Support Care Cancer (2010) 18:1023–1031
DOI 10.1007/s00520-010-0897-7

REVIEW ARTICLE

A systematic review of orofacial pain in patients receiving cancer therapy

Joel B. Epstein · Catherine Hong · Richard M. Logan · Andrei Barasch · Sharon M. Gordon · Lorree Oberlee-Edwards · Deborah McGuire · Joel J. Napenas · Linda S. Elting · Fred K. L. Spijkervet · Michael T. Brennan

Received: 22 October 2009 / Accepted: 23 April 2010 / Published online: 11 June 2010

Abstract
Purpose We present the findings of a structured systematic review of the literature assessing orofacial pain induced by malignant disease and/or its therapy (excluding mucositis). This evaluation of the literature published after the 1989 NIH Development Consensus conference on the oral complications of cancer therapies is an effort to assess the prevalence of pain, quality of life and economic impact, and management strategies for cancer therapy-induced orofacial pain.
Methods A systematic medical literature search was conducted with assistance from a research librarian in MEDLINE/PubMed and EMBASE databases for articles

J. B. Epstein (✉)
Department Oral Medicine and Diagnostic Sciences,
Otolaryngology and Head and Neck Surgery and Cancer Center,
MC 838, University of Illinois,
Chicago, IL 60612, USA
e-mail: jepstein@uic.edu

C. Hong
Department of Oral Medicine, Carolinas Medical Center,
P. O. Box 32861, Charlotte, NC 28232, USA
e-mail: catherine.hong@carolinas.org

R. M. Logan
Oral Pathology, School of Dentistry, Faculty of Health Sciences,
The University of Adelaide, Consultant Oral Pathologist,
Division of Surgical Pathology, SA Pathology,
Adelaide, Australia
e-mail: richard.logan@adelaide.edu.au

A. Barasch
Department of General Dental Sciences,
University of Alabama at Birmingham,
SDB 111, Birmingham, AL 35294-0007, USA
e-mail: abarasch@uab.edu

S. M. Gordon
University of Maryland,
650W Baltimore St., Baltimore, MD, USA
e-mail: sgordon@umaryland.edu

L. Oberlee-Edwards
Scripps Center for Dental Care,
9850 Genesee Ave, La Jolla, CA 92037, USA
e-mail: loree@empowerpeople.com

D. McGuire
University of Maryland School of Nursing,
Program in Oncology, University of Maryland Marlene
and Stewart Greenebaum Cancer Center,
655 West Lombard Street, 325B, Baltimore, MD 21201, USA
e-mail: dmcguire@son.umaryland.edu

J. J. Napenas
Department of Oral Medicine, Carolinas Medical Center,
P. O. Box 32861, Charlotte, NC 28232, USA
e-mail: joel.napenas@carolinas.org

L. S. Elting
Department of Biostatistics,
The University of Texas M.D. Anderson Cancer Center,
1515 Holcombe Blvd, Houston, TX 77030, USA
e-mail: lelting@mdanderson.org

F. K. L. Spijkervet
Department of Oral & Maxillofacial Surgery,
University Medical Center Groningen, University of Groningen,
Hanzeplein 1, 9700 RG, Groningen, The Netherlands
e-mail: f.k.l.spijkervet@kchir.umcg.nl

M. T. Brennan
Department of Oral Medicine, Carolinas Medical Center,
P. O. Box 32861, Charlotte, NC 28232, USA
e-mail: mike.brennan@carolinas.org

published between January 1, 1990 and December 31, 2008. Each study was independently assessed by two reviewers with expertise in the field of oral oncology.
Results Thirty-nine studies assessed pain in the head and neck region. The measure was commonly embedded in quality of life studies. Most of these studies described pain in head and neck cancer (HNC) patients, which therefore became the focus of the report.

Pain is common in patients with HNC and is reported by approximately half of patients prior to cancer therapy, 81% during therapy, 70% at the end of therapy, and by 36% at 6 months after treatment. Pain is experienced beyond the 6-month period by approximately one third of patients and is typically more severe than pre-treatment cancer-induced pain.
Conclusions This systematic review identified the presence of pain before cancer therapy, likely attributable to the cancer; an increase in pain during therapy and the common persistence of pain following cancer treatment. Continuing research should use validated tools to prospectively assess orofacial pain, its causes and pathophysiology, and its effect on quality of life and economic impact. Clinical trials of pain management in this setting are also warranted.

Keywords Cancer therapy · Head and neck and orofacial pain

Introduction

Cancer-associated pain in the orofacial region is common and is typically associated with significant psychological and physical suffering. In the vast majority of cases, pain is directly related to the malignancy or is a consequence of curative treatment. Cancer-induced pain may be due to nociceptive and neuropathic mechanisms. In some cases, pain may be coincidental and unrelated to cancer.

Historical perspective

This systematic review represents evaluation of the medical literature published since the *1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies* [1]. Germaine to this review of orofacial pain in cancer were the following goals established by consensus at the above conference:

- To establish baseline data with which all subsequent examinations can be compared.
- To identify risk factors for the development of oral complications.

Advances in cancer therapies since 1989 resulting in improved survival have included changes in chemotherapy, radiation therapy and surgical cancer care, rehabilitation, and prosthetic management. In hematopoietic stem cell transplantation, improved supportive care, non-myeloablative transplantation, peripheral and cord blood transplant, and advances in chemotherapy have occurred, which produced a net increase in survivorship. These changes have also had significant effects on orofacial pain.

Aims of the systematic review

The general purpose of this systematic review was to update the findings of the *1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies* related to orofacial pain excluding mucositis-related pain in cancer patients. Oropharyngeal mucositis was specifically excluded due to the work of the Multinational Association of Supportive Care in Cancer (MASCC) Mucositis Study Group that has focused upon this complication of therapy. However, the exclusion of mucositis created challenges in the review due to the overlap of pain during and following treatment, which may be due to multiple causes and because the overwhelming cause of acute mucosal pain is related to oropharyngeal mucositis. We attempted to assess orofacial pain not attributable to oropharyngeal mucositis that may include pain in the head and neck region due to tumor, pain due to infection, post-surgical pain, and pain following cancer therapy, in order to determine:

1. the prevalence and severity of pain due to cancer or cancer therapy,
2. the impact of orofacial pain on quality of life,
3. the socioeconomic impact of orofacial pain in the cancer setting, and
4. recommendations for management strategies.

Methodology

Search strategy and criteria for selecting articles

A systematic literature search was conducted with databases in MEDLINE/PubMed and EMBASE for articles published between January 1, 1990 and December 31, 2008. We used the following MeSH terms in a Boolean search: Pain AND [Neoplasms] OR [Head and Neck Neoplasms/Radiotherapy] OR [Radiotherapy] OR [Antineoplastic Agents] OR [Antineoplastic Combined Chemotherapy Protocols] OR [Combined Modality Therapy] OR [Whole-Body Irradiation] OR [Bone Marrow Transplantation] OR [Hematopoietic Stem Cell Transplantation] AND [Humans] AND [1990/01/01:2008/12/31]. In addition, we

targeted orofacial pain and quality of life in cancer patients using a similar strategy. The search results were imported into a computerized database (Reference Manager Version 12). The results from MEDLINE/PubMed and EMBASE were then combined, and duplicate publications were eliminated. The methodology is described in more detail in Brennan et al. [2].

Types of publications excluded

We excluded the following publication types from the systematic review: previous systematic and non-systematic reviews; studies not reporting actual data, or data from previous publications, or if later, relevant follow-up publications were identified; phase I and II clinical studies, opinion papers, editorials and case reports; articles published before 1990 and articles from the 1990 NCI *Monographs*. The search was limited to English language. We included studies that reported orofacial pain, but not those where the location of pain was not specifically stated to be from the head and neck region. We excluded interventional studies with a focus on oral mucositis and not oral pain, as well as studies where cancer treatment was not provided or was not clearly stated.

Review methodology

The review team was recruited from the Oral Care Study Group, MASCC/International Society of Oral Oncology (ISOO) and calibrated by teleconferences and email correspondence. The abstract of each article was reviewed by the section head (JBE) and the systematic review organizer (MTB). Citations were included if they met criteria listed above resulting in a preliminary set of 89 potentially relevant publications. The full text articles were electronically distributed to the review team along with an evaluation form customized for the pain review [2]. Two reviewers extracted information independently related to study design, study population, interventions, outcome measures, methods, results, and conclusions for each article. Results were compared and re-evaluated in group sessions until consensus was obtained between reviewers. The final analysis included 39 articles, which met the criteria for the present review. Reasons for exclusion of 50 of the original 89 articles included: study with oral mucositis focus=18; oral pain not assessed=16; review article=6; interventional study, but not for oral pain=3; study with no cancer therapy=2; cancer treatment unclear=1; phase 1 study=1; case report=1; editorial=1, and not English=1.

The quality of selected articles was assessed and scored with respect to sources of bias, representativeness, scale validity, and sample size. These parameters were utilized to determine the weighted prevalence of pain. Further details of this methodology can be reviewed elsewhere in this monograph [2].

Results

A total of 39 studies assessed pain in the head and neck region. These studies included 33 observational studies and 6 clinical trials (Table 1). Thirty-four of the 39 studies assessed oral pain in patients with head and neck cancer (HNC). A summary of patient characteristics is summarized in Table 1. Pain was often reported using quality of life questionnaires (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQC30], EORTC Head and Neck [H&N 35], University of Washington Quality of Life questionnaire [UWQOL], visual analog scale [VAS], and study-specific questionnaires: Epstein Addendum, French Schaub, Hospital Anxiety and Depression Scale [HADS], Oral Mucositis Daily Questionnaire [OMDQ]).

Prevalence of pain in the head and neck region

Pain is common in patients with HNC and reported by approximately half of patients prior to cancer therapy, 81% during therapy, 70% at the end of therapy and still 36% at 6 months post-treatment (Table 2). Assessment of the prevalence of pain throughout treatment and on follow-up has been conducted in six studies [3–8]. Only a few studies assessed the prevalence of pain following cancer therapy [3–5, 7–10]. However, orofacial pain has been identified during treatment, and continuing pain of lower intensity is common at 1 year.

The findings using the EORTC QLQ C30, the most common Patient Reported Outcome (PRO) tool used in recent literature, are shown (Fig. 1). Pain experienced with conventional radiation therapy (CRT) and intensity-modulated radiation therapy (IMRT) has been compared in one study using EORTC QLQC30 questionnaires (scale 0–10). In this study, similar levels of pain were identified in the pre-treatment IMRT and CRT cohorts (7.6 and 7.1, respectively), 3-month post-RT (7.6, 7.9), 6-month post-RT (6.3, 7.1), and 12-month post-RT (2.8 and 9.5) [11]. Another study comparing IMRT and CRT at 12-month post-RT demonstrated pain levels of 30.1 and 21.9 (p= 0.11), following radiation therapy up to 1 year [11] and at 1 year in another study [4].

Another study assessed pain by the EORTC H&N questionnaire and showed that 2 years following cancer therapy (surgery/RT), pain was improved in 31% of patients, unchanged in 36%, and worse than pre-treatment

Table 1 Study and patient characteristics in oral and pharyngeal pain studies (n=39)

Study and patient characteristics	Number of studies [references] or patients
Study design of all pain studies (39)	
RCT	3 [20, 21, 27]
Non-randomized controlled	1 [23]
Before and after	2 [22, 24]
Cohort	21 [5–7, 9, 11, 12, 14–17, 28–38]
Case–control	2 [39, 40]
Cross sectional	10 [3, 4, 8, 10, 13, 41–45]
Cancer diagnosis from observation studies (n=33)	
Squamous cell carcinoma	3,161 pts.
Head and neck cancer (diagnosis not specified)	882 pts.
Cancer staging	
Stage I	465 pts.
Stage II	554 pts.
Stage III	637 pts.
Stage IV	1,163 pts.
TNM cancer staging	
T1	51 pts.
T2	247 pts.
T3	213 pts.
T4	104 pts.
T1/T2	302 pts.
T3/T4	124 pts.
Breast cancer	123 pts.
Thyroid cancer	71 pts.

in 33% [12]. Pain intensity was higher in HNC patients who received combined modality therapy (Fig. 2). Pain did not return to baseline in patients receiving combined radiation and chemotherapy, and pain levels often remain elevated for more than a year.

Similarly, the presence of pain has been noted in a number of studies using the EORTC HN35 questionnaire. The impact of oncology treatment upon pain was reported prior to treatment (20), at 2 months [11], after 6 months [11], and more than 1-year post-treatment [4, 11]. Similar findings from the EORTC HN35 questionnaire are seen in studies using the EORTC QLQ C30 questionnaire (Fig. 2).

UWQOL is a validated QOL tool, initially developed to assess complex outcomes in patients who received head and neck surgery; therefore, the UWQOL has been most often used in HNC patients with treatment that included surgery [13, 14].

Two studies that utilized the VAS showed an increase in pain during therapy followed by reduction at 1 month, with pain levels that were nevertheless higher than pre-treatment (Fig. 3) [6, 15].

One study assessed pain in patients with advanced HNC following combined modality therapy including surgery/RT/CT [16]. Pain was reported by 84% of patients in the week preceding death, while 18% reported emergency department admissions due to pain. Complica-

Table 2 Weighted prevalence of orofacial pain by cancer therapy and diagnosis

Cancer therapy—cancer diagnosis	Prevalence pre-tx: mean (SE), [confidence interval]	Prevalence during tx: mean (SE), [confidence interval]	Prevalence end of tx: mean (SE), [confidence interval]	Prevalence 6months post-tx: mean (SE), [confidence interval]
Chemotherapy and radiation—head and neck cancer	49.5% (0.07) [29.0–70.0]	80.8% (0.17) [0.0–100]	69.7% (0.08) [43.6–95.8]	36.2% (0.08) [14.2–58.2]
Chemotherapy—breast cancer	NA	45.1% (0.01) [33.1–57.0]	NA	NA

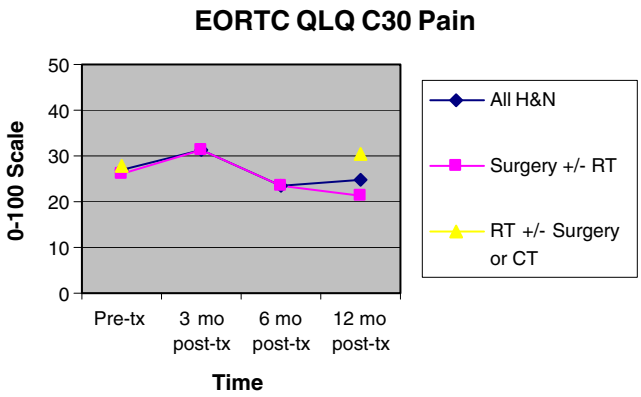

Fig. 1 Orofacial pain as reported using EORTC QLQ C30 before, during, and following cancer therapy. References: pre-treatment [10, 12, 28, 34, 38], 3 months post-tx, [34], 6 months post-tx, [34, 38], 12 months post-tx [12, 28, 34, 38]

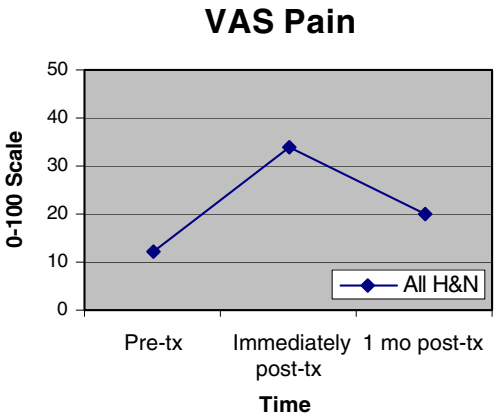

Fig. 3 VAS pain in HNC patients. References: [6, 15, 45]

tions were more frequent in patients with advanced stages of disease.

Most of these studies have reported orofacial pain despite the use of analgesics during cancer therapy.

Orofacial pain in breast cancer patients

Two studies evaluated the prevalence of orofacial pain during chemotherapy in a breast cancer cohort [9, 17]. Approximately half (45%) of these patients experienced orofacial pain as measured by the EORTC QLQ C30 [9] or study-specific questions about oral pain from neurotoxicity related to chemotherapy [17].

Economic impact

While there have been studies that have evaluated the economic impact of mucositis [18], there were no studies evaluating this dimension for orofacial pain.

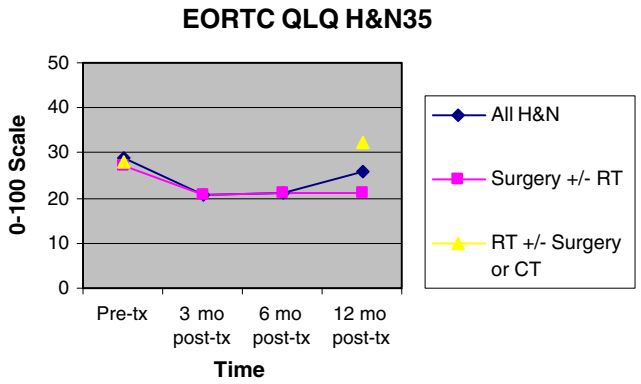

Fig. 2 Orofacial pain in HNC patients before, during, and following therapy. References: pre-treatment [10, 12, 28, 34, 38], 3 months post-tx [34], 6 months post-tx [34, 38], 12 months post-tx [12, 28, 34, 38]

Prevention and/or management strategies

Orofacial pain is commonly reported with oral mucositis, therefore prevention or management strategies in oncology patients often includes both pain and mucositis. The Clinical Practice Guidelines from the Mucositis Study Section of MASCC/ISOO have evaluated numerous prevention and treatment strategies for the management of oropharyngeal mucositis; therefore, due to the overlap with mucositis and pain, the reader is referred to this publication for management recommendation [19]. Treatment recommendation from these guidelines included patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing hematopoietic stem cell transplantation. No other treatment recommendations or suggestions could be made due the paucity of the literature on this topic.

We assessed studies that reported management of orofacial pain as a primary outcome. We identified five studies that evaluated pain management strategies in HNC and four of these were directed at pain from mucositis but may also include tumor-related pain. A randomized placebo-controlled study of antioxidants (α-tocopherol and ß-carotene) was initiated to moderate the adverse events of radiation therapy for HNC [20]. No benefit was identified for pain with EORTC QLQ C30. Additionally, the ß-carotene supplement was discontinued as the rate of local tumor recurrence tended to be higher in the supplement arm. A study of Gelclair compared to sucralfate/mucaine, found no difference between the study rinses, suggesting that Gelclair is equally effective to sucralfate/mucaine in relieving radiotherapy-induced oral mucositis pain [21]. Doxepin rinse was assessed in an open-label clinical trial, in patients with mucositis and oral pain [22]. This rinse may provide significant pain relief for patients with pain due to oral mucosal damage from cancer or

therapy, with pain suppression lasting up to 4 h. Repeated use of the rinse for 1 week was effective despite increasing severity of mucositis over time, suggesting possible cumulative pain relief.

A muco-adhesive film sheet versus a control (topical and systemic anesthetics) was shown to be useful in alleviating pain due to acute radiation-induced mucositis and maintain good oral feeding [23]. Similarly, benzocaine hydrochloride in a mucoadherent film was assessed in an open-label trial of 23 subjects with chemotherapy-induced mucositis and found to reduce discomfort with acidic beverage challenge within a 3-h follow-up time [24].

Due to the limitation of studies specifically related to management of orofacial pain in cancer patients, no guideline recommendations beyond the Mucositis Study Section of MASCC/ISOO are possible.

Discussion

We reviewed the literature from 1990–2008 to determine the prevalence, impact on quality of life, socioeconomic impact, and recommendations for management strategies. Several points can be learned from this review:

1. Orofacial pain is frequently present at initiation of therapy, typically attributed to the malignancy, and increases in prevalence during treatment, from 50% to over 75% at the end of treatment. Orofacial pain improves following treatment; however, in many cases, pain never returns to its baseline value.
2. The studies in this review demonstrate increased pain intensity in HNC patients who received combined modality therapy (Fig. 1) and that orofacial pain does not return to baseline in patients receiving combined RT and CT. The visual analog pain score in the available studies shows increased pain during therapy and reduction at 1 month, but higher levels than pre-treatment pain [6, 15]. These and other studies suggest persisting pain months and possibly years following cancer therapy. Pain at 2 years following surgery and radiation therapy compared to baseline pre-treatment was increased in 33% and unchanged in 36% of patients [12].
3. While much of the increase in pain during treatment appears to be due to oral mucositis, it may also have other causes including pain due to the cancer, inflammation, and infection following surgery and chemotherapy or damage to the sensory nerves in the region. Furthermore, it is important to recognize that pain continues despite current standard clinical approaches to pain management.
4. Cancer pain significantly increases disease morbidity, reduces performance status, increases anxiety and depression, and diminishes QOL [25, 26]. Head and neck and oropharyngeal pain affect social functions of communication (e.g., speech, facial expression), social and physical interaction (e.g., kissing and eating), may lead to inability to eat by mouth, and take oral medications, which may compound the affective and cognitive impact of the pain.
5. The socioeconomic impact of orofacial pain has not been adequately assessed.
6. The reviewed studies show that pain was experienced during cancer treatment despite the use of analgesics, indicating the severity of symptoms and the limited ability to control pain with standard current clinical care. This review documents the need for improvement in pain management, and the limited success of current common approaches for orofacial pain management in oncology.

Limitations of this review include the majority of studies included pain in assessment of more broadly evaluated QOL. There are a limited number of prospective studies assessing pain during therapy, and very few following treatment, those that do use a general assessment of pain and QOL. Furthermore, in many of these studies, analgesic use was not reported, possibly confounding assessment, but reflecting patient experience. Changing approaches for HNC may be associated with different pain experience, and further clinical study is indicated. Future studies should assess pain experience associated with the therapy of cancer provided, the stage of cancer, the site of the primary tumor, and the presence or absence of lymph node metastases. These studies will require sufficient power to allow analysis of these variables. Orofacial pain following cancer therapy requires study, as indicated in this review, where pain continues for 1 year and longer following therapy. Future investigation should also include the mechanisms of pain, as current therapy focuses upon nociceptive pain using NSAIDs and opioids, with little emphasis upon neurologically active medications. As seen in the current review, the study of orofacial and head and neck pain in oncology is complicated by the multifactorial etiology of pain during therapy which may include pain due to tumor, pain due to treatment-related toxicity, and secondary causes such as infection. Most studies that assess QOL do not attempt to distinguish potential cause(s) of pain, but assess overall symptom burden upon QOL. Furthermore, the nature of pain and mechanisms of symptom that may guide treatment and yield improved symptom control are not included in QOL studies. Future study should also consider the etiopathogenesis of pain in

oncology and address directed management to the cause(s) and pathogenesis of pain during and following cancer therapy. Study of the impact of pain management approaches is needed.

The heterogeneity of diagnoses, treatment, and outcome measures within studies result in difficulties in interpretation. Additionally, it is often difficult to determine if orofacial pain is related directly to the cancer, to cancer therapy, or a combination of these factors. Studies of chronic pain are important due to increasing awareness of the persistence of complications of cancer therapy for months to years and likely indefinitely and increasing patient survivorship. This review points out the common persistence of pain following cancer therapy that was previously reported in few studies. The issue of pain management and survivorship upon QOL has received only limited attention to date. The findings indicate the need for large, multi-institutional, randomized studies to assess cancer treatments. Validated tools are available for PRO and QOL.

The literature reviewed has utilized a variety of methods to assess pain, the majority of which represent quality of life tools in which pain is a component. The various tools used result in similar patterns of pain in cancer patients. There is limited study of orofacial pain in cancers other than in HNC, and the literature does not address orofacial pain in pediatric, geriatric, and potential ethnic differences in orofacial pain. Studies to date have focused on mucositis-related pain. There have been no studies assessing comorbidities that may affect orofacial pain in cancer.

- Areas in particular need of continuing research include: developing criteria for assessing and classifying orofacial pain in cancer patients.
- Determine incidence and prevalence of orofacial pain related to different anticancer therapies and related risk factors.
- Study the mechanisms of orofacial pain at the molecular and cellular level and determine how these affect the oral environment.
- Determine the most effective pain management strategies for patients with orofacial pain.

Limited studies have been conducted assessing oral outcomes in pediatric/adolescent cancer populations and in geriatric populations. Also, new therapy including altered fractionation radiation therapy, chemotherapy (induction, concurrent) with or without targeted therapies requires investigation for acute and chronic side effects of therapy. No studies assessing pain and cost of care were identified, while most data was compiled from QOL studies.

Appendix

Table 3 Levels and sources of evidence and grade of recommendation

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, non-experimental 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 level I or II evidence
Suggestion	Guideline based on level 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

Conflict of interest statement None to declare.

References

1. Oral complications of cancer therapies: diagnosis, prevention, and treatment (1989) Available from: http://consensus.nih.gov/1989/1989OralComplicationsCancerTherapy073html.htm[cited Apr 17] 7:1–11
2. Brennan MT, Spijkervet FK, Elting LS (2010) Systematic reviews of oral complications from cancer therapies, Oral Care Study Group, MASCC/ISOO: methodology and quality of the literature (in press). Support Care Cancer
3. Pow EH, McMillan AS, Leung WK, Wong MC, Kwong DL (2003) Salivary gland function and xerostomia in southern Chinese following radiotherapy for nasopharyngeal carcinoma. Clin Oral Investig 7:230–234

4. Graff P, Lapeyre M, Desandes E, Ortholan C, Bensadoun RJ, Alfonsi M, Maingon P, Giraud P, Bourhis J, Marchesi V, Mege A, Peiffert D (2007) Impact of intensity-modulated radiotherapy on health-related quality of life for head and neck cancer patients: matched-pair comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys 67:1309–1317
5. Epstein JB, Robertson M, Emerton S, Phillips N, Stevenson-Moore P (2001) Quality of life and oral function in patients treated with radiation therapy for head and neck cancer. Head Neck 23:389–398
6. Epstein JB, Stewart KH (1993) Radiation therapy and pain in patients with head and neck cancer. Eur J Cancer B Oral Oncol 29B:191–199
7. Magne N, Marcy PY, Chamorey E, Guardiola E, Pivot X, Schneider M, Demard F, Bensadoun RJ (2001) Concomitant twice-a-day radiotherapy and chemotherapy in unresectable head and neck cancer patients: a long-term quality of life analysis. Head Neck 23:678–682
8. Langius A, Bjorvell H, Lind MG (1993) Oral- and pharyngeal-cancer patients' perceived symptoms and health. Cancer Nurs 16:214–221
9. Macquart-Moulin G, Viens P, Palangie T, Bouscary ML, Delozier T, Roche H, Janvier M, Fabbro M, Moatti JP (2000) High-dose sequential chemotherapy with recombinant granulocyte colony-stimulating factor and repeated stem-cell support for inflammatory breast cancer patients: does impact on quality of life jeopardize feasibility and acceptability of treatment? J Clin Oncol 18:754–764
10. Hammerlid E, Bjordal K, hlner-Elmqvist M, Boysen M, Evensen JF, Biorklund A, Jannert M, Kaasa S, Sullivan M, Westin T (2001) A prospective study of quality of life in head and neck cancer patients. Part I: at diagnosis. Laryngoscope 111:669–680
11. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, Leung WK (2006) Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 66:981–991
12. Fang FM, Chien CY, Kuo SC, Chiu HC, Wang CJ (2004) Changes in quality of life of head-and-neck cancer patients following postoperative radiotherapy. Acta Oncol 43:571–578
13. Duke RL, Campbell BH, Indresano AT, Eaton DJ, Marbella AM, Myers KB, Layde PM (2005) Dental status and quality of life in long-term head and neck cancer survivors. Laryngoscope 115:678–683
14. Winter SC, Cassell O, Corbridge RJ, Goodacre T, Cox GJ (2004) Quality of life following resection, free flap reconstruction and postoperative external beam radiotherapy for squamous cell carcinoma of the base of tongue. Clin Otolaryngol Allied Sci 29:274–278
15. Ohrn KE, Wahlin YB, Sjoden PO (2001) Oral status during radiotherapy and chemotherapy: a descriptive study of patient experiences and the occurrence of oral complications. Support Care Cancer 9:247–257
16. Ethunandan M, Rennie A, Hoffman G, Morey PJ, Brennan PA (2005) Quality of dying in head and neck cancer patients: a retrospective analysis of potential indicators of care. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 100:147–152
17. McCarthy GM, Skillings JR (1992) Orofacial complications of chemotherapy for breast cancer. Oral Surg Oral Med Oral Pathol 74:172–178
18. Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB (2003) The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. Cancer 98:1531–1539
19. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, Migliorati CA, McGuire DB, Hutchins RD, Peterson DE, Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (2007) Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 109:820–31
20. Bairati I, Meyer F, Gelinas M, Fortin A, Nabid A, Brochet F, Mercier JP, Tetu B, Harel F, Abdous B, Vigneault E, Vass S, Del VP, Roy J (2005) Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients [see comment]. J Clin Oncol 23:5805–5813
21. Barber C, Powell R, Ellis A, Hewett J (2007) Comparing pain control and ability to eat and drink with standard therapy vs Gelclair: a preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis. Support Care Cancer 15:427–440
22. Epstein JB, Truelove EL, Oien H, Allison C, Le ND, Epstein MS (2001) Oral topical doxepin rinse: analgesic effect in patients with oral mucosal pain due to cancer or cancer therapy. Oral Oncol 37:632–637
23. Oguchi M, Shikama N, Sasaki S, Gomi K, Katsuyama Y, Ohta S, Hori M, Takei K, Arakawa K, Sone S (1998) Mucosa-adhesive water-soluble polymer film for treatment of acute radiation-induced oral mucositis. Int J Radiat Oncol Biol Phys 40:1033–1037
24. LeVeque FG, Parzuchowski JB, Farinacci GC, Redding SW, Rodu B, Johnson JT, Ferretti GA, Eisenberg PD, Zimmer MB (1992) Clinical evaluation of MGI 209, an anesthetic, film-forming agent for relief from painful oral ulcers associated with chemotherapy. J Clin Oncol 10:1963–1698
25. Epstein JB, Elad S, Eliav E, Jurevic R, Benoliel R (2007) Orofacial pain in cancer: part II—clinical perspectives and management. J Dent Res 86:506–518
26. Benoliel R, Epstein J, Eliav E, Jurevic R, Elad S (2007) Orofacial pain in cancer: part I—mechanisms. J Dent Res 86:491–505
27. Stiff PJ, Emmanouilides C, Bensinger WI, Gentile T, Blazar B, Shea TC, Lu J, Isitt J, Cesano A, Spielberger R (2006) Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. J Clin Oncol 24:5186–5193
28. Fang FM, Tsai WL, Chien CY, Chiu HC, Wang CJ, Chen HC, Hsiung CY (2005) Changing quality of life in patients with advanced head and neck cancer after primary radiotherapy or chemoradiation. Oncology 68:405–413
29. Borggreven PA, Verdonck-de LI, Muller MJ, Heiligers ML, de BR, Aaronson NK, Leemans CR (2007) Quality of life and functional status in patients with cancer of the oral cavity and oropharynx: pretreatment values of a prospective study. Eur Arch Otorhinolaryngol 264:651–657
30. Kita T, Yokoyama K, Higuchi T, Kinuya S, Taki J, Nakajima K, Michigishi T, Tonami N (2004) Multifactorial analysis on the short-term side effects occurring within 96 hours after radioiodine-131 therapy for differentiated thyroid carcinoma. Ann Nucl Med 18:345–349
31. Roh JL, Kim AY, Cho MJ (2005) Xerostomia following radiotherapy of the head and neck affects vocal function. J Clin Oncol 23:3016–3023
32. Claus F, Duthoy W, Boterberg T, De Gersem W, Huys J, Vermeersch H, De Neve W (2002) Intensity modulated radiation therapy for oropharyngeal and oral cavity tumors: clinical use and experience. Oral Oncol 38:597–604
33. Schwartz DL, Montgomery RB, Yueh B, Donahue M, Anzai Y, Canby R, Buelna R, Anderson L, Boyd C, Hutson J, Keegan K (2005) Phase I and initial phase II results from a trial investigating weekly docetaxel and carboplatin given neoadjuvantly and then concurrently with concomitant boost radiotherapy for locally advanced squamous cell carcinoma of the head and neck. Cancer 103:2534–2543

34. Schliephake H, Jamil MU (2002) Prospective evaluation of quality of life after oncologic surgery for oral cancer. Int J Oral Maxillofac Surg 31:427–433
35. Hainsworth JD, Meluch AA, McClurkan S, Gray JR, Stroup SL, Burris HA III, Yardley DA, Bradof JE, Yost K, Ellis JK, Greco FA (2002) Induction paclitaxel, carboplatin, and infusional 5-FU followed by concurrent radiation therapy and weekly paclitaxel/carboplatin in the treatment of locally advanced head and neck cancer: a phase II trial of the Minnie Pearl Cancer Research Network. Cancer J 8:311–321
36. Weymuller EA, Yueh B, Deleyiannis FW, Kuntz AL, Alsarraf R, Coltrera MD (2000) Quality of life in patients with head and neck cancer: lessons learned from 549 prospectively evaluated patients. Arch Otolaryngol Head Neck Surg 126:329–335
37. Derks W, de Leeuw RJ, Hordijk GJ, Winnubst JA (2004) Quality of life in elderly patients with head and neck cancer one year after diagnosis. Head Neck 26:1045–1052
38. de Graeff A, de Leeuw JRJ, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM (1999) A prospective study on quality of life of patients with cancer of the oral cavity or oropharynx treated with surgery with or without radiotherapy. Oral Oncol 35:27–32
39. Rogers SN, Miller RD, Ali K, Minhas AB, Williams HF, Lowe D (2006) Patients' perceived health status following primary surgery for oral and oropharyngeal cancer. Int J Oral Maxillofac Surg 35:913–919
40. van Wilgen CP, Dijkstra PU, van der Laan BF, Plukker JT, Roodenburg JL (2004) Shoulder and neck morbidity in quality of life after surgery for head and neck cancer. Head Neck 26:839–844
41. Epstein JB, Emerton S, Kolbinson DA, Le ND, Phillips N, Stevenson-Moore P, Osoba D (1999) Quality of life and oral function following radiotherapy for head and neck cancer. Head Neck 21:1–11
42. Chaturvedi SK, Shenoy A, Prasad KM, Senthilnathan SM, Premlatha BS (1996) Concerns, coping and quality of life in head and neck cancer patients. Support Care Cancer 4:186–190
43. Gellrich NC, Schimming R, Schramm A, Schmalohr D, Bremerich A, Kugler J (2002) Pain, function, and psychologic outcome before, during, and after intraoral tumor resection. J Oral Maxillofac Surg 60:772–777
44. Ingram SS, Seo PH, Sloane R, Francis T, Clipp EC, Doyle ME, Montana GS, Cohen HJ (2005) The association between oral health and general health and quality of life in older male cancer patients. J Am Geriatr Soc 53:1504–1509
45. Connelly ST, Schmidt BL (2004) Evaluation of pain in patients with oral squamous cell carcinoma. J Pain 5:505–510