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REVIEW ARTICLE

Systematic reviews of oral complications from cancer therapies, Oral Care Study Group, MASCC/ISOO: methodology and quality of the literature

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Abstract
Background Oral complications are commonly experienced by patients undergoing cancer therapies. The Oral Care Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has completed nine systematic reviews including Bisphosphonate Osteonecrosis of the Jaw, Odontogenic/Periodontal Infection, Dysgeusia, Oral Fungal Infection, Osteoradionecrosis, Trismus, Oral Pain, Oral Viral Infection, and Xerostomia.
Methods The aims of these reviews were to determine the prevalence of each oral complication, relationship with quality of life, economic impact, and formulation of guidelines based on the quality of the literature. The present article described the details of the methodology and statistical analysis utilized in these nine systematic reviews. Additionally, a summary of the quality of the literature from these oral complications is presented.
Conclusion Oral complications associated with cancer therapies are common among cancer patients. The systematic reviews by the Oral Care Study Group of MASCC/ISOO provide a thorough assessment of the available literature for these oral complications.

Keywords Oral care · Oral complications · Cancer therapies

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Introduction

To fully understand which oral complications from cancer therapies are important targets for prevention and better management, it is important to understand the burden of illness from cancer and from cancer therapies. Numerous studies have identified, and report a wide range of incidence and severity for different oral complications from cancer therapies. These include: mucositis, xerostomia, bleeding, dysphagia, dysgeusia, caries, periodontal disease, infection (bacterial, viral, and fungal), pain, trismus, osteoradionecrosis, growth and developmental disturbances, and salivary gland dysfunction [1].

In 1989, the National Institutes of Health Development Consensus Conference on the Oral Complications of Cancer Therapies provided recommendations for oral assessment and oral/dental management prior, during and following cancer therapy [2]. These recommendations served to summarize

our understanding of the subject at the time. The 20 years following the Consensus Conference, and up to the present time, there has been a gradual increase in the understanding of the impact of these problems. During this time, there was a movement towards developing preventive and management strategies. The 1989 conference brought together leading experts in the field and clearly catalyzed and legitimized the development of a formal specialty discipline of oral oncology. However, there has not been such a review of the subject area since 1989, and as a result, current preventive and treatment strategies largely rely on non-evidence-based, anecdotal evidence that is often decades old (e.g., mouth care protocols for chemotherapy).

Since the consensus conference, cancer therapies have changed significantly in the past 10–15 years, with increased specificity but also increased intensity of treatment regimens. For example, intensity-modulated radiation therapy and the selective use of amifostine and other radioprotective agents are thought to spare some parotid function. It is unclear if the incidence/prevalence, nature, and severity of oral complications has increased or decreased with current cancer therapies and the impact of these oral complications on short- and long-term morbidity. Additionally, the 1989 consensus conference did not systematically review the quality of the literature.

Considering our limited understanding of the burden of illness in the oral cavity from various cancer therapies, it is difficult to produce evidence-based, preventive and management protocols. It is essential first to establish a structured assessment of this topic. With a full knowledge of the primary oral complications from cancer regimens, a prospective multicenter trial can be planned to collect data on the burden of illness from various cancer regimens.

The aims of the systematic reviews reported in the subsequent articles include the following: (1) determine the prevalence rates for each oral complications by cancer regimen (chemotherapy (CT), radiation therapy (RT), stem cell transplant (SCT), surgery, or any combination of these therapies); (2) evaluate the impact of oral complications on economic (e.g., increased medical costs) and quality of life issues; and (3) evaluate the evidence to support various management strategies for oral complications.

Methodology

A thorough literature search was completed with MEDLINE, Cochrane Library, and Best Evidence (Appendix-online). A more in-depth search was completed with CancerLit and EMBASE utilizing a similar search strategy with MEDLINE. CancerLit provides a bibliographic database containing more than a million citations and abstracts related to cancer from over 4,000 different sources [3]. The importance of searching EMBASE, the European counterpart to MEDLINE, is seen in the low overlap of articles recovered between these two databases, estimated at 34% by Smith [4]. Although MEDLINE and EMBASE searches tend to identify different sets of references, they have been found to return similar numbers of relevant references [5]. For each oral complication identified, an additional search was completed from MEDLINE, CancerLit, EMBASE, Cochrane Library, and Best Evidence for clinical trials for the management of these oral complications of cancer therapy. More specific literature searches were completed for each of the oral complications and these additional studies supplemented the articles identified in the main literature search previously described. If completed, these additional searches are described in the methodology section of the specific oral complication.

Inclusion criteria

After completion of the search of the cancer literature, articles for review were selected based on original data of oral complications associated with cancer therapies. Articles were selected from January 1, 1990–December 31, 2008 unless otherwise noted. Searches were limited to human subjects and the English language (searches were expanded to languages other than English on a case-by-case basis). Age was not limited, except when a specific clinical objective applies only to a particular age group.

Exclusion criteria

We excluded the following types of publications:

- Systematic or narrative reviews
- Studies without original data on oral complications
- Opinion papers and case reports
- Articles before 1990
- Articles from the 1990 NCI Monograph [6]

Definition of variables

We assessed the prevalence and severity of the oral complications by cancer therapy regimen, for example, the prevalence (Y/N) and grade of xerostomia following RT for head and neck cancer. Considering the numerous types of CT regimens utilized, we examined the most commonly reported regimens available in the literature, as well as the regimens with the highest reported oral complications.

Depending on the amount and quality of data, the level of evidence, grade of recommendation, and guideline classification based on the American Society of Clinical Oncology Clinical Practice Guidelines for individual management strategies for oral complications was completed [7]. The economic data and resource utilization (e.g.,

emergency department visits, number of hospital days, diet alterations, fluid replacement, antifungal agents, and antiviral agents) and quality of life measures associated with individual oral complications were summarized if available.

Oral complication group section

Each review group included a Section Head and multiple Reviewers, much of whom were members of the Oral Care Study Group of MASCC/ISOO. The Review Organizers completed distribution of articles and study forms and held separate calibration sessions for each oral complication review group. Data collection forms were pilot tested by the Review Organizers prior to use by all Reviewers to ensure complete results were gathered for the systematic review. This form was modified by the Review Organizers from the data entry forms utilized for the systematic reviews of World Workshop Oral Medicine IV [8].

At least two reviewers independently assessed each study with the use of Form C (Appendix-online). Disagreements between the two reviewers were resolved by the Section Head of the group and the final determination was recorded in a database.

Numerical estimates of prevalence and severity of oral complications were obtained from each article using Form C, which utilized outcomes of a form used previously for estimating the incidence of oral mucositis. Additionally, each article was evaluated with respect to its design, methods of ascertainment, scale utilized for oral complications, and sample size. These study characteristics were numerically scored as described below and the scores were used to produce quality weighted estimates of prevalence (Table 1).

A similar strategy was used for estimation of outcomes (i.e., mean reduction in QOL score) if numerical estimates were available from at least three different articles. If fewer than three articles were identified, descriptions were limited to qualitative assessments indicating only the direction of outcomes ("reduced", "increased", "no difference").

Each oral complication review group was asked to apply the guideline development methods of the American Society of Oncology for assessment of level of evidence, grade of recommendation, and guideline classification (Table 2). These guidelines were utilized for the MASCC/ISOO Mucositis Consensus Conferences, and many review members were familiar with this process [9].

Statistical analysis

Statistical analyses were limited to estimation of prevalence of oral complications and outcomes data. Recommendations for management strategies were based on qualitative evaluation of the level of evidence as described above, rather than quantitative analysis.

Prevalence of oral complications from cancer therapies

Each oral complication was evaluated according to cancer therapy regimen to include standard-dose CT, high-dose CT with or without HSCT, RT alone, and RT with CT. If insufficient data were available for prevalence estimates, all CT regimens were merged and compared to RT with or without CT. Prevalence was reported as the proportion affected and computed (as described below) as the mean of the proportion affected from each study in the group, weighted by the assigned quality points, along with 95% confidence intervals. This method was used successfully in a previous analysis of the incidence of oral mucositis related to cancer therapy [10].

We defined the overall quality-adjusted oral complication prevalence, p_{overall} as

$$p_{\text{overall}} = \sum_{j=1}^{J} \frac{qs_j p_j}{\sum_{i=1}^{J} qs_i},$$

where qs_j is the quality score for the jth study and p_j is the proportion of subjects with oral complications observed in the jth study [11]. We anticipated that many studies would have small sample sizes and, thus, the Gaussian approximation to the binomial distribution, which is a large sample result, would not be appropriate. Therefore, we computed an estimate of the 95% confidence interval for the overall quality-adjusted oral complication prevalence using the bootstrap method as follows [12]. One thousand bootstrap samples were generated for each treatment regimen (or treatment type) and the overall quality-weighted oral complication prevalence was calculated for each bootstrap sample. The bootstrap oral complication prevalences were ordered from smallest to largest, and the 2.5th percentile and 97.5th percentile bootstrap oral complication prevalences were used to approximate the 95% bootstrap confidence interval for the treatment regimen (or treatment type).

Prevalence by severity grade was computed similarly, where sufficient information was available. All analyses were conducted using STATA 10.1 (Statacorp, College Station, TX, USA).

Quality of life impact of oral complications from cancer therapies

The mean changes in quality of life scores related to oral complications were analyzed. In each case, point estimates from the quality weighted, aggregated data was computed along with 95% confidence intervals as described above. If fewer than three studies were identified, quantitative analysis was forgone in favor of qualitative descriptions of economic and quality of life outcomes.

Table 1 Quality grading strategy for incidence and outcomes evaluation [9]

Quality measures	Definitions	Quality points assigned
Representativeness	Multi-institution, consecutive patients representative of underlying population	2
	Single institution, consecutive patients, representative of underlying population	1
	Convenience sample	0
Sources of bias in oral complication measurement		
Ascertainment bias	CT: daily or weekly assessment RT: >4 assessments during or after RT	2
	CT: >1 assessment per cycle, <weekly assessment RT: 2–4 assessments during or after RT	1
	CT: 1 assessment per cycle RT: 1 assessment during or after RT	0
Misclassification bias	Prospective (patient or professional)	1
	Retrospective (patient recall)	0
Examiner bias	Blinded	1
	Unblinded	0
Oral complication assessment validity	Standard validated scale	2
	Well-defined, study-specific scale	1
	Not defined	0
Estimate precision	Sample size sufficient to estimate a prevalence of 20% within	
	±5%	2
	±10%	1
	Greater than 10%	0

CT chemotherapy, *RT* radiotherapy

Quality measures of oral complications literature: summary of results

The current systematic reviews evaluated the literature for nine oral complications associated with cancer therapies. A total of 543 articles met the inclusion criteria and were evaluated by approximately 70 reviewers- most members of the Oral Care Study Group of MASCC/ISOO. The largest group was the Xerostomia Section with 255 article and the other eight groups reviewed between 20 and 64 articles

Table 2 Oral complications treatment trials: level of evidence, recommendation grade, and guideline classification [7]

Measure	
Level of evidence	Source of evidence
I	Meta-analysis of multiple well-designed studies. High-powered randomized trials
II	At least one well-designed experimental trial. Low-powered randomized trials
III	Well-designed, quasi-experimental studies (e.g., nonrandomized, controlled, single-group, pre–post, cohort)
IV	Well-designed, nonexperimental studies (e.g., comparative and correlational descriptive and case studies)
V	Case reports and clinical examples
Grade of recommendation	
A	Evidence of type I or consistent findings of multiple types II, III, or IV
B	Evidence of types II, III, or IV with generally consistent findings
C	Evidence of types II, III, or IV, but generally inconsistent findings
D	Little or no systematic empirical evidence
Guideline classification	
Recommendation	This is reserved for guidelines based on levels I or II evidence
Suggestion	Guideline based on levels III, IV, V evidence; implies panel consensus on the interpretation of the evidence
No guideline possible	Used with insufficient evidence to base a guideline because (1) little or no evidence on the practice in question or (2) the panel lacks consensus on the interpretation of existing evidence

Table 3 Types of studies reviewed in the oral complications literature (1990–2008)

	Total # of studies	RCT	Non-RCT	Before and after	Cohort	Cross-sectional	Case control
Bisphosphonate osteonecrosis of the jaw	22	0	0	0	18	0	4
Odontogenic/periodontal infection	64	10	3	2	27	14	8
Dysgeusia	26	5	0	5	14	1	1
Oral fungal infection	43	15	5	2	18	2	1
Osteoradionecrosis	46	2	0	9	33	0	2
Oral pain	40	3	1	2	21	11	2
Trismus	22	0	3	2	17	0	0
Oral viral infection	25	7	2	1	14	0	1
Xerostomia	255	45	0	19	148	40	3
Total	543	87	14	42	310	68	22

(Table 3). The most common study design was the observational cohort study (57%) followed by the randomized controlled trial (RCT) design (16%). The Fungal Section had the highest percentage of RCT studies with 35%, while the Bisphosphonate Osteonecrosis of the Jaw Section and Trismus Section did not have any RCT studies.

As previously noted, many quality measures were evaluated to determine the weighted prevalence for each oral complication. A summary of some of these quality measures is presented in Table 4. In general, a wide range of each of these quality measures was found. A multicenter study design can often improve the generalizability of a study. In the present reviews, multicenter studies were reported in 12–41% of the literature reviewed with the highest percentage in the Bisphosphonate Osteonecrosis of the Jaw Section.

Two measures to minimize selection bias included accrual of consecutive patients and concurrent controls. Enrollment of consecutive patients was the highest in the Dysgeusia Section (88%), but lowest in the Bisphosphonate Osteonecrosis of the Jaw Section (5%). Accrual of concurrent controls ranged from 0–44% with the highest in the Fungal Section and lowest in the Trismus Section.

Blinding is another important study design consideration. Blinding of the examiner was infrequent across all groups (0–19%), but as few of the studies were interventional trials, blinding of the examiner was uncommon. The Fungal Section had the highest blinding in this regard, but this group of literature also had the highest percentage of RCTs.

Use of validated scales is of vital importance in study design. Unfortunately, not all oral complications have well-validated scales for use in clinical trials. The Bisphosphonate Osteonecrosis of the Jaw Section reported no studies that utilized a standardized, validated scale, while most studies (92%) in the Odontogenic/Periodontal Infection Section had validated scales available for use in clinical studies. The Oral Pain Section also had a high percentage (85%) of validated scales—many associated with available quality of life scales.

Table 4 Quality measures of the oral complications literature

Oral complication	Total # of studies	Multicenter *N* (%)	Consecutive accrual *N* (%)	Concurrent controls *N* (%)	Examiner blinded *N* (%)	Outcome measure		Groups comparable *N* (%)
						Standard, validated *N* (%)	Study-specific *N* (%)	
Bisphosphonate osteonecrosis of the jaw	22	9 (41%)	1 (5%)	4 (18%)	0 (0%)	0 (0%)	11 (50%)	3 (14%)
Odontogenic/periodontal infection	64	10 (16%)	38 (59%)	25 (39%)	9 (14%)	59 (92%)	3 (5%)	Not assessed
Dysgeusia	26	8 (31%)	23 (88%)	5 (19%)	0 (0%)	14 (54%)	7 (27%)	3 (12%)
Oral fungal infection	43	9 (21%)	31 (72%)	19 (44%)	8 (19%)	27 (63%)	10 (23%)	16 (37%)
Osteoradionecrosis	46	5 (11%)	19 (41%)	5 (11%)	1 (2%)	12 (26%)	9 (20%)	3 (7%)
Oral pain	40	12 (30%)	20 (50%)	5 (13%)	0 (0%)	34 (85%)	5 (13%)	4 (10%)
Trismus	22	4 (18%)	12 (55%)	0 (0%)	0 (0%)	9 (41%)	6 (27%)	1 (5%)
Oral viral infection	25	5 (20%)	18 (72%)	7 (28%)	4 (16%)	6 (24%)	15 (60%)	4 (16%)
Xerostomia	255	31 (12%)	141 (55%)	79 (31%)	24 (9%)	74 (29%)	150 (59%)	29 (11%)

Finally, studies testing differences between groups must demonstrate appropriate measurement and adjustment of potential baseline/confounding variables. A minority of studies overall were determined to have comparable groups (5–37%), but again this may be related to the low percentage of study designs (26%) that were considered interventional trials (i.e., RCT, non-RT, or before and after study design) in the present group of literature reviewed. Not surprisingly, the Fungal Section with the highest percentage of RCT had the most studies with comparable groups.

Conclusions

An assessment of quality measures from the oral complications literature points to numerous opportunities to reduce bias and confounding in future studies through improved designs. Such improvements of study design will enhance our understanding of the burden of illness of the oral complications associated with cancer therapy.

The overall findings from these systematic reviews will shape our current understanding of oral complications from cancer therapies, and will help clarify the gaps in the literature that can be addressed with future observational and interventional studies. Taking into account areas that lack sufficient scientific evidence, future prospective, multicenter clinical studies can be designed with the goal of expanding our knowledge of the impact of oral complications from cancer therapies. With the availability of newer research into these areas, these systematic reviews can be updated in the future with the continued goal to expand our understanding of oral complications associated with cancer therapy.

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Conflict of interest statement None to declare.

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