Evidence of dental screening for oral foci of infection in oncology patients
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Chapter 2

Evidence supporting pre-radiation elimination of oral foci of infection in head and neck cancer patients to prevent oral sequelae. A systematic review.

JM Schuurhuis, MA Stokman, MJH Witjes, PU Dijkstra, A Vissink, FKL Spijkervet

Edited version of:
Abstract

**Background and purpose:** Pre-radiation dental screening of head-neck cancer patients aims to identify and eliminate oral foci of infection to prevent post-radiation oral problems. The evidence for the efficacy of dental screening is unclear. In this systematic review, we analyzed available evidence on the efficacy of pre-radiation elimination of oral foci of infection in preventing oral sequelae.

**Materials and Methods:** A search was conducted (MEDLINE/EMBASE) for papers published up to May 2014. Papers on head-neck cancer patients subjected to pre-radiation dental screening, (chemo)radiation and oral follow-up were included.

**Results:** Of the 1770 identified papers, 20 studies fulfilled the inclusion criteria of which 17 were retrospective. A great heterogeneity in patient groups, dental screening techniques, definitions of oral foci of infection and techniques for eliminating foci was found. Most papers lacked essential details on how dental screening was performed and a clear definition of an oral focus of infection. The evidence for efficacy of elimination of oral foci of infection to prevent post-radiotherapy oral sequelae was inconclusive.

**Conclusions:** Consequently, the efficacy of pre-radiation elimination of oral foci of infection remains unclear. No conclusions can be drawn about a definition of an oral focus of infection and whether pre-radiation elimination of these foci should be mandatory. We therefore suggest prospective studies with well-defined criteria for oral foci of infection, a clear description of which foci were eliminated and how, a detailed description of pre-radiation dental screening, clearly described patient and tumor characteristics, and a detailed dental history and dental status. Subsequently, oral problems that occur post-radiation should be systematically recorded.

Introduction

Radiotherapy is an effective treatment option for a wide variety of head and neck neoplasms. Unfortunately, it causes acute and long term adverse oral effects. While some adverse effects are unavoidable, others, in particular the risk of developing jaw osteoradionecrosis (ORN), are thought to be reduced by a thorough pre-radiation dental screening to detect oral foci of infection [1,2]. In this review we have operationalized the concept of oral focus of infection as a pathologic process in the oral cavity that does not cause major problems in healthy individuals, but may lead to severe local or systemic inflammation under certain circumstances [3,4]. A pre-radiation dental screening aims to locate and eliminate oral foci of infection, such as caries profunda, periodontal attachment loss, periapical problems and partially or completely impacted teeth [3-5], thus prevent radiation-related oral complications. Little evidence exists on the efficacy of elimination of oral foci of infection to prevent post-radiotherapy oral sequelae [5,6]. Nevertheless, pre-radiation dental screening of patients is daily practice in head and neck cancer centers [7,8]. Head and neck oncology patients are known to have poor dental status compared to healthy subjects [9-12]. The poorer dental status is thought to be related to the more frequent alcohol and tobacco abuse and lower dental awareness in these patients.

Prevention of jaw osteonecrosis associated with radiotherapy, known as osteoradionecrosis (ORN), a feared late complication of radiotherapy, is probably the main reason that dental teams all over the world perform a pre-radiation dental screening of patients [3]. Despite the extensive literature on this topic, the mechanisms underlying ORN are not well understood. One risk factor for ORN, identified in the systematic review by Nabil et al. [3], is post-irradiation extraction of the mandibular tooth within the radiation field. Consequently, post-irradiation extractions should be avoided as much as possible, and pre-radiation screening for oral foci of infection is necessary. Other risk factors for developing ORN are tumor characteristics [13,14], total radiation dose [14-16], bacterial infections [17,18], dental status [19], periodontitis [12], and surgical interventions [20].

In this systematic review we analyzed the available evidence for the efficacy of pre-radiation elimination of oral foci of infection in head and neck cancer patients to prevent post-radiotherapy oral sequelae. We focused specifically on the following questions: Is pre-radiation elimination of oral foci of infection in head and neck cancer patients efficient and should pre-radiation elimination of these oral foci be mandatory?
Materials and methods

Search strategy
A broad literature search was conducted in MEDLINE/PubMed and EMBASE for papers published up to May 2014 (Supplementary Table 1). No language filters were applied. Meta-analysis, systematic reviews, randomized controlled trials, clinical studies and cohort studies were considered as sources for evidence to answer the research question.

Review strategy
After the search was conducted, duplicates were removed and the remaining papers were subjected to title and abstract analysis by 2 reviewers (JMS, MAS) independently. Title and abstract were included for full text analysis if the terms ‘head and neck cancer’ and ‘(chemo)radiation’ or synonyms were present, combined with mention of pre-radiation oral or dental care, oral or dental screening, or pre-radiation extraction, or oral status or synonyms. Single case reports, opinion papers, narrative or expert reviews, surveys, and letters to the editor were excluded, as were papers about pre-adult patients (<18 years), chemotherapy as a single treatment, surgery as a single treatment, effects of radiation on tooth structures, mucositis, and microbiology. The papers selected after title and abstract analysis were classified by study type.

The selected studies were included for full text analysis if head and neck cancer patients received external beam radiotherapy, a pre-radiation dental screening had been performed, criteria for oral foci were described (what was considered an oral focus) and patients were assessed for oral sequelae at least once after radiation (Supplementary Table 2). Two reviewers (JMS, MAS) independently analyzed the studies for the inclusion criteria and extracted data if the study was included, using a self-developed evaluation form (Supplementary Table 2). Disagreements about including or excluding studies or about extracted data were resolved after discussion. In case of insufficient information in the manuscripts for adequate assessment, the corresponding authors were contacted for more details.

Results
The search resulted in 1770 papers, 540 hits in PubMed and 1230 hits in EMBASE (figure 1). After removing duplicates, 1469 papers remained for title and abstract analysis. Out of the 234 papers eligible for full text analysis, 205 papers (63%) were available in full text on the internet and after contacting international library databases. Of these 205 papers, 124 papers (60%) were guidelines, protocols and descriptive papers that did not investigate or analyze effects of dental screening on prevention of oral sequelae, so they were excluded. The remaining 81 papers were subjected to full text analysis using the evaluation form (Supplementary Table 2). No randomized controlled trials were found.

In 3 out of 81 papers, an oral focus of infection was not clearly defined. The authors of these studies were contacted for more details [9,21,22]. One author [9] did not respond and one author [21] could not provide more details. These papers were excluded. Niewald et al. [22] did provide more details on their definition of oral foci of infection.

Table 2). No randomized controlled trials were found.

In 3 out of 81 papers, an oral focus of infection was not clearly defined. The authors of these studies were contacted for more details [9,21,22]. One author [9] did not respond and one author [21] could not provide more details. These papers were excluded. Niewald et al. [22] did provide more details on their definition of oral foci of infection.
The included papers
After full text analysis, 20 studies met the inclusion criteria (Table 1). Three papers were prospective [23-25], the others were retrospective [2,12,22,26-39]. References of the 20 included studies were checked to find any additional relevant studies. None were found.

Study characteristics
The number of patients in the included studies ranged from 28 [25] to 1140 [32] (Table 1). Duration of follow-up ranged from 6 [25,27] to 60 months [29]. Five studies did not describe the duration of follow-up [26,31,33,38,39]. Tumor location was well described in most studies (Table 1). Some studies included a great variety of tumor locations in the head and neck region. Although these were not always specified in the article, most studies included other tumor sites as well, such as unknown primary tumors, non-Hodgkin lymphoma and Hodgkin lymphoma [2,23,25,27-29,31,34,35,37,39]. Two studies [33,38] included only nasopharynx carcinoma patients. Some studies also included edentulous patients in their study population.

Pre-radiation dental screening
Most papers lacked details on how dental screening was performed (Table 2), but commonly, radiographic examination (n=14) and periodontal probing (n=19) were performed.

Oral foci of infection
The descriptions of oral foci of infection in the papers varied greatly: we found 7 definitions for periodontitis, 4 for caries, 2 for pulpal pathology and 5 for radiographic findings (Table 3). Four of the studies provided a very precise description of what was assumed to be a focus of infection, such as “caries in which excavation may lead to pulpal exposure” [12,26,34,35], but other studies lacked adequate detail in the descriptions. They used more general terms such as “active moderate periodontal disease” [37] or “advanced/severe periodontal disease” without defining the severity of periodontitis [22-24,26-32,34-38].

Nine studies reported on the findings of the dental screening [12,24,25,28,30,31,34-36] (Table 1). In six studies [12,24,30,31,34,36] the percentage of patients presenting with oral foci was described, ranging from 20% [30] to 79% [31]. Detailed information on the type of oral foci of infection found was provided in 6 studies [12,24,25,28,34,35] (Table 1).

Generally, more recent studies reported on the presence of periodontal disease as focus of infection at pre-radiation screening, whereas in most of the older studies the periodontal condition of the patients was not reported. Prevalence of periodontitis in pre-radiation dental screening in the more recent studies ranged from 54% to 93% in dentate subjects [12,24,25].

As shown in Table 1, we found a wide variation of pre-radiation interventions to eliminate oral foci of infection, including tooth extraction (all studies), scaling and root planing (6 studies), restoration (9 studies), surgical removal of root or wisdom tooth (10 studies), endodontic treatment (4 studies), and apexification (2 studies).

Other interventions
In 16 studies, oral hygiene instructions were given before the start of radiotherapy, either as part of the dental screening or early in the treatment process [2,12,22-26,28-32,35,36,38,39]. Dental calculus removal was described as part of the dental screening or as a procedure early in the treatment process in 12 studies [12,22,24-29,31,33,36,38]. Fluoride application during and after radiotherapy was advised in 18 studies [2,12,22-30,33-39]. Most studies advised daily application of a fluoride gel. Neutral fluoride gel was prescribed in 8 studies [2,12,25,29,30,33,34,39]. The other studies did not report the type of fluoride gel [22,36] or prescribed a 1% NaF-gel [27], 2% NaF-gel or 1.23% APF-gel [38], 1.23% NaF-gel, 0.4% stannous [26,35,37] or 1.1% NaF-gel [37], NaF-gel without percentage [23] or 3% NaF-rinse [28].

Evidence for effects of pre-radiation elimination of oral foci of infection in preventing oral sequelae

Oral sequelae after radiotherapy
ORN was reported in 17 studies (Table 1). In 4 studies, ORN was defined as exposed bone through an opening in the overlying mucosa, persisting as a non-healing wound for 3 months or more [12,29,35,37]. One study used ORN of grade 2 or higher according to the classification by Glanzmann and Grätz [36]. Another study used the Common Terminology Criteria for Adverse Events version 3.0 [2]. No clear definition for ORN was found in 11 studies [22,24,26-28,30,32,34,38,39]. Prevalence of ORN ranged from 0% [2,38] to 23% [22]. In studies with a short follow-up, ORN was seldom seen [27,34]. In a study with a mean follow-up of 35 months, no cases of ORN were reported [2].

Post-radiotherapy dental extractions were reported in 13 studies [2,12,22,23,26-30,34,35,37,39]. Post-radiotherapy extractions ranged from 4% [27] to 57% of patients [34]. In 5 studies ORN was seen in patients who were subjected to post-radiotherapy extractions, but no significantly increased risk was reported for developing ORN after post-radiotherapy extractions [12,26,27,29,37]. The reason for post-radiotherapy extraction, if reported, was periodontal disease [12,28,30] or caries [30].

Prospective studies
The prospective study by Pochanugool et al. [23] analyzed the effects of three fluoride-regimes: fluoride gel, fluoride rinse or both. Patients were subjected to a pre-radiation dental screening and subsequent extraction of unrestorable teeth.
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Study design</th>
<th>Nr of pts</th>
<th>FU in months</th>
<th>Location (n)</th>
<th>Findings dental</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral foci</td>
<td>Perio</td>
</tr>
<tr>
<td>1976</td>
<td>Keys</td>
<td>R</td>
<td>246</td>
<td>-</td>
<td>Head and neck cancer</td>
<td>-</td>
</tr>
<tr>
<td>1976</td>
<td>Regezi</td>
<td>R</td>
<td>130</td>
<td>≥12</td>
<td>Nasopharynx (15) Oral cavity (101) Pharynx (5) Other (15)</td>
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</tr>
<tr>
<td>1981</td>
<td>Horiot*</td>
<td>R</td>
<td>528</td>
<td>≤6</td>
<td>Nasopharynx (12) Oral cavity (155) Pharynx (167) Others (206)</td>
<td>-</td>
</tr>
<tr>
<td>1987</td>
<td>Epstein</td>
<td>R</td>
<td>146</td>
<td>60</td>
<td>Head and neck cancer (115) Others (31)</td>
<td>-</td>
</tr>
<tr>
<td>1989</td>
<td>Levendor</td>
<td>R</td>
<td>100</td>
<td>48</td>
<td>Oral cavity</td>
<td>20</td>
</tr>
<tr>
<td>1990</td>
<td>Brown*</td>
<td>R</td>
<td>92</td>
<td>-</td>
<td>Nasopharynx (7) Oral cavity (47) Pharynx (22) Others (22)</td>
<td>79</td>
</tr>
<tr>
<td>1992</td>
<td>Kumar</td>
<td>R</td>
<td>1140</td>
<td>48</td>
<td>Oral cavity</td>
<td>-</td>
</tr>
<tr>
<td>1994</td>
<td>Pochanugool</td>
<td>P</td>
<td>29 gel</td>
<td>44.1</td>
<td>Nasopharynx (50) Pharynx (4) Other (19)</td>
<td>-</td>
</tr>
<tr>
<td>1996</td>
<td>Niewald</td>
<td>R</td>
<td>52 HF</td>
<td>34</td>
<td>Oral cavity (168)</td>
<td>-</td>
</tr>
<tr>
<td>1999</td>
<td>Epstein</td>
<td>R</td>
<td>57</td>
<td>-</td>
<td>Nasopharynx</td>
<td>-</td>
</tr>
<tr>
<td>2003</td>
<td>Sulaiman</td>
<td>R</td>
<td>187</td>
<td>22.1</td>
<td>Nasopharynx (29) Oral cavity (68) Pharynx (29) Other (6)</td>
<td>41</td>
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<td>2004</td>
<td>Oh</td>
<td>R</td>
<td>55 extr</td>
<td>33.5</td>
<td>Nasopharynx (17) Oral cavity (28) Pharynx (1) Other (37)</td>
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</tr>
<tr>
<td>2006</td>
<td>Bonan*</td>
<td>P</td>
<td>40</td>
<td>28.7</td>
<td>Nasopharynx (2) Oral cavity (36) Pharynx (2)</td>
<td>-</td>
</tr>
<tr>
<td>2007</td>
<td>Ben-David</td>
<td>R</td>
<td>176</td>
<td>35</td>
<td>Oral cavity (152) Pharynx (20) Other (4)</td>
<td>-</td>
</tr>
<tr>
<td>2007</td>
<td>Chang</td>
<td>R</td>
<td>413</td>
<td>Median 45.6</td>
<td>Oral cavity</td>
<td>Others</td>
</tr>
<tr>
<td>2008</td>
<td>Wang</td>
<td>R</td>
<td>181</td>
<td>-</td>
<td>Nasopharynx</td>
<td>-</td>
</tr>
<tr>
<td>2011</td>
<td>Schuurhuis</td>
<td>R</td>
<td>80</td>
<td>26</td>
<td>Oral cavity</td>
<td>75</td>
</tr>
<tr>
<td>2011</td>
<td>Studer</td>
<td>R</td>
<td>143 conv</td>
<td>40</td>
<td>Oral cavity</td>
<td>73</td>
</tr>
<tr>
<td>2013</td>
<td>Bueno</td>
<td>P</td>
<td>9 healthy</td>
<td>6</td>
<td>Oral cavity (18) Pharynx (4) Others (6)</td>
<td>-</td>
</tr>
<tr>
<td>2014</td>
<td>Duarte</td>
<td>R</td>
<td>158</td>
<td>-</td>
<td>Oral cavity (28) Pharynx (89) Nasopharynx (21)Others (20)</td>
<td>-</td>
</tr>
</tbody>
</table>
In another prospective study [24], 40 patients with squamous cell carcinoma in the head and neck region and with a low socioeconomic status received pre-radiation treatment. Multiple teeth were extracted due to poor dental conditions and inadequate oral care. It could not be shown that extraction of poor teeth prevented ORN. ORN developed in the mandibles of 5 patients who were heavy users of tobacco and alcohol. These patients had received >63 Gy.

The prospective study by Bueno et al. [25] compared 2 groups of patients with malignant tumors of the upper aerodigestive tract subjected to radiotherapy. One group had periodontal disease (pockets 4-5 mm) and was treated accordingly. The controls were patients with a healthy periodontium and were not periodontally treated. Despite the radiation or chemoradiation, periodontal status improved in cancer patients subjected to pre-radiation periodontal treatment for up to 6 months after cancer treatment. Outcomes on ORN were not reported.

### Retrospective studies

One retrospective study [26] compared head and neck cancer patients who had been subjected to a program of dental care with a historic control group treated with radiotherapy prior to the start of the dental care program. The patients subjected to the dental care program, fewer extractions, fewer clinic visits, and less caries were reported. No data on ORN were provided.

Another study [29] assessed the relationship between ORN and tooth extractions by reviewing dental records of irradiated head and neck cancer patients. A greater risk of ORN was shown when teeth were extracted after radiotherapy. Of the patients who were subjected to post-radiotherapy extractions, 5% (3 out of 42) developed ORN as opposed to 7% (5 out of 92)(p=1.000) in patients who had extractions before radiotherapy. One retrospective study [32] reported on ORN incidence in a cohort of patients after dental screening and elimination of oral foci. ORN was observed in 14 out of 1140 patients (1%).

A third retrospective study [22] compared ORN frequency after hyperfractionated radiotherapy to conventionally fractionated radiotherapy (n=168 patients). Hyperfractionation led to an ORN frequency of 23%, compared to 9% in the conventionally treated group, whereupon hyperfractionation was discontinued.

A fourth retrospective study [35] compared two groups of head and neck cancer patients with impacted third molars: extraction (n=55 patients) and non-extraction (n=38 patients). Twelve patients were included in both groups as they had at least one, but not all, impacted molars removed before radiotherapy. The aim of this study was to determine how pre-irradiation extractions vs retention of impacted third molars affected the risk of ORN: 4 patients (2 in each group) developed ORN.

A fifth study [37] involved a cohort of head and neck cancer patients subjected to radiotherapy to determine whether pre-radiation elimination of oral foci could prevent ORN. Pre-radiation extractions were accompanied by a higher incidence of ORN compared to patients who did not have pre-radiation extractions (15% ORN vs 9%). The overall conclusion of that study was that pre-radiation extractions did not reduce the risk of ORN of the mandible following radiotherapy in dentate patients.

In three of the retrospective studies [2,36,39], patients were treated with intensity modulated radiation therapy (IMRT). In the other 17 studies, conventional radiotherapy was given. In the study by Ben-David et al. [2], strict prophylactic oral care in IMRT patients was evaluated. No ORN was found after a mean follow-up of 35 months. The IMRT-study by Studer et al. [36] evaluated minimally invasive oral care compared to conventional oral care in patients undergoing IMRT, using the ORN rate as outcome variable for efficacy of oral care. Based on their data, risk-adapted minimally invasive oral care was recommended before starting IMRT. ORN was seen in 2% of patients in the conventional oral care group after a mean follow-up of 40 months. In the minimally invasive group, 1% of patients developed ORN after a mean follow-up of 19 months.

The third IMRT study [39] compared dental health of head and neck cancer patients receiving IMRT compared to conventional radiotherapy. After dental screen-
ing, only patients without dental disease were included. Patients treated with IMRT exhibited significantly less ORN (0% vs 10%). The conclusion of this study was that the number of post-radiotherapy extractions has been reduced following the introduction of IMRT, even more so with a complete dental evaluation prior to radiotherapy.

Discussion

In our review, we found only low-level evidence to answer the questions of whether pre-radiation elimination of oral foci of infection in head and neck cancer patients is efficient and whether pre-radiation elimination of these oral foci should be mandatory. Most studies did not even use a univocal definition of an oral focus of infection, or it was unclear what was considered an oral focus.

Generally, an oral focus has been defined in the literature as ‘a pathologic process in the oral cavity that does not cause major problems in healthy individuals, but may lead to severe (local or systemic) inflammation under certain circumstances’ [3,4]. This definition does not indicate which pathology may lead to post-radiation oral problems such as ORN. One inclusion criterion for our review (Supplementary Table 2) was that a particular study should clearly define an oral focus of infection. Remarkably, in almost a quarter of the papers of which we read the full text, criteria for oral foci were not described. This resulted in the exclusion of those papers, even when the other inclusion criteria were met. Furthermore, when analyzing the included papers, we found no consensus about which foci of infection should be eliminated. This was due to the variety of definitions of an oral focus of infection (see Table 3). However, we did find agreement that “hopeless teeth” have to be extracted and “healthy teeth” have to be retained.

Another major issue that prevented us from drawing a more straightforward conclusion from the included papers was that the content of the dental screening performed was often not described clearly (Table 2). For example, most papers reported periodontal probing, but the periodontal examination was not clearly described. Moreover, in some papers periodontal probing was not described in the methods section, but probing, pocket depth and/or periodontitis results were described in the results, tables and figures. In these cases, we assumed that periodontal probing had actually been performed. This was also the case for furcation involvement, recession, plaque and mobility. Since radiotherapy may aggravate periodontal disease [40] or increase the risk of ORN [12], a full periodontal examination is advised as part of the dental screening, including probing depth, gingival recessions, mobility, furcation involvement, dental calculus, plaque and bleeding index.

Dental radiographs were often part of dental screening (Table 2). We advise to routinely make a panoramic radiograph, based on ALARA (as low as reasonably achievable) principles, to determine any impacted teeth, root tips, periapical problems, cysts and other radiological problems, as was done in 7 out of 19 studies. In addition, bitewings, periapical radiographs or both have to be made on indication.

Future studies in this field should therefore report in detail on how the dental screening was performed; otherwise the effects of dental screening on the post-radiation oral sequelae, such as ORN, cannot be assessed.

Although we gathered demographic data on age, tumor site, TNM-classification, histology, oncologic treatment and cumulative radiation dose during the assessment of the included studies (Supplementary Table 2), only tumor location is provided in Table 1 since the other data were reported in a great variety and could not be summarized in a compact table. In order to analyze the effects of pre-radiation elimination of oral foci of infection to prevent ORN, which etiology is multifactorial and not fully understood [41], there is a need for prospective studies with clearly described oncologic treatment modalities and well defined criteria for oral foci of infection. In addition, the studies should report which foci were eliminated and which oral sequelae occurred after radiotherapy. The follow-up period should at least be 2 years, since late side effects such as ORN take time to develop [3]. Moreover, the onset of ORN is influenced by many factors, including baseline dental hygiene, dental history, dental IQ, time between foci elimination and radiotherapy, post-radiation oral care, patient compliance to preventive post-radiotherapy regimens and genetics [41]. Unfortunately, these factors were not described in the majority of the included studies and could therefore not be analyzed.

In the majority of the included studies, patients were treated with conventional radiotherapy. However, in the last decade treatment modalities have changed substantially, for instance due to the introduction of IMRT around 2003 [42]. The exact effects of IMRT on the oral tissues and jaw bone in particular are not yet clear. It has been shown that IMRT results in less xerostomia due to sparing of the parotid and/or submandibular glands [43]. But at the same time, sparing of glands may result in higher doses to the other tissues in the radiation field, such as the jawbone [44]. These potentially higher doses to the jawbone increase the risk of developing ORN.

The reported outcomes in the included studies on occurrence of ORN after IMRT were limited due to a rather short follow-up [2,36]. Recently, a study was published with a longer follow-up (median of 37.4 months) [45] showing a low incidence of ORN (1%). However, 54% of the patients included in the latter study had a tumor located outside the oral cavity or oropharynx, resulting in a lower radiation dose to the jaws. This might be accompanied by a lower incidence of ORN. We therefore conclude that it is mandatory to assess the exact effects of IMRT on the oral tissues and jaw bone and the incidence of ORN.

Periodontal disease, either pre- or postradiotherapy [12,19,22], is possibly related to a higher risk of ORN. The effects of IMRT on periodontally diseased teeth should be further assessed, since many head and neck cancer patients with oral foci present with periodontal disease. Bueno et al. [25] evaluated the effects of pre-radiation periodontal treatment in patients with pockets of 4-5mm. Six
months after radiotherapy, periodontal status had improved. However, the follow-up period of six months is too short to evaluate whether periodontal breakdown recurred and to evaluate whether periodontal treatment may increase the risk of ORN. All patients in this study received oral hygiene instructions, which would probably lead to improvement of the periodontal status. The study made no distinction between the effects of oral hygiene instructions and the effects of periodontal treatment. The results of initial periodontal treatment of teeth with pockets ≥6 mm in patients scheduled for radiotherapy are unclear and hardly any literature on this topic is available \[40,46\]. Thus, prognostic research designs might be useful to answer the question of whether or not teeth with pockets ≥6 mm should be removed or periodontally treated.

Another risk factor for ORN mentioned in various studies is alcohol/tobacco abuse \[12,22,24,28,29,32,33\]. Future studies might reveal that patients who use tobacco and/or alcohol abusively require extraction of their remaining teeth, due to the increased risk of developing ORN and the lack of compliance of many of these patients with oral hygiene instructions and caries prophylaxis.

The consensus in the dental field appears to be that a high level of oral hygiene is important during and after radiotherapy; oral hygiene instructions, removal of dental calculus and fluoride application were described in detail in the included studies. The study by Pochanugool \[23\] concluded that daily home fluoride application will prevent radiation caries. However, an increase of filling rate after radiation was reported, and extraction rate decreased. An increased number of fillings implies that more caries lesions occurred, although the authors concluded that fluoride application prevented radiation caries. Extraction rates will decrease if more teeth are preserved by filling. Consequently, it is difficult to interpret the results and conclusions.

Of the oral sequelae occurring after radiotherapy, ORN was most often reported (in 16 of 19 studies). Post-radiotherapy dental extractions (17 studies) were also described. Most studies (84%) did not report why post-radiotherapy extractions were needed. It would be valuable to know if all oral foci of infection were eliminated before the onset of radiotherapy, or if oral foci remained. The rationale for pre-radiation removal of oral foci can be justified only when such information is provided.

We included no randomized controlled trials in our systematic review. If only randomized controlled trials were accepted as appropriate evidence, then our research questions would have remained unanswered. By including prospective and retrospective cohort studies in this review, we aimed to answer the research questions, albeit with a lower level of evidence, to provide the field with up-to-date information on the assumed efficacy of pre-radiation elimination of oral foci of infection in head and neck cancer, and to point out the need for higher level of evidence from future well-designed and well-written studies.
In summary, after systematically reviewing the literature, the efficacy of pre-radiation elimination of oral foci of infection on preventing oral sequelae remains unclear. We were also unable to find an unequivocal definition of an oral focus of infection and determine whether pre-radiation elimination of foci should be mandatory. This was due to a great heterogeneity in patient groups, dental screening techniques, definitions of oral foci of infection and techniques for eliminating these oral foci, and a lack of detail in the included studies on how screening on oral foci of infection was performed and what was considered as such an oral focus.

Notwithstanding the low level of evidence in the literature regarding the efficacy of screening and/or elimination of oral foci present, we hypothesize that the following should be considered as significant oral foci of infection and should be either effectively treated before onset of radiotherapy or be eliminated before onset of radiotherapy, when effective treatment of a particular focus of oral infection is not feasible:

- deep caries in which excavation may lead to pulpal exposure;
- active periodontal disease with pockets ≥ 6 mm, furcation ≥ grade 1, mobility > grade 1, gingival recession ≥ 6mm and especially a combination of these periodontal problems;
- non-restorable teeth with large restorations, especially those extending the gum line or with root caries, or those with severe erosion or abrasion;
- periapical granuloma and avital teeth;
- (partially) impacted or partially erupted teeth not fully covered by bone or showing radiolucency; cysts and other radiographic abnormalities.

To test this hypothesis, we recommend that future trials should include:
- a description in detail of what is considered to be an oral focus of infection;
- a description in detail of the treatment given to eliminate these oral foci of infection;
- a clear description of the content of the pre-radiation dental screening;
- a detailed description of patient and tumor characteristics, including age, tumor site, TNM-classification, histology, oncologic treatment, alcohol/tobacco use and cumulative radiation dose;
- a detailed description of the dental history and baseline dental status;
- an in detail description of the oral sequelae that occurred after head and neck radiotherapy;
- the follow-up period should be >2 years to be able to detect late sequelae of radiotherapy.

### Table 3. Definition of oral focus of infection.

<table>
<thead>
<tr>
<th>Periodontitis</th>
<th>Advanced/severe periodontal disease [6,9,10,12-18,20,21,23-25]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Furcation involvement [11,12,19,21,22]</td>
</tr>
<tr>
<td></td>
<td>Mobility (with furcation involvement)* [11,12,20*,22,26]</td>
</tr>
<tr>
<td></td>
<td>Periodontal disease pockets ≥ 6 mm [5,11,22,26]</td>
</tr>
<tr>
<td></td>
<td>Active moderate periodontal disease [24]</td>
</tr>
<tr>
<td></td>
<td>Advanced recession [22]</td>
</tr>
<tr>
<td></td>
<td>Periodontal disease pockets &gt; 5 mm [19]</td>
</tr>
<tr>
<td>Caries</td>
<td>(Deep*) caries (in which excavation may lead to pulpal exposure**) [5**,6,10*,12**, 13*-15,18,20**,21**,23]**</td>
</tr>
<tr>
<td></td>
<td>Unrestorable carious teeth [9,16,17,19,20,22,25,26]</td>
</tr>
<tr>
<td></td>
<td>Caries that extended to the gum line [22,26]</td>
</tr>
<tr>
<td></td>
<td>Teeth with large, compromised restorations [22,26]</td>
</tr>
<tr>
<td>Pulpal pathology</td>
<td>Apically pathology [5,14,16-18,21,23,25]</td>
</tr>
<tr>
<td></td>
<td>Nonvital teeth [6,17,23]</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td>(Partially) Impacted teeth [5,12,16,17,20,21,25]</td>
</tr>
<tr>
<td></td>
<td>Root tips (not fully covered by bone or showing radiolucency*) [5,6,12,20*,25]</td>
</tr>
<tr>
<td></td>
<td>Incomplete eruption [6,20,21]</td>
</tr>
<tr>
<td></td>
<td>Cysts [5]</td>
</tr>
<tr>
<td></td>
<td>Radiographic abnormalities [5]</td>
</tr>
</tbody>
</table>

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References


[35] Oh HK, Chambers MS, Garden AS, Wong PF, Martin JW. Risk of osteoradionecrosis after extraction of impacted third molars in


