Chapter 1

Introduction and aim of the thesis
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Pre-treatment dental screening aims to locate and eliminate oral foci of infection in order to prevent local, loco-regional or systemic complications during and after treatment [1-3]. An oral focus of infection is defined as a pathologic process in the oral cavity that does not cause major infectious problems in healthy individuals, but may lead to severe local or systemic inflammation under certain circumstances [4,5].

Acute and chronic oral foci of infection can be distinguished:
- An oral focus of infection is considered acute when that focus showed one or more of the following clinical symptoms or those symptoms were reported by the patient to have occurred during the last 3 months: 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.
- An oral focus of infection is considered chronic when that focus had not exacerbated and was asymptomatic during the previous 3 months [6].

Dental screening usually involves clinical examination of the oral cavity, including oral mucosa, dentition, and periodontium, combined with radiographic imaging of the dentition and jaw bones [1]. Dental screening on oral foci of infection is done for a variety of patient groups at risk including head and neck cancer (HNC) patients subjected to radiotherapy and/or chemoradiation, hematologic patients subjected to high-dose or intensive chemotherapy, patients on intravenous bisphosphonates and patients with fever of unknown origin [7,8].

Frequently observed potential oral foci of infection include caries profunda, periodontal disease, periapical problems, (partially) impacted or partially erupted teeth not fully covered by bone or showing radiolucency, cysts, non-vital pulps and ulcerations [9-11]. However, which pathologic oral process should be considered as an oral focus of infection is dependent on the underlying medical problem. For example, patients with an oral squamous cell carcinoma treated with curative ionizing radiation therapy to the head and neck region possess a lifelong risk to develop treatment related sequelae, such as osteoradionecrosis (ORN) of the jaws [12,13]. Therefore, it is commonly accepted, although not evidence driven, that such patients have to be free of oral foci of infection 10-14 days before the onset of radiotherapy to allow possible tooth extraction wounds to heal [1,10]. On the contrary, the effects of chemotherapy on healthy oral tissues are essentially temporary and reversible. Thus, the risk of developing complications related to chronic oral foci of infection is probably not higher than in healthy subjects once patients have recovered from chemotherapy and their blood levels have normalized [9]. Removal of oral foci of infection can therefore be less aggressive in chemotherapy patients and can probably be limited to acute oral foci of infection and chronic oral foci of infection that have recently caused complaints.

Although frequently executed, dental screening on oral foci of infection is, as mentioned before, hardly evidence based [1-3,10]. Screening on oral foci of infection is mainly based on clinical experience and retrospective cohort studies. Moreover, even until today there is a great national and international variety between institutions when it comes to the groups of patients that are routinely seen for a dental screening as well as which oral foci of infection have to be considered as an oral focus of infection [3,14,15]. Not much seems to be changed over the years because of a lack of evidence due to a lack of well-designed studies.

In this thesis, two groups of patients in whom usually a dental screening is performed before onset of therapy are assessed, viz., HNC patients subjected to radiotherapy and hematology patients undergoing intensive chemotherapy or high-dose chemotherapy and ASCT, in order to gain more evidence for this screening on oral foci of infection.

Head and neck cancer

Radiotherapy to the head and neck region results in multiple acute and late side effects such as a reduced salivary flow (hyposalivation), a sensation of oral dryness (xerostomia), dental caries, fungal and bacterial infections, loss of taste, oral mucositis, trismus and skin-fibrosis [9,12,16]. The main reason for dental screening on oral foci of infection is to prevent acute and long-term oral sequelae, especially ORN. Comparison of the data on ORN reported in the literature is hard as no unequivocal definition of ORN is applied which may result in under- or overreporting of ORN. For example, many patients may have low-grade jaw complications, such as exposed bone, which is not unequivocally reported as ORN [17].

The last decade, radiation treatment of HNC has changed substantially, amongst others due to the introduction of intensity modulated radiation therapy (IMRT) and concomitant chemoradiation (CIMRT) [18]. The exact effects of IMRT on the oral microflora, oral tissues and jaw bone are not yet clear, including its impact on what oral foci of infection have to be considered an oral focus of infection needing treatment before onset of therapy. For example, it has been shown that IMRT results in less xerostomia due to sparing of the parotid and/or submandibular glands [19-21]. But at the same time, sparing of, e.g., salivary glands may result in higher doses to the other tissues in the radiation field, such as the jaw bone [22]. Higher doses to jaw bone bear the risk of a higher risk of developing ORN. Therefore, a prospective cohort study has to be conducted to assess the effects of IMRT on post-radiation oral sequelae as well as to assess the efficacy of dental screening and elimination of oral foci of infection in IMRT-patients. Additionally, the effects of IMRT on oral microbial composition have to be assessed as a possible factor underlying certain post-radiotherapy oral sequelae.
Hematologic patients

Patients undergoing chemotherapy are prone to develop, often reversible, oral side effects, such as oral mucositis, xerostomia, taste changes, and local and systemic infections [23]. Intensive or high-dose chemotherapy given to hematologic patients could cause severe neutropenia (absolute neutrophil count <500/µL), which puts patients at high risk of infections, sepsis and septic shock [24]. Chemotherapy can also be given be given as adjuvant treatment in HNC patients, often combined with radiotherapy, but in a lower dose that does not cause neutropenia. It is in fact the neutropenia that makes the problems occurring in high-dose chemotherapy patients dissimilar from the problems occurring in irradiated patients, as high-dose chemotherapy neutropenia significantly increases the risk for infectious complications. However, once chemotherapy has ended, neutrophil counts return to normal thereby reducing the risk of developing oral complications related to oral foci of infection to that of healthy subjects. However, in hematologic patients undergoing high-dose chemotherapy and allogeneic stem cell transplant, oral complications may last longer and be of a different kind due to graft versus host disease [25]. These patients were not assessed in this thesis.

The efficacy of dental screening for oral foci of infection in intensively treated chemotherapy patients is questionable: Do acute and chronic oral foci of infection indeed have to be removed before onset of therapy or can the treatment of certain chronic oral foci of infection be postponed until after treatment?

In many institutions, like at the University Medical Center Groningen, the Netherlands, hematologic patients subjected to intensive chemotherapy or high-dose chemotherapy and ASCT are routinely screened for oral foci of infection before starting intensive treatment [26]. Acute exacerbation of oral foci of infection is presumed to result in bacterial translocation from the oral cavity to the blood. To minimize the risks of developing oral sequelae and to reduce the chance of developing neutropenic fever, oral foci of infection which are anticipated to potentially cause problems during chemotherapy are routinely eliminated. The literature suggests that acute oral foci of infection should be eliminated, but that certain types of chronic oral foci of infection can be left untreated [6,27,28]. The underlying studies had mixed patient groups and/or a small number of patients [6,27,28] or reported on the need for treatment of postendodontic asymptomatic periapical radiolucencies only [27]. Therefore, the hypothesis has to be tested that chronic oral foci of infection that did not cause complaints for at least the last 3 months do not have to be eliminated before chemotherapy in leukemic patients subjected to intensive chemotherapy and multiple myeloma (MM), non-Hodgkin’s lymphoma (NHL) or Hodgkin’s lymphoma patients subjected to high-dose chemotherapy and autologous stem cell transplantation (ASCT).

Aim of the thesis

The general aim of this thesis was to assess the efficacy of pre-treatment dental screening in HNC patients subjected to radiotherapy as well as in hematology patients subjected to intensive chemotherapy or high-dose chemotherapy and ASCT regarding complications during treatment and follow-up.

Sub-goals

To systematically review the literature on the efficacy of pre-radiation dental screening in head and neck cancer patients (Chapter 2).
To retrospectively assess whether pre-radiation dental screening for oral foci of infection in head and neck cancer patients is effective (Chapter 3).
To retrospectively identify risk factors, related to the oral problems as observed prior to radiotherapy, for oral sequelae after radiotherapy (Chapter 3).
To assess the effects of radiation therapy in head and neck cancer patients on oral microbial composition in a prospective cohort study comparing patients who had surgery, postoperative or primary IMRT and postoperative or primary CHIMRT (Chapter 4).
To prospectively assess oral sequelae that may occur during follow-up in head and neck cancer patients treated with IMRT/CHIMRT (Chapter 5).
To prospectively assess the effect of leaving chronic oral foci untreated on infectious complications during intensive chemotherapy in a cohort of hematology patients (Chapter 6).
References


