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Doke J.M. Buurman

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De impact van het kauwstelsel op de functionele revalidatie
en kwaliteit van leven bij patiënten met hoofd-halskanker

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by

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Contents

CHAPTER 1

GENERAL INTRODUCTION

General Introduction

Head and Neck Cancer

Head and neck cancer (HNC) includes malignancies of the upper aerodigestive tract above the level of the clavicles [1]. It encompasses the lip and oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, nasal cavity and paranasal sinuses, salivary glands, lymph node metastases from unknown primary tumors, ear canal/middle ear carcinomas (lateral skull base), and various skin tumors in the head and neck region. To this are added: thyroid carcinomas with involvement of the larynx, cervical esophagus and tracheal tumors, malignant orbital, non-ocular tumors and HNC in children [2]. The vast majority of HNCs are squamous cell carcinomas [1]. The complex head and neck region is responsible for many different functions such as eating, speaking and swallowing. At the same time, the appearance of the face plays a very important role in social interaction. HNC and its treatment affects these important functions in most patients and regularly also the appearance.

Epidemiology and etiology

Head and neck cancer is the seventh most common cancer worldwide. In 2020, there were 930,000 new patients with HNC and 470,000 related deaths [3, 4]. In the Netherlands, HNC accounts for about three percent of the total number of malignant neoplasms, making it one of the ten most common forms of cancer. The incidence of HNC in the Netherlands has ranged from 3000 to 3250 new cases per year over the past 10 years, with an increase in the incidence of oral cavity and oropharyngeal tumors and a decrease in laryngeal cancer [5].

This increase in the incidence of oropharyngeal cancer is consistent with global figures, in which the increased incidence of human papilloma virus (HPV) related oropharyngeal squamous cell carcinoma accounts for most of this growth [6]. While tobacco and alcohol use remain the leading causes of HNC, the incidence of laryngeal cancer is slowly declining, in part due to decreased tobacco use [3].

Treatment of head and neck cancer

Due to the complexity of diagnostic procedures and therapeutic modalities, HNC treatment is centralized in dedicated multidisciplinary HNC centers [7]. According to the Dutch Cooperative Head & Neck Group, treatment should start within 30 calendar days after the first consultation in 80% of the patients [2]. To minimize the time between the first consultation and the start of treatment, a multidisciplinary consultation on the first day has been introduced in several

institutions [8]. At the Comprehensive Cancer Center of Maastricht University Medical Center (MUMC+) and the Maastro Clinic, the patient is seen during the first consultation by a head and neck surgeon in oral and maxillofacial surgery (OMS), a head and neck surgeon in otolaryngology (ENT) and a head and neck radiation-oncologist. On the same day, the patient is examined by an oral hygienist, a maxillofacial prosthodontist and, if necessary, an anaplastologist. If a biopsy has not yet been performed, it will also be scheduled on the day of the initial consultation. Day 2 is primarily used for imaging, including CT or MRI and ultrasound of the neck. On day 3, the multidisciplinary tumor board (MDT) of the head and neck working group is held, in which the patient is discussed including all the results of the diagnostic tests. The TNM-staging system is used for classification and a proposal for the therapeutic concept is determined based on this [3, 9, 10]. The multidisciplinary team is complemented by plastic surgery, medical oncology, dermatology, oncology nursing care, dietetics, speech therapy, physiotherapy and psychosocial care to achieve structural and functional preservation, improve morbidity when possible and maintain long-term quality of life (QoL) [3]. Following the MDT, the recommended treatment plan is discussed with the patient.

For early-stage cancers of the oral cavity and paranasal sinuses, surgery is the treatment of choice with high cure rates and limited morbidity. Early-stage oropharyngeal cancer can be treated by primary surgery or radiotherapy (RT), with RT playing an important role in preserving the larynx in patients with laryngeal cancer [3]. In locally advanced disease, the preferred therapy depends largely on the size and anatomic location of the primary tumor, disease stage, patient age, patient preferences, performance status, and coexisting diseases. For cancer of the oral cavity surgical resection remains the treatment of choice, followed by adjuvant RT, which may be combined with chemotherapy (CRT). At other anatomical sites, surgical resection would likely result in poor long-term functional outcomes, and RT combined with chemotherapy (CRT) is the curative standard of care. CRT is reserved for nonelderly patients who do not have serious comorbidities. RT is usually administered five days per week for seven weeks in fractions of 2Gy up to 66Gy in 33 fractions or 70Gy in 35 fractions in case of postoperative and primary RT, respectively. This is combined with cisplatin administered intravenously every three weeks at a dose of 100 mg/m2 [11, 12]. Cetuximab is considered in patients ineligible for cisplatin and consists of a loading dose of 400 mg/m2 followed by 250 mg/m2 weekly, combined with accelerated fractionated RT up to 68Gy in 34 fractions in 38 days [13].

Side-effects of the treatment

Surgical resection can be mutilating and result in altered oral anatomy, tooth loss, reduction in maximum mouth opening (MMO), and soft tissue and bone defects. These side-effects can have an impact on patients' outer appearance, social interaction and oral functions, such as mastication, deglutition, and phonetics [14-17].

For example, treatment of malignant diseases of the tongue and/or floor of mouth can significantly worsen tongue function, masticatory performance, bite force, and dental status [17-20]. Treatment of malignant diseases of the maxilla and midface, can lead to leakage through the nose, impaired speech intelligibility due to loss of air, and impaired masticatory performance [21, 22].

RT also causes damage to normal tissues located within the radiation field, e.g. skin, soft tissues of the neck, salivary glands, oral mucosa, bones, dentition, chewing and swallowing muscles, and the temporomandibular joint. The clinical consequences of RT can be divided in acute and late (lifelong) side effects. Acute side effects include mucositis, hyposalivation, loss of taste, dermatitis, pain, hair loss, and dysphagia. Late side effects include soft tissue fibrosis, xerostomia, osteoradionecrosis (ORN), radiation caries, and trismus [23].

Hyposalivation leads to a deterioration of the lubrication of the oral cavity. This can cause radiation caries, an increase in periodontal problems, dysphagia, speech problems and problems wearing dentures. These side effects impact QoL and may persist forever [16, 24-26].

The most feared side effect is ORN [27]. ORN is defined as 'irradiated bone that becomes devitalized and is exposed through the overlying skin or mucosa, without tumor recurrence, and does not heal within 3 months' [28]. Although the risk of ORN has decreased to nearly 5% today [27, 29] due to careful patient selection, improved pre- and post-treatment dental care and individualized RT dose calculation algorithms, the impact of ORN on oral function and QoL remains catastrophic [30-33].

CRT or bioradiotherapy (BRT) can cause severe toxicity both during treatment (acute symptoms) and in the longer term. In addition to the acute symptoms of RT itself, dysphagia, oral pain, taste (dysgeusia or hypogeusia) and smell (dysosmia or hyposmia) disturbances, nausea, and vomiting are more common when chemotherapy or biotherapy is added to RT. These symptoms interfere

with oral intake and often lead to weight loss and dehydration during and immediately after CRT [34]. Unintentional weight loss and low muscle mass, the clinical features of cachexia [35], negatively impact treatment-related toxicity and oncologic outcome. Patients with HNC and unintentional weight loss and/or low muscle mass experience higher toxicity, more unplanned hospitalizations, and poorer overall survival [36-38].

Worldwide, patients with HNC cite fear of the cancer relapse as by far the greatest concern after cancer treatment [39, 40]. However, this main concern is closely followed by the side effects of cancer treatment, with the most important side effects being: Dry mouth, chewing/eating, swallowing, speech/voice/being understood, and dental health/teeth [40]. Young age at diagnosis combined with a better prognosis for HPV-positive HNC and thus a longer life expectancy has increased awareness of late treatment-related toxicity [41].

Consequences of the loss of dental functions

Teeth may be lost due to surgical resection of an oral cavity tumor, but also due to the removal of potential oral sources of infection prior to RT, CRT or BRT to prevent ORN [42, 43]. Tooth extractions result in a reduced number of functional units and impair the ability to chew and swallow [44, 45]. The implications of disrupting our masticatory system are great. Qualitative studies have shown that this multiple tooth loss negatively affects patients' ability to chew and eat, and thus their quality of life [46-48]. Specifically, a greater number of missing teeth is associated with a reduced maximum bite force (MBF), decreased masticatory performance, and self-perceived oral health status [44, 49, 50]. Compared to the non-cancer general dental practitioners group, patients with HNC rated oral function issues as more important than other domains. Other issues such as pain, appearance, activity, recreation, mood, and anxiety were considered less important [51].

Despite the fact that masticatory performance can often return to pre-treatment levels after surgery, even in patients who survive for five years, some degree of masticatory impairment persists and may affect the ability to eat [17, 44]. RT and its side effects on the quantity and quality of saliva, oral mucosa, and masticatory muscles, exacerbate masticatory problems [17].

The masticatory performance of patients with oral cavity cancer is positively affected by having full dentures or better, a higher number of occlusal units (OU), an increased MMO, and an increased maximum bite force (MBF). The location of the tumor also plays an important role [44].

Role of the maxillofacial prosthodontists in rehabilitation

Therefore, there is a need and demand among patients for dental rehabilitation aimed at restoring orofacial form and function as well as overall well-being. Dental rehabilitation begins at the time of diagnosis, and a multidisciplinary approach is critical for optimal treatment outcomes [49]. Dental and prosthodontic rehabilitation and the planning required to achieve it are preferably performed by a maxillofacial prosthodontist and should preferably begin on the day of the initial admission [52].

Rehabilitation is performed in concert with reconstructive surgical options and requires cooperation with oral and maxillofacial surgeons, head and neck oncologists, radiation oncologists, anaplastologists, general and differentiated dentists, and allied health care providers.

Maxillofacial prosthodontics is a differentiation of dentistry that involves rehabilitation of patients with defects or disabilities that were present when born or acquired due to disease or trauma. The patients with HNC belong to the group of acquired defects. The rehabilitation consists of replacing missing bone and other tissues and restoring oral functions such as chewing, swallowing, and speaking. Often this rehabilitation is combined with traditional dental therapy to restore oral health, function and esthetics, especially when the oral cavity is compromised by RT [53, 54].

During the initial consultation, a comprehensive assessment of the patients and their oral condition is critical. A thorough pretreatment oral and dental screening, including the patient's medical and dental history and clinical and radiographic examination, should be performed considering patient-related factors such as age, patient preferences, dental awareness, level of oral hygiene, and cancer treatment-related factors such as clinical staging and tumor location, cure or palliation decisions, treatment modality, type, dose, and range of RT, and immediacy of treatment [17, 42, 43].

The dentate patient

In patients with remaining natural teeth, removal of teeth with limited prognosis identified as potential cause of oral cavity infection before head and neck RT is associated with a lower risk of developing ORN than tooth extractions after or during RT [55]. In the Netherlands, oral health recommendations prior to RT are based on a 1992 protocol, which was revised in 2018 [42, 43, 56]. To give extraction wounds sufficient time (at least 10 to 14 days) to heal before starting RT, decisions

are made based on the expected radiation dose. Because the risk of developing ORN begins at an RT dose of approximately 40Gy [27], it is desirable to eliminate oral sources of infection that are likely to be within the radiation field and receive a cumulative dose of ≥40Gy [43, 57].

Ideally, the dentition should be preserved as much as possible to allow optimal rehabilitation of masticatory function and QoL, but treatment plans should be based on basic principles of prosthodontics, including a philosophy of preventive and conservative restorative dentistry [17]. This includes the role of natural teeth as an anchor point for a removable partial denture or as a pillar for (semi)fixed prosthetic rehabilitation [49].

The edentulous patient
In a completely edentulous patient, successful prosthetic rehabilitation depends on the existing anatomical base. The hard palate in the upper jaw provides a stable base for this prosthetic rehabilitation. In de mandible, only a horseshoe-shaped base is available, so the tongue, lips and cheeks play an important role in stabilizing the prosthesis. When oral anatomy changes due to HNC treatment, it can be very difficult to place a stable and retentive prosthesis. In addition, altered lubrication of the oral cavity may cause the prosthesis to damage the mucosa [23]. Implant-retained dentures (IODs) are a standard treatment for patients with HNC and appear to contribute to successful overall treatment [58-60]. However, the percentage of patients in HNC therapy who receive dental implants varies widely from 22% to 91% [25].

In the maxilla, the stable prosthetic base of the hard palate may be lost due to trauma, infection or tumor resection. This can lead to leakage through the nose, impaired speech intelligibility due to loss of air and inability to chew resulting in enormous limitations in daily life [21, 22, 61]. Reconstruction of these defects remains a challenge for both surgeons and prosthodontists due to the complex three-dimensional anatomy of the maxilla and midface and is controversial [62-65]. Valid arguments have been presented for choosing the best reconstruction and rehabilitation method based on parameters such as QoL and functional outcomes [66-69]. Regardless of the rehabilitation method, defects that encompass a significant portion of the alveolus must be rehabilitated to allow optimal masticatory behavior and appearance of teeth [64]. A significant number of surgically reconstructed patients will remain excluded from dental rehabilitation and will not return to normal eating [70].

Therefore, prosthetic obturation seems to be the preferred treatment modality for many patients, generally leading to an improvement in masticatory function [22, 71, 72]. However, this prosthetic treatment is challenging due to insufficient retention, among other reasons [71]. As in the mandible, implant retention, especially in edentulous patients, has also proven successful in prosthetic rehabilitation in the maxilla [64, 73-76].

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Aims and outline of this thesis

With the changing head and neck cancer (HNC) population, advances in surgical techniques and innovative radiation systems, the focus is shifting from survival to survival with the best possible quality of life (QoL). As a result, attention to the side effects of cancer treatment is increasing. Fear of cancer recurrence is now closely followed by concerns about dry mouth, chewing, swallowing, speach, and dental health. Therefore, it is becoming increasingly important to optimize each patient's masticatory system to improve QoL. Patient-related factors such as age, patient preferences, dental awareness and factors related to cancer treatment should be considered.

The overall aim of this thesis is to evaluate the masticatory function after prosthetic rehabilitation of edentulous HNC patients and to assess the accuracy and possible consequences of tooth extractions prior to radiotherapy (RT).

The first section of this thesis focuses on the prosthetic rehabilitation of edentulous patients with an acquired defect and/or side effects after RT (**Chapters 2-4**). The second section examines the initial steps in the search for optimal preservation of the existing masticatory system of the patient with HNC (**Chapters 5-6**).

In **Chapter 2** we examined the overall percentage of functioning mandibular prostheses with and without implant retention in irradiated patients with HNC. In addition, we determined patient satisfaction with dental rehabilitation in terms of QoL.

The available general QoL questionnaires, such as the EORTC QLQ-C30 en QLQ-H&N35, lack the discriminating ability to measure the effect of prosthodontic treatment on chewing, swallowing, speech, aesthetics, retention, and pain. In 2004 the Liverpool Oral Rehabilitation Questionnaire (LORQ) was developed to provide a more sophisticated measure of the impact of prosthetic treatment on QoL in patients with HNC. In order to be able to use the LORQv3 for Dutch-speaking patients we translated the questionnaire into Dutch and evaluated the internal consistency, reliability, and validity of the resulting LORQv3-NL in **Chapter 3**.

Mastication with an obturator prosthesis is challenging, especially when retention is limited, as in edentulous patients. In **Chapter 4,** we evaluated the potential benefits of implant placement on masticatory performance and

QoL of edentulous maxillectomy patients after prosthetic obturation (**4a**), and compared the objective and subjective masticatory function of patients with implant-supported obturators with patients with surgically reconstructed maxillae (**4b**).

Removal of teeth with limited prognosis, identified as a potential cause of oral cavity infection prior to head and neck RT, is associated with a lower risk of developing osteoradionecrosis (ORN). At the same time, tooth extractions result in a reduced number of functional units and impair both chewing and swallowing. To ensure that extraction wounds have adequate time to heal (at least 10 to 14 days) before starting RT, the decision of whether extraction is warranted is made based on the expected radiation dose. However, for some of the extracted teeth, it may be found after completion of RT that the extraction was not indicated due to the RT dose received being lower than expected.

In **Chapter 5** we examined the number and patient and tumor characteristics associated with this number of redundantly extracted teeth.

After HNC treatment, sufficient time must be allowed for adequate wound healing before successful prosthetic rehabilitation can begin. This means that patients who have to undergo RT have a deteriorated masticatory system during this RT. This impairment in mastication has been associated with oropharyngeal dysphagia, and oropharyngeal dysphagia is significantly related to involuntary weight loss.

In **Chapter 6,** we examined the effects of incomplete dentition and tooth extractions on weight loss during RT combined with chemotherapy (CRT) or biotherapy (BRT) and the need for tube feeding during CRT or BRT for patients with oropharyngeal carcinoma.

CHAPTER 2

PROSTHETIC REHABILITATION OF HEAD AND NECK CANCER PATIENTS FOCUSING ON MANDIBULAR DENTURES IN IRRADIATED PATIENTS.

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Abstract

Purpose: This retrospective study assessed treatment outcomes and patient satisfaction of irradiated head and neck cancer patients treated with mandibular implant overdentures (IODs) or conventional dentures (CDs).

Materials and Methods: Fifty-one irradiated head and neck cancer patients, out of a total of 158 patients included, completed the standardized questionnaire and underwent a clinical assessment. Nineteen patients were treated with removable CDs and 32 patients received IODs between January 2006 and January 2011. The mean follow up of the patients after diagnosis was 5.75 years (range: 1 to 23 years).

Results: A total of 45 (88,3%) mandibular dentures were in function at the time of assessment. The overall denture satisfaction was 7.3 (range 1 to 10, SD: 2.14). Patients being treated with adjuvant concepts, including surgical tumor ablation, scored worse than patients after radiation therapy alone. Edentulous patients seem to benefit from implants, especially with respect to prosthesis retention. Men take more benefit from IODs compared to women.

Conclusions: The results are comparable to other studies in head and neck cancer patients and also of healthy individuals. Surgical interventions in adjuvant therapy concepts lead to reduced denture satisfaction. The concept of prosthetic rehabilitation as part of oncologic treatment can be judged as successful.

Introduction

Treatment of head and neck cancer has an enormous impact on patients' lives. Therapy-related functional and esthetic problems directly influence the outer appearance, social interaction and oral functions, such as mastication, swallowing, speech and nutrition of patients [1-3]. Current advances in microsurgery in combination with dental implants have led to better functional and esthetic outcomes [4]. However, radiation therapy and chemotherapy still cause unfavorable side effects such as reduced swallowing ability, xerostomia, and a painful and tender mucosa [2, 3, 5]. These side effects have an impact on the quality of life (QoL) and may last forever [3, 6-8].

In the rehabilitation process, after tumor treatment, prosthetic rehabilitation plays a prominent role in improving oral functions and QoL [7, 9]. Implant-retained dentures (IODs) are a standard treatment in head and neck cancer patients. Several studies in irradiated and nonirradiated patients presented high implant survival rates varying from 69% to nearly 99% [4, 10, 11]. However, the percentage of head and neck oncology patients, who are rehabilitated with the use of implants widely varies from 22% to 91% [7]. There are different reasons for this variation. Among others, survival rate, length of follow-up, and financial aspects play important roles depending on local insurance regulations.

A positive correlation can be found between denture satisfaction and overall QoL in head and neck cancer patients [12]. There is some evidence regarding better outcomes for IODs in edentulous individuals compared with conventional dentures (CDs) [13, 14]. For irradiated edentulous patients, the same assumptions have been made [10, 11, 15]. This might imply that IODs increase denture satisfaction and the overall QoL in head and neck cancer patients. Thus, prosthetic rehabilitation appears to aid in a successful overall treatment of head and neck cancer.

The objectives of this retrospective study were threefold: to assess the overall percentage of functioning IODs and CDs and to determine patient satisfaction with dental rehabilitation with respect to QoL in both the IOD and CD groups.

Data acquisition was based on patients treated for primary head and neck cancer at the Maastricht University Medical Center (MUMC) who had to undergo radiation therapy at the Maastro clinic between January 2006 and January 2011.

Materials and Methods

One hundred fifty-eight patients suffering from head and neck cancer were extracted from the overall population of head and neck cancer patients of the Department of Cranio-Maxillofacial Surgery, MUMC). The authors made a list of patients for whom dental technician work had been done. Their medical files were then reviewed to determine if they were edentulous, had received an IOD or CD between January 2006 and January 2011, and if radiation therapy had been mentioned. All patients received an invitation and response letter for participation in this study. The total response rate was 68.4% (n = 108).

Sixty-nine patients agreed to participate, 30 patients refused, 5 patients were not irradiated for various reasons, 1 patient died, 3 patients moved, and 50 patients did not respond to the letter. All patients ready to participate in the study were invited to visit the clinic to complete a questionnaire. They were assisted by a researcher. Of the 69 people invited by phone, 13 failed to show up for their appointment, 2 fell ill, 1 responded too late to the invitation, and 2 appeared but refused to answer the questions.

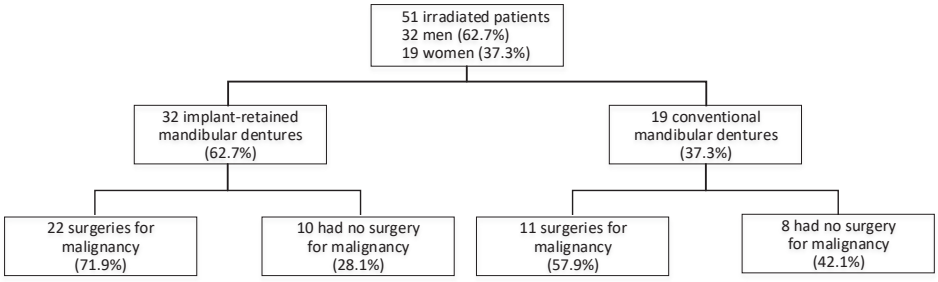

Figure 1 - Classification of the patients who completed the assessment and questionnaires.

A total of 51 patients, 32 (62.7%) men and 19 (37.3%) women, completed the questionnaires (Fig 1). All patients were seen by the same researcher (LV). The oncological and medical history, as well as any current medications, were recorded. The following data were obtained: tumor classification according to the TNM classification, tumor location, oncological treatment, and whether or not the patient was irradiated by intense modulated radiation therapy (Table 1). The dimensions of the surgical defect in the mandible were classified as partial defects (box and slice osteotomies) and continuity defects, with or without bony reconstruction. There were five cases of maxillary resections. The center

of attention, however, was on the mandible as the radiation doses were focused on the lower third of the face and the neck. This region is more susceptible to functional impairment due to the fact that the tongue is situated in the irradiation field and, therefore, speech and swallowing are affected. A dental anamnesis was done followed by an oral examination (Table 2). The oral conditions and the state of the prosthetic rehabilitation were noted. The medical and dental anamnesis were standardized and completed with information from the patients' medical records.

Table 1 - Patient and Tumor Characteristics

Patient	**n**	**Minimum**	**Maximum**	**Mean**	**SD**
Mean age (y)	51	52	84	67.2	7.586
Edentulous mandibule (y)	50	1	46	12.8	14.739
Follow-up (y)	51	1	23	5.75	4.293
Sex					
M	32	62.7%			
F	19	37.3%			
Tumor location					
Oral	23	45.1%			
Oropharynx	14	27.5%			
Laryngopharynx	11	21.6%			
Other	3	5.9%			
Surgery					
Y	33	64.7%			
N	18	35.3%			
Bony defect					
Without	44	86.3%			
Partial	0	0%			
Continuity	7	13.7%			

The questionnaire entitled "Satisfaction of the denture" was filled in together with the researcher (LV). General QoL was assessed with the Linear Analogue Self-Assessment method (one-item version). Overall denture satisfaction was expressed on a 10-point rating scale, range 1 to 10, 1 being completely dissatisfied and 10 being completely satisfied [9]. More detailed information about denture satisfaction was assessed using a validated questionnaire consisting of eight

separate items focusing on the function of maxillary and mandibular dentures and on specific features such as esthetics, retention and functional comfort. All questions could score 1 to 5, 1 being most satisfied and 5 being most unsatisfied [16]. All data were evaluated using SPSS (IBM, version 18.0 for Mac).

Table 2 - Dental Anamnesis and Oral Assessment as Administered

Dental anamnesis:
Edentulous since?
Age at first mandibular denture?
Do you wear your mandibular denture? Why not?
Oral assessment:
Dental status? Maxilla edentulous?
Implant status for mandibule? How many implants? Stable implants?
Dutch Periodontal Screening Instrument for implants and possible teeth in the maxilla.
Condition of oral mucosa? Blister or ulcer by denture?
Soft tissue defect?

Results

Of the total number of patients (n = 51), 32 had an IOD and 19 a CD (Fig 1). The patient characteristics are shown in Table 1.

In the 32 patients with an IOD, a total of 73 implants were placed in the mandible. Overall implant survival was 97.3% (71/73), and 95.9% (70/73) of the implants were in function after a mean time of 48.6 months (range: 14 to 132 months, SD: 32.1 months). Two implants were lost, one at stage-two surgery and the other due to malpositioning. In one patient, one of three implants was not activated, as it was not needed for the prosthetic rehabilitation.

Most of the patients (n = 45, 88.3%) used their mandibular dentures (Table 3). Reasons for being unable to wear the mandibular denture were: anatomical changes in the oral cavity due to ablative surgery, pain, temporomandibular joint dysfunction, and dissatisfaction with design and esthetic aspects of the denture.

Table 3 - Frequencies of Patients Wearing Their Dentures

	Frequency	%
Yes	39	76.5
Most of the time	6	11.8
Mostly not	4	7.8
Never	2	3.9
Total	51	100

Patients answering "yes" or "most of the time" were scored as "wearing their denture". Patients answering "mostly not" or "never" were scored as "not wearing their denture".

Table 4 - Denture Satisfaction Scores for the Total Group

	n	Minimum	Maximum	Mean
Overall Denture Satisfaction	49	1	10	7.3
Mandibular Denture Satisfaction	48	1	10	7.4

Range: 0 to 10 with 0 being completely dissatisfied and 10 being completely satisfied. The missing patients were not able to wear their dentures because of changes in anatomy due to recent surgery.

Overall denture satisfaction was obtained separately for the complete prosthetic restoration and for the mandibular denture (Table 4). There was no difference in overall denture satisfaction between the CD group (mean: 7.33, SD: 1.97) and the IOD group (mean: 7.29, SD: 2.26) (Table 5). The slight difference in overall mandibular denture satisfaction between the CD group (mean: 6.88, SD: 1.80) and the IOD group (mean: 7.73, SD: 2.50) was not significant. A detailed analysis showed a significant difference for the item "retention" in favor of the IOD group (mean: 1.77, SD: 0.83) versus de CD group (mean: 2.50, SD: 1.16) (Table 5).

Table 5 - Comparing the CD Group with the IOD Group

	CD mean (n = 18)	IOD mean (n = 31)	Total (mean)	*p*
Overall denture satisfaction	7.3333	7.2903	7.3061	.947
Mandibular denture satisfaction	6.8824	7.7258	7.4271	.227
Retention	2.5000	1.7742	2.0408	.014

For the items "overall denture satisfaction" and "mandibular denture satisfaction" the range was 0 to 10 with 0 being completely dissatisfied and 10 being completely satisfied. For "retention", 1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied.

In regard to sex, there were no significant differences found in the CD group; however, significant differences were found in the IOD group. Men scored better in "overall denture satisfaction" and "overall mandibular denture satisfaction", specifically with regard to "mandibular denture" and "appearance". The items "functional comfort" and "speaking" were also judged more favorably by men than women (Table 6).

Regarding men, the difference in "overall mandibular denture satisfaction" became significant in favor of the IOD group, and in addition to the item "retention", "mandibular denture" also scored significantly better in the IOD group (Table 7).

When comparing patients after adjuvant therapy with patients after radiation therapy alone, there was a significantly better score for "appearance and speaking" from the group that underwent radiation therapy alone. For "eating" there was a strong trend in favor of the radiation therapy alone group (Table 8). Patients with mandibular continuity resection scored significantly worse on the items "eating and speaking" (Table 9).

Table 6 - Mean Scores for the IOD Group

	Men (n = 20)	Women (n = 11)	Total	*p*
Overall denture satisfaction	8.0250	5.9545	7.2903	**.012**
Mandibular denture satisfaction	8.4750	6.3636	7.7258	**.022**
Denture satisfaction				
General	1.9444	2.7273	2.2414	.076
Maxillary denture	2.1765	2.8000	2.4074	.217
Mandibular denture	1.6000	2.4545	1.9032	**.037**
Appearance	1.7000	2.5455	2.0000	**.017**
Retention	1.6500	2.0000	1.7742	.265
Functional comfort	1.8750	2.8182	2.2097	.052
Eating	1.9500	2.6364	2.1935	.109
Speaking	1.8500	2.6364	2.1290	.060

For the items "overall denture satisfaction" and "mandibular denture satisfaction", the range was 0 to 10 with 0 being completely dissatisfied and 10 being completely satisfied. For items under the "denture satisfaction" heading, 1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied.
Bold numbers indicate statistical significance ($p \leq .05$).

Table 7 - Significant Differences for Men with CDs versus Men with IODs

	CD (n = 10)	IOD (n = 20)	Total	*p*
Mandibular denture satisfaction	6.5556	8.4750	7.8793	.003
Mandibular denture	2.4444	1.6000	1.8621	.009
Retention	2.6000	1.6500	1.9667	.016

For the item "mandibular denture satisfaction" the range was 0 to 10 with 0 being completely dissatisfied and 10 being completely satisfied. For "mandibular denture" and "retention", 1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied.

Table 8 - Differences Between Patients Who Underwent Surgery and Radiation Therapy vs Patients Who Underwent Radiation Therapy Alone

	Surgery and radiation therapy (n = 31)	Radiation therapy alone (n = 18)	Total	*p*
Appearance	2.1613	1.4444	1.8980	.012
Speaking	2.2903	1.5000	2.0000	.006
Eating	2.3548	1.7778	2.1429	.087

For the items "appearance", "speaking", and "eating", 1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied.

Table 9 - Differences Between Patients Without a Bony Defect vs Patients With a Total Mandibular Defect

	Without bony defect (n)	Total mandibular defect (n)	Total	*p*
Overall denture satisfaction	7.4091 (44)	6.4000 (5)	7.3061	.323
Mandibular denture satisfaction	7.5114 (44)	6.5000 (4)	7.4271	.405
Denture satisfaction				
General	1.9767 (43)	2.7500 (4)	2.0426	.174
Maxillary denture	2.0732 (41)	2.5000 (4)	2.1333	.329
Mandibular denture	1.9545 (44)	2.5000 (4)	2.0000	.326
Appearance	1.8409 (44)	2.4000 (5)	1.8980	.233
Retention	2.0455 (44)	2.0000 (5)	2.0408	.926
Functional comfort	2.1705 (44)	2.2000 (5)	2.1735	.960
Eating	2.0227 (44)	3.2000 (5)	2.1429	**.027**
Speaking	1.8864 (44)	3.0000 (5)	2.0000	**.017**

For the items "overall denture satisfaction" and "mandibular denture satisfaction" the range was 0 to 10 with 0 being completely dissatisfied and 10 being completely satisfied. For items under the "denture satisfaction" heading, 1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied.
Bold numbers indicate statistical significance ($p \leq .05$)

Discussion

According to the Dutch guidelines for the treatment of head and neck cancer, many patients are bound to lose some or even all of their teeth. Prosthetic rehabilitation in these cases is mostly done with partial or complete dentures. Today, the Dutch health care system supplies two interforaminal dental implants in the mandible for patients having trouble using their dentures and who have a strongly resorbed mandible.

In comparison to the literature, good results were registered, with 88.3% (45 of 51, Table 3) of mandibular dentures in function after a variable time of follow-up (range: 1 to 23 years) (Table 1) [10, 11].

The overall denture satisfaction in the examined population was relatively high, with a mean of 7.3 out of 10. This is comparable to other studies of patients with oral cancer as well as of healthy patients [9, 10, 17].

Prospective randomized studies show that patients are more satisfied with an IOD comparing to a CD [13]. This study on irradiated head and neck cancer patients also found a better, but non significant, overall mandibular denture satisfaction for IOD rehabilitation. The only significant factor found was “retention”. If we split the group into men and women, the men scored significantly higher in “overall mandibular denture satisfaction” and “mandibular denture”. In the women’s group, no significant difference between IODs and CDs was noted. These results may have been influenced by the fact that the women more frequently underwent surgery. Only 17 of 32 (53%) men underwent surgery, but 15 out of 18 (83%) women did. Unfortunately, the remaining group of women that were only irradiated was too small to confirm these assumptions.

Comparable differences were also found between men and women in the Pan et al study [17]. However, Pan et al found these differences in the CD group, whereas the present study found them in the IOD group. Although the present group was compromised by the oncological treatment, it can be concluded that women are less satisfied with their dentures than men.

Concerning the items “appearance and speaking”, surgical patients scored worse than irradiation only patients. Significance was found for patients after continuity resections of the mandible. The items “eating and speaking” were

judged significantly worse by this group of patients. Although these findings were significant, one has to consider that only seven patients had continuity resection, of whom only five were able to wear dentures.

The total response rate was 68.4%. This is higher than reported in literature; however, of those having responded to the invitation letter, only 47% (51 out of 108) were willing to participate. This is comparable to other retrospective questionnaire studies [3, 18].

Conclusions

Irradiated edentulous patients seem to benefit from implant-retained prosthesis in the mandible, especially with respect to prostheses retention. Men appear to benefit more from IODs than women. Mandibular surgery has a negative influence on denture satisfaction.

From the standpoint of prosthetic rehabilitation, any operation that changes the anatomical structure of the mandible has to be avoided. This demand is difficult to practice as todays oncologic studies still present high rates of T3 and T4 cancers of the oropharyngeal region affecting the jaw. The only means of achieving this goal is prevention and education through better information for patients and professionals concerning premalignant lesions and early cancer treatment to avoid mutilating operations.

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CHAPTER 3

TRANSLATION, CROSS-CULTURAL ADAPTATION, AND VALIDATION OF THE LIVERPOOL ORAL REHABILITATION QUESTIONNAIRE (LORQ) INTO THE DUTCH LANGUAGE.

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Abstract

Statement of problem: The Liverpool Oral Rehabilitation Questionnaire (LORQ) is a health-related quality of life instrument assessing the impact of oral rehabilitation on patients' health-related quality of life. Because a validated Dutch version of the LORQ is not available, the questionnaire cannot be used in the Netherlands.

Purpose: The purpose of this study was to translate and adapt the LORQv3 into a Dutch-language version and to evaluate the internal consistency, reliability, and validity of the resulting LORQv3-NL.

Material and methods: The original English-language LORQv3 was translated into Dutch via the forward-backward approach. The reliability and construct validity of the LORQv3-NL was tested on a sample of 158 participants. The participants were enrolled at the dental faculty of Radboudumc, at the Centre for Special Oral Care of the Radboudumc and Maastricht UMC+ and in general practices. Internal consistency was assessed by calculating the Cronbach α, and the test-retest reliability (n = 34; 2-week interval) was assessed by weighted kappa coefficient. Furthermore, convergent validity was measured by comparing the outcomes with those of the Dutch version of the Oral Health Impact Profile 14-item (OHIP-NL14) (n = 17), and patients with head and neck cancer (n = 25) were added to test discriminative validity.

Results: Internal consistency and test-retest reliability were satisfactory (Cronbach α = 0.75–0.89; interclass correlation coefficient = 0.89). In addition, all associations were in the expected direction.

Conclusions: The LORQv3-NL appears to be a good tool for assessing denture complaints and denture incompatibility.

Introduction

Current research on denture satisfaction mainly focuses on the oral health-related quality of life (OHRQoL). Different instruments have been developed for measuring OHRQoL, such as the Oral Health Impact Profile (OHIP)-49 [1] and its shortened version for patients with edentulism OHIP-edent [2]. Although these questionnaires concentrate on the influence of dental/denture problems on quality of life, they miss denture functionality details like mastication, swallowing, speech, esthetics, retention, and pain. It is to be expected that patients with poor adaptation to their dentures report a higher influence of denture problems on quality of life than do satisfied patients. To investigate satisfaction in patients with poor adaptation to their dentures, a questionnaire is needed that contains various detailed aspects of oral function, such as more specific information on the maxillary and mandibular dentures separately and different aspects of esthetics, food intake, pain, and social interaction, and also focuses on OHRQoL.

The Liverpool Oral Rehabilitation Questionnaire (LORQ) was developed in 2004 to improve the assessment of issues and problems related to patients undergoing oral rehabilitation after oncologic treatment of the head and neck [3]. After some modifications, version 3 of the LORQ could be used in the clinical setting [4, 5]. The LORQv3 demonstrated satisfactory psychometric properties of acceptability, reliability, and validity. This tool was able to differentiate between cancer and noncancer groups and demonstrated significant correlations between items on the LORQ and in coadministered questionnaires [6]. The high variation among items and the level of detail in this questionnaire make it suitable for assessing denture complaints in patients with poor adaption.

Given the significance of identifying and evaluating denture complaints in Dutch patients with denture problems, the objective of this study was to translate and adapt the LORQv3 into a Dutch-language version and to evaluate the internal consistency, reliability, and validity of the resulting LORQv3-NL. The null hypotheses were that the LORQv3-NL would not identify differences between data from patients visiting general practices, patients visiting the university dental clinic, and head and neck oncology patients, and that the LORQv3-NL would not identify differences between test-retest data at an interval of 2 weeks.

Materials and Methods

The English-language LORQv3 consists of 40 items divided into 2 primary sections. The first section contains 17 items that assess oral function, orofacial appearance, and social interaction. The second section assesses issues specific to prostheses and patient denture/prosthetic satisfaction [5].

LORQ items refer to problems and symptoms experienced during the previous week and are rated 1 through 4, representing “never,” “sometimes,” “often,” and “always” [6]. Finally, there is a comment section for patients to identify issues not adequately addressed by the questionnaire. The questionnaire is self-administered and takes approximately 10 minutes to complete. It is available online (http://www.headandneckcancer.co.uk).

The LORQv3 was translated by 6 different translators into Dutch through the use of the forward-backward approach, following guidelines for cross-cultural adaptation of health-related quality of life (self-administered) measures [7, 8]. Four independent bilingual translators whose native language was Dutch performed the forward translation into Dutch. One of them was a prosthodontist and another a maxillofacial surgeon; the remaining 2 were professional translators with no medical or clinical background. The 4 forward translations were compared and synthesized into one common version by an expert panel (M.E., D.B.), consisting of 2 dentists/prosthodontists and 1 psychologist specializing in the field of dentistry. Competing options for a translation were debated until consensus was reached. The resulting consensus forward translation was translated back into English by 2 independent, professional translators whose native language was English. The 2 back-translations were again discussed by the expert panel, comparing equivalence between the 2 versions. The back-translations were reviewed against the original English language LORQv3 by the expert panel. Finally, the resulting LORQv3-NL was read and commented upon by a prosthodontist (C.vH.) outside the expert panel.

To study the reliability and construct validity of the LORQv3-NL, a sample of 158 participants was recruited over a period of 2 years. The participants were enrolled during their procedure for new dentures at the dental faculty of Radboudumc in Nijmegen, or during regular examinations at the Centre for Special Oral Care of the Radboudumc in Nijmegen and Maastricht UMC+ in Maastricht and in general practices in the Nijmegen area. Dentists from general practice were

contacted and asked to participate through letters and telephone calls. Dentists who agreed to participate asked their patients to fill out the questionnaire. Participants completed the LORQv3-NL during their dental appointment.

The internal consistency of a questionnaire relates to its homogeneity. All items should measure different aspects of the same trait. Therefore, different items should correlate moderately with each other and with the total score [9]. The internal consistency of the total LORQv3-NL, as well as its 2 sections, was assessed by calculating Cronbach α values. Values of 0.70 to 0.80 are considered satisfactory for a reliable comparison between groups. For clinical purposes, a minimum of 0.90 is required, while values of at least 0.95 are normally considered desirable [10]. However, according to Streiner [11], α values over 0.90 most likely indicate unnecessary redundancy rather than a desirable level of internal consistency when there are more than 20 or so items.

A subsample of 34 participants received a second LORQv3-NL questionnaire and completed it during another dental appointment, or they received and returned a second questionnaire by mail. The interval between the first and second questionnaire was 2 weeks. This interval was selected because the measured variable was assumed not to have changed in this time, and participants were unlikely to remember their first response over this interval. The test-retest reliability of the LORQv3-NL and its 2 sections was determined by calculating the weighted kappa coefficient.

Discriminative validity and convergent validity were used to measure construct validity. For convergent validity, the correlation between the questionnaire and other related measures was assessed. In this study, a subsample of 17 participants also filled out the OHIP-NL14, the Dutch version of the OHIP-14. A positive correlation between the 2 scores would indicate convergent validity. The LORQ-questionnaire was originally designed for patients with head and neck cancer. To test discriminative validity, a group of 25 patients with head and neck cancer also filled out the LORQv3-NL. These patients were expected to have higher scores than the noncancer group because of their compromised oral environment as a result of surgery or radiotherapy [12, 13]. Furthermore, a difference can be expected between the patients visiting the university dental clinics and patients going to a general practitioner for routine examinations. We hypothesized that the patients visiting the university dental clinic actively reached out for help, so they would have more complaints and therefore demonstrate higher scores. The LORQv3-NL scores were compared among those 3 groups.

Results

No serious difficulties were encountered during any part of the translation and adaption procedure. Items discussed were questions 18 and 19 and related to whether or not the participant had any natural dentition. The English word 'teeth' refers to anteroir teeth as well as premolars and molars. In Dutch, the straightforward translation of 'teeth' refers only to the anterior teeth. Therefore, in the Dutch translation, this term was changed to 'front teeth' and 'back teeth'. Instead of the straightforward translation, some idiomatic equivalent had to be found for the following words or phrases: 'food particles', 'upset' and 'denture'. For these words, several translations are possible that would have been understood by a Dutch-speaking person. Discussion was mainly based on which word would be most appropriate. Twelve out of 158 participants did not answer all of the first 17 questions of the LORQv3-NL, but each of these questions was answered by at least 153 participants.

The internal consistency of the Dutch version of the LORQ can be considered satisfactory. Items 11 through 14, 29, and 37 had a low corrected item-total correlation. (0.42, 0.43, 0.30, 0.31, 0.24, and 0.21, respectively). Results compared with the original LORQ are shown in Table 1.

Table 1 - Cronbach α values for difference in internal consistency between English LORQv3 and Dutch version

Item Nos.	LORQv3	LORQv3-NL
Items 1-17	0.92	0.89
Items 20-23	0.87	0.83
Items 26-31	0.84	0.75
Items 34-39	0.92	0.81

Abbreviations: LORQv3, Liverpool Oral Rehabilitation Questionnaire, version 3; NL, Netherlands

The explained variance of the mean score between the 2 time measurements was 0.89, indicating that 89% of the variance in the 2-week mean scores of the first 17 items can be explained or predicted correctly by the baseline scores. Table 2 shows various result measures on each item separately. Items 9, 14, and 16 had a low *p* value, indicating a structural difference between test and retest. The weighted kappa values were very good, with 0.401 as the lowest score for LORQ-item 2. Figure 1 shows that participants tended to report fewer complaints at the second measurement.

Table 2 - Mean scores and test-retest reliability measured for first 17 general items of LORQ: distribution per item

LORQ Item	No. per Score 1/2/3/4	Weighted Kappa	Reliability	Decision Making Error	Mean Score	*p*	95% CI
1	72/51/21/11	0.574	0.583	0.66	0.18	.280	[-0.15...0.50]
2	89/45/13/6	0.401	0.408	0.70	0.15	.392	[-0.20...0.49]
3	113/27/12/4	0.822	0.824	0.39	0.00	1.000	[-0.19...0.19]
4	138/13/4/1	0.730	0.755	0.27	0.29	.661	[-0.11...0.16]
5	104/36/11/3	0.614	0.637	0.48	0.29	.801	[-0.21...0.26]
6	73/69/10/3	0.686	0.694	0.47	0.89	.447	[-0.14...0.32]
7	88/53/9/5	0.743	0.752	0.44	0.29	.786	[-0.19...0.25]
8	72/56/23/6	0.699	0.708	0.45	0.12	.292	[-0.11...0.34]
9	108/36/8/5	0.743	0.765	0.42	0.21	.051	[-0.00...0.41]
10	106/31/11/9	0.729	0.780	0.48	0.18	.136	[-0.06...0.41]
11	132/19/3/2	0.705	0.713	0.37	0.03	.744	[-0.15...0.21]
12	127/24/3/2	0.809	0.831	0.32	0.09	.263	[-0.07...0.25]
13	135/15/4/1	0.696	0.726	0.35	0.06	.488	[-0.11...0.23]
14	124/23/3/5	0.622	0.753	0.43	0.24	.030	[0.02...0.45]
15	106/31/14/6	0.830	0.840	0.39	0.15	.134	[-0.05...0.34]
16	70/50/23/13	0.708	0.743	0.54	0.29	.031	[0.03...0.56]
17	126/20/6/5	0.672	0.681	0.51	-0.03	.812	[-0.28...0.22]

Abbreviations: CI, confidence interval; LORQ, Liverpool Oral Rehabilitation Questionnaire

For measuring the convergent validity, the LORQv3-NL was compared with the OHIP14-NL. The results can be seen in Figure 2. The association was in the expected direction, $R^2 = 0.642$.

The oncology patients scored higher on the first 17 items of the LORQ than the other patient groups. Furthermore, the general practice group reported fewer problems with their oral rehabilitation than the university dental clinic group. Box plots of this variable for the different patient groups are shown in Figure 3.

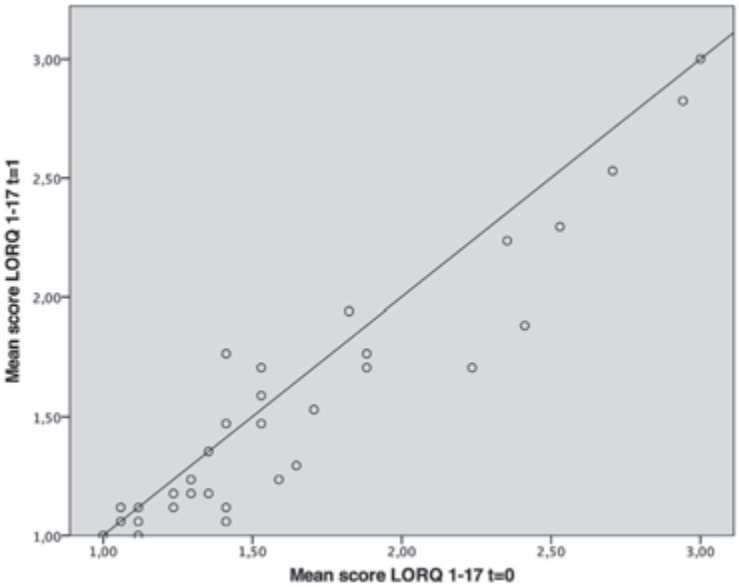

Figure 1 - Test-retest reliability shown in scatterplot. T = 0 first moment of registering, T = 1 after 2 weeks. Line shows equation x = y, ideal curve.

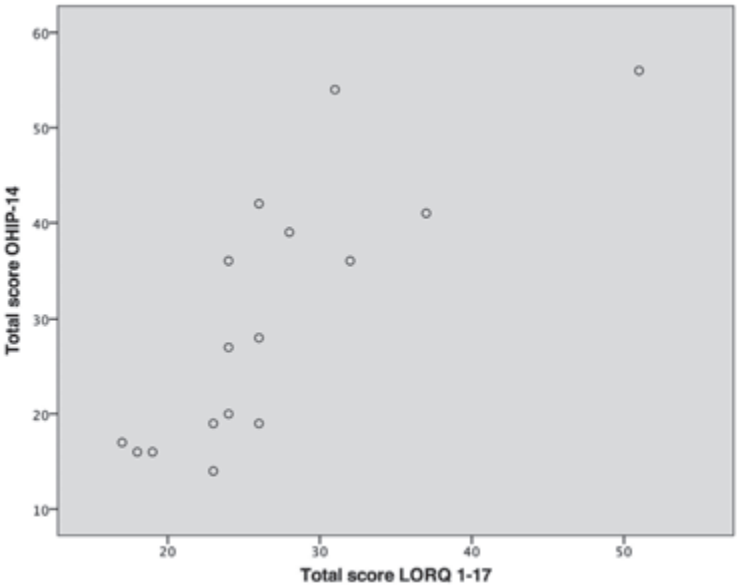

Figure 2 - Association between total score on first 17 items of LORQ and OHIP-14 questionnaires. LORQ, Liverpool Oral Rehabilitation Questionnaire; OHIP-NL14, Dutch version of the Oral Health Impact Profile 14-item.

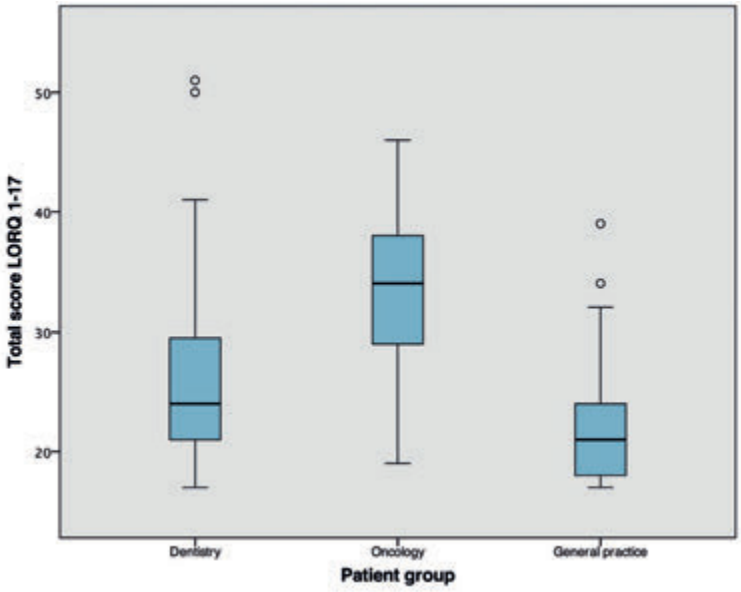

Figure 3 - Boxplots of results of different patient groups on first 17 items of Liverpool Oral Rehabilitation Questionnaire (LORQ).

Discussion

The results from this study support the rejection of the first null hypothesis, as the LORQv3-NL identified differences among the data from patients visiting general practices, patients visiting the university dental clinic, and patients with head and neck cancer. The second null hypothesis was retained, as the LORQv3-NL could not identify differences between test-retest data at an interval of 2 weeks.

This study describes the translation, cultural adaptation, and validation of the LORQ into Dutch settings. To achieve a comparable version of an instrument to be used in a new country and culture, a cross-cultural adaptation of the instrument is necessary. A cross-cultural adaptation involves both linguistic translation and cultural adaptation to maintain the content validity of the instrument at a conceptual level across different cultures [8, 14].

The reliability and validity of the Dutch version of the LORQ were assessed to decide whether it could be recommended as a reliable and discriminating questionnaire. The LORQv3-NL showed good psychometric properties. The general internal consistency of the LORQv3-NL can be considered satisfactory and comparable with the original version. In general, the Cronbach α value of the Dutch version was slightly lower than the original English version. This might be due to the group size or the group composition. The English version has been tested mostly on patients with head and neck cancer. Their responses are probably more divergent than a general practice group, because in general they have more complaints.

A few items showed a low correlation with the total. Items 11 through 14 deal with esthetics and express how much the patient feels disturbed by his or her appearance. The rest of the questionnaire focuses more on other functional aspects such as mastication, swallowing, and pain. This might explain the lower item-total correlation of these questions. Items 29 and 37 ask whether, during eating, the patient has ever removed his or her maxillary or mandibular denture. These questions are very specific and might not relate to pain or lack of masticatory ability directly, leading to low item-total correlations. For a few items, the item-total correlation was high (highest was 0.76 for item 34). This might suggest that these items are redundant. The original LORQv3 questionnaire formed the basis for this translation. To keep the LORQv3-NL comparable with the original questionnaire LORQv3, no items were deleted despite the possibility of some items being redundant.

The test-retest reliability was observed to be good. In Figure 1 a slight tendency to report fewer complaints after 2 weeks than at baseline can be noted. Most participants filled out the first questionnaire during a dental appointment. The second questionnaire was sent by mail. Maybe the dental evaluation itself resulted in a slight decrease in complaints because patients were able to discuss their problems and were reassured.

Three groups of patients were compared: patients visiting general practices, patients visiting the university dental clinic, and head and neck oncology patients. Overall group scores followed the expected pattern, with the oncology group reporting the most problems and the general practice group the least. This supports the discriminative validity of the LORQv3-NL. Remarkably, no difference could be found on items 11-14 concerning facial appearance. One might expect the oncology group to have a compromised appearance because of surgery and/or radiotherapy. Therefore, either this oncology group was not compromised in their facial appearance or they did not perceive it as a burden. As expected, only the oncology group was experiencing difficulty swallowing liquids and opening the mouth. This can be fully explained by the compromised oral environment after oncologic treatment.

Conclusions

Based on the findings of this study, the following conclusions were drawn:

1. The translation, cultural adaptation, and validation of the LORQv3 in Dutch has resulted in an instrument that can be used in Dutch-speaking populations.
2. LORQv3-NL not only measures OHRQoL but also focuses on different aspects of denture functionality. The Dutch version has proven, like the original version, to be reliable and valid with respect to internal consistency, construct validity, and test-retest reproducibility.
3. The LORQv3-NL will provide a new tool for studying denture complaints and denture incompatibility.

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CHAPTER 4.1

MASTICATORY PERFORMANCE AND ORAL HEALTH-RELATED QUALITY OF LIFE IN EDENTULOUS MAXILLECTOMY PATIENTS: A CROSS-SECTIONAL STUDY TO COMPARE IMPLANT-SUPPORTED OBTURATORS AND CONVENTIONAL OBTURATORS.

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Abstract

Objective: The aim of this cross-sectional study was to compare the masticatory performance and oral health-related quality of life (OHRQoL) of edentulous maxillectomy patients with and without implant-supported obturator prostheses.

Material and methods: Nineteen edentulous maxillectomy patients with completed prosthetic obturator treatment in the upper jaw participated in this study. In nine patients, the obturator prosthesis was supported by implants in the remaining bone of the midface and/or skull base to improve retention. Masticatory performance was measured objectively by the mixing ability test (MAT) and subjectively by three OHRQoL questionnaires: (a) the Oral Health Impact Profile for EDENTulous people (OHIP-EDENT), (b) the Obturator Function Scale (OFS), and (c) the Dutch Liverpool Oral Rehabilitation Questionnaire version 3 (LORQv3-NL). The independent *t* test and the Mann-Whitney *U* test were used to test for differences in outcomes of patients with and without implant-retention of their obturator prostheses.

Results: Patients with implant-supported obturator prostheses had significantly better masticatory and oral function, reported fewer chewing difficulties, and had less discomfort during food intake than did patients with a conventional obturator.

Conclusion: Supporting prosthetic obturators after maxillectomy with implants improves oral functioning, chewing, and eating comfort. This treatment modality is a viable technique to improve the functionality of prosthetic rehabilitation in patients who have undergone maxillectomy.

Introduction

Maxillary defects due to trauma, infections, or tumour resections can result in tremendous limitations in daily life, depending on the size and anatomical location of the defect [1, 2]. Surgical reconstruction of these defects remains challenging and controversial due to the complex three-dimensional anatomy of the maxilla and midface [3-5]. Preserving the oronasal separation and a clear nasal airway is important for optimal mastication, deglutition, and phonetics [5]. These oral functions are essential for the total rehabilitation of the patient and, therefore, directly related to quality of life issues [6, 7]. Microsurgical repair is regarded as the standard option in reconstructive surgery of the face, depending on the defect size and the indication [3, 8]. However, excellent facial contour, function, and acceptable aesthetics can seldom be achieved with a single-stage procedure [9]. A considerable number of these patients will consequently remain deprived of dental rehabilitation and will not return to normal food intake [10]. Nonetheless, prosthetic obturation appears to be the preferred treatment modality for many patients, which generally leads to an improvement of masticatory performance [2, 11, 12]. However, prosthodontic treatment is challenging due to technical limitations, such as poor retention, instability of the obturator prosthesis, and oronasal incompetence [11]. Retention of the obturator prosthesis is very difficult to achieve, especially in edentulous patients. Nevertheless, implants have been placed successfully in the residual maxillary alveolar process, the pterygoid, and zygomatic bone for maxillary prosthetic rehabilitation [13, 14]. To the best of our knowledge, the literature lacks objective masticatory performance testing that is combined with patient-reported oral health-related quality of life (OHRQoL) after prosthetic obturation of edentulous maxillectomy patients [15-20]. Therefore, the aim of this study was to compare the masticatory performance and OHRQoL of edentulous maxillectomy patients with and without implant-supported obturator prostheses.

Materials and methods

Patients

All patients that were referred to the Department of Cranio-Maxillofacial Surgery at Maastricht University Medical Centre (MUMC+) for surgical and prosthetic rehabilitation in the maxilla/midface between 2005 and 2015 were asked to participate in this comparative cross-sectional study. We compared patients with implant-supported obturator prostheses (Group 1) with patients wearing conventional obturator prostheses (Group 2). Patients with maxillary/midface defects in edentulous upper jaws were included when the prosthetic obturator treatment was completed. Brown's classification was used to determine the defect size in the maxilla/midface [21]. The study was approved by the Ethics Committee of the MUMC+ (METC 15-4-123). Informed consent was obtained from all participating patients.

Procedure

Patients with a status eligible for implants after partial or total maxillectomy or partial or total loss of the maxilla/midface were treated according to the "surgical and prosthetic reconsiderations in patients with maxillectomy protocol" as defined by Lethaus, Lie et al. [8]. Implants were not placed if it was expected that there would be sufficient prosthetic options for a conventional obturator. Furthermore, some patients refused implant treatment. The decision of using implants was not based on the prognosis of the patient. Imaging for digital planning was based on computerized tomography (CT) scans acquired by multi-slice CT (Siemens) or cone-beam CT (ICAT, Hatfield). Implant sites in the remaining facial skeleton or skull base were planned based on the CT-data with the Simplant 3D® program (Dentsply Sirona, Wals bei Salzburg). When standard abutments did not comply with the required distances or angulations of our protocol, individual abutments were designed by hand or by using the Cinema 4D® planning program (Design Express). If possible, a bar construction was made on the dental implants to support the obturator. Magnet abutments were used as an alternative retention method when the space between two implants was too wide. (Figures 1 and 2).

Data acquisition

The mixing ability test (MAT) was used to measure the masticatory performance objectively [22, 23]. Subjective aspects were measured with three OHRQoL questionnaires: (a) the Oral Health Impact Profile for EDENTulous people (OHIP-EDENT) [24], (b) the Obturator Function Scale (OFS) [7], (c) and the Dutch Liverpool Oral Rehabilitation Questionnaire version 3 (LORQv3-NL) [25-28].

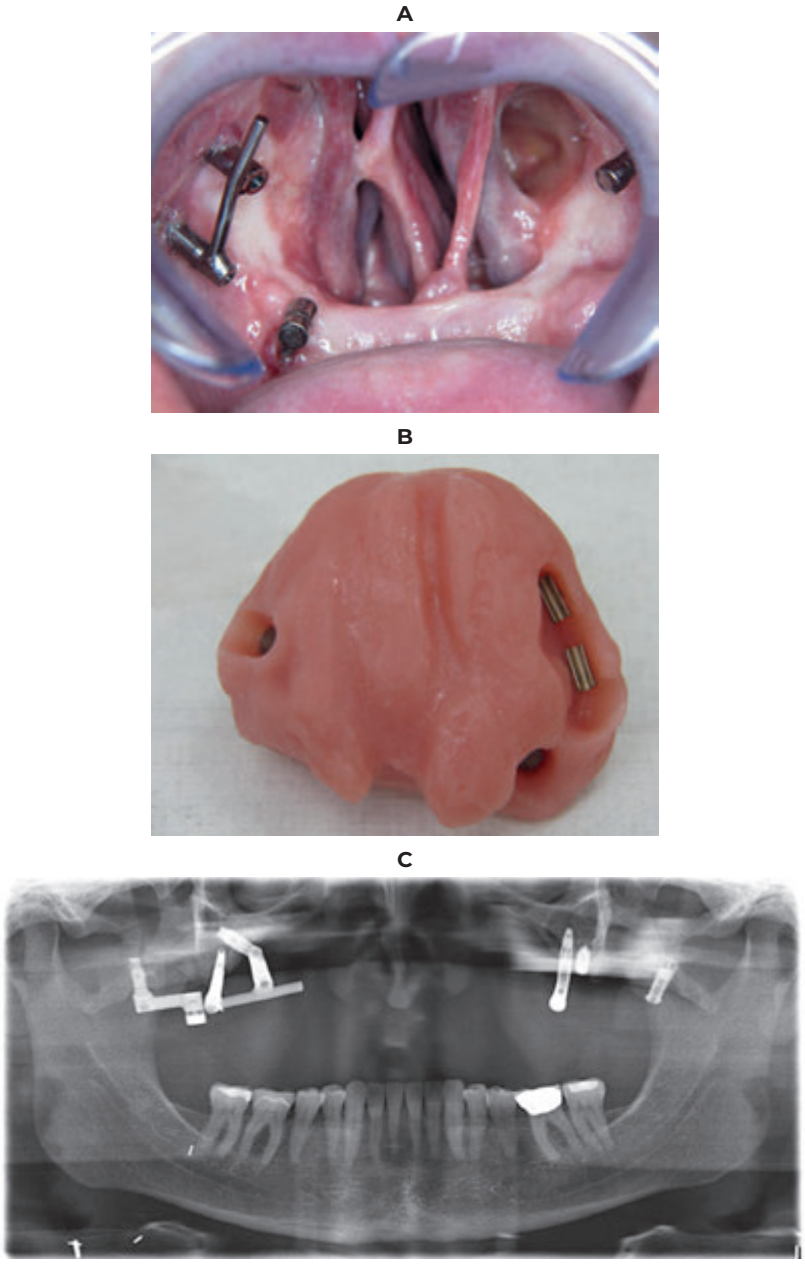

Figure 1 - A patient presented with a Brown class IId defect [21] after avascular necrosis after Le Fort I osteotomy. (a) Bar construction was made on the dental implants to support the obturator, where the space was too large between two implants, magnet abutments were used as alternative retention method. (b) Retentive parts in the obturator prosthesis.(c) Panoramic radiography showed the position of dental implants in remaining bony parts of the midface or skull base.

*Masticatory performance_*

The MAT measures how well a subject can mix a two-coloured wax tablet by chewing on it. The tablet has a diameter of 20 mm and consists of two 3 mm layers of red and blue wax. The test-wax is a soft material (Plasticine modelling wax, non-toxic DIN EN-71) that forms a compact bolus during chewing and was offered at room temperature (20 ˚C). After chewing, the wax is flattened between foils to a thickness of 2.0 mm to avoid shadows. Then, the test-wax is illuminated by a scanner lamp and photographed on both sides using a high-quality scanner (Epson V750). The images of the wax were analysed and processed using a commercially available program for image analysis (Adobe Photoshop CS3). Intermediate colour intensities appear, and the spreads of the intensities for red and blue decrease. A lower mixing ability index (MAI) score implies a better-mixed tablet and, hence, better masticatory performance [22, 23].

Oral Health Impact Profile for EDENTulous people

The OHIP-EDENT is based on the original 49 items of OHIP and adapted for edentulous patients. The internal consistency of the OHIP-EDENT has a Cronbach's alpha of .86-.97 [29-31]. The test-retest reliability has an intraclass correlation (ICC) of .57-.76 [29, 31]. The aim of the OHIP-EDENT is to detect OHRQoL changes, as influenced by the clinical aspects of edentulism and its treatment. The in total 19 items are defined to measure seven domains: (1) functional limitation (3 items), (2) pain (4 items), (3) psychological discomfort (2 items), (4) physical disability (3 items), (5) psychological disability (2 items), (6) social disability (3 items), and (7) handicap (2 items). Each item is scored on a Likert scale from 1 ('Never') to 5 ('Very often'). The outcomes of the OHIP-EDENT can have a range from 19 to 95. A score of 19 means that dental problems do not affect daily life at all, whereas a score of 95 means that dental problems affect daily life very often.

Obturator Function Scale

The OFS assesses patients' satisfaction and the quality of their obturator prosthesis [7]. The total scale of the questionnaire has an excellent internal consistency, and the eating and speech sub-scales have a Cronbach's alpha of .86, .82, and .87, respectively [7]. This questionnaire consists of 15 items in total and three subcategories: (a) eating problems (3 items), (b) speech problems (5 items), and (c) other problems (7 items). Each item is scored on a Likert scale from 1 ('Not at all a problem') to 5 ('Always a problem').

Dutch Liverpool Oral Rehabilitation Questionnaire version 3

The LORQv3-NL evaluates the impact of oral rehabilitation on OHRQoL in patients treated for oral cancer. The LORQv3-NL is divided into four sections and consists of (a) oral function, oral-facial appearance and social interaction (17 items), (b) patient satisfaction of prostheses (4 items), (c) patient satisfaction of upper dentures (6 items), and (d) patient satisfaction of lower dentures (6 items). The internal consistency of these sections has a Cronbach's alpha of .89, .83, .75, and .81, respectively [25]. All items are rated on a 1 to 4 Likert scale from 1 ('Never') to 4 ('Always') and refer to recent symptoms or problems experienced during the previous week.

Statistics

The presentation of results is primarily descriptive with means, standard deviations (SD), and medians. Fisher's exact test, the Chi-square-test, and Independent *t* tests were used to assess whether there are differences in demographic and clinical data. Values of the implant-retained group versus the conventional group of the MAI score (continued data) were compared with Independent *t* tests when data were normally distributed; otherwise, the Mann-Whitney *U* test was applied. Normal distribution was verified by using the Shapiro-Wilk test. The Mann-Witney U Test was used to compare the outcome of the OHIP-EDENT, OFS, and LORQv3-NL questionnaires (ordinal data) for the two patient groups. Statistical analyses were regarded as significant if the *p*-value was equal to or lower than .05. Data were evaluated using SPSS (IBM version 24 for Mac).

A *post hoc* power analysis was performed on the primary outcome MAI score by G*Power [32, 33].

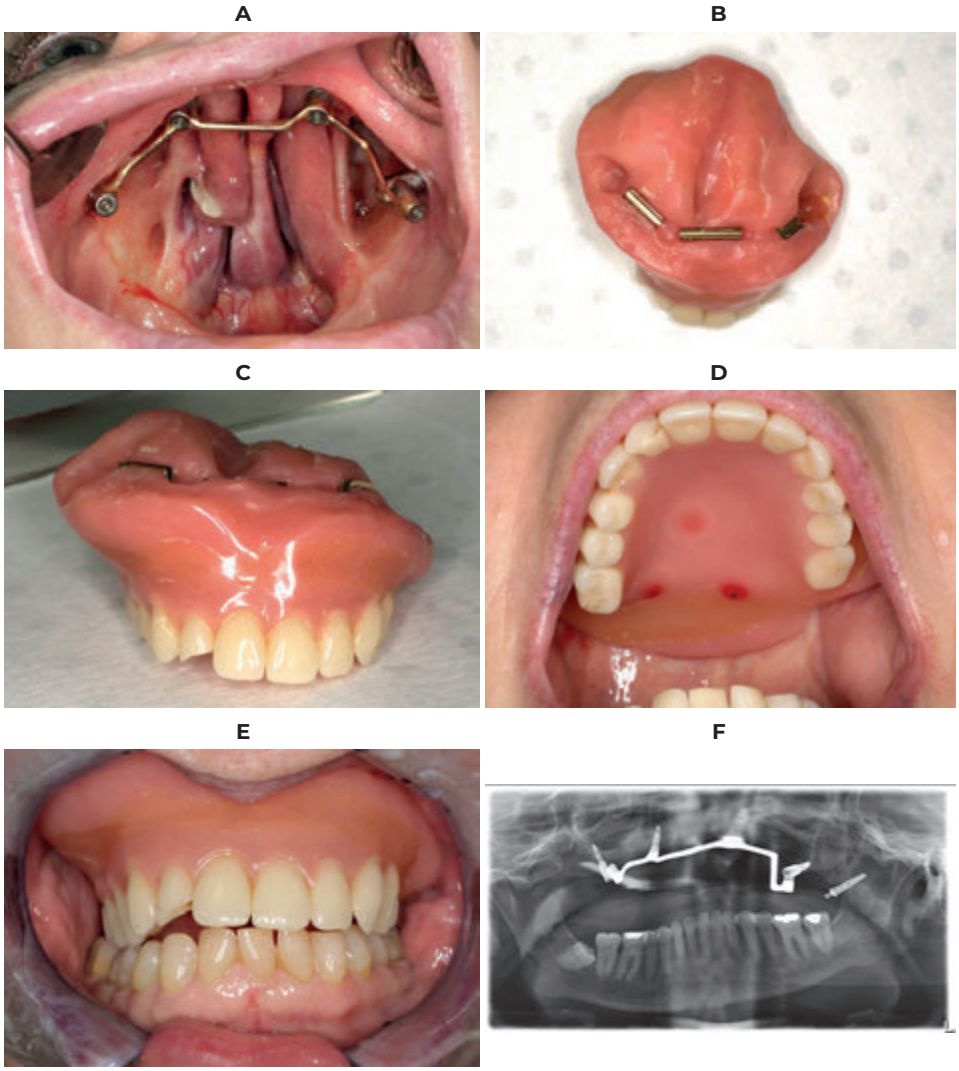

Figure 2 - A patient presented with a Brown class IId defect [21] after treatment of ameloblastoma. (a) Bar construction was made on the dental implants to support the obturator. (b) Retentive parts in the obturator prosthesis. (c) Frontal view of the obturator. (d) Palatal view of the final prosthesis. (e) Frontal view many years (>8) after implant-supported obturator delivery. (f) Panoramic radiography showed the position of dental implants in remaining bony parts of the midface or skull base.

Results

Clinical features of patients

Twenty-two patients with substantial loss of maxillary/midfacial substance and edentulism in the remaining maxillae were eligible to participate in this cross-sectional study. Nineteen patients agreed to participate, two patients rejected the invitation, and one patient did not respond. The medical history and demographic data of the 11 men (57.9%) and eight women (42.1%) are shown in Table 1. Regarding sex, age, reason for maxillectomy, adjuvant radiotherapy, and dental status in the lower jaw, no significant differences were found between the two patient groups. According to Brown's classification, the maxillary defects ranged from Ia to IId. Two patients only had a defect of the soft palate (SP), which is not included in Brown's classification. The defects in the group of patients with an implant-supported obturator prosthesis were significantly larger and more ventral than the defects in the group with conventional obturator prostheses, making prosthetic rehabilitation more challenging (see also Table 1). On average, the patients with implant-supported obturating prostheses were interviewed 3.8 years after prosthetic rehabilitation (range: 1 month-7.4 years), and 4.8 years (range: 4 months-8.7 years) in the conventional obturator group. Thirteen patients, five with implant-supported prostheses and nine with conventional obturator prostheses, had a history of adjuvant radiotherapy (56-70Gy) due to cancer treatment.

In Group 1 (nine patients), the mean age was 64 years (range 47-78). Four of these patients received implants in the remaining parts of the maxilla; one patient received implants after bone-augmentation. In the remaining five cases, no viable maxillary structure was left for implant placement. These patients received implants in the remaining bone structures useful for implantation, such as the pterygoid bone, the zygomatic bone, or the paranasal pillars of the nasal aperture. In total, 42 implants were placed to support the obturator prostheses, of which four were lost in a total of three patients. Three implants were lost before loading due to lack of osseointegration; the fourth showed good osseointegration but was lost 3 years after loading. These patients had undergone radiation treatment: two after implant placement, and one before implant placement. In three patients of Group 1, the natural dentition in the lower jaw was preserved. In four of the remaining six patients, the lower jaw dentures were implant-retained.

Ten patients with a mean age of 71 years (range 59-85) were treated with conventional obturator prostheses (Group 2). A partial natural dentition was preserved in the lower jaw in only one patient of Group 2. In three of the remaining nine patients, the lower jaw dentures were implant-retained.

Table 1 - Demographic and clinical characteristics of patients with implant-supported obturators and patients with conventional obturators

Patient characteristics	**Implant-supported obturators n = 9**	**Conventional obturators n = 10**	***p*-value**
Gender (%)			
Male	7 (78%)	4 (40%)	0.170[c]
Female	2 (22%)	6 (60%)	
Age			
40-49	2	0	
50-59	2	1	
60-69	2	3	0.327[a]
70-79	3	4	
80-89	0	2	
Follow-up time (Mean ± SD)	45.38 ± 34.67	57.09 ± 31.46	0.453[b]
Origin of maxillectomy			
Gingival squamous cell carcinoma	5	6	
Polymorf lowgrade adenocarcinoma	0	2	
Adenoidcystic carcinoma	1	1	
Muco-epidermoid carcinoma	0	1	0.417[a]
Ameloblastoma	1	0	
Avascular necrosis after Le Fort I osteotomy	1	0	
Traumata	1	0	
Radiotherapy	5 (56%)	8 (80%)	0.350[c]

Table 1 - Continued

Patient characteristics	Implant-supported obturators n = 9	Conventional obturators n = 10	*p*-value
Brown-classification			
Ia	1	0	
IIa	0	3	
IIb	2	5	0.021[a,*]
IIc	1	0	
IId	5	0	
soft palate	0	2	
Dental status mandibular			
Natural dentition	3	1	
Implant-supported lower denture	4	3	0.091[a]
Conventional lower denture	2	6	

Note: Brown vertical classification. I: maxillectomy not causing an oronasal fistula; II: not involving the orbit. Brown horizontal classification. a: palatal defect only. not involving the dental alveolus; b: less than or equal to 1/2 unilateral; c: less than or equal to 1/2 bilateral or transverse anterior; d: greater than 1/2 maxillectomy. Soft palate not part of Browns classification with only a defect in the soft palate.

[a] *χ^2-test.*

[b] *t Test.*

[c] *Fisher's exact test.*

**p<.05.*

Quality of life related to masticatory performance

The Shapiro-Wilk test showed a non-normal distribution of the MAT outcomes; therefore, the Mann-Whitney *U* test was used.

Table 2 - OHIP-EDENT scores of patients with implant-supported obturators and patients with conventional obturators

Item No	Description
Functional limitation	
1	Difficulty chewing
2	Food catching
3	Dentures nog fitting
Subtotal	
Physical pain	
4	Painfull aching
5	Uncomfortable to eat
6	Sore spots
7	Uncomfortable dentures
Subtotal	
Psychologic discomfort	
8	Worried
9	Self-conscious
Subtotal	
Physical disability	
10	Avoid eating
11	Unable to eat
12	Interrupt meals
Subtotal	
Psychologic disability	
13	Upset
14	Been embarrassed
Subtotal	
Social disability	
15	Avoid going out
16	Less tolerant of others
17	Irritable with others
Subtotal	

Implant supported obturators		Conventional obturators		
Mean ± SD	**Median**	**Mean ± SD**	**Median**	***p*-value**
2.00 ± 0.71	2.00	3.40 ± 0.70	3.00	0.001**
3.44 ±1.33	4.00	3.40 ± 1.17	3.00	0.799
1.78 ±0.83	2.00	2.00 ± 0.94	2.00	0.601
7.22 ±2.17	7.00	8.80 ± 1.93	9.00	0.115
2.22 ±1.48	2.00	2.45 ± 1.26	2.25	0.612
2.11 ±1.17	2.00	3.40 ± 0.97	3.50	0.026*
2.22 ±1.30	2.00	1.70 ± 1.06	1.00	0.295
1.44 ±0.53	1.00	1.40 ± 0.52	1.00	0.849
8.00 ±3.57	8.00	8.95 ± 2.71	9.50	0.412
1.44 ± 0.73	1.00	1.50 ± 0.85	1.00	1.000
2.22 ± 1.64	2.00	2.60 ± 1.27	3.00	0.473
3.67 ± 2.24	3.00	4.10 ± 1.52	4.00	0.297
3.00 ± 1.12	3.00	3.60 ± 1.17	4.00	0.247
1.67 ± 1.00	1.00	1.80 ± 0.79	2.00	0.534
1.33 ± 0.71	1.00	1.70 ± 0.82	1.50	0.254
6.00 ± 2.45	6.00	7.10 ± 2.13	7.50	0.233
1.78 ± 1.30	1.00	1.80 ± 1.23	1.00	0.927
1.89 ± 1.36	1.00	1.80 ± 1.14	1.00	0.927
3.67 ± 2.60	3.00	3.60 ± 2.01	3.00	0.931
1.44 ± 0.73	1.00	2.10 ± 1.37	1.50	0.314
1.67 ± 1.12	1.00	1.30 ± 0.68	1.00	0.460
1.67 ± 1.12	1.00	1.80 ± 0.92	1.50	0.614
4.78 ± 2.77	3.00	5.20 ± 1.75	5.00	0.293

Table 2 - Continued

Item No	Description
Handicap	
18	Unable to enjoy company
19	Life unsatisfying
Subtotal	
Total	

***** $p<.05$. ****** $p<.01$.

Table 3 - OFS-scores of patients with implant-supported obturators and patients with conventional obturators

Item No	Description
Eating problems	
1	Difficulty in chewing food
2	Leakage when swallowing liquids
3	Leakage when swallowing food
Subtotal	
Speech problems	
4	Voice different from before surgery
5	Difficulty in talking in public
6	Speech is nasal
7	Difficulty in pronouncing words
8	Speech is difficult to understand
Subtotal	
9	Mouth feels dry
10	Dissatisfaction with looks
11	Clasps on front teeth are noticeable
12	Upper lip feels numb
13	Avoidance of family/social events
14	Difficulty inserting obturator
15	Upper lip looks funny
Total	

***** $p<.05$. ** $p<.01$.

Implant supported obturators		Conventional obturators		
Mean ± SD	**Median**	**Mean ± SD**	**Median**	***p*-value**
1.56 ± 0.88	1.00	1.90 ± 1.20	1.00	0.567
1.56 ± 1.33	1.00	1.70 ± 0.82	1.50	0.296
3.11 ± 2.03	2.00	3.60 ± 1.84	3.00	0.376
36.44 ±13.79	31.00	41.35 ± 9.16	43.25	0.253

Implant supported obturators		Conventional obturators		
Mean	**Median**	**Mean**	**Median**	***p***
1.67 ± 0.87	1.00	3.00 ± 0.82	3.00	0.007**
3.11 ± 1.36	3.00	3.60 ± 1.08	4.00	0.446
2.44 ± 1.24	3.00	2.10 ± 1.37	2.00	0.497
7.22 ± 2.68	8.00	8.70 ± 2.41	9.00	0.323
1.89 ± 1.76	1.00	2.70 ± 0.82	2.50	0.034*
1.78 ± 1.56	1.00	2.20 ± 1.40	2.00	0.236
2.22 ± 1.48	2.00	2.60 ± 1.35	2.00	0.367
1.89 ± 1.27	1.00	2.30 ± 1.25	2.00	0.367
2.00 ± 1.50	1.00	1.80 ± 0.79	2.00	0.790
9.78 ± 6.55	6.00	11.60 ± 4.30	10.50	0.174
2.67 ± 1.58	2.00	1.90 ± 1.10	1.50	0.250
2.11 ± 1.54	1.00	1.50 ± 1.08	1.00	0.276
2.11 ± 1.45	2.00	1.70 ± 0.95	1.00	0.563
1.56 ± 0.73	1.00	1.70 ± 1.25	1.00	0.899
1.56 ± 1.13	1.00	1.40 ± 0.84	1.00	0.818
1.11 ± 0.33	1.00	1.50 ± 0.97	1.00	0.301
2.00 ± 1.41	1.00	1.30 ± 0.95	1.00	0.126
30.11 ± 13.52	26.0	31.30 ± 6.40	30.0	0.413

Table 4- LORQv3-NL scores of patients with implant-supported obturators and patients with conventional obturators

Item No	Description
Chewing	
1	Did you experience difficulty with chewing?
2	Did you have pain when you chew?
16	Did your chewing ability influence your choice of foods?
Subtotal	
Swallowing	
3	Did you experience difficulty with swallowing solids?
4	Did you experience difficulty with swallowing liquids?
Subtotal	
Salivation	
5	Did food particles collect under your tongue?
6	Did food particles stick to your palate?
7	Did food particles stick inside your cheeks?
8	Did you have mouth dryness?
9	Did you have problems with drooling?
Subtotal	
10	Did you experience problems with speech?
17	Did you experience difficulty with opening your mouth?
Subtotal Oral function (1-10, 16, 17)	
Orofacial appearance	
11	Were you upset by your facial appearance?
12	Were you upset by the appearance of your mouth?
13	Were you upset by the appearance of your lips?
14	Were you upset by the appearance of your teeth?
Subtotal	
Social interaction	
15	Did your chewing ability affect your social life?
Total (1-17)	
Patient satisfaction	
20	Were you embarrassed about conversing because of your dentures/implant-retained teeth?
21	Did you refuse dinner invitations because of embarrassment about your dentures/implant-retained teeth?

Implant supported obturators		Conventional obturators		
Mean ± SD	**Median**	**Mean ± SD**	**Median**	***p*-value**
1.67 ± 1.00	1.00	2.00 ± 0.67	2.00	0.183
1.33 ± 0.71	1.00	1.30 ± 0.48	1.00	0.832
1.78 ± 0.97	2.00	2.50 ± 1.18	2.00	0.153
4.78 ± 2.05	4.00	5.80 ± 1.81	6.00	0.199
1.00 ± 0.00	1.00	2.30 ± 0.68	2.00	0.000***
1.44 ± 0.73	1.00	1.70 ± 0.82	1.50	0.461
2.44 ± 0.73	2.00	4.00 ± 0.94	4.00	0.002**
1.33 ± 0.50	1.00	2.00 ± 1.16	1.50	0.216
1.56 ± 0.53	2.00	1.70 ± 0.68	2.00	0.678
1.78 ± 0.83	2.00	2.10 ± 1.37	1.50	0.793
2.33 ± 0.87	2.00	2.30 ± 0.95	2.00	0.965
1.56 ± 0.73	1.00	2.00 ± 1.33	1.00	0.648
8.56 ± 1.81	8.00	10.10 ± 2.85	9.50	0.282
1.44 ± 1.01	1.00	2.00 ± 1.16	1.50	0.237
1.56 ± 1.01	1.00	2.30 ± 1.34	2.00	0.196
18.78 ± 4.35	19.00	24.20 ± 5.25	22.50	0.030*
1.44 ± 1.01	1.00	1.10 ± 0.32	1.00	0.440
1.56 ± 1.01	1.00	1.20 ± 0.42	1.00	0.458
1.44 ± 1.01	1.00	1.00 ± 0.00	1.00	0.126
1.33 ± 0.71	1.00	1.00 ± 0.00	1.00	0.126
5.78 ± 3.56	4.00	4.30 ± 0.68	4.00	0.215
1.33 ± 1.00	1.00	2.00 ± 1.05	2.00	0.065
25.89 ± 8.37	25.00	30.50 ± 5.91	29.0	0.078
1.33 ± 0.71	1.00	1.20 ± 0.63	1.00	0.530
1.22 ± 0.67	1.00	1.70 ± 1.06	1.00	0.187

Table 4- Continued

Item No	Description
22	Did you feel loss of self-confidence because of embarrassment about your dentures/implant-retained teeth?
23	Did you find it difficult to open your mouth because of your dentures/implant-retained teeth?
Subtotal	
Maxillary prosthetic satisfaction	
26	Were you dissatisfied with your upper denture/implant-retained teeth?
27	Did your upper denture/implant-retained teeth cause soreness or ulceration of the gum?
28	Did you find food particles collecting under your upper denture/implant-retained teeth?
29	Did you take out your upper denture/implant-retained teeth for eating?
30	Did you feel insecure with your upper denture/implant-retained teeth?
31	Were you worried that your upper denture/implant-retained teeth might fall out?
Subtotal	
Mandibular prosthetic satisfaction	
34	Were you dissatisfied with your lower denture/implant-retained teeth?
35	Did your lower denture/implant-retained teeth cause soreness or ulceration of the gum?
36	Did you find food particles collecting under your lower denture/implant-retained teeth?
37	Did you take out your lower denture/implant-retained teeth for eating?
38	Did you feel insecure with your lower denture/implant-retained teeth?
39	Were you worried that your lower denture/implant-retained teeth might fall out?
Subtotal	

***** $p<.05$. ** $p<.01$. ******* $p<.001$.

Implant supported obturators		Conventional obturators		
Mean ± SD	**Median**	**Mean ± SD**	**Median**	***p*-value**
1.44 ± 1.01	1.00	1.20 ± 0.42	1.00	0.818
1.11 ± 0.33	1.00	2.20 ± 1.23	2.00	0.023*
5.11 ± 2.32	4.00	6.30 ± 1.57	7.00	0.049*
1.33 ± 1.00	1.00	1.10 ± 0.32	1.00	0.878
1.11 ± 0.33	1.00	1.40 ± 0.52	1.00	0.165
2.33 ± 0.87	2.00	1.70 ± 0.68	2.00	0.098
1.00 ± 0.00	1.00	1.00 ± 0.00	1.00	1.000
1.44 ± 1.01	1.00	1.10 ± 0.32	1.00	0.440
1.22 ± 0.67	1.00	1.20 ± 0.42	1.00	0.699
8.44 ± 2.65	8.00	7.50 ± 0.97	7.00	0.493
1.17 ± 0.41	1.00	1.11 ± 0.33	1.00	0.765
1.17 ± 0.41	1.00	1.22 ± 0.44	1.00	0.799
1.50 ± 0.55	1.50	2.00 ± 0.87	2.00	0.255
1.17 ± 0.41	1.00	1.67 ± 1.32	1.00	0.673
1.00 ± 0.00	1.00	1.44 ± 1.01	1.00	0.232
1.00 ± 0.00	1.00	1.56 ± 1.01	1.00	0.129
7.00 ± 0.89	7.00	9.00 ± 4.06	8.00	0.276

Patients with an implant-supported obturator prosthesis had a significantly better MAI score (18.66 ± 1.37) than patients with conventional prostheses (22.36 ± 3.16; *p* = .015). Thereby, the subdomain of 'chewing difficulty' showed better results in patients with an implant-supported obturator in both the OHIP-EDENT (*p* = .001; Table 2) and OFS (*p* = .007; Table 3). The subdomain of 'eating comfort' of the OHIP-EDENT also showed a significantly better eating comfort in patients with an implant-supported prosthesis (*p* = .026). Likewise, the domain of 'oral functioning' of the LORQv3-NL was better in patients with an implant-supported obturator prosthesis (*p* = .030; Table 4). The difficulties in swallowing solids are noteworthy. The results were worse in patients wearing conventional obturator prostheses in comparison to those with implant-supported devices (LORQv3-NL; *p* = .000). Voice modifications were more obvious in patients of Group 2 (OFS; *p* = .034).

Post hoc power calculation

We computed the sample size given α = .05, power = 0.8, and the expected effect size for two independent means (matched pairs) with the MAI score outcomes of this study. The mean MAI score was 18.66 (± 3.16) for the patients with implant-supported obturator prostheses and 22.36 (± 1.37) for the patients with conventional obturators. Therefore, the required sample size was estimated at 16 subjects (eight per group).

Discussion

In this cross-sectional comparative study, we explored whether implant-supported obturator prostheses in maxillectomy patients improved masticatory performance and OHRQoL. Therefore, we evaluated both objective outcomes from the MAT and subjective outcomes from the OHRQoL questionnaires, as objective information of oral functioning may be different from personal experiences. The MAT evaluates the ability to mix a bi-coloured wax tablet and results in the MAI score. It has proven to be valid and reliable in test candidates with compromised masticatory performance [23, 34].

The study indicates that implant-supported obturator prostheses are useful in the oral functional rehabilitation of maxillectomy patients. The results show a significantly better MAI score outcome in patients of Group 1, notwithstanding the larger and more ventral defects. The patients with implant-supported obturator prostheses show similar MAI score results (18.66 ± 1.37) compared with dentate obturator patients (18.4 ± 4.2) despite severely compromised oral function due to the maxillectomy. Likewise, healthy edentulous non-maxillectomy individuals with conventional maxillary dentures and implant-supported mandibular overdentures (MAI 18.5 ± 3.1) have shown similar results. The mean MAI score of Group 2 patients (22.36 ± 3.16) was comparable to healthy full denture patients (21.2 ± 3.6) and other edentulous obturator patients (25.1 ± 5.3) [23, 35].

The added value of dental implants in prosthetic rehabilitation of patients after maxillectomy has been reported previously, both in patients receiving obturator prostheses, as well as in surgically reconstructed patients. The use of zygomatic implants increases reconstructive treatment options, especially for maxillectomy patients. To date, functional differences have not been established between the obturator and surgically reconstructed patients [20, 36, 37].

We reached an overall implant survival of 90.5%, with four out of 42 implants lost in patients in Group 1. Since the four lost implants have failed in irradiated bone, our overall implant survival in non-irradiated bone of 100% is comparable with the results published by Huang et al. [14]. In their study, implant survival in irradiated patients was 82.6%. Other studies have reported similar results; however, these studies did not refer to dental implant survival in extra-maxillary bony structures of the midface or skull base [38-40]. Moreover, current literature does not explicitly reveal information about the radiation doses at the specific implant sites. Instead, studies have reported whether the patient was irradiated

or not. In our study, the implant sites of the lost implants had been irradiated with more than 50Gy. Nevertheless, the patients could continue to wear their prosthetic obturators despite singular implant loss, which we considered a successful overall result of functional rehabilitation.

In addition to objective results such as MAI scores, functional aspects must be assessed subjectively using the OHRQoL. The OHIP-EDENT is a modified shorted version of the OHIP-49 questionnaire which, in contrast to the more commonly used OHIP-14, includes items related to chewing and denture problems [24]. The OHIP-EDENT showed significantly better results after implant-retained prosthetic rehabilitation in a study on five edentulous hemi-maxillectomy patients [18].

The Memorial Sloan Kettering Cancer Centre Obturator Functioning Scale (OFS) has proven to be a viable questionnaire to assess self-reported obturator functioning and to predict quality of life in maxillectomy patients [7, 41, 42]. It has shown the negative impact of (adjuvant) radiotherapy [15, 16, 42, 43] and defect size on obturator functioning [16, 35].

The LORQv3 is a health-related questionnaire assessing the impact of oral rehabilitation on patients' OHRQoL [26-28]. It has recently been translated and validated into the Dutch language, resulting in the LORQv3-NL [25]. This questionnaire has shown the added value of prosthetic rehabilitation in improving HRQoL of patients treated for head and neck cancer, including maxillectomy patients rehabilitated with obturator prostheses [44-46].

Our OHIP-EDENT, OFS, and LORQv3-NL results did not disclose significant differences in summary scales between the two patient groups. This is probably due to the long-time interval between prosthetic rehabilitation and data acquisition (range: 1 month-7.4 years). Patients tend to adapt over time and under-report deficits, also called response shifts [47].

On the subscale level, the 'Oral function' subscale and the 'Patient Satisfaction' subscale of the LORQv3-NL showed that implant retainment has an added value for the obturator prostheses. Although these benefits are underlined in response choices by all three questionnaires, the small patient groups should be considered. The same carefully interpretation should be applied for the promising results in the speaking and swallowing domains, which have proven to be important for quality of life [7, 41].

There are benefits for microsurgical reconstruction of extended maxillary and midface defects. Patients requiring adjuvant radiotherapy will take advantage of reconstructive surgery, as the risk of post-radiogenic changes in the irradiated tissues will be less pronounced. Tissue atrophy, fibrosis, and the most feared risk of osteoradionecrosis can be prevented by vascularized tissue transfer into the defect site. Moreover, surgical defect repair can lead to aesthetic benefits, and implant-retained fixed dentures can be applied. However, risks, as well as costs of reconstructive surgery, should not be underestimated. For class IIb and smaller defects, very good results can be achieved by either prosthetic obturation or surgical reconstruction [21]. Our results endorse the previously mentioned advantages of implant-supported prosthetic rehabilitation, especially in (a) preventing donor site morbidity, (b) surgical risks, and (c) longer hospitalization needed for a vascularized flap transfer [48]. The overall treatment time until adequate prosthetic rehabilitation is achieved is much shorter in prosthetic obturation. In oncologic cases, the inspection of the resection defect offers advantages during the follow-up.

Strengths and limitations

To our knowledge, this is the first study to objectively examine masticatory performance in patients rehabilitated with implant-supported obturator prostheses in comparison to conventional prosthetic devices. Moreover, patient-reported OHRQoL-results appear to support the objective results of this study. The inclusion of only edentulous maxillectomy patients has the advantage of eliminating the bias of residual dentition, which has proven to be beneficial for masticatory performance [2, 15, 35, 49, 50].

Limitations are the cross-sectional study design, the small population, the inhomogeneous anamnesis, and the wide time span between prosthetic rehabilitation and data acquisition. Although patients in Group 1 had a mean follow-up time of 4.8 years, only four out of these nine patients had a follow-up of more than five years. Quality of life 1 year after surgery has been shown to be a good indicator of long-term quality of life [51]. Implant survival rates, however, ask for a minimum of five years, and preferably ten years, of follow-up [14, 39, 52, 53].

Future research

Long-term longitudinal prospective research with a larger number of participants is required, as well as objective measurements of speech and swallowing. Comparison of functional outcomes and HRQoL after prosthetic obturation, preferably implant-supported, with surgical reconstruction would give support in the individual decision making for maxillectomy patients.

Conclusion

Implant-supported prosthetic obturation after maxillectomy appears to improve chewing ability, oral functioning, and patient satisfaction. More research is needed to confirm the advantages in speech and swallowing after implant-supported prosthetic obturation. This treatment modality is a viable alternative to surgical reconstruction after maxillectomy, especially in medically compromised and older patients. If implant placement is possible in maxillectomy patients, implant-retained obturator prostheses should be preferred.

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CHAPTER 4.2

MASTICATION IN MAXILLECTOMY PATIENTS: A COMPARISON BETWEEN RECONSTRUCTED MAXILLAE AND IMPLANT SUPPORTED OBTURATORS: A CROSS-SECTIONAL STUDY.

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Abstract

Objective: The aim of this study was to compare masticatory performance and patient reported eating ability of maxillectomy patients with implant-supported obturators and patients with surgically reconstructed maxillae.

Methods: This cross-sectional study was conducted at the University of Alberta, Edmonton, Canada and at Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands. Eleven surgically reconstructed maxillectomy patients have been included at University of Alberta and nine implant-supported obturator patients at MUMC+. The mixing ability test (MAT) was used to measure masticatory performance. In addition, the oral health related quality of life (OHRQoL) was measured with shortened versions of the oral health impact profile (OHIP) questionnaire. Values of the implant-supported obturator group versus the surgical reconstruction group were compared with independent t-tests in case of normal distribution, otherwise the Mann-Whitney U test was applied.

Results: Patients with reconstructed maxillae and patients with implant-supported obturator prostheses had similar mean mixing ability indices (18.20 ± 2.38 resp. 18.66 ± 1.37; p = .614). The seven OHRQoL questions also showed no differences in masticatory ability between the two groups.

Conclusion: With caution, the results of this study seem to confirm earlier results that implant-supported obturation is a good alternative to surgical reconstruction for all Class II maxillary defects. With both techniques, the masticatory performance is sufficiently restored, with careful planning being highly desirable.

Introduction

Ablative cancer surgery, extended resection of benign lesions, or trauma involving the maxilla will result in complex three-dimensional defects in the region of the upper jaw and midface. Reconstruction of these defects is a major challenge for both surgeons and prosthodontists [1-3]. Researchers have presented valid arguments in choosing the best reconstruction and rehabilitation method for maxillectomy patients, based on parameters such as quality of life (QoL) and functional outcomes [4-7]. Implant-supported obturation represents an alternative for surgical reconstruction of defects where the orbital floor is intact and no substantial loss of soft tissues exists [3, 8, 9]. The advantages of implant-supported obturation include a shorter treatment period, no need for extensive reconstructive surgery with donor and recipient site morbidity, reduced post-treatment morbidity, and lower costs [8]. Disadvantages of prosthetic obturation include nasal leakage, cleaning, and constant prosthetic refinement [10]. Regardless of the rehabilitation route, defects that comprise a significant part of the dental alveolus, require dental rehabilitation to allow for optimal mastication and dental appearance [3]. Regarding mastication, comparative studies between surgical reconstruction and obturation seem to favour surgical reconstruction, especially in patients with larger maxillary defects [11-13]. At the same time, QoL-research shows equivalent results for both options[14-17]. To our knowledge no studies are available comparing masticatory performance between surgically-reconstructed and implant-supported prosthetic obturation. Therefore, the aim of this study was to compare masticatory performance and patient reported eating ability of patients with implant supported obturators and patients with surgically reconstructed maxillae.

Materials and methods

This cross-sectional study was conducted at the University of Alberta, Edmonton, Canada and at Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands. The surgical reconstruction group consisted of patients treated at the University of Alberta Hospital and rehabilitated at the Institute for Reconstructive Sciences in Medicine (iRSM). Patients treated for benign tumours, or malignant tumours with a curative intent were included [12]. Eligible tumour locations were upper alveolar process, tuber maxillae, palate and maxillary sinus. Reconstruction was performed according to the Alberta Reconstructive Technique (ART) protocol [18, 19] for malignant tumours or the Rohner-protocol [20] for benign tumours. The Rohner prefabricated fibula technique allows for a two-stage approach. The primary surgery comprises prefabrication of the fibula with implant placement according to the surgical design and simulation (SDS) plan, followed by a healing period. Subsequently, the fibular flap is harvested in a second operation, and the reconstruction of the maxilla is carried out using cutting guides and the occlusion of the final prosthesis as a transfer template. In malignant tumours, the ART-technique, is based on 3D-printed surgical guides and positioning splints. Neck dissection, tumour resection, microsurgical reconstruction and implant placement are done in the first surgical stage, followed by exposing the implants in a second operation.

In the obturator group, patients with edentulous upper jaws were included when maxillary defects were rehabilitated with an implant-supported obturator at Maastricht UMC+ [21]. Maastricht patients were treated according to the "surgical and prosthetic reconsiderations in patients with maxillectomy protocol" as defined by Lethaus et al. in 2010 [22]. Implant sites in the remaining facial skeleton or skull base were planned based on CT-data with the Simplant 3D® program (Dentsply Sirona, Charlotte, USA). When standard abutments did not comply with the required distances or angulation of our protocol, individual abutments were designed by hand or by using Cinema 4D® planning program (Design Express, Gouda, The Netherlands). If possible, a bar construction was made on the dental implants to support the obturator prosthesis. Magnet abutments were used as an alternative retention method, when the space between two implants was too wide.

Exclusion criteria were cognitive impairment or the inability to understand English for the Canadian participants and an inability to understand Dutch for the Dutch participants.

Patients at the University of Alberta have been included as part of the HREBA.CC-17-0167 study [12], and at Maastricht UMC+ as part of the METC.15-4-123 study [21]. For both studies medical-ethical approval was given. Written informed consent was obtained from each participant before entering the study.

Clinical patient charts were examined for age, sex, duration since dental oral rehabilitation, origin of defect, type of tumour, type of treatment (surgery alone or surgery with adjuvant radiotherapy), radiation dose as well as number of dental implants. The initial defect was recorded by the classification of the extents of maxillary defects according to Brown [23]. The horizontal, or dentoalveolar component of this classification describes the functional side of the defect.

Dental status was examined and scored according to present natural dentition, dental implants, and prostheses in both jaws. Furthermore, the occluding pairs were scored as premolar equivalents [24]. Occluding fixed dental prostheses were included in the number of occluding pairs. In contrast third molars and tissue- or implant-supported prostheses were not included.

Masticatory performance
The mixing ability test (MAT) was used to measure masticatory performance [25, 26]. This test measures how well a participant mixes a two-coloured wax tablet by chewing on it. The tablet has a diameter of 20 mm and consists of two 3 mm layers of red and blue wax. The test-wax is a soft material (Plasticine modelling wax, non-toxic DIN EN-71) that forms a compact bolus during chewing and was presented to the participant at room temperature (20 ˚C). After chewing, the wax was flattened between foils to a thickness of 2 mm to avoid shadows. Then the test wax was illuminated by a scanner lamp and photographed on both sides using a high-quality scanner (Epson V750). The images of the wax were analysed and processed using a commercially available program for image analysis (Adobe Photoshop CS3). Intermediate colour intensities appear and the spreads of the intensities for red and blue decrease. A lower mixing ability index score (MAI) implies a better colour-mixed tablet, hence better masticatory performance.

Patient reported eating ability
Oral health related quality of life (OHRQoL) was measured with the OHIP-14 at iRSM and the OHIP-EDENT at MUMC+. Both questionnaires are based on the original OHIP consisting of 49 items and have a symptom scale, with higher scores representing stronger symptoms. The overlapping seven questions of OHIP-14 [27] and OHIP-EDENT [28] were used in this study (see Appendix A).

These seven items measure six domains: (a) pain (2 items), (b) psychological discomfort (1 item), (c) physical disability (1 item), (d) psychological disability (1 item), (e) social disability (1 item), and (f) handicap (1 item). Each item was scored on a Likert scale from 1 'Never' to 5 'Very often'.

Statistics

Statistical analysis was done by calculating means and standard deviations (SD) for continuous variables; medians and inter quartile range (IQR) for ordinal and non-normal distributed data. Cross-tabulations were made for categorical variables. A Chi^2 test was used for categorical outcomes; when the table was two by two the Fisher's exact test was used. Given the small amount of patients available for contacting, no sample size calculation was performed. Values of the implant-supported obturator group versus the surgical reconstruction group were compared with independent t-tests in case of normal distribution, otherwise the Mann-Whitney U test was applied. Normal distribution was verified by using the Shapiro-Wilk test. The Mann-Witney U Test was used to test between the two patient groups for the OHIP item outcomes (ordinal data). Statistical analyses were regarded as significant, if the *p*-value was equal to or lower than .05. Data were evaluated using SPSS (IBM version 24 for Mac).

Results

A total of 20 patients were included in this cross-sectional study. Of these 20 patients, eleven (six according to the ART protocol, five according to Rohner's technique) had maxillae reconstructed by free vascularized fibula flaps in Edmonton and nine patients had received an implant supported obturator prosthesis in Maastricht. The medical history and demographic data of the ten men (50%) and ten women (50%) are presented in Table 1. No significant differences were found between the reconstruction group and the obturator group with regard to sex, duration since dental oral rehabilitation, cause for maxillectomy, and adjuvant radiotherapy. Most patients had a defect not involving the orbit, corresponding a vertical Brown component I (n = 1) or II (n = 15). However, some of the data were different between the two groups. Patients with an obturator were older, had a larger horizontal Brown component than the reconstructed patients (p = .034). In addition, the dental status of the maxilla (p = .000), mandible (p = .014), and number of occlusal units (p = .000) were less for the obturator group.

Eleven patients with a mean age of 45 years (range 19–66) were surgically reconstructed and received a total of 46 implants in the (neo)maxilla. One received an implant supported denture, the other ten received fixed dental prosthesis on implants. A natural dentition was preserved in the lower jaw in ten patients. In one patient, the lower jaw was rehabilitated with a fixed dental prosthesis on implants.

In the implant supported obturator group the mean age was 64 years (range 47-78). Four of these patients received implants in the remaining parts of the maxilla, in one patient after bone-augmentation. In the remaining five cases, no viable maxillary structure was left for implant placement. These patients received implants in remaining bone structures useful for implantation, such as the pterygoid bone, the zygomatic bone or paranasal pillars of the nasal aperture. In total 42 implants were placed in the maxillary structures of which 32 were used to support the obturator prostheses. Of the ten unused implants, five were lost, two were damaged and two were non-functional. In the lower jaw: 3 patients had a natural dentition, 5 patients had an implant supported denture, and 1 patients had a conventional denture added to an implant supported obturator.

Patients with a reconstructed maxilla and patients with an implant supported obturator prosthesis had similar mean MAI (18.20 ± 2.38 resp. 18.66 ± 1.37; p = .614). The seven overlapping questions of the OHIP-14 and OHIP-EDENT also showed no differences in masticatory ability between the two groups (Table 2).

Table 1 - Demographic and clinical characteristics of patients with implant supported obturators and a reconstructed maxilla

Patient characteristics	**Implant supported obturators n = 9**	**Reconstructed Maxilla n = 11**	***p*-value**
Gender; n (%)			
Male	7 (78%)	8 (73%)	0.604[a]
Female	2 (22%)	3 (27%)	
Age; mean (SD)	63.78 (12.05)	45.00 (14.28)	0.006[b]
Days since stage II; median (Q1)	1339.12 (359.58)	446.00 (276.00)	0.370[c]
Origin maxilla defect; n (%)			
Malignant tumour	6 (67%)	6 (55%)	
Benign tumour	1 (11%)	5 (45%)	0.105[d]
Trauma	2 (22%)	0 (0%)	
Treatment; n (%)			
Surgery	4 (44%)	8 (73%)	0.205[a]
Surgery and radiotherapy	5 (56%)	3 (27%)	
Vertical Brown defect; n (%)			
I	1 (11%)	0 (0%)	
II	8 (89%)	7 (64%)	0.086[d]
III	0 (0%)	4 (36%)	
Horizontal Brown defect; n (%)			
A	1 (11%)	3 (27%)	
B	2 (22%)	7 (64%)	0.034[d,*]
C	1 (11%)	1 (9%)	
D	5 (56%)	0 (0%)	
Dental status mandible; n (%)			
Natural dentition	3 (33%)	10 (91%)	
Fixed dental prosthesis on implants	0 (0%)	1 (9%)	0.014[d,*]
Implant supported denture	5 (56%)	0 (0%)	
Complete denture	1 (11%)	0 (0%)	

Table 1 - Continued

Patient characteristics	Implant supported obturators n = 9	Reconstructed Maxilla n = 11	*p*-value
Dental status maxilla; n (%)			
Natural dentition	0 (0%)	2 (18%)	
Fixed dental prosthesis on implants	0 (0%)	8 (73%)	0.000[d,***]
Implant supported denture	9 (100%)	1 (9%)	
Occlusal units; mean (SD)	0.00 (0.00)	7.45 (3.80)	0.000[b,***]
Masticatory performance; mean (SD)	18.66 (1.37)	18.20 (2.38)	0.614[b]

Note: Brown vertical classification. I: maxillectomy not causing an oronasal fistula; II: not involving the orbit; III: involving the orbital adnexae with orbital retention.
Brown horizontal classification. a: palatal defect only. not involving the dental alveolus; b: less than or equal to 1/2 unilateral; c: less than or equal to 1/2 bilateral or transverse anterior; d: greater than 1/2 maxillectomy.
Abbreviations: n, number; Q1, first quartile; SD, standard deviation.
[a]*Fisher's exact test.*
[b]*Independent T-test.*
[c]*Mann-Withney U test.*
[d]χ^2*-test.*
**p<.05;*
****p<.001.*

Table 2 - OHIP-49 scores of patients with implant supported obturators and patients with a reconstructed maxilla

Domain	Description
Pain	Painful aching
Pain	Uncomfortable to eat
Psychological discomfort	Self-conscious
Physical disability	Interrupt meals
Psychological disability	Been embarrassed
Social disability	Irritable with others
Handicap	Life unsatisfying

Abbreviation: IQR, Interquartile range.

Implant supported obturators	Reconstructed maxilla	
Median (IQR)	**Median (IQR)**	***p*-value**
2.00 (2.50)	2.00 (1.00)	0.552
2.00 (2.00)	2.00 (1.00)	0.603
2.00 (2.50)	2.00 (2.00)	0.766
1.00 (0.50)	1.00 (2.00)	0.370
1.00 (1.50)	2.00 (2.00)	0.552
1.00 (1.50)	2.00 (1.00)	0.766
1.00 (0.50)	2.00 (1.00)	0.175

Discussion

The results of this study appear to demonstrate comparable masticatory performance and patient reported eating ability for patients with surgically reconstructed maxillae and patients with implant supported obturator prostheses. The mean MAI for both groups (18.20 ± 2.38 resp. 18.66 ± 1.37) are comparable with other compromised groups, like dentate obturator patients (18.4 ± 4.2) and healthy edentulous non-maxillectomy individuals with conventional maxillary dentures and implant-supported mandibular overdentures (18.5 ± 3.1) [25, 29]. Both maxillectomy groups remained below the MAI-level of the natural dentition group (15.8 ± 2.0), confirming previous research into chewing performance in maxillectomy patients [11, 25].

Several authors advocate for the benefits of surgical reconstruction over obturation of maxillary defects, especially for larger defects. Amongst them are authors mainly describing a personal preference solely based on experience [30, 31], or combining the best available literature with clinical experience [3, 17, 32]. Unfortunately, the best available literature is limited, and study populations are usually small. A recently published systematic review describes a risk of selection bias and heterogeneous measurements for studies comparing masticatory efficiency [7]. Additionally, the different methods of measuring masticatory performance: mixing ability test, colour changing chewing gum, and sieving method used in maxillectomy patients [11-13, 21, 25, 29, 33-36] complicate the comparison of the study results.

Recent research confirms the benefits of implant-support to obturators [8, 21] and even suggests equivalent functional results as compared to surgical reconstruction [15, 16]. Our surgically reconstructed group has previously been compared with patients with an conventional obturator, most of them without implants [12, 37-39]. In contrast to our obturator group, the obturator group of this previous cross-sectional study had a significant lower mean MAI index (27.3 ± 0.5) which represents very limited masticatory performance. The retention method of these obturators might be a limiting factor, with only two obturators being implant-supported. Another possible explanation might be found in the feeding-tube item of the EORTC-QLQH&N35. With eleven of the thirteen patients with an obturator scoring positive on the feeding-tube item, there is a possibility that those patients are not masticating at all and with that losing the physical fitness of the masticatory system to do so.

When choosing between obturation or surgical reconstruction, it is important to inform the patient as well as possible. Although the Rohner-procedure gives immediate chewing ability like obturators do, for patients with a malignant tumour, the obturator offers a faster recovery of chewing capacity than the ART-procedure. Since dental oral rehabilitation under the ART procedure is initiated after completion of all cancer treatments and tissue healing, it can easily take up to 6 months to start. The choice of surgical reconstruction has the advantage of avoiding the discomfort of placing and cleaning obturators. There is also less nasalance for hard palate defects reconstructed with a SDS fibula free flap, which may be due to potential retention problems of the obturators [40]. However, all this comes with a higher price. Patients should take into account longer operating times and longer hospital stays. In addition to the higher costs, operations with a longer duration have a higher chance of increased pain, increased functional limitations, poor global recovery and decreased HRQoL 6 months after surgery [41]. Finally, despite all advances in radiology, it remains difficult to distinguish between benign post-treatment changes and recurrent malignancy [42]. In addition to the fact that the oncologist with the surgical reconstruction loses direct visual inspection, the assessment of post-surgical radiological images also becomes more difficult.

Strengths and limitations of this study

To our knowledge this is the first study to objectively compare masticatory performance in patients with surgically reconstructed maxillae and patients with implant supported obturator prostheses. The reliability of the MAT [43, 44] in these rare compromised patient groups are the strengths of this study.

Amongst the limitations are the great variance in time between the end of treatment and the data acquisition and the cross-sectional study design. The differences between the groups, especially cultural differences in this cohort international study, and the small absolute number of patients also remain limitations. However, the most important differences; age, horizontal defect size, dental status and the number of occlusal units would be expected to benefit the masticatory function of the surgically reconstructed group. Our results therefore endorse all the more caution in favouring surgical reconstruction when it comes to masticatory function.

Future research

The choice between surgical reconstruction or obturation of maxilla defects remains controversial and will largely be determined by personal preferences and financial possibilities.

Ideally, future research should consist of prospective comparative research into the short and long term functional results of both modalities. Adding diet consistency questionnaires to the MAT is likely to provide valuable information to further support the decision making [45]. However, to be able to include enough patients, multicentre or even multinational research will be required.

Conclusion

With caution, the mastication results in this study seem to confirm earlier results that implant-supported obturation is a good alternative to surgical reconstruction for all Class II maxillary defects. With both techniques, the masticatory performance is sufficiently restored, with careful planning being highly desirable.

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Appendix A:

The overlapping questions of OHIP-14 and OHIP-EDENT, based on the OHIP-49 [27, 28]

a) Have you had a sore jaw?
b) Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?
c) Have you been self-conscious because of your teeth, mouth or dentures?
d) Have you had to interrupt meals because of problems with your teeth, mouth or dentures?
e) Have you been a bit embarrassed because of problems with your teeth, mouth or dentures?
f) Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures?
g) Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?

CHAPTER 5

THE EXTENT OF UNNECESSARY TOOTH LOSS DUE TO EXTRACTIONS PRIOR TO RADIOTHERAPY BASED ON RADIATION FIELD AND DOSE IN PATIENTS WITH HEAD AND NECK CANCER.

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Abstract

Background and purpose: Prior to radiotherapy (RT), teeth with poor prognosis that pose a risk for post-RT osteoradionecrosis (ORN) are removed. To allow enough time for adequate wound healing prior to RT, decisions are made based on the estimated radiation dose. This study aimed to gain insight into (1) the overall number of teeth extracted and (2) the patient and tumor characteristics associated with the number of redundantly extracted teeth.

Materials and methods: Patients with head and neck cancer (HNC), treated with RT between 2015 and 2019, were included in this cross-sectional study. For each extracted tooth the radiation dose was calculated retrospectively. The cut-off point for valid extraction was set at ≥40Gy in accordance with the national protocol. Potential factors for doses ≥40Gy were identified, including age, sex, tumor location, tumor (T) and nodal stage (N), overall tumor stage and number of teeth extracted.

Results: A total of 1759 teeth were removed from 358 patients. Of these 1759 teeth, 1274 (74%) appeared to have been removed redundantly, based on the mean dose (D_{mean}) of <40Gy. Using the maximum dose (D_{max}) of <40Gy, 1080 teeth (61%) appeared to have been removed redundantly. Tumor location and N-classification emerged as the most important associative variables in the multivariable regression analysis.

Conclusion: To our knowledge this is the first study to provide insight into the amount of teeth redundantly extracted prior to RT and represents a step forward in de-escalating the damage to the masticatory system prior to RT.

Introduction

Osteoradionecrosis (ORN) of the jaw is among the most feared late complications observed in patients with head and neck cancer (HNC) treated with radiotherapy (RT) [1].

Removal of teeth with a limited prognosis and identified as a potential cause of infection in the oral cavity prior to head and neck RT can be associated with a lower risk of developing ORN compared to performing tooth extractions after or during RT [2]. Therefore, it is important that the jaw areas receiving significant doses of radiation are free of potential sources of infection prior to RT. However, tooth extractions result in a decreased number of functional units and impair mastication and swallowing, contributing to a decreased health-related quality of life (QoL) [3-8]. In a recent study on patients with oropharyngeal squamous cell carcinoma (OPSCC), tooth extractions prior to therapy contributed to significant weight loss during RT combined with chemotherapy (CRT) or biotherapy (BRT) [9]. Since maintaining body weight is important for completion of planned RT and to support the recovery period, further weight loss caused by tooth extractions should be minimized or avoided as much as possible [10].

The original Dutch protocol which was re-evaluated in 2018 recommends comprehensive dental assessment of potential oral sources of infection at least 10 to 14 days prior to RT to allow adequate time for wound healing [11-13].

As described by Spijkervet et al., the risk of developing ORN starts at a RT dose of about 40Gy and increases with increasing radiation dose [1]. It is therefore desirable to eliminate oral sources of infection where the radiation fields will achieve an expected cumulative radiation dose of ≥40Gy [13, 14]. However, some of the extracted teeth may be redundantly extracted, due to the fact that the estimated radiation dose prior to RT appeared to be lower after completion of RT planning. Considering the impact of pre-RT tooth extractions on patients with HNC and the advancements in RT techniques, there is a growing demand to adopt a less radical approach to pre-RT extractions [3, 5, 6, 15, 16]. The first objective of this study was to gain insight into the number of teeth not necessarily extracted prior to planned RT. The second objective was to determine which patient or tumor characteristics are associated with the number of redundantly extracted teeth prior to RT.

Materials and Methods

Study design and population

This cross-sectional study included all patients who were treated by primary or adjuvant RT, CRT of BRT with curative intent for HNC at the Comprehensive Cancer Center of Maastricht University Medical Center (MUMC+) and Maastro Clinic between 2015 and 2019. Patients were excluded who were edentulous, did not need tooth extractions pre-RT, had a tooth extraction after RT instead of before, or neglected their teeth to such an extent that extraction of all remaining teeth was required. In addition, patients were excluded if they had previous head and neck RT, proton- or brachytherapy, or RT with palliative intent. Finally, patients with an unknown primary, centrally located, or bilateral proven tumor spread were excluded to allow for reporting of dose distributions in the jaws according to laterality: ipsi- versus contralateral. Data on age, sex, tumor location, tumor size (T), and lymph node status (N), as well as information on tooth extractions were extracted from the electronic health records by an experienced maxillofacial prosthodontist (DB). If a TNM classification was stated according to the 7th edition, it was converted to the TNM classification according to the 8th edition [17, 18]. This study was approved by the medical ethics committee of the MUMC+ (METC 2019-1241). The institutional review board of MUMC+ allowed us to invoke the institutional "no objection regulation", so no patient informed consent was needed.

Tumor location

The patient cohort was divided into eight groups according to the anatomical region of the expected radiation fields: 1) larynx, 2) hypopharynx, 3) parotid region, 4) oropharynx, 5) oral cavity, 6) maxillary complex, 7) nasopharynx, and 8) other (Table 1). The group of patients with parotid gland tumors was supplemented with patients presenting with pre-auricular skin cancers with a radiation field including the parotid gland (due to metastasis or elective coverage) and formed the 'parotid region' group. Patients with a salivary gland tumor of the submandibular or sublingual gland were included in the 'oral cavity' group, because of the close anatomical relation with the mandible. Patients with a tumor in the maxillary region/hard palate were combined with patients with a nasal, paranasal sinus or nasal cavity tumor and formed: the 'maxillary complex' group.

Table 1 – Baseline characteristics of the 358 patients

	n = 358
Age (years)	
Mean ± SD	63.6 ± 11.3
median (IQR)	60.0 (16)
Sex (n; %)	
Female	109 (30.4)
Male	249 (69.6)
Anatomical region of the expected radiation fields (n; %)	
Larynx	60 (16.8)
Hypopharynx	37 (10.3)
Parotid region	35 (9.8)
Oropharynx	117 (32.9)
Oral cavity	51 (14.2)
Maxillary complex	22 (6.1)
Nasopharynx	11 (3.1)
Other	25 (7.0)
Tumor stage (n; %)	
T0	6 (2)
T1	63 (18)
T2	93 (27)
T3	106 (30)
T4	81 (23)
Missing	*9*
Node stage (n; %)	
N0	148 (42)
N1	76 (22)
N2	87 (25)
N3	42 (12)
Missing	*5*

Table 1 – Continued

	n = 358
Tumor stage group (n; %)	
Stage 0 (cis)	1 (0)
Stage I	62 (18)
Stage II	63 (18)
Stage III	91 (26)
Stage IV	134 (38)
Missing	*7*
Type of tumor (n; %)	
Mucosal	289 (81)
Salivary gland	35 (10)
Skin, incl. Melanoma	22 (6)
Other types of tumor	12 (3)

Abbreviation: SD, standard deviation; IQR, interquartile range; TNM-classification: T, tumor; N, node; M, metastasis classification according to the 8th edition.[15, 16]

Radiotherapy

RT was delivered using volumetric modulated arc therapy (VMAT) five days per week for six or seven weeks, to a total dose of 66 to 70Gy in 33 to 35 fractions depending on the RT setting: adjuvant versus primary RT. Twenty-four patients underwent RT in a randomized trial on dose-escalation for the primary tumor (ARTFORCE, clinicaltrials.gov ID NCT01504815) in which the FDG-avid part of the primary tumor was irradiated at a total dose of 84Gy [19]. If indicated, RT was combined with systemic therapy, including cisplatin (CRT) or cetuximab (BRT) [20].

Dental assessment

According to national standard procedures, dental assessment of potential oral sources of infection was performed by oral and radiographic examination (e.g. orthopantomography), at least 14 days before the start of RT. Teeth with a poor prognosis due to extensive caries, advanced periodontal disease, and non-restorable teeth were considered a potential source of infection. Radiographic abnormalities such as apical radiolucency, (partially) impacted teeth, residual root apices, root resorption, and dental cysts were also considered as potential source of infection [11-13]. Teeth with poor prognosis were treated by extraction if the expected radiation dose to the jaws was ≥40Gy [1, 13].

Radiation dose calculations

All RT dose planning was performed in Eclipse (Aria version 15.5; Varian Medical Systems Inc, Palo Alto, California, United States) [21] in which the targets (gross tumor volume (GTV), clinical target volumes (CTV) and planning target volumes (PTV)) were delineated according to international guidelines [22] and the organs at risk (OAR's) according to the Brouwer's Atlas [23]. The radiation dose for each extracted tooth was calculated retrospectively: An experienced RT technologist (MG) delineated the location of the extracted teeth on the planning CT. First, the window level was set to bone density. Second, for each extracted tooth a new structure was created and named according to the Fédération Dentaire Internationale (FDI) World Dental Federation notation [24]. If the maxilla and/or mandible had received a maximum dose (D_{max}) of less than 25Gy (defined as: the 25Gy isodose line not touching the bone of the mandible/maxilla), this particular extracted tooth was not delineated, but was recorded as <25Gy. To delineate the location of the extracted tooth, the contouring tool was converted to a high-resolution segment and a 6 mm wide brush was selected. For each extracted tooth, the position on each CT slice (3 mm slice thickness) where the bone was visible was delineated (Figure 1). After all locations of the extracted teeth were delineated, the mean dose (D_{mean}) and the D_{max} in these locations were exported. All exported data were converted to ipsilateral or contralateral, according to the laterality of the primary tumor region. RT dose was converted to a binary variable comparing sites that received ≥40Gy with sites that received <40Gy, including sites recorded as <25Gy. To calculate the mean values, standard deviations and ranges of D_{mean} and D_{max}, the sites recorded as <25Gy were not included.

Statistical analyses

Descriptive statistics were reported as numbers and percentages, means with standard deviations (SDs), medians with interquartile ranges (IQRs), and total radiation dose ranges in Gy. Univariable logistic regression analyses was used to test the association between different demographic and clinical variables with dose ≥40Gy, for both D_{mean} and D_{max}. These factors included: age at first dental assessment, sex, tumor location, tumor (T) and nodal stage (N), overall tumor stage (I, II, III, IV), early vs. advanced tumor stage, and number of teeth extracted. Factors with $p<.05$ were selected as potentially relevant associative variables and subsequently tested using multivariable logistic regression analyses. Data were analysed using SPSS (IBM version 28 for Windows, Armonk, New York, USA). A *p*-value of less than .05 was considered statistically significant.

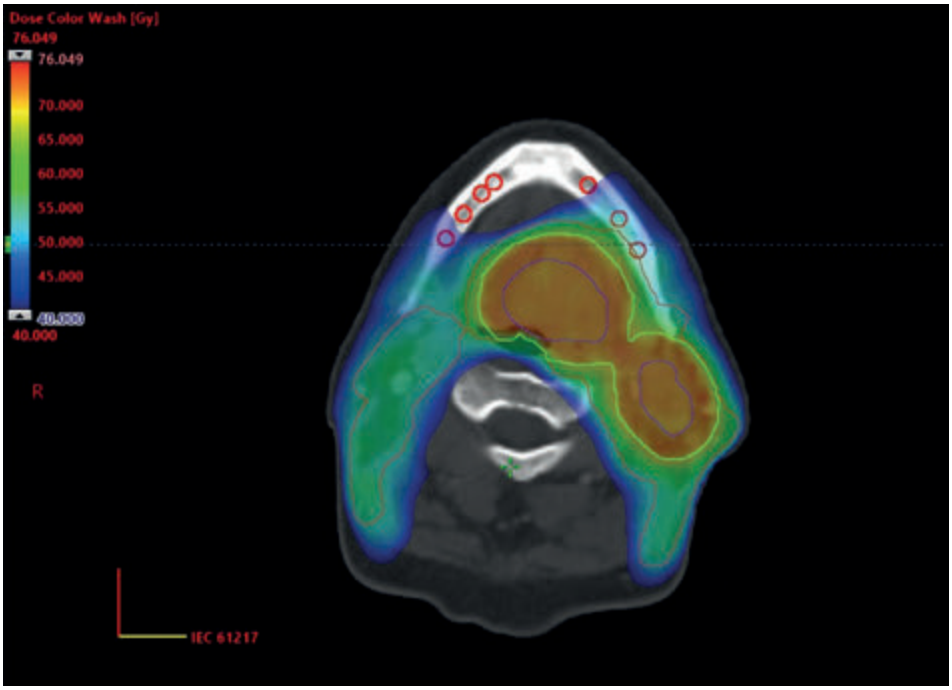

Figure 1 - Delineation of the location of the extracted teeth.

Results

One thousand six hundred and sixteen patients were seen for dental assessment prior to RT of whom 1258 were excluded (Figure 2). In total, 358 patients were included, 249 males (69.6%) and 109 females (30.4%). The mean age was 63.6 years (SD 11.3). Baseline characteristics are presented in Table 1. A total of 1759 teeth were removed from these 358 patients. Of these 1759 teeth, 1274 teeth (74%) appeared to have been removed redundantly, based on the D_{mean} of <40Gy. Using the D_{max} of <40Gy, 1080 teeth (61%) appeared to have been removed redundantly (Table 2).

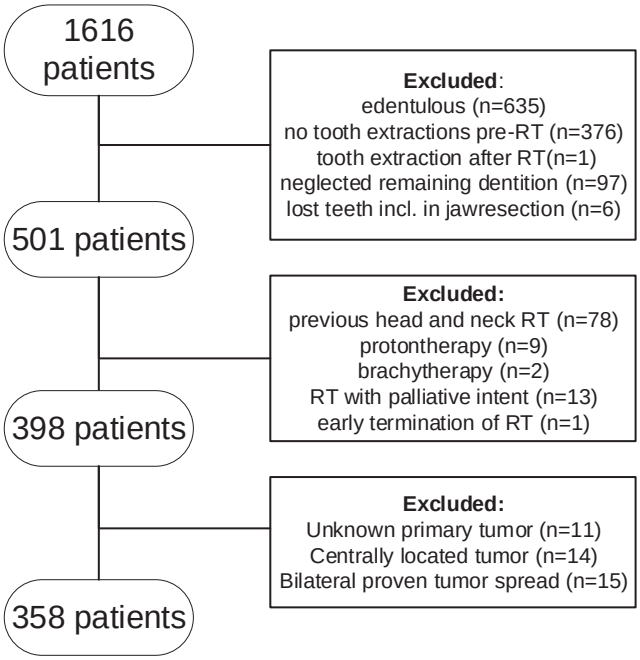

Figure 2 - Exclusion criteria.

Of the potential factors contributing to teeth receiving a cumulative RT dose ≥40Gy, tumor location and N-classification emerged as the most important factors in the multivariable regression analysis (Figure 3). Logistic regression outcomes for each factor per individual tooth in Figure 3 can be found in Supplementary Table 1.

Table 2 - Number of removed teeth per location

Region	No. of extracted teeth	D_{mean}<40Gy n (%)	D_{mean}≥40Gy n (%)	D_{max}<40Gy n (%)	D_{max}≥40Gy n (%)
Larynx	217	209 (96)	8 (4)	204 (94)	13 (6)
Hypopharynx	163	145 (89)	18 (11)	127 (78)	36 (22)
Parotid region	94	81 (86)	13 (14)	72 (77)	22 (23)
Oropharynx	667	480 (72)	187 (28)	383 (57)	284 (43)
Oral cavity	378	177 (47)	201 (53)	139 (37)	239 (63)
Maxillary complex	87	52 (60)	35 (40)	43 (49)	44 (51)
Nasopharynx	72	62 (86)	10 (14)	54 (75)	18 (25)
Other	81	68 (84)	13 (16)	58 (72)	23 (28)
Total	1759	1274 (72)	485 (28)	1080 (61)	679 (39)

Abbreviation: n, number; $D_{max,}$ maximum dose; $D_{mean,}$ mean dose

The highest percentages of redundantly removed teeth were found in the patients with tumors in the laryngeal (94-96%), hypopharyngeal (78-89%) and 'parotid region' (77-86%) (Table 2). In all but one of these 132 patients, the regions that received a dose of ≥40Gy were the mandibular molar and mandibular second premolar regions on both sides in the hypopharyngeal and laryngeal group. In patients from the 'parotid region' group, this affected only the ipsilateral side. Detailed information on the doses for each tooth and the number and percentage of redundantly removed teeth can be found in Supplementary Tables 2A1-2H2.

In patients with an oropharyngeal tumor the percentages of redundantly removed teeth were 57-72%, with the areas of the four incisors, the two canines and the two contralateral premolars of the maxilla all exposed to a RT dose <40Gy. For other regions of the maxilla and for the entire mandible, the radiation dose for each tooth varied widely, resulting in percentages of redundantly removed teeth from 0% to 100% (Supplementary Tables 2D1-2D2).

In the 'oral cavity group' the number of redundantly removed teeth was the lowest. Eleven percent of the mandibular teeth on the ipsilateral side and 40% on the contralateral side were extracted redundantly due to a D_{mean} of <40Gy. Considering the D_{max} of <40Gy, 5% of the ipsilateral and 23% of the contralateral mandibular teeth were redundantly extracted. For maxillary teeth it was 89% and 81% for D_{mean} and D_{max} <40Gy, respectively (Supplementary Tables 2E1-2E2).

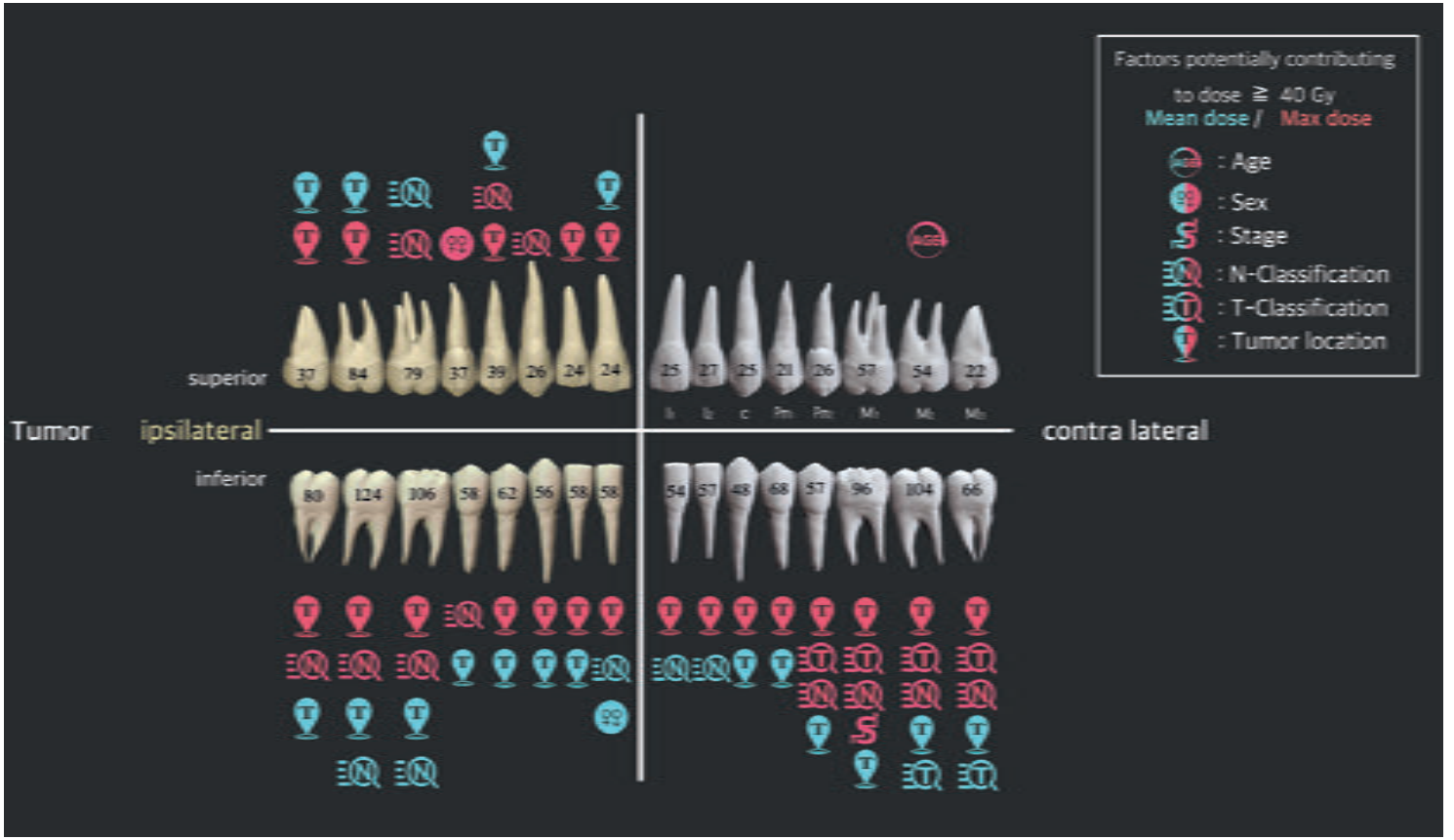

Figure 3 - Factors potentially contributing to RT dose ≥40Gy.

Illustration by Keisuke Koyama, Maastricht University Medical Center+.

Patients with a tumor in the 'maxillary complex' were at risk of receiving a radiation dose of ≥40Gy for all maxillary teeth and ipsilateral mandibular molars. The percentage of redundantly removed teeth in this group was 60% for D_{mean} and 49% for D_{max} (Table 2 and Supplementary Table 2F1-2F2).

In the nasopharyngeal group, the only jaw regions that ultimately received a dose of ≥40Gy were the molar regions in the maxilla and ipsilateral mandible and the second premolar on the contralateral side of the mandible. This resulted in a percentage of redundantly extracted maxillary teeth of 76% for D_{mean} and 61% for D_{max}. For mandibular teeth the percentages were 95% for D_{mean} and 87% for D_{max} (Supplementary Tables 2G1-2G2).

All but one of the 25 patients from group "other" consisted of skin tumors located in the face, scalp and or neck region, treated with radiation. The percentage of redundantly removed teeth ranged from 84% for the D_{mean} to 72% for the D_{max} (Table 2 and Supplementary Tables 2H1-2H2).

Discussion

The results of this study show that up to 61% of teeth were unnecessarily extracted at D_{max} <40Gy and up to 74% at the D_{mean} <40Gy. To our knowledge, this is the first study to provide insight into the amount of teeth redundantly extracted prior to RT. It therefore provides arguments to drastically reduce the number of tooth extractions prior to RT for HNC. This de-escalation can help maintain the masticatory system and reduce the loss of functional units, which has a direct effect on food intake [3-9]. Not only the crushing of food, the maintenance of body weight, but also a person's social integration is often linked to the presence of functional teeth [25]. Patients suffer not only from the underlying oncological diseases, but also from the demands of therapy. The removal of teeth is generally negatively connoted [7, 8]. The procedure itself and the expected pain can lead to a deterioration in the patient's general situation before the start of oncological therapy. For these reasons, de-escalation in the sensitive area of the oral cavity is extremely desirable.

Tumor location had a high association with unnecessarily extracted teeth. In patients with tumors located in the laryngeal, and hypopharyngeal region, only the mandibular molars and the second mandibular premolar received a dose of ≥40Gy. In these regions the primary tumor is relatively further away from the teeth. In the oral cavity, oropharynx and 'maxillary complex' group the number of redundantly extracted teeth was less due to the closer proximity of the primary tumor to the mandible or maxilla. This led to a higher radiation dose in the jaw bones, consistent with the delineation of GTV, CTV and PTV according to international guidelines [22].

N-state was also associated with unnecessarily extracted teeth. The presence of positive lymph nodes located near the mandible (high level II or retropharyngeal), and submandibular lymph nodes of level Ib of the neck included in the clinical (elective) target volume resulted in a higher RT dose in the mandible.

In this study, a cut-off point of ≥40Gy was chosen as the threshold as indication for tooth extraction [12, 13]. Studies focusing on vascular changes at microscopic level after RT showed changes in tissue structure that occur at much lower doses [26, 27]. Studies dealing with radiation doses in typical anatomical locations of the head and neck skeleton showed average doses of 24.4 and 28.2Gy, which can be sufficient to trigger an ORN. The maximum doses measured at these specific ORN-sensitive regions were 44.3 and 48.4Gy [28, 29]. The choice of 40Gy

as the threshold dose for the risk of developing ORN as described in the Dutch National Protocol is empirical [12, 13]. Several other studies suggest using 50Gy or 60Gy for the mandible or even 70Gy for the maxilla as a reference value for the development of ORN [28-32], with only one Delphi study discussing a critical radiation threshold for prophylactic removal of teeth [33]. While the Canadian Dental Oncology Network seems to accept a certain risk of developing ORN, the Dutch guidelines prefer minimizing this risk as much as possible.

There are previous publications describing radiation doses to portions of the mandible and maxilla [34-37]. One study retrospectively delineated each tooth within the radiation fields in 18 HNC patients and used a D_{mean} cut-off point of >50Gy to assess the need for pre-RT extractions or similarly invasive procedures [34]. Two studies did not report the doses in ipsi- and contralateral which made it difficult to compare the results [35, 36]. Another study looked at the mandibular volume percentages receiving >55Gy for 28 patients with base of tongue malignancies [37].

The strength of our study includes the large sample size (358 patients with 1759 precisely delineated extraction sites) and the detailed information on radiation doses (mean and maximum dose). Another strength of this comprehensive study is the fact that all extraction sites were delineated by a single experienced radiation technician (MG) in close collaboration with an experienced prosthodontist (DB). This contributes significantly to the consistency of the results.

A limitation of the present study is that the exact diagnosis for tooth extraction is missing. For some teeth, the prognosis might have been so poor that extraction would be the treatment of choice regardless of planned radiotherapy. Tooth extractions in these patients is also partly triggered by the insurance system in the Netherlands. The treatment of possible oral infection sites and the resulting prosthetic rehabilitation are covered by the national insurance system in the Netherlands. This opportunity leads to acceptation of more frequent tooth extractions in order to favorably access standardized prosthetic denture rehabilitation. This means that the actual percentage of redundantly removed teeth for reasons of planned radiotherapy is probably lower.

Another limitation is the indication of the location of the radiation field at the time of the comprehensive dental assessment. This can lead to a bias in judgement, especially since the guidelines for the expected dose still date from the early days of IMRT and have not yet been adapted to the much more appropriate VMAT-RT.

Extrapolation of the results described here is difficult since it is linked to the RT technique used (3D RT, IMRT or VMAT) and to the local experience in aspects of treatment planning with consequent differences in sparing of normal tissues. Therefore, in addition to properly assessing the tumor location and the location of the positive lymph nodes, good consultation with the radiation-oncologist remains of great clinical importance.

Future research to define a true radiation dose cut-off point for ORN in the head and neck area is needed to achieve a potential further de-escalation in preventive measures with the result of a functional destruction of the masticatory organ. Thereby, it is important that it is clearly described whether the mean or the maximum dose must be used. Artificial intelligence (AI) algorithms using Deep Learning (DL) may be able to accurately predict the radiation dose for new patients, based on an input of cohorts of previously treated cases with imaging and dose to the teeth available. This would allow a fast and reliable dose-prediction based on CT imaging, without the need to await the results of the labor-intensive manual treatment planning process [38, 39].

Conclusion

This study represents insights in how to de-escalate damage to the masticatory system before RT without neglecting the risk of developing ORN. Especially in patients undergoing RT for cancer of the larynx, the hypopharynx or the 'parotid region', guidelines have been given to support decision making during comprehensive dental assessment. To prevent redundant tooth loss and functional damage close cooperation between all specialists involved in head and neck cancer therapy is of great importance. Guidelines must be adapted where appropriate.

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Supplementary data

Abbreviations Tables

Cic:	Cuspid inferior contralateral = Mandibular cuspid on the contralateral side
Cii:	Cuspid inferior ipsilateral = Mandibular cuspid on the ipsilateral side
Csc:	Cuspid superior contralateral = Maxillary cuspid on the contralateral side
Csi:	Cuspid superior ipsilateral = Maxillary cuspid on the ipsilateral side
CI-95%:	95% confidence interval
Dmax:	maximum dose
Dmean:	mean dose
I1ic:	Incisor 1 inferior contralateral = Mandibular first incisor on the contralateral side
I1ii:	Incisor 1 inferior ipsilateral = Mandibular first incisor on the ipsilateral side
I1sc:	Incisor 1 superior contralateral = Maxillary first incisor on the contralateral side
I1si:	Incisor 1 superior ipsilateral = Maxillary first incisor on the ipsilateral side
I2ic:	Incisor 2 inferior contralateral = Mandibular second incisor on the contralateral side
I2ii:	Incisor 2 inferior ipsilateral = Mandibular second incisor on the ipsilateral side
I2sc:	Incisor 2 superior contralateral = Maxillary second incisor on the contralateral side
I2si:	Incisor 2 superior ipsilateral = Maxillary second incisor on the ipsilateral side
M1ic:	Molar 1 inferior contralateral = Mandibular first molar on the contralateral side
M1ii:	Molar 1 inferior ipsilateral = Mandibular first molar on the ipsilateral side
M1sc:	Molar 1 superior contralateral = Maxillary first molar on the contralateral side
M1si:	Molar 1 superior ipsilateral = Maxillary first molar on the ipsilateral side

M2ic:	Molar 2 inferior contralateral = Mandibular second molar on the contralateral side
M2ii:	Molar 2 inferior ipsilateral = Mandibular second molar on the ipsilateral side
M2sc:	Molar 2 superior contralateral = Maxillary second molar on the contralateral side
M2si:	Molar 2 superior ipsilateral = Maxillary second molar on the ipsilateral side
M3ic:	Molar 3 inferior contralateral = Mandibular third molar on the contralateral side
M3ii:	Molar 3 inferior ipsilateral = Mandibular third molar on the ipsilateral side
M3sc:	Molar 3 superior contralateral = Maxillary third molar on the contralateral side
M3si:	Molar 3 superior ipsilateral = Maxillary third molar on the ipsilateral side
N- classification:	node classification according to the TNM-classification 8th edition.[17, 18]
OR:	odds ratio
Pm1ic:	Premolar 1 inferior contralateral = Mandibular first premolar on the contralateral side
Pm1ii:	Premolar 1 inferior ipsilateral = Mandibular first premolar on the ipsilateral side
Pm1sc:	Premolar 1 superior contralateral = Maxillary first premolar on the contralateral side
Pm1si:	Premolar 1 superior ipsilateral = Maxillary first premolar on the ipsilateral side
Pm2ic:	Premolar 2 inferior contralateral = Mandibular second premolar on the contralateral side
Pm2ii:	Premolar 2 inferior ipsilateral = Mandibular second premolar on the ipsilateral side
Pm2sc:	Premolar 2 superior contralateral = Maxillary second premolar on the contralateral side
Pm2si:	Premolar 2 superior ipsilateral = Maxillary second premolar on the ipsilateral side
SD:	Standard Deviation
T- classification:	tumor classification according to the TNM-classification 8th edition.[17,18]

Supplementary Table 1A - I1s ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95% lower**	**upper**	**p value**
Age	1.038	0.910	1.183	0.580
Sex (male vs. female)	0.179	0.016	2.065	0.168
Tumor location	2.136	1.054	4.329	**0.035**
T-classification	1.260	0.390	4.075	0.700
N-classification	0.000	0.000		0.997
Total no of removed teeth	0.750	0.559	1.007	0.056
Tumor stage (I, II, III or IV)	0.855	0.337	2.171	0.742
Tumor stage (Early vs Adv)	1.286	0.110	15.003	0.841

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1B - I2s ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95% lower**	**upper**	**p value**
Age	0.996	0.855	1.161	0.958
Sex (male vs. female)	0.222	0.019	2.533	0.226
Tumor location	1.553	0.989	2.439	0.056
T-classification	1.612	0.473	5.495	0.446
N-classification	0.000	0.000		0.998
Total nr of removed teeth	0.834	0.669	1.040	0.107
Tumor stage (I, II, III or IV)	0.965	0.389	2.390	0.938
Tumor stage (Early vs Adv)	1.615	0.140	18.581	0.700

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				1.038	0.910	1.183	0.580				
				0.179	0.016	2.065	0.168				
2.136	1.054	4.329	**0.035**	2.136	1.054	4.329	**0.035**	2.136	1.054	4.329	**0.035**
				1.260	0.390	4.075	0.700				
				0.000	0.000		0.997				
				0.750	0.559	1.007	0.056				
				0.855	0.337	2.171	0.742				
				1.286	0.110	15.003	0.841				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				1.028	0.898	1.178	0.687				
				0.318	0.046	2.223	0.248				
				1.717	1.058	2.786	**0.029**	1.717	1.058	2.786	**0.029**
				1.000	0.375	2.664	1.000				
				0.000	0.000		0.997				
				0.825	0.678	1.004	0.054				
				0.705	0.327	1.520	0.373				
				1.000	0.141	7.099	1.000				

Supplementary Table 1C - Cs ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.907	0.741	1.111	0.348
Sex (male vs. female)	0.600	0.033	10.822	0.729
Tumor location	1.425	0.864	2.351	0.165
T-classification	109554010.5	0.000		0.997
N-classification	0.000	0.000		0.997
Total nr of removed teeth	0.908	0.732	1.127	0.382
Tumor stage (I, II, III or IV)	53541804.78	0.000		0.998
Tumor stage (Early vs Adv)	190055869.5	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1D - Pm1s ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	1.050	0.969	1.138	0.234
Sex (male vs. female)	0.289	0.060	1.395	0.122
Tumor location	1.998	1.247	3.203	**0.004**
T-classification	1.061	0.492	2.288	0.881
N-classification	0.267	0.097	0.737	**0.011**
Total nr of removed teeth	0.854	0.734	0.993	**0.040**
Tumor stage (I, II, III or IV)	1.066	0.484	2.347	0.873
Tumor stage (Early vs Adv)	2.667	0.282	25.249	0.392

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				1.031	0.926	1.149	0.574				
				0.214	0.031	1.504	0.121				
				1.461	1.007	2.118	**0.046**	1.473	0.898	2.416	0.125
				1.154	0.493	2.704	0.741				
				0.129	0.019	0.867	**0.035**	0.129	0.019	0.867	**0.035**
				0.906	0.793	1.036	0.149				
				0.876	0.375	2.044	0.759				
				2.143	0.204	22.478	0.525				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				1.021	0.953	1.095	0.551				
				0.226	0.048	1.067	0.060				
1.704	1.065	2.724	**0.026**	1.862	1.207	2.872	**0.005**	1.557	1.003	2.415	**0.048**
				1.250	0.585	2.674	0.564				
0.338	0.102	1.120	0.076	0.231	0.082	0.653	**0.006**	0.279	0.086	0.902	**0.033**
0.863	0.692	1.075	0.188	0.875	0.769	0.996	**0.043**	0.893	0.745	1.071	0.224
				1.012	0.481	2.126	0.976				
				3.200	0.342	29.900	0.308				

Supplementary Table 1E - Pm2s ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy			
	Univariable analysis			
	OR	CI-95% lower	CI-95% upper	p value
Age	0.938	0.840	1.047	0.256
Sex (male vs. female)	0.222	0.031	1.578	0.133
Tumor location	0.952	0.643	1.409	0.807
T-classification	2.489	0.728	8.513	0.146
N-classification	0.358	0.108	1.184	0.092
Total nr of removed teeth	0.967	0.847	1.104	0.618
Tumor stage (I, II, III or IV)	1.673	0.479	5.844	0.420
Tumor stage (Early vs Adv)	3366557254.8	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1F - M1s ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy			
	Univariable analysis			
	OR	CI-95% lower	CI-95% upper	p value
Age	1.029	0.969	1.093	0.358
Sex (male vs. female)	0.310	0.095	1.014	0.053
Tumor location	0.955	0.755	1.207	0.698
T-classification	1.574	0.872	2.838	0.132
N-classification	0.373	0.178	0.781	**0.009**
Total nr of removed teeth	0.908	0.794	1.039	0.160
Tumor stage (I, II, III or IV)	0.965	0.577	1.613	0.892
Tumor stage (Early vs Adv)	0.744	0.216	2.564	0.640

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				0.998	0.923	1.079	0.956				
				0.109	0.020	0.589	**0.010**	0.113	0.018	0.707	**0.020**
				1.036	0.770	1.394	0.816				
				1.676	0.752	3.735	0.206				
				0.410	0.178	0.949	**0.037**	0.440	0.184	1.052	0.065
				0.970	0.876	1.075	0.562				
				1.439	0.576	3.592	0.436				
				615418998.7	0.000		0.999				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				1.003	0.955	1.055	0.893				
				0.375	0.138	1.015	0.054				
				0.930	0.749	1.131	0.465				
				1.375	0.861	2.195	0.182				
0.373	0.178	0.781	**0.009**	0.504	0.300	0.849	**0.010**	0.504	0.300	0.849	**0.010**
				0.969	0.897	1.046	0.419				
				0.835	0.550	1.268	0.399				
				0.513	0.185	1.421	0.199				

Supplementary Table 1G - M2s ipsi – Univariable and multivariable analysis of factors potentially contribut

	D_{mean} ≥40Gy			
	Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.962	0.916	1.011	0.124
Sex (male vs. female)	0.864	0.340	2.197	0.758
Tumor location	0.775	0.630	0.953	**0.016**
T-classification	1.343	0.875	2.064	0.178
N-classification	0.984	0.622	1.557	0.945
Total nr of removed teeth	1.018	0.953	1.086	0.601
Tumor stage (I, II, III or IV)	1.102	0.739	1.642	0.635
Tumor stage (Early vs Adv)	0.903	0.356	2.292	0.830

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1H - M3s ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy			
	Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.997	0.952	1.044	0.883
Sex (male vs. female)	1.354	0.271	6.758	0.712
Tumor location	0.583	0.370	0.920	**0.020**
T-classification	1.046	0.585	1.870	0.879
N-classification	1.114	0.609	2.040	0.725
Total nr of removed teeth	0.991	0.904	1.087	0.855
Tumor stage (I, II, III or IV)	0.781	0.463	1.320	0.357
Tumor stage (Early vs Adv)	0.583	0.151	2.256	0.435

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

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D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				0.978	0.935	1.024	0.341				
				0.557	0.226	1.372	0.203				
0.775	0.630	0.953	**0.016**	0.781	0.646	0.943	**0.010**	0.781	0.646	0.943	**0.010**
				1.435	0.944	2.179	0.091				
				0.854	0.547	1.333	0.487				
				0.999	0.937	1.064	0.967				
				1.017	0.695	1.487	0.930				
				0.969	0.396	2.371	0.945				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				0.998	0.954	1.045	0.947				
				1.231	0.257	5.900	0.795				
0.583	0.370	0.920	**0.020**	0.566	0.368	0.870	**0.010**	0.566	0.368	0.870	**0.010**
				1.044	0.584	1.866	0.886				
				1.194	0.649	2.193	0.569				
				0.988	0.902	1.082	0.794				
				0.674	0.391	1.159	0.154				
				0.409	0.102	1.640	0.207				

Supplementary Table 1I - I1s contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95% lower**	**upper**	**p value**
Age	1.088	0.929	1.273	0.295
Sex (male vs. female)	0.000	0.000		0.998
Tumor location	1.338	0.847	2.050	0.181
T-classification	0.856	0.254	2.881	0.802
N-classification	0.000	0.000		0.997
Total nr of removed teeth	0.878	0.717	1.076	0.209
Tumor stage (I, II, III or IV)	0.651	0.233	1.820	0.413
Tumor stage (Early vs Adv)	0.750	0.057	9.871	0.827

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1J - I2s contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95% lower**	**upper**	**p value**
Age	1.092	0.931	1.281	0.278
Sex (male vs. female)	0.000	0.000		0.998
Tumor location	1.360	0.887	2.085	0.158
T-classification	0.890	0.282	2.812	0.843
N-classification	0.000	0.000		0.997
Total nr of removed teeth	0.895	0.735	1.091	0.274
Tumor stage (I, II, III or IV)	0.629	0.223	1.776	0.382
Tumor stage (Early vs Adv)	0.667	0.051	8.729	0.757

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				1.088	0.929	1.273	0.295				
				0.000	0.000		0.998				
				1.338	0.847	2.050	0.181				
				0.856	0.254	2.881	0.802				
				0.000	0.000		0.997				
				0.878	0.717	1.076	0.209				
				0.651	0.233	1.820	0.413				
				0.750	0.057	9.871	0.827				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				1.092	0.931	1.281	0.278				
				0.000	0.000		0.998				
				1.360	0.887	2.085	0.158				
				0.890	0.282	2.812	0.843				
				0.000	0.000		0.997				
				0.895	0.735	1.091	0.274				
				0.629	0.223	1.776	0.382				
				0.667	0.051	8.729	0.757				

Supplementary Table 1K - Cs contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	CI-95% lower	upper	p value
Age	1.054	0.826	1.345	0.671
Sex (male vs. female)	0.000	0.000		0.999
Tumor location	1.511	0.748	3.054	0.250
T-classification	45283923.76	0.000		0.998
N-classification	0.000	0.000		0.998
Total nr of removed teeth	0.931	0.679	1.275	0.655
Tumor stage (I, II, III or IV)	23577335.37	0.000		0.998
Tumor stage (Early vs Adv)	89748602.70	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1L - Pm1s contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	CI-95% lower	upper	p value
Age	1.149	0.813	1.624	0.430
Sex (male vs. female)	0.000	0.000		0.999
Tumor location	8522.325	0.000		0.998
T-classification	51827021.55	0.000		0.998
N-classification	0.000	0.000		0.998
Total nr of removed teeth	0.936	0.708	1.236	0.639
Tumor stage (I, II, III or IV)	20386717.23	0.000		0.998
Tumor stage (Early vs Adv)	115391059.7	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				1.057	0.885	1.262	0.540				
				0.643	0.036	11.631	0.765				
				1.081	0.594	1.965	0.800				
				2.493	0.345	18.023	0.365				
				0.000	0.000		0.997				
				0.915	0.721	1.160	0.463				
				1.399	0.249	7.871	0.703				
				190055868.8	0.000		0.999				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				1.149	0.813	1.624	0.430				
				0.000	0.000		0.999				
				8522.325	0.000		0.998				
				51827021.55	0.000		0.998				
				0.000	0.000		0.998				
				0.936	0.708	1.236	0.639				
				20386717.23	0.000		0.998				
				115391059.7	0.000		0.999				

Supplementary Table 1M - Pm2s contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy			
	Univariable analysis			
	OR	CI-95%		p
		lower	upper	value
Age	1.156	0.881	1.517	0.295
Sex (male vs. female)	0.000	0.000		0.998
Tumor location	1.279	0.507	3.221	0.602
T-classification	2.612	0.335	20.383	0.360
N-classification	0.000	0.000		0.998
Total nr of removed teeth	0.921	0.761	1.114	0.395
Tumor stage (I, II, III or IV)	1.252	0.249	6.300	0.785
Tumor stage (Early vs Adv)	170049980.7	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1N - M1s contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy			
	Univariable analysis			
	OR	CI-95%		p
		lower	upper	value
Age	1.038	0.939	1.147	0.464
Sex (male vs. female)	0.144	0.015	1.383	0.093
Tumor location	1.039	0.689	1.566	0.856
T-classification	5.764	0.833	39.876	0.076
N-classification	0.816	0.350	1.901	0.637
Total nr of removed teeth	0.983	0.867	1.115	0.791
Tumor stage (I, II, III or IV)	1.661	0.522	5.283	0.390
Tumor stage (Early vs Adv)	224371514.1	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				1.151	0.948	1.397	0.155				
				0.571	0.067	4.875	0.609				
				1.313	0.654	2.636	0.444				
				0.835	0.270	2.580	0.754				
				0.000	0.000		0.997				
				0.867	0.732	1.027	0.099				
				0.590	0.236	1.476	0.259				
				0.667	0.054	8.196	0.751				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				0.967	0.903	1.034	0.322				
				0.394	0.107	1.446	0.160				
				0.872	0.631	1.206	0.409				
				1.727	0.853	3.498	0.129				
				0.863	0.485	1.536	0.617				
				0.945	0.857	1.042	0.256				
				1.489	0.731	3.031	0.273				
				5.133	0.602	43.768	0.135				

Supplementary Table 1O - M2s contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.955	0.883	1.032	0.245
Sex (male vs. female)	0.950	0.145	6.221	0.957
Tumor location	0.845	0.520	1.373	0.496
T-classification	0.818	0.350	1.912	0.643
N-classification	2.050	0.774	5.431	0.149
Total nr of removed teeth	0.877	0.687	1.120	0.294
Tumor stage (I, II, III or IV)	2.763	0.570	13.387	0.207
Tumor stage (Early vs Adv)	260560455.5	0.000		0.998

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1P - M3s contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	**0.994**	**0.857**	**1.154**	**0.940**
Sex (male vs. female)	115391059,81	0.000		0.999
Tumor location	0.533	0.109	2.616	0.438
T-classification	0.000	0.000		0.997
N-classification	2.150	0.288	16.081	0.456
Total nr of removed teeth	0.999	0.778	1.281	0.991
Tumor stage (I, II, III or IV)	1.000	0.169	5.919	1.000
Tumor stage (Early vs Adv)	107698322.6	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				0.919	0.852	0.992	**0.030**	0.919	0.852	0.992	**0.030**
				0.425	0.085	2.128	0.298				
				0.898	0.610	1.322	0.585				
				0.788	0.378	1.643	0.525				
				1.138	0.546	2.372	0.729				
				0.917	0.773	1.087	0.318				
				1.436	0.642	3.210	0.378				
				3.200	0.354	28.945	0.301				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				0.990	**0.914**	**1.072**	**0.805**				
				0.385	0.042	3.523	0.398				
				1.021	0.670	1.557	0.921				
				1.580	0.581	4.297	0.370				
				0.869	0.317	2.382	0.784				
				0.994	0.866	1.139	0.926				
				1.840	0.510	6.628	0.351				
				538491623.0	0.000		0.999				

Supplementary Table 1Q - I1i ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.966	0.901	1.037	0.340
Sex (male vs. female)	0.201	0.053	0.764	**0.018**
Tumor location	0.000	0.000		0.994
T-classification	1.116	0.605	2.059	0.726
N-classification	3.573	1.593	8.016	**0.002**
Total nr of removed teeth	1.093	0.999	1.195	0.052
Tumor stage (I, II, III or IV)	4.341	1.116	16.878	**0.034**
Tumor stage (Early vs Adv)	656286618.2	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1R - I2i ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.968	0.908	1.033	0.329
Sex (male vs. female)	0.259	0.073	0.918	**0.036**
Tumor location	0.113	0.033	0.383	**<0.001**
T-classification	1.062	0.577	1.955	0.848
N-classification	2.845	1.448	5.589	**0.002**
Total nr of removed teeth	1.104	1.006	1.212	**0.038**
Tumor stage (I, II, III or IV)	4.056	1.226	13.416	**0.022**
Tumor stage (Early vs Adv)	706770224.0	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				0.973	0.913	1.036	0.395				
0.186	0.040	0.871	**0.033**	0.273	0.085	0.874	**0.029**	0.496	0.066	3.739	0.497
				0.112	0.039	0.319	**<0.001**	0.122	0.039	0.319	**<0.001**
				1.305	0.741	2.297	0.356				
3.652	1.556	8.568	**0.003**	2.257	1.260	4.042	**0.006**	0.786	0.249	2.481	0.681
				1.073	0.987	1.167	0.096				
1.648	0.375	7.230	0.508	3.424	1.276	9.189	**0.015**	2.846	0.669	12.105	0.157
				1076983257	0.000		0.999				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				0.939	0.880	1.001	0.054				
0.580	0.051	6.595	0.661	0.159	0.048	0.531	**0.003**	0.285	0.044	1.850	0.189
0.070	0.014	0.361	**0.001**	0.178	0.078	0.408	**<0.001**	0.178	0.078	0.408	**<0.001**
				1.383	0.773	2.474	0.274				
0.445	0.078	2.545	0.363	2.126	1.230	3.675	**0.007**	0.639	0.206	1.981	0.438
1.179	0.984	1.413	0.075	1.052	0.968	1.144	0.231				
2.723	0.486	15.254	0.255	2.947	1.226	7.083	**0.016**	2.638	0.768	9.058	0.123
				1136815206	0.000		0.999				

Supplementary Table 1S - Ci ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.991	0.936	1.049	0.752
Sex (male vs. female)	0.618	0.197	1.946	0.411
Tumor location	0.052	0.012	0.232	**<0.001**
T-classification	1.191	0.670	2.119	0.551
N-classification	2.195	1.224	3.934	**0.008**
Total nr of removed teeth	1.032	0.950	1.121	0.454
Tumor stage (I, II, III or IV)	2.861	1.257	6.510	**0.012**
Tumor stage (Early vs Adv)	10.000	1.199	83.376	**0.033**

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1T - Pm1i ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.998	0.931	1.069	0.948
Sex (male vs. female)	0.438	0.137	1.401	0.164
Tumor location	0.135	0.052	0.352	**<0.001**
T-classification	1.184	0.661	2.120	0.570
N-classification	2.938	1.539	5.609	**0.001**
Total nr of removed teeth	1.057	0.974	1.147	0.181
Tumor stage (I, II, III or IV)	4.047	1.494	10.964	**0.006**
Tumor stage (Early vs Adv)	9.643	1.170	79.462	**0.035**

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				0.985	0.933	1.040	0.584				
				0.321	0.106	0.972	**0.044**	0.342	0.068	1.718	0.193
0.052	0.012	0.232	**<0.001**	0.192	0.082	0.451	**<0.001**	0.192	0.082	0.451	**<0.001**
				1.268	0.739	2.177	0.389				
0.746	0.173	3.207	0.693	1.946	1.149	3.297	**0.013**	0.911	0.341	2.438	0.853
				1.015	0.938	1.098	0.708				
0.000	0.000		0.995	1.921	1.061	3.479	**0.031**	1.197	0.552	2.596	0.649
4.724	0.160	139.302	0.368	2.714	0.747	9.866	0.129				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				1.010	0.951	1.074	0.738				
				0.373	0.128	1.087	0.071				
0.133	0.047	0.378	**<0.001**	0.211	0.097	0.459	**<0.001**	0.211	0.097	0.459	**<0.001**
				1.411	0.836	2.384	0.197				
1.687	0.567	5.025	0.347	2.244	1.352	3.724	**0.002**	1.137	0.520	2.487	0.747
				1.047	0.971	1.129	0.230				
1.847	0.419	8.145	0.418	2.138	1.203	3.802	**0.010**	1.254	0.628	2.502	0.521
0.998	0.008	131.270	0.999	2.933	0.898	9.578	0.075				

Supplementary Table 1U - Pm2i ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy			
	Univariable analysis			
	OR	CI-95%		p
		lower	upper	value
Age	0.989	0.942	1.039	0.661
Sex (male vs. female)	0.530	0.181	1.552	0.247
Tumor location	0.229	0.103	0.510	**<0.001**
T-classification	1.501	0.893	2.522	0.125
N-classification	1.682	1.027	2.755	**0.039**
Total nr of removed teeth	1.079	0.998	1.168	0.057
Tumor stage (I, II, III or IV)	2.296	1.255	4.200	**0.007**
Tumor stage (Early vs Adv)	3.763	1.049	13.504	**0.042**

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1V - M1i ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy			
	Univariable analysis			
	OR	CI-95%		p
		lower	upper	value
Age	1.009	0.973	1.047	0.630
Sex (male vs. female)	0.416	0.171	1.011	0.053
Tumor location	0.568	0.433	0.745	**<0.001**
T-classification	1.347	0.950	1.910	0.095
N-classification	1.905	1.284	2.827	**0.001**
Total nr of removed teeth	1.085	1.003	1.174	**0.043**
Tumor stage (I, II, III or IV)	1.485	1.036	2.130	**0.031**
Tumor stage (Early vs Adv)	2.129	0.926	4.893	0.075

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				1.021	0.968	1.077	0.440				
				0.393	0.109	1.413	0.153				
0.229	0.103	0.510	**<0.001**	0.702	0.522	0.944	**0.019**	0.784	0.574	1.070	0.125
				1.632	0.915	2.911	0.097				
0.746	0.309	1.805	0.516	2.580	1.376	4.836	**0.003**	2.580	1.376	4.836	**0.003**
				1.095	0.989	1.211	0.081				
1.663	0.804	3.438	0.170	2.012	1.173	3.449	**0.011**	1.159	0.568	2.364	0.686
0.144	0.002	10.177	0.372	3.160	0.946	10.554	0.061				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value	OR	CI-95% lower	CI-95% upper	p value
				0.981	0.942	1.020	0.332				
				0.557	0.211	1.467	0.236				
2.215	1.325	3.407	**0.002**	0.652	0.522	0.813	**<0.001**	0.615	0.476	0.794	**<0.001**
				1.308	0.911	1.878	0.146				
2.125	1.325	3.407	**0.002**	2.801	1.693	4.634	**<0.001**	3.048	1.765	5.264	**<0.001**
1.009	0.924	1.102	0.845	1.124	1.012	1.247	**0.029**	1.041	0.926	1.170	0.501
0.999	0.593	1.683	0.98	1.644	1.131	2.389	**0.009**	0.910	0.517	1.602	0.744
				2.260	0.968	5.280	**0.060**	0.964	0.103	8.997	0.975

Supplementary Table 1W - M2i ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p value**
		lower	**upper**	
Age	0.968	0.936	1.001	0.060
Sex (male vs. female)	0.697	0.307	1.583	0.388
Tumor location	0.649	0.538	0.782	**<0.001**
T-classification	1.372	0.978	1.925	0.067
N-classification	1.894	1.302	2.756	**<0.001**
Total nr of removed teeth	1.102	1.015	1.195	**0.020**
Tumor stage (I, II, III or IV)	1.561	1.094	2.226	**0.014**
Tumor stage (Early vs Adv)	1.985	0.910	4.333	0.085

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1X - M3i ipsi – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p value**
		lower	**upper**	
Age	0.957	0.918	0.998	**0.041**
Sex (male vs. female)	1.598	0.514	4.969	0.418
Tumor location	0.674	0.536	0.847	**<0.001**
T-classification	1.159	0.755	1.780	0.500
N-classification	1.925	1.154	3.210	**0.012**
Total nr of removed teeth	1.108	0.986	1.245	0.086
Tumor stage (I, II, III or IV)	0.917	0.636	1.322	0.643
Tumor stage (Early vs Adv)	0.542	0.212	1.387	0.201

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				0.963	0.929	0.998	**0.039**	0.971	0.929	1.014	0.178
				0.659	0.274	1.585	0.352				
0.645	0.531	0.783	**<0.001**	0.681	0.570	0.812	**<0.001**	0.651	0.530	0.799	**<0.001**
				1.454	1.021	2.070	**0.038**	1.130	0.736	1.736	0.576
1.897	1.246	2.887	**0.003**	2.664	1.685	4.212	**<0.001**	2.564	1.567	4.194	**<0.001**
1.005	0.921	1.096	0.917	1.148	1.036	1.272	**0.008**	1.054	0.945	1.175	0.347
1.111	0.677	1.824	0.676	1.741	1.203	2.518	**0.003**	0.971	0.342	2.756	0.955
				2.447	1.101	5.439	**0.028**	0.782	0.214	2.852	0.710

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
0.970	0.929	1.014	0.180	0.970	0.929	1.013	0.173				
				1.412	0.422	4.723	0.576				
0.702	0.556	0.887	**0.003**	0.636	0.500	0.809	**<0.001**	0.673	0.524	0.864	**0.002**
				1.314	0.816	2.118	0.261				
1.641	0.964	2.792	0.068	2.566	1.356	4.858	**0.004**	2.071	1.087	3.944	**0.027**
				1.152	0.993	1.336	0.062				
				1.097	0.741	1.623	0.644				
				0.914	0.337	2.475	0.859				

Supplementary Table 1Y- I1i contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.982	0.913	1.057	0.630
Sex (male vs. female)	0.221	0.055	0.895	**0.034**
Tumor location	0.000	0.000		0.995
T-classification	1.179	0.602	2.309	0.630
N-classification	3.973	1.642	9.611	**0.002**
Total nr of removed teeth	1.112	1.010	1.226	**0.031**
Tumor stage (I, II, III or IV)	7.685	1.076	54.874	**0.042**
Tumor stage (Early vs Adv)	573233007.2	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1Z - I2i contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.978	0.909	1.051	0.538
Sex (male vs. female)	0.250	0.063	0.993	**0.049**
Tumor location	0.000	0.000		0.994
T-classification	1.157	0.597	2.241	0.666
N-classification	4.090	1.673	10.000	**0.002**
Total nr of removed teeth	1.118	1.015	1.232	**0.024**
Tumor stage (I, II, III or IV)	7.803	1.089	55.884	**0.041**
Tumor stage (Early vs Adv)	538491595.6	0.000		0.999

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p	OR	CI-95%		p	OR	CI-95%		p
	lower	upper	value		lower	upper	value		lower	upper	value
				0.977	0.918	1.041	0.475				
0.230	0.044	1.194	0.080	0.385	0.119	1.248	0.112				
				0.093	0.029	0.297	**<0.001**	0.093	0.029	0.297	**<0.001**
				1.285	0.721	2.292	0.395				
3.963	1.571	9.999	**0.004**	1.861	1.082	3.203	**0.025**	0.794	0.265	2.383	0.681
1.050	0.935	1.178	0.409	1.048	0.965	1.138	0.269				
2.368	0.320	17.507	0.398	2.468	1.081	5.635	**0.032**	1.814	0.353	9.320	0.476
				7.480	0.882	63.438	0.065				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p	OR	CI-95%		p	OR	CI-95%		p
	lower	upper	value		lower	upper	value		lower	upper	value
				0.968	0.910	1.031	0.310				
0.230	0.045	1.188	0.079	0.314	0.098	1.005	0.051				
				0.122	0.044	0.334	**<0.001**	0.122	0.044	0.334	**<0.001**
				1.361	0.765	2.422	0.295				
4.211	1.644	10.785	**0.003**	2.029	1.166	3.531	**0.012**	0.708	0.224	2.233	0.555
1.059	0.945	1.186	0.325	1.056	0.972	1.147	0.196				
2.485	0.327	18.893	0.379	2.497	1.104	5.651	**0.028**	1.330	0.438	4.039	0.615
				7.556	0.899	63.473	0.063				

Supplementary Table 1AA - Ci contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95% lower**	**upper**	**p value**
Age	0.986	0.921	1.056	0.695
Sex (male vs. female)	0.636	0.171	2.371	0.501
Tumor location	0.132	0.039	0.450	**0.001**
T-classification	1.515	0.735	3.123	0.261
N-classification	2.189	1.149	4.169	**0.017**
Total nr of removed teeth	1.068	0.976	1.168	0.151
Tumor stage (I, II, III or IV)	2.730	1.047	7.123	**0.040**
Tumor stage (Early vs Adv)	6.217	0.719	53.757	0.097

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1BB - Pm1i contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95% lower**	**upper**	**p value**
Age	0.980	0.924	1.039	0.493
Sex (male vs. female)	0.367	0.103	1.311	0.123
Tumor location	0.119	0.035	0.406	**<0.001**
T-classification	1.167	0.571	2.384	0.673
N-classification	2.082	1.089	3.981	**0.027**
Total nr of removed teeth	1.104	1.012	1.204	**0.026**
Tumor stage (I, II, III or IV)	2.388	0.981	5.814	0.055
Tumor stage (Early vs Adv)	5.211	0.624	43.520	0.127

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p	OR	CI-95%		p	OR	CI-95%		p
	lower	upper	value		lower	upper	value		lower	upper	value
				0.976	0.917	1.040	0.453				
				0.489	0.147	1.629	0.244				
0.132	0.039	0.450	**0.001**	0.133	0.047	0.375	**<0.001**	0.133	0.047	0.375	**<0.001**
				1.824	0.924	3.597	0.083				
1.155	0.503	2.653	0.733	2.237	1.242	4.030	**0.007**	0.700	0.203	2.415	0.572
				1.045	0.962	1.136	0.297				
1.002	0.207	4.842	0.998	3.620	1.429	9.167	**0.007**	0.715	0.043	12.011	0.816
				11.556	1.356	98.465	**0.025**	9.998	0.620	161.122	0.105

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p	OR	CI-95%		p	OR	CI-95%		p
	lower	upper	value		lower	upper	value		lower	upper	value
				0.965	0.918	1.015	0.167				
				0.414	0.147	1.163	0.094				
0.119	0.035	0.406	**<0.001**	0.178	0.082	0.390	**<0.001**	0.178	0.082	0.390	**<0.001**
				1.560	0.857	2.842	0.146				
1.094	0.457	2.616	0.840	1.591	0.977	2.590	0.062				
1.097	0.960	1.254	0.172	1.070	0.994	1.151	0.070				
				1.970	1.068	3.634	**0.030**	1.386	0.631	3.045	0.417
				3.678	0.946	14.307	0.060				

Supplementary Table 1CC - Pm2i contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95% lower**	**upper**	**p value**
Age	0.967	0.897	1.042	0.376
Sex (male vs. female)	0.581	0.152	2.212	0.426
Tumor location	0.439	0.233	0.828	**0.011**
T-classification	1.171	0.595	2.306	0.647
N-classification	1.511	0.811	2.816	0.193
Total nr of removed teeth	1.032	0.950	1.122	0.453
Tumor stage (I, II, III or IV)	1.771	0.729	4.302	0.207
Tumor stage (Early vs Adv)	2.778	0.317	24.371	0.357

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1DD - M1i contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95% lower**	**upper**	**p value**
Age	0.942	0.884	1.003	0.061
Sex (male vs. female)	0.834	0.260	2.677	0.761
Tumor location	0.435	0.273	0.693	**<0.001**
T-classification	2.410	1.265	4.591	**0.007**
N-classification	5.074	2.215	11.625	**<0.001**
Total nr of removed teeth	1.086	1.008	1.171	**0.029**
Tumor stage (I, II, III or IV)	2.728	1.294	5.751	**0.008**
Tumor stage (Early vs Adv)	4.766	1.013	22.414	**0.048**

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				0.967	0.909	1.029	0.289				
				0.370	0.119	1.156	0.087				
0.439	0.233	0.828	**0.011**	0.495	0.300	0.819	**0.006**	0.419	0.230	0.763	**0.004**
				2.070	1.093	3.922	**0.026**	2.419	1.136	5.153	**0.022**
				1.763	1.036	3.002	**0.037**	2.001	1.029	3.892	**0.041**
				1.033	0.962	1.109	0.370				
				2.012	0.975	4.152	0.058				
				7.037	0.830	59.678	0.074				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p value	OR	CI-95%		p value	OR	CI-95%		p value
	lower	upper			lower	upper			lower	upper	
				0.976	0.929	1.027	0.351				
				0.717	0.264	1.944	0.513				
0.461	0.263	0.808	**0.007**	0.523	0.357	0.766	**<0.001**	0.560	0.345	0.909	**0.019**
1.705	0.760	3.829	0.196	2.599	1.482	4.561	**<0.001**	3.632	1.466	8.998	**0.005**
5.486	1.974	15.247	**0.001**	3.014	1.715	5.298	**<0.001**	3.811	1.609	9.023	**0.002**
0.999	0.896	1.114	0.985	1.067	0.996	1.144	0.065				
1.238	0.168	9.132	0.834	1.666	1.052	2.639	**0.030**	0.392	0.168	0.916	**0.031**
0.359	0.038	3.419	0.373	2.624	0.880	7.826	0.084				

Supplementary Table 1EE - M2i contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.933	0.883	0.985	**0.012**
Sex (male vs. female)	0.651	0.251	1.692	0.379
Tumor location	0.530	0.363	0.775	**0.001**
T-classification	2.551	1.458	4.461	**0.001**
N-classification	2.190	1.351	3.553	**0.001**
Total nr of removed teeth	1.048	0.976	1.125	0.201
Tumor stage (I, II, III or IV)	1.618	0.997	2.625	0.051
Tumor stage (Early vs Adv)	2.591	0.880	7.628	0.084

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

Supplementary Table 1FF - M3i contra – Univariable and multivariable analysis of factors potentially contributing to

	D_{mean} ≥40Gy Univariable analysis			
	OR	**CI-95%**		**p**
		lower	**upper**	**value**
Age	0.987	0.944	1.032	0.564
Sex (male vs. female)	0.583	0.193	1.761	0.339
Tumor location	0.494	0.313	0.781	**0.003**
T-classification	1.809	1.035	3.162	**0.038**
N-classification	1.722	1.023	2.897	**0.041**
Total nr of removed teeth	1.020	0.949	1.096	0.590
Tumor stage (I, II, III or IV)	1.792	1.057	3.040	**0.030**
Tumor stage (Early vs Adv)	3.988	1.023	15.544	**0.046**

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis.*

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p	OR	CI-95%		p	OR	CI-95%		p
	lower	upper	value		lower	upper	value		lower	upper	value
0941	0.880	1.006	0.075	0.948	0.904	0.994	**0.026**	0.961	0.908	1.017	0.165
				0.797	0.332	1.915	0.612				
0.486	0.303	0.779	**0.003**	0.583	0.418	0.814	**0.002**	0.557	0.378	0.821	**0.003**
2.245	1.208	4.173	**0.011**	2.137	1.352	3.377	**0.001**	1.916	1.166	3.151	**0.010**
1.740	0.987	3.069	0.056	2.010	1.307	3.093	**0.001**	1.658	1.029	2.672	**0.038**
				1.014	0.947	1.084	0.696				
				1.175	0.794	1.739	0.419				
				1.207	0.514	2.838	0.666				

D_{mean} ≥40Gy (Continued)				D_{max} ≥40Gy							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95%		p	OR	CI-95%		p	OR	CI-95%		p
	lower	upper	value		lower	upper	value		lower	upper	value
				0.990	0.948	1.033	0.632				
				0.611	0.209	1.785	0.368				
0.494	0.310	0.785	**0.003**	0.614	0.425	0.886	**0.009**	0.614	0.425	0.886	**0.009**
1.897	0.010	3.564	**0.047**	1.479	0.899	2.432	0.123				
1.615	0.870	3.000	0.129	1.586	0.972	2.588	0.065				
				1.014	0.946	1.088	0.694				
0.919	0.232	3.645	0.905	1.423	0.921	2.200	0.112				
1.918	0.295	12.485	0.496	2.333	0.763	7.133	0.137				

Supplementary Table 2A1 – Larynx Dmean

min. Dmean		0,9		1.6	1.6
max. Dmean		2,2		1.6	1.6
mean Dmean		1,6		1.6	1.6
(SD)		(0.6)			
percentage redundantly removed teeth (<40Gy)	100%	100%	100%	100%	100%
number redundantly removed teeth (<40Gy)	1	5	1	2	1
total number of extracted teeth	1	5	1	2	1
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	11	22	20	8	15
number redundantly removed teeth (<40Gy)	10	21	19	7	15
percentage redundantly removed teeth (<40Gy)	**91%**	**95%**	**95%**	**88%**	100%
mean Dmean	23,8	16,8	17,0	19,9	8,1
(SD)	(13.9)	(12.8)	(12.7)	(22.7)	(6.1)
min. Dmean	8,5	4,0	6,8	3,5	2,9
max. Dmean	**52,7**	**58,8**	**57,5**	**56,9**	22,2

number of patients n = 60

M1sc, Pm2si, M1si, M2si, M3si, and all inferior teeth: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

								1.6		2.2
								1.6		2.2
								1.6		2.2
								100%		100%
								2		1
0	0	0	0	0	0	0	0	2	0	1
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
9	9	8	7	9	9	13	5	22	25	12
9	9	8	7	9	9	13	4	21	24	11
100%	100%	100%	100%	100%	100%	100%	**80%**	**95%**	**96%**	**92%**
7,6	6,1	6,6	6,7	6,4	7,8	8,9	27,5	15,0	14,7	19,8
(4.8)	(4.5)	(4.5)	(4.9)	(4.8)	(5.7)	(5.9)	(24.6)	(10.7)	(11.6)	(14.3)
2,6	1,9	1,9	2,1	2,0	2,4	2,6	6,3	4,3	2,9	4,6
15,7	14,9	14,5	14,7	16,0	17,7	19,7	**54,5**	**52,6**	**53,3**	**53,1**

Supplementary Table 2A2 – Larynx Dmax

min. Dmax		1,2		2.2	3.3
max. Dmax		2,5		2.2	3.3
mean Dmax		1,9		2.2	3.3
(SD)		(0.7)			
percentage redundantly removed teeth (<40Gy)	100%	100%	100%	100%	100%
number redundantly removed teeth (<40Gy)	1	5	1	2	1
total number of extracted teeth	1	5	1	2	1
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	11	22	20	8	15
number redundantly removed teeth (<40Gy)	10	20	18	6	15
percentage redundantly removed teeth (<40Gy)	**91%**	**91%**	**90%**	**75%**	100%
mean Dmax	34,7	24,5	25,1	29,0	13,9
(SD)	(14.0)	(14.7)	(14.7)	(27.2)	(6.9)
min. Dmax	23,2	8,8	10,8	8,7	8,1
max. Dmax	**65,5**	**66,5**	**66,7**	**67,7**	26,1

number of patients n = 60

M1sc, Pm2si, M1si, M2si, M3si, and all inferior teeth: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

								2.4		2.5
								2.4		2.5
								2.4		2.5
								100%		100%
								2		1
0	0	0	0	0	0	0	0	2	0	1
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
9	9	8	7	9	9	13	5	22	25	12
9	9	8	7	9	9	13	4	21	24	9
100%	100%	100%	100%	100%	100%	100%	**80%**	**95%**	**96%**	**75%**
14,0	12,0	12,5	12,6	12,4	13,7	15,9	36,3	23,6	23,2	31,5
(6.7)	(6.7)	(6.6)	(7.0)	(6.8)	(7.4)	(8.1)	(29.1)	(13.3)	(14.0)	(17.0)
5,5	5,0	6,3	7,7	5,1	6,4	6,5	11,1	8,4	7,5	13,9
25,1	23,7	23,1	23,8	24,6	26,2	28,0	**68,2**	**68,5**	**64,2**	**62,2**

Supplementary Table 2B1 – Hypopharynx Dmean

min. Dmean	1,8	2,2	1,2	1,1	1,3
max. Dmean	**64,5**	**56,6**	15,3	10,9	9,4
mean Dmean	25,1	29,4	6,7	4,5	5,4
(SD)	(28.1)	(38.5)	(7.2)	(5.6)	(5.7)
percentage redundantly removed teeth (<40Gy)	**75%**	**50%**	100%	100%	100%
number redundantly removed teeth (<40Gy)	3	1	7	4	3
total number of extracted teeth	4	2	7	4	3
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	11	14	13	4	4
number redundantly removed teeth (<40Gy)	6	9	9	4	4
percentage redundantly removed teeth (<40Gy)	**55%**	**64%**	**69%**	100%	100%
mean Dmean	36	30,8	28,9	16,7	14,11
(SD)	(15.5)	(14.7)	(14)	(6.7)	(9.2)
min. Dmean	16,3	9,3	8,3	10,7	5,2
max. Dmean	**65,9**	**55,6**	**50,0**	22,8	23,5

number of patients n = 37

I1sc, I2sc, Csc, M1sc, Pm1si, Pm2si, M1si, Cii, Pm1ii, M1ii, I2ic, Pm1ic, M3ic, number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

	1,1	1,1	1,0	1,0		1,3	0,8	1,0	2,1	27,2
	1,1	1,1	1,0	1,0		6,3	6,6	17,3	25,3	27,2
	1.1	1.1	1,0	1,0		3,8	2,4	6,8	16,3	27.2
						(3.5)	(2.8)	(6.5)	(12.5)	
	100%	100%	100%	100%	100%	100%		100%	100%	100%
	1	1	2	2	1	2	4	6	3	1
0	1	1	2	2	1	2	4	6	3	1
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
2	5	5	5	5	2	5	8	20	11	6
2	5	5	5	5	2	5	8	19	11	5
100%	100%	100%	100%	100%	100%	100%	100%	**95%**	100%	**83%**
3.5	9,2	8,4	7,9	6,9	8,1	8,4	14,5	19,7	19,1	21,2
	(4.8)	(4.0)	(3.3)	(2.7)	(5.7)	(2.4)	(3.5)	(9.7)	(10.5)	(13.7)
3,5	3,2	3,1	3	3	4	5,3	8,9	8	8,7	8,1
3,5	16,3	14,1	12,2	9,2	12,1	10,9	19,1	**40,4**	37,9	**40,9**

Supplementary Table 2B2 – Hypopharynx Dmax

min. Dmax	2,1	2,6	1,4	1,7	1,5
max. Dmax	**69,3**	**67,2**	23,2	13,0	10,9
mean Dmax	29,7	34,9	9,1	5,5	6,2
(SD)	(29.2)	(45.7)	(10.2)	(6.4)	(6.6)
percentage redundantly removed teeth (<40Gy)	**75%**	**50%**	100%	100%	100%
number redundantly removed teeth (<40Gy)	3	1	7	4	3
total number of extracted teeth	4	2	7	4	3
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	11	14	13	4	4
number redundantly removed teeth (<40Gy)	4	6	6	2	4
percentage redundantly removed teeth (<40Gy)	**36%**	**43%**	**46%**	**50%**	100%
mean Dmax	47,8	42,2	40,5	31,8	24,7
(SD)	(16.5)	(16.4)	(15.8)	(19.1)	(9.0)
min. Dmax	24,3	13,0	12,2	15,4	14,7
max. Dmax	**72,8**	**63,6**	**58,7**	**53,0**	32,1

number of patients n = 37

I1sc, I2sc, Csc, M1sc, Pm1si, Pm2si, M1si, Cii, Pm1ii, M1ii, I2ic, Pm1ic, M3ic, number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

	1,3	1,4	1,3	1,2		1,6	1,0	1,1	2,6	30,0
	1,3	1,4	1,3	1,2		7,5	7,5	19,1	30,5	30,0
	1,3	1,4	1,3	1,2		4,5	2,9	9,1	19,1	30.0
						(4.2)	(3.1)	(7.8)	(14.7)	
	100%	100%	100%	100%	100%	100%		100%	100%	100%
	1	1	2	2	1	2	4	6	3	1
0	1	1	2	2	1	2	4	6	3	1
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
2	5	5	5	5	2	5	8	20	11	6
2	5	5	5	5	2	5	7	16	8	4
100%	100%	100%	100%	100%	100%	100%	**88%**	**80%**	**73%**	**67%**
9,1	20,5	18,3	16,7	14,9	16,6	19,7	28,2	29,2	27,5	28,3
	(11.1)	(8.6)	(6.9)	(6.2)	(6.0)	(3.5)	(8.6)	(12.4)	(11.8)	(17.0)
9,1	7,4	7,7	7,6	7,3	12,4	15,5	19,4	13,5	14,3	13,3
9,1	35,0	28,6	23,4	20,5	20,8	22,7	**41,0**	**55,8**	**46,3**	**50,6**

Supplementary Table 2C1 - Parotid region Dmean

min. Dmean	15,9	5,0	4,5	8,0	14,4
max. Dmean	24,2	24,0	24,3	15,9	14,4
mean Dmean	19,4	13,0	14,0	11,9	14,4
(SD)	(3.0)	(7.3)	(7.5)	(5.6)	
percentage redundantly removed teeth (<40Gy)	100%	100%	100%	100%	100%
number redundantly removed teeth (<40Gy)	5	10	10	2	1
total number of extracted teeth	5	10	10	2	1
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	11	14	11	3	2
number redundantly removed teeth (<40Gy)	5	8	10	3	2
percentage redundantly removed teeth (<40Gy)	**45%**	**57%**	**91%**	100%	100%
mean Dmean	37,6	31,1	26,8	18,0	8,5
(SD)	(11.8)	(14.0)	(12.6)	(6.7)	(3.2)
min. Dmean	18,8	13,3	8,9	13,3	6,3
max. Dmean	**49,1**	**49,6**	**43,2**	25,8	10,8

number of patients n = 35

M2si, M1si, M1sc, M2sc: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean mean dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

								8,0		6,4
								8,0		7,6
								8,0		7,0
										(0.8)
								100%	100%	100%
								2	1	2
0	0	0	0	0	0	0	0	2	1	2
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
4	2	2	2	2	1	1	1	2	0	3
4	2	2	2	2	1	1	1	2		3
100%	100%	100%	100%	100%	100%	100%	100%	100%		100%
12,7	13,2	10,3	7,9	6,9	8,1	10,3	7,7	6,3		7,2
(4.9)	(0.1)	(2.0)	(3.6)	(3.7)				(2.6)		(3.3)
5,4	13,2	8,9	5,4	4,3	8,1	10,3	7,7	4,5		4,5
16,0	13,3	11,7	10,5	9,5	8,1	10,3	7,7	8,1		10,9

Supplementary Table 2C2 - Parotid region Dmean

min. Dmax	18,8	7,7	7,5	10,4	17,7
max. Dmax	31,6	27,7	28,8	18,4	17,7
mean Dmax	25,4	16,6	17,3	14,4	17,7
(SD)	(5.2)	(7.4)	(7.8)	(5.6)	
percentage redundantly removed teeth (<40Gy)	100%	100%	100%	100%	100%
number redundantly removed teeth (<40Gy)	5	10	10	2	1
total number of extracted teeth	5	10	10	2	1
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	11	14	11	3	2
number redundantly removed teeth (<40Gy)	3	7	5	2	2
percentage redundantly removed teeth (<40Gy)	**27%**	**50%**	**45%**	**67%**	100%
mean Dmax	48,4	39,1	37,2	27,4	13,9
(SD)	(12.0)	(15.3)	(17.2)	(11.5)	(6.7)
min. Dmax	28,6	19,1	17,2	20,6	9,1
max. Dmax	**63,2**	**56,7**	**54,3**	**40,6**	18,6

number of patients n = 35

M2si, M1si, M1sc, M2sc: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

								11,4		8,7
								11,4		10,3
								11,4		9,5
										(1.1)
								100%	100%	100%
								2	1	2
0	0	0	0	0	0	0	0	2	1	2
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
4	2	2	2	2	1	1	1	2	0	3
4	2	2	2	2	1	1	1	2		3
100%	100%	100%	100%	100%	100%	100%	100%	100%		100%
17	18,8	15,2	12	9,8	9,9	27,7	20,1	8,9		9,2
(5.9)	(0.5)	(0.8)	(1.7)	(3.0)				(2.1)		(4.2)
8,2	18,4	14,6	10,8	7,7	9,9	27,7	20,1	7,4		5,7
20,6	19,1	15,8	13,2	11,9	9,9	27,7	20,1	10,4		13,8

Supplementary Table 2D1 – Oropharynx Dmean

min. Dmean	9,1	4,3	3,1	2,5	2,1
max. Dmean	**70,2**	**71,2**	**70,0**	**56,0**	**47,4**
mean Dmean	45.5	38.1	23.9	20.8	15.9
(SD)	(18.2)	(21.3)	(20.7)	(17.4)	(14.2)
percentage redundantly removed teeth (<40Gy)	**27%**	**49%**	**78%**	**85%**	**93%**
number redundantly removed teeth (<40Gy)	4	18	25	11	13
total number of extracted teeth	15	37	32	13	14
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	30	37	39	23	22
number redundantly removed teeth (<40Gy)	2	5	10	14	20
percentage redundantly removed teeth (<40Gy)	**7%**	**14%**	**26%**	**61%**	**91%**
mean Dmean	54.5	52.7	45.3	38.8	31.2
(SD)	(8.3)	(9.5)	(9.4)	(11.8)	(10.5)
min. Dmean	33,6	29,4	23,3	16,9	15,6
max. Dmean	**67,1**	**66,8**	**65,2**	**67,2**	**64,9**

number of patients n = 117

Csi: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with the total tooth baring part of the jaw receiving <25Gy, the extraction sites are not delineated in the planning software.

1,5	1,3	1,3	1,2	1,3	1,3	1,5	1,7	1,8	2,0	3,6
18,5	7,1	17,5	17,2	17,7	18,5	25,5	32,4	**53,8**	**47,3**	34,6
56.1	3.4	5.4	5.5	5.5	6.7	7.2	10.8	16.6	15.9	22.5
(5.6)	(1.9)	(4.8)	(4.8)	(4.7)	(5.8)	(7.8)	(9.5)	(15.9)	(13.0)	(11.1)
100%	100%	100%	100%	100%	100%	100%	100%	**90%**	**92%**	100%
9	7	10	9	10	11	12	12	19	23	8
9	7	10	9	10	11	12	12	21	25	8
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
21	19	19	17	19	17	27	24	32	47	29
20	18	19	17	19	16	26	22	25	29	17
95%	**95%**	100%	100%	100%	**94%**	**96%**	**92%**	**78%**	**62%**	**59%**
27.0	24.1	22.0	21.5	21.4	23.8	25.2	25.8	30.8	36.0	36.1
(10.2)	(7.9)	(7.3)	(7.3)	(8.4)	(13.0)	(11.5)	(13.5)	(13.3)	(14.1)	(13.6)
12,3	10,8	9,9	10,2	8,5	8,2	8,9	10,3	9,1	10,2	12,3
63,9	**40,4**	39,4	38,5	37,2	**65,6**	**66,6**	**67,5**	**63,6**	**66,2**	**64,0**

Supplementary Table 2D2 – Oropharynx Dmax

min. Dmax	21.8	13.6	6.7	4.9	4.9
max. Dmax	**73.6**	**74.6**	**71.9**	**63.0**	**55.3**
mean Dmax	55.8	49.8	33.9	28.1	24.6
(SD)	(16.7)	(20.4)	(22.4)	(19.8)	(16.2)
percentage redundantly removed teeth (<40Gy)	**13%**	**35%**	**59%**	**77%**	**86%**
number redundantly removed teeth (<40Gy)	2	13	19	10	12
total number of extracted teeth	15	37	32	13	14
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	30	37	39	23	22
number redundantly removed teeth (<40Gy)	0	1	3	5	11
percentage redundantly removed teeth (<40Gy)	**0%**	**3%**	**8%**	**22%**	**50%**
mean Dmax	63.3	63.2	56.1	50.6	42.1
(SD)	(8.3)	(9.4)	(10.1)	(12.7)	(12.4)
min. Dmax	43.2	36.3	30.8	24.7	22.6
max. Dmax	**72.6**	**74.3**	**73.7**	**73.1**	**71.5**

number of patients *n = 117*

Csi: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with the total tooth baring part of the jaw receiving <25Gy, the extraction sites are not delineated in the planning software.

3.3	1.8	1.8	1.5	1.6	1.7	2.1	2.5	2.7	2.5	8.6
25.9	12.7	22.5	22.1	26.5	29.1	31.5	39.2	**63.1**	**55.3**	**61.0**
11.8	5.5	8.7	9.0	9.2	12.6	11.1	15.5	21.7	21.7	31.1
(8.7)	(3.5)	(6.7)	(6.5)	(7.3)	(9.1)	(9.8)	(11.0)	(18.0)	(13.5)	(16.4)
100%	100%	100%	100%	100%	100%	100%	100%	**81%**	**92%**	**88%**
9	7	10	9	10	11	12	12	17	23	7
9	7	10	9	10	11	12	12	21	25	8
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
21	19	19	17	19	17	27	24	32	47	29
14	15	17	15	16	14	20	17	20	19	13
67%	**79%**	**89%**	**88%**	**84%**	**82%**	**74%**	**71%**	**63%**	**40%**	**45%**
35.6	32.3	29.0	28.4	28.4	30.3	32.3	32.7	38.2	43.6	43.4
(11.5)	(9.7)	(8.0)	(8.4)	(10.8)	(14.6)	(12.6)	(15.8)	(15.5)	(15.1)	(14.8)
17.8	15.2	13.8	16.8	11.2	10.3	10.7	11.7	11.9	14.2	14.9
72.1	**50.2**	**44.1**	**45.1**	**47.5**	**73.8**	**72.1**	**71.8**	**71.6**	**73.0**	**69.6**

Supplementary Table 2E1 - Oral cavity group Dmean

min. Dmean	4.4	3.6	1.3	0.9	0.8
max. Dmean	**52.0**	**66.9**	**62.8**	**61.8**	**53.4**
mean Dmean	16.2	24.3	13.9	13.5	8.6
(SD)	(20.4)	(23.1)	(18.4)	(21.9)	(15.1)
percentage redundantly removed teeth (<40Gy)	**80%**	**77%**	**87%**	**86%**	**91%**
number redundantly removed teeth (<40Gy)	4	10	13	6	10
total number of extracted teeth	5	13	15	7	11
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	8	20	15	16	17
number redundantly removed teeth (<40Gy)	0	0	1	0	3
percentage redundantly removed teeth (<40Gy)	**0%**	**0%**	**7%**	**0%**	**18%**
mean Dmean	56.3	60.6	57.2	60.2	50.9
(SD)	(5.6)	(5.8)	(10.2)	(5.8)	(15.7)
min. Dmean	48.8	49.3	30.5	50.6	7.0
max. Dmean	**64.6**	**71.3**	**70.4**	**68.8**	**69.7**

number of patients n = 51

M2si and M1si: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with the total tooth baring part of the jaw receiving <25Gy, the extraction sites are not delineated in the planning software.

0.8	0.8	0.7	0.7	0.7	0.7	2.2	2.8	1.0	3.1	3.4
38.9	**52.6**	**50.8**	**51.0**	**53.2**	11.1	3.8	**48.7**	**61.1**	13.6	12.2
8.0	8.9	9.4	9.4	9.7	3.6	2.7	12.1	13.6	7.7	8.2
(12.9)	(16.8)	(18.3)	(18.4)	(19.2)	(3.5)	(0.7)	(16.7)	(17.6)	(4.2)	(4.0)
100%	**89%**	**86%**	**86%**	**86%**	100%	100%	**86%**	**91%**	100%	100%
8	8	6	6	6	7	4	6	10	7	4
8	9	7	7	7	7	4	7	11	7	4
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
17	17	18	17	16	15	17	15	13	16	12
1	4	5	6	5	4	6	8	6	9	4
6%	**24%**	**28%**	**35%**	**31%**	**27%**	**35%**	**53%**	**46%**	**56%**	**33%**
52.7	49.7	47.2	41.9	39.9	44.4	42.6	35.2	32.5	29.1	37.6
(14.7)	(15.8)	(15.2)	(17.7)	(19.5)	(17.6)	(17.5)	(18.3)	(19.5)	(17.9)	(17.4)
5.9	5.6	5.6	5.8	6.3	7.1	5.0	4.0	3.8	4.0	4.7
69.1	**65.5**	**64.1**	**64.3**	**63.7**	**63.7**	**64.0**	**57.3**	**62.2**	**53.2**	**55.0**

Supplementary Table 2E2 - Oral cavity group Dmax

min. Dmax	5.9	5.2	1.77	1.7	1.7
max. Dmax	**63.3**	**68.7**	**69.3**	**69.5**	**70.0**
mean Dmax	26.1	34.4	25.4	28.9	19.5
(SD)	(26.1)	(24.1)	(21.4)	(27.9)	(21.3)
percentage redundantly removed teeth (<40Gy)	**60%**	**69%**	**80%**	**71%**	**91%**
number redundantly removed teeth (<40Gy)	3	9	12	5	10
total number of extracted teeth	5	13	15	7	11
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	8	20	15	16	17
number redundantly removed teeth (<40Gy)	0	0	0	0	1
percentage redundantly removed teeth (<40Gy)	**0%**	**0%**	**0%**	**0%**	**6%**
mean Dmax	65.2	67.6	67.3	68.6	59.9
(SD)	(6.9)	(4.3)	(5.5)	(3.9)	(15.4)
min. Dmax	54.4	56.4	53.3	59.6	8.8
max. Dmax	**73.0**	**74.4**	**75.4**	**75.1**	**75.2**

number of patients n = 51

M2si and M1si: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with the total tooth baring part of the jaw receiving <25Gy, the extraction sites are not delineated in the planning software.

1.5	1.6	1.2	1.2	1.3	1.2	3.3	3.7	1.3	4.3	12.4
70.9	**69.7**	**69.0**	**65.7**	**67.5**	**48.7**	9.1	**70.4**	**67.5**	21.9	24.0
22.6	18.4	16.8	14.4	14.8	13.1	6.5	21.2	18.2	12.0	17.2
(25.6)	(24.0)	(24.0)	(23.1)	(23.7)	(16.5)	(3.0)	(26.1)	(20.4)	(7.2)	(5.6)
75%	**78%**	**86%**	**86%**	**86%**	**86%**	100%	**71%**	**82%**	100%	100%
6	7	6	6	6	6	4	5	9	7	4
8	9	7	7	7	7	4	7	11	7	4
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
17	17	18	17	16	15	17	15	13	16	12
1	2	2	1	1	1	1	5	6	9	4
6%	**12%**	**11%**	**6%**	**6%**	**7%**	**6%**	**33%**	**46%**	**56%**	**33%**
62.5	60.2	59.0	57.8	57.8	57.0	54.6	47.1	44.7	37.7	42.7
(15.5)	(17.1)	(16.3)	(16.1)	(15.8)	(15.6)	(14.8)	(16.9)	(15.6)	(16.8)	(20.3)
7.4	7.5	8.6	8.0	9.2	10.1	10.9	11.7	22.2	6.4	7.7
76.0	**75.1**	**74.3**	**74.4**	**72.6**	**72.1**	**71.4**	**72.6**	**68.5**	**61.8**	**62.2**

Supplementary Table 2F1 - Maxillary complex Dmean

min. Dmean	3,0	4,4	39,1	2,5	9,6
max. Dmean	36,0	**52,3**	**65,7**	**71,4**	**71,5**
mean Dmean	14,3	34,0	48,7	42,4	49,6
(SD)	(18.8)	(18.9)	(9.4)	(30.0)	(22.2)
percentage redundantly removed teeth (<40Gy)	100%	**50%**	**17%**	**50%**	**17%**
number redundantly removed teeth (<40Gy)	3	3	1	2	1
total number of extracted teeth	3	6	6	4	6
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	2	4	2	0	0
number redundantly removed teeth (<40Gy)	1	1	0		
percentage redundantly removed teeth (<40Gy)	**50%**	**25%**	**0%**		
mean Dmean	27,4	36,6	44,2		
(SD)	(29.3)	(24.1)	(0.2)		
min. Dmean	6,7	1,1	44,1		
max. Dmean	**48,1**	**55,0**	**44,4**		

number of patients n = 22

I2ii, I1ii, I1ic, I2ic: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

9,0	8,8	8,5	6,9	6,6	6,7	6,6	6,4	6,1	4,7	15,9
71,4	**71,3**	**71,8**	**58,4**	**58,7**	**57,7**	**53,0**	**59,5**	**51,9**	**49,7**	32
49,3	47,7	47,2	32,6	32,7	32,2	29,8	33,0	26,9	21,6	26,6
(34.9)	(34.0)	(33.9)	(36.5)	(36.8)	(36.1)	(32.8)	(26.6)	(16.4)	(14.5)	(9.3)
33%	**33%**	**33%**	**50%**	**50%**	**50%**	**50%**	**67%**	**75%**	**89%**	100%
1	1	1	1	1	1	1	2	6	8	3
3	3	3	2	2	2	2	3	8	9	3
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
0	2	2	2	2	1	1	0	1	2	1
	2	2	2	2	1	1		1	2	1
	100%	100%	100%	100%	100%	100%			100%	100%
	0,8	0,8	0,8	0,8	19,7	20,0		8,2	8,3	4,7
									(1.4)	
	0,8	0,8	0,8	0,8	19,7	20,0		8,2	7,3	4,7
	0,8	0,8	0,8	0,8	19,7	20,0		8,2	9,3	4,7

Supplementary Table 2F2 - Maxillary complex Dmax

min. Dmax	5,5	24,4	53,6	9,4	26,3
max. Dmax	**54,2**	**70,1**	**74,0**	**74,3**	**74,3**
mean Dmax	22,7	48,7	62,1	51,5	62,5
(SD)	(27.3)	(16.4)	(7.3)	(29.5)	62.5
percentage redundantly removed teeth (<40Gy)	**67%**	**33%**	**0%**	**25%**	**17%**
number redundantly removed teeth (<40Gy)	2	2	0	1	1
total number of extracted teeth	3	6	6	4	6
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	2	4	2	0	0
number redundantly removed teeth (<40Gy)	1	1	0		
percentage redundantly removed teeth (<40Gy)	**50%**	**25%**	**0%**		
mean Dmax	48,0	43,8	62,2		
(SD)	(21.2)	(28.5)	(11.7)		
min. Dmax	33,1	1,8	53,9		
max. Dmax	**63,0**	**65,5**	**70,4**		

number of patients n = 22

I2ii, I1ii, I1ic, I2ic: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

25,2	22,0	17,4	14,0	14,3	12,7	12,2	12,2	14,7	11,6	20,9
74,1	**22.0-**	**74,2**	**70,5**	**68,8**	**67,7**	**64,3**	**68,6**	**57**	**53,4**	**45,5**
56,1	55,1	53,9	42,3	41,5	40,2	38,3	44,3	35,7	29,3	35,9
(26.9)	(28.8)	(31.7)	(40.0)	41.5	(38.9)	(36.8)	(29.0)	(15.0)	(14.5)	(13.1)
33%	**33%**	**33%**	**50%**	**50%**	**50%**	**50%**	**33%**	**63%**	**78%**	**33%**
1	1	1	1	1	1	1	1	5	7	1
3	3	3	2	2	2	2	3	8	9	3
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
0	2	2	2	2	1	1	0	1	2	1
	2	2	2	2	1	1		1	2	1
	100%	100%	100%	100%	100%	100%			100%	100%
	1,2	1,2	1,2	1,2	34,8	36,7		12,8	11,8	6,7
									(0.2)	
	1,2	1,2	1,2	1,2	34,8	36,7		12,8	11,7	6,7
	1,2	1,2	1,2	1,2	34,8	36,7		12,8	12,0	6,7

Supplementary Table 2G1 – Nasopharynx Dmean

min. Dmean	41.1	41.3	28.4	21	29,2
max. Dmean	60.0	42	38.6	21	29,2
mean Dmean	48.5	41.7	33.5	21.0	29.2
(SD)	(10.1)	(0.5)	(7.2)		
percentage redundantly removed teeth (<40Gy)	**0%**	**0%**	100%	100%	100%
number redundantly removed teeth (<40Gy)	0	0	2	1	1
total number of extracted teeth	3	2	2	1	1
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	2	3	2	2	2
number redundantly removed teeth (<40Gy)	2	2	2	2	2
percentage redundantly removed teeth (<40Gy)	100%	**67%**	100%	100%	100%
mean Dmean	34.8	29.4	26.2	25.4	22.7
(SD)	(7.0)	(13.9)	(17.7)	(1.6)	(3.0)
min. Dmean	29.9	15.0	13.7	24.2	20.6
max. Dmean	39.8	**42.8**	38.7	26.5	24.9

number of patients *n = 11*

	17.0	19.7	21.0	20.4	13.4	14.5	19.4		29.6	28.7	64,4
	19.8	25.5	24.2	23.9	24.9	18.0	19.4		36.0	59.6	64,4
	18.3	22.6	22.6	22.2	19.3	16.3	19.4		32.4	42.3	64.4
	(1.4)	(4.1)	(2.3)	(2.4)	(5.8)	(2.4)			(2.7)	(12.9)	
	100%	100%	100%	100%	100%	100%	100%		100%	**50%**	**0%**
	3	2	2	2	3	2	1		4	2	0
	3	2	2	2	3	2	1	0	4	4	1
	Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
	Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
	2	2	3	3	3	2	4	3	2	2	2
	2	2	3	3	3	2	4	2	2	2	2
	100%	100%	100%	100%	100%	100%	100%	**67%**	100%	100%	100%
	20.3	19.1	18.4	17.9	18.4	19.3	22.0	30.0	23.0	27.0	22.9
	(4.2)	(4.3)	(3.0)	(2.4)	(1.4)	(0.1)	(1.7)	(10.2)	(5.6)	(3.6)	(3.9)
	17.4	16.0	15.0	15.2	16.8	19.2	19.5	23.4	19.0	24.5	20.1
	23.3	22.1	20.9	19.7	19.4	19.3	23.5	**41.8**	27.0	29.5	25.7

Supplementary Table 2G2 – Nasopharynx Dmax

min. Dmax	47.7	52.9	36.1	29,6	35,4
max. Dmax	63.1	57.2	46.4	29,6	35,4
mean Dmax	**54.3**	**55.0**	**41.2**	29.6	35.4
(SD)	(7.9)	(3.1)	(7.3)		
percentage redundantly removed teeth (<40Gy)	**0%**	**0%**	**50%**	100%	100%
number redundantly removed teeth (<40Gy)	0	0	1	1	1
total number of extracted teeth	3	2	2	1	1
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	2	3	2	2	2
number redundantly removed teeth (<40Gy)	0	2	1	2	2
percentage redundantly removed teeth (<40Gy)	**0%**	**67%**	**50%**	100%	100%
mean Dmax	61.7	38.9	35.4	30.9	28.6
(SD)	(9.6)	(16.0)	(26.1)	(4.1)	(2.8)
min. Dmax	54.9	24.0	16.9	28.0	26.6
max. Dmax	**68.5**	**55.8**	**53.8**	33.8	30.6

number of patients *n = 11*

	24.2	23.5	22.6	22.5	19.5	20.9	26,9		37.7	33.7	67,4
	26.9	28.2	27.5	29.5	31.2	22.9	26,9		47.1	64.3	67,4
	25.3	25,8	25.0	26.0	24.9	21.9	26.9		**42.0**	**53.3**	**67.4**
	(1.4)	(3.3)	(3.4)	(5.0)	(5.9)	(1.4)			(3.9)	(13.6)	
	100%	100%	100%	100%	100%	100%	100%		**25%**	**25%**	**0%**
	3	2	2	2	3	2	1		1	1	0
	3	2	2	2	3	2	1	0	4	4	1
	Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
	Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
	2	2	3	3	3	2	4	3	2	2	2
	2	2	3	3	3	2	4	2	2	2	2
	100%	100%	100%	100%	100%	100%	100%	67%	100%	100%	100%
	26.0	25.2	23.7	23.6	24.0	25.6	27.3	**38.2**	29.7	36.7	35.2
	(6.4)	(5.7)	(3.3)	(1.2)	(0.4)	(1.6)	(2.9)	(12.6)	(9.5)	(2.8)	(3.6)
	21.5	21.2	21.5	22.3	23.6	24.5	24.7	27.6	23.0	34.7	32.6
	30.5	29.3	27.4	24.7	24.4	26.7	31.4	**52.2**	36.4	38.7	37.7

Supplementary Table 2H1 – Other Mean

min. Dmean	11,4	0,6	7,6	5,8	41,6
max. Dmean	11,4	**46,6**	38,2	38	**48**
mean Dmean	11,4	19,9	21,0	19,1	44,8
(SD)		(16.2)	(12.7)	(14.4)	(4.5)
percentage redundantly removed teeth (<40Gy)	100%	**89%**	100%	100%	**0%**
number redundantly removed teeth (<40Gy)	1	8	6	4	0
total number of extracted teeth	1	9	6	4	2
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	5	10	4	2	0
number redundantly removed teeth (<40Gy)	4	7	2	2	0
percentage redundantly removed teeth (<40Gy)	**80%**	**70%**	**50%**	100%	
mean Dmean	23,4	29,1	26,0	29,8	
(SD)	(15.1)	(18.6)	(24.3)	(0.8)	
min. Dmean	0,6	0,4	0,3	29,2	
max. Dmean	**42**	**50,8**	**51,5**	30,4	

number of patients n = 25

M1sc, M2sc, M3sc, M1si, M2si: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean mean dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

7,1	19,2	49,7	5,2	5,1	5,1			4,1	4,2	0,4
36,6	**50,1**	**49,7**	**47,9**	**48,2**	8,6			17,7	11,2	0,4
19,5	34,7	49,7	21,9	21,2	6,8			10,9	7,7	0,4
(15.2)	(21.9)		(22.8)	(23.5)	(2.5)			(9.6)	(3.6)	
100%	**50%**	**0%**	**67%**	**67%**	100%			100%	100%	100%
3	1	0	2	2	2	0	0	3	5	2
3	2	1	3	3	2	0	0	3	5	2
Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
1	2	1	1	1	1	0	1	4	1	1
1	2	1	1	1	1	0	1	4	1	1
100%	100%	100%	100%	100%	100%		100%	100%	100%	100%
20,1	0,2	0,1	7,9	6,9	8,1	10,3	7,7	6,3		7,2
	(0.1)		(3.6)	(3.7)				(2.6)		(3.3)
20,1	0,1	0,1	5,4	4,3	8,1	10,3	7,7	4,5		4,5
20,1	0,3	0,1	10,5	9,5	8,1	10,3	7,7	8,1		10,9

Supplementary Table 2H2 – Other Dmax

min. Dmax	13,6	0,7	11,9	7,0	54,5
max. Dmax	13,6	**50,4**	**50,8**	**52,8**	**57,6**
mean Dmax	13,6	24,1	29,8	25,5	56,1
(SD)		(17.4)	(16.3)	(20.3)	(2.2)
percentage redundantly removed teeth (<40Gy)	100%	**78%**	**83%**	**75%**	**0%**
number redundantly removed teeth (<40Gy)	1	7	5	3	0
total number of extracted teeth	1	9	6	4	2
teeth upper jaw	M3si	M2si	M1si	Pm2si	Pm1si
teeth lower jaw	M3ii	M2ii	M1ii	Pm2ii	Pm1ii
total number of extracted teeth	5	10	4	2	0
number redundantly removed teeth (<40Gy)	4	5	2	0	0
percentage redundantly removed teeth (<40Gy)	**80%**	**50%**	**50%**	**0%**	
mean Dmax	29,2	37,3	38,4	50,6	
(SD)	(17.9)	(22.6)	(35.9)	(2.8)	
min. Dmax	0,8	0,6	0,5	48,6	
max. Dmax	**48,0**	**68,9**	**70,0**	**52,5**	

number of patients n = 25

M1sc, M2sc, M3sc, M1si, M2si: number of teeth with cut-off point 40Gy is greater than the number of teeth available for the mean max dose. In patients with both jaws receiving <25Gy, the extraction sites are not delineated in the planning software.

	8,2	45,9	59,1	6,3	6,6	6,8			4,9	5,3	0,4
	54,1	**60,1**	**59,1**	**53,4**	**53,1**	20,3			30,5	14,8	0,4
	35,1	53,00	59,1	29,5	27,8	13,5			17,7	9,9	0,4
	(23.9)	(10.1)	59,1	(23.6)	(23.5)	(9.5)			(18.1)	(5.1)	
	33%	**0%**	**0%**	**67%**	**67%**	100%			100%	100%	100%
	1	0	0	2	2	2	0	0	3	5	2
	3	2	1	3	3	2	0	0	3	5	2
	Csi	I2si	I1si	I1sc	I2sc	Csc	Pm1sc	Pm2sc	M1sc	M2sc	M3sc
	Cii	I2ii	I1ii	I1ic	I2ic	Cic	Pm1ic	Pm2ic	M1ic	M2ic	M3ic
	1	2	1	1	1	1	0	1	4	1	1
	1	2	1	1	1	1	0	1	4	1	1
	100%	100%	100%	100%	100%	100%		100%	100%	100%	100%
	29,9	0,4	0,1	0,1	0,1	17,5		21,6	11,0	0,3	34,5
		(0.4)							(11.1)		
	29,9	0,1	0,1	0,1	0,1	17,5		21,6	0,3	0,3	34,5
	29,9	0,7	0,1	0,1	0,1	17,5		21,6	26,5	0,3	34,5

CHAPTER 6

TOOTH EXTRACTIONS PRIOR TO CHEMORADIATION OR BIORADIATION ARE ASSOCIATED WITH WEIGHT LOSS DURING TREATMENT FOR LOCALLY ADVANCED OROPHARYNGEAL CANCER.

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Abstract

Purpose: Prior to radiotherapy combined with chemotherapy (CRT) or biotherapy (BRT) for oropharyngeal squamous cell carcinoma (OPSCC), teeth with poor prognosis that pose a risk for post-RT osteoradionecrosis (ORN) are removed. The effect of tooth loss on body weight loss and tube feeding (TF) dependency during CRT/BRT is unknown. This study aimed to evaluate the effect of incomplete dentition, tooth extractions prior to CRT/BRT, and the subsequent loss of functional units on (1) weight loss during CRT/BRT and (2) the need for TF during CRT/BRT for OPSCC.

Methods: OPSCC patients treated with CRT/BRT between 2013 and 2016 were included in this retrospective cohort study. Dental status was determined during the dental assessment at first visit and after tooth extractions prior to the start of CRT/BRT. Weight loss during CRT/BRT was scored dichotomously, comparing weight loss >5% to stable or increased weight. Potential factors associated with weight loss were identified, including patient, tumor, and treatment characteristics.

Results: Seventy-seven OPSCC patients were included. Forty patients (52%) experienced weight loss >5% during CRT/BRT. Extractions were performed in 66% of the OPSCC patients. The mean number of extracted teeth was 4.1 ± 5.6 per patient. Tooth extractions prior to CRT/BRT were associated with weight loss >5% during CRT/BRT (HR 1.130 (95% CI 1.011 - 1.262), p = .031). None of the dental status-related parameters showed any significant associative value for TF during CRT/BRT.

Conclusions: Pre-CRT/BRT tooth extractions intended to reduce the risk of ORN, are a risk factor for weight loss during CRT/BRT for OPSCC.

Introduction

The incidence of oropharyngeal cancer, predominantly squamous cell carcinoma, has increased over the past 30 years from less than 300 new diagnoses in the early 1990s to nearly 700 in 2018 in the Netherlands alone [1]. This is consistent with global figures, in which the increased incidence of Human Papilloma Virus (HPV) related oropharyngeal squamous cell carcinoma (OPSCC) has the largest share in this growth, especially among men in developed countries [2]. A better prognosis for HPV-positive OPSCC, combined with young age at diagnosis and thus a longer life expectancy, has increased awareness of late treatment-related toxicity [3]. Radiotherapy (RT) alone or in combination with chemotherapy (cisplatin) (CRT) or biotherapy (cetuximab) (BRT) is the main therapy for OPSCC with osteoradionecrosis (ORN) as one of the most feared toxicities. Although the risk of ORN has decreased with current advancements in radiotherapy techniques and better oral health regimens, cancer located in the oropharynx remains a risk factor for ORN due to its location proximate to the mandible [4-7]. Comprehensive dental assessment of potential oral sources of infection (poor prognosis teeth) prior to RT is an example of improved oral health regimes. In the Netherlands, oral health recommendations prior to RT are based on a protocol that dates from 1992, which has been revisited in 2018 [8-10]. Removal of poor prognosis teeth that are identified as potential oral source of infection is a common recommendation in the prevention of ORN. This is however complex and controversial. Tooth extractions result in a reduced number of functional units (Table 1) and impair the ability to masticate and swallow, contributing to decreased health-related quality of life (QoL) [6, 11-13]. Indeed, this deterioration in mastication has been associated with oropharyngeal dysphagia [14, 15]. Furthermore, it has been demonstrated that oropharyngeal dysphagia is significantly related to involuntary weight loss [16, 17]. Cachexia, clinically characterized by unintended weight loss and low muscle mass [18], has a negative effect on treatment-related toxicity and oncological outcome. Head and neck cancer patients with weight loss and/or low muscle mass experienced higher levels of toxicity, more unplanned hospital admissions, and poorer overall survival [19-21]. Therefore, it is of utmost importance to prevent weight loss during oncological treatment and to elucidate contributing risk factors [21].

Nutritional management targeting malnutrition to prevent or limit weight loss is an essential part of head and neck oncological treatment. Regularly, tube feeding (TF) may be necessary to achieve these goals [22].

A systematic review of longitudinal studies revealed inconsistent findings on the association between tooth loss and nutritional status in adults [23]. To our knowledge, to date, no studies have investigated the effect of incomplete dentition or loss of functional units due to tooth extraction prior to CRT/BRT, on body weight and TF dependency in patients with head and neck cancer.

Therefore, the aim of this study was to evaluate the effect of incomplete dentition, tooth extractions prior to CRT/BRT, and the subsequent loss of functional units on the following: (1) weight loss during CRT/BRT and (2) the need for TF during CRT/BRT for OPSCC. We hypothesized that OPSCC patients who underwent tooth extractions prior to RT, experienced greater weight loss during CRT/BRT and were more prone to TF dependency compared to patients whose teeth were not removed.

Materials and Methods

Study design and population

Patients with OPSCC, who were treated with primary or postoperative CRT/BRT in the Comprehensive Cancer Center of Maastricht University Medical Center (MUMC+) and Maastro Clinic between January 2013 and December 2016, were included in this retrospective cohort study. Exclusion criteria were single modality treatment with radiotherapy only, previous head and neck radiation, and TF dependency at start of the oncological treatment. Patients were part of a larger MUMC+ sample from a cohort study on alterations in body composition in locally advanced head and neck squamous cell carcinoma (LAHNSCC) [21]. Additional data extraction on dental status from the electronic health records was performed by an experienced maxillofacial prosthodontist (DB). This study was approved by the medical ethics committee of the MUMC+ (METC 2020-1589).

All patients received primary CRT or BRT (cisplatin or cetuximab, respectively) or postoperative CRT (cisplatin) with curative intent. RT was administered using intensity-modulated RT (IMRT) for five days per week for six (BRT) or seven (CRT) weeks, in fractions of 2Gy. Cisplatin was administered intravenously in doses of 100 mg/m^2 every 3 weeks [24, 25] concurrently with daily fractionated IMRT up to 66Gy in 33 fractions or 70Gy in 35 fractions in case of postoperative and primary RT, respectively. Cetuximab was indicated in patients not fit for cisplatin and consisted of a 400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly, combined with accelerated fractionated IMRT up to 68Gy in 34 fractions in 38 days [26]. According to the national standard procedures, the dental status was assessed through oral and radiographic examination (e.g. orthopantomography), at least 14 days before the start of CRT/BRT [8-10]. Teeth with a poor prognosis due to extensive caries, advanced periodontal disease, and non-restorable teeth were considered as potential source of infection for ORN. Radiographic abnormalities like apical radiolucency, (partially) impacted teeth, residual root tips, root resorption, and dental cysts were also considered as potential source of infection. Poor prognosis teeth within the estimated radiation fields were treated, usually by extraction.

During CRT/BRT, 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 8 to 10 times a day [8, 9]. Patients received custom-made fluoride trays in combination with a neutral 1% sodium fluoride gel to be used every other day [8, 9]. To relieve the symptoms of mucositis, patients were sprayed with saline 3 times a week by the dental hygienist [27].

Patients were counselled by a dietician on a weekly basis according to the Dutch malnutrition guideline as part of standard clinical care [28]. TF was indicated if oral intake including oral nutritional supplements did not meet >75% of the calculated nutritional requirements [29]. TF was administered through a nasogastric tube, percutaneous endoscopic gastrostomy or radiologically inserted gastrostomy.

Anthropometric measurements
Weight was measured weekly at the start of RT during the standard visits to the Comprehensive Cancer Center of MUMC+. Height was measured only once before the start of CRT/BRT to calculate the body mass index (BMI). Pretreatment weight loss was a patient-reported outcome measure. Weight loss during the course of CRT/BRT was converted into a binary variable, comparing losses of more than 5% to stable or increased weight, based on the definition of grade 1 weight loss in the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE).

The same CTCAE version was also used by the radiation oncologists to report the severity of oropharyngeal dysphagia at start of RT. At the same time, the World Health Organization Performance Status (WHO PS) was assessed. The Charlson comorbidity index (CCI) was determined based on the medical history in the individual electronic health records [29]. The p16 status was used as surrogate marker for HPV infection [30].

Dental status was determined at two time points: during the dental assessment at first visit (dental sources of infection and functional dental status) and after tooth extractions prior to the start of CRT/BRT (functional dental status). The dental terminology and classification systems used are listed in Table 1. Whether or not patients underwent tooth extractions, the number of extracted teeth, and additional dental interventions including the removal of exostoses and implant insertion were recorded. The use of TF during CRT/BRT was treated as a binary measure, consisting of TF started during CRT/BRT for any duration versus remaining on a total oral diet.

Statistical analyses
Descriptive statistics were reported as means and standard deviations (SDs) for normally distributed, continuous variables, and medians and inter quartile ranges (IQRs) for non-normally distributed data. Comparisons between groups were performed with independent t-tests in case of a normal distribution or the

Mann-Whitney *U* test in case of non-normal distribution. Normal distribution was verified using the Shapiro-Wilk test. Cross-tabulations were made for categorical variables. A Chi^2 test was used for categorical outcomes. When more than 20% of cells had expected frequencies <5, we used Fisher's exact test.

Table 1 – Terminology clarification

Edentulous	No functional teeth in place
Functional tooth	A tooth was considered functional if it could make contact with an opposing (prosthetic) tooth. Roots or impacted teeth are considered as nonfunctional.
Functional Unit	Functional tooth, bridge pontic, or crown (on implants), which could make contact with an opposing (prosthetic) tooth, is considered a functional unit.
Occlusal Unit [41]	A measure to represent the chewing surface of the postcanine functional unit. One pair of occluding premolars is equal to one occlusal unit. One pair of occluding molars is considered as two occlusal units. Third molars are excluded.
Eichner Index [42, 43]	A validated measure describing the existing posterior functional units in support zones. It is divided into 3 main classes
Eichner Index A	Functional units exist in all 4 posterior support zones
Eichner Index B	Functional units are present in one to three posterior support zones or within the anterior area only
Eichner Index C	No functional units left

All potential associative variables for weight loss underwent screening through univariable logistic regression. Factors with $p<.10$ were selected as potentially relevant associative variables and subsequently tested using multivariable logistic regression. Due to limited sample size, the influence of potential associative factors was tested individually, with a maximum of three variables in the multivariable model.

Statistical analyses were regarded as significant if the *p* value was equal to or lower than .05. Data were evaluated using SPSS (IBM version 25 for Windows, Armonk, NY, USA). For the Fisher's exact test with more than 2 by 2 items, the R software (R Core Team (2021) R Foundation for Statistical Computing, Vienna, Austria) was used.

Results

Seventy-seven patients with OPSCC met the inclusion criteria and were included in this study. Extractions were performed in 66% of the OPSCC patients. The mean number of extracted teeth was 4.1 ± 5.6 per patient. During CRT/BRT, 40 patients (52%) experienced significant weight loss of more than 5%. Baseline characteristics are presented in Table 2. Patients with significant weight loss during CRT/BRT had a higher BMI at start of treatment compared to patients without significant weight loss. In addition, a higher proportion of patients with significant weight loss had teeth removed to clear them from potential sources of infection.

Table 2 – Baseline characteristics

	Stable weight or less than 5% loss during CRT/BRT n = 37 (48%)	***>5% weight loss during CRT/BRT n = 40 (52%)***	***p* value**
Patient characteristics			
Age (years)			
mean ± SD	58.4 ± 9.5	59.4 ± 6.0	
median (IQR)	60.0 (13)	59.5 (9)	0.971[c]
Male	25 (68%)	29 (73%)	0.637[d]
Female	12 (32%)	11 (28%)	
Smoking history	33 (89%)	35 (88%)	1.000[a]
No history of smoking	4 (11%)	5 (13%)	
Alcohol consumption	19 (51%)	27 (68%)	0.149[d]
No alcohol consumption	18 (49%)	13 (33%)	
BMI at start RT (kg/m^2); mean ± SD	24.5 ± 5.0	26.7 ± 4.2	**0.039[b]**
Percentage weight loss prior to CRT/BRT; mean ± SD	2.4 ± 3.7	1.7 ± 3.2	0.373[b]
Dysphagia (CTCAE grade)			
0 - No symptoms of dysphagia	18 (49%)	15 (38%)	0.077[d]
1 - Symptomatic, regular diet	7 (19%)	17 (43%)	
2 - Symptomatic, altered eating/swallowing	12 (32%)	8 (20%)	

Table 2 – Continued

	Stable weight or less than 5% loss during CRT/BRT n = 37 (48%)	***>5% weight loss during CRT/BRT n = 40 (52%)***	***p* value**
WHO PS 0	9 (24%)	14 (35%)	0.325[a]
WHO PS 1	28 (76%)	25 (63%)	
WHO PS 2	0 (0%)	1 (3%)	
CCI 0	7 (19%)	2 (5%)	0.231[a]
CCI 1	7 (19%)	12 (30%)	
CCI 2	10 (27%)	17 (43%)	
CCI 3	7 (19%)	4 (10%)	
CCI 4	2 (5%)	3 (8%)	
CCI 5	1 (3%)	1 (3%)	
CCI 6	3 (8%)	1 (3%)	
Tumor characteristics			
T1	5 (14%)	7 (18%)	0.287[a]
T2	8 (22%)	12 (30%)	
T3	10 (27%)	4 (10%)	
T4	14 (38%)	17 (43%)	
N0	8 (22%)	6 (15%)	0.886[a]
N1	1 (3%)	1 (3%)	
N2	27 (73%)	32 (80%)	
N3	1 (3%)	1 (3%)	
Stage II	0 (0%)	1 (3%)	0.829
Stage III	3 (8%)	2 (5%)	
Stage IV	34 (92%)	37 (93%)	
p16+	20 (54%)	26 (65%)	0.328[d]
p16-	17 (46%)	14 (35%)	
Dental status			
Edentulous at start RT	13 (35%)	9 (23%)	0.220[d]
Dentate at start RT	24 (65%)	31 (78%)	

Table 2 – Continued

	Stable weight or less than 5% loss during CRT/BRT n = 37 (48%)	***>5% weight loss during CRT/BRT n = 40 (52%)***	***p* value**
Eichner Index A at first assessment	7 (19%)	12 (30%)	0.427[d]
Eichner Index B at first assessment	11 (30%)	8 (20%)	
Eichner Index C at first assessment	19 (51%)	20 (50%)	
Eichner Index A at start RT	4 (11%)	8 (20%)	0.547[a]
Eichner Index B at start RT	13 (35%)	11 (28%)	
Eichner Index C at start RT	20 (54%)	21 (53%)	
Decrease in Eichner Index (ABC) due to tooth extractions prior to CRT/BRT	4 (11%)	5 (13%)	1.000[a]
No decrease in Eichner Index (ABC) due to tooth extractions prior to CRT/BRT	33 (89%)	35 (88%)	
OU at first assessment; mean ± SD	3.5 ± 4.5	4.0 ± 4.7	0.642[b]
OU at start RT; mean ± SD	2.1 ± 3.6	3.2 ± 4.4	0.249[b]
Loss of OU due to tooth extractions prior to CRT/BRT			
mean ± SD	1.4 ± 2.3	0.8 ± 1.8	
median (IQR)	0.0 (3)	0.0 (1)	0.317[c]
Tooth extractions prior to CRT/BRT	20 (54%)	31 (78%)	**0.030[d]**
No tooth extractions prior to CRT/BRT	17 (46%)	9 (23%)	
Tooth extractions and/or additional interventions	23 (62%)	32 (80%)	0.083[d]
No tooth extractions and/or additional interventions	14 (38%)	8 (20%)	
Number of removed teeth; mean ± SD	3.4 ± 5.0	4.8 ± 6.1	0.289[b]
Treatment characteristics			
Primary CRT/BRT	35 (95%)	38 (95%)	1.000[a]
Postoperative CRT	2 (5%)	2 (5%)	
Cisplatin	27 (73%)	29 (73%)	0.963[d]
Cetuximab	10 (27%)	11 (28%)	

Table 2 – Continued

	Stable weight or less than 5% loss during CRT/BRT n = 37 (48%)	***>5% weight loss during CRT/BRT n = 40 (52%)***	***p* value**
RT dose to contralateral submandibular gland (Gy); mean ± SD	48.1 ± 12.0*	49.7 ± 10.6*	0.529[b]
RT dose to contralateral parotid salivary gland (Gy); mean ± SD	24.2 ± 10.5	22.2 ± 7.1	0.345[b]
RT dose to superior PCM (Gy); mean ± SD	59.3 ± 11.6	59.3 ± 7.5	0.995[b]
RT dose to middle PCM (Gy); mean ± SD	59.8 ± 6.4	60.1 ± 7.1	0.870[b]
RT dose to inferior PCM (Gy); mean ± SD	49.4 ± 10.8	49.5 ± 8.4	0.939[b]
RT dose to oral cavity (Gy); mean ± SD	45.9 ± 11.0	45.2 ± 9.5	0.740[b]
RT dose to cricopharyngeal muscle (Gy); mean ± SD	44.5 ± 7.3	43.3 ± 6.5	0.433[b]
RT dose to cervical esophagus (Gy)			
mean ± SD	41.5 ± 8.3	37.0 ± 11.1	
median (IQR)	42.0 (8.0)	40.1 (17.7)	0.129[c]
TF during CRT/BRT (any duration)	24 (65%)	23 (58%)	0.508[d]
No TF	13 (35%)	17 (43%)	

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CRT/BRT, chemoradiotherapy or bioradiotherapy; WHO PS, World Health Organization performance status; p16+/-, p16 positive/negative tumor as surrogate marker for Human Papilloma Virus; PCM, pharyngeal constrictor muscles; RT, radiotherapy; TF, tube feeding; TNM-classification, tumor (T), node (N), metastasis (M) classification according to the 7th edition [44].

Bold values denote statistical significance at the p<.05 level.

[a]*Fisher's exact test.*

[b]*Independent T-test.*

[c]*Mann-Whitney U test.*

[d]*Chi²-test.*

**two missing values due to a bilateral neck dissection*

Univariable logistic regression analysis for significant weight loss during CRT/BRT revealed a potential associative value (*p* value <.10) for the factors BMI, tooth extractions, tooth extractions and/or additional interventions, and RT dose to the cervical esophagus (Table 3).

Table 3 – Univariable and multivariable analysis of factors potentially contributing to significant weight loss of >5% during CRT/BRT and to TF dependency

	significant weight loss of >5% during CRT/BRT			
	Univariable analysis			
	OR	CI-95% lower	CI-95% upper	p value
Age	1.018	0.960	1.078	0.556
Sex (male vs. female)	1.265	0.476	3.363	0.637
Smoking	0.848	0.210	3.434	0.818
Alcohol	1.968	0.781	4.956	0.151
BMI	1.113	1.003	1.236	**0.044**
Weight loss prior to CRT/BRT	0.941	0.823	1.075	0.370
Dysphagia at start RT (CTCAE grade 2 vs. 0 or 1)	0.521	0.185	1.468	0.217
WHO PS (1 or 2 vs. 0)	0.597	0.221	1.611	0.309
CCI (≥4 vs. <4)	0.738	0.205	2.659	0.642
T3 or T4 vs. T0, T1 or T2	0.599	0.239	1.498	0.273
N2 or N3 vs. N0 or N1	1.821	0.578	5.739	0.306
p16+ vs. p16-	1.579	0.631	3.948	0.329
Edentulous vs. dentate	0.536	0.197	1.462	0.223
Decrease in Eichner Index (ABC) due to tooth extractions prior to CRT/BRT (binary)	1.179	0.291	4.771	0.818
Tooth extractions (yes vs. no)	2.928	1.094	7.834	**0.032**
Tooth extractions and additional interventions (yes vs. no)	2.435	0.877	6.756	0.087
Number of removed teeth	1.047	0.961	1.140	0.291
Loss of OU due to tooth extractions prior to CRT/BRT	0.867	0.687	1.095	0.232
Cetuximab vs. cisplatin (ref)	1.024	0.375	2.795	0.963
RT dose to contralateral parotid gland	0.975	0.925	1.028	0.347
RT dose to contralateral submandibular gland	1.013	0.973	1.056	0.523
RT dose to superior PCM	1.000	0.954	1.048	0.995
RT dose to median PCM	1.006	0.941	1.075	0.868
RT dose to inferior PCM	1.002	0.956	1.050	0.938
RT dose to oral cavity	0.992	0.950	1.037	0.737
RT dose to cricopharyngeus muscle	0.974	0.911	1.040	0.428
RT dose to cervical esophagus	0.952	0.904	1.002	0.060
TF use	0733	0.292	1.841	0.508

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CRT/BRT, chemoradiotherapy or bioradiotherapy; WHO PS, World Health Organization performance status; OU, occlusal units; PCM, pharyngeal constrictor muscles; RT, radiotherapy; TF, tube feeding;

significant weight loss of >5% during CRT/BRT (Continued)				TF dependency							
Multivariable analysis*				Univariable analysis				Multivariable analysis*			
OR	CI-95% lower	upper	p value	OR	CI-95% lower	upper	p value	OR	CI-95% lower	Upper	p value
				0.980	0.922	1.041	0.509				
				0.776	0.281	2.141	0.624				
				0.759	0.175	3.297	0.713				
				0.982	0.386	2.501	0.970				
1.130	1.011	1.262	**0.031**	0.987	0.895	1.089	0.799				
				1.187	1.001	1.407	**0.049**				
				1.256	0.435	3.627	0.673				
				1.689	0.627	4.547	0.300				
				0.732	0.202	2.650	0.634				
				1.765	0.696	4.476	0.232				
				1.056	0.333	3.342	0.927				
				0.487	0.185	1.283	0.145				
				0.892	0.325	2.447	0.825				
				0.465	0.114	1.894	0.285				
3.360	1.185	9.529	**0.023**	0.756	0.283	2.019	0.577				
				0.484	0.165	1.425	0.188				
				0.995	0.917	1.080	0.909				
				1.125	0.877	1.445	0.354				
				0.355	0.127	0.995	**0.049**	0.226	0.070	0.731	**0.013**
				1.018	0.964	1.075	0.524				
				1.048	1.001	1.096	**0.044**	1.067	1.013	1.124	**0.015**
				1.013	0.966	1.063	0.584				
				1.040	0.970	1.115	0.272				
				1.044	0.990	1.102	0.112				
				1.031	0.983	1.081	0.211				
				1.088	1.010	1.173	**0.026**				
				1.044	0.995	1.096	0.077				

Bold values denote statistical significance at the p<.05 level.
**Step-backward analysis of all variables with p<.05 in univariable analysis*

In multivariable step backward logistic regression analyses, tooth extractions prior to CRT/BRT and BMI at start of CRT/BRT remained as associative factors for weight loss >5% during CRT/BRT, independent of weight loss prior to CRT/BRT, WHO PS, CCI, dental status at first assessment or at start CRT/BRT, number of occlusal units (OU), and number of removed teeth (Table 3). When evaluating the individual influence of potential associative factors, the associative value of extractions was reduced to a trend when corrected for alcohol use (p = .057).

Univariable logistic regression analysis for TF dependency during CRT/BRT revealed a potential associative value (p value <.10) for the following factors: Weight loss prior to CRT/BRT, type of systemic therapy (cisplatin or cetuximab), RT dose to the contralateral submandibular gland, RT dose to the cricopharyngeal muscle, and RT dose to the cervical esophagus. None of the dental state parameters showed any significant associative value for TF dependency. In multivariable analysis, only a higher RT dose to the contralateral submandibular gland and type of systemic therapy (cisplatin) remained significant associative factors for the risk of TF dependency (Table 3).

Discussion

The results of the current study showed that OPSCC patients who underwent tooth extraction(s) prior to IMRT intended to reduce the risk of ORN are more likely to experience significant weight loss of more than 5% during CRT/BRT. Interestingly, the number of teeth extracted and the number of functional units lost did not influence the degree of weight loss and the need for TF.

Few researchers studied the effect of dental status on weight loss or nutritional status in head and neck cancer patients. Thereby, uniform methods or widely accepted standardized protocols for dental status assessment are lacking. Despite the use of different study methods and dental status assessment methods, our results are in line with a study published in 2008 suggesting that dental condition, defined by the decayed, missing, and filled teeth index and the masticatory coefficient are risk factors for weight loss at the outset of management of head and neck cancer (HNC) [31]. Another study evaluated dental status by using the Eichner Index in a sample of 104 treatment-naïve HNC patients [32]. These authors reported that a reduced number of functional units was associated with the total nutrition impact symptoms score, but the absence of functional units was not necessarily an absolute impairment to achieve normal dietary intake. In our study, a reduced number of functional units were not associated with weight loss of more than five percent.

Limiting factors in previous studies were amongst others a mixture of tumor sites and limited information on possible associative factors. Also, no information was available on tooth loss in the context of pre-treatment tooth extractions or during oncological surgery, and data on weight loss during oncological therapy was underreported as well.

Research in the general population has shown a relationship between the number of natural teeth and weight loss. Having fewer teeth or being edentulous increased the risk of clinically relevant weight loss [33-36]. However, this concerns research among elderly people of at least 65 years of age, in which the dental status was examined and not the effect of tooth extractions as an intervention.

It remains unclear if the negative effect of tooth extractions on body weight is the result of a decrease in functional units or that it is the result of disrupting the existing masticatory system in its motor-sensory functionality and/or willingness to eat. Previous studies suggested that extractions, masticatory, and swallowing

function are interrelated. The number of OU and having functional dentures were positively associated with masticatory performance in a prospective cohort study [11]. A retrospective single center study in oral cancer patients showed that patients lacking OU had an increased risk for swallow impairment [37].

Therefore, an association between a deterioration of dental status, resulting in reduced masticatory performances, and weight loss seems conceivable.

Tooth extractions or functional units did not predict TF dependency. In a recent study in 450 LAHNSCC patients, nine associative values were added to a prediction model for the need for TF, including amongst others BMI and percentage weight change at baseline [38]. Since we only found type of systemic therapy (cisplatin vs. cetuximab) and RT dose to the submandibular gland as independent TF predictors in the present study population, we have to assume that the study is underpowered and that these preliminary results should be interpreted with caution.

This is the first study addressing the impact of pre-CRT/BRT tooth extractions to reduce the risk of ORN, on weight loss. This weight loss is known to have a negative effect on treatment-related toxicity and oncological outcome. By evaluating the CRT/BRT trajectory, including neat weight reporting, a reliable retrospective assessment was possible. The addition of chemotherapy to RT as radiosensitizer does not only enhance RT efficacy, but may also intensify side effects, including nausea, vomitus, mucositis, and weight loss [39, 40]. As a result, the percentage of patients who become TF-dependent during CRT/BRT could be higher than during RT as a single modality. Therefore, we focused on the vulnerable CRT/BRT group to answer our research question.

Despite the fact that the research was set up on the basis of strictly standardized usual care protocols, we have some limitations to address. The relatively small sample size impeded extensive subgroup stratification and multivariable corrections. The number of patients who were edentulous at baseline was relatively high. Edentulous patients may have had extractions (e.g., root tips or impacted wisdom teeth), but loss of a functional unit or decrease of the Eichner index is not possible. This may explain why extractions emerged as an associative factor for >5% weight loss and the decline in OU and Eichner Index did not reveal an association with weight loss. Although we were able to identify many factors associated with weight loss after tooth extractions, information on socio-economic and education status, factors associated with health perception, could not be retrieved from the electronic health records, as this information was not reported.

The patient's financial and intellectual ability to modify their diet after tooth extractions may also have affected their capability to maintain weight, but accessing this privacy-sensitive data remains challenging. Following the procedure of tooth extraction, a reduced oral intake for approximately one or two weeks might lead to weight loss. Due to its retrospective character, we were not able to extract information on weight on the exact day of tooth extractions and on a standardized day after the procedure. However, a uniform moment of baseline measurements was defined, namely right before CRT/BRT initiation. Neither could we evaluate the effect of pain on oral intake since this was not reported in a standardized way and levels of treatment toxicity (mucositis, xerostomia) were not included in this study.

Conclusion

Our study suggests that tooth extractions contribute to significant weight loss during treatment. Since body weight maintenance is important for completing planned oncological treatment and for supporting the recovery phase, further weight loss caused by tooth extractions should be minimized or avoided as much as possible. More careful consideration of teeth removal prior to CRT/BRT seems appropriate, but demands close communication with the HNC team. As RT protocols and thus the doses to the tooth-bearing part of the jaws vary widely, interdisciplinary consultation with the radiation oncologist is highly recommended in order to reduce the risk of ORN due to potential oral sources of infection.

This study prompts further investigation into the adverse effects of tooth extractions and disruption of the masticatory system. That, along with the current improvements in RT techniques, may fuel the discussion to review and deescalate the current tooth extraction protocols aimed at reducing the risk of ORN.

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CHAPTER 7

GENERAL DISCUSSION

General discussion

The shift in the focus of head and neck cancer (HNC) treatment from survival to survival with the best possible quality of life (QoL) has increased scientific research attention to the side effects of HNC treatments. Acute and lifelong side effects of HNC treatment include limitations in chewing and swallowing, speech, dry mouth, and social integration associated with decreased quality of life and possible follow-up surgery. Masticatory function and dental health are among the effects that are considered very important by HNC survivors [1].

Chewing or mastication is controlled by teeth, tongue, cheeks, lips, jaw muscles, neuromuscular control, and saliva. The loss of teeth leads to a decrease in functional units and impairs masticatory performance (objective masticatory function) [2, 3]. Impaired masticatory performance leads to the consumption of predominantly soft, easy-to-chew foods, which may result in poor dietary habits and low nutrient intake [2]. In addition, deterioration of masticatory function has been associated with oropharyngeal dysphagia [4, 5] which has significant associations with involuntary weight loss [6, 7].

Therefore, it is important to optimize each patient's masticatory system by minimizing the loss of functional units and optimally restoring the loss.

In this thesis, we evaluated masticatory function and oral health-related quality of life (OHRQoL) after prosthetic rehabilitation of edentulous patients with HNC, as well as the accuracy and possible consequences of tooth removal prior to radiotherapy (RT).

The edentulous jaw

Toothless people are impaired in their chewing function, and even clinically satisfactory full dentures are a poor alternative to natural teeth. The ability of denture wearers to grind food is very poor compared to people with natural teeth. Full denture wearers require, on average, four to eight times more chewing than dentate individuals to achieve the same degree of comminution. This poor chewing performance is compensated for by chewing longer and swallowing coarser food particles. One of the factors leading to the decrease in masticatory performance is the decreased bite force that denture wearers may develop due to the lack of retention and stability of the denture [2]. This lack of retention and stability is exacerbated in patients with HNC by the effects of cancer treatment. Surgical treatment of oral cavity cancer often results in soft tissue and bone defects

that may limit the neutral zone and restrict the area of support for complete dentures. RT can cause lifelong side effects such as fibrosis, xerostomia, dysphagia, osteoradionecrosis (ORN), radiation caries, and trismus [8]. Hyposalivation leads to worsening of the lubrication of the oral cavity, resulting in reduced retention of the prosthesis and increased risk of mucosal damage.

Dental implants have been used worldwide for more than 60 years and have proven to be very successful. Implant treatment significantly improves masticatory function and patient satisfaction over a long period of time [2, 9, 10]. These long-lasting successful treatment results have also been achieved in edentulous patients after treatment of oral cavity cancer [11, 12]. The improved masticatory function with implant-retained overdentures (IOD) compared with conventional dentures (CD) and no functional dentures (NFD) is mainly due to the higher maximum bite force of the IODs [13].

Rehabilitation of the edentulous mandible

In **Chapter 2**, we investigated functional treatment outcomes and patient satisfaction using patient-reported outcomes (PROMs) in 51 patients with HNC who received a full mandibular prosthesis with or without implants after completion of RT. Compared with the literature, good results were obtained, with 88.3% of these prostheses functioning at the time of evaluation (range: 1 to 23 years) [14, 15]. Overall satisfaction with the prosthesis was relatively high, with a mean score of 7.3 out of 10. This was comparable to other studies in patients with cancer of the oral cavity as well as healthy patients [15-17].

Patients who received additional treatment, such as surgery, performed worse than patients who received RT alone. Recent publications, mainly in patients with carcinomas of the oral cavity, have clearly demonstrated the additional benefit of implants. Edentulous oral cancer patients with full dentures on implants had higher bite force, reported fewer problems with the dentures, and had less difficulty chewing, especially solid and soft foods [13]. For patients with oral cavity cancer who are scheduled for ablative surgery, it is possible to place implants during ablative surgery, which offers several advantages. During the wound healing phase of tumor surgery, the initial osseointegration of the implants takes place, and if adjuvant RT is required, the onset of RT is not (additionally) delayed by implant placement. The individual cost of implant placement during ablative surgery is lower than deferred implant placement [18]. In addition, earlier prosthetic rehabilitation after cancer treatment is possible, which may also lead to higher bite force and masticatory function [13, 19].

In patients with pharyngeal or laryngeal cancer who are primarily treated with RT, implantation may delay the onset of RT because the wound area must be healed before RT is started [20]. Since the introduction of intensity-modulated radiotherapy (IMRT), it has been possible to avoid high doses of RT to normal structures, including the anterior mandible [21]. With the development of volumetric modulated arc therapy (VMAT) and intensity modulated proton therapy (IMPT), even further dose adjustments are possible [19]. Therefore, delayed implantation may be preferred for patients treated with these current RT techniques. Implant placement after RT is primarily indicated in patients who have retention or chewing problems with their conventional prosthesis. However, in patients without functional problems who have received high doses of RT doses in the posterior portion of the mandible, implant placement should be considered. Despite the promising dose reduction in the tooth-bearing parts of the jaw, the dorsal parts of the mandible still receive relatively high RT doses in HNC patients [19, 22]. Placement of interforaminal implants offers the advantage that the prosthesis-bearing mucosa in these dorsal regions of the mandible can be unloaded to avoid soft tissue ulceration and necrosis.

An exception should be made for patients who become edentulous during the removal of sources of infection prior to RT. A period of 10 to 14 days for wound healing until the start of RT is needed anyway, so implant placement does not cause any additional delay. However, in these patients, there is a potential risk of insufficient intermaxillary space remaining for prosthetic rehabilitation after RT because the jaws did not resorb. This can be assessed during the dental examination prior to RT. If one is to be expected, it is desirable to lower the alveolar process sufficiently before placing the implants.

In our study, men appeared to benefit more from implants than women. While our differences between men and women may have been influenced by the fact that more women underwent surgery, other studies show differences between men and women in terms of prosthetic satisfaction [17, 23-25]. Consideration of gender differences in future research may contribute to better personalized care [26].

The Liverpool Oral Rehabilitation Questionnaire version 3 (LORQv3)

In our initial study in **Chapter 2**, we encountered two limitations with our methods. First, we lacked an objective measure of masticatory performance, which we remedied in the studies in **Chapter 4** by using the mixing ability test (MAT) [27]. In addition, available general QoL questionnaires, such as the EORTC

QLQ-C30 and the QLQ-H&N35, lack the discriminatory power to measure the effects of prosthetic treatment on mastication, swallowing, speech, aesthetics, retention, and pain. In 2004, the Liverpool Oral Rehabilitation Questionnaire (LORQ) was developed to better measure the impact of prosthetic treatment on the quality of life of patients with HNC [28-31]. However, a validated Dutch version of the LORQ was not available. To be able to use the LORQv3 for Dutch-speaking patients, we translated the LORQv3 into Dutch and adapted it to the Dutch situation in **Chapter 3**.The original English LORQv3 was translated into Dutch using the forward–backward approach, resulting in the LORQv3-NL. The internal consistency of the LORQv3-NL was tested in 158 participants from the Radboudumc Faculty of Dentistry, the Center for Special Oral Care of Radboudumc and Maastricht UMC+ and in general practices. We also evaluated internal consistency, reliability, and validity. Test-retest reliability was performed in 34 of these 158 patients. For convergent validity, the correlation between the LORQv3-NL and the OHIP-NL14 was examined in 17 of 158 patients. Internal consistency (Cronbach's $\alpha = 0.89$ for items 1-17) and test-retest reliability (weighted kappa values ranging from 0.401 to 0.830 for items 1-17), and convergent validity ($R^2 = 0.642$) were satisfactory. With the LORQv3-NL, we seem to have a good instrument for the assessment of prosthesis discomfort and prosthesis intolerance. To date, the LORQv3 has been translated and validated in a Turkish version [32] and a German version [33], and shows high validity and reliability in all four languages. The questionnaire has been successfully used in the United Kingdom, Turkey, the Netherlands, Germany, and for several studies in India, making it a suitable questionnaire for multinational research on OHRQoL in patients with HNC.

Rehabilitation of the edentulous maxilla with defects

In the maxilla, the lack of retention and stability of the full denture may be due to the effects of cancer treatment or to trauma or infection. In particular, if the hard palate is defective, the stable denture base is lost. Such a palatal defect results in leakage through the nose, decreased speech intelligibility due to air loss, and decreased masticatory performance, leading to limitations in daily life [34-36]. Reconstruction of these defects remains a challenge for both surgeons and prosthodontists due to the complex three-dimensional anatomy of the maxilla and midface [37-40]. The complexity of these defects is reflected in the various classification systems that have been developed, of which the Okay classification and the Brown classification are the most commonly used [41, 42]. The Brown classification has the advantage of describing a horizontal or dentoalveolar component that corresponds to the functional side of the defect

[42]. Valid arguments have been made for choosing the best reconstruction and rehabilitation method based on parameters such as quality of life and functional outcomes [43-46]. The most appropriate reconstruction is ultimately determined by many factors, such as defect size, dental status, patient motivation for oral rehabilitation, comorbidities, facility experience, and clinician preferences [47]. Regardless of the rehabilitation method, defects that encompass a significant portion of the alveolus must be rehabilitated to allow for optimal masticatory behavior and appearance of the teeth [39, 48].

Low-level defects are less detrimental to facial appearance and primarily require treatment of the oronasal defect and dental rehabilitation. In many parts of the world, prosthetic obturation of these defects is still the treatment of choice, allowing the patient to speak, swallow, and chew. The obturator also continues to play a useful role for patients who cannot undergo complex autogenous reconstruction or in whom access to the surgical site is considered important for monitoring [35, 49-51]. However, inadequate retention makes this prosthetic rehabilitation of the maxilla challenging [50] where, as in the mandible, implant retention, especially in edentulous patients, has also proven useful [39, 52-56].

In **Chapter 4a**, we evaluated the potential benefits of implant placement on masticatory function and QoL of edentulous maxillectomy patients after prosthetic obturation.

We evaluated both objective outcomes from the mixing ability test (MAT) and subjective outcomes from the OHRQoL questionnaires, as objective information of oral functioning may be different from personal experiences [57]. We used the oral health impact profile for edentulous people (OHIP-EDENT) [58], the Memorial Sloan Kettering Cancer Centre obturator functioning scale (OFS) [59] and the Dutch version of the Liverpool oral rehabilitation questionnaire version 3 (LORQv3-NL) [60]. The results of the nine patients with implant supported obturator prostheses showed a significantly better mixing ability index (MAI) score outcome, notwithstanding the larger and more ventral defects. These MAI score results (18.7 ± 1.37) were similar to dentate obturator patients (18.4 ± 4.2) and healthy edentulous non-maxillectomy individuals with conventional maxillary dentures and implant-supported mandibular overdentures (MAI 18.5 ± 3.1). The mean MAI score of the ten patients with conventional obturator prostheses (22.4 ± 3.16) were comparable to healthy full denture patients (21.2 ± 3.6) and other edentulous obturator patients (25.1 ± 5.3) [27, 61].

We reached an overall implant survival of 90.5%, losing 4 of 42 implants, all 4 in irradiated bone. These results are similar to other studies, most of which did not address dental implant survival in extra-maxillary bony structures of the midface or skull base [53, 62-65]. As the patients were able to continue wearing their prosthetic obturators despite single implant loss, we considered this a successful overall outcome of functional rehabilitation.

Our OHIP-EDENT, OFS, and LORQv3-NL results did not disclose significant differences in summary scales between the two patient groups. This is probably due to the long-time interval between prosthetic rehabilitation and data acquisition (range: 1 month-7.4 years). Patients tend to adapt over time and under-report deficits, also called response shifts [66].

On the subscale level, the 'Oral function' subscale and the 'Patient Satisfaction' subscale of the LORQv3-NL showed that implant retainment has an added value for the obturator prostheses. Although these benefits are underlined in response choices by all three questionnaires, the small patient groups should be considered. The same carefully interpretation should be applied for the promising results in the speaking and swallowing domains, which have proven to be important for quality of life [59, 67].

In **Chapter 4b** we compared the objective and subjective masticatory function of patients with implant-supported obturators with patients with surgically reconstructed maxillae in a collaboration with UMC Utrecht and University of Alberta, Edmonton, Canada.

The implant-supported obturator group, consisted of the nine patients with edentulous upper jaws and implant-supported obturators from **Chapter 4a** [68]. The surgically reconstructed maxillae group consisted of 11 patients: 6 reconstructed according to the Alberta Reconstructive Technique (ART) protocol [69, 70] for malignant tumors and 5 according to the Rohner-protocol [71] for benign tumors from the HREBA.CC-17-0167 study [72].

The results demonstrated comparable masticatory performance and patient reported eating ability for patients with surgically reconstructed maxillae and patients with implant supported obturator prostheses. The mean MAI for both groups (18.2 ± 2.38 resp. 18.7 ± 1.37) remained below the MAI-level of the natural dentition group (15.8 ± 2.0), confirming previous research into chewing performance in maxillectomy patients [27, 73].

Several authors advocate for the benefits of surgical reconstruction over obturation of maxillary defects, especially for larger defects. Amongst them are authors mainly describing a personal preference solely based on experience [74, 75], or combining the best available literature with clinical experience [39, 66, 76]. Unfortunately, the best available literature is limited, and study populations are usually small.

Our study in **Chapter 4a** and an South-African study in 2007 confirm the benefits of implant-support to obturators [54, 68] and other studies even suggests equivalent functional results as compared to surgical reconstruction [77, 78].

When choosing between obturation or surgical reconstruction, it is important to inform the patient as well as possible. There are benefits for microsurgical reconstruction of extended maxillary and midface defects. Surgical reconstruction has the advantage of avoiding the discomfort of placing and cleaning obturators. There is also less nasalance for hard palate defects reconstructed with a surgical design and simulation fibula free flap [79]. Patients requiring adjuvant RT will take advantage of reconstructive surgery, as the risk of post-radiogenic changes in the irradiated tissues will be less pronounced. Tissue atrophy, fibrosis, and the most feared risk of osteoradionecrosis can be prevented by vascularized tissue transfer into the defect site. Moreover, surgical defect repair can lead to aesthetic benefits, and implant-retained fixed dentures can be applied. However, all this comes with a higher price. Patients should take into account longer operating times and longer hospital stays. In addition to the higher costs, operations with a longer duration have a higher chance of increased pain, increased functional limitations, poor global recovery and decreased HRQoL 6 months after surgery [80]. Finally, despite all advances in radiology, it remains difficult to distinguish between benign post-treatment changes and recurrent malignancy [81]. In addition to the fact that the oncologist with the surgical reconstruction loses direct visual inspection, the assessment of post-surgical radiological images also becomes more difficult.

Related to mastication, the Rohner-procedure gives immediate chewing ability like obturators do, but for patients with a malignant tumor, the obturator offers a faster recovery of chewing capacity than the ART-procedure. Since dental oral rehabilitation under the ART procedure is initiated after completion of all cancer treatments and tissue healing, it can easily take up to 6 months to start.

The Liverpool group has presented good results with the zygomatic implant perforated (ZIP) flap technique [82]. This technique for the immediate reconstruction and rapid dental rehabilitation of the low-level maxillectomy defect was first published in 2017 [83] and combines the use of soft-tissue free flap reconstruction of the oral defect combined with the early loading of zygomatic implants whose abutments perforate the flap at the time of primary surgery. With this technique, there is less reliance on bone transfer. Despite the significant challenges, the ZIP flap technique provides full dental rehabilitation within 30 days of surgery and prior to radiotherapy if this is required, with excellent published patient reported outcomes.

The choice between surgical reconstruction or (implant retained) obturation of maxilla defects remains controversial, especially for the low-level maxillectomy defects and will largely be determined by comorbidities, institutional experience, personal preferences and financial possibilities.

The accuracy and possible consequences of tooth removal prior to radiotherapy
Osteoradionecrosis of the jaw is among the most feared late complications observed in patients with HNC treated with RT [84].

To lower the risk of developing ORN, it is important that the jaw areas receiving significant doses of radiation are free of potential sources of infection prior to RT [85]. However, tooth extractions result in a decreased number of functional units and impair mastication and swallowing, contributing to a decreased HRQoL [1, 3, 86-89].

The original Dutch protocol [90] which was re-evaluated in 2018 [20, 91] recommends comprehensive dental assessment and elimination of oral sources of infection where the radiation fields will achieve an expected cumulative radiation dose of ≥40Gy at least 10 to 14 days prior to RT [84, 92]. However, some of the extracted teeth may be extracted redundantly, due to the fact that the estimated radiation dose prior to RT appeared to be lower after completion of RT planning.

In **Chapter 5**, we retrospectively investigated how many of the teeth extracted prior to RT turned out to have been removed redundantly. In addition, we investigated which patient or tumor characteristics were associated with the number of redundantly extracted teeth prior to RT. In **Chapter 6**, we evaluated the effect of incomplete dentition, tooth extractions prior to RT combined with chemotherapy (CRT) or biotherapy (BRT), and the subsequent loss of functional units on (1) weight loss during CRT/BRT and (2) the need for TF during CRT/BRT for oropharyngeal squamous cell carcinoma (OPSCC).

In the 358 patients included in **Chapter 5**, 1759 teeth were extracted of which 1274 teeth (74%) appeared to have been removed redundantly, based on the mean dose (D_{mean}) of <40Gy. Using the maximum dose (D_{max}) of <40Gy, 1080 teeth (61%) appeared to have been removed redundantly. Of the potential factors contributing to teeth receiving a cumulative RT dose ≥40Gy, tumor location and N-classification emerged as the most important factors in the multivariable regression analysis. The patients with OPSCC in **Chapter 6** who underwent tooth extraction(s) prior to IMRT were more likely to experience significant weight loss of more than 5% during CRT/BRT. The number of teeth extracted and the number of functional units lost did not influence the degree of weight loss and the need for tubefeeding (TF).

These results provided arguments to drastically reduce the need and number of tooth extractions prior to RT for HNC.

Accuracy of tooth removal

Cut-off point

In this study, a cut-off RT dose of ≥40Gy was chosen as the threshold as indication for tooth extraction [20, 91]. The choice of 40Gy as the threshold dose for the risk of developing ORN as described in the Dutch National Protocol is empirical [20, 91]. Vascular changes in tissue structure after RT occur at much lower doses [93, 94] and average doses of 24.4 and 28.2Gy corresponding with maximum doses of 44.3 and 48.4Gy have been shown sufficient to trigger an ORN [95, 96]. Several other studies suggest using 50Gy or 60Gy for the mandible or even 70Gy for the maxilla as a reference value for the development of ORN [95-99], with only one Delphi study discussing a critical radiation threshold for prophylactic removal of teeth [100]. Further research is needed before the Dutch guidelines that aim to minimize this risk as much as possible are amended. Thereby, it is important that it is clearly described whether the mean or the maximum dose must be used.

Dose-distribution

There are previous publications describing radiation doses to portions of the mandible and maxilla [22, 101-104], whereby reporting the doses in ipsi- and contralateral is very crucial. This was clearly illustrated by our results for tumors in the “parotid region” where only the mandibular molars and second mandibular premolar on the ipsilateral side received a dose ≥40Gy. While some studies looked at RT dose in terms of a volume percentage of the jaw [103], others outlined the teeth individually [22, 101, 102] or used a cylinder [104], like our study. We drew one

cylinder per tooth over the full length of the jaw, while Alberga et al. used a 6 mm high cylinder at standardized locations in the jaw [104]. These different methods for determining RT doses to jaw areas limit the ability to compare these studies.

Tumor location had a high association with dose-distribution and thus unnecessarily extracted teeth. In patients with tumors located in the laryngeal, and hypopharyngeal region, only the mandibular molars and the second mandibular premolar received a dose of ≥40Gy. In these regions the primary tumor is relatively further away from the teeth. In the oral cavity, oropharynx and 'maxillary complex' group the number of redundantly extracted teeth was less due to the closer proximity of the primary tumor to the mandible or maxilla. This led to a higher radiation dose in the jaw bones, consistent with the delineation of gross tumor volume (GTV), clinical target volume (CTV) and planning target volume PTV according to international guidelines [105].

N-state, describing the spread of cancer to nearby lymph nodes, was also associated with unnecessarily extracted teeth. The presence of positive lymph nodes located near the mandible (high level II or retropharyngeal), and submandibular lymph nodes of level Ib of the neck included in the clinical (elective) target volume resulted in a higher RT dose in the mandible.

Further research, preferably in a multicenter setting, is needed to extrapolate our results to other treatment centers, as local experience aspects of treatment planning and normal tissue sparing differ. With the introduction of IMPT further dose-sparing effect on the dentition, especially for tumors located further away from the tooth-bearing regions, seems likely but single radiation dosages exceeding 40Gy still exist [104]. Therefore, in addition to properly assessing the tumor location and the location of the positive lymph nodes, good consultation with the radiation-oncologist remains of great clinical importance. The development of artificial intelligence may contribute in the estimation of expected RT doses in the head and neck to make dental assessment more predictable [106, 107].

Possible consequences of tooth removal

Our study in **Chapter 6** suggests that tooth extractions contribute to significant weight loss during treatment, but a reduced number of functional units was not associated with weight loss of more than 5 percent. The latter may be due to the relatively high number of edentulous patients in our cohort who were able to undergo extractions (e.g., root tips or impacted wisdom teeth), but whose number of functional units could not decrease any further.

Previous studies suggested dental conditions to be risk factors for weight loss [108, 109]. It has also been suggested that extractions, mastication, and swallowing are interrelated. Such as having functional dentures and the number of occlusal units (OU), which are positively associated with masticatory performance [3], and patients with oral cancer lacking OU who had an increased risk for swallow impairment [110].

For now, it remains unclear whether the negative effect of tooth extractions on body weight is the result of a decrease in functional units or that it is the result of disrupting the existing masticatory system in its motor-sensory functionality and/or willingness to eat.

Since body weight maintenance is important for completing planned oncological treatment and for supporting the recovery phase, further weight loss caused by tooth extractions should be minimized or avoided as much as possible.

Besides the maintenance of body weight, a person's social integration is often linked to the presence of functional teeth [111]. Patients suffer not only from the underlying oncological diseases, but also from the demands of therapy. The removal of teeth is generally negatively connoted [1, 89]. With greater accuracy of tooth extraction, the masticatory system will be better preserved and the loss of functional units will be limited, which has a direct effect on food intake [1, 3, 86-89, 112]. So further research into the adverse effects of tooth extractions and disruption of the masticatory system is desirable.

The support provided by the insurance system in the Netherlands will continue to be important in this regard. The treatment of possible oral infection sites and the resulting prosthetic rehabilitation are currently covered by the national insurance schemes in the Netherlands. It would be ideal if later preventive care to prevent further damage to the masticatory system in these vulnerable mouths does not depend on someone's financial possibilities.

In conclusion, masticatory function and patient satisfaction of edentulous patients with HNC significantly improves with implant treatment. The placement of implants should therefore be considered for every patient with a edentulous mandible who is having retention problems and for every patient with a maxillary defect who is being rehabilitated with an obturator prosthesis. For dentate patients with HNC who will undergo RT treatment, there is an indication to reduce the number of tooth extractions prior to RT. More research is needed to safely de-escalate the current guidelines, without increasing the risk of ORN.

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CHAPTER 8

SUMMARY IN ENGLISH AND DUTCH

Summary

The patient population presenting with head and neck cancer (HNC) is changing. On the one hand, the prevalence of tobacco use is decreasing, with a synchronous decrease in the incidence of laryngeal cancer in particular. At the same time, the incidence of oropharyngeal cancer is increasing, mainly due to the human papilloma virus (HPV). The young age at diagnosis combined with better prognosis for HPV-positive HNC and the associated longer life expectancy, has increased awareness of late treatment-related toxicity. Advances in surgical and radiation techniques are also contributing to the shift in focus from survival to survival with the best quality of life (QoL) possible. Fear of the cancer recurrence is now closely followed by the side effects of cancer treatment, such as dry mouth, limitations in chewing and swallowing, speech and social integration, decreased QoL and follow-up surgery.

Therefore, optimizing the masticatory system and thus improving the QoL of each patient is becoming increasingly important. Optimizing the masticatory system should take into account patient related factors such as age, patient preferences, dental awareness and, of course, cancer treatment-related factors itself.

The overall aim of this thesis was to evaluate masticatory function after prosthetic rehabilitation of edentulous patients with HNC and to assess the accuracy and potential consequences of tooth extractions prior to radiotherapy (RT).

The first section of this thesis addressed the prosthetic rehabilitation of edentulous patients with an acquired defect and/or side effects after RT (**Chapters 2-4**). The second section examined the initial steps in the search for optimal preservation of the existing masticatory system of the patient with HNC (**Chapters 5-6**).

In **Chapter 2,** we investigated the functional treatment outcomes and patient satisfaction of mandibular prostheses with and without implant retention using patient-reported outcomes (PROs) in 51 irradiated patients with HNC. Nineteen patients were treated with removable conventional dentures and 32 patients with implant-retained mandibular prostheses between January 2006 and January 2011. A total of 45 (88.3%) of these 51 mandibular prostheses, were in function at the time of assessment. Overall satisfaction with the prostheses was 7.3. Patients treated with additional approaches, such as surgical tumor removal, scored lower than patients who received RT alone. In addition, edentulous patients appeared to benefit from implants, particularly in terms of denture retention. Men benefited more from IODs than women.

The above study has shown that the available general QoL questionnaires, such as the EORTC QLQ-C30 and QLQ-H&N35, do not capture details of prosthetic functionality such as chewing, swallowing, speaking, aesthetics, retention, and pain to measure the effects of prosthetic treatment. The Liverpool Oral Rehabilitation Questionnaire (LORQ) had shown better discriminatory power. Until then, no validated Dutch version of the LORQv3 was available. Therefore, the aim of **Chapter 3** was to translate and adapt the LORQv3 into Dutch and to assess the internal consistency, reliability, and validity of the resulting LORQv3-NL.

The original English LORQv3 was translated into Dutch using the forward-backward approach. The internal consistency of the LORQv3-NL was tested in 158 participants from the Radboudumc Faculty of Dentistry, the Center for Special Oral Care of Radboudumc and Maastricht UMC+ and in general practices. Test-retest reliability was performed in 34 of these 158 patients. For convergent validity, the correlation between the LORQv3-NL and the OHIP-NL14 was examined in 17 of the 158 patients. Internal consistency (Cronbach's $\alpha = 0.89$ for items 1-17), test-retest reliability (weighted kappa values of 0.401 to 0.830 for items 1-17), and convergent validity ($R^2 = 0.642$) were satisfactory. The LORQv3-NL appeared to be a good instrument for assessing denture satisfaction and perceived fit.

One of the most difficult prosthetic treatments is rehabilitating a patient with a maxillary defect due to tumour resection or trauma, for example. With a maxillary defect, oronasal separation is lost, allowing air, fluid, and often even food to escape. This impairs functions such as eating, swallowing and speaking, and thus has a significant impact on social well-being and QoL.

Prosthetic treatment aims to restore the nasal-oral separation as well as possible and replace the missing teeth. Traditionally, this is done with an obturator prosthesis, in which retention is sought on the remaining teeth. This hold is more difficult to find when there are no natural teeth left. As in the mandible, implants can also be considered in the maxilla. In **Chapter 4** we investigated whether implant-retainment actually leads to functional improvement and a better QoL.

In the first cross-sectional study (**Chapter 4.1**), we compared masticatory performance and oral health-related QoL of edentulous patients with obturator prostheses with or without implants. In 19 edentulous patients with a (partial) maxillectomy whose prosthetic treatment had been completed, masticatory performance was measured objectively and three questionnaires were completed. Masticatory performance was measured by the mixing ability

test (MAT) and the questionnaires were: (1) the Oral Health Impact Profile for EDENTulous People (OHIP-EDENT), (2) the Obturator Function Scale (OFS), and (3) the LORQv3-NL. The nine patients with implant-supported obturator prostheses had a significantly better masticatory and oral function, reported fewer chewing difficulties, and had less discomfort during food intake than did the ten patients with a conventional obturator.

A second cross-sectional study (**Chapter 4.2**) was conducted in collaboration with UMC Utrecht and the University of Alberta, Edmonton, Canada. The masticatory performance and patient reported eating ability of the nine patients with implant-supported obturator prostheses (Maastricht) were compared to 11 surgically reconstructed maxillectomy patients (Edmonton). Again, masticatory performance was measured by the mixing ability test (MAT). Oral health-related QoL was measured with shortened versions of the OHIP questionnaire. Patients with reconstructed maxillae and patients with implant-supported obturator prostheses had similar MAT scores. The seven oral health-related QoL questions also showed no differences in chewing ability between the two groups.

In conclusion, supporting prosthetic obturators after maxillectomy with implants improves oral functioning, chewing, and eating comfort. With caution, the results of this study seem to confirm earlier results that implant-supported obturation is a good alternative to surgical reconstruction for all Class II maxillary defects according to Brown's classification. With both techniques, the masticatory performance is sufficiently restored, with careful planning being highly desirable.

The final part of this thesis addressed tooth extractions prior to RT. Patients with HNC who were eligible for RT were seen by a dental team for a comprehensive dental assessment prior to RT. Teeth with a limited prognosis at risk of developing osteoradionecrosis (ORN) during or after RT were extracted. ORN, or radiation-induced osteomyelitis, is a serious and late complication of RT, characterized by irradiated bone that becomes devitalized and is exposed through the overlying skin or mucosa, without tumor recurrence and failing to heal within three months. ORN can lead to pathologic fractures, intra- or extra-oral fistulas and infection and often requires extensive surgery. These procedures are risky and complex, can lead to new side effects, and have a negative impact on QoL.

Available evidence on the efficacy of pre-RT tooth extractions in preventing ORN is limited. At the same time, tooth extractions result in a reduced number of functional units and impair the ability to chew and swallow. To allow extraction

wounds sufficient time, at least 10 to 14 days, to heal before starting RT, decisions are made based on the expected radiation dose. However, for some extracted teeth, it may be found after completion of RT that extraction was not indicated because the RT dose applied was lower than expected.

In **Chapter 5** we examined the number and patient and tumor characteristics associated with this number of redundantly extracted teeth. For this purpose, 358 patients with HNC, treated with RT between 2015 and 2019, were included in this cross-sectional study. Radiation dose was calculated retrospectively for each extracted tooth. The cut-off point for valid extraction was set at ≥40Gy in accordance with the national protocol. Because this guideline does not specify whether this is the mean or maximum dose, we evaluated both values separately. A total of 1759 teeth were removed from 358 patients. Of these 1759 teeth, 1274 (74%) appeared to have been removed redundantly, based on the mean dose (D_{mean}) of <40Gy. At the maximum dose (D_{max}) of <40Gy, 1080 teeth (61%) appeared to have been removed redundantly. Tumor location and the spread of cancer to nearby lymph nodes were found to be the most important associative variables in multivariable regression analysis.

The impact of tooth loss on body weight loss and tube feeding (TF) dependence during RT combined with chemotherapy (CRT) or biotherapy (BRT) was previously unknown. In **Chapter 6**, we retrospectively examined the effect of incomplete dentition, tooth extractions prior to CRT/BRT, and subsequent loss of functional units on (1) weight loss during therapy and (2) the need for TF during CRT/BRT for oropharyngeal squamous cell carcinomas (OPSCC). Weight loss during CRT/BRT was assessed dichotomously, comparing weight loss >5% with stable or increased weight. Potential factors associated with weight loss were identified, including patient, tumor, and treatment characteristics. Of the 77 OPSCC patients included, 40 patients (52%) experienced weight loss >5% during CRT/BRT. Tooth extractions prior to CRT/BRT were associated with >5% weight loss during treatment. None of the dental-related parameters showed a significant associative value for TF.

In conclusion, dental extractions pre-RT to reduce the risk of ORN, are a risk factor for weight loss during CRT/BRT in OPSCC. Unintended weight loss, one of the clinical features of cachexia, negatively impact treatment-related toxicity and oncologic outcome. Therefore, it is of utmost importance to avoid weight loss during cancer treatment.

Nederlandse samenvatting

De populatie van mensen met hoofd-halskanker is aan het veranderen. Enerzijds neemt de prevalentie van tabaksgebruik af, met synchroon een afname van met name de incidentie van larynxkanker. Daarnaast neemt de incidentie van orofarynxkanker toe, voornamelijk als gevolg van het humaan papillomavirus (HPV). De jongere leeftijd en een betere prognose voor patiënten met HPV-positieve hoofd-halskanker, en de bijbehorende langere levensverwachting, heeft geleid tot een groter bewustzijn van bijwerkingen op de langere termijn. Ook de vooruitgang in chirurgische technieken en innovatieve bestralingssystemen dragen bij aan de verschuiving van de focus op alleen overleven, naar overleven met de best mogelijke kwaliteit van leven. De angst voor terugkeer van de tumor wordt nu op de voet gevolgd door bezorgdheid over de bijwerkingen van de tumorbehandeling, zoals een droge mond, beperkingen in het kauw- en slikvermogen, spraak en sociale integratie, verminderde kwaliteit van het leven en vervolgoperaties.

Zodoende wordt het steeds belangrijker om het kauwsysteem van elke patiënt te optimaliseren en daarmee de kwaliteit van leven te verbeteren. Bij het optimaliseren van het kauwsysteem moet rekening worden gehouden met patiëntgebonden factoren zoals leeftijd, voorkeuren van de patiënt, tandheelkundig bewustzijn en uiteraard factoren die verband houden met de behandeling van de kanker zelf.

Het algemene doel van dit proefschrift was het evalueren van het kauwvermogen na prothetische herstel van tandeloze patiënten met hoofd-halskanker en het evalueren van de nauwkeurigheid en mogelijke gevolgen van het verwijderen van tanden en kiezen voorafgaand aan de bestraling (RT).

Het eerste deel van dit proefschrift richt zich op het prothetisch herstel van tandeloze patiënten met een verworven defect en/of bijwerkingen van de bestraling (**hoofdstukken 2-4**). Het tweede deel bestudeert de eerste stappen in een zoektocht naar optimaal behoud van het bestaande kauwstelsel van de patiënt met hoofd-halskanker (**hoofdstukken 5-6**).

In **hoofdstuk 2** hebben we met patiënt gerapporteerde uitkomsten (PROs) gekeken naar de functionele behandelresultaten en patiënttevredenheid bij 51 bestraalde patiënten met hoofd-halskanker die een onderprothese hadden gekregen, al dan niet op implantaten. Tussen januari 2006 en januari 2011

kregen 19 patiënten een conventionele onderprothese en 32 patiënten een overkappingsprothese op implantaten. Van deze 51 protheses waren er in totaal 45 (88,3%) in functie op het moment van de beoordeling. De algehele tevredenheid met de gebitsprothese was een 7,3. Patiënten die aanvullend waren behandeld met bijvoorbeeld chirurgie, scoorden slechter dan patiënten die alleen werden bestraald. Verder leken tandeloze patiënten, voornamelijk voor het houvast van de prothese, profijt te hebben van implantaten. Daarbij hadden mannen meer profijt dan vrouwen.

We ontdekten bij bovengenoemd onderzoek ook dat de beschikbare algemene kwaliteit van leven vragenlijsten, zoals de EORTC QLQ-C30 en QLQ-H&N35, onvoldoende discriminerend waren om het effect van een prothetische behandeling te meten op het gebied van kauwen, slikken, spreken, esthetiek, retentie en pijn. Dit discriminerend effect bleek veel beter voor de Liverpool Oral Rehabilitation Questionnaire (LORQ). Tot dan toe was er geen gevalideerde Nederlandse versie van de LORQ beschikbaar. Zodoende was het doel van **hoofdstuk 3** om de LORQv3 te vertalen in het Nederlands en aan te passen aan de Nederlandstalige situatie. Tevens wilden we de interne consistentie, betrouwbaarheid en validiteit van de resulterende LORQv3-NL beoordelen.

De originele Engelstalige LORQv3 werd naar het Nederlands vertaald volgens de methode vertalen-en-terugvertalen. De interne consistentie van de LORQv3-NL werd getest bij 158 patiënten van de opleiding tandheelkunde van het Radboudumc, het Centrum voor Bijzondere Tandheelkunde van het Radboudumc en Maastricht UMC+ en in algemene tandartspraktijken. De test-hertest betrouwbaarheid werd bij 34 van deze 158 patiënten uitgevoerd. Voor de convergente validiteit werd de correlatie tussen de LORQv3-NL en de OHIP-NL14 beoordeeld bij 17 van de 158 patiënten. De interne consistentie (Cronbach's $\alpha = 0.89$ voor items 1-17) en de test-hertest betrouwbaarheid (gewogen kappa waarden van 0,401 tot 0,830 voor items 1-17), en convergente validiteit ($R^2 = 0,642$) waren bevredigend. Met de LORQv3-NL bleken we over een goed instrument te beschikken voor het uitvragen van de tevredenheid over en ervaren pasvorm van de gebitsprothese.

Eén van de meest uitdagende prothetische behandelingen is het rehabiliteren van een patiënt waarbij, een deel van, de bovenkaak (maxilla) verloren is gegaan als gevolg van het verwijderen van een tumor of door bijvoorbeeld een trauma. Als er een deel van de maxilla verloren is gegaan, is er een open verbinding tussen de mond- en neusgangen en -bijholtes, waar lucht, vocht en vaak zelfs voedsel

door kunnen lekken. Dit heeft impact op functies als spreken, eten en slikken, en daarmee ook een aanzienlijke impact op het sociale welzijn en de kwaliteit van leven. Het doel van de prothetische behandeling is dan ook om deze opening zo goed als mogelijk af te dichten en de ontbrekende tanden en kiezen weer aan te vullen. Dat wordt van oudsher gedaan met een klosprothese (obturator) waarvoor houvast gezocht wordt aan de resterende tanden en kiezen. Als geen natuurlijke tanden of kiezen meer aanwezig zijn, is het vinden van houvast voor de klosprothese dan ook moeilijker. Net als in de onderkaak, kan ook in de bovenkaak het plaatsen van implantaten worden overwogen. Of deze houvast middels implantaten ook daadwerkelijk voor een functionele verbetering zorgt en leidt tot een grotere kwaliteit van leven, onderzochten we in **hoofdstuk 4**.

Bij de eerste cross-sectionele studie (**hoofdstuk 4.1**) vergeleken we de kauwprestaties en de mondgezondheid gerelateerde kwaliteit van leven van tandeloze patiënten met klosprotheses al dan niet op implantaten. Hiervoor werden bij 19 tandeloze patiënten bij wie (een deel van) de maxilla verloren was gegaan en bij wie het vervaardigen van de klosprothese was voltooid, de kauwprestaties objectief gemeten en werden er 3 vragenlijsten afgenomen. De kauwprestaties werden gemeten met de kleurenmengtest en de vragenlijsten waren: (1) de Oral Health Impact Profile voor tandeloze mensen (OHIP-EDENT), (2) de Obturator Functie Schaal (OFS) en (3) de LORQv3-NL. De negen patiënten met een klosprothese op implantaten hadden een significant betere kauw- en mondfunctie, rapporteerden minder kauwproblemen en hadden minder ongemak tijdens het eten dan de tien patiënten met een klosprothese zonder implantaten.

Aanvullend werd een tweede cross-sectionele studie (**hoofdstuk 4.2**) uitgevoerd in samenwerking met het UMC Utrecht en de Universiteit van Alberta, Edmonton, Canada. Hierbij werden de kauwprestaties en het door de patiënten gerapporteerde eetvermogen van de negen patiënten met klosprotheses op implantaten (Maastricht) vergeleken met 11 patiënten bij wie het maxilladefect chirurgisch was gereconstrueerd (Edmonton). Ook hierbij werd de kauwprestatie gemeten met de kleurenmengtest. De mondgezondheid gerelateerde kwaliteit van leven werd gemeten met verkorte versies van de OHIP vragenlijst. Hierbij werd aangetoond dat de patiënten met de chirurgisch gereconstrueerde bovenkaak en patiënten met de klosprothese op implantaten vergelijkbaar presteerden met de kleurenmengtest. Ook bij de zeven mondgezondheid gerelateerde kwaliteit van leven vragen werden geen verschillen in kauwvermogen tussen deze twee groepen gevonden.

Hieruit kunnen we dan ook concluderen dat het verbeteren van de houvast van de klosprothese door het plaatsen van implantaten nadat (een deel van) de maxilla verloren is gegaan, de mondfunctie, het kauwvermogen en het eetcomfort verbetert. Bovendien kunnen we met de nodige voorzichtigheid vaststellen dat de resultaten van deze studie eerdere resultaten lijken te bevestigen dat de klosprothese op implantaten een goed alternatief is voor de chirurgische reconstructie voor alle Klasse II maxillaire defecten volgens de klassering van Brown. Met beide technieken wordt de kauwprestatie voldoende hersteld, waarbij zorgvuldige planning zeer wenselijk is.

Het laatste deel van dit proefschrift richt zich op het verwijderen van tanden en kiezen in de voorbereidingsfase van een bestralingsbehandeling. Patiënten met hoofd-halskanker die in aanmerking komen voor een bestraling, werden voorafgaand gezien door een tandheelkundig team voor een uitgebreid mondonderzoek. Tanden en kiezen met een matige prognose die tijdens en na de bestraling een risico vormen voor het ontstaan van osteoradionecrose (ORN) werden verwijderd. ORN, ofwel een bestralingsgeïnduceerde osteomyelitis, is een ernstige en late complicatie van de bestraling, die wordt gekarakteriseerd door verzwakt blootliggend bestraald bot dat niet is geheeld na een periode van drie maanden zonder de aanwezigheid van kanker. ORN kan leiden tot onder meer pathologische fracturen, vorming van intra- of extra-orale fistels en infectie, en heeft veelal uitgebreide chirurgische behandelingen nodig. Deze behandelingen zijn risicovol, complex, kunnen tot nieuwe bijwerkingen leiden en hebben een negatieve impact op de kwaliteit van leven.

Het beschikbare bewijs over de effectiviteit van het verwijderen van tanden en kiezen voor de bestraling om ORN te voorkomen is beperkt. Tegelijkertijd resulteert het verwijderen van tanden en kiezen in een verminderd aantal functionele eenheden en belemmert dit zowel het kauwen als het slikken. Om de extractiewonden voldoende tijd te geven (minstens 10 tot 14 dagen) om te genezen voordat met de bestraling wordt begonnen, worden beslissingen genomen op basis van de verwachte stralingsdosis. Echter, voor een deel van de getrokken tanden kan na voltooiing van de bestraling blijken dat de extractie achteraf (nog) niet nodig was, omdat de gegeven dosis lager was dan de dosis die verwacht werd.

In **hoofdstuk 5** hebben we gekeken naar het aantal overtollig getrokken tanden en welke patiënt- of tumorkarakteristieken hiermee geassocieerd waren. Hiervoor werden 358 patiënten die tussen 2015 en 2019 waren bestraald

voor hoofd-halskanker opgenomen in deze cross-sectionele studie. Voor elke getrokken tand werd achteraf de stralingsdosis berekend. Overeenkomstig met ons landelijke protocol, werd het afkappunt voor terechte extractie vastgesteld op ≥40Gy. Omdat deze richtlijn niet beschrijft of dit over de gemiddelde of maximale dosis gaat, hebben wij naar beide waarden apart gekeken. In totaal werden bij deze 358 patiënten 1759 tanden verwijderd. Van deze 1759 tanden bleken er 1274 (74%) overbodig te zijn verwijderd, gebaseerd op de gemiddelde bestralingsdosis van <40Gy. Voor de maximale bestralingsdosis van <40Gy, bleken 1080 tanden (61%) overbodig te zijn verwijderd. Tumorlocatie en mate van uitzaaiing in de halsklieren kwamen naar voren als de belangrijkste factoren in de multivariabele regressieanalyse.

De impact van tandverlies op gewichtsverlies en afhankelijkheid van sondevoeding tijdens een bestralingsbehandeling gecombineerd met chemotherapie (CRT) of biotherapie (BRT) was niet bekend. In **hoofdstuk 6** onderzochten we retrospectief het effect van een onvolledig gebit, het verwijderen van tanden en kiezen voorafgaand aan CRT/BRT en het daaropvolgende verlies van functionele eenheden op: (1) gewichtsverlies tijdens de behandeling en (2) de noodzaak van sondevoeding tijdens CRT/BRT voor orofarynxkanker. Daarbij werd gewichtsverlies tijdens CRT/BRT dichotoom gescoord, waarbij gewichtsverlies >5% werd vergeleken met stabiel of verhoogd gewicht. Mogelijke factoren die geassocieerd werden met gewichtsverlies werden geïdentificeerd, waaronder patiënt-, tumor- en behandelingskenmerken. Van de 77 geïncludeerde patiënten met orofarynxkanker werd bij 40 patiënten (52%) een gewichtsverlies >5% tijdens CRT/BRT geconstateerd. Het verwijderen van tanden en kiezen voorafgaand aan CRT/BRT bleek geassocieerd met gewichtsverlies >5% tijdens de behandeling. Geen van de tandheelkundige parameters toonde enige significante associatieve waarde voor sondevoeding. Concluderend, het verwijderen van tanden en kiezen voorafgaand aan de bestraling, bedoeld om het risico op ORN te verkleinen, is een risicofactor voor gewichtsverlies tijdens CRT/BRT voor patiënten met orofaynxkanker. Dit onbedoelde gewichtsverlies, één van de klinische kenmerken van cachexie, heeft een negatief effect op de behandeling gerelateerde toxiciteit en oncologische uitkomst. Het is dan ook van het grootste belang om gewichtsverlies tijdens de behandeling van kanker te voorkomen.

CHAPTER 9

IMPACT PARAGRAPH

Impact

The scientific knowledge in the development, diagnosis and treatment of oropharyngeal squamous cell carcinoma has expanded significantly over the last 15 years. New insights into the importance and role of the immune system in carcinogenesis, the response of the immune system to cancer, and aspects of the growth and recurrence behavior of malignant tumors of the oral cavity have led to new therapeutic approaches on a molecular basis. In the near future, imaging will also keep up with biological elements in tumor visualization. Our knowledge is growing, but still surgical resection of the tumor and appropriate reconstructive measures remain the first choice of treatment.

The patient population with HNC is changing. First, the patient population developing HNC is changing, with traditional risk factors such as tobacco and alcohol use taking a back seat and a greater proportion of HNC being caused by human papillomavirus (HPV), especially in young people. At the same time, overall life expectancy is increasing, so there is also a group of patients who do not develop HNC until they are older, which in turn again is related to HPV infections. Second, care in the field of HNC is changing. Known reconstruction methods and radiation techniques are evolving and being refined. In dentistry, prophylaxis efforts at all levels have greatly improved oral health over the past 50 years. As a result, a growing number of patients still have most of their own teeth when diagnosed with HNC.

Patients who have recovered from HNC regularly cite teeth and dental health as a major concern when asked about the side effects of treatment. These side effects greatly impact quality of life, which has become an essential part of the treatment goal for HNC treatment. In order to adequately inform the patient of all options prior to treatment, it is important to critically review existing treatment options in addition to developing new treatments. In this work, we addressed the following two fundamental questions: a) we evaluated masticatory function and oral health-related quality of life (OHRQoL) after prosthodontic rehabilitation of edentulous patients with HNC, and b) we evaluated the accuracy and potential consequences of tooth removal prior to radiation therapy (RT).

Our results showed that implant-retained prostheses in both jaws improve masticatory function and significantly increase patient satisfaction over a long period of time. In particular, we studied a group of edentulous patients with maxillary defects who had been rehabilitated with obturator prostheses. In half of

this group, the prostheses were implant-retained, resulting in significantly better masticatory performance. The statistical power calculation of this study showed the strength of our results. We would therefore strongly recommend that any edentulous patient with a maxillary defect who is rehabilitated with an obturator prosthesis consider implant placement. This recommendation is opposed to surgical reconstruction of maxillary defects as well. Surgical reconstruction of maxillary defects is morbidity prone, costs time, resources and leads to masticatory functional rehabilitation much later than the recommendation we make.

Chewing is the prerequisite for being able to swallow and digest adequately. Future research should not be limited to chewing. The inclusion of other functions, such as swallowing and speech, as well as the maintenance of healthy nutrition through peroral food intake should be the focus of masticatory functional rehabilitation. The combination of objective testing methods supplemented by subjective research through questionnaires or interviews will provide a more complete picture.

Questionnaires should be available and validated in different languages to facilitate subjective multinational studies. By translating the Liverpool Oral Rehabilitation Questionnaire Version 3 (LORQv3) into Dutch and adapting it to Dutch conditions, we made this questionnaire available to the Dutch population. This questionnaire was developed to provide a more sophisticated measurement of the impact of prosthetic treatment on the quality of life of patients with HNC. Together with the validated Turkish and German versions and the original English version, international research with the same questionnaire on the effects of prosthetic care is now possible.

Reducing tooth extractions prior to HNC-induced RT results in improved quality of life. With 61% (based on maximum dose) to 74% (based on mean dose) of teeth removed at sites that ultimately received a dose of <40Gy, we limited the chewing ability of the 358 patients more than absolutely necessary. We provided tools for initial de-escalation steps in patients with tumors in the head and neck region. However, further research is needed to de-escalate current guidelines based on valid data without increasing other risks to patients. Future research should preferably be directed to the threshold RT dose for dental extractions prior to RT to prevent ORN to gain evidence-based data.

APPENDIX

LIST OF PUBLICATIONS

List of publications

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APPENDIX

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APPENDIX

CURRICULUM VITAE

Curriculum Vitae

Doke Johanna Maria Buurman was born on March 24, 1977, in Gendt, The Netherlands. She is married and has two sons. In 1995, she completed her education at Canisiuscollege - Mater Dei in Nijmegen, graduating from Atheneum. That same year, she enrolled in dental school at KU Leuven, but later transferred to KU Nijmegen in 1996. In 2000, she completed an internship at the University of Stellenbosch in South Africa and obtained her Dentist degree on February 21, 2002.

From 2002 to 2009, Doke worked part-time as a general practitioner in various dental practices. In September 2002, she joined the Center of Special Dental Care at Radboudumc in Nijmegen, where she pursued a part-time differentiation in maxillofacial prosthodontics. In 2008, she was officially recognized as a dentist-maxillofacial prosthodontist by the Nederlandse Vereniging voor Gnathologie and Prosthetische Tandheelkunde (NVGPT).

In 2009, Doke commenced her work at the Cranio-Maxillofacial Surgery department under the supervision of Prof. Dr. Dr. P.A.W.H. Kessler at Maastricht University Medical Center+ (MUMC+). During this time, she was entrusted with the responsibility to carry forward and enhance the Center for Special Dentistry established by the esteemed Dr. Henk Verdonck. Furthermore, she seized the opportunity to immerse herself in scientific research, which ultimately culminated in the successful completion of her PhD research. Doke presented her research at several national and international conferences.