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# Patients with advanced periodontal disease before intensity-modulated radiation therapy are prone to develop bone healing problems: a 2-year prospective follow-up study

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## Abstract

**Purpose** Intensity-modulated radiation therapy (IMRT) has changed radiation treatment of head and neck cancer (HNC). However, it is still unclear if and how IMRT changes oral morbidity outcomes. In this prospective study, we assessed the outcome of reducing post-IMRT sequelae by means of pre-radiation dental screening and eliminating oral foci.

**Methods** All consecutive dentate patients > 18 years, diagnosed with primary oral or oropharyngeal carcinoma, referred for pre-treatment dental screening between May 2011 and May 2013, were included and followed for 2 years. Patients were treated with IMRT or IMRT with chemotherapy (CHIMRT). Dental screening data, demographic data, and data on oral sequelae during follow-up were recorded. Diagnosed oral foci were treated before start of the radiation therapy.

**Results** Oral foci were found in 44/56 (79%) patients, consisting predominantly of periodontal breakdown. Bone healing problems after radiotherapy occurred more often in patients with periodontal pockets  $\geq 6$  mm at baseline (19 vs. 4% in patients with pockets < 6 mm). Osteoradionecrosis developed in 4/56 patients (7%) during follow-up. In line with this observation, multiple logistic regression analysis showed

that the periodontal inflamed surface area, which is higher in patients with more severe periodontal disease, predicted that a patient has a higher risk on developing osteoradionecrosis or bone healing problems ( $p = 0.028$ ).

**Conclusions** Patients with severe periodontal disease before IMRT/CHIMRT are more prone to develop bone healing problems post-radiotherapy.

**Keywords** Head and neck cancer · Intensity-modulated radiotherapy · Chemoradiotherapy · Dental focal infection · Osteoradionecrosis · Periodontitis

## Introduction

Head and neck cancer (HNC) patients treated by radiotherapy are at risk of developing severe oral sequelae. Periodontal disease, an inflammatory disease affecting the tissues surrounding the teeth resulting in inflammation of the gums and loss of bone adjacent to the affected teeth, and radiation-associated dental caries may require dental extractions and consequently result in an increased risk of developing osteoradionecrosis (ORN) of the jaw [1–4]. ORN is radiation-induced destruction of the bone. ORN is difficult to treat, not self-limiting, and may require extensive invasive surgery and/or adjuvant treatment with hyperbaric oxygen (HBO). Hypovascularity and hypocellularity of irradiated tissues are considered the predominant underlying pathophysiological mechanisms, which have low reparative ability [5, 6]. The majority of ORN cases develop within 3 years after radiotherapy [7].

Risk factors for developing ORN include post-irradiation extractions [1], periodontal attachment loss/periodontitis [2],

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oral surgical interventions [8], and poor dental status [9]. To prevent oral morbidity after radiotherapy, in particular ORN, pre-radiation dental screening is commonly performed to locate and eliminate oral foci, although the efficacy of these interventions is unclear [3]. An oral focus is defined 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 [1, 10].

During the last decade, treatment of HNC has changed substantially, particularly due to the introduction of intensity-modulated radiation therapy (IMRT) and concomitant chemoradiation [11]. The effects of IMRT on oral tissues and jaw bone in particular are not yet clearly understood. IMRT results in less reduction of salivary flow due to sparing of the parotid and/or submandibular glands [12]. However, dose redistribution resulting from salivary gland sparing may lead to higher doses to other tissues in the radiation field, in particular to the oral mucosa, which can result in “beam path toxicities” [13]. These potentially higher doses to jaw bone and oral tissues entail a higher risk of developing ORN post-radiotherapy [6].

Current pre-radiation dental screening protocols are based on conventional radiotherapy and require an update to take account of the IMRT effects. We therefore conducted a prospective 2-year follow-up cohort study to assess the outcome of pre-radiation dental screening and elimination of oral foci in HNC patients treated with IMRT. Results were compared to those of historical controls treated with three-dimensional conformal radiation therapy [2].

## Methods

### Patients

All consecutive dentate or partially dentate patients > 18 years, diagnosed with primary oral or oropharyngeal carcinoma, referred to the University Medical Center Groningen (UMCG), the Netherlands, for pre-treatment dental screening between May 2011 and May 2013, were included if IMRT to the head and neck region was part of the treatment plan. Patients who had undergone previous oncologic treatment (surgery and/or radiotherapy and/or chemotherapy) to this region were excluded as well as patients with unknown primary or parotid gland tumors. A standardized follow-up of 2 years' post-oncologic treatment related to oral and dental morbidity was completed (JMS). Written informed consent was obtained from all patients. The medical ethical committee of the UMCG approved the study (METC 2012/091).

### Dental screening

All patients were evaluated before their oncologic treatment as part of routine clinical practice by means of oral and dental screening, including radiographic examination [14]. Plaque and bleeding scores were assessed as a percentage of the total number of sites with plaque respectively bleeding on probing. To quantify periodontal disease, the periodontal inflamed surface area (PISA) was used [15]. Patients were asked about their smoking and drinking habits. Self-reported smoking options were “current smoker,” “past smoker,” or “never smoked.” Self-reported alcohol consumption options were “never drink alcohol” or “drink alcohol.”

All data obtained at baseline and follow-up visits (Table 1) were collected in pre-determined order and recorded using a standardized study form.

### IMRT

All included patients were subjected to definitive primary or postoperative IMRT or definitive primary or postoperative chemoradiation (CHIMRT). Patients treated with concomitant CHIMRT were irradiated with a conventional fractionation schedule (2 Gy per fraction, five times per week up to 70 Gy in 7 weeks). In case of primary radiotherapy of tumors considered ineligible for CHIMRT, an accelerated schedule (six times per week) with concomitant boost technique was used, either or not combined with cetuximab. IMRT treatments attempted to spare the parotid glands without compromising dose to target volumes. In general, 7-field equidistant, non-opposing beams were applied. All IMRT treatments applied a simultaneous integrated boost. Most patients received bilateral elective irradiation of the neck nodes to a total dose of 54.25 Gy, in fractions of 1.55 Gy. Primary tumor and pathological lymph nodes were treated to a total dose of 70 Gy, in 2 Gy fractions.

If applied, chemotherapy was given concurrently with fractionated IMRT and consisted of Carboplatin on day 1 (300–350 mg/m<sup>2</sup> in 30 min intravenously) and 5-fluorouracil (5-FU) from day 1 to 4 by continuous infusion (600 mg/m<sup>2</sup>/24 h), consisting of three courses given with an interval of 3 weeks. Postoperative chemotherapy consisted of 6 × 50 mg Cisplatin weekly. When chemotherapy was considered to be infeasible, patients were treated with cetuximab using a loading dose of 400 mg/m<sup>2</sup> 1 week prior to radiotherapy and a weekly dose of 250 mg/m<sup>2</sup> during radiotherapy.

### Treatment of oral foci

Before onset of IMRT or CHIMRT, oral foci were eliminated (Table 2), if teeth related to the foci were within the radiation field receiving a cumulative dose > 40 Gy. An oral focus was defined as follows [3]:

- severe dental caries in which excavation may lead to pulp exposure;
- severe periodontal disease, defined as pockets on probing  $\geq 6$  mm, furcation  $\geq$  grade 1, mobility  $>$  grade 1, gingival recession  $\geq 6$  mm, and especially a combination of these periodontal problems;
- non-restorable teeth with large restorations, especially those extending beyond the gum line or with root caries, or those with severe erosion or abrasion;
- periapical pathosis and non-vital teeth;
- impacted, partially impacted, or partially erupted teeth not fully covered by bone or showing radiolucency;
- cysts and other radiographic abnormalities.

Dental pathology not defined as an oral focus was treated according to professional dental standards. Before the onset of IMRT or CHIMRT, patients were seen by a dental hygienist for dental prophylaxis and oral hygiene instructions.

### Oral care during radiotherapy

During IMRT and CHIMRT, patients were seen daily (Monday to Friday) by a dental hygienist for spraying the oral cavity with saline according to standard protocol [16]. Instructions were given to continue normal daily oral care (tooth brushing and/or interdental cleaning) as long as possible, and to rinse the mouth with salt-baking soda solution at home, 8–10 times per day [14]. Dentate IMRT and CHIMRT patients received custom-made fluoride trays and were prescribed a neutral 1% sodium fluoride gel to be used every second day [14, 17, 18].

### Follow-up

Regular oncology follow-up visits to the oral and maxillofacial surgeon, dental hygienist, and/or hospital dentist were combined with visits to the researcher (JMS) (Table 1). Dental follow-up by the dental hygienist and hospital dentist is standard for IMRT and CHIMRT patients every 3–6 months, depending on the patient's needs, during at least 5 years after treatment. Oral sequelae during follow-up were recorded, including caries and restorative problems, periodontal disease, bone healing problems, and ORN. According to the prevailing definition, ORN is an area of exposed devitalized irradiated bone that fails to heal over a period of 3 months in the absence of local neoplastic disease [5, 19–21]. All other phenomena of a delayed bone healing, such as bone sequestration after radiation and areas with non-healing bone after tooth extraction less than 3 months, were defined as bone healing problems. Antibiotic prophylaxis was given in case of surgical intervention and, if the dose in the specific region of surgical treatment was  $\geq 40$  Gy, application of HBO was considered depending on patient factors, such as smoking, general

**Table 1** Overview of data collection in chronological order

Data collection and sampling	Dental screening	Before onset of IMRT or CHIMRT	6 weeks after IMRT or CHIMRT	Every 6 months until end of follow-up
Panoramic X-ray	X			X
General health and medication	X	X	X	X
Alcohol/Tobacco	X	X	X	X
Oral examination	X	X	X	X
Periodontal examination incl. plaque and bleeding score	X			X

IMRT intensity modulated radiation therapy, CHIMRT IMRT with chemotherapy

health, and complexity of removal of affected teeth. Moreover, when oral sequelae occurred during follow-up and if they were within the radiation field ( $\geq 40$  Gy), all efforts were made to prevent tooth extraction. All data (dental screening and follow-up visits) were recorded using the standardized study form.

### Historical control group

The historical control group consisted of 80 adult HNC patients who had been subjected to pre-radiation dental screening for oral foci. They received postoperative or primary curative three-dimensional conformal radiation therapy or chemoradiation, as part of primary cancer treatment for carcinoma in the oral cavity or oropharynx [2].

### Statistical analysis

Data were analyzed using IBM SPSS Statistics 23.0 for Windows. Values of  $p < 0.05$  were considered significant. Testing for significance was done using Chi-square tests for binary data (developing ORN, having bone healing problems) and Kruskal-Wallis tests for quantitative data (PISA). The Wilcoxon signed rank test was used for comparing baseline PISA scores with follow-up data.

Age at dental screening, smoking and alcohol use at baseline, treatment applied for foci elimination, pocket depth  $\geq 6$  mm, PISA score, T-stage, radiotherapy dose, conventional or accelerated radiotherapy, surgical treatment, and chemotherapy were explored for their predicted value influencing the development of ORN or bone healing problems at the follow up assessment with multiple logistic regression analysis. Variables that were significantly associated with the outcome variable ( $p \leq 0.10$ ) were entered in the logistic regression analyses. Variables not significantly contributing to the regression equation were removed ( $p > 0.10$ ).

**Table 2** Assessment and treatment of oral foci within or outside the radiation field

Assessed tooth problems	Treatment if cumulative dose > 40 Gy <sup>a</sup>	Treatment if cumulative dose < 40 Gy or outside the radiation portal <sup>a</sup>
Caries profunda	Tooth extraction	Restoration, if necessary combined with endodontic treatment, or tooth extraction
Periapical pathosis (on radiographs) without symptoms and/or additional problems	In teeth <i>without</i> root canal filling: endodontic treatment and/or apexification In teeth <i>with</i> root canal filling: endodontic re-treatment, apexification, or tooth extraction (needed in case of pre-radiotherapy time limitations)	In teeth <i>without</i> root canal filling: endodontic treatment In teeth <i>with</i> root canal filling: endodontic re-treatment, apexification, or tooth extraction Treatment can be postponed until after radiotherapy
Extensive periapical pathosis (on radiographs) combined with periodontal disease, in afunctional teeth or <i>with symptoms</i>	Tooth extraction	In teeth <i>without</i> root canal filling: endodontic treatment combined with initial periodontal treatment In teeth <i>with</i> root canal filling: endodontic re-treatment, apexification, or tooth extraction depending on the prognosis
Avital pulp <i>with symptoms</i> without periapical radiolucency on radiographs	Endodontic treatment or tooth extraction (which might be necessary in case of pre-radiotherapy time limitations)	Endodontic treatment or tooth extraction depending on the prognosis
Avital pulp <i>without symptoms</i> and without periapical radiolucency on radiographs	Endodontic treatment or tooth extraction (needed in case of pre-radiotherapy time limitations)	Endodontic treatment (which can be postponed until after radiotherapy)
Periodontal disease with: Pockets 4–5 mm	Initial periodontal therapy	Initial periodontal therapy
Pockets ≥ 6 mm	Tooth extraction	Initial periodontal therapy
Gingival recessions ≥ 6 mm	Tooth extraction	Only recession requires no treatment
Impacted teeth or roots fully covered by bone without radiographic abnormalities	No treatment	No treatment
Impacted teeth or roots <i>not fully covered</i> by bone or with radiographic abnormalities (e.g., cysts, apical radiolucency)	If problems are expected in the future: tooth extraction Tooth extraction	No treatment or, in case of symptoms, surgical removal Roots with periapical radiolucency might be worth preserving by endodontic treatment and restoration (which can be postponed until after radiotherapy)
Cysts	Surgical removal	Surgical removal
Internal or external root resorption	Tooth extraction	Endodontic treatment or tooth extraction depending on the prognosis

<sup>a</sup> If an irradiated patient needed treatment, radiation fields were always verified with the department of Radiation Oncology, and depending on the dose in the specific region where treatment was needed, antibiotic prophylaxis was given to the patient

## Results

### Demographics

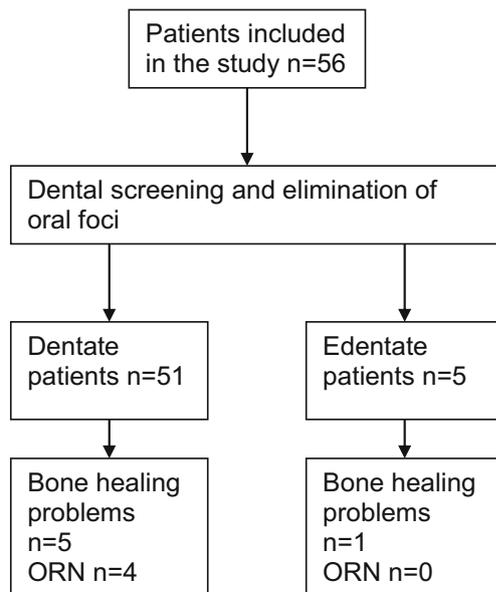
Between May 2011 and May 2013, 56 patients met the inclusion criteria (Fig. 1). Follow-up ranged from 11 to 27 months, with a median of 24 [22; 24] months (Fig. 2). Demographics, clinical characteristics, and baseline dental data of all patients are summarized in Table 3.

After dental screening and pre-radiation treatment of foci, 5/56 patients needed a full mouth clearance (Fig. 1). Results on oral sequelae during follow-up are therefore based on the

remaining 51 dentate patients. Results on dental screening and bone healing problems are based on the original 56 patients.

### Dental screening and treatment of oral foci

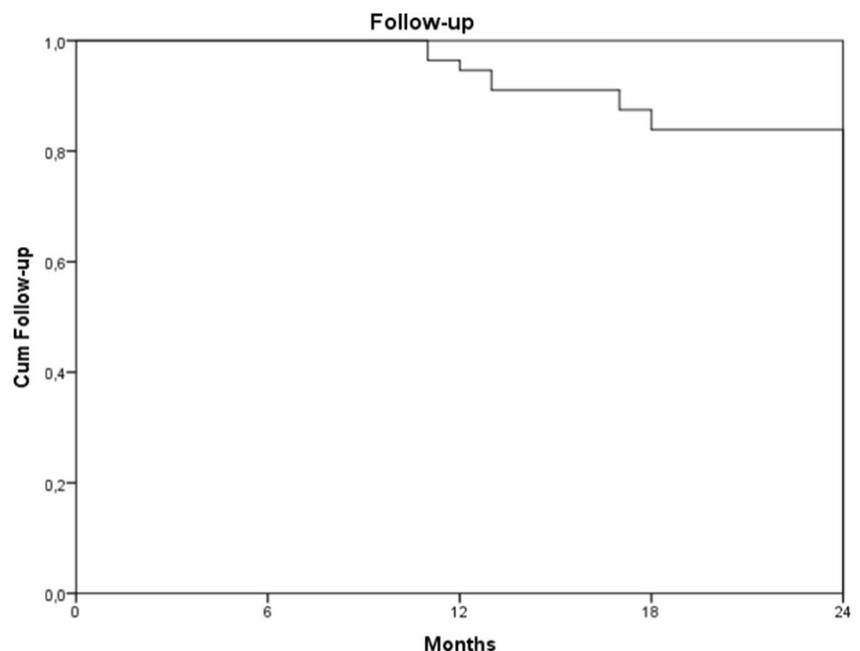
Out of 56 dentate patients, 44 (79%) had 1 or more oral foci at dental screening (Fig. 3). Baseline periodontal condition was healthy (no pockets) in 3 patients. Pocket depths of 4–5 and ≥ 6 mm were found in 25 and 28 patients, respectively. Thus, 53/56 patients (95%) had periodontal disease to some extent at baseline. Median pre-treatment PISA was 349 mm<sup>2</sup> [131; 863] (Table 3).



**Fig. 1** Flow chart of included patients showing dentate and edentate patients

Pre-radiotherapy dental extractions were needed in 43 patients, viz., for 1 patient with no pockets, in 15 patients with pockets 4–5 mm, and 27 in patients with pockets  $\geq 6$  mm. Five patients (11%) needed full mouth clearance: 4 patients had generalized severe periodontitis with pockets  $\geq 6$  mm, and 1 patient never visited a dentist because of anxiety. A median of seven teeth [2; 10] were extracted per patient. One patient had a dental cyst that was surgically removed. After focus elimination, the periodontal condition was healthy in 3 patients, while 48 dentate patients had remaining pockets of 4–5 mm.

**Fig. 2** Kaplan Meier plot of follow-up in months. Nine patients dropped out before the end of the study: two were lost to follow-up, two patients died, and five patients were diagnosed with metastatic or recurrent disease and declined health care



## Oral sequelae during follow-up

### Oral hygiene and fluoride prophylaxis

All dentate patients were instructed to brush their teeth daily and to use fluoride gel every other day during follow-up. Comparing baseline and 2 years of follow-up, plaque scores reduced from a median of 50 to 30% ( $p = 0.016$ ) and bleeding scores from 30 to 10% ( $p = 0.027$ ).

### Post-radiotherapy periodontal health

Post-radiotherapy, 12/51 dentate patients (24%) had progression of periodontal pocket depth (4–5 mm pockets deepened) and/or developed new periodontal pockets ( $\geq 4$  mm on a site that was  $\leq 3$  mm before). Eight out of these 12 patients needed tooth extraction after dental screening before radiation because of pockets  $\geq 6$  mm, and all 12 had remaining pockets of 4–5 mm (not considered as oral foci that needed extraction) before the onset of radiotherapy.

PISA scores decreased significantly during follow-up from 349 mm<sup>2</sup> [131; 863] at baseline to 225 mm<sup>2</sup> [139; 408] ( $p = 0.006$ ) and 149 mm<sup>2</sup> [77; 357] ( $p = 0.003$ , Table 3) at 6 months and 2 years follow-up, respectively, probably due to elimination of oral foci and improved oral hygiene.

### Post-radiotherapy tooth extractions

Six patients (12%) needed one to three post-radiotherapy tooth extractions because of deep dental caries ( $n = 4$ ) or periodontal disease ( $n = 2$ ).

**Table 3** Demographics, clinical characteristics, and baseline dental data of the study group ( $n = 56$ )

	Variable	Category	Number of patients dentate during follow-up Total $n = 51$	Number of patients edentate during follow-up <sup>a</sup> Total $n = 5$
Demographics	Age, years	Mean (SD)	59 (8.5)	62 (5.4)
	Gender	Male/Female	32/19	4/1
Clinical characteristics	Tumor site	Oral cavity	25	1
		Oropharynx	26	4
	T-classification	T1	10	1
		T2	17	2
		T3	6	0
		T4	17	2
		Not reported	1	0
	N-classification	N0	17	1
		N1	7	0
		N2	25	4
		N3	1	0
		Not reported	1	0
	Cumulative IMRT dose	Median [IQR]	70 [66–70]	70 [70–70]
	Frequency of IMRT	5/week	42	3
		6/week	9	2
Primary IMRT		10	1	
Postoperative IMRT		14	0	
Primary CHIMRT		17	4	
Postoperative CHIMRT		10	0	
Chemotherapy type	Carboplatin/5-FU	18	4	
	Cisplatin	7	0	
	Cetuximab	2	0	
Wound closure	Primary	9	0	
	Skin graft/flap	15	0	
Self-reported smoking	Yes/In the past/No/NR	16/17/17/1	4/0/1/0	
Alcohol consumption	Yes/No	40/11	3/2	
Baseline dental data	Number of teeth	Median [IQR]	24 [18–27]	11 [8.5–17]
	Plaque score	Median [IQR]	50 [25–75]	70 [45–80]
	Bleeding score	Median [IQR]	30 [20–60]	70 [33–95]
	PISA	Median [IQR]	349 [131–863]	533 [170–1509]
	DMFS	Median [IQR]	77 [60–102]	118 [88–120]

*SD* standard deviation, *IQR* inter quartile range, *IMRT* intensity modulated radiation therapy, *CHIMRT* intensity modulated radiation therapy with chemotherapy, *DMFS* decayed missing filled surfaces. The range of scores is 0–128, *NR* not reported

<sup>a</sup> After dental screening and pre-radiation treatment of oral foci, five patients needed a full mouth clearance

### Post-radiotherapy dental caries

Out of 51 dentate patients, 13 (25%) developed 1 or more carious lesions.

### Post-radiotherapy periapical pathosis

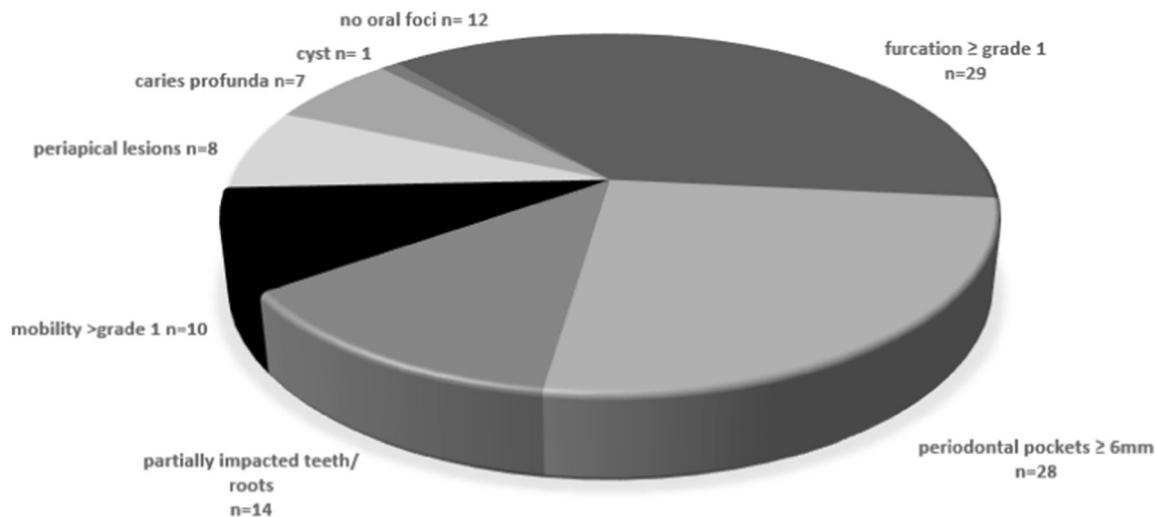
Out of 51 patients, 3 patients (6%) developed deep dental caries with periapical pathosis during follow-up. Endodontic treatment or tooth extraction was performed.

### Post-radiotherapy bone healing problems and ORN

None of the 3 patients without periodontal pockets at baseline developed bone healing problems or ORN during 2-year follow-up.

Bone healing problems were observed in 10 out of 56 patients (18%) in the mandible: 3 patients were diagnosed with delayed wound healing after pre-radiotherapy tooth extraction, 3 with lingual mandibular sequestration (unrelated to tooth extraction), and 4 with ORN (more details below). Of

### ORAL FOCI OF INFECTION AT DENTAL SCREENING IN 56 PATIENTS



**Fig. 3** Oral foci were found in 44 out of 56 patients. Since patients were occasionally diagnosed with more than one oral focus, the sum of the numbers exceeds 44. Patients had one to six oral foci with a mean of 2.3 foci per patient (SD = 1.1)

these 10 patients, 1 patient developed bone healing problems after pre-radiotherapy full mouth clearance. The other 9 patients had teeth left after elimination of oral foci and during the 2 years of follow-up.

In the group of patients with baseline periodontal pockets  $\geq 6$  mm ( $n = 28$ ), 5 developed bone healing problems, not yet diagnosed as ORN, during follow-up (19%) and 1 patient (4%) in the group with pocket depths of 4–5 mm at baseline ( $n = 25$ ). No increased risk for developing bone healing problems was found in patients with periodontal pockets  $\geq 6$  mm at baseline compared to patients with pockets  $< 6$  mm at baseline, although there was strong tendency pointing in this direction ( $p = 0.084$ ).

Of the 28 patients with periodontal pockets  $\geq 6$  mm at baseline, 2 developed ORN (7%) as well as in 2 out of 25 patients with pockets  $< 6$  mm at baseline (8%). Therefore in our study, no increased risk for developing ORN was found in patients with periodontal pockets  $\geq 6$  mm at baseline compared to patients with pockets  $< 6$  mm at baseline ( $p = 1.000$ ).

ORN developed in 1 patient, 3 months after completion of postoperative IMRT in an area where a severely periodontal compromised mandibular molar was removed before radiotherapy. In a second patient, ORN developed, 7 months after postoperative CHIMRT. Extended caries developed in the most distal mandibular molar in this patient. Endodontic treatment was impossible to perform and the molar was extracted post-radiotherapy resulting in a non-healing socket and eventually ORN. This patient was free of oral foci at baseline, but had pockets of 4–5 mm at baseline.

Idiopathic ORN of the angle of the mandible resulting in a pathologic fracture developed in 1 patient 2 months after

CHIMRT had ended. This patient was free of periodontal disease during follow-up. In another patient, ORN was unrelated to pre- or post-radiotherapy tooth extractions, as it was observed 2 months after postoperative IMRT in the transplanted fibula bone used for reconstruction of the mandible. The patient had post-radiotherapy surgery, however, to remove reconstruction plates. This patient had periodontal pockets 4–5 mm at baseline.

Many factors might influence development of bone healing problems after radiotherapy. Patients with ( $n = 10$ ) and without ( $n = 46$ ) bone healing problems were compared for number of teeth extracted after dental screening ( $p = 0.052$ ), number of teeth at dental screening ( $p = 0.357$ ), T-stage ( $p = 0.093$ ), having diabetes ( $p = 0.186$ ), smoking at baseline ( $p = 0.755$ ), drinking alcohol at baseline ( $p = 0.275$ ), baseline plaque ( $p = 0.949$ ), bleeding ( $p = 0.355$ ) and PISA scores ( $p = 0.072$ ), and having periodontal pockets  $\geq 4$  mm ( $p = 0.406$ ) or  $\geq 6$  mm at dental screening ( $p = 0.163$ ).

#### Multiple logistic regression analysis

Multiple logistic regression analysis showed that of the variables assessed (see section on statistical analysis), only the PISA score predicted a higher risk on developing ORN or bone healing problems.

#### Comparison historical control group

Comparison with historical controls [2], on baseline, showed no difference for the presence of oral foci (75 vs. 79%;  $p = 0.630$ ), patient with pockets depths  $\geq 6$  mm (54 vs.

50%;  $p = 0.668$ ), and extractions (average of 7.7 extracted teeth vs. 7.0;  $p = 0.266$ ). In this study, 7% of the patients developed ORN compared to 11% of the historical controls ( $p = 0.424$ ).

## Discussion

This study showed that patients with periodontal disease before IMRT/CHIMRT are prone to develop bone healing problems post-radiotherapy. The assessed protocol for elimination of oral foci pre-IMRT was compared to historical controls with conventional radiotherapy [2]; the protocol was equally effective for patients treated with IMRT/CHIMRT. Post-radiotherapy oral and dental morbidity seen in IMRT/CHIMRT patients is comparable to that seen in patients treated with conventional radiotherapy.

### Periodontal inflamed surface area

The relationship between periodontal disease and bone healing problems is supported by our finding that baseline PISA scores predicted a higher risk on developing ORN or bone healing problems. Presence of periodontal pockets  $\geq 6$  mm at dental screening was different between patients with and without bone healing problems, although not significant. There seems to be a strong trend, however, and our study may have been underpowered to find a significant difference. The correlation of PISA with ORN deserves further study.

### Oral foci

Compared to our retrospective study [2] that included 80 patients subjected to conventional radiotherapy (mean follow-up 26 months), a comparable percentage of patients presented with oral foci. Again, oral foci consisted mainly of periodontal disease, which is comparable to the percentage of patients with periodontal problems (68%) in the small study of Bueno et al. [22]. Approximately 10% of Dutch adults have severe periodontal disease [23]. Apparently, poor periodontal health is more common among HNC patients [2, 4, 24, 25] and might be a major cause of bone-related oral sequelae post-radiotherapy.

### Bone healing problems and ORN

Bone healing problems were observed in 10/56 patients (18%). We diagnosed 5 patients with delayed wound healing and 1 with lingual mandibular sequestration, which was not defined as ORN because healing occurred within 3 months after minimally invasive surgery (sequestrectomy). Immediate surgical intervention in case of exposed bone, as done in our

hospital, may result in a more rapid healing compared to observation.

ORN was reported in 7% of our patients after IMRT compared to 11% in our retrospective three-dimensional conformal radiation therapy (3D-CRT) study [2]. The prevalence of ORN as reported in the literature is highly variable [7] and the reported outcomes on occurrence of ORN after IMRT are limited. Our findings suggest a reduced rate of ORN following the clinical introduction of IMRT [26–28]. It has been suggested, however, that the latency time to develop jaw complications after IMRT is longer. Nevertheless, after 3 years, the risk of developing jaw complications appears to be equal to that for non-IMRT treatment [29]. Nabil et al. [7] suggested a median/mean follow-up of  $> 3$  years, since 90% of ORN cases were reported within 3 years after radiotherapy. Our median follow-up was shorter than in the studies referred to, and more cases of ORN may develop in our cohort in the future. However, all cases of ORN in this study occurred in the first 7 months after IMRT.

Studer et al. [26] reported 5 cases of ORN in 304 patients (1.6%) with oropharyngeal or oral cavity carcinoma treated with IMRT, with a follow-up between 5 and 86 months [26]. Gomez et al. [28] included 168 patients with a follow-up between 0.8 and 89.6 months; they reported a low incidence of ORN (1%). However, 54% of the included patients in the latter study had a tumor located outside the oral cavity or oropharynx, resulting in a lower radiation dose to the jaws, which might be accompanied by a lower incidence of ORN. Both studies did not report how many patients received post-operative or primary IMRT, which may have influenced the outcomes on ORN since it is a known risk factor [8]. A complete lack of ORN was reported by Ben-David et al. [27]. They suggested that the reduction in the ORN rates could be attributed to more conformal dose distributions and to better prophylactic care and ongoing dental care.

Our oral care protocol was similar for our retrospective and prospective study, although it was more strictly executed prospectively, with only 1 patient that was not treated according to protocol compared to 15 patients in the retrospective study [2]. Those 15 patients received pre-radiotherapy initial periodontal therapy for teeth with pockets  $\geq 6$  mm, instead of tooth extraction, and they were particularly at risk of developing ORN. The improved implementation of the dental screening protocol may have decreased our ORN prevalence, as suggested by others [27], and this might explain the weaker relationship between periodontal disease and ORN found in the present study compared to the retrospective study [2]. Nevertheless, periodontal disease, derived as PISA scores, is still the only factor that we found to be associated with bone healing problems.

Periodontal treatment might have a short-term (6 months) positive effect on periodontal breakdown [22], but the present study (median follow-up 24 months) showed that progression

of periodontal pocket depth was frequently observed after IMRT (24%). This percentage is even higher than the 18% reported in the retrospective study [2].

In our study on oral microflora [30], we found an almost immediate effect after the elimination of oral foci, with a decrease of periodontal pathogens. However, rather high percentages of periodontal pathogens were still present in our HNC patients 1 year after IMRT and may be involved in progression of pocket depths.

## Conclusion

This study showed that patients with severer periodontal disease present before IMRT/CHIMRT, i.e., a higher PISA, were more prone to develop bone healing problems post-radiotherapy. Furthermore, it was shown that post-radiotherapy oral and dental morbidity seen in IMRT/CHIMRT patients was comparable to that of patients treated with three-dimensional conformal radiation therapy under the condition of pre-radiation screening and treatment of oral foci.

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## Compliance with ethical standards

**Conflict of interest** J.M. Schuurhuis declares, on behalf of all authors, that we have no conflict of interest. We have full control of all primary data and agree to allow the journal to review the data if requested.

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