Original Article

Mucositis-Related Morbidity and Resource Utilization in Head and Neck Cancer Patients Receiving Radiation Therapy With or Without Chemotherapy

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Abstract

The objective of this study was to estimate health care-resource utilization in head and neck cancer (HNC) patients. This was a prospective, longitudinal, multicenter, noninterventional study of mucositis in patients receiving radiation with or without chemotherapy for HNC. Mouth and throat soreness and functional impairment were measured using the Oral Mucositis Weekly Questionnaire-HNC. Resource utilization data were obtained from patient interviews and recorded from the patient's medical chart. Seventy-five patients were enrolled from six centers. Fifty (67%) patients received concurrent chemoradiation therapy; 34 (45%) received intensity-modulated radiation therapy. Over the course of treatment, 57 (76%) patients reported severe mouth and throat soreness. Pain and functional impairment because of mouth and throat soreness increased during the course of therapy despite the use of opioid analgesics in 64 (85%) of the patients. Complications of radiation therapy resulted in increased patient visits to physicians, nurses, and nutritionists. Thirty-eight (51%) patients had a feeding tube placed. Twenty-eight patients (37%) were hospitalized, five of whom were hospitalized twice; of the 33 admissions, 10 (30%) were designated as secondary to mucositis by their treating physician. Mean length of hospitalization was 4.9 days (range: 1–16). This study demonstrates that mucositis-related pain and functional impairment is associated with increased use of costly health resources. Effective treatments to reduce the pain and functional impairment of oral mucositis are needed in this patient population. J Pain Symptom Manage 2009;38:522–532.

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Key Words
Head and neck cancer, mucositis, patient-reported outcomes, functional impairment, nutrition, hospitalization, resource utilization

Introduction

Mucositis is a debilitating, almost universal complication of radiation therapy (RT) or concurrent chemoradiation (CCR) for head and neck cancer (HNC) and presents a formidable obstacle for delivering aggressive, curative-intent therapy.[1] Given the severity of this toxicity, comparatively little data about its symptom and functional sequelae or economic impact are available. In bone marrow transplantation, where the effects of mucositis have been assessed with greater rigor, mucositis has been associated with worse clinical and economic outcomes, including increased risk of infection, prolonged total parenteral nutrition, intravenous opioid administration, and hospitalization.[2] The paucity of similar data in patients with HNC stems from inadequate toxicity reporting, the lack of validated patient-reported outcomes (PROs) for mucositis and its sequelae, and the scarcity of trials designed to capture supportive and economic outcome data.[3]

In a systematic literature review of 33 randomized clinical trials of HNC,[4] only three studies reported oral pain, four reported dysphagia, one reported opioid use, three reported feeding-tube placement, and three reported mucositis-related hospitalization. Although mucositis grade is documented in most randomized clinical treatment trials involving RT, the data generally are reported only as the worst grade of toxicity. The duration of mucositis, its associated symptom burden, and its effects on patient function are rarely documented unless the study specifically investigates a mucosal protective agent. Thus, comparison of toxicities because of treatment-related factors, such as chemotherapy regimen or radiation techniques, is difficult at best.

The lack of validated PROs for mucositis-related symptoms and function loss compounds the problem. Gross measures of function, such as the presence of a feeding tube during and after treatment, often are used as surrogates of functional assessment. The Functional Assessment of Cancer Therapy-Head and Neck Scale[5] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35[6] modules are commonly used to assess function in patients with HNC, but these modules were not developed to target mucositis and its sequelae. When used in clinical trials, they often are administered at infrequent intervals, thus providing insufficient data to compare the symptom burden of various treatment regimens. Finally, there has been little systematic investigation of the effects of mucositis on resource utilization.

A PRO that is designed to assess the acute and late effects of mucositis would address many of the issues outlined earlier. We performed a prospective, longitudinal, multicenter, observational study of the validity, reliability, and feasibility of the Oral Mucositis Weekly Questionnaire-HNC (OMWQ-HN), a PRO questionnaire for the assessment of mucositis. In the primary analysis of that study,[7] the OMWQ-HN was demonstrated to be a valid and reliable tool to assess mucositis-related pain and function loss. A secondary objective of the study was to estimate health resource utilization in HNC patients as they relate to mucositis sequelae; the results of the secondary analyses are presented here.

Patients and Methods

Patient Eligibility

Patients were recruited from six centers in the United States. Eligibility criteria included the following: 1) histologically confirmed carcinoma of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx, or neck disease of unknown origin; 2) radiotherapy with or without chemotherapy as either primary or postoperative therapy; 3) at least 18 years of age; and 4) ability to read English. No restrictions were made based on histopathology. Patients who had received prior RT

to the head and neck were not included on this study. The treating physician determined the treatment plan, including RT dose and schedule, chemotherapy dosing and schedule, and use of supportive measures, such as feeding-tube placement, intravenous hydration, and opioid administration. Patients receiving an investigational agent for mucositis were excluded. Written informed consent was obtained, and the protocol was approved by institutional review boards of participating institutions.

Study Procedures

The study was six weeks in duration, beginning with the initiation of RT. Demographic and clinical characteristics recorded at baseline included sex, age, primary tumor site and stage, scheduled RT, and Karnofsky scores. The OMWQ-HN was administered once at baseline and Week 2, twice during Week 4 (24–48 hours apart), and once at Week 6 or the end of treatment (whichever came first). The OMWQ-HN uses 5-point scales (0 = none to 4 = extreme) to quantify the degree of mouth and throat soreness (MTS) and associated limitations of swallowing, drinking, eating, talking, sleeping, and brushing teeth. Other items use 7-point scales to quantify overall health and quality of life, and scales from 0 (no pain/soreness) to 10 (worst possible pain/soreness) to quantify the severity of MTS, mouth pain, and throat pain.

The following resource utilization data were collected from the patient's chart at the end of Weeks 2, 4, and 6, or at the time of early discontinuation: opioid analgesic use, prescription nonsteroidal anti-inflammatory drug (NSAID) use, feeding-tube placement, and use of total parenteral nutrition (TPN). Hospitalization during the previous two weeks was recorded and the reason for hospitalization was categorized as related or unrelated to mucositis. The study coordinator interviewed the patient biweekly at the end of Weeks 2, 4, and 6, and recorded the number of visits in the previous two weeks to physicians, nurses, and nutritionists; the number of extra (unscheduled) visits; and the primary reason for any extra visits (management of pain, hydration/nutrition difficulties, other complications of treatment, or other).

Statistical Analysis

Baseline demographic and clinical characteristics were summarized using percents, means, and standard deviations. The percentages of patients with severe MTS, functional impairments, opioid use, NSAID use, and feeding-tube placement were calculated for the overall sample and for groups of patients defined by treatment type, opioid use, or degree of MTS. Reasons for opioid analgesic or NSAID use and for feeding-tube placement were summarized. Using the approach validated by Epstein et al.,[7] all OMWQ-HN item responses except overall health, overall QOL, and limits brushing teeth were summed to create an OMWQ-HN score, where a higher score represented worse symptom burden. OMWQ-HN scores were compared between patients taking and not taking opioid analgesics at each assessment using two-sample *t*-tests. General linear models for longitudinal data were used to evaluate change over time in MTS. The relationship was evaluated between maximum patient-reported MTS during the study and the following: hospitalization days (analysis of variance [ANOVA]), nonprophylactic feeding-tube placement (Chi-square), TPN days (Kruskal-Wallis) and nutritionist visits (ANOVA). The extent and reasons for hospitalizations and health care provider visits were tabulated. The proportion of patients reporting severe MTS and function loss was compared between those receiving intensity-modulated radiation therapy (IMRT) vs. other RT using Fisher's exact test. SAS v9.1 (SAS Institute, Inc., Cary, NC) was used for all analyses.

Results

Study Population

The study was conducted from March through September 2004. Seventy-five patients were enrolled. Seven (9%) patients withdrew before completing the six-week study, including four after Week 2 and three after Week 4. Reasons for withdrawal were death ($n = 1$), hospitalization ($n = 1$), patient refusal ($n = 1$), and other/reason not specified ($n = 4$). Baseline patient demographic and clinical characteristics are shown in Table 1. Sixty-eight (91%) patients were treated with once-daily fractionation, including 34 (45%) patients who were treated with IMRT. Seven

Table 1
Patient Characteristics

Characteristics	No. of Patients	%
Sex		
Male	61	81
Female	14	19
Age (years)		
Mean (SD)	58.8 (10.2)	
Range	40–86	
Region of primary tumor		
Oral cavity	17	23
Oropharynx	28	37
Hypopharynx	6	8
Nasopharynx	3	4
Larynx	17	23
Unknown	4	5
Stage at diagnosis		
I	2	3
II	8	11
III	12	16
IVA	35	47
IVB	6	8
IVC	2	3
Unknown	10	13
Scheduled treatment[a]		
Intensity-modulated radiation therapy	34	45
Conventional radiotherapy	34	45
Concomitant boost	7	9
Induction chemotherapy	10	13
Concurrent chemoradiation	50	67
Karnofsky Performance Status		
<80	6	8
80	11	15
90	30	40
100	28	37

SD = standard deviation.
[a]Does not sum to 100% because patients may have received more than one type of treatment.

(9%) patients were treated with concomitant boost (CB) fractionation. Fifty (67%) patients were treated with CCR.

Mucositis Sequelae

Pain. A total of 57 (76%) patients (95% confidence interval [CI]: 65%–85%) reported severe MTS (i.e., "quite a lot" or "extreme" on the 5-point scale) at any time during the study. The percentage of patients reporting severe MTS increased significantly over time ($P < 0.001$ overall), from 36% to 55% and 60% during Weeks 1–2, 3–4, and 5–6, respectively. The rates of severe pain were not significantly different ($P = 0.175$) between patients receiving IMRT (68%) and patients receiving conventional RT or CB (83%) (Fig. 1).

Function Loss. Patients also reported high degrees of functional impairment as a result of MTS (Table 2). The degree of functional impairment increased over time despite increased use of opioids. During Weeks 1–2 of RT, 38% of patients reported severe impairment of swallowing (i.e., "limited a lot" or "unable to do") because of MTS; of these patients, 67% were taking opioids for MTS. By Weeks 5–6 of RT, the percentage of patients who reported severe difficulty swallowing had increased to 59%, of whom 84% were taking opioids for MTS. Similar results were found for eating, drinking, and talking. Function loss was similar between patients treated with IMRT and those treated with non-IMRT techniques (Table 2).

Resource Utilization

Analgesic Use. Sixty-four (85%) patients (95% CI: 75%–92%) were prescribed opioid analgesics at least once during the study, with 78% of all opioid prescriptions specifically for mouth and throat pain, and 18% for skin burn/irritation or other reasons alone or in combination with mouth and throat pain. The reason for opioid use was not recorded for the remaining 4% of prescriptions. Thirteen (17%) patients were prescribed prescription NSAIDs. Prescription NSAID use was highest during Weeks 1–2, when 12 (16%) patients were prescribed these medications.

Opioid route of administration changed over the six-week study period (Fig. 2a). During Weeks 1–2 of RT, 76% of opioids prescribed were in oral form alone, 18% were oral plus transdermal, and the route was not specified for 6%; no opioids were prescribed in parenteral form during Weeks 1–2. By Weeks 5–6, 52% of opioids prescribed were in oral form alone, 34% were oral plus transdermal, 8% were transdermal alone, and 6% were intravenous or subcutaneous (alone or combined with other routes). Hydrocodone, fentanyl, and morphine were the three most commonly prescribed opioids. Nearly two-thirds (64%) of patients received combinations of opioids.

The percentage of patients who reported severe pain while taking opioids increased from 25% during Weeks 1–2 to 51% during Weeks 5–6 (Fig. 2b). The degree of functional

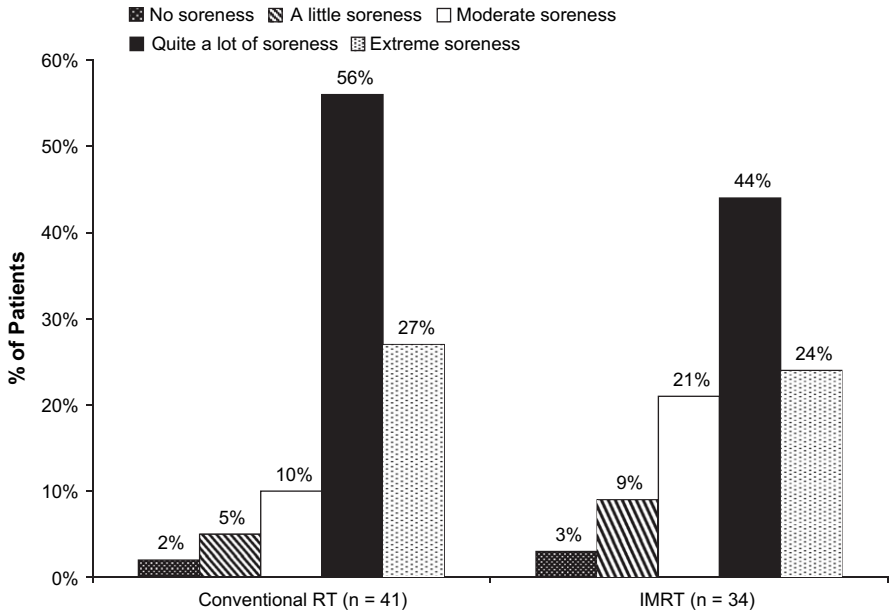

Fig. 1. Maximum severity of mouth and throat soreness by type of radiation therapy. The rates of severe pain were not significantly different ($P = 0.175$ by Fisher's exact test) with regard to radiation technique. Conventional RT = conventional RT ± CB.

impairment also increased over time despite increased use of opioid analgesics (Fig. 2c).

Nutritional Support. Feeding tubes were placed a total of 41 times in 38 (51%) patients (95% CI: 39%–62%) at any time during the study. Many feeding tubes were placed prophylactically at baseline ($n = 23$). The remaining feeding tubes were placed at Weeks 1–2 ($n = 6$), 3–4 ($n = 5$), and 5–6 ($n = 7$). Three patients received parenteral nutrition (one during Weeks 3–4 and two during Weeks 5–6). The average duration of parenteral nutrition in these patients was eight days (range: 3–14).

Health Care Provider Visits. On average, patients had regular visits to a radiation oncologist 5.9 times (once per week), a radiation oncology nurse 8.0 times (1.3 times per week), and a nutritionist 2.4 times (once every 2.5 weeks). Patients required a mean of 0.5 and 0.4 additional visits to the radiation oncologist and nurse, respectively, during the six-week study. Most extra visits to the radiation oncologist and nurse occurred during Weeks 3–4; eight (11%) patients made extra visits to these health care providers during this time. The most common reasons for extra visits to the physician or nurse were management of pain or other complications of treatment (Table 3). There were 0.3 mean additional visits to a nutritionist; most extra visits to a nutritionist occurred during Weeks 5–6, and all were for management of hydration/nutrition difficulties.

Hospitalization. A total of 28 (37%; 95% CI: 26%–49%) patients were hospitalized at least once during the study. A total of 33 hospitalizations occurred during the course of the study: six during Weeks 1–2; 14 during Weeks 3–4; and 13 during Weeks 5–6. The primary reasons for hospitalization were categorized as mucositis or decreased oral intake ($n = 7$), acute renal failure ($n = 5$), miscellaneous medical conditions ($n = 4$), percutaneous endoscopic gastrostomy (PEG)-related ($n = 3$), nausea/vomiting ($n = 3$), respiratory disorders ($n = 3$), dehydration ($n = 2$), infection ($n = 2$), and unknown ($n = 4$).

Of the 33 admissions, health care providers considered 10 (30%) to result directly from mucositis. The proportion of hospitalizations considered to result from mucositis increased over time (Fig. 3). The most common admission (ICD-9-CM) code related to mucositis was 787 (symptoms involving digestive system). Verbatim reasons noted on the case-report

Table 2
OMWQ-HN Scores According to Radiation Therapy

	Baseline, *n* (%)			Weeks 5–6, *n* (%)		
OMWQ-HN Item	All RT (*n* = 75)	Conventional RT (*n* = 41)	IMRT (*n* = 34)	All RT (*n* = 63)	Conventional RT (*n* = 33)	IMRT (*n* = 30)
Sleeping						
Not limited	52 (69.3)	23 (56.1)	29 (85.3)	18 (28.6)	7 (21.2)	11 (36.7)
Limited a little	8 (10.7)	6 (14.6)	2 (5.9)	10 (15.9)	5 (15.2)	5 (16.7)
Limited some	11 (14.7)	9 (22.0)	2 (5.9)	18 (28.6)	13 (39.4)	5 (16.7)
Limited a lot	4 (5.3)	3 (7.3)	1 (2.9)	16 (25.4)	7 (21.2)	9 (30.0)
Unable to do	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (3.0)	0 (0.0)
Swallowing						
Not limited	46 (61.3)	21 (51.2)	25 (73.5)	5 (7.9)	2 (6.1)	3 (10.0)
Limited a little	10 (13.3)	5 (12.2)	5 (14.7)	7 (11.1)	5 (15.2)	2 (6.7)
Limited some	9 (12.0)	8 (19.5)	1 (2.9)	14 (22.2)	6 (18.2)	8 (26.7)
Limited a lot	9 (12.0)	6 (14.6)	3 (8.8)	31 (49.2)	15 (45.5)	16 (53.3)
Unable to do	1 (1.3)	1 (2.4)	0 (0.0)	6 (9.5)	5 (15.2)	1 (3.3)
Drinking						
Not limited	52 (69.3)	23 (56.1)	29 (85.3)	7 (11.1)	2 (6.1)	5 (16.7)
Limited a little	9 (12.0)	7 (17.1)	2 (5.9)	8 (12.7)	4 (12.1)	4 (13.3)
Limited some	8 (10.7)	6 (14.6)	2 (5.9)	15 (23.8)	9 (27.3)	6 (20.0)
Limited a lot	5 (6.7)	4 (9.8)	1 (2.9)	26 (41.3)	12 (36.4)	14 (46.7)
Unable to do	1 (1.3)	1 (2.4)	0 (0.0)	7 (11.1)	6 (18.2)	1 (3.3)
Eating						
Not limited	48 (64.0)	22 (53.7)	26 (76.5)	8 (12.7)	4 (12.1)	4 (13.3)
Limited a little	11 (14.7)	7 (17.1)	4 (11.8)	1 (1.6)	0 (0.0)	1 (3.3)
Limited some	6 (8.0)	5 (12.2)	1 (2.9)	8 (12.7)	6 (18.2)	2 (6.7)
Limited a lot	9 (12.0)	6 (14.6)	3 (8.8)	26 (41.3)	9 (27.3)	17 (56.7)
Unable to do	1 (1.3)	1 (2.4)	0 (0.0)	20 (31.7)	14 (42.4)	6 (20.0)
Talking						
Not limited	47 (62.7)	19 (46.3)	28 (82.4)	9 (14.3)	3 (9.1)	6 (20.0)
Limited a little	11 (14.7)	8 (19.5)	3 (8.8)	10 (15.9)	5 (15.2)	5 (16.7)
Limited some	9 (12.0)	8 (19.5)	1 (2.9)	16 (25.4)	8 (24.2)	8 (26.7)
Limited a lot	7 (9.3)	6 (14.6)	1 (2.9)	24 (38.1)	13 (39.4)	11 (36.7)
Unable to do	1 (1.3)	0 (0.0)	1 (2.9)	4 (6.3)	4 (12.1)	0 (0.0)

Conventional RT = conventional RT ± CB.

form for admissions included "dehydration," "unable to swallow because too painful," "odynophagia/mild dehydration/uncontrolled pain," and "decreased (oral) intake and increasing odynophagia." Among hospitalized patients, mean length of stay was 4.9 days (range: 1–16, standard error: 0.72). The mean length of stay was three days for hospitalized patients with a maximum MTS score of "none" and 5.2 days for hospitalized patients with a maximum MTS score of "quite a lot" or "extreme."

Association Between Resource Utilization and Mucositis Severity

Table 4 summarizes the relationship between the maximum severity of MTS during the study and resource utilization, including hospitalization days, incidence of nonprophylactic feeding-tube use, days of parenteral nutrition, and number of nutritional visits. Higher maximum MTS scores were associated with greater resource use compared with lower maximum pain scores, including a statistically significant association with nutritional visits ($P < 0.029$) and with nonprophylactic feeding-tube use ($P < 0.048$).

Discussion

The present study describes the substantial symptom burden and functional sequelae of radiation-induced mucositis and the resulting use of costly health care resources in HNC patients with locally advanced disease. The most notable symptom associated with mucositis is pain. The OMWQ-HN is a validated instrument that assesses mucositis-associated mouth and throat pain, as well as its impact on function and overall well-being.[7] As expected, the results of our study demonstrate

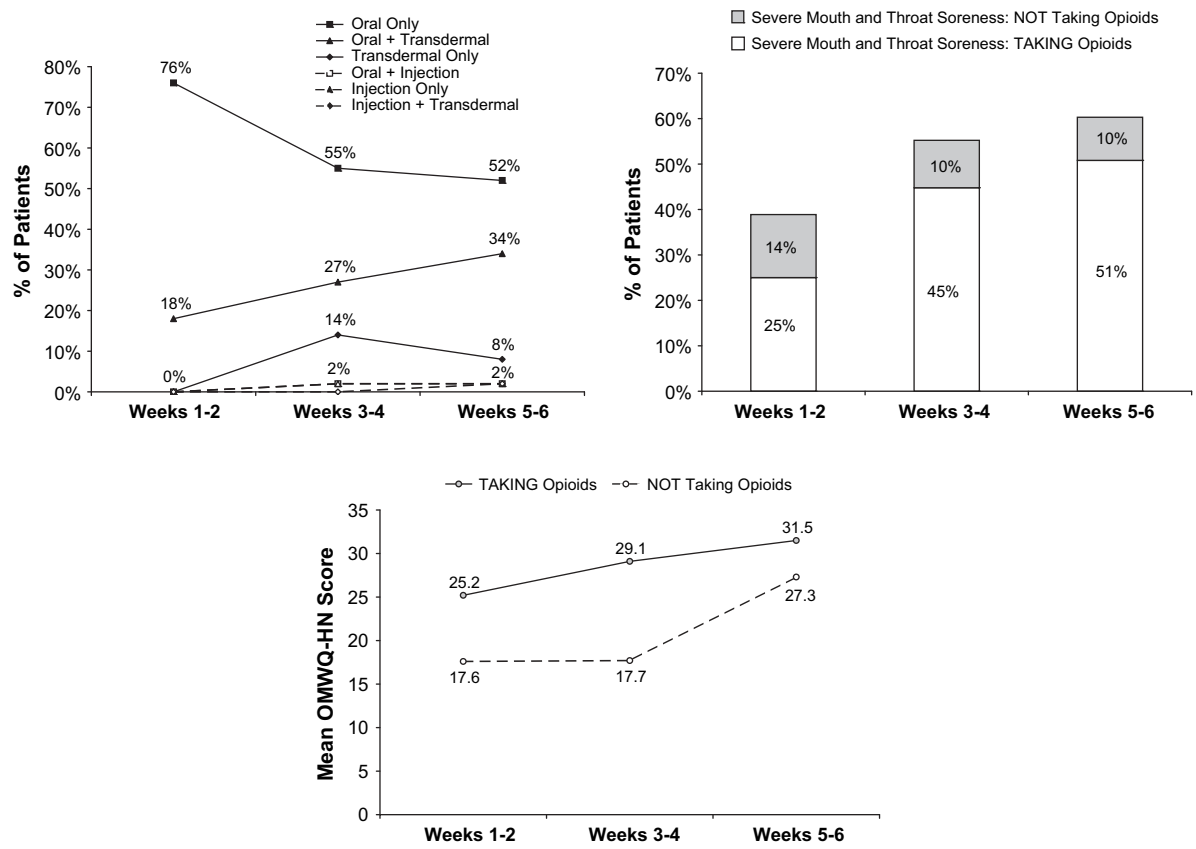

Fig. 2. Opioid use. a) Route of administration. b) Severity of mouth and throat soreness over time, according to opioid use. The overall test for the effect of time was statistically significant ($P < 0.001$ by general linear model). Changes in mouth and throat soreness at each time point compared with baseline were also statistically significant ($P < 0.001$ by general linear model). c) Mean OMWQ-HN scores over time, according to opioid use. Scores among patients taking opioids were significantly greater than those among patients not taking opioids at Weeks 1–2 ($P = 0.025$) and 3–4 ($P = 0.001$), and were not significantly different at Weeks 5–6 ($P = 0.256$).

that the percentage of patients with severe pain related to radiation-induced mucositis increased over time, with 39% and 60% of patients reporting severe pain during Weeks 1–2 and 5–6, respectively. Most patients (85%) received opioid therapy during the study, but pain remained poorly controlled in opioid-treated patients. This supports previous reports that mucositis-induced pain is difficult to control with systemic analgesic therapy.[8]

Mouth and throat pain may result in marked function loss. Initially, patients shift from solid food to nutritional supplements. Progressive pain complicated by increased mucous production, dry mouth, altered taste, and tissue edema may result in unintentional weight loss because of decreased oral intake of food and medications. Our results show that increasing pain was associated with severe limitations of drinking and eating.

Patients who are unable to swallow sufficient calories to maintain adequate caloric intake require a feeding tube. In our study, 51% of patients had one or more feeding tubes placed at some point in their therapy. Twenty-three (31%) patients received a feeding tube prophylactically, whereas another 18 feeding tubes were placed during therapy as a result of treatment-related alterations in oral intake. We noted a significant association between the severity of MTS and the use of nonprophylactic feeding tubes. Furthermore, patients with severe pain were significantly more likely than those with milder pain to require nutritional visits.

As oral intake decreased secondary to progressively worse mucositis, the pattern of

Table 3
Additional Visits to Health Professionals

Reason for Visit	Weeks 1–2 ($n=69$)	Weeks 3–4 ($n=65$)	Weeks 5–6 ($n=57$)
Any extra physician visit	6 (8.7)	7 (10.8)	2 (3.5)
Pain management	1 (1.4)	2 (3.1)	2 (3.5)
Other complications	1 (1.4)	4 (6.2)	0
Other	3 (4.3)	1 (1.5)	0
Not available	1 (1.4)	0	0
Any extra nurse visit	6 (8.7)	7 (10.8)	4 (7.0)
Pain management	2 (2.9)	3 (4.6)	1 (1.8)
Hydration/nutrition	0	1 (1.5)	2 (3.5)
Other complications	0	2 (3.1)	1 (1.8)
Other	3 (4.3)	1 (1.5)	0
Not available	1 (1.4)	0	0
Any extra nutrition visit	3 (4.3)	4 (6.2)	5 (8.8)
Hydration/nutrition	3 (4.3)	4 (6.2)	5 (8.8)

opioid use shifted from predominantly oral formulations toward the use of transdermal and parenteral formulations. Transdermal and parenteral formulations are associated with marked increase in cost when compared with oral formulations, thus adding to cost of therapy.

Because of the frequency and severity of radiation-induced acute toxicities, health care providers usually see HNC patients on a frequent basis during therapy. This allows the timely identification and management of treatment-related toxicities. The frequency of health care provider visits was not specified in the protocol for this study; however, patients at all sites were scheduled to see both the treating physician and the nurse on a weekly basis. Nutritional assessments were also conducted on a frequent basis (average of 2.5 times over the six-week course of the study). Despite the high frequency with which patients were scheduled to be evaluated, 11% of patients required unplanned visits for the management of pain, hydration, nutrition, or other complications of therapy. This represents a significant commitment of health care provider time for the care of this patient population.

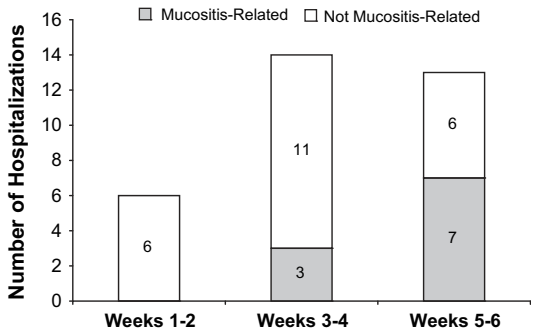

Fig. 3. Hospitalizations and their relationship with mucositis.

Impaired swallowing may result in a number of complications that require aggressive medical intervention and hospitalization. Most notably, patients require admission for placement of a feeding tube because of decreased oral intake; however, patients may also be admitted for complications stemming from altered swallowing function. For example, patients may develop pulmonary complications, such as aspiration pneumonia with respiratory compromise. Dysphagia may also result in decreased fluid intake, dehydration, and the need for IV fluids. Failure to adequately hydrate patients may lead to renal insufficiency.

Patients with mucositis-related sequelae are generally admitted under the diagnosis of the sequela, not mucositis itself. Furthermore, most admissions are related to the aggregate insult of multiple factors. Thus, it can be challenging to determine whether any single admission is attributable, as a whole or in part, to mucositis. In our study, 37% of patients were hospitalized at least once during the six-week study, and investigators considered 30% of these hospitalizations to be directly attributed to oral mucositis. However, in review of the data, mucositis may have played a role in a substantially higher number of admissions. Five patients had acute renal failure and two had dehydration; decreased oral intake because of painful mucositis may

Table 4
Resource Utilization According to Maximum Mouth and Throat Soreness Pain Score

Maximum Pain Score	Total (Mean) Length of Hospitalization (Days)	Nonprophylactic Feeding Tube (No. [%] of Subjects)	Total (Mean) Parenteral Nutrition (Days)	Total (Mean) Nutritional Visits
0: None ($n=2$)	3 (1.5)	0 (0)	0 (0)	4 (2.0)
1: A little ($n=5$)	5 (1.0)	0 (0)	0 (0)	8 (1.6)
2: Moderate ($n=11$)	13 (1.2)	1 (9)	0 (0)	20 (1.8)
3: Quite a lot ($n=38$)	62 (1.6)	10 (26)	3 (0.1)	93 (2.4)
4: Extreme ($n=19$)	43 (2.3)	6 (32)	22 (1.2)	69 (3.6)
P-value: 0–2 vs. 3 vs. 4	0.573[a]	0.048[b]	0.211[c]	0.029[a]

[a]ANOVA.
[b]Chi-square test for ordinal data.
[c]Kruskal-Wallis test.

have contributed, at least in part, to the severity of the renal insufficiency and dehydration. In addition, three patients were admitted for PEG-related issues. Although the primary reason was not mucositis, PEG tubes are placed to ensure adequate intake either in anticipation or as a result of mucositis. Finally, mucositis may result in altered swallow function and an increased risk for aspiration and its associated sequelae. Thus, the vast majority of admissions were either directly or indirectly related to mucositis.

There are numerous treatment-related factors that may impact the incidence and severity of mucositis and mucositis-related toxicities, including baseline function, tumor stage, primary site, the use of concurrent chemotherapy, and the intensity of concurrent chemotherapy.[9] In addition, RT parameters, such as technique, target volume, and radiation dose significantly impact the rates of mucositis and function loss.[10] Recently, IMRT has become a commonly used technique for HNC patients. Although the studies are generally small, the data indicate that IMRT is associated with decreased xerostomia because of salivary gland sparing. Data regarding other radiation-related symptoms are limited. We therefore analyzed the data to determine whether there was any indication that IMRT was associated with greater or lesser degrees of mucositis-related symptoms. In this study, there was no statistically significant difference in pain and function scores between patients treated with non-IMRT techniques vs. those treated with IMRT. Such a comparison must be seen as hypothesis generating, not as conclusive evidence of the comparability of mucositis between non-IMRT and IMRT, because the study was not adequately powered to make such comparisons. However, similar findings have been supported by others in preliminary studies of IMRT for HNC.[11–13]

The present study was not designed to evaluate costs directly, but resource utilization data revealed that 37% of patients were admitted to the hospital, and 30% of these admissions were directly attributed to mucositis, for an overall rate of mucositis-related hospitalization of 11%. In 2004, the mean hospitalization charge was $23,048 for patients with a primary diagnosis of mucositis in the United States.[14] Therefore, head and neck radiation may be associated with an average additional cost of approximately $2500/patient ($23,048/patient × 11%) directly resulting from hospitalizations, which is consistent with previous estimates in HNC patients.[3] Although the other hospitalizations in this study were not directly attributed to mucositis, it is possible that mucositis contributed to them indirectly (e.g., hospitalizations for feeding-tube placement); hence, the mucositis-related cost of hospitalization may be greater than estimated by this analysis.

Other potential contributors to medical costs were common in the present study, including opioids and other medications, nutritional supplements, feeding-tube placement and supplies, and increased medical staff visits. A previous analysis that considered several cost drivers (incremental professional time, outpatient support, prescription medications, and hospitalizations) found that mean total incremental costs because of mucositis were between $2949 and $4037 per HNC patient.[3] Mucositis has been shown to increase resource utilization and costs in patients with other solid tumors and lymphomas as well.[15]

It is clear from the extensive use of costly health care resources that the economic burden of mucositis is high; unfortunately, a theoretical framework for assessment of mucositis-related health care costs in HNC is lacking. In this study, we have confined our assessment to the acute effects of therapy; however, it is recognized that the economic cost of late effects may be substantial. As noted earlier, patients experience numerous symptoms and substantial function loss, but it is often unclear which acute effects should be attributed directly to the consequences of mucositis.

Limitations

This study is subject to limitations. Demographics and treatment characteristics in this study generally were similar to those of a systematic review[4] of 6181 patients who received RT for HNC in clinical studies between 1996 and 1999. Use of CCR was more common in the present study than in that analysis (67% vs. 29%), but this is consistent with evolving strategies for HNC treatment. The study did not include clinical assessments of mucositis; the findings were based solely on PRO. Many patients reported severe MTS despite receiving opioids, but patient compliance to prescribed therapy was not evaluated. Poor compliance may have contributed to inadequate pain control in some patients. Not all clinical consequences of mucositis (e.g., weight loss, saliva consistency and quantity) were measured. In designing the study, it was well recognized that 1) the duration of RT was variable depending on the setting (primary vs. postoperative) and the RT technique; and 2) that mucositis and mucositis-related symptoms may last for a protracted period after the completion of therapy. As the primary objective of the study was to assess the validity, reliability, and feasibility of the OMWQ-HN, it was felt that a study six weeks in length would provide sufficient data to achieve the primary objective. Thus, only the acute consequences of mucositis were measured; the long-term clinical, functional, and economic consequences of mucositis were not captured by this study. Finally, treatment-related factors, such as the use of CCR, the intensity of CCR, and the use of IMRT may impact the incidence and severity of mucositis and mucositis-related symptoms. Because this study was designed primarily to validate a new assessment tool, the small sample size limited the statistical power of these analyses and the conclusions that can be made. However, these data provide compelling preliminary evidence of an association that deserves further study in larger populations.

Conclusion

Mucositis-related morbidity is a significant problem for HNC patients. Mucositis-related pain impairs oral function and is uncontrolled for a substantial number of patients despite the use of opioids, which suggests that once mucositis develops, it is difficult to be treated effectively. Mucositis in HNC patients receiving RT also may be costly, accounting for approximately one-third of hospital admissions, and increased visits to health care providers resulting in increased provider and hospital charges, pharmacy costs, and costs for nutritional support. Additional studies are warranted to clarify 1) the clinical and economic consequences of radiation-induced mucositis in HNC and 2) the impact that effective interventions may have in not only relieving patient suffering but also reducing health care resource utilization and related downstream costs.

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