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Review article

Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review

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Abstract

Background and purpose: To determine the frequency of mucositis and associated outcomes in patients receiving radiotherapy (RT) for head and neck cancer through a systematic review of recently published literature.

Materials and methods: According to the study protocol, databases were searched for randomized clinical trials (English only, 1996–1999) of patients with head and neck cancer receiving RT with or without chemotherapy that reported one or more outcomes of interest.

Results: Thirty-three studies ($n = 6181$ patients) met inclusion criteria. Mucositis was defined using a variety of scoring systems. The mean incidence was 80%. Over one-half of patients (56%) who received altered fractionation RT (RT-AF) experienced severe mucositis (grades 3–4) compared to 34% of patients who received conventional RT. Rates of hospitalization due to mucositis, reported in three studies ($n = 700$), were 16% overall and 32% for RT-AF patients. Eleven percent of patients had RT regimens interrupted or modified because of mucositis in five studies ($n = 1267$) reporting this outcome. Data insufficiency or heterogeneity prohibited analysis of mucositis severity and other associated outcomes, such as oral pain, dysphagia and opioid use.

Conclusions: Mucositis is a frequent, severe toxicity in patients treated with RT for head and neck cancer. While it appears that mucositis may lead to hospitalization and treatment interruptions, its overall impact on outcomes has not been adequately investigated.

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Keywords: Head and neck cancer; Radiotherapy; Mucositis; Toxicity; Outcome

1. Introduction

Growing evidence indicates more aggressive regimens improve local tumor control and survival of patients with head and neck cancer [19]. Better treatment outcomes, however, have come at the expense of increased patient morbidity, notably an increase in severe (grades 3–4) mucositis that causes substantial pain, interferes with the patient's ability to chew and swallow, and worsens the patient's quality of life [44]. Patients report that mucositis is the most debilitating side effect of their head and neck

cancer therapy (Alison Rose-Ped, unpublished observations, January 1999). Management of mucositis may require feeding tube placement, hospitalization, and intensive supportive care. We undertook a systematic review of the published literature in order to better characterize the incidence and clinical and economic consequences of mucositis in the head and neck cancer population. The results may inform the design of future intervention trials for mucositis. We limited our review to 'acute' mucositis which occurs during or shortly after active therapy, with no intention to capture the potential delayed consequences of mucositis.

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2. Materials and methods

2.1. Search strategy

The methods of systematic review used in this study have been well described elsewhere [12,31,39] and include the goal of minimizing bias in the collection and interpretation of clinical data. To further minimize the possibility of bias (or appearance thereof), a firm specializing in the conduct of systematic reviews (MetaWorks Inc.) was engaged to help design the study as well as to perform the data abstraction and analysis and write a summary of the results. Medline and Current Contents were searched for all papers published between January 1, 1996 and December 31, 1999. This publication time frame was chosen in order to capture data from clinical trials conducted in the recent past. Search terms included head and neck, neoplasms, radiation therapy or drug therapy, cancer, tumors, malignancy, carcinoma, human, stomatitis, and trial types. Reference lists in accepted and rejected studies were reviewed manually to identify other potentially relevant papers not indexed by the two electronic databases.

2.2. Study selection

Two reviewers (one research analyst and one physician) assessed study eligibility using predefined criteria, applied to abstracts of citations and full papers when appropriate. The first level of screening was to exclude abstracts of animal or in vitro studies; study designs other than parallel-group, randomized, controlled trials (RCTs); non-English language publications; publications before 1996; diseases other than head and neck cancer; or studies lacking treatment with radiotherapy (RT) or chemotherapy (CT). In a second level of screening, full papers were reviewed and screened against predefined inclusion criteria. Outcomes of interest for this review were pain, dysphagia, weight loss, interruptions in RT or modifications to RT and/or CT (including lowering or delaying dose), hospitalization, incidence of feeding tube insertions, use of opioids, quality of life, tumor response and survival. Only randomized controlled trials (RCTs) with at least ten patients, reporting the incidence of mucositis or stomatitis, and at least one outcome of interest were included.

2.3. Assessment of study quality

The quality of the selected RCTs was scored using an instrument developed by Jadad et al. [24] that assigns quality points based on three reported methodological features of the trial: randomization method, blinding procedures, and accounting for withdrawals. The level of quality of the evidence was assigned using a previously published method [11].

2.4. Data selection and management

One investigator extracted all data elements from accepted studies, which were verified against the source study by a second investigator, always a physician. Data (study and patient characteristics, treatment information, and outcomes) were entered onto data extraction forms designed specifically for the study, and then entered into a relational database. Intent-to-treat outcomes were preferentially extracted if presented.

2.5. Statistical methods

Summary statistics were computed for characteristics of studies, patients, and treatments, using means weighted for sample size. For computations of proportions, total number of patients randomized or enrolled (per study or treatment group) was the preferred denominator; if not reported, the total number analyzed either for safety or for efficacy was used, whichever was higher. Aggregate incidence of mucositis was calculated across all the studies, weighted by the number of patients enrolled. Overall severity of mucositis (where reported) was calculated similarly, using the number of patients in each grade. Subgroup analyses and Spearman correlations [13,16] with incidence of mucositis were conducted based upon the covariates of patient characteristics, including age, sex, tumor stage and location; treatment characteristics, including RT only, RT type (conventional vs. altered fractionation), CT only, RT + CT; mucositis intervention (active vs. placebo); and clinical outcome (mucositis severity by treatment group). The correlations of grade 3–4 mucositis incidence with clinical outcomes (oral pain, dysphagia, weight loss, RT and/or CT interruptions/modifications, tumor response and survival rate at 3 years) as well as utilization outcomes (hospitalization rates, feeding tube placement) were also measured using Spearman correlation coefficients, where the units of analysis were the treatment groups. All analyses were performed using SAS Version 8.0 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Study characteristics

Thirty-three studies ($n = 6181$) were accepted for inclusion in the analysis (Appendix). Table 1 summarizes the study characteristics. The majority of studies (21 studies, 64%) were performed in Europe. Fifteen of the 33 studies (45%) were considered adequately powered (Level of Evidence I) even though the median quality score in these studies was only 2 (scale 1–5, mean 2.7), implying questionable internal validity. Study duration was reported in 16 studies, ranging from 1.4 to 3 months.

Table 1
Study characteristics^a

Characteristic	No. of studies	No. of patients	No. of treatment arms	References
Total accepted (all RCTs)	33	6181	69	Appendix A
Geographic location ^b				
Europe	21	4258	45	[3,5,6,8,14,15,17,23,25,27,28,29,30,33,35,37,38,41,42,45,47]
North America	8	1083	16	[1,2,4,7,21,22,32,41]
Other	5	1084	10	[9,10,26,36,43]
Study quality (Jadad score)				
1	1	90	3	[15]
2	16	2822	34	[1,2,5,6,8,14,22,25,28,30,32,35,37,38,41,45]
3	11	2407	22	[4,9,10,17,21,23,26,27,36,43,47]
4	2	377	4	[7,42]
5	3	485	6	[3,29,33]
Level of evidence				
I	15	4626	30	[2,4,6,7,10,14,17,23,27,30,33,36,41,42,45]
II	18	1555	39	[1,3,5,8,9,15,21,22,25,26,28,29,32,35,37,38,43,47]
Study duration reported	16	2346	34	
1–2 months	11	1634	23	[3,5,6,7,9,17,25,26,35,28,42]
> 2 months	5	712	11	[10,30,32,37,38]
Year published				
1998–1999	15	2198	31	[2,3,4,5,6,7,8,10,29,33,35,38,41,45,47]
1996–1997	18	3983	38	[1,9,14,15,17,21,22,23,25,26,27,28,30,32,36,37,42,43]
Industry sponsored	5	1365	10	[10,17,35,36,41]

^a RCT, randomized controlled trial.

^b One study included centers in both Europe and North America [41].

3.2. Treatment characteristics

Treatment characteristics are shown in Table 2. More than two-thirds ($n = 4358$) of the patients in these studies received RT alone, almost one-fourth ($n = 1505$) received

Table 2
Treatment characteristics^a

	No. of studies	No. of patients
Total	33	6181
RT only ^b	10	4358
RT-C	9	2875
RT-AF	4	1096
RT + CT ^b	21	1505
RT-C + CT	19	1156
RT-AF + CT	4	214
CT only	2	318
Mucositis intervention	9	688
Active	9	555
Placebo	6	133
No mucositis intervention	24	5493
Surgery total ^c	8	1561
Before RT/CT	2	477
After RT/CT	6	914

^a RT, radiation treatment; CT, chemotherapy; RT-C, conventional radiation treatment; RT-AF, altered fractionation radiation treatment.

^b Four treatment arms (containing 387 patients) in the RT only group and four (135 patients) in the RT + CT group contained a mix of conventional and hyperfractionated accelerated radiation treatment, or did not specify the type of RT.

^c Includes two treatment arms for which the timing of surgery was not specified and 1 treatment arm for which surgery both before and after RT/CT was reported.

RT + CT, and a small fraction ($n = 318$) received CT alone. In four studies [7,29,32,42], the type of RT was not specified or a mix of conventional fractionation RT (RT-C) and altered fractionation RT (RT-AF) was used. For patients randomized to RT only for which the type of RT was known, 72% ($n = 2875$) received RT-C and 28% ($n = 1096$) received RT-AF. The mean dose to tumor was 67 Gy for RT-C (1.8 to 2.5 Gy/session) and 63 Gy for RT-AF (1.25 to 2.00 Gy/session); the range of mean treatment duration was 4–8 weeks for RT-C and 8 days to 7 weeks for RT-AF. In the RT + CT treatment arms, 77% of patients ($n = 1156$) received RT-C and 23% ($n = 214$) received RT-AF along with their CT. The most common CT agents were cisplatin, 5-fluorouracil (5-FU), and carboplatin.

Surgery, which was not the sole therapeutic modality in any trial (based on the inclusion criteria), was a protocol-specified treatment in seven studies and was reported in three additional studies ($n = 1561$). In the majority of cases ($n = 915$), surgery was performed following RT and/or CT as a salvage procedure.

While the majority of studies in this database reported mucositis incidence as an ancillary outcome in the evaluation of different head and neck cancer treatments, nine studies were RCTs specifically studying mucositis interventions (prevention or treatment). Interventions studied were sucralfate [7,8], antibiotic lozenges/pastilles [32,42], amifostine [5,35], low energy laser [3], povidone iodine [37], or biperiden + pilocarpine [38]. Amifostine was administered intravenously (IV); the other agents were given orally. Five of the nine intervention studies used RT-C with three reporting on RT-C alone [3,8,38] and two

Table 3
Patient characteristics^a

Characteristic	Total	
	<i>n</i>	%
Total	6181	100
Mean/median age (years)		
< 55	1344	32
≥ 55	2873	68
Gender		
Male	4382	81
Female	1039	19
Primary tumor site		
Oral cavity	617	11
Oropharynx	1545	28
Larynx	1315	24
Hypopharynx ^b	611	11
Paranasal sinuses	39	1
Nasopharynx	1129	21
Unknown, Other	171	3
Tumor stage (I–IV)		
I	318	11
II	167	6
III	783	28
IV	1298	47
III–IV ^c	2290	83

^a For all categories, percentages given are of the patients for whom this information was available. Numbers of patients for each category do not sum to total due to under-reporting of patient characteristics at baseline.

^b Includes pyriform sinus.

^c Includes patients with tumor stages III, IV, and those reported as III–IV ($n = 209$, or 8%).

reporting on RT-C + CT [5,37], one was in the setting of CT only [35], one utilized unspecified RT [32], and two were mixed RT-C and RT-AF [7,42].

3.3. Patient characteristics

Patient characteristics are described in Table 3. Median age was 56 years (range 14–87 years) among the 23 reporting studies ($n = 4217$). Gender was reported in 26 studies ($n = 5421$); males predominated (81%). The largest

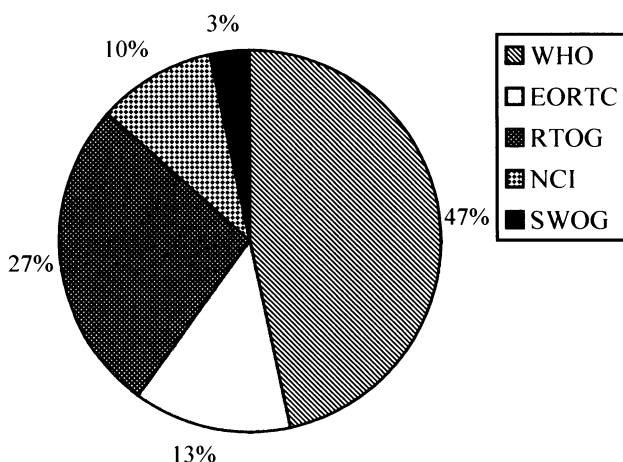


Fig. 1. Distribution of mucositis scales used in trials.

Table 4
Frequency and severity of mucositis by cancer treatment^a

Treatment	<i>n</i>	Mucositis incidence (% of patients)	Grade 3–4 mucositis (% of patients)
Total ^b	6181	80	39
RT-C	2875	97	34
RT-AF	1096	100	57
RT + CT ^c	1505	89	43
CT only	318	22	0

^a RT, radiation therapy; C, conventional; AF, altered fractionation; CT, chemotherapy.

^b Includes four RT only treatment arms of 387 patients who could not be categorized as RT-C or RT-AF (mixed or unknown fractionation regimens).

^c Includes one treatment arm of 56 patients who received RT-AF + chemotherapy.

share of the patients for whom the primary tumor location was reported had oropharyngeal tumors ($n = 1519$, 28%), followed by tumors of the larynx ($n = 1302$, 24%) and of the nasopharynx ($n = 1140$, 21%). The most prevalent tumor stage in studies reporting this information was American Joint Commission for Cancer (AJCC) stage III–IV ($n = 2290$, 83%). Only two studies [35,41] had patients with recurrent or metastatic disease.

3.4. Reporting of mucositis

Thirteen studies reported all grades of mucositis, nine reported grades 3–4 only, five reported combination grades, and the remaining studies reported some (but not all) grades or combination grades other than grades 3–4. Most (25/33) of the studies specified the scale used to assess mucositis severity. The most commonly used scale was the World Health Organization (WHO) classification (1 = soreness, erythema; 2 = erythema, ulcers, can eat solids; 3 = confluent ulcers, requires liquid diet only; 4 = oral alimentation not possible, hemorrhage) [46], although it was used in less than one-half (14/33) of all studies. The next most commonly used scale was the Radiation Therapy Oncology Group instrument (RTOG, eight studies), followed by the European Organization for Research and Treatment of Cancer (EORTC, four studies), the National Cancer Institutes Common Toxicity Criteria (NCI-CTC, three studies), and the Southwest Oncology Group (SWOG, one study). Fig. 1 depicts the distribution of mucositis scales used in the trials.

The mean overall incidence of mucositis was 80% among the patients in all 33 studies (Table 4). The frequency of mucositis was highest in patients treated with RT-AF, affecting 100% of patients overall. Nearly all patients receiving RT-C (97%) or RT + CT (90%) experienced mucositis. Mucositis incidence was lowest (22%) in patients receiving CT alone. Patients treated with RT-AF also experienced the most severe mucositis, with more than one-half (57%) experiencing grades 3–4 mucositis. Severe mucositis (grades 3–4) also affected a sizable proportion

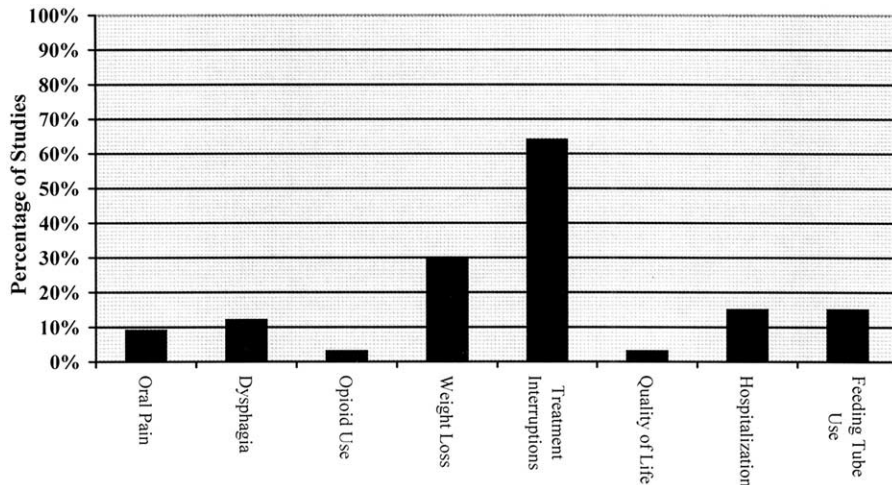


Fig. 2. Reporting of selected outcomes of interest from 33 studies

(43%) of patients receiving RT + CT and over one-third (34%) of patients receiving RT-C. No patients receiving CT alone experienced grades 3–4 mucositis.

The weighted mean duration of mucositis was 39.7 days (range 7–98 days) in the three studies ($n = 264$) reporting this information [4,7,37]. Two of these studies were intervention studies [7,37], with mean duration of mucositis of 35.7 days in the active mucositis intervention groups and 52.1 days in the placebo groups.

3.5. Clinical outcomes

The objective of this review was to explore the relationship between mucositis and outcomes of interest. Given that most studies were head and neck cancer treatment studies, the most frequently studied outcomes were tumor response (64%, 21/33 studies) and survival (45%, 15/33 studies). Few studies reported on other clinical outcomes of interest relevant to mucositis (Fig. 2). Oral pain, considered the hallmark and most troublesome symptom of mucositis, was reported in fewer than 10% (3/33) of studies. Dysphagia was reported in 12% (4/33) of studies, dehydration in 3% (1/33) of studies, opioid use in 3% (1/33) of studies, and weight loss in 30% (10/33) of studies. Overall quality of life was reported in only one study. Treatment modifications, whether planned or unplanned, were reported more often (64%, 21 studies), but the extent or link to mucositis was rarely noted by study authors.

3.5.1. Oral pain

Oral pain occurred in 69% of patients in the three studies reporting this outcome ($n = 405$). In these studies, the incidence of grades 3–4 mucositis was 23% and the treatment settings of these studies were either mixed [7,42] or RT-C only [8], precluding any comparison of oral pain between patients who received RT-AF and those treated with RT-C.

3.5.2. Dysphagia

The overall incidence of dysphagia was 56% in the four studies reporting this outcome ($n = 660$) [5,7,41,42], three of which were mucositis intervention studies. In one of these studies, a lower incidence of dysphagia was reported for the group that received active drug (polymyxin, tobramycin, amphotericin (PTA) lozenge) versus the group that received placebo ($P = 0.006$) [42]. Similarly, in another study [5], less dysphagia was reported for the active treatment arm (amifostine) compared to patients receiving no study drug ($P = 0.001$). The third study [8] showed no benefit of mucositis intervention (sucralfate), with the incidence of dysphagia similar for both arms.

3.5.3. Opioid use

Opioid use was reported in only one study ($n = 30$) in which chemotherapy was administered: the incidence of opioid use was 53% and the incidence of grades 3–4 mucositis was 33% [3].

3.5.4. Weight loss

Only ten studies (30%) reported mean weight loss for treatment groups; none reported body-mass index, mean baseline weight, or height. Mean weight loss ranged from 3.0 to 6.7 kg (6–12% of body weight). In the eight studies ($n = 880$) [1,2,6–8,25,28,35] that reported incidence of weight loss, 34% of patients lost weight. The mean incidence of $\geq 10\%$ weight loss among the three studies reporting this assessment was 17% (range 5–70%; $n = 485$). In one trial of mucositis intervention, investigators reported less weight loss in patients who received active study drug (PTA) compared with those who received placebo ($P = 0.009$) [42].

3.5.5. Quality of life

Only one study [14] reported quality of life, but no breakdown by mucositis incidence or severity was given.

Table 5
Outcomes reported as attributable to mucositis^a

Treatment		Hospitalizations		RT interruption/modification ^b		Feeding tube placement	
		Overall	Due to mucositis	Overall	Due to mucositis	Overall	Due to mucositis
Total	%	35	16	11	1	19	1
	<i>n</i>	893	700	3852	1267	819	275
RT only	%	40	17	9	1	10	2
	<i>n</i>	703	650	3191	1058	500	275
RT-C	%	21	5	9	1	18	NR
	<i>n</i>	411	358	2012	446	165	0
RT-AF	%	66	32	8	0.2	28	NR
	<i>n</i>	292	292	1067	612	60	0
RT + CT	%	14	6	19	1	33	NR
	<i>n</i>	190	50	661	209	319	0

^a *n*, number of patients; NR, not reported; RT, radiation therapy; C, conventional; AF, altered fractionation; CT, chemotherapy.

^b Unplanned modification of regimen, treatment interruption, or delay in scheduled treatment.

3.5.6. Planned treatment interruptions/modifications

Three studies (*n* = 932) reported planned treatment breaks for grades 3–4 mucositis [4,23,45]. All three studies included RT-AF and two of these also included CT. One study [4] evaluated the addition of CT (cisplatin and 5-FU) to a hyperfractionated RT regimen of 1.25 Gy twice per day, 5 days a week, for 6 weeks. A 1-week interruption was planned after a 40 Gy dose for the 56 patients in the RT-AF + CT group. Rates of grades 3–4 mucositis were 75% in the RT-AF alone group and 76% in the patients treated with RT-AF + CT. Another study [23] compared the effects of RT-C (*n* = 253) at 70 Gy over 7 weeks without interruption vs. planned split course accelerated radiotherapy (RT-AccF, *n* = 247) at 38.4 Gy over 8 days, followed by a 12–14-day rest period, followed by another 43.2 Gy over 17 days. The rate of grades 3 and 4 mucositis was higher in the RT-AF group (65%) than in the RT-C group (49%), as was the rate of grade 4 mucositis (17 vs. 5%, respectively). In the third study reporting planned treatment breaks, a regimen of RT-AF with or without concurrent cisplatin, 5-FU, and leucovorin was evaluated [45]. Thirty-nine fractions in 51 days were given to both groups in three cycles of 23.4 Gy each, separated by a rest period of 11 days. In this study, 16% of the RT-AF recipients and 38% of the RT-AF + CT recipients developed grades 3–4 mucositis.

3.5.7. Unplanned treatment interruptions/modifications

Eighteen studies (*n* = 3852) reported deviations from the RT or CT treatment plan, including interrupting treatment, delaying or lowering radiation or CT dose. Studies involving a scheduled break were not entered as interruptions or modifications to planned treatment. Overall, 11% of patients (*n* = 424) experienced a deviation in their treatment plan (Table 5). The incidence of treatment modifications or interruptions was higher when CT was also administered (19%) than when RT-C (9%) or RT-AF (8%) was administered alone. Five studies [1,3,4,14,27] (*n* = 1267) reported unplanned interruption or modification

of RT specifically due to mucositis. Overall, 11% of patients with RT modifications in these studies were noted as having had their RT regimens modified as a result of mucositis (range 8–27%). Ten studies (*n* = 1029) reported interruptions or modifications in CT. One-half (53%) of patients in these studies required changes to planned treatment regimens for a variety of reasons including hematological, neurological, and local toxicities such as mucositis. One study reported that more patients in the RT-C group required modification or interruption of their RT regimen (21%) than in the RT-AF group (10%) [23]. The authors explained this finding by the ‘almost invariable’ occurrence of the peak effects of acute toxicity in the RT-C arm during the last 2 weeks of treatment, as opposed to the week following treatment completion in the RT-AF arm.

3.6. Utilization outcomes

Utilization outcomes were also reported infrequently (Fig. 2). Insertion of feeding tubes was reported in 15% (5/33) of studies and hospitalization was reported in 15% (5/33) of studies. No studies reported the use of outpatient resources in the management of mucositis.

3.6.1. Hospitalization due to mucositis

Hospitalization due to mucositis was reported in three studies (*n* = 700). The overall incidence was 16% (Table 5), with a higher proportion in groups that received RT-AF (32%) than in those treated with RT-C (5%), coinciding with the higher incidence and severity of mucositis in RT-AF recipients. Mean duration of hospitalization for mucositis was reported in one study [23], and was similar for the RT-AF group (35 days) and the RT-C group (42 days). In another study, the authors reported that although RT-AF treatment was associated with a higher rate of grades 3–4 mucositis (95%) than RT-C (42%), only one RT-AF recipient required hospitalization (for hyperalimentation), compared to no hospitalizations in the RT-C arm [43]. In a separate study, the rates of hospitalizations due to mucositis

were higher in patients who received RT and CT than in those who received CT alone (6% in the RT + CT group vs. 2% in the RT-only group) [1].

3.6.2. Feeding tube insertion

Feeding tube insertion was reported in five studies ($n = 819$), with a mean frequency of 19%. In one mucositis intervention study, the author reported that four of 139 patients in the placebo arm were subjected to feeding tube insertion specifically due to mucositis; none of the 136 patients in the active mucositis intervention group required feeding tube placement [42].

3.7. Correlational analysis

The relationship between mucositis and clinical outcomes was explored with correlational analyses where data permitted. Correlational analyses were limited by the small size of many of the studies, under-reporting of outcomes of interest, and ‘ceiling’ or ‘floor’ effects (incidence of one of the two variables consistently high or consistently low). Strong positive correlations were found for the incidence of grades 3–4 mucositis and the proportion of patients requiring feeding tube insertion (eight treatment arms reporting; $r = 0.88$, $P = 0.004$), and for the incidence of mucositis and the proportion of patients with weight loss (eight treatment arms reporting; $r = 0.83$, $P = 0.001$).

In the 11 treatment arms for which the total number of patients who had a complete response (CR) or partial response (PR) and the complete grades 3–4 mucositis incidence data were available, there was no correlation between the proportion of patients with grades 3–4 mucositis and the number of patients with a CR or PR ($r = 0.24$, $P = 0.47$). In the 11 treatment arms for which survival at 3 years and the complete grades 3–4 mucositis incidence data were available, there was a trend toward a moderate, but not statistically significant, positive correlation noted between the incidence of grades 3–4 mucositis and survival at 3 years ($r = 0.56$, $P = 0.07$).

4. Discussion

This systematic review confirms the high incidence of mucositis in patients receiving RT, with rates of 97% reported during RT-C, 100% during RT-AF, and 89% during chemoradiation therapy. The results underscore the impact of fractionation on the severity of mucositis: 56% of patients receiving RT-AF experienced grades 3–4 mucositis, compared with 34% of patients receiving RT-C and 43% of patients on RT + CT. These rates of severe mucositis are slightly higher than, but similar to, those recently reported by the RTOG in a large fractionation trial (RT-C: 25%, RT-AF: 41–47%) [20].

Improvements in tumor control and survival have prompted the routine use of altered fractionation regimens

[19]. Since 100% of patients receiving RT-AF in our review developed mucositis, with a majority of these experiencing severe (grades 3–4) mucositis, the impact of mucositis on intensive treatment regimens deserves increased attention. Unplanned treatment breaks or changes to the treatment regimen were forced by development of severe mucositis in 11% of cases in the five studies reporting this outcome. In three other studies in our review, a treatment break was planned specifically to allow for recovery from expected acute toxicities. The rate of treatment interruptions overall and those specifically due to mucositis may well be higher in ‘real world’ treatment settings than in randomized controlled trials where investigators are monitored for adherence to protocol treatment. While our review uncovered no clear connection between mucositis and tumor response or survival, the lack of a straightforward relationship may be due to the contrasting forces at work: on one hand, treatment interruptions caused by mucositis may drive tumor response lower; on the other hand, the occurrence of severe mucositis may also be a marker for more aggressive treatment, with higher tumor response rates.

Mucositis is also thought to affect patient experience as well as treatment course, although data that fully characterize its sequelae are surprisingly scarce. Reporting of key clinical outcomes potentially associated with mucositis was rare: only 9% of studies reported oral pain, 12% reported dysphagia, and 30% reported weight loss. The literature was also notably sparse in reporting of other outcomes potentially attributable to mucositis, such as hospitalization (15%, 5/33 studies), and feeding tube placement (3%, 1/33 studies). The paucity of data on outcomes likely reflects the view that mucositis is an inevitable toxicity, rather than a complication that may be prevented or mitigated.

Notwithstanding limited data, our review provides some evidence of the impact of mucositis on selected outcomes including hospitalization, weight loss, and feeding tube placement. In the setting of RT-AF, nearly one-third of patients were hospitalized due to mucositis in studies reporting this outcome. These patients were likely hospitalized because of dehydration, malnutrition, and/or pain control. A statistical correlation was found between the incidence of mucositis and weight loss, and between the severity of mucositis and the need for a gastrostomy tube. Such correlations must be interpreted cautiously because of the small sample size of many of the studies in this review, reporting biases, and other confounding factors; however, these findings are consistent with evidence that mucositis is a significant cause of morbidity in head and neck cancer patients.

Finally, although not part of our review, recent, preliminary data suggests that mucositis adversely affects quality of life. An analysis of quality of life data from a large multicenter randomized clinical trial (RTOG 9003) comparing four fractionation schedules found significant correlations between declining quality of life and pharyngeal

($P < 0.0001$) and mucositis ($P < 0.0001$) toxicities using the Functional Assessment of Cancer Therapy (FACT) scale [18]. A growing number of tools are being used to assess quality of life, performance status, and functional outcomes in head and neck cancer patients. The validity and sensitivity of these tools to capture the acute effects of mucositis have not, however, been documented.

4.1. Limitations

As with any systematic review, conclusions from this data set may be subject to change based on additional published evidence. For this review, one eligible study remained outstanding on inter-library loan at the time of a prospectively determined cut-off date for inclusion in the database. This study was a small RCT of 14 patients in the setting of RT-C, in which filgrastim was compared with placebo for mucositis prevention/treatment and where outcomes of weight loss and interruption of RT-C were reported [40]. New, recently reported studies, particularly RTOG 9003 [20], were not captured in our search, and thus may have significant implications for this analysis. As most of the studies reviewed here were conducted in Europe, our findings may be influenced by European practice patterns, potentially limiting their extrapolation to the United States and elsewhere.

4.2. Implications for future research

As has been previously noted, toxicity in general is not uniformly collected nor reported in clinical trials [44]. This is in part due to lack of a widely accepted grading system for scoring toxicity during the period of time these trials were conducted. Five different grading systems were used in the publications we reviewed. These systems contain significant differences in language, detail and severity scaling. This introduces another measure of uncertainty regarding the reliability and completeness of toxicity reporting. In 1998 the U.S. NCI disseminated a revised set of toxicity criteria, NCI-CTC v 2.0 (<http://ctep.cancer.gov/>). The CTC has since become widely adopted by multiple cooperative groups, regulatory agencies and pharmaceutical firms. The use of a single ‘yardstick’ for measuring toxicity should facilitate reporting and comparison between trials.

Important clinical and utilization endpoints in future intervention trials for mucositis secondary to RT for head and neck cancer include oral pain (using standard tools such as the visual analog scale), dysphagia, weight loss, interruptions in treatment, opioid use, hospitalization, feeding tube use, and the cost associated with the treatment of this complication. The impact of mucositis on quality of life is an important consideration, and a tool sensitive to this outcome should be developed. Studies that directly quantify the health and economic impact of mucositis in these patients are also needed. Given that the management of mucositis in head and neck patients is largely performed on

an outpatient basis, an accounting of physician, dietician/nutritionist, nursing, and pharmacy services should be captured in economic analyses [34].

4.3. Conclusion

Mucositis is a frequent and severe consequence of RT, occurring in the majority of patients being treated for head and neck cancer. Mucositis causes substantial morbidity in these patients. Its full impact on the clinical course, however, may not be recognized due the lack of data on the relationship between mucositis and treatment outcomes. Further study on both the impact of mucositis, and its prevention and treatment, is urgently needed.

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Appendix A. Studies included in the analyses

Adelstein et al., 1997 [1] ^a	Jeremic et al., 1997 [25] ^{a,d}
Al-Sarraf et al., 1998 [2] ^a	Kumar et al., 1996 [26] ^a
Bensadoun et al., 1999 [3] ^b	Lefebvre et al., 1996 [27] ^d
Brizel et al., 1998 [4] ^a	Maciejewski et al., 1996 [28] ^c
Buntzel et al., 1998 [5] ^b	Mantovani et al., 1998 [29] ^d
Calais et al., 1999 [6] ^a	Merlano et al., 1996 [30] ^a
Carter et al., 1999 [7] ^b	Okuno et al., 1997 [32] ^b
Cengiz et al., 1999 [8] ^b	Overgaard et al., 1998 [33] ^a
Chatani et al., 1996 [9] ^d	Planting et al., 1999 [35] ^b
Chua et al., 1998 [10] ^a	Rahn et al., 1997 [37] ^b
Dische et al., 1997 [14] ^c	Rode et al., 1999 [38] ^b
Dobrowsky et al., 1996 [15] ^{a,c}	Schrijvers et al., 1998 [41] ^d
Eschwege et al., 1997 [17] ^a	Symonds et al., 1996 [42] ^b
Haffty et al., 1997 [21] ^d	Teo et al., 1996 [43] ^c
Haffty et al., 1997 [22] ^a	Wendt et al., 1998 [45] ^a
Horiot et al., 1997 [23] ^c	Zakotnik et al., 1998 [47] ^a
International Nasopharynx Cancer Study Group et al., 1996 [36] ^a	

^a Study of RT only vs. RT + CT.

^b Study of mucositis intervention (treatment or prophylaxis).

^c Study of RT-AF vs. RT-C.

^d Other primary objective (including studies of the effect of radiation field size, larynx-sparing vs. larynx-preserving regimens, or comparison of two different RT + CT regimens).

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