Chapter 7

General discussion
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This thesis assessed the efficacy of pre-treatment dental screening in head and neck cancer (HNC) patients subjected to radiotherapy and in hematology patients subjected to intensive chemotherapy regarding complications during treatment and follow-up.

At the start of this PhD project, there was a lack of evidence for dental screening and elimination of oral foci of infection, especially considering new treatment modalities, such as intensity modulated radiation therapy (IMRT) with or without adjuvant chemotherapy. Based on the studies performed in this PhD study, it can be concluded that the assessed dental screening protocol was equally effective in patients treated with IMRT, IMRT combined with chemotherapy (CHIMRT) and in patients treated with conventional radiotherapy, since post-radiotherapy oral and dental morbidity seen was comparable. However, not all oral sequelae can be prevented and the need for further research remains.

It was found that in particular HNC patients with periodontal disease before radiotherapy were prone to develop bone healing problems after radiotherapy. Furthermore, in hematology patients, it was shown that chronic oral foci of infection can be left untreated as leaving these foci untreated does not increase infectious complications during intensive chemotherapy.

What to consider as an oral focus of infection?

Little evidence exists on the efficacy of elimination of oral foci of infection to prevent post-radiotherapy oral sequelae [1,2], nor is it clear what to consider as an oral focus of infection in specific patient groups. In our systematic review (Chapter 2), we found only low-level evidence to answer the questions of whether pre-radiation elimination of oral foci of infection in HNC patients is efficient and whether pre-radiation elimination of these oral foci should be mandatory. This review confirmed that most studies yet published did not even use a univocal definition of an oral focus of infection, or it was unclear what was considered an oral focus [3]. After using the same efficient dental screening protocol in both a retrospective (Chapter 3) and a prospective study (Chapter 5), we suggest that the following should be considered as an oral focus of infection in HNC patients:

- deep caries in which excavation may lead to pulpal exposure;
- active periodontal disease with pockets ≥6mm, 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.

As mentioned before, we showed that chronic oral foci of infection can be left untreated in hematology patients subjected to intensive chemotherapy, as this does not increase infectious complications during intensive chemotherapy (Chapter 6). The study described in chapter 6 also showed that what to consider as an oral focus of infection is dissimilar in chemotherapy patients than in patients submitted to radiotherapy. This is due to the fact that the adverse effects of chemotherapy are mainly reversible and that the risk of developing complications related to oral foci of infection is probably not higher than in healthy subjects, once the patient had recovered from oncologic treatment and blood levels have normalized. This is in contrast to radiotherapy, where the effects are mainly irreversible and the risk to develop complications remains a lifelong. Unlike previous studies that focused on acute conversions of previously diagnosed chronic dental disease [4], we focused on systemic complications of chronic oral foci of infection. Based on the outcomes of this prospective study, we recommend pre-chemotherapy dental screening and treatment of acute oral foci of infection in intensively treated leukemia patients and patients subjected to high-dose chemotherapy and autologous stem cell transplantation (ASCT) as follows:

- ask and examine patients if they had any symptoms like tooth related or oral mucosa related pain, percussion or palpation tenderness of oral structures, fever related to oral pathology, swelling of oral tissues and/or tooth related purulent drainage that might be caused by a pathology related to the oral mucosal and/or dental hard tissues during the past 3 months. These acute oral problems and pathologies should be eliminated before the onset of chemotherapy.

Osteoradionecrosis

The results of our retrospective study (Chapter 3) suggest that patients presenting with severe periodontal disease at dental screening are prone to develop osteoradionecrosis (ORN), particularly when the periodontally affected teeth in these patients are not (aggressively) treated. Our prospective study (Chapter 5) showed that patients with periodontal disease before IMRT/CHIMRT were indeed prone to develop bone healing problems after IMRT/CHIMRT. The better execution of the dental screening protocol (teeth with pockets ≥6mm were extracted instead of maintained and treated with initial periodontal therapy) may have lowered our ORN prevalence and this might explain the less strong relation between periodontal disease and ORN found in the prospective study than in the retrospective study [5]. It has to be mentioned, however, that our study may have been underpowered to find a significant difference, but the results of our prospective study at least point towards the hazard of periodontal disease with regard to a higher risk of developing bone healing problems post-radiotherapy.

This hazard might increase during long-term follow-up, because due to the less reduced salivary flow rate seen after IMRT compared to conventional radiotherapy, the risk of developing rapidly progressing dental caries may reduce. As a result, teeth will be longer preserved in IMRT patients, increasing the risk to develop peri-
To quantify periodontal disease, the periodontal inflamed surface area (PISA) was used in the prospective studies (Chapter 5 and 6) described in this thesis [6]. As PISA is a measure for inflammation load, it was very suitable to use in our hematology study (Chapter 6) assessing the effect of leaving chronic oral foci, such as periodontally affected teeth, on infectious systemic complications. However, when assessing the relation between periodontal disease and bone healing problems/ORN, which is a local problem, we preferred to look at pocket progression at the tooth level (Chapter 5) as removal of teeth already greatly reduced the PISA score. Thus, PISA scores are not preferred in radiotherapy studies.

In our study on oral microflora (Chapter 4), we found an almost immediate effect after the elimination of oral foci of infection, with a decrease of periodontal pathogens. However, rather high percentages of periodontal pathogens were present after 1 year of follow-up and may have caused the progression of pocket depth observed. It is also suggested in literature that changes in cellularity, vascularity and reduced healing/remodeling potential of the periodontium contribute to the increased risk of periodontal involvement after radiotherapy [7]. Also, compromised oral hygiene and reduced salivary flow may underlie the progression of periodontal disease.

Guidelines pre-radiotherapy dental screening in head and neck cancer
Although no strict guidelines for pre-radiotherapy dental screening and elimination of oral foci exist, the studies in HNC patients in this thesis have shown that a strict execution of a dental screening protocol is mandatory. Not aggressively treating periodontally affected teeth pre-radiotherapy resulted in an increased risk for ORN (Chapter 2) and patients with periodontal disease before IMRT were prone to develop bone healing problems after IMRT (Chapter 5). Progression of periodontal pocket depth was observed in 24% of HNC patients after IMRT/CHIMRT. The patients’ periodontal status at dental screening and the probability of progression of periodontal disease after IMRT/CHIMRT should be considered carefully in dental treatment planning before radiotherapy. A strict execution of a well-defined dental screening protocol is likely to result in fewer post-radiotherapy extractions and therefore, less ORN since post-radiotherapy extractions are a well-known risk factor [8,9]. Although there is no literature available evaluating the economic impact of ORN [10], high costs are inevitable when for example surgical intervention and hyperbaric oxygen therapy are mandatory. Reducing the incidence of ORN is likely to reduce health care costs and more importantly, may prevent suffering from the patients.

It is recommended to perform a pre-radiotherapy dental screening for HNC patients subjected to radiotherapy according to an (as far as yet available) evidence-based protocol, as applied in our prospective study (Chapter 5). This screening should preferably be done at least 10-14 days before the start of radiotherapy to allow for healing of, e.g., extraction sites. Additionally, oral hygiene instructions should be given. All patients need to be evaluated for periodontal disease, as periodontal disease, according to the results presented in Chapters 3 and 5, probably is a condition making subjects prone to develop ORN. Thus, the starting point of a pre-radiotherapy dental screening should be which teeth can be maintained, when considering (1) the long term prognosis of the teeth in relation to the disease status of the patient, (2) the patient’s ability to maintain a proper level of oral hygiene depending on, amongst others, motivation and physical abilities and (3) the patient’s susceptibility to develop ORN. A careful, frequent (at least twice a year), standardized oral follow-up with repeated oral hygiene instructions is needed after radiotherapy, at least in dentate patients.

Guidelines dental screening in intensively treated hematologic patients
Although no strict guidelines for pre-chemotherapy dental screening and elimination of oral foci exist, the hematology study in this thesis has shown that a less aggressive approach can be executed in leukemic patients subjected to intensive chemotherapy and in multiple myeloma (MM), non-Hodgkin’s lymphoma (NHL) or Hodgkin’s lymphoma (HL) patients subjected to high-dose chemotherapy and ASCT (Chapter 6). Such an approach is likely to be beneficial for these hematologic patients, as removal of teeth just before or during neutropenic phases of their disease may compromise nutrition, and malnutrition is associated with a lower quality of life [11]. Tooth extraction directly before the start of intensive chemotherapy also leads to a risk for infection, bleeding or delayed wound healing, which may require postponing oncologic treatment [12], or otherwise increase bacteremia with a higher chance of septic complications. For survivors, treatment of diseased teeth can be postponed until oncologic treatment is completed and blood levels have normalized. Moreover, pre-chemotherapy dental work-up will be less time consuming and therefore less expensive, when only acute oral foci of infection, seen in less than 10% of our patients, have to be treated instead of all the chronic oral foci seen in over 70% of our patients scheduled for intensive chemotherapy.

Based on our study outcomes it is recommended to perform pre-chemotherapy dental screening in leukemic patients subjected to intensive chemotherapy and in MM/NHL/HL patients subjected to high-dose chemotherapy and ASCT. With regard to the dental screening, oral foci of infection should be defined as acute or chronic. Chronic oral foci of infection can be left untreated, while acute oral foci of infection should be eliminated, preferably before onset of chemotherapy or otherwise early thereafter.

Recommendations for future research
More prospective studies are needed with well-defined criteria for oral foci of infection, a clear description of which foci were eliminated and how, a detailed description of how dental screening was done, clearly described patient and tumor characteristics, and a detailed dental history and dental status. Although our pro-
spective study was a good start, a larger patient group would be preferable, especially regarding low incidence of oral sequelae such as ORN. In future studies, the oral problems that occur post-IMRT should be systematically recorded. Doing so would allow for a sound comparison of prospective studies which would result in a higher level of evidence for performing dental screening and eliminating oral foci of infection pre-radiotherapy than the mainly retrospective cohort studies that are currently available. Amongst others, the relation between periodontal disease and bone healing problems can be assessed in a meta-analysis once sufficient comparable prospective studies are available.

We will continue to follow our HNC cohort, which will provide the readership with long term data on the efficacy of dental screening in preventing oral sequelae such as ORN in IMRT/CHIMRT patients.

Regarding intensive chemotherapy patients, prospective studies with larger patient groups are needed, to assess whether leaving chronic oral foci untreated may lead to a significantly longer duration of fever and neutropenia, as our results showed a strong trend when comparing duration of neutropenia (p=0.066) and fever (p=0.059) in patients with and without chronic oral foci of infection. If this trend would be found statistically significant, patient factors such as the level of oral hygiene and PISA scores may play an important role and have to be assessed, as bad oral hygiene and a large periodontal inflamed surface area may increase the risk for bacteremia with oral microorganisms. Frequent bacteremia may result in a longer duration of neutropenia and fever. The assessed protocol of leaving chronic oral foci of infection untreated could still be executed, however, since we did not see infectious complications related to oral microorganisms. The alternative, which is tooth extraction, leads to a risk for infection, bleeding or delayed wound healing, which may require postponing oncologic treatment [12], or otherwise increase bacteremia with a higher chance of septic complications.

To be able to find a significant difference between patients with and without chronic oral foci of infection, regarding the number of positive blood cultures (respectively, 73% and 69% of those patients had positive blood cultures in our study) a sample size calculation showed that over 4000 patients will be needed. As such high numbers are needed to find a significant difference, it is important that the applied methods in future studies allow comparison between studies, since it is not feasible for a single institution or even multicenter studies to include such a high number of patients.

References


