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REVIEW ARTICLE

Osteoradionecrosis in cancer patients: the evidence base for treatment-dependent frequency, current management strategies, and future studies

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Abstract
Purpose The purpose of this study is to review the evidence base from 1990 to 2008 to (1) clarify the impact of cancer therapies on prevalence of osteoradionecrosis (ORN) in head and neck cancer patients, and to (2) evaluate management strategies and their consequences on quality of life and cost of care.

Methods Articles were selected for the time period beginning after 1989, excluding the 1990 NCI monograph articles from the 1989 NIH-sponsored Oral Complications in Cancer Therapy Symposium that was published in 1990. The search included both Medline/PubMed and Embase and was limited to humans. The search was limited to publications in the English language. No abstracts were utilized in the current

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review. Each article was evaluated by two reviewers. A weighted prevalence was calculated for the prevalence of ORN while incorporating predetermined quality measures. The level of evidence, recommendation grade, and guideline (if possible) were provided for published preventive and management strategies for ORN.

Results A total of 43 articles between 1990 and 2008 were reviewed. The weighted prevalence for ORN included conventional radiotherapy (RT)=7.4%, intensity modulated RT (IMRT)=5.1%, chemoradiotherapy (CRT)=6.8%, and brachytherapy=5.3%. Hyperbaric oxygen may contribute a role in management of ORN. However, no clear guideline recommendations could be established for the prevention or treatment of ORN based on the literature reviewed.

Conclusions New cancer treatment modalities such as IMRT and concomitant CRT have had minimal effect on prevalence of ORN. No studies to date have systematically addressed impact of ORN on either quality of life or cost of care.

Keywords Osteoradionecrosis · Head and neck radiation · Cancer

Introduction

Definition of oral complication and unanswered questions

Osteoradionecrosis (ORN) is characterized by a non-healing area of exposed bone of at least 6 months duration in a patient who has been treated with radiation therapy for cancer. ORN is associated with pain and morbidity and, in advanced stages, typically requires surgical resection and reconstruction for management. An example of a case of ORN of several years duration in a cancer patient is presented (Figs. 1 and 2).

Risk of ORN increases with radiation dosages above 6,000 cGy, previous cancer resection, advanced dental disease status, and postradiation dental extractions [1, 2]. In a cohort of 68 patients with ORN, 34 (50%) had a tooth extraction closely associated with the onset of ORN [2]. However, not all patients who develop ORN have identifiable specific causes. Furthermore, not all risk factors (e.g., severely compromised dentition) predictably cause ORN.

The prevention or treatment of ORN often includes surgical debridement with adjunctive therapies such as antibiotics and hyperbaric oxygen (HBO) therapy. Thus, a major issue relative to ORN is the need to determine optimal preventive or treatment strategies that may or may not include HBO.

A summary of unanswered questions is listed in "Recommendations for future research directions" at the end of this report.

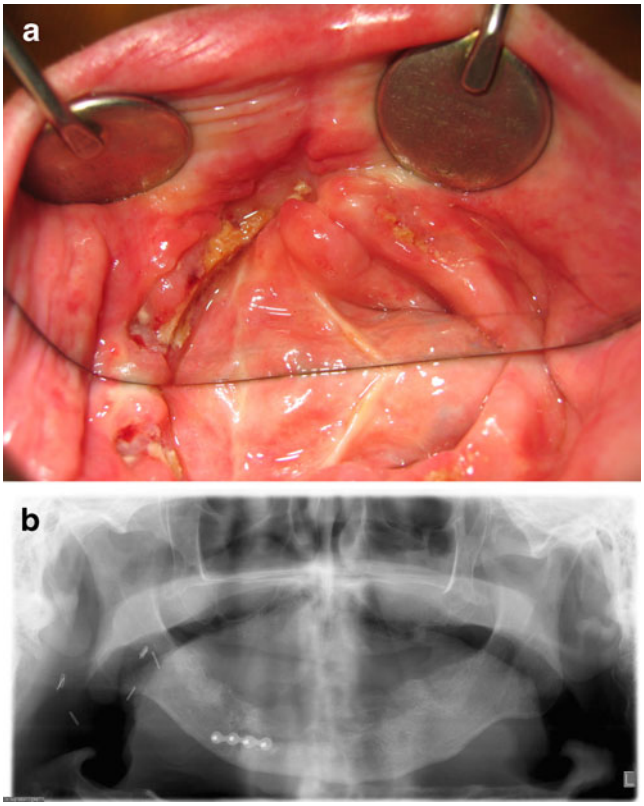

Fig. 1 **a** This patient presented with osteoradionecrosis 2 years after computer-planned curative radiotherapy. Lesion causation was possibly related to an ill-fitting prosthesis. **b** Panoramic image with bony sequestum visible. Treatment included osteosynthesis during ablative surgery, with mandibular splinting

Historical perspective—prior to 1990

The modeling for ORN and its management was initially delineated in the 1980s. It was addressed as a component of the NIH Consensus Conference in 1989 [3]. Key Conference outcomes relative to ORN included the following:

- ORN is one of the most serious complications arising from head and neck radiation therapy.
- Current research has shown that ORN represents non-healing, necrotic bone and is not an infection.
- ORN results from functional and structural bony changes that may not be expressed for months or years. Furthermore, ORN may occur either spontaneously or in response to wound causation.
- Predisposing factors include absorbed radiation dose, fractionation, delivery modality, and dental status.
- Timing of dental extractions and other factors affect incidence.
- ORN may be reduced through early intraoral evaluation, treatment, and adequate healing time prior to beginning radiation therapy.

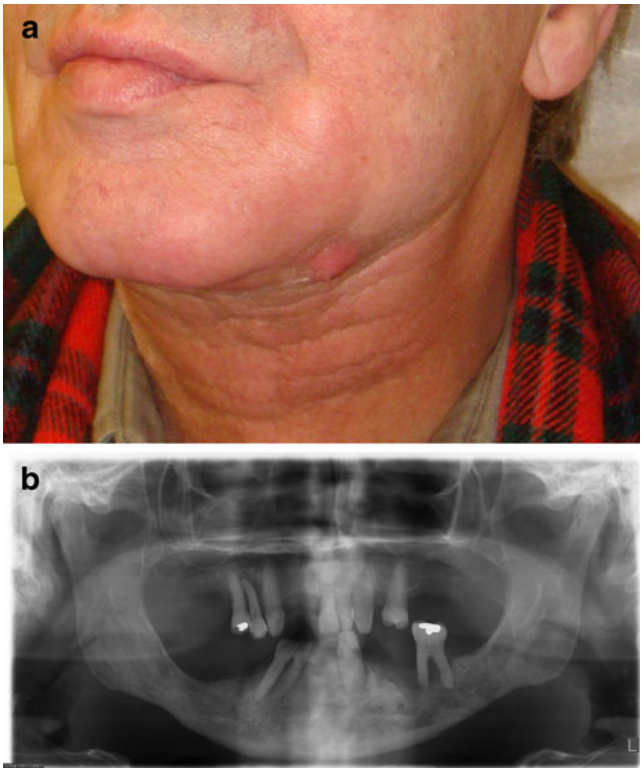

Fig. 2 **a** This patient developed osteoradionecrosis (ORN) 5 years after curative postoperative radiotherapy. Note the extra-oral fistula from ORN of the mandible, in association with periodontal disease with the mandibular molar. No cancer recurrence was identified via biopsy. **b** Panoramic image of the patient demonstrating ORN contiguous with the periodontally compromised mandibular molar. Courtesy of Dr. M. Witjes, University Medical Center Groningen, The Netherlands

- HBO therapy has been beneficial in the prevention and treatment of ORN. It is of paramount importance for the medical community to recognize the factors that may reduce ORN incidence, endorse oral care protocols, and acknowledge the value of HBO therapy in the prevention and treatment of this disease.

Twenty years later, another expert panel convened in April 2009 in Bethesda, Maryland to address oral complications of emerging cancer therapies, including ORN [4]. As noted above, key questions from this conference are summarized in "Recommendations for future research directions" at the end of this report.

Advances in cancer therapies since 1989

New advances in cancer therapy since 1989 are being used to provide more targeted and effective modalities of radiotherapy (RT; e.g., appearance and optimizing of 3D treatment planning, conformal radiation techniques, and intensity modulated RT (IMRT) and proton beam radiation therapy). Since 1989, the standard of care for treatment of more advanced head and neck cancers includes concurrent chemotherapy and RT that frequently incorporates IMRT technology.

New directions in treatment of ORN include ultrasound, biologics, distraction osteogenesis, and antioxidant agents. Given the relative recent use of these technologies, their relationship to ORN incidence and severity has not been systematically reported to date. Therefore, these technologies will not be addressed in further detail in this review.

Aims of systematic review

To extend on the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [3], the goals of this systematic review of ORN as an oral complication of cancer therapies were as follows:

1. Determine the prevalence of ORN by cancer therapy regimen;
2. Determine the impact of ORN on quality of life;
3. Determine the economic impact of ORN;
4. Assess prevention and management strategies for ORN and determine the quality of recommendations for different treatment strategies.

Methodology

Summary of methodology

A systematic literature search was conducted for articles published between January 1, 1990 and December 31, 2008 [5]. The goals of this search were delineation of the prevalence of ORN in head and neck cancer patients treated with RT alone or combined treatment modalities, its impact on quality of life and health care costs, and evaluation of prophylactic or treatment strategies for the lesion.

Literature search utilized

An initial literature search was completed with MEDLINE, CancerLit, EMBASE, Cochrane Library, and Best Evidence [5]. A more specific literature search was completed for the keywords "ORN" and "Cancer" to determine if additional literature was not identified in the initial literature search. Additional studies identified in the references of reviewed articles were also included in this review.

The senior author (MB) compiled of list of articles to be reviewed. A search for additional articles in each section was then performed by the authors.

The search included both Medline and Embase and was limited to humans.

No abstracts were utilized in the current review.

Types of publications excluded

The search was limited to English language [5]. Gender and age were not limited. The following publication types were eliminated by the review panel from the present systematic review: systematic and non-systematic reviews, studies not reporting actual data on ORN, studies reporting redundant data from previous publications or if later follow-up publication relevant, opinion papers and case reports, articles published before 1990, and articles from the 1990 NCI Monograph [3].

Review method

Each article was independently evaluated by two reviewers (WD, AH, AP, DS, and MB) with pilot-tested collection forms [5]. ORN was assessed by the presence (Y/N) when available. Measures of QOL and economic variables were documented if available. Further data collected for each article such as type of study, blinding, presence of control group, scale validity, and samples size were used to determine the quality grading.

Prevalence and weighting

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 utilized and reported in a previous analysis of the incidence of oral mucositis related to cancer therapy [6].

The overall quality adjusted ORN prevalence (p_{overall}) was defined as

$$p_{\text{overall}} = \sum_{j=1}^{J} \frac{\text{qs}_j p_j}{\sum_{i=1}^{J} \text{qs}_i}$$

where q_{sj} is the quality score for the jth study, and p_j is the proportion of subjects with oral complications observed in the jth study [7]. 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 ORN prevalence using the bootstrap method as follows [8]:

One thousand bootstrap samples were generated for each treatment type, and the overall quality weighted oral complication prevalence was calculated for each bootstrap sample. The bootstrap ORN prevalences were ordered from smallest to largest, and the 2.5th percentile and 97.5th percentile bootstrap ORN prevalences were used to approximate the 95% bootstrap confidence interval for the treatment regimen. All analyses were conducted using STATA 10.1 (Statacorp, College Station, TX, USA).

Table 1 presents the raw as well as weighted data. The weighted prevalence data are included in order to enhance the accuracy of estimation of the true prevalence of ORN, by taking into account the study quality parameters as described.

Results

Articles reviewed

Forty-three articles were reviewed as a result of the literature search. The cancer types evaluated included the following: nasopharynx or sinus squamous cell carcinoma (SCCA)—one study; oropharynx, oral cavity, or tonsil SCCA—15 studies; and mixed head and neck SCCA—28 studies. Conventional RT was evaluated in 38 studies, IMRT in four studies, and brachytherapy in one study. Fifteen studies evaluated combined RT and CT, and 13 studies assessed patients treated with brachytherapy (with or without CT). The study design

Table 1 Weighted prevalence of osteoradionecrosis in relation to type of cancer therapy

	Number of studies (reference number)	Number of patients	Mean raw prevalence (%)	Mean weighted prevalence (%)	Standard error	95% confidence interval
During cancer therapy						
Conventional RT	26 [27–52]	3,607	7.3	7.4	0.01	4.8–10.0
IMRT	4 [23–26]	680	3.1	5.2	0.02	0.0–12.0
Radiotherapy and chemotherapy	11 [24, 25, 27, 38, 42–44, 49–52]	673	6.2	6.8	0.01	3.6–10.1
Brachytherapy	10 [26, 28, 31, 32, 34, 35, 40, 45, 49, 53]	2,457	7.0	5.3	0.01	2.7–7.9

types included randomized clinical trials (n=2), before and after studies (n=10), cohort studies (n=29), and case–control studies (n=2).

Prevalence

Prevalence of ORN could be determined from 31 studies where the presence of ORN was appropriately assessed (Table 1). The weighted prevalence for ORN in patients treated with conventional RT was 7.4%, with IMRT=5.2%, with RT+chemotherapy (CT)=6.8%, and with brachytherapy with or without additional RT=5.3%.

Impact on quality of life

There were no studies evaluating the quality of life impact of ORN.

Economic impact

There were no studies evaluating the economic impact of ORN.

Prevention and/or treatment strategies

Description of number of articles and types of strategies evaluated

A total of 13 studies that addressed intervention for the prevention or treatment of ORN was evaluated.

Summary of results for the different prevention and treatment strategies

(A) Prevention of ORN (Table 2)

1. Spacers in brachytherapy

One study evaluated if spacers could prevent ORN in a cohort of patients treated with brachytherapy. There was a much higher prevalence of ORN in patients that were treated without spacers (40%) vs. those that were treated with spacers (2%) [9].

2. HBO therapy

HBO therapy is commonly recommended for prevention of ORN, but the clinical efficacy and the cost-effectiveness of

Table 2 Prevention of osteoradionecrosis

Prevention strategy	First author (reference number)	Prevention regimen	Sample size	Number of cases of ORN (%)
Targeted cancer therapies				
IMRT	[23–26]	All four studies utilized IMRT	N=503	10 (0.2%)
			N=14	1 (7.1%)
			N=90	9 (10%)
			N=73	1 (1.4%)
Prevention of ORN with spacers	[9]	Brachytherapy with spacers	N=48	1 (2.1%)
		Brachytherapy without spacers	N=55	22 (40%)
Prevention of ORN prior to dental extractions				
Hard tissue replacement	[37]	Placed bioplant hard tissue replacement therapy: nonresorbable, microporous polymeric composite that consists of a polymethyl methacrylate (PMMA) substrate sintered with polyhydroxyethyl methacrylate (pHEMA), and a calcium hydroxide graft coating	N=8 (44 teeth extracted)	0 (0%)
Postoperative antibiotics	[48]	Post-op antibiotics 1 week (pen 250 mg 4×/day) or longer until epithelialization of socket with 0.2% chlorhexidine 1–2 weeks after extraction	N=43 (237 teeth extracted)	2 (5%) patients 4 (2%) of all teeth extracted
Removal of third molars pre-RT	[51]	Group 1: extraction of impacted third molars before radiotherapy	N=58	2 (3%)
		Group 2: no extraction of impacted third molars before radiotherapy	N=38	2 (5%)
HBO therapy	[11]	Group 1: received prophylactic HBO prior to extractions postradiation	N=29	1 (3.4%)
		Group 2: did not receive prophylactic HBO prior to extractions postradiation	N=7	1 (14.3%)
HBO therapy	[12]	Group 1: received prophylactic HBO prior to extractions postradiation	N=7	0 (0%)
		Group 2: did not receive prophylactic HBO prior to extractions postradiation	N=100	2 (2%)
HBO therapy	[13]	HBO therapy: 20 pre-extraction and 10 post-extraction sessions at 2.4 ATA for 90 min on 100% oxygen once a day, 5 days a week	N=40 (456 teeth)	7 (2%) of all teeth

this therapy is unclear. As previously noted, dental extractions increase the risk of ORN; therefore, effective preventive therapies would be an important strategy to avoid this problematic long-term side effect of radiation therapy. In an earlier prospective clinical trial in 1985, Marx et al. showed pre- and postoperative antibiotics with atraumatic extractions in postradiation patients had a complication rate of 29.9%, while HBO decreased the complication rate to 5.4% [10]. Following the 1989 NIH Consensus Conference [3], two retrospective cohort studies have assessed the prevalence of ORN in patients receiving post-RT dental extractions that either did or did not receive HBO prior to extractions. A study by Vudiniabola et al. demonstrated one case of ORN in 29 postradiation patients (3.4%) treated with prophylactic HBO prior to extractions, while one of seven patients (14.3%) who did not receive prophylactic HBO developed ORN [11]. In another study by Sulaiman et al., two cases of ORN developed in 100 post-RT patients (2%) not treated with prophylactic HBO prior to extractions, while none of the seven patients who did receive prophylactic HBO developed ORN [12]. Of the seven patients who did receive HBO therapy, one developed a secondary tumor, and another patient developed a new primary solid tumor. In a report by Adkinson et al., ORN did not develop in 40 patients receiving prophylactic HBO therapy for dental extractions post-RT, but no comparison group was evaluated in this study [13].

3. Other preventive strategies

Limited prevention studies regarding hard tissue replacement in extraction sites, use of postoperative antibiotics, and removal vs. leaving impacted third molar preradiation treatment are also reported in Table 2. Additional studies are required to further evaluate these preventive options.

(B) Treatment of ORN (Table 3)

1. HBO therapy alone

HBO therapy provides a pressurized environment where patients breathe 100% oxygen. Originally developed for the

Table 3 Treatment of osteoradionecrosis

Treatment strategy	First author (reference number)	Treatment regimen	Sample size	Response to treatment: ORN resolution
HBO therapy	[20]	Protocol I: 10 pre- and 5 post-op HBO sessions Surgery: decortication with periosteal grafting	*N*=7	6 (86%)
		Protocol II: 5–10 pre- and 5–7 post-op HBO sessions Surgery: decortication with periosteal grafting	*N*=29	27 (93%)
	[19]	Experimental group: HBO with conservative therapies of augmentin, analgesics, quinolone, debridement/curettage, with irrigation	*N*=31	6 (19%)
		Control group: "placebo" HBO with conservative therapies of augmentin, analgesics, quinolone, debridement/curettage with irrigation	*N*=37	12 (32%)
	[18]	HBO only group	*N*=20	13 (65%)
		Surgery group: included a wide range of surgical treatments such as partial mandibulectomy and microvascular transplantation, additional debridements	*N*=21	14 (67%)
	[17]	HBO only group	*N*=19	7 (37%)
		HBO with sequestrectomy	*N*=20	18 (90%)
		HBO with resection	*N*=12	11 (92%)
	[16]	HBO and sequestrectomy	*N*=5	2 (40%)
		Sequestrectomy only	*N*=3	2 (67%)
	[13]	30 pre-debridement sessions: each treatment at 2.4 ATA for 90 min on 100% oxygen once a day, 5 days a week	*N*=106	45 (42%)
	[15][a]	Conservative therapy: antibiotics, curettage, debridement, and small sequestrectomy	*N*=58	23 (40%)
		Surgery I: extensive sequestrectomy and marginal resection of the mandible with or without soft tissue reconstruction	*N*=14	7 (50%)
		Surgery II: segmental resection of the mandible with or without reconstruction of soft tissue and/or the mandible	*N*=15	13 (87%)
Pentoxifylline	[21]	Pentoxifylline (800 mg) and vitamin E (1,000 IU) for 6 months	*N*=10	9 (90%)
		Pentoxifylline (800 mg) and vitamin E (1,000 IU), along with 1,600 mg/day clodronate, 1 g/day ciprofloxacin, and 16 mg/day methylprednisolone 2 days a week for 6 months	*N*=8	7 (88%)
Vascularized bone-containing flap	[22]	Surgical reconstruction with vascularized bone-containing free flaps harvested from fibula, iliac crest, and scapula	*N*=9	9 (100%)

[a] Only seven patients received HBO therapy

treatment of decompression sickness, it is primarily used today as a management strategy of wound care. The mechanisms of action for HBO are thought to include enhanced perfusion, stimulation of collagen matrix for new blood vessels, improved resting oxygen levels, and bactericidal activity [14].

Seven studies were identified that evaluated the efficacy of HBO therapy with or without varying degrees of surgical management [13, 15–20]. In general, HBO therapy does not appear to have a significant advantage in resolution of ORN compared to surgical management. Resolution rates of ORN with HBO ranged from 19% to 93% and seemed to improve with concomitant surgical intervention. A 2004 randomized, placebo-controlled multicenter trial demonstrated no benefit of HBO therapy in the management of active ORN [19].

2. Pentoxifylline

One study assessed the efficacy of pentoxifylline and vitamin E in a cohort of 18 patients that were refractory to prior therapy including antibiotics (n=9), HBO therapy (n=6), and/or sequestrectomy (n=6) [21]. All patients received 2–4 weeks of amoxicillin/clavulanate (2 g/day), fluconazole (50 g/day), and methylprednisolone (16 mg/day) prior to pentoxifylline and vitamin E. This open-label study design demonstrated an 89% resolution of ORN, but additional, larger cohort studies that are placebo-controlled are needed to determine the efficacy of this treatment option.

3. Vascularized bone-containing flap

A small open label study of nine patients with ORN demonstrated 100% resolution with the use of a vascularized bone-containing flap [22]. Confirmation with larger studies is necessary to demonstrate the efficacy of this surgical therapy.

Summary

This systematic review identified the following overall trends in the literature:

(A) Prevention of ORN

- Four studies included consideration of IMRT, a targeted cancer therapy, relative to ORN prevention [23–26]. These studies collectively demonstrated that although the weighted prevalence with IMRT was lower than with conventional RT (5.2% vs. 7.3%, respectively), additional studies are needed to determine if this difference is clinically significant.
- Three studies evaluated the use of HBO therapy for the prevention of ORN in patients requiring dental extractions. In two non-randomized studies [11, 12], a comparison was made between patients who did vs. those who did not receive preventive HBO prior to dental extractions. Together, these two studies demonstrated a similar prevalence of ORN with 1/36 (2.8%) in the HBO group and 3/107 (2.8%) in the non-HBO group. In another study that assessed 40 patients who all receive preventive HBO prior to dental extractions, ORN was identified in seven of 456 (1.5%) of the teeth extracted [13].
- Four other studies were identified that reported on clinical interventive strategies to prevent ORN. Of these,
  - One study involved brachytherapy with or without spacers (randomized study, n=103). A statistically significant difference in prevalence of ORN was observed (brachytherapy with spacers, 2.1%; brachytherapy without spacers, 40%).

  The three other studies were directed to,
  - Hard tissue replacement (open label study, n=8);
  - Postoperative antibiotics (open label study, n=43);
  - Removal of third molars pre-RT (randomized, n=96).

(B) Treatment of ORN

- HBO-based treatment of ORN has received the most comprehensive analysis and reporting, accounting for seven of the nine studies evaluated. The clinical research has been both retrospectively as well as prospectively based.
- The remaining two, non-HBO treatment strategies reported in the literature include pentoxyfilline (one randomized study; n=18) and vascularized bone-containing graft (one open label study, n=9).

This status of literature reported to date has resulted in limitations of the current evidence base, as summarized in "Summary of limitations of current literature" below. These limitations in turn permit generation of only selected clinical preventive or treatment recommendations relative to ORN, as described below. Current clinical decision-making for prevention or treatment of ORN is thus based on the relatively limited scope of research to date combined with professional judgment and experience.

Research opportunities exist relative to each domain cited below and as then summarized in "Recommendations for future research directions." If successful, such research may provide the evidence base for a more comprehensive list of recommendations for prevention and treatment of ORN in the future.

Prevalence

A total of 43 articles between 1990 and 2008 were reviewed. The weighted prevalence for ORN was similar between the different cancer therapies: conventional RT (RT)=7.4%, IMRT=5.1%, chemoradiotherapy=6.8%, and brachytherapy=5.3%.

It is important to note that few studies were available for assessment of prevalence in relation to type of cancer therapy. Therefore, the weighted prevalence may not be an accurate representation of the true prevalence of ORN associated with IMRT. The difference in the mean raw prevalence and the mean weighted prevalence reflects the range of differences in study quality with the four studies evaluated in the present review.

It is also noteworthy that there was a wide range of cancer therapies reported in the literature that was reviewed. Therefore, we stratified by the four groups as delineated in Table 1. Further stratification by other specific cancer therapies was not relevant to this analytic approach, given the small number of studies (example, n=one or two) that would have otherwise resulted from this strategy. This current limitation of the collective literature could be obviated by increasing the number of high quality studies in the future. This expansion of number of published studies could in turn lead to further delineation of the relationship of IMRT and other therapies to prevalence for ORN.

QOL and economic impact

No studies to date have systematically addressed either the quality of life or health care cost impact of ORN.

High quality new clinical research in these fields is needed.

Prevention strategies with level of evidence, recommendation grade, and guideline classification

Use of prophylactic HBO therapy for the prevention of ORN in patients requiring post-RT dental extractions

Level of evidence III, recommendation grade C: no guideline possible.

Management strategies with level of evidence, recommendation grade, and guideline classification

HBO therapy for treatment of ORN

Level of evidence II, recommendation grade B: single therapy HBO not recommended for treatment of ORN.

(Note: This conclusion is directed to single therapy HBO only vs. HBO in combination with other treatment including surgery).

Summary of limitations of current literature

The current literature is collectively limited in scope and/or quality by the following issues:

- Limited number of randomized, double-blind, placebo-controlled trials;
- Evolving protocols relative to delivery techniques for RT;
- Dynamic nature of concurrent chemotherapy regimens and introduction of novel drugs (e.g., biologics) with unknown effects on the ORN trajectory;
- Clinical trial design issues, including the following:
  - Definitions of clinical endpoints and grading of ORN;
  - Variations in follow-up periods;
  - Assessment/reporting of patient-related factors (e.g., vasculo-connective tissue and other systemic disease conditions;
  - Limited reporting of local RT dose/distribution to the mandible.

Recommendations for future research directions

New research, particularly large prospective observational and clinical trials, is needed to answer the questions listed below. These questions have emerged from both the current systematic review as well as the April 2009 conference "Oral complications of emerging cancer therapies" [4].

Questions that ideally should be addressed in large, prospective, multi-center, observational studies of risk, outcomes, and cost of ORN for various treatment strategies are as follows:

- What is the role of radiation treatment strategy and dental planning in relation to ORN?
- Are there specific valid predictors of risk for ORN?
- What is the impact of ORN on quality of life and cost of care?
- How do the emerging, novel cancer therapies affect prevalence of ORN?

Questions that ideally should be addressed in prospective clinical trials are as follows:

- Is prevention of ORN possible?
- What is the role of "adjuvant preventive therapy" (e.g., HBO; antibiotics)?
- Is there a subset of patients at risk for ORN for whom HBO is or is not effective?
- What is the most effective method of treatment of ORN?
- What are the mechanistic and clinical relationships of novel ORN treatment modalities (e.g., ultrasound, biologics, distraction osteogenesis, and antioxidants) in relation to ORN management?

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