologist (A.S.G.). Information was collected from the date RT was initiated through 6 weeks after RT completion. Radiotherapy was categorized by use of intensity-modulated RT (IMRT) and by use of altered fractionation regimens, including concomitant boost and hyperfractionation. Patients who received IMRT typically received once-daily fractionation. All clinical targets were treated in every fraction, with the gross disease and margin (or high-risk target volumes in the postoperative setting) treated to the highest dose per fraction, and subclinical target volumes treated to lower doses per fraction (6). Infrequently, all targets were treated at the same dose and fraction size to 50–54 Gy, and the gross disease with margin boosted separately either with sequential or concomitant boost fractionation schedule.

Cost information was obtained from the hospital accounting system. We analyzed cost from the provider's perspective and reported it in 2006 U.S. dollars. We included the direct costs of providing the services and excluded professional fees (which were unavailable) and accounting costs (*i.e.*, depreciation, overhead). Cost was computed by applying our center's service-specific cost-to-charge ratios to charges obtained from billing records for each patient. The 2002 costs were inflated to 2006 U.S. dollars using the Consumer Price Index for Medical Care. Mean inpatient and outpatient costs were categorized by maximum grade of mucositis and receipt of IMRT and chemotherapy. Because of the significant differences among patients in these groups, mean costs were adjusted for site and stage of disease, lymph node involvement, RT fractionation, age, and presence of chronic comorbid conditions. Extreme values of cost in a few patients skewed mean cost values. Therefore, the mean of the natural logarithm of cost was computed.

In addition to cost, we measured the resources used by each patient. These included the number and duration of hospitalizations and the number of visits to the emergency department, dental oncologist, and dietician. We also measured the number of days receiving opioid, nonopioid, and topical analgesics, oral and intravenous antimicrobials, and gastrostomy tubes. The use of gastrostomy tubes was further characterized by timing of insertion, as either present at onset of RT or inserted during RT. Although it is not possible to accurately determine the indication for gastrostomy tube insertion in a retrospective study, we assumed that those present before RT were not required because of mucositis and that

those inserted during RT possibly were required because of mucositis.

Oral mucositis was measured weekly according to the Common Toxicity Criteria, version 2 (7). For analytic purposes, patients were characterized by their highest grade of mucositis during RT. Because of the frequent use of concomitant boost fractionation, we also examined the highest grade of mucositis during 6 weeks after RT. Only 6 patients experienced a higher grade after RT (Grade 3) than during RT (Grade 2), and in all cases it occurred among patients who received chemotherapy after completion of RT and resolution of RT-induced mucositis. None of these patients received concomitant boost. Thus we used the maximum grade during RT for all analyses. Pain was measured on a scale of 0–10, with 10 reflecting the worst pain possible. Breaks in RT were defined by a delay of 3 treatment days or more in the planned RT schedule.

The proportions of patients with clinical and treatment factors were compared between those with and without mucositis and between those who received IMRT and those who received standard RT, using Pearson's chi-square test (or Fisher's exact test, when appropriate). Mean resources used were compared using *t* tests. All tests of significance were two-tailed. Separate analyses were done for those who received RT alone and those who received chemotherapy in addition to RT (chemo-RT). We modeled the risk of developing mucositis using logistic regression to examine the unique contribution of each of the clinical and treatment factors. We also modeled the risks of developing serious clinical outcomes (dose reduction or delay, hospitalization, weight loss, or gastrostomy tube insertion), using logistic regression to estimate the unique contribution of oral mucositis while accounting for other confounding factors. The impact of mucositis on the total costs of inpatient and outpatient care was modeled similarly using linear regression. However, in this case, the natural logarithm of costs was modeled to reduce the influence of outliers.

The study was approved by the institutional review board at M. D. Anderson Cancer Center, and waivers of informed consent and authorization were granted. The research was conceived and conducted by the investigators, who also were solely responsible for analysis and interpretation of data and for preparation of the manuscript. The sponsor reviewed and commented on the design of the study and the manuscript but was not involved in interpretation of data or in the decision to publish.

RESULTS

A total of 204 patients met the criteria for inclusion. Most (78%) were men, their mean age was 56 years (95% confidence interval [CI], 55–58), and 57% were employed at the time of treatment (Table 1). Non-Hispanic whites predominated, although 9% were black and 10% Hispanic. The majority had primary cancers in the oral cavity or oropharynx, although 22% had larynx or hypopharynx primaries. Patients' primary tumors were evenly divided between early and advanced T stage: 103 patients had T1–2 tumors and 101 had T3–4. One hundred forty-three (70%) had nodal involvement. None of the patients had distant metastases. All but 16 patients (8%) had good performance status at baseline, and only 59 (29%) had comorbid conditions. Seventy-six patients (37%) received IMRT, and 95 (47%) received chemo-RT. All but

Table 1. Characteristics of patients

Characteristic	IMRT ($n = 76$)		No IMRT ($n = 128$)		Total ($N = 204$)
	RT only ($n = 47$)	RT + Chemo ($n = 29$)	RT only ($n = 62$)	RT + Chemo ($n = 66$)	
Male	31 (66)	27 (93)	47 (76)	54 (82)	159 (78)
Mean age (range)	53 (20–72)*	56 (38–82)	58 (27–82)*	56 (42–80)	56 (20–82)
Age > 70 y	3 (6)	2 (7)	11 (18)	5 (8)	21 (10)
Race					
White	40 (85)	21 (73)	50 (81)	48 (73)	159 (78)
Black	0	5 (17)	6 (9)	7 (11)	18 (9)
Hispanic	7 (15)	1 (3)	5 (8)	7 (11)	20 (10)
Other	0	2 (7)	1 (2)	4 (5)	7 (30)
Employed	31 (66)	17 (59)	30 (48)	38 (58)	116 (57)
Primary cancer					
Oral cavity, oropharynx	47 (100)	29 (100)	34 (55)	50 (76)	160 (78)
Larynx, hypopharynx	0	0	28 (45)	16 (24)	44 (22)
Primary stage					
T1	12 (25)	3 (10)	20 (32)	2 (3)	37 (18)
T2	28 (60)	5 (17)	22 (36)	11 (17)	66 (32)
T3	1 (2)	6 (21)	10 (16)	33 (50)	50 (25)
T4	6 (13)	15 (52)	10 (16)	20 (30)	51 (25)
Nodal stage					
N0	17 (36)	8 (28)	26 (42)	10 (15)	61 (30)
N1	11 (23)	5 (17)	13 (21)	7 (11)	36 (18)
N2	19 (41)	10 (34)	20 (32)	41 (62)	90 (44)
N3	0	6 (21)	3 (5)	8 (12)	17 (8)
Comorbidity					
0	38 (81)[†]	24 (83)	34 (55)[†]	49 (74)	145 (71)
1	3 (6)	2 (7)	17 (27)	9 (14)	31 (15)
2 or more	6 (13)	3 (10)	11 (18)	8 (12)	28 (14)
Diabetic	3 (6)	2 (7)	7 (11)	8 (12)	20 (10)
Zubrod performance status					
0	17 (36)	5 (17)	21 (34)	10 (15)	53 (26)
1	30 (64)	20 (69)	37 (60)	48 (73)	135 (66)
2 or more	0	4 (14)	4 (6)	8 (12)	16 (8)
Edentulous	4 (9)	2 (7)	14 (23)	9 (14)	29 (14)
Mean RT dose (Gy) to primary (CI)	64 (62–65)	70 (70–71)	64 (65–67)	70 (68–72)	67 (67–68)
Altered fractionation	2 (4)[‡]	5 (17)[§]	20 (32)[‡]	36 (55)[§]	63 (31)

Abbreviations: IMRT = intensity-modulated radiotherapy; Chemo = chemotherapy; CI = confidence interval; RT = radiotherapy.
Data are presented as number (percentage), unless otherwise noted.
* $p = 0.02$; † $p = 0.005$; ‡ $p < 0.001$; § $p = 0.001$.

8 of the 95 patients received concurrent chemotherapy. Because they were too few to analyze separately, the 8 patients who received chemotherapy before RT were combined with the 87 patients who received concurrent RT. All patients who received chemotherapy received platinum-based regimens; 71% also received a taxane. Altered fractionation RT schedules were used in 63 patients (31%); in 62 of these it was the concomitant boost fractionation schedule (8, 9).

There were prognostically important differences among patients who received different treatment modalities. Overall, patients who received IMRT were younger than those who received standard RT (53.9 vs. 57.4 years; $p = 0.03$). This difference was confined to patients who received RT without chemotherapy (Table 1). None of the patients with larynx or hypopharynx primaries received IMRT, and those who did receive IMRT were more likely to have low T stage (T1, T2) primary tumors than those who received standard

RT (63% vs. 43%; $p = 0.005$). This difference was most profound among patients who did not receive chemotherapy, in whom low T stage was observed in 85% of patients who received IMRT and only 68% of those who received standard RT ($p = 0.04$). Altered fractionation was used significantly less frequently among patients who received IMRT (9%) than in those receiving standard RT (44%; $p < 0.001$).

Patients who received chemo-RT were more likely to have locally advanced primaries (78% vs. 25%; $p < 0.001$) and nodal involvement (81% vs. 61%; $p = 0.001$) than those who received RT alone. They also were more likely to have poor performance status at baseline (13% vs. 4%; $p = 0.02$). Patients who received standard RT were more likely to receive chemotherapy than those who received IMRT (52% vs. 38%; $p = 0.06$), thus the unfavorable clinical factors that characterized chemotherapy recipients were more common in the conventional RT group.

Table 2. Risk and duration of oral mucositis

	Maximum grade of mucositis (CTC v. 2.0)					Duration of mucositis (wk)	
Factor (n)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Any mucositis	Grade 3–4
Overall (204)	18 (9)	8 (4)	43 (21)	122 (60)	13 (6)	4.9 (4.6–5.2)	2.1 (1.8–2.4)
RT only (109)	16 (15)	4 (3)	25 (23)	62 (57)	2 (2)	4.2 (3.8–4.6)*	1.7 (1.4–2.1)†
RT plus chemotherapy (95)	2 (2)	4 (4)	18 (19)	60 (63)	11 (12)	5.8 (5.4–6.1)*	2.5 (2.0–2.9)†
IMRT (76)	1 (1)	2 (3)	20 (26)	48 (63)	5 (7)	5.4 (5.1–5.8)‡	2.2 (1.8–2.7)§
No IMRT (128)	17 (13)	6 (5)	23 (18)	74 (58)	8 (6)	4.6 (4.2–5.1)‡	2.0 (1.6–2.4)§
Conventional fractionation (141)	16 (11)	7 (5)	34 (24)	78 (55)	6 (4)	4.9 (4.5–5.3)‖	1.9 (1.5–2.2)¶
Altered fractionation (63)	2 (3)	1 (2)	9 (14)	44 (70)	7 (11)	5.0 (4.5–5.6)‖	2.6 (2.1–3.1)¶
Oral cavity, oropharynx (160)	2 (1)	4 (2)	33 (21)	109 (68)	12 (8)	5.5 (5.3–5.8)#	2.5 (2.1–2.8)**
Larynx, hypopharynx (44)	16 (36)	4 (9)	10 (23)	13 (30)	1 (2)	2.8 (2.1–3.5)#	0.8 (0.3–1.2)**
Age ≥70 y (21)	8 (38)	1 (5)	5 (24)	7 (33)	0	5.2 (4.9–5.5)††	2.2 (1.9–2.5)
Age <70 y (183)	10 (5)	7 (4)	38 (21)	115 (63)	13 (7)	2.8 (1.6–3.9)††	1.4 (0.4–2.3)
Diabetic (20)	0	0	2 (10)	18 (90)	0	5.3 (4.4–6.1)	2.6 (1.7–3.4)
Not diabetic (184)	18 (10)	8 (4)	41 (22)	104 (57)	13 (7)	4.9 (4.6–5.2)	2.0 (1.7–2.3)
Edentulous (29)	2 (7)	0	13 (45)	13 (45)	1 (3)	4.6 (3.8–5.5)	1.5 (0.8–2.2)‡‡
Dentate (175)	16 (9)	8 (5)	30 (17)	109 (62)	12 (7)	5.0 (4.7–5.3)	2.2 (1.9–2.5)‡‡

Abbreviations: CTC = Common Toxicity Criteria; RT = radiation therapy; IMRT = intensity-modulated RT.

Data are presented as number (percentage) or mean (95% confidence interval).

* $p < 0.001$; † $p = 0.008$; ‡ $p = 0.01$; § $p = 0.44$; ‖ $p = 0.68$; ¶ $p = 0.02$; # $p < 0.001$; ** $p < 0.001$; †† $p < 0.001$; ‡‡ $p = 0.08$.

Risk of OM among RT recipients

Overall, 91% of patients developed OM; in 66% it was severe (Grade 3–4) (Table 2). Univariate analyses showed that the risk of OM was significantly higher among patients who received chemo-RT compared with those who received RT alone (98% vs. 85%; $p = 0.002$), those who had oral cavity or oropharynx primaries compared with those with larynx or hypopharynx primaries (99% vs. 64%; $p < 0.001$), and among IMRT recipients compared with standard RT recipients (99% vs. 87%; $p = 0.004$). However, as previously mentioned, unfavorable risk factors (high T stage and altered fractionation) were not equally distributed among these groups. Therefore, the unique contribution of each of these factors to the risk of OM was examined in multiple
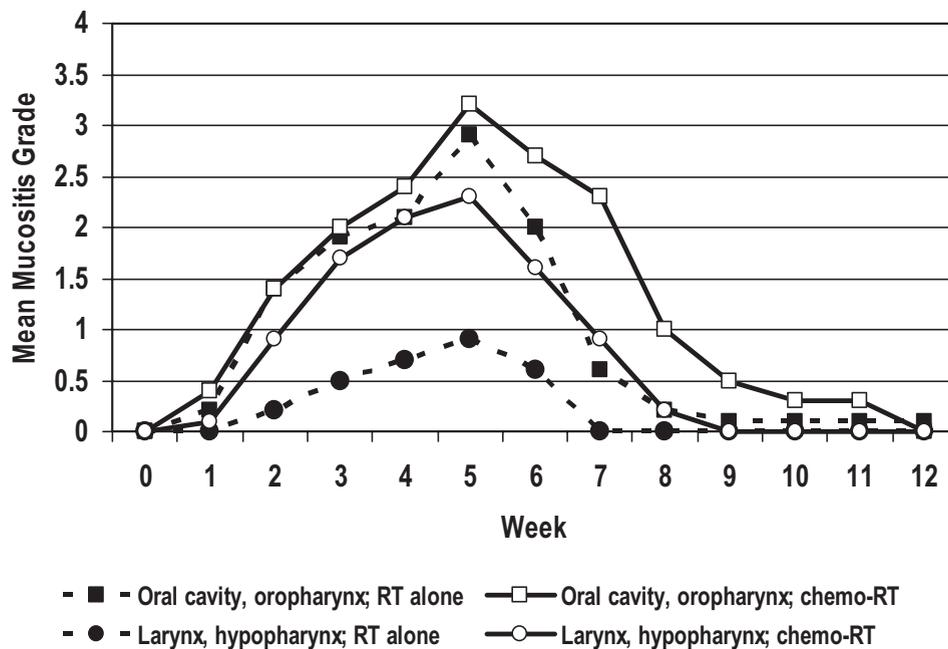
CTC V 2.0 scale 0 - 4

Fig. 1. Distribution of mean grade of mucositis during 6 weeks of radiotherapy (RT) and 6 weeks of follow-up.

Table 3. Clinical outcomes and associated symptoms among patients with and without mucositis

| | Maximum mucositis grade (CTC v. 2.0) | | | | | |
| | RT only ($n = 109$) | | | RT + chemo ($n = 95$) | | |
Clinical outcome	0 ($n = 16$)	1–2 ($n = 29$)	3–4 ($n = 64$)	0 ($n = 2$)	1–2 ($n = 22$)	3–4 ($n = 71$)
RT delay/dose reduction	0	1 (3)	5 (8)	0	0	7 (10)
Maximum oral pain score						
0	6 (38)	6 (20)	0	1	2 (9)	2 (3)
1–4	9 (56)	11 (38)	32 (50)	1	8 (36)	25 (35)
5–8	1 (6)	8 (28)	19 (30)	0	10 (46)	32 (45)
9–10	0	4 (14)	13 (20)	0	2 (9)	12 (17)
Weight loss (% of baseline)						
0	3 (19)	4 (14)	13 (20)	0	4 (18)	2 (3)
0.1–4.9	10 (62)	11 (38)	18 (28)	1	9 (41)	13 (18)
5.0–9.9	2 (13)	10 (34)	23 (36)	0	4 (18)	34 (48)
≥10	1 (6)	4 (14)	10 (16)	1	5 (23)	22 (31)
Most abnormal diet						
Normal	8 (50)	2 (7)	1 (2)	1	1 (5)	2 (3)
Soft	7 (44)	11 (38)	20 (31)	0	3 (14)	4 (6)
Liquid	0	12 (41)	21 (33)	0	10 (45)	20 (28)
NPO	1 (6)	4 (14)	22 (34)	1	8 (36)	45 (63)
Dehydration	0	6 (21)	21 (33)	1	7(33)	32 (45)
Reduced Zubrod performance status	1 (6)	9 (31)	29 (45)	1	12 (55)	41 (58)
Associated conditions						
Fever	0	0	1 (2)	0	5 (23)	18 (25)
Febrile neutropenia	0	0	0	0	0	4 (6)
Oral/esophageal fungal/viral infection	2 (13)	5 (17)	9 (14)	0	9 (41)	30 (42)
Local gastrostomy tube infection	0	0	2 (3)	0	2 (9)	4 (6)
Aspiration pneumonia	0	0	2 (3)	0	1 (5)	1 (1)
Non-oral mucositis	8 (50)	7 (24)	5 (8)	2	5 (23)	12 (17)
Xerostomia	0	2 (7)	11(17)	0	3 (14)	8 (11)

Abbreviations: CTC = Common Toxicity Criteria; RT = radiation therapy; chemo = chemotherapy; NPO = nothing by mouth.
Data are presented as number (percentage).

variable analyses. These analyses revealed that patients with oral cavity or oropharynx primaries (odds ratio [OR], 44.5; 95% CI, 5.2 to >100; $p < 0.001$), those who received chemo-RT (OR, 7.8; 95% CI, 1.5–41.6; $p = 0.02$), and those who were treated with altered fractionation schedules (OR, 6.3; 95% CI, 1.1–35.1; $p = 0.03$) were significantly more likely to develop OM, whereas the use of IMRT was not associated with higher risk ($p = 0.68$). Patients with oral cavity or oropharynx primaries (OR, 9.4; 95% CI, 4.1–21.8; $p < 0.001$), diabetes (OR, 6.6; OR, 1.3–34.1; $p = 0.02$) and those who received altered fractionation schedules (OR, 3.7; 95% CI, 1.6–8.5; $p = 0.002$) were most likely to develop Grade 3–4 mucositis.

Clinical course of OM

On average, OM persisted for almost 5 weeks and Grade 3–4 OM for more than 2 weeks. The severity of OM peaked during Week 5 of therapy, irrespective of cancer site or treatment modality; OM typically persisted through Week 7 among patients who also received chemotherapy (Fig. 1). On univariate analysis, receipt of chemotherapy ($p < 0.001$) and IMRT ($p = 0.01$) were associated with significantly longer durations of OM, as were oral cavity or oropharynx primaries ($p < 0.001$) (Table 2). Altered fractionation

schedules were not associated with longer duration of OM overall ($p = 0.68$), but were associated with significantly longer duration of Grade 3–4 OM ($p = 0.02$). This finding was supported in multivariate analyses. Factors significantly associated with an increased duration of any grade OM included chemotherapy use ($p < 0.001$) and oral cavity or oropharynx primaries ($p < 0.001$), whereas oral cavity or oropharynx primaries ($p < 0.001$) and altered fractionation schedules ($p = 0.04$) were associated with longer durations of Grade 3–4 OM.

Clinical outcomes of OM

Despite the prognostically significant differences in patient characteristics described above, there were no significant differences in outcomes between patients who received IMRT and those who received standard RT (data not shown). Therefore, the two groups were combined for outcome analysis. Considering only those patients who received RT alone, 5.5% of patients experienced a delay in RT (Table 3). The RT dose was also reduced in 1 of these patients. Radiotherapy breaks averaged 5.8 days in duration (range, 3–11 days). All but 1 of the 6 patients with delays had severe (Grade 3–4) OM. The maximum oral pain score was correlated with the maximum grade
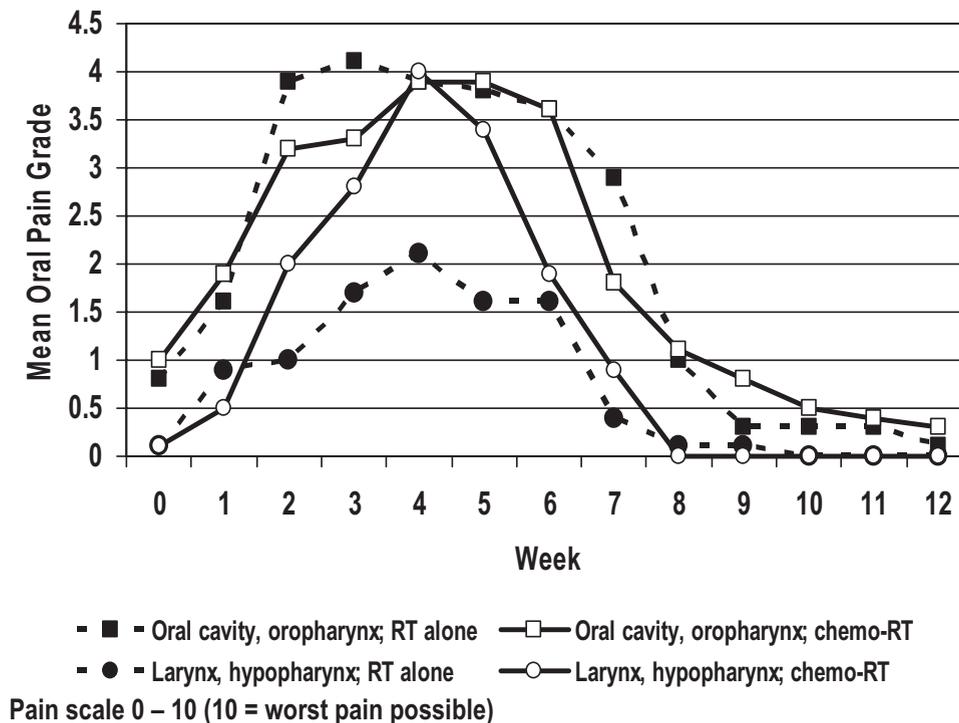
Fig. 2. Distribution of mean pain scores during 6 weeks of radiotherapy (RT) and 6 weeks of follow-up.

of OM; a higher proportion of patients with severe (Grade 3–4) OM had oral pain scores ≥5, compared with those with Grade 0–2 OM (50% vs. 29%; $p = 0.03$). Oral pain scores peaked earlier than the maximum grade of OM, between Weeks 2 and 4 of RT, depending on cancer site and treatment modality (Fig. 2). However, mean pain scores remained high through Week 6, then decreased rapidly, demonstrating a pattern very similar to that of OM. It is important to note, however, that oral pain was present among 10 of the 16 patients who did not develop OM, including 1 patient with a pain score ≥5.

Two thirds of patients (67%) with Grade 3–4 OM were unable to tolerate solid or soft diets during therapy. However, this finding was not restricted to patients with severe OM; those with Grades 0, 1, or 2 mucositis also were unable to eat in 38% of cases. The inability to eat was accompanied by significant weight loss. Forty-seven percent of patients with Grade 3–4 OM experienced a loss of ≥5 kg, compared with 22% of patients with Grade 0–2 OM ($p = 0.009$) (data not shown). Compared with Grade 0, Grade 3–4 OM doubled the risk of loss of >10% of baseline body weight (6% vs. 16%; $p = 0.30$) and tripled the risk of a loss between 5% and 10% of body weight (13% vs. 36%; $p = 0.07$) (Table 3). Local fungal and viral infections of the oral cavity and esophagus occurred in 15% of patients. None of these infections were accompanied by fever, and most were managed with oral antifungal and/or antiviral agents. Two patients (3%) developed aspiration pneumonias, and 2 developed local infections at their gastrostomy tube sites. Outcomes among patients who received chemo-RT displayed similar patterns (Table 3). Radiotherapy delays

(mean, 4.3 days; range, 3–10 days), severe oral pain, significant weight loss, reduced performance status, and inability to eat were more common among patients with Grade 3–4 OM than in those with Grade 0–2 OM. Owing to their higher risk of Grade 3–4 OM, serious clinical outcomes were more frequent among patients who received chemo-RT. Compared with those who received RT alone, severe oral pain (41% vs. 59%; $p = 0.01$), weight loss (37% vs. 56%; $p = 0.006$), reduced performance status (36% vs. 57%; $p = 0.003$), and inability to eat solid foods (55% vs. 88%; $p < 0.001$) were more common among those who received chemo-RT. Infections were more common among those who received chemo-RT than in those who received RT alone (72% vs. 18%; $p < 0.001$). In contrast to patients who received RT alone, local fungal or viral infections of the oral cavity or esophagus were accompanied by fever in 44% of cases. Overall, 24% of patients who received chemo-RT developed fever. Four of these developed fever during chemotherapy-induced neutropenia.

Considering all patients, infections were more common among diabetics than among those without diabetes (55% vs. 33%; $p = 0.04$). This difference was restricted to local infections at gastrostomy tube insertion sites, which occurred in 5 of the 20 diabetics and only 3 of the 184 nondiabetics (25% vs. 2%; $p < 0.001$).

Economic outcomes of OM

Overall, the presence of OM was associated with increased use of costly resources, such as hospital days and emergency department (ED) visits. Only 6% of patients without OM were hospitalized or visited the ED during RT,

Table 4. Resource utilization among patients with and without mucositis

| | Maximum mucositis grade (CTC v. 2.0) | | | | | |
| Resource | RT only (n = 109) | | | RT + chemo (n = 95) | | |
	0 (n = 16)	1–2 (n = 29)	3–4 (n = 64)	0 (n = 2)	1–2 (n = 22)	3–4 (n = 71)
Mean hospital days per patient	0	0.5	1.0	1.5	2.7	2.6
No. (%) hospitalized	0	4 (14)	9 (14)	1	8 (36)	24 (34)
Mean length of stay (d)	—	3.6	6.8	3.0	7.4	7.8
Mean ED visits	0.1	0.3	0.5	0	0.9	0.9
No. (%) with ED visit	1 (6)	7 (24)	21 (33)	0	10 (45)	37 (52)
Mean dental oncologist visits	0.6	1.6	2.3	0.5	1.0	1.9
No. (%) with dental oncologist visit	5 (31)	18 (62)	57 (89)	1	11 (50)	50 (70)
Mean dietician visits	1.5	3.0	3.8	5.0	4.0	4.1
No. (%) with dietician visit	9 (56)	27 (93)	62 (97)	2	21 (95)	70 (98)
Mean days using analgesics						
Opioids	15.9	27.6	28.6	14.5	33.9	34.3
Other systemic	1.0	2.4	6.4	18.5	1.0	3.3
Topical	1.7	10.9	15.9	5.0	9.5	14.8
No. (%) using analgesics						
Opioids	10 (63)	24 (83)	60 (94)	1	21 (95)	67 (94)
Other systemic	1 (6)	3 (10)	15 (23)	1	1 (5)	8 (11)
Topical	3 (19)	15 (52)	42 (66)	1	13 (59)	45 (63)
Mean days antimicrobials						
Oral	0.8	1.4	0.8	0	7.5	6.3
Intravenous	0	0.7	0.4	0	1.0	1.3
No. (%) using antimicrobials						
Oral	2 (13)	5 (17)	7 (11)	0	11 (50)	33 (46)
Intravenous	0	1 (3)	4 (6)	0	6 (27)	11 (15)
Gastrostomy tube						
Mean days during RT (all patients)	1.3	7.4	8.5	0.5	17.2	16.3
Mean duration during RT* (d)	10.5	31	22	1.0	32	24
Mean total duration* (d)	70.5	104.7	81	42	106.8	79.2
Gastrostomy tube insertion						
None	14 (88)	22 (76)	39 (61)	1	10 (45)	23 (32)
At onset	1 (6)	2 (7)	7 (11)	0	7 (32)	10 (14)
Inserted during RT†	1 (7)	5 (19)	18 (32)	1	5 (33)	38 (62)

Abbreviations: CTC = Common Toxicity Criteria; RT = radiation therapy; ED = emergency department.
* From among those with gastrostomy tube at any time during RT.
† From among those without gastrostomy tube at onset of RT.

whereas 23% of patients with OM ($p = 0.09$) were hospitalized and 40% visited the ED ($p = 0.004$).

Considering only those patients who received RT alone, resource use was related to the presence and the severity of OM (Table 4) but was unrelated to use of IMRT when compared with standard RT (data not shown). Approximately one third of patients with Grade 3–4 OM visited the ED, and half of these patients were admitted to the hospital (Table 4). Compared with patients with Grade 0–2 OM, those with Grade 3–4 OM had an increased number of visits to dental oncologists (2.3 vs. 1.2 visits; $p < 0.001$) and dieticians (3.8 vs. 2.4 visits; $p < 0.001$) and increased use of opioid analgesics (29 vs. 23 days; $p = 0.04$). Insertion of gastrostomy tubes during RT was significantly associated with OM grade, occurring in 18 of the 57 patients (32%) who did not have gastrostomy tubes at RT initiation and developed Grade 3–4 OM, compared with 6 of the 42 patients (14%) who developed Grade 0–2 OM ($p = 0.047$). Not surprisingly, gastrostomy was required during RT most

frequently among patients with Grade 3–4 OM who could not eat (47% vs. 10%; $p < 0.001$).

In contrast, among patients who received chemo-RT, there were no significant differences in resource use between patients with Grade 3–4 OM compared with those with Grade 0–2 OM (Table 4). As expected, those who received chemo-RT generally used more resources than those who received RT alone.

The increased use of resources among patients with OM led to a corresponding increase in cost, averaging approximately $1700 among patients who experienced Grade 1–2 OM and $3600 among those who developed Grade 3–4 OM. After adjustment for differences in site and stage of disease, lymph node involvement, fractionation, age, and comorbidities, the mean cost of RT alone was $14,646 (95% CI, $11,801–$18,178) among patients without OM and $20,624 (95% CI, $19,227–$22,122) among those with OM ($p = 0.006$). Among those who received chemo-RT, the costs were $28,660 (95% CI, $19,283–$42,597) and

Table 5. Total cost, in US$, of care during and 6 weeks after radiotherapy

| | Mucositis grade | | | | | |
| | IMRT | | | No IMRT | | |
Regimen	0	1–2	3–4	0	1–2	3–4
Radiotherapy alone						
During RT						
Total	—	19,450 (17,182–22,018)	21,736 (19,185–24,626)	16,206 (13,433–19,551)	18,111 (16,328–20,088)	20,239 (18,025–22,726)
Inpatient	—	1 (0–4)	2 (1–8)	1 (0–5)	1 (0–4)	2 (1–7)
Outpatient	—	18,878 (17,011–20,949)	20,100 (18,100–22,321)	16,252 (13,883–19,025)	17,304 (15,862–18,877)	18,424 (16,716–20,307)
6-wk follow-up						205 (52–812)
Total	—	108 (24–470)	394 (89–1742)	15 (2–142)	56 (16–191)	2 (1–1)
Inpatient	—	1 (0–1)	1 (1–3)	1 (0–1)	1 (0–1)	164 (41–646)
Outpatient	—	99 (22–428)	303 (69–1328)	17 (2–160)	53 (16–182)	
Chemoradiotherapy						
During RT						
Total	29,160 (23,080–36,842)	31,426 (27,410–36,031)	33,896 (30,210–37,970)	30,898 (24,641–38,744)	33,299 (29,671–37,371)	35,887 (33,263–38,719)
Inpatient	48 (1–4055)	20 (1–262)	8 (1–68)	80 (1–5544)	32 (4–276)	13 (3–54)
Outpatient	27,255 (7084–104,866)	33,339 (15,145–73,390)	40,781 (21,191–78,482)	13,003 (3580–47,228)	15,906 (8290–30,515)	19,456 (12,664–29,891)
6-wk follow-up						
Total	303 (16–5901)	893 (157–5080)	2,631 (621–11,132)	79 (5–1356)	233 (55–979)	686 (266–1768)
Inpatient	4 (0–101)	3 (1–22)	3 (1–14)	3 (0–70)	3 (1–13)	2 (1–6)
Outpatient	182 (9–3858)	549 (92–3285)	1,658 (376–7314)	48 (3–893)	145 (33–635)	438 (165–1158)

Values (US$) are given as mean (95% confidence interval). Values adjusted for site and stage of disease, lymph node involvement, radiotherapy (RT) fractionation, age, and comorbidity. Mucositis graded according to Common Toxicity Criteria v. 2.0.

$34,706 (95% CI, $32,846–$36,671), respectively, although this difference did not reach statistical significance ($p = 0.35$).

Among patients who received RT alone, the presence of Grade 1–2 OM was associated with an increase in total cost of care of approximately $1900, virtually all of which represented outpatient costs. Development of Grade 3–4 OM was associated with an incremental cost of an additional $2100–$2200 (Table 5). Among those who received chemo-RT, the incremental cost of Grade 1–2 OM was $2200–$2400 compared with those without OM. Grade 3–4 OM was associated with an additional $2400–$2500 per patient compared with Grade 1–2 OM. Follow-up costs were minimal among patients who received RT alone, although they were higher among patients who had experienced OM. These costs were somewhat higher among patients who received chemo-RT, although they were still low compared with the cost of care during RT. Despite similar resource use, IMRT was more expensive than conventional RT, irrespective of fractionation and use of chemotherapy (Table 5).

DISCUSSION

Oral mucositis is an expected complication of RT to head-and-neck tumors, although previous estimates of incidence vary widely between 50% and 90%, depending on RT field, dose, fractionation, and use of chemotherapy (1, 5, 10–13). There are few descriptions of the clinical and economic outcomes of OM in this population, particularly among patients who receive chemo-RT, IMRT, and altered fractionation (1, 5). Therefore, we examined the risk of OM and its outcomes and cost among newly diagnosed patients who were treated in 2002.

There are a number of limitations of this study, which should be considered before interpreting the results. First, complete ascertainment of events is a major concern in any retrospective study. We limited the study to patients who received all care at our institution to eliminate incomplete ascertainment caused by care delivered by other providers. We also used multiple data sources to improve ascertainment, including paper and electronic medical records, billing records, and the tumor registry and Division of Radiation Oncology Database. We found that ascertainment of the presence of OM was improved substantially by including review of nursing, dental oncology, and dietician records. After incorporation of data from these sources, we can say with confidence that Grade 0 OM reflected a clear statement that OM was not present rather than the absence of information. In contrast, patients may not have been rigorously examined for nonoral mucositis, particularly laryngeal mucositis. We reported nonoral mucositis when it was documented; however, the low incidence of oral and nonoral mucositis among patients with laryngeal primaries should not be construed to reflect a similar absence of laryngeal mucositis.

Second, studies conducted in a single institution may suffer from poor generalizability, particularly in the case of a referral institution. To evaluate this source of bias, we compared the characteristics of our patients to those of newly diagnosed patients in the Surveillance Epidemiology and End Results (SEER) database for the same time period. We found that our patients were generally similar, with the following exceptions. Our patients were significantly younger than those in SEER (56 vs. 60 years), more likely to have nodal involvement (70% vs. 44%), and less likely to have distant metastases (0 vs. 12%). We do not believe that the difference in age is large enough to invalidate our findings. Furthermore, we intentionally excluded patients who received only palliative RT to produce a homogeneous population for risk estimation, hence the disparity in frequency of distant metastases. Although we do not view this as a flaw, it is important to remember that our results apply only to patients who receive RT with curative intent. In contrast, the difference in nodal involvement is clinically important because it reflects larger RT fields, which probably increase the risk or severity of OM. Indeed, the presence of nodal involvement was so strongly associated with increased risk of OM in our analysis (OR, 21.0; 95% CI, 2.4–102.7; $p = 0.007$) that we adjusted for this factor in all multivariate analyses. To the degree that our patients differ from those in the community with respect to nodal involvement, we may have overestimated the risk of OM and its clinical and economic outcomes that would be experienced in the general population.

Other possible sources of bias also should be considered. First, concomitant boost was used in altered-fraction regimens rather than hyperfractionation schedules. Although the incidence of mucosal toxicity has been shown to be similar in concomitant boost and hyperfractionation schedules (8, 9), it is possible that the timing, clinical course, or duration might vary depending on the altered schedule chosen. Second, the study was conducted in an academic research institution. It is possible that delays and dose reductions were less frequent in our study owing to a more aggressive approach to therapy. Although it is difficult to measure approach to therapy, the high rate of delays (20–60%, depending on severity of OM) seen in a previous community-based study supports this notion (13). Third, although we limited the study to patients who received all their care during RT and completed scheduled follow-up visits at our institution, some received additional follow-up care from referring physicians. We were unable to collect resource use information from referring physicians. Thus, we may have underestimated the total resource use and cost for the follow-up period, particularly for the 21% of patients from other states. Finally, hospitalization for management of all but the most life-threatening complications is strongly influenced by the available capacity of the hospital. Our hospital operated at maximum capacity during this period. Thus, it is possible that we underestimated the frequency of hospitalization that would be seen in the community, as well as the cost of care, owing to the short supply of hospital beds.

OM is common among recipients of RT to head-and-neck primaries

Few patients in our study escaped OM. It developed in more than 90% of recipients of head-and-neck RT and was considered severe in more than 60% of them. This finding is not unique; most trials of modern, accelerated regimens, particularly those that include chemotherapy, report rates exceeding 50% (10, 14). The consistency of these findings substantiates the clinical significance of this problem.

OM is associated with serious clinical outcomes and increased resource use

The association between OM and pain, inability to eat, and weight loss is biologically and temporally plausible. It comes as no surprise that similar observations have been made in the past (3, 10, 15–17). However, it is likely that other factors also contribute to these outcomes, particularly symptoms of the primary cancer and other treatment modalities, such as chemotherapy. This notion is supported by the pain, weight loss, and reduced performance status observed occasionally among patients without OM in our study, as well as the resource use that accompanied those symptoms.

The link between OM and infection is also plausible owing to damage to mucosal barriers, requirement for feeding tubes, and aspiration caused by difficulty swallowing. Significant associations between bacteremia and OM among neutropenic patients have been reported previously (18–20). However, in the head-and-neck RT setting, the association remains unclear. In our study, antibiotic use was significantly higher among patients with OM (42%) than among those without OM (11%; $p = 0.01$). However, compared with patients with Grade 1–2 OM, antibiotic use was no greater among patients with Grade 3–4 OM, in whom interruption of the oral mucosa would be expected to facilitate colonization and infection (45% vs. 41%; $p = 0.59$). This finding suggests that factors other than the grade of OM also may influence fever and antibiotic use.

There is a growing literature to support our observations. Cancer patients' symptoms (*e.g.*, fever, anorexia, weight loss, fatigue) are known to occur in clusters (21–24). The mechanism for this clustering is a common, cytokine-mediated pathobiologic response to exposure to a damaging agent (*i.e.*, chemotherapy, RT, bacterial colonization, or cancer), a model based on the biology of the "sickness behaviors" noted in all animal species (21–23, 25). The pathobiology of mucositis has been modeled similarly by Sonis, who describes upregulation of genes that control production of pro-inflammatory cytokines (14, 26). These cytokines result in damage to the mucosa, which permits invasion by bacteria and further activation of cytokines. This shared, cytokine-mediated response to insult provides a biologic explanation for the clinically observed clustering of common symptoms and suggests a pathway for development of effective preventive and therapeutic interventions. It also suggests a possible genetic explanation for the between-patient variability in severity of symptoms, namely genetic differences in susceptibility to cytokine expression. These are certainly intriguing areas for future research.

OM is associated with increased costs

The increased resource use observed in patients with OM causes a corresponding increase in costs. We found that OM was associated with an incremental cost of $1,700–$6,000, depending on grade of OM. These findings are similar to those of Peterman *et al.* (27), who observed an incremental cost of approximately $3,000 per patient in 1996, with higher costs among patients with more severe mucositis. These also are comparable to the incremental costs previously observed during myelosuppressive chemotherapy of $2,700 to $5,600 per cycle (28). Taken together, these findings point to a significant cost of OM and to the potential value of interventions to prevent or minimize OM.

Given the clustering of OM with other symptoms, however, it is unclear whether decreased incidence or severity of OM would lead to corresponding reductions in costs. If these symptoms share a common pathobiology, interruption of that process by a preventive intervention would be expected to alter the incidence and outcomes of all symptoms in the cluster, as well as their associated costs. However, in the absence of a mechanistically based intervention, it is conceivable that OM could be eliminated, but the associated fever, weight loss, reduced performance status, and fatigue could continue unabated, along with their associated costs. Therefore, although it is clear that OM is associated with increased costs, it is not clear that eliminating OM would result in decreased costs. This logic again exposes the potential economic value of mechanistically based interventions, as well as the potential to target these interventions to patients with genetic profiles that predict increased cytokine response.

CONCLUSIONS

We have provided strong evidence that OM occurs in virtually all recipients of RT to head-and-neck primaries, particularly those who have oral cavity or oropharynx primaries and those who receive chemo-RT. Oral mucositis is associated with an increased risk of severe oral pain, decreased performance status, inability to eat, and weight loss, as well as increased resource use and an incremental cost of approximately $6,000. We anxiously await the development of new mechanistically based interventions to prevent and treat this clinically and economically important condition.

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