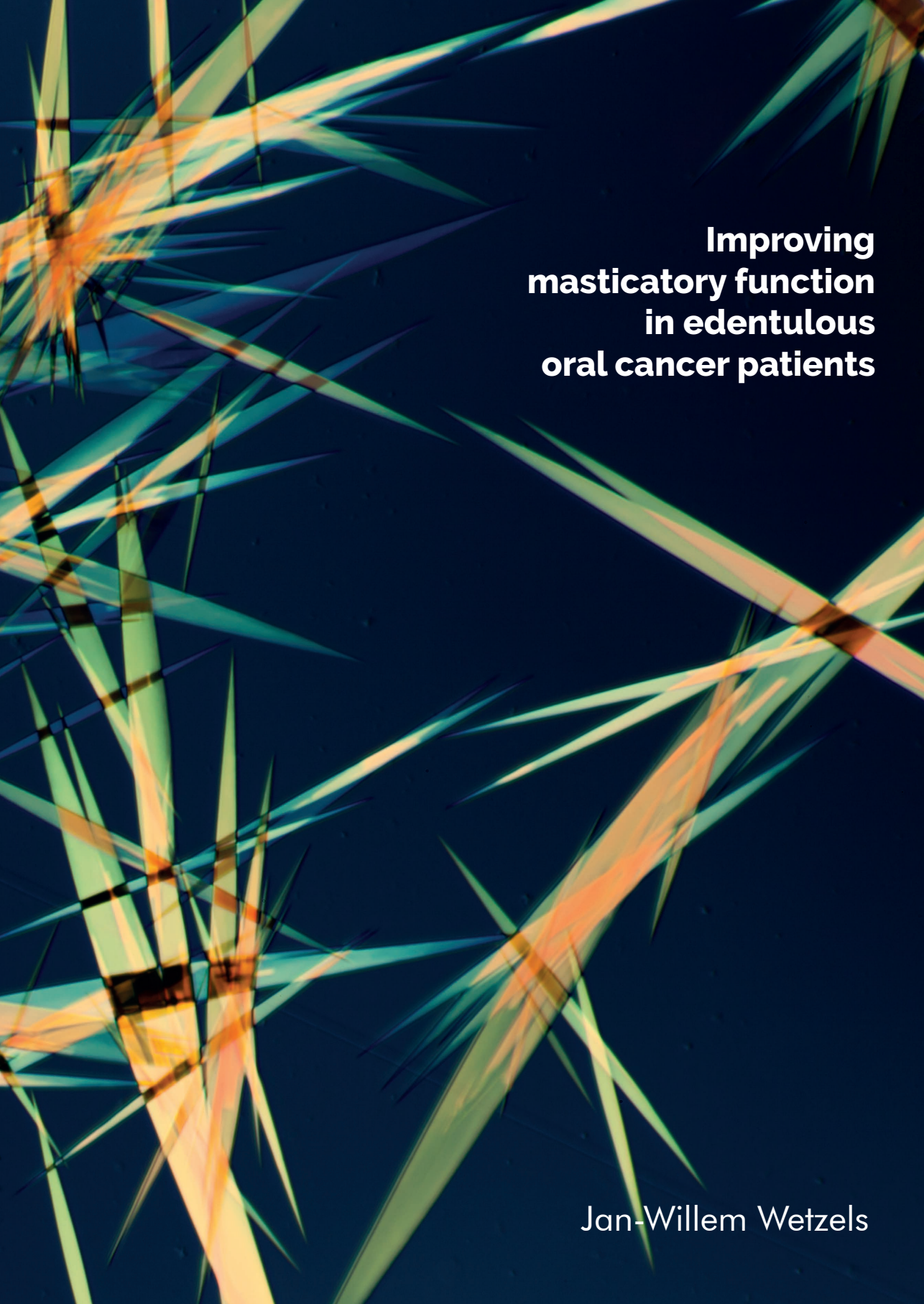

Improving masticatory function in edentulous oral cancer patients

Jan-Willem Wetzels

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ISBN: 9789464191127

Cover: Linden Gledhill, food coloring under a microscope, lindengledhill.com
Artwork from the album ‘Immunity’ by Jon Hopkins

Design: Eduard Boxem, persoonlijkproefschrift.nl

Printing: Gildeprint Enschede, gildeprint.nl

Improving masticatory function in edentulous oral cancer patients

Proefschrift

ter verkrijging van de graad van doctor

aan de Radboud Universiteit Nijmegen

op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,

volgens besluit van het college van decanen

in het openbaar te verdedigen op vrijdag 19 februari 2021

om 14.30 uur precies

door

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geboren op 26 mei 1986

te Roermond

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Paranimfen:

Mattijs de Waard

Rene van den Bosch

Improving masticatory function in edentulous oral cancer patients

Doctoral Thesis

to obtain the degree of doctor

from Radboud University Nijmegen

on the authority of the Rector Magnificus prof. dr. J.H.J.M. van Krieken,

according to the decision of the Council of Deans

to be defended in public on Friday, February 19, 2021

at 14.30 hours

by

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Contents

CHAPTER 1

General Introduction

Oral cancer

Oral cancer is a serious problem worldwide. In 2018, an estimated 355.000 patients were newly diagnosed globally, constituting 2.0% of all new patients with cancer[1]. The incidence of oral cancer is highest in South Central Asia, followed by Europe and Northern America. The most common subtype of oral cancer is the oral squamous cell carcinoma (OSCC) (more than 90%)[2,3]. The global distribution between men and women is roughly 2 to 1, which is mainly attributed to the level of tobacco and alcohol consumption[4]. Smoking and alcohol use are the main risk factors for OSCC, and are estimated to be responsible for 75% of all cases[5]. Toxins from smoking and alcohol directly, or indirectly, activate oncogenes or inactivate tumor suppressor genes[6]. The accumulation of multiple genetic mutations, combined with genetic predisposition, ultimately leads to the formation of OSCC[7].

Smokers have a 2 to 5 times increased risk of developing OSCC compared to non-smokers, depending on the number of years of smoking and the number of cigarettes per day[8-10]. Although light alcohol consumption (1 unit per day) does not seem to increase the risk of OSCC[11,12], this risk increases with every extra unit of alcohol that is consumed. An average of 4 units of alcohol equals the effect of 20 cigarettes per day[8], and more alcohol consumption can multiply the risk of OSCC up to 9 times[13]. Daily smoking and drinking alcohol often coexist, and the combination of both factors leads to an exponential risk of OSCC[8,14]. When an average of 6 drinks and 10 cigarettes are consumed daily over many years, the chance of developing OSCC is multiplied by a factor 35[15].

Other environmental factors that are associated with OSCC include betel nut chewing, oral tobacco use, chronic inflammation, viral infection and immune deficiency. The chewing of betel nut quid is common practice in South Central Asia, and increases the risk of OSCC 3 to 8 times[16-19]. Infection with human papillomavirus (HPV), mainly with high-risk HPV type 16, is associated with the recent increasing incidence in oropharyngeal cancer. HPV infection also seems to be a risk for OSCC, since there has been a rise in the incidence of HPV-positive OSCCs[5,20]. However, this association appears to be limited, since there is greater variability in the type of HPV seen in oral cancer[4].

In the Netherlands, 916 patients were diagnosed with oral cancer in 2018[21]. The incidence has been rising steadily by around 1% per year since 1990, and more prominently in women; possibly due to increased alcohol and tobacco consumption in this group[2,22]. Therefore, women currently account for 47% of new oral cancer patients in the

Netherlands. However, in other Western countries the average incidence of oral cancer appears to be declining, which is mainly attributed to decreased alcohol and tobacco use[23-26].

Most patients are diagnosed between 50 and 80 years of age (76%), with a peak between 60 and 70 years[21]. Unfortunately, an increase in the occurrence of oral cancer in young patients has been observed in Western countries in the past years[27], many of whom never smoked or consumed alcohol[28]. The predominant location for oral cancer is the tongue (40%), followed by the floor of the mouth (28%), buccal mucosa (16%), lower alveolar process (10%), upper alveolar process (4%) and hard palate (2%)[22]. The current 5-year survival for oral cancer is 62% in the Netherlands, and has regrettably not improved in the last decade[2,22].

Treatment

Upon the diagnosis of oral cancer, the patient undergoes extensive clinical and radiological evaluation. In addition, biopsies are taken from cervical lymph nodes when metastasis is suspected. The tumor is staged according to the TNM classification system (Tumor size, lymph Node metastasis, distant Metastasis)[29]. Oral cancer is classified as stage I and II (early) when the tumor is up to 2 cm (T1) or 4 cm (T2) in size, the depth of invasion is less than 1 cm, and no metastasis is found. Stage III and IV (locoregionally advanced) oral cancer involves tumors that are larger than 4 cm or have a depth of more than 1 cm, or when metastasis is present.

For oral cancer, the current curative treatment of choice is surgery, followed by (chemo) radiotherapy on indication[30]. The tumor is resected with a margin of at least 1 cm[31,32]. To achieve this margin, often large parts of the tongue, lower jaw, upper jaw, cheek or lips have to be removed. When the tumor is adjacent to, or involves the lower jaw, a marginal (rim) or segmental resection has to be performed[33]. A marginal resection is preferred, because this way much of the strength and function of the lower jaw is preserved[34,35]. For tumors in the upper jaw, resection often leads to an opening between the oral cavity and the maxillary sinus or nasal cavity[36]. In general, the tumor can be removed with a transoral approach, however, sometimes a transcervical or a lip-splitting technique is necessary.

The defect after removal of the tumor is generally reconstructed during the same operation. Small defects can be closed with locally available tissue, with a skin graft or be

left open to granulate. Large defects may require reconstruction with a free vascularized flap from outside the mouth; commonly used flaps are the radial forearm, fibula and anterolateral thigh flaps[37,38]. When a segment has been removed from the lower jaw, reconstruction with a fibula flap is preferred, since it shows better functionality and long-term success than reconstruction with solely a titanium plate[39,40]. The scapula or iliac flap are also used for reconstruction of the mandible[41,42]. Defects in the upper jaw can be closed with a free vascularized flap or with a removable obturator prosthesis; the latter has the advantage that it enables a better inspection of the surgical area for tumor recurrences.

When a metastasis in a cervical lymph node is present, the metastasis and surrounding lymph nodes are removed in a so-called selective neck dissection. When no metastasis is found during pretreatment evaluation, but the risk of undiscovered (occult) metastasis is increased (N0 patients in stage III and IV disease), a selective neck dissection is also performed. For stage I and II oral cancer, the sentinel-node biopsy has been recently introduced as an additional diagnostic tool. By removing and analyzing the first draining lymph node, or group of nodes, the accuracy of tumor staging is increased[43-45]. Postoperative radiotherapy is administered, typically within 6 weeks after surgery, when remaining tumor or cervical metastasis is present or likely to be present. This includes patients with tumor-positive surgical margins, tumor invasion around nerves, blood vessels or advanced lymph node metastasis (N2 or N3) [30]. In patients younger than 70 years, chemotherapy or immunotherapy can be added to increase the effect of radiotherapy[46,47]. When patients cannot undergo primary curative surgery, they receive curative or palliative (chemo)radiotherapy[48]. This includes patients who are medically inoperable, or have an unresectable tumor; for instance when the base of the tongue or soft palate is involved bilaterally.

Function after treatment

Early staged tumors (T1 and T2) can generally be managed with simple surgical resection without the need for any major reconstructive effort or adjuvant therapy. Advanced cancers however often require major surgical resection, reconstructive surgery and adjuvant therapy with (chemo)radiotherapy[49]. The sequelae of these treatments may lead to significant impairment of facial appearance[50] and oral functions, including eating[51], drinking[52] and speaking[53]. Patients without remaining teeth (edentulous patients) are particularly at risk for functional problems after their oncological treatment for oral cancer,

because functioning conventional dentures are often difficult to fabricate. This concerns a large group, as it is estimated that between 54% and 92% of oral cancer patients are edentulous after curative ablative surgery[54-56].

Several factors are of influence. Ablative surgery changes the anatomy of the mouth, which often restricts the denture-bearing surface and neutral zone necessary for denture fabrication. Especially in the lower jaw, this may lead to stability and retention problems of a conventional full denture[57]. Damage to the mucosa, nerves and disorientation of muscles may result in a disturbed tactile and kinaesthetic sense, making adaptation to new dentures difficult[58]. Resection of the tongue may lead to a loss of volume, motor and sensory function[59,60]. When tongue function is impaired, problems with food transportation, denture stability, swallowing and speech can arise[61,62].

Radiotherapy forms an extra burden for edentulous oral cancer patients. One of the main complications is a dry mouth (xerostomia) caused by a permanently reduced salivary secretion. Swallowing and chewing problems may arise due to insufficient moistening of food[63]. Due to the lack of saliva, dentures have less retention and produce more friction during function. Because the mucosa is often thin and ischemic after radiotherapy[64,65], sore areas, ulcers and sequesters may arise, which often lead to complete intolerance to wearing dentures[66,67]. Taste impairment can sometimes affect the nutritional status of the patients, because of loss of appetite and altered food intake[63]. Furthermore, a reduced mouth opening (trismus) after radiotherapy can cause problems with food ingestion and with fabrication of full dentures[68].

To conclude, prosthodontic loading of the oral mucosa in edentulous oral cancer patients who have completed their oncological treatment, is often not well-tolerated or even impossible. Functioning conventional full dentures, that are worn during meals, can only be fabricated in around 50% of these patients[54,56,69]. Therefore, many patients end up without functioning dentures, or an upper denture used only for aesthetics or speech.

Implant placement

Value of Dental implants

Placing dental implants to support full dentures may improve the rehabilitation of edentulous oral cancer patients. Such endosseous implants offer specific benefits, like enlarging the retention and stability of dentures, which may lead to an increased chewing

ability. By rehabilitating patients with functioning dentures, often other functions such as clarity of speech, the ability to swallow and facial appearance also improve.

In healthy edentulous adults, installation of 2 to 4 implants in the mandible delivers more stability and retention to the lower denture. Benefits of such implant-retained overdentures have been extensively documented for this group. Mandibular implant-retained overdentures result in a significantly better masticatory function and denture satisfaction compared to conventional dentures[70-76], and should be considered as the first choice of treatment[77,78]. Furthermore, functioning implants prevent jawbone resorption and loss of bone mineral content, due to a more favorable stress distribution of the edentulous jaw[79,80].

In oral cancer patients, implant-retained overdentures also seem to result in more favorable masticatory function compared to conventional dentures[61,81,82], although comparative studies are lacking. Furthermore, most studies use only questionnaires on masticatory function and health-related quality of life, which by themselves are insufficient to discriminate between implant-retained and conventional dentures[83]. More studies using objective outcome measures, such as the ability to comminute or mix food and the maximum bite force, are needed to fully assess the effect of implants on the masticatory function of edentulous oral cancer patients.

Timing of Implant Placement

In most oncology centers, edentulous oral cancer patients first receive conventional dentures when possible after oncological treatment. When patients are dissatisfied with these dentures, implant placement is performed optionally after a disease-free survival of at least six to twelve months[84]. Postponing implant placement offers the advantage that positioning of implants is easier to plan, as the soft tissues are already healed. Another advantage, is that patients can be carefully selected depending on their oncological and medical prognosis. A drawback of this approach, however, is that many patients are unwilling to undergo further implant surgery, thus accepting no or less-than-optimally functioning dentures[69]. Furthermore, when patients received postoperative radiotherapy, implant placement into highly irradiated bone might be contraindicated due to the risk for developing osteoradionecrosis of the jaw[56,85], or might require additional hyperbaric oxygen therapy; which is costly and burdensome to the patient[86].

An alternative treatment is immediate implant placement at the time of the ablative tumor surgery, followed by primary rehabilitation with implant-retained overdentures. This approach seems to lead to a larger number of patients rehabilitated with implants and functioning implant-retained overdentures, which patients receive at an earlier time[55,87]. Patients do not need an extra session to install the implants, and the implantation site has not been compromised as a result of radiotherapy; thereby bypassing the need for preventive antibiotics and hyperbaric oxygen therapy. Implant survival seems to be high and similar to postponed placement, and the negative effect of postoperative radiotherapy is reported to be equal for both protocols[88-91], although studies on immediate placement are sparse and often report pooled data[84]. A disadvantage, is that many implants will not be loaded due to death of the patient, or may have to be removed in case of tumor recurrence; the incidences of which are highest during the first postoperative year. Furthermore, the risk of improper implant positioning is higher when implants are placed during ablative surgery[92]. Especially for tumors near the interforaminal region, the healing pattern of the soft tissue is difficult to predict, and the underlying implants may not be suitable for prosthodontic rehabilitation[87]. It has also been suggested that immediate implant placement possibly interferes with postoperative chemotherapy or radiotherapy, and that backscattering of radiation may lead to osteoradionecrosis due to a higher radiation dose near the implants[93,94]; but no clinical evidence has been provided.

In conclusion, currently two protocols for the prosthodontic rehabilitation of edentulous oral cancer patients with implants exist: immediate implant placement during ablative surgery and optional (postponed) implant placement at a later stage. Differences regarding the masticatory function, the number of patients successfully rehabilitated with dentures, implant survival, costs and complications between both protocols are unclear. Furthermore, there is a need for objective outcome measures in determining the masticatory function of edentulous oral cancer patients.

Study objectives

The main objective of this thesis is to improve the masticatory function of edentulous oral cancer patients. To achieve this objective, the effect of implant-retained overdentures on the masticatory function is assessed. Secondly, the optimal timing of implant placement is studied: immediate implant placement during ablative surgery or postponed implant placement at a later stage.

To assess masticatory function accurately, objective outcome measures are necessary. These measures were lacking in previous studies, which mainly used questionnaires on masticatory function. Possible influencing factors on masticatory function, such as the maximum mouth opening, also have to be taken into account. Therefore, the following questions have to be answered in this thesis:

1. What is the masticatory function of edentulous oral cancer patients who are rehabilitated with implant-retained overdentures, with conventional dentures and of those without functioning dentures?
2. Which factors influence the masticatory function before and after oral oncological treatment?
3. Which factors influence the maximum mouth opening, and which risk factors are responsible for developing a reduced mouth opening (trismus)?
4. What are the clinical outcomes and costs of immediate implant placement during ablative surgery versus optional (postponed) implant placement?
5. What are the long-term results of immediate implant placement?

Thesis outline

In **chapter 2**, the masticatory function of edentulous oral cancer patients was assessed. Patients with conventional dentures, implant-retained overdentures and patients without functioning dentures were compared prospectively at different time points before and up to five years after oncological treatment. For a full comparison, a group of healthy control subjects with either conventional or implant-retained dentures was also recruited. Objective outcome measures of masticatory function included masticatory performance and bite force. Masticatory performance was measured with a mixing ability test, using a two-colored wax tablet[95,96]. Bite force was calculated as the maximum amount of force a patient could exert between the upper and lower jaw[97]. As subjective outcome measures, masticatory ability and denture function were evaluated with a questionnaire.

Possible factors of influence on the masticatory function of oral cancer patients were investigated in **chapter 3.** Prospective measurements were performed before and up to five years after oncological treatment, and were compared with healthy subjects. Objective measures included masticatory performance, bite force and mouth opening.

Dental status, including the number of occlusal units for patients with a functioning natural dentition, was recorded at every assessment and included in further analysis. Demographics, tumor details and details regarding the oncological treatment were also incorporated.

For a full comprehension, the course of mouth opening was investigated separately (**chapter 4**). Maximum mouth opening was measured with an extra-oral method instead of interincisal measurements, because the dental status frequently changed during the oncological treatment and follow-up period. Factors of influence on mouth opening were studied prospectively up to one year after oral oncological treatment, and mouth opening in oral cancer patients was compared with healthy subjects. Furthermore, risk factors for the occurrence of trismus (defined as maximum mouth opening < 35 mm) were identified.

Two protocols for the prosthodontic rehabilitation of edentulous oral cancer patients were compared in **chapter 5**: immediate implant placement during ablative surgery and optional (postponed) implant placement at a later stage. In the first protocol, implants were placed immediately during ablative surgery, and patients were primarily rehabilitated with implant-retained overdentures. In the second protocol, patients first received conventional dentures after oncological treatment, followed by optional implant placement when these dentures were not satisfying. The number of patients rehabilitated with functioning dentures (conventional or implant-retained) as well as the speed of prosthodontic rehabilitation were assessed up to five years after tumor surgery. Implant outcome measures (including implant loading, implant loss, implant failure and improper positioning) were compared between protocols. Possible complications, including delaying of postoperative radiotherapy and the occurrence of osteoradionecrosis, were also assessed. Lastly, the costs of both protocols were calculated.

The long-term results of immediate implant placement were evaluated in **chapter 6**. Factors that influence successful prosthodontic rehabilitation and implant outcomes were studied with a follow-up period ranging from five to seventeen years. Survival analysis was performed to measure the durability of the implants and implant-retained overdentures, and possible complications were analyzed.

Conclusions drawn from the aforementioned studies, their clinical impact and broad future perspectives are discussed in **chapter 7**.

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CHAPTER 2

Functional benefits of implants placed during ablative surgery: a 5-year prospective study on the prosthodontic rehabilitation of 56 edentulous oral cancer patients

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Head & Neck 2016; 38: E2103-2011

ABSTRACT

Background: The timing of placement as well as the functional benefit of interforaminal implants in edentulous patients treated for oral cancer is unclear.

Methods: Fifty-six patients were recruited at two hospitals. In one hospital, interforaminal implants were placed during ablative surgery. The other hospital used conventional prosthodontics with optional placement of implants post-surgery (postponed-placement). Masticatory performance, maximum bite force and subjective masticatory function were assessed before and 6 months, 1 year, and 5 years after surgery.

Results: Implant-retained overdentures (IODs) demonstrated the highest bite force and the least problems with solid food and food choice. Masticatory performance was equal for IODs and conventional dentures. After 5 years, IODs from patients in the during-ablative-surgery protocol tend to have higher bite force and masticatory performance than those from patients in the postponed-placement protocol.

Conclusion: IODs produce the highest overall masticatory function. Implant placement during ablative surgery seems to be functionally beneficial.

INTRODUCTION

Edentulous oral cancer patients, who account for 54% – 92% of oral cancer patients after curative ablative surgery[1-3], pose a prosthodontic challenge. Surgical resection changes the anatomy of the mouth and frequently affects the neutral zone, restricting the area of support for full dentures[4]. Resection of the jawbone may cause problems with denture retention, especially the mandible, where a rim or segment resection only allows for a partial denture that has little contribution to masticatory performance[5]. Furthermore, postoperative radiotherapy causes xerostomia and atrophy of mucous membranes[6,7], which may lead to complete intolerance of mucosa-bearing dentures[8]. Patients receiving radiotherapy report more complications after denture placement, such as sore areas, ulcers and sequesters[9]. Patients often experience a restricted mouth opening after oncological therapy, making any dental procedure difficult[10,11]. Due to these limitations, many edentulous oral cancer patients end up with less-than-optimally functioning dentures, with an upper denture for aesthetic purposes only, or without both dentures[3,8].

A common solution to increase the retention and stability of full dentures, is the placement of dental implants followed by the fabrication of implant-retained overdentures (IODs). In healthy edentulous adults, the functional benefit of IODs, especially in the mandible, has been well documented. Mandibular IODs offer better masticatory function and more denture satisfaction, in particular for those patients who had retention problems with their previous mandibular conventional denture (CD)[12-20]. Furthermore, bite force tends to be higher in healthy patients with IODs[21-23]. In addition, functioning implants may prevent further resorption of the jawbone[24-26].

The role of dental implants and the timing of implant placement in edentulous oral cancer patients is still subject of debate. Current practice in most oncology centers, is optional (postponed) implant placement in patients who are dissatisfied with their CDs, after a disease-free survival of at least 1 year[27]. However, many patients refrain from further implant surgery or hyperbaric oxygen therapy, thus accepting their less-than-optimally functioning dentures[28]. Another strategy is placement of implants during ablative surgery, which provides significantly more edentulous patients with implants. The fact that these patients receive functioning overdentures nearly 2 years earlier than those with postponed implants is advantageous. However, 17% of the implants placed during ablative surgery will never be loaded[1,29]. Overall, IODs seem to result in the most favorable masticatory

outcome compared to CDs in oral cancer patients[30,31]. Since most studies on functionality so far have focused on subjective measurements of masticatory function and health-related quality of life[27], the suggested benefits for objective masticatory function and bite force remain to be seen. Furthermore, functional differences between implant placement during ablative surgery and postponed placement have yet to be addressed.

The aim of this two-center study was to compare the rehabilitation of edentulous oral cancer patients with mandibular implant-retained dentures, conventional dentures, and no functioning dentures with regard to objective and subjective masticatory function. Functional differences between implant placement during ablative surgery and postponed placement were also investigated.

MATERIAL AND METHODS

Subjects

This study was conducted at the UMC Utrecht (UMCU) and Radboud University Medical Center (Radboudumc), with patients who were treated for a primary malignant tumor of the oral cavity in the period between 2007 and 2009. Patients were included if they received ablative tumor surgery with curative intent, were edentulous prior to surgery, or became edentulous during surgery. Exclusion criteria were the presence of dental implants before surgery, the presence of upper jaw implants inserted during ablative surgery, a previous and/or synchronous malignancy, cognitive impairment, and the inability to understand or read Dutch. Written informed consent for participation in the study was obtained from all patients. The experimental protocol was authorized by the Ethics Committees of both the UMCU and Radboudumc. Based on the histological findings of the resected specimens, patients received postoperative radiotherapy within 6 weeks after surgery, according to the guidelines of the Dutch Head and Neck Society, with a total dose between 56 and 66 Gy. Forty age-matched healthy individuals were recruited, of whom 20 had functioning CDs, and 20 had functioning full dentures with a mandibular IOD. Details of this group have been previously published[32]. Sex, tumor location, tumor size (T of TNM, 6th edition)[33], surgical reconstruction, implant and prosthodontic details were obtained from the medical records. Age, tobacco use, and alcohol consumption were recorded at the pretreatment session. A distinction was made between patients who smoked daily and those who either did not smoke or smoked infrequently. With respect to alcohol consumption, a distinction was made between patients who consumed an

average of more than one alcoholic beverage per day and those who consumed less than this amount of alcohol per day.

Prosthodontic rehabilitation

All patients with a remaining natural dentition were screened by the hospital dental services in both medical centers. Teeth lost due to extensive dental caries, periodontitis, or periapical periodontitis were removed during ablative surgery. Patients with few remaining teeth, in whom prosthodontic problems could be expected, were made edentulous during the ablative surgery. Regarding the rehabilitation of the edentulous patients, the Radboudumc used the during-ablative-surgery (DAS) protocol in which implants were placed during ablative surgery when feasible. The UMCU chose to use the postponed-placement (P) protocol in which implants were placed at a later stage; that is at least 1 year after the ablative surgery.

DAS protocol

All patients assigned to the DAS protocol who were edentulous or who became edentulous at the time of ablative surgery received two or three two-phase implants (Brånemark® Mk III [Nobel Biocare AB, Göteborg, Sweden]) in the interforaminal area, providing that there was sufficient bone height and quality (i.e. no implants were placed in microvascularized or homologous bone grafts), no mucosal problems were present, and the oral hygiene and compliance of the patient was expected to be sufficient[34]. When necessary, the alveolar ridge was lowered, additional bone was augmented from the iliac crest or retromolar region, and the mucosa was corrected. Abutments were placed after a minimum healing period of 3 months. Irradiated patients received the abutments at least 6 months after radiotherapy. Full dentures with a mandibular IOD were fabricated by the maxillofacial prosthodontist, with the use of a bar attachment or Locator® abutments [Zest Anchors LLC, Escondido, CA, USA]; depending on the anatomical conditions and prosthodontic needs.

P protocol

All edentulous patients assigned to the P protocol were seen postoperatively by the maxillofacial prosthodontist, and CDs were fabricated when possible. Patients who were not satisfied with their dentures, or patients in whom functioning dentures could not be placed due to anatomical conditions, were eligible for placement of two or three two-phase implants (Astra® Osseospeed [Astra Tech AB, Mölndal, Sweden] or Straumann® [Institut Straumann AG, Basel, Switzerland]) in the interforaminal area,

after a disease-free period of at least 6 months. Patients who received postoperative radiotherapy underwent 20 sessions of hyperbaric oxygen before and 10 sessions after implant placement. The preimplantation surgery, abutment placement, and prosthodontic treatment were comparable to the DAS protocol.

Measurements

All patients were assessed within 4 weeks before surgery, and at 0.5, 1, and 5 years after surgery. The healthy control group was assessed once[32]. During all measurements, patients were instructed to wear their dentures only if they used them routinely to eat their meals. We distinguished 3 groups: 1, full dentures with a mandibular IOD (IODs); 2, conventional dentures (CDs); and 3, no functioning dentures (NFD). Patients who were not accustomed to wearing both upper and lower dentures during mastication were regarded as having no functioning dentures. The number of days that the current dentures were functioning was noted and used in further analysis. At the preoperative assessment, some patients had remaining natural dentition and were scored as 4, dentate.

Bite force

Maximum vertical interocclusal bite force was measured using a bite-force transducer, which consisted of one (unilateral) strain gauge mounted on a mouthpiece[35]. With the patient seated in an upright position, the strain gauge element was placed between the first molars to measure the interocclusal force. The bite force experiments consisted of clenching as hard as possible, twice on the right side of the jaw and twice on the left. The presented outcome measure is the mean of the highest bite force on the left side and the highest bite force on the right side. When patients could not perform the maximum bite force test due to trismus, we interpreted this as the worst possible score.

Masticatory performance

Masticatory performance was measured with a previously validated mixing ability test[32,36], which uses a wax tablet that consists of a layer of red and a layer of blue wax. Chewing the tablet mixes the colors, and the gradual decrease in the spread of color intensities represents the masticatory performance. This mixing ability test uses a linear scale of 0 – 30, with a score of 30 representing a perfectly mixed tablet and a score of 0 representing a non-mixed tablet. Patients were seated in an upright position and instructed to perform 20 chewing cycles on the wax tablet, which was offered at room temperature. When patients could not perform the mixing ability test due to pain, we interpreted this as the worst possible score.

Functional questions

Masticatory ability and denture function were measured at every assessment using an eight-item questionnaire (Table 1). For each question, there were four possible answers on an ordinal scale. In further analysis these answers were dichotomized; answers 1 (never) and 2 (sometimes) were labeled “unlikely” and answers 3 (often) and 4 (always) were labeled “likely” with regard to having problems in a certain functional domain.

Statistical analysis

Chi-Square Tests were used to analyze differences in patient characteristics between patients assigned to the DAS and P protocols, one-way Analysis of Variance (ANOVA) was used to analyze age differences. The Chi-Square Test was furthermore used to analyze the influence of preoperative dental status on the type of dentures that would be made. Outcome measures were analyzed at 0.5, 1, and 5 years after surgery. To analyze maximum bite force and masticatory performance, a linear mixed-effects model was constructed for both outcome measures.

Table 1. Eight questions on masticatory function and denture function

1. Have you experienced problems with your dentures?
2. Have you experienced chewing problems?
3. Have you experienced pain while chewing?
4. Have you experienced problems eating solid food (e.g. carrots, peanuts, or meat)?
5. Have you experienced problems eating soft food (e.g. cake, bread, or pasta)?
6. Have you experienced problems eating fluid food (e.g. custard or apple sauce)?
7. Has your ability to chew interfered with your social life?
8. Has your ability to chew interfered with your food choice?
Possible answers were: 1, never; 2, sometimes; 3, often; 4, always

The assessment period, use of the current dentures (in years), and postoperative radiotherapy were added as fixed effects. To account for within-patient correlations, a random patient factor was added.

To compare the DAS and P protocols, we distinguished four typical patient groups: patients assigned to the DAS protocol who received IODs (at 0.6 years after surgery); patients assigned to the P protocol who received IODs (at 2.4 years); patients assigned to the P protocol who received CDs (at 1.1 years); and patients from both cohorts who

received NFD. The aforementioned time of denture placement was obtained from a previous study[1], and imputed into the mixed-effects models to calculate a mean and standard error at each time point. To analyze possible bias, differences between the observed and the predicted values from the models at 0.5, 1, and 5 years (residuals) were obtained, and were analyzed with one-way ANOVA. Statistical differences between the four typical patient groups and the healthy control groups at 5 years after surgery were analyzed using normalized tests.

The eight functional questions (on the dichotomized scale) were analyzed with logistic regression models. The assessment period was added as main effect. The use of the current dentures (in years), and postoperative radiotherapy were also added to the models, but removed when significance was unlikely ($P > 0.100$). The within-subjects correlation between the functional questions (on the four-point ordinal scale), and bite force or masticatory performance, were calculated using multiple regression analyses[37]. Missing values were not imputed. All tests were two-sided, and differences with a P-value < 0.050 were considered to be statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

In total, 56 patients were included, of whom 23 were assigned to the DAS protocol, and 33 to the P protocol (Figure 1). All patient characteristics were equally distributed among patients assigned to both treatment protocols at the preoperative assessment (Tables 2 and 3). Dental status before surgery was not correlated with the type of dentures the patient would receive after surgery ($P = 0.199$). Of the patients with CDs, four had a mandibular overdenture on two to four natural roots at some point during the study. One complete measurement was missing due to time constraints. A total of 155 out of 1840 functional questions (8%) were missing, due to misunderstanding or misreading of parts of the questionnaire by the patients or because some questions were not applicable.

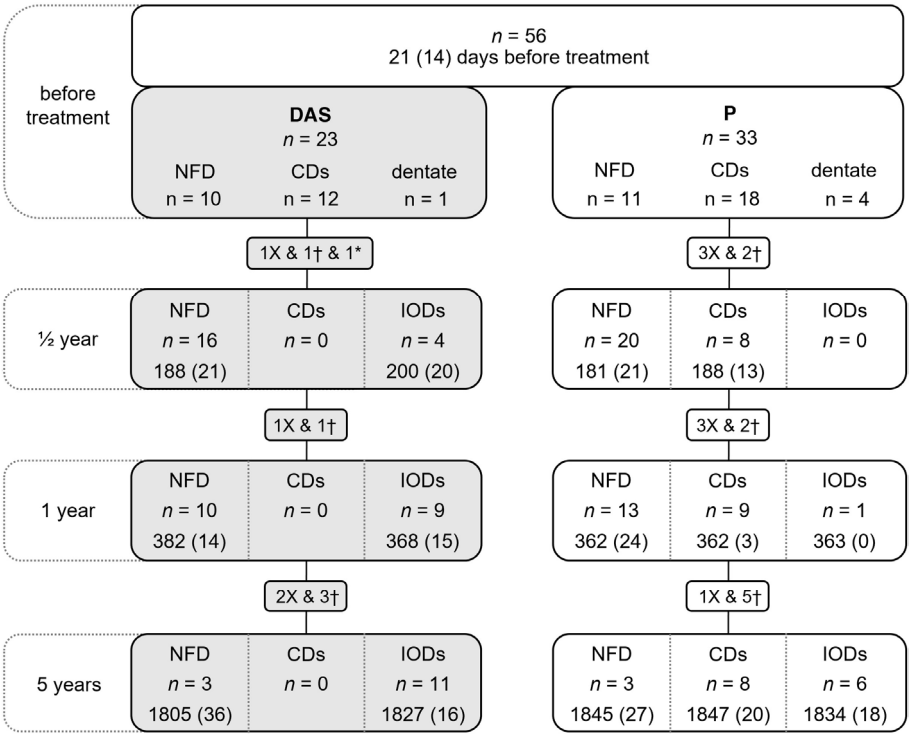

Figure 1. Flowchart showing the number of patients (*n*) measured at each assessment and the average time in days (SD) since the ablative surgery. SD, standard deviation; DAS, during-ablative-surgery protocol; P, postponed-placement protocol; NFD, no functioning dentures; CDs, conventional dentures; IODs, implant-retained overdentures; X, patient(s) stopped participating; †, patient(s) died; *, missing measurement

Table 2. Demographics and tumor details of patients in the DAS and P protocols

	DAS (*n* = 23)		P (*n* = 33)		
	n	%	*n*	%	P-value
Sex					0.425
Male	15	67	18	53	
Female	8	33	15	47	
Smoking (daily)					0.256
Yes	9	42	18	53	
No	14	58	15	47	
Alcohol use (> 1 daily)					0.903
Yes	8	38	12	34	
No	15	62	21	66	
Tumor size (pT of TNM)					0.131
T1	2	8	10	31	
T2	12	50	9	28	
T3	1	4	3	10	
T4	8	38	11	31	
Tumor location					0.236
Maxilla	2	12	8	22	
Mandible	11	46	16	50	
Tongue and/or floor of the mouth	10	42	9	28	
Preoperative dental status					0.521
NFD	10	44	11	33	
CDs	12	52	18	55	
Dentate	1	4	4	12	
Mean age, years (SD)	68.0 (11.4)		71.0 (9.8)		0.296

DAS, during-ablative-surgery protocol; P, postponed-placement protocol; NFD, no functioning dentures; CDs, conventional dentures; SD, standard deviation

Table 3. Details regarding the oncological treatment of patients in the DAS and P protocols

	DAS (*n* = 23)		P (*n* = 33)		
	n	%	*n*	%	P-value
Treatment					0.258
Surgery	7	29	15	47	
Surgery and radiotherapy	16	71	18	53	
Mandibular resection					0.321
No resection	11	48	16	49	
Rim	9	39	8	24	
Segment	3	13	9	27	
Reconstruction of soft tissue					0.614
Primary closure	10	43	16	49	
Local flap	0	0	2	6	
Split-thickness skin graft	5	22	6	18	
Vascularized flap	8	35	9	27	
Reconstruction of bone defect					0.312
No reconstruction needed	17	74	17	52	
Free vascularized bone flap	2	9	4	12	
Reconstruction plate	1	4	6	18	
Obturator prosthesis	3	13	6	18	

DAS, during-ablative-surgery protocol; P, postponed-placement protocol; NFD, no functioning dentures; CDs, conventional dentures; SD, standard deviation

Implants

In the DAS cohort, a total of 40 interforaminal implants were placed in 18 patients. In the remaining five patients from this cohort, implant placement was either not possible due to bone height or quality, or due to poor compliance. Out of 18 patients, 15 received functioning IODs at a mean time of 325 days after surgery. One patient with three implants died before their dentures could be made.

In two patients with two implants, functioning dentures could not be made because of limited mouth opening. At the 5-year assessment, 13 patients in the DAS cohort had functioning dentures and two additional patients had died. Three implants were lost (7.5%) in two separate patients, all at 19 months after placement. One patient, who did not receive postoperative radiotherapy, lost two implants due to tumor recurrence. The other patient, who received postoperative radiotherapy, lost one implant due to

peri-implantitis. Out of 40 implants, 31 became functional at some point (78%). At the 5-year assessment, 27 out of 40 implants were still functional. No patients from the DAS cohort received CDs after tumor surgery. One patient from the DAS cohort developed osteoradionecrosis of the posterior mandible, for which resection and reconstruction were required. The implants were not removed during this operation, and became functional at a later stage.

In the P cohort, nine out of 33 patients received a total of 19 interforaminal implants at an average time of 568 days after surgery. Four of these patients received postoperative radiotherapy, all of which underwent 30 sessions of hyperbaric oxygen therapy. Out of these nine patients, eight received functioning IODs at a mean time of 862 days after surgery. These overdentures were still functioning 5 years after surgery. Implant loss was 16% (3/19) 5 years after tumor surgery. One patient, who did not receive postoperative radiotherapy, lost all three implants when the infected fibula flap was removed after 12 months. In total, 16 implants (84%) became functional and were still functional 5 years after surgery. Of the patients in the P cohort, 17 out of 33 had functioning CDs (newly fabricated or still the same as before surgery), six of whom wore an obturator prosthesis. Of these 17 patients, five received interforaminal implants in combination with a mandibular IOD (one with an obturator prosthesis). The remaining 12 patients received functioning CDs at an average period of 396 days after surgery. At the 5-year assessment, nine CDs were still functioning.

Bite force

Having IODs significantly improved the maximum bite force and was the major contributor to bite force (Table 4). Conventional dentures also improved bite force, but this was not significant. The estimated bite force of the four typical patient groups from the DAS and P protocols is displayed in Figure 2. At the 5-year assessment, bite force was superior in patients from the DAS cohort who received overdentures and was significantly higher than the other 3 patient groups ($P < 0.001$). Patients from the P cohort who received IODs showed a larger bite force than patients from the same cohort who received CDs ($P = 0.043$), and patients with NFD ($P < 0.001$). The difference between patients from the P cohort who received CDs and patients with NFD was not significant ($P = 0.482$). Healthy controls with CDs did not differ significantly from patients with IODs from the DAS or P cohort or from patients with CDs at the 5-year assessment. Healthy controls with overdentures had a significantly higher bite force than all four patient groups.

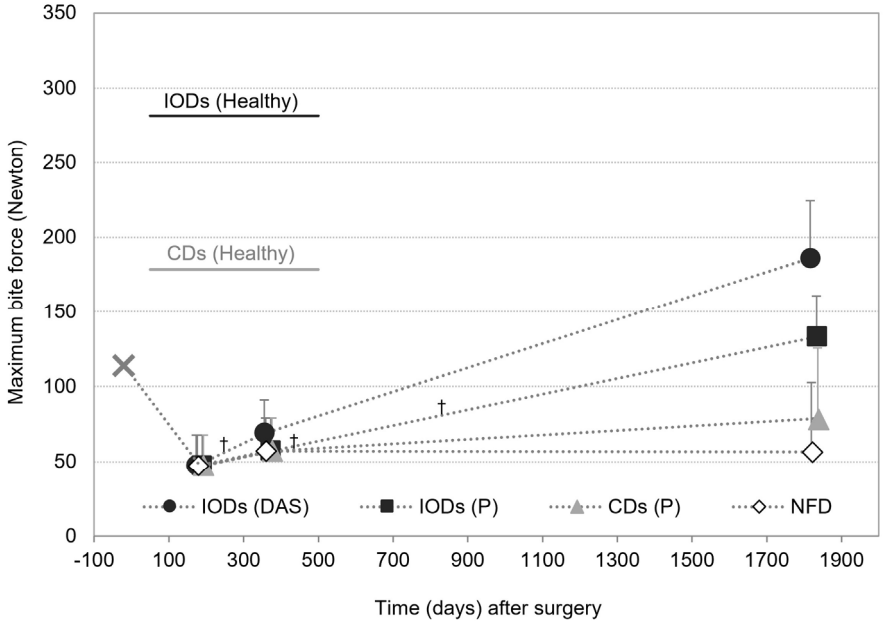

Figure 2. Estimated maximum bite force (with 95% confidence intervals) of the four typical patient groups, at 0.5-, 1-, and 5-years after tumor surgery. The symbol X represents the mean bite force of all patients at the preoperative assessment. The healthy controls were measured once. Values were calculated with a linear mixed-effects model, using the average time of denture placement (symbol †) from a previous study,[1] the type of dentures, the time since surgery, and the use of radiotherapy as fixed effects. Residuals between the observed and estimated values were small and did not differ significantly between patients and between measurements. The dashed lines are for visual aid only. DAS, during-ablative-surgery protocol; P, postponed-placement protocol; IODs, implant-retained overdentures; CDs, conventional dentures; NFD, no functioning dentures

Masticatory performance

Regarding the masticatory performance, the use of IODs had a positive effect and so did the use of CDs (Table 5). However, there was also a marked improvement in masticatory performance independent of the type of dentures (IODs, CDs, or NFD): masticatory performance improved significantly between 0.5 and 1 year in all patients and up to 5 years, but the latter was not significant.

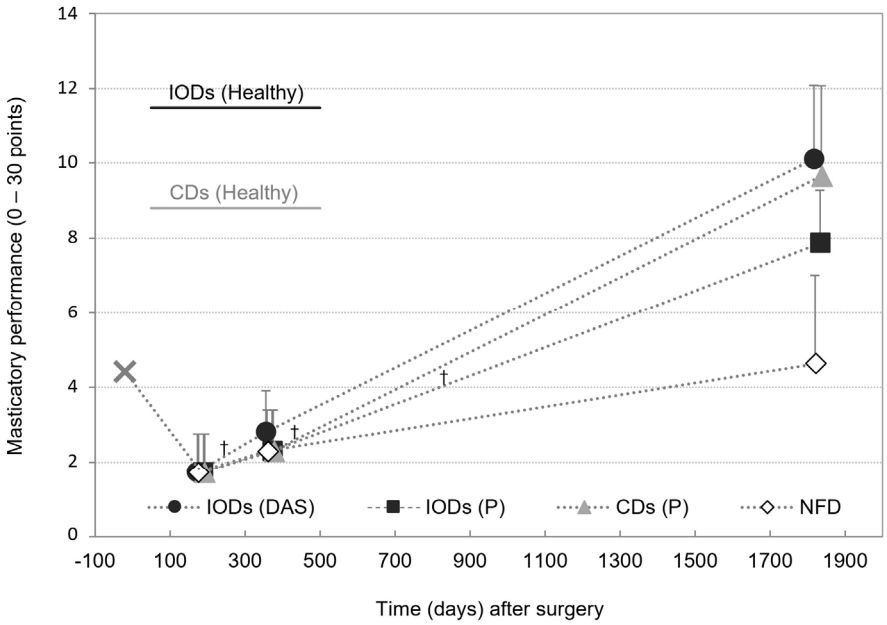

Figure 3. Estimated masticatory performance (with 95% confidence intervals) of the four typical patient groups, at 0.5-, 1-, and 5-years after tumor surgery. The symbol X represents the mean masticatory performance of all patients at the preoperative assessment. The healthy controls were measured once. Values were calculated with a linear mixed-effects model, using the average time of denture placement (symbol †) from a previous study,[1] the type of dentures, the time since surgery, and the use of radiotherapy as fixed effects. Residuals between the observed and estimated values were small and did not differ significantly between patients and between measurements. The dashed lines are for visual aid only. DAS, during-ablative-surgery protocol; P, postponed-placement protocol; IODs, implant-retained overdentures; CDs, conventional dentures; NFD, no functioning dentures

Figure 3 shows the estimated masticatory performance of four typical patient groups treated according to the DAS and P protocols. At the 5-year assessment, patients with IODs from the DAS cohort and patients with CDs had the highest masticatory performance, and did not differ significantly from both control groups.

Table 4. Mixed-effects model for bite force (in Newton)

	Estimate	SE	P-value
Dentures			
Use of CDs (per year)	5.982	8.067	0.460
Use of IODs (per year)	29.428	7.253	< 0.001
NFD	0		
Time after surgery			
0.5 years	-9.012	23.556	0.703
1 year	0.703	22.983	0.976
5 years	0		
Radiotherapy	-9.258	16.735	0.583

SE, standard error; CDs, conventional dentures; IODs, implant-retained overdentures; NFD, no functioning dentures. The estimate of the intercept is 61.711

Table 5. Mixed-effects model for masticatory performance (on a scale of 0-30)

	Estimate	SE	P-value
Dentures			
Use of CDs (per year)	1.340	0.416	0.002
Use of IODs (per year)	1.260	0.377	0.001
NFD	0		
Time after surgery			
0.5 years	-2.807	1.233	0.025
1 year	-2.259	1.206	0.064
5 years	0		
Radiotherapy	-1.202	0.764	0.124

SE, standard error; CDs, conventional dentures; IODs, implant-retained overdentures; NFD, no functioning dentures. The estimate of the intercept is 5.248

Patients with IODs from the P cohort had a worse masticatory performance than patients with IODs from the DAS cohort (P = 0.001) and the IOD control group (P = 0.001), but did not differ significantly from patients with CDs (P = 0.197) and the CD control group (P = 1.000). Patients with NFD had a significantly worse masticatory performance compared to all other patient and control groups.

Table 6. Factors of influence found for each of 8 functional questions

	Factor(s) of influence	OR	P-value
1. Denture problems	Radiotherapy	3.746	0.024
2. Chewing problems	Radiotherapy	3.190	0.054
3. Pain while chewing			
4. Problems with solid food	Use of IODs (per year)	0.494	0.016
5. Problems with soft food			
6. Problems with fluid food			
7. Problems with social life			
8. Problems with food choice	Use of IODs (per year)	0.453	0.031
	Use of CDs (per year)	0.495	0.055

OR, odds ratio; IODs, implant-retained overdentures; CDs, conventional dentures

Table 7. Correlation between bite force/masticatory performance and each of 8 functional questions

	Bite force		Masticatory performance	
	Correlation	P-value	Correlation	P-value
1. Denture problems	-0.22	0.014	-0.23	0.008
2. Chewing problems	-0.34	< 0.001	-0.30	< 0.001
3. Pain while chewing	-0.10	0.211	-0.18	0.026
4. Problems with solid food	-0.40	<0.001	-0.46	< 0.001
5. Problems with soft food	-0.23	0.003	-0.22	0.005
6. Problems with fluid food	-0.09	0.220	-0.08	0.274
7. Problems with social life	-0.20	0.010	-0.11	0.155
8. Problems with food choice	-0.37	< 0.001	-0.36	< 0.001

The correlation coefficient between bite force and masticatory performance was 0.63 ($P < 0.001$)

Functional questions

The use of IODs resulted in significantly fewer problems with solid food and interference with the patients' food choice (Table 6). Patients who received radiotherapy reported significantly more problems with their dentures. Furthermore, a lower maximum bite force and lower masticatory performance were associated with significantly more functional problems (Table 7).

DISCUSSION

In summary, edentulous oral cancer patients who received full dentures with a mandibular implant-retained overdenture (IODs) demonstrated the highest maximum bite force, but their masticatory performance did not differ significantly from patients who received conventional dentures (CDs). IODs in patients from the DAS cohort seemed to be superior to those from the P cohort with regard to bite force and masticatory performance 5 years after surgery. When bite force and masticatory performance improved, fewer problems with chewing, dentures, solid food, soft food, and food choice were reported. Patients who had no functioning dentures (NFD) demonstrated a worse bite force and masticatory performance compared to all other groups.

Masticatory function

Edentulous oral cancer patients who received implant-retained overdentures had a significantly higher bite force than those receiving conventional dentures, which was comparable to having no functioning dentures at all. This effect seems to be in concordance with studies in healthy edentulous patients, which show that bite force is higher in patients with implant-retained overdentures, and significantly increases when patients with conventional dentures receive implant-retained overdentures[16,21,22,32,38]. This effect is explained by the increase in retention of the lower denture due to implant attachment, allowing the patient to exert larger bite forces before their lower dentures become loose.

CDs and IODs did not differ significantly with regard to masticatory performance, and both resulted in a significant improvement. This is in contrast with two other studies on head and neck cancer, which reported better masticatory performance for IODs compared to CDs[30,31]. However, both studies only included patients reconstructed with vascularized bone grafts, and did not differentiate between full and partial dentures. The literature on healthy edentulous patients shows that IODs tend to be favorable to CDs with regard to masticatory performance[19,20,38], also when the mixing ability test is used as test food[32]. This discrepancy with our study is at least partially due to selection bias in favor of CDs: only patients who were not satisfied with their conventional dentures either received implants, or did not wear their dentures during mastication (and were therefore scored as NFD). As such, based on our results, a positive effect on masticatory performance of IODs compared to CDs in oral cancer patients cannot be ruled out. In this study, masticatory performance improved over time in the group with NFD. Apparently, patients

can partially compensate for having no functioning dentures by using their edentulous jaws in combination with their tongue to masticate and thereby increasing its strength; an effect that was also demonstrated in previous studies[39,40].

After a postoperative period of 5 years, IODs in patients from the DAS cohort appeared to have higher bite force and masticatory performance than those from the P cohort; even though the implants in patients from the P cohort were ideally placed with careful preoperative planning and therefore provided maximum support for the lower denture. This finding indicates that receiving functioning overdentures at an early stage (7.4 months vs 27.4 months after ablative surgery)[1], may result in a higher bite force and masticatory performance in the long-term. Due to early prosthodontic rehabilitation, thickness and activity of masticatory muscles (as measured by electromyography) might increase in the long-term, as was also demonstrated in healthy edentulous patients[41,42]. In other domains, such as neck–shoulder function and mouth opening, early rehabilitation after oral cancer treatment seems to be beneficial as well[43,44].

The use of implant-retained overdentures gave fewer problems with solid food such as peanuts or carrots; probably because of the higher maximum bite force which is needed for this kind of food. Logically, these patients also reported fewer problems with their food choice. This is in concordance with a review on head and neck cancer patients, which showed that IODs allowed for a normal diet, while patients with CDs could only chew soft foods, and those with NFD were restricted to liquid diets or feeding tubes[30]. Maximum bite force and masticatory performance were correlated with denture problems, chewing problems, problems with solid and soft food, and problems with food choice. However, this correlation was only partial, which indicates that other factors also play a role in patient satisfaction and experience. This effect is also known in healthy edentulous patients, in whom denture satisfaction is highly individual and only partially correlated with denture stability, retention and objective functionality[45]. Furthermore, patient's increased satisfaction from using IODs compared to CDs may be caused by the increase in stability, retention and masticatory function; but it can also be attributed to osseoperception in the peri-implant bone, or a perceived effect[12,46-48]. Patients who received postoperative radiotherapy reported significantly more denture problems and more chewing problems (although the latter were not significant), regardless of their maximum bite force and masticatory performance. This indicates that, even when bite force, masticatory performance, and quality of the dentures are objectively adequate, patients who received radiotherapy might still experience chewing and dentures. Previous

studies have also demonstrated this independent effect of postoperative radiotherapy on denture satisfaction and subjective masticatory function[29,49,50].

Strengths and limitations

The strengths of this study are its prospective design, inclusion of patients assigned to both the DAS and P protocols, different types of dentures (IODs, CDs and NFD) and repeated measurements at the preoperative assessment and at 0.5, 1, and 5 years after tumor surgery. So far, this is the only study to evaluate the masticatory function using both protocols for prosthodontic rehabilitation of edentulous oral cancer patients. Not only subjective outcome measures were used, but also independent outcome measures (maximum bite force and masticatory performance) were tested. Furthermore, the outcomes were compared with two groups of healthy controls. By using linear mixed-effects models and adding a patient factor, it was possible to adjust for repeated observations and loss of participants. Postoperative radiotherapy was added to the models, because it is strongly associated with other treatment variables, such as tumor size and surgical reconstruction, and is widely used in other studies on this subject.

The relatively small number of patients (56 at inclusion) is a limitation of this study, making it difficult to find small effects in the mixed-effects models. However, the effect of the type of dentures on maximum bite force and masticatory performance was clearly demonstrated in this study. Differences between IODs in patients from the DAS and P protocols were estimated by imputing the average time of denture placement into the mixed-effects model. This estimation appeared valid, because patient characteristics were equally distributed among the DAS and P protocols, and residuals from the models were small and equal among the four patient groups. However, because of the relatively small sample size, this study can only provide a strong indication of functional superiority of IODs from the DAS protocol compared to those from the P protocol. In the present study, measurement time points were related to time since surgery. In addition, the number of days that the current dentures were functioning was used in our statistical analysis. Because of the heterogeneity among patients with regard to the time of denture placement, a measurement shortly after placement would have estimated the effect of the dentures even more accurately.

Clinical implications and future research

This study has shown that both IODs and CDs give reasonable functional results, and are acceptable treatment modalities for the prosthodontic rehabilitation of edentulous

oral cancer patients, although the IODs were clearly superior with regard to maximum bite force. However, it is difficult to predict which patients will be satisfied with CDs after oral cancer therapy or which patients will have suboptimal or no functioning dentures at all. Although the patients in the P cohort desired the extra functionality of IODs, the required surgical interventions and possible need for additional hyperbaric oxygen therapy reduced their motivation. Therefore, the DAS protocol is more predictable with regard to functional outcome, and will leave fewer patients without functioning dentures. Having no functioning dentures will result in a totally inadequate bite force, and a less-than-optimal masticatory performance. Providing functioning dentures should therefore be a prime goal in oral cancer rehabilitation. Not only does the DAS protocol provide a larger portion of edentulous patients with IODs; its beneficial effect starts nearly 2 years earlier than in the P protocol.[1] In this study, we found a strong indication of superior bite force and masticatory performance after 5 years compared to the patients with IODs from the P cohort.

Literature shows that implant failure is low and equal for DAS and P protocols (3% - 10%)[1,51-54]. Some authors speculate that in the DAS protocol, backscattering of postoperative radiotherapy might increase the risk of implant failure or osteoradionecrosis due to higher irradiation doses in the bone adjacent the implants[55-57], although no in vivo studies so far have demonstrated such negative effects. In our study, there was only one case of implant failure (1.7%), in a patient from the DAS cohort who had received postoperative radiotherapy. Furthermore, only one patient developed osteoradionecrosis, and this was not adjacent to the implants which were still functioning after 5 years. Therefore backscattering does not seem to play a significant role in our study.

The number of implants that were loaded was only slightly lower in the DAS cohort compared to the P cohort (83% versus 95%)[1]. Given the functional benefits demonstrated in this study, it seems that the DAS protocol is superior to the P protocol. However, a cost-effectiveness analysis should be performed in the future for a full comparison of both protocols, since the number of implants that were not utilized in the DAS protocol increased costs. Also, the need for hyperbaric oxygen in patients receiving postoperative radiotherapy who have been assigned to the P protocol is still unclear[53,54,58,59].

In conclusion, implant-retained overdentures resulted in the highest overall masticatory function in the prosthodontic rehabilitation of edentulous oral cancer patients. Implant placement during ablative surgery seems to be functionally beneficial.

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CHAPTER 3

Masticatory function and related factors after oral oncological treatment, a 5-year prospective study

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Head & Neck 2019; 41: 216-224

ABSTRACT

Background: Chewing ability is often compromised in patients with oral cancer. The aim of this study was to identify which factors affect masticatory performance in these patients.

Methods: Patients with primary oral cancer were assessed for up to five years after primary treatment. Healthy controls were assessed once. A mixed-model analysis was performed, with masticatory performance as outcome measure.

Results: A total of 123 patients were included in the study. Factors positively associated with masticatory performance were: number of occlusal units, having functional dentures, and maximum mouth opening. The impact of tumor location and maximum bite force differed per assessment moment. Masticatory performance declined for up to one year, but recovered at 5 years after treatment.

Conclusion: Masticatory performance in patients treated for oral cancer is affected by maximum bite force, maximum mouth opening, number of occlusal units, and dental status. These should be the focus of post-treatment therapy.

INTRODUCTION

The aim of curative treatment for oral malignancies is disease remission achieved by radical resection and, on indication, postoperative irradiation. A great challenge for this curative treatment is trying to maintain or restore acceptable functional and esthetical outcomes after treatment. Oral function (eating, speaking, drinking, and swallowing) is known to be worse in patients who have had tumor surgery in the oral cavity than in healthy subjects[1–3]. Masticatory performance is an important aspect of post-treatment quality of life in patients treated for head and neck cancer[4–6].

Oncological surgery removes malignancies at the cost of functional anatomy[7]. After ablation of the tumor, where primary closure is impossible, reconstruction is necessary either immediately after the ablation of the tumor or in a secondary stage, and is achieved using a local flap, bone grafts, or microvascular free-tissue transfer and/or implant surgery. Often, dental rehabilitation with a prosthesis is used to restore oral function and aesthetics[8]. Despite successful rehabilitation, different phases of mastication may still be affected, such as the transportation, trituration, and consolidation of the food bolus[9,10]. Patients who undergo a glossectomy may, for example, have difficulty with the transportation of food, while patients who have had a mandibulectomy can experience difficulty in trituration and vertical mobility during mastication[11]. Radiotherapy can cause masticatory impairment due to tooth loss, mucositis, fibrosis, trismus, or xerostomia. Additionally, a lack of saliva can unable patients to tolerate dentures[3,12,13].

Oral rehabilitation can improve masticatory performance. To achieve optimal oral rehabilitation, it is important to identify factors that affect masticatory performance in patients treated for oral cancer. Previous studies on this patient group focused mainly on the subjective appraisal of chewing ability using questionnaires; very few studies have assessed masticatory performance with an objective method[14–16].

The primary aim of this study was to identify and quantify factors involved in objective masticatory performance for patients who have been treated for oral cavity malignancies, with a follow-up of five years post-treatment. We also compared these results to healthy controls.

MATERIAL AND METHODS

Subjects

In this two-center prospective cohort research, the study population consisted of patients with a primary malignant tumor involving the oral cavity who were referred to University Medical Center Utrecht (UMCU) or Radboud University Medical Center (Radboudumc) between January 2007 and August 2009. Patients were included if they were being treated with a curative intent, using surgery or surgery followed by radiotherapy. Exclusion criteria included inoperability, a previous and/or current second primary malignancy, cognitive impairment, or the inability to understand Dutch. Sixty age-matched healthy controls were also recruited, whose details were published previously[17]. Of these control subjects, 20 had a functioning natural dentition, 20 had functioning conventional full dentures, and 20 had functioning full dentures with a mandibular implant-retained overdenture. The experimental protocol was approved by the Ethics Committees of the UMCU and Radboudumc. All patients received written information and provided their signed informed consent.

Pre-treatment oral screening and dental management was performed for all patients. Adjuvant radiotherapy, when given, started within 4 to 6 weeks after surgery, in accordance with the Dutch Head and Neck Society treatment guidelines, with a total radiation dose of 64 to 70 Gy. Tumor locations included in this study were included codes C00, C02-C06, and C31, defined by the World Health Organization International Classification of Diseases Oncology third edition[18]. Maxillary tumors included the upper alveolar process, maxillary tuber, palate, and maxillary sinus (C03.0, C05, C31.0). Mandibular tumors included the lower alveolar process, the retromolar trigone, the cheek, and the lower lip (C00.4, C03.1, C06.0, C06.1, C06.2). Tongue and/or floor of the mouth (TFM) tumors included the tongue and the anterior floor of the mouth (C02, C04).

Patient information, including sex, tumor location and size (pT of TNM-classification, 6th edition[19]), resection site, and details of reconstruction, were extracted from medical records. Age, smoking habit, and alcohol consumption were charted at the pre-treatment session. Smoking habit was scored as ‘No’ for non- or infrequent smokers and ‘Yes’ for daily smokers. Alcohol consumption scored ‘Yes’ if it exceeded one unit per day on average.

Assessments

Patients were assessed no more than four weeks before primary treatment (baseline, t_0), then at 4–6 weeks after surgery (t_{1a}) and/or 4–6 weeks after radiotherapy (t_{1b}), six months (t_2), one year (t_3), and five years (t_5) after their primary treatment. At every assessment, masticatory performance, maximum bite force, and maximum mouth opening were evaluated, as well as dental status and the presence of an obturator prosthesis. The healthy controls were assessed once.

Masticatory performance

The mixing ability test (MAT) measures how well a subject mixes a two-colored wax tablet by chewing on it[17,20]. The wax is a soft material (Plasticine modelling wax, non-toxic DIN EN-71) that forms a compact bolus during chewing. The tablet was offered to patients at room temperature (20°C), and patients were instructed to chew on the tablet 20 times. The tablet had a diameter of 20 mm and consisted of two 3-mm layers of bright red and blue wax. Chewing mixes the colors to yield intermediate shades of red and blue. After being chewed, the wax was flattened to a thickness of 2.0 mm and photographed on both sides using a high-quality scanner (Epson V750, Long Beach, California). The wax images were analyzed using Adobe Photoshop CS3 (San Jose, California) to generate a measure for the spread of red and blue intensities: the Mixing Ability Index (MAI). A higher index implies a better-mixed tablet, hence better masticatory performance. The MAI ranges from 0 to 30.

Maximum bite force

Maximum bite force (MBF) was measured using a bite force transducer[21]. The device consists of a unilateral strain gauge with a surface area of 100 mm^2 and a vertical height of 2.8 mm. It was covered with a hard putty for dental protection and mounted on a mouthpiece. The strain gauge element was placed between the first molars to measure the occlusal forces when subjects clenched their jaws together as hard as possible. Two measurements each were taken from the left and right sides. The mean of the highest measurements on the left and right sides is presented as the MBF.

Maximum mouth opening

Maximum mouth opening (MMO) was measured extra-orally using a previously published protocol[22]. Briefly, the distance between applied markings on the inferior border of the chin and the tip of the nose was measured in patients in a resting position, as well as when opening the mouth as far as possible. Both positions were measured twice at

every assessment. The difference between the average of the two resting positions and the highest value of the two maximum opening positions was defined as the MMO.

Dental status

Dental status was assessed and stratified into the following groups: edentulous without functioning dentures (ED), full dentures in upper and lower jaw (FD), full dentures with implant retention in one jaw (upper or lower) (FD&FDI), full denture in upper or lower jaw and dentate in the other jaw (FD&D), full dentures with implant retention in both jaws (FDI&FDI), full denture with implant retention in upper or lower jaw and dentate in the other jaw (FDI&D), or dentate in both jaws (D). Partially dentate jaws were classified as dentate. Additionally, pairs of natural occluding premolars and molars were counted and scored respectively as 1 and 2 occlusal units (OU)[23]. When maxillary defects could not be closed primarily, a temporary obturator was fabricated based on preoperative assessments and dental casts. After approximately one year, the patient was provided with the definite obturator, made of acrylic resin, based on Beumer's method[24]. The presence or absence of an obturator prosthesis was scored as 'Yes' or 'No', respectively.

Statistical analysis

Chi-Square Tests were used to analyze differences in patient characteristics with respect to nominal and ordinal variables, such as tumor location, while a one-way Analysis of Variance (ANOVA) was used to examine age differences among the groups. Independent Samples T-Tests were used to calculate the differences between mean values. The mean values of MAI, MMO, MBF, OU (Paired T-Test), and dental status (Wilcoxon Signed Rank Test) did not differ between the t_{1a} and t_{1b} time points, thus only the t_{1b} values were presented when the patient had undergone both these assessments (t_1).

A linear mixed-effects model with the MAI as outcome was constructed to assess both the changes over time and the effect of patient characteristics and clinical parameters. To account for within-patient correlations, a random patient factor was added. Fixed-effect factors such as age, sex, tumor location, alcohol consumption at baseline, tumor extent (pT classification), treatment modality, surgical reconstruction, assessment moment (t_0–t_5), smoking habit, dental status, number of occlusal units, the presence of an obturator prosthesis, MMO, and MBF during the follow-up were assessed, as well as all two-way interactions of the factors during the assessment period. The factors that were not significant at a $P < 0.050$ level were removed in a backwards fashion, beginning with the interactions, to build a parsimonious model with sufficient fit while maintaining a

hierarchical structure; meaning that if an interaction was included in the model, the main effects were also represented in the model. When an interaction with the assessment moment was found for a specific variable, there was a different coefficient for all levels of the variable at each assessment moment. The coefficients of the significant covariates, together with the value of the intercept of the mixed model analysis were combined into a formula for the estimated mixing ability index. The intercept is the value of the estimated MAI in the event that all following coefficients remain zero. The addition of coefficients of the significant covariates will, depending on the coefficient being positive or negative, either increase or decrease the estimated MAI. The formula was used to compare the chewing performance of patients with tumors in the three location groups during the follow-up period. For each time point, we filled the formula with the average variable values for the significant coefficients in the three tumor location groups, as calculated by a restricted maximum likelihood approach.

A P-value less than 0.050 was considered statistically significant. The mixed model analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). The remaining tests were performed using SPSS version 21.0 (IBM Corp. Armonk, NY, USA).

RESULTS

At t_0, a total of 123 patients were enrolled in this study. After five years, 69 patients were still in the study; 30 patients died during the follow-up period, and 24 patients chose to stop participating for various reasons (Figure 1). Baseline demographics and clinical characteristics categorized on primary tumor location are displayed in Tables 1 and 2.

Thirty patients had a maxillary tumor, 48 had a mandibular tumor and 45 had a tumor of the tongue and/or floor of the mouth (TFM). Of the 30 patients who underwent a maxillectomy, 20 received an obturator prosthesis. In 10 of these 20 patients, the obturator was placed without further tissue to cover the defect, in 1 patient it was combined with a local flap, and in the other 9 patients the obturator was combined with a split-thickness skin graft. Of the 48 patients with mandibular tumors, 18 had segmental defects. Two patients with primary floor of the mouth tumors had mandibular invasion to an extent that necessitated segmental resection. Nine patients were reconstructed using a reconstruction plate, of whom 3 combined with a vascularized flap due to soft tissue deficiency. Seven patients were reconstructed with a free vascularized bone flap and one with a non-vascularized

iliac crest graft. One patient's segmental defect was not reconstructed due to comorbidity. Sixty-four patients (52%) received postoperative radiotherapy (Table 1).

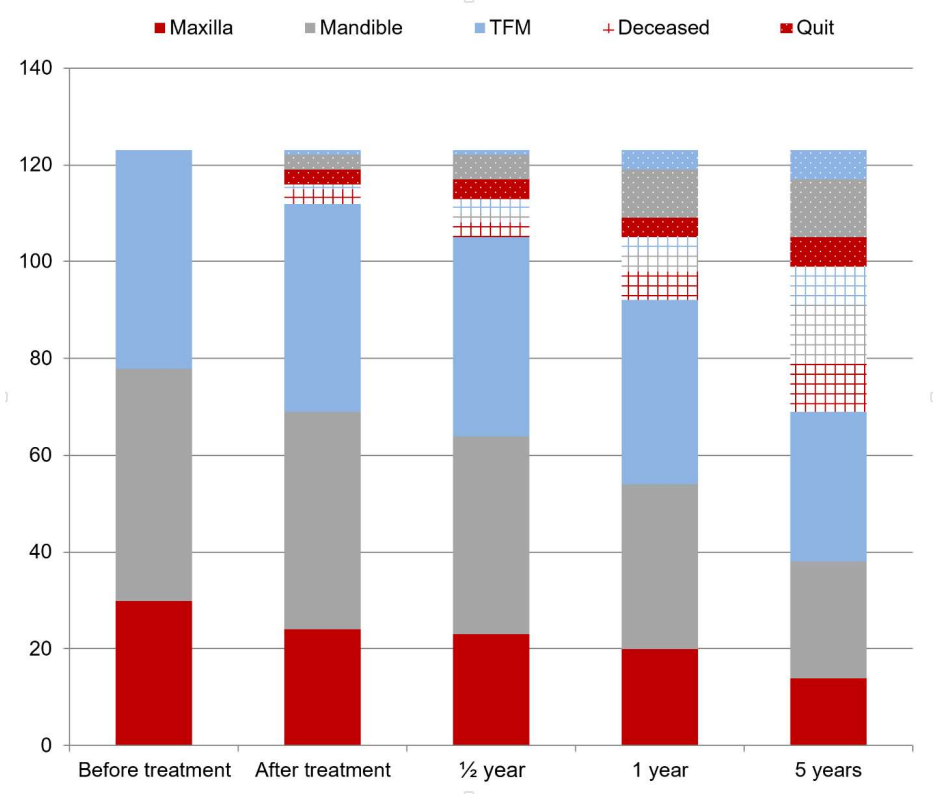

Figure 1. Flowchart showing the number of patients (*n*) at each assessment and the average time since the ablative surgery. TFM, tongue and/or floor of the mouth

At baseline, sex, smoking status, alcohol use, and the number of occlusal units did not differ between patients with tumors in different locations; however, significant differences were observed between their MBF and masticatory performance, dental status, pT-classification, treatment, reconstruction, and age (Tables 1 and 2).

Table 1. Baseline demographics and oncological details, categorized by tumor location

	Maxilla (*n* = 30)		Mandible (*n* = 48)		TFM (*n* = 45)		Healthy (*n* = 60)		
	n	%	*n*	%	*n*	%	*n*	%	P-value
Sex									0.291
Male	14	47	25	52	30	67	31	52	
Female	16	53	23	48	15	33	29	48	
Smoking (daily)									0.252
Yes	8	27	18	38	16	36	13	22	
No	22	73	30	62	29	64	47	78	
Alcohol use (> 1 daily)									0.096
Yes	8	27	15	31	19	42	30	50	
No	22	73	33	69	26	58	30	50	
Tumor size (pT of TNM)									0.000
T1	5	17	14	29	23	51			
T2	11	37	13	27	14	31			
T3	1	3	3	6	4	9			
T4	13	43	18	38	4	9			
Treatment									0.000
Surgery	12	40	24	50	23	51			
Surgery & radiotherapy	18	60	24	50	22	49			
Surgical reconstruction									0.000
Primary closure	17	56	16	33	23	51			
Local flap	2	7	2	4	0	0			
Split-skin or free flap†	11	37	12	25	19	42			
Bone graft/flap	0	0	18	38	3	7			
Mean age, years (SD)	68.7 (12.3)		66.7 (12.7)		61.4 (13.1)		60.3 (7.2)		0.001

TFM, tongue and/or floor of the mouth; †, split-thickness skin graft (25), free vascularized flap (17); SD, standard deviation

Table 2. Dental status and functional assessments at baseline, categorized by tumor location

	Maxilla (*n* = 30)		Mandible (*n* = 48)		TFM (*n* = 45)		Healthy (*n* = 60)		
	n	%	*n*	%	*n*	%	*n*	%	P-value
Dental status									0.000
ED	7	23	13	27	5	11	0		
FD	7	23	8	17	13	29	20	33	
FD&FDI	0	0	2	4	4	9	20	33	
FD&D	4	14	8	17	3	7	0		
FDI&FDI	0	0	0	0	0	0	0		
FDI&D	1	3	0	0	0	0	0		
D	11	37	17	35	20	44	20	33	
Mean number of OUs	2.4 (4.1)		2.3 (3.9)		3.8 (5.1)		3.8 (5.4)		0.267
Mean MMO (mm)	52.9 (11.8)		46.6 (11.4)		56.0 (9.8)		53.7 (7.5)		0.000
Mean MBF (Newton)	224 (233)		257 (330)		377 (344)		446 (384)		0.006
Mean MAI	5.9 (5.9)		6.6 (5.0)		9 (4.6)		11.5 (3.7)		0.000

ED, edentulous (no functioning dentures); FD, full denture; FDI, full denture with implant retention; D, dentate; OU, occlusal unit; MMO, maximum mouth opening; MBF, maximum bite force; MAI, mixing ability index; TFM, tongue and/or floor of the mouth

Masticatory performance

The mixed model analysis showed that age, sex, smoking and alcohol use, pT classification, treatment modality, presence of an obturator prosthesis, and the type of reconstruction did not significantly contribute to the MAI; therefore, these factors were removed from the model. The assessment moment, dental status, number of occlusal units, and MMO did significantly affect MAI. The location of the tumor and the MBF also contributed significantly to the MAI, but the relative effects differed at every assessment moment.

The formula for the estimated MAI with significant variables and their coefficients is displayed in Table 3. Figure 2 shows the relative impact of all significant variables, and can be interpreted as a visual presentation of the formula. All assessment moments except t_5 (t_0, t_1, t_2, and t_3) decreased the MAI (thus had a worse masticatory performance); with the assessment immediately after surgery (t_1) having the lowest coefficient. A dental status better than edentulous without functioning dentures, a higher number of occlusal units, and an increased MMO increased the MAI. An edentulous state without dentures

decreased the MAI more than any other dental state. A higher MBF increased the MAI; however, its impact was greatest before treatment and five years after treatment. The influence of the tumor location differed between the assessments.

Table 3. Mixed-effects model for the mixing ability index (MAI)

Factors without time interaction (equal at every assessment)					
Dental status					
ED	-4.18				
FD	-0.22				
FD&FDI	0.43				
FD&D	-0.04				
FDI&FDI	1.91				
FDI&D	-0.17				
D	0				
Occlusal units (per unit)	0.26				
MMO (per mm)	0.04				
Factors with time interaction	**before**	**after**	**½ year**	**1 year**	**5 years**
MBF (per Newton)	0.005	0.003	0.001	0.002	0.005
Tumor location					
Maxilla	-0.77	0.13	-3.28	-2.41	1.19
Mandible	-0.35	1.40	-1.38	-0.84	0.37
TFM	0	0	0	0	0
Intercept	4.05	1.88	4.24	3.48	6.10

Estimates of the mixing ability index are on a linear scale of 0 – 30, with a score of 30 representing the best score and 0 the worst possible score. The contribution of a single coefficient can only be interpreted when all other variables remain stable. ED, edentulous (no functioning dentures); FD, full denture; FDI, full denture with implant retention; D, dentate; MMO, maximum mouth opening; MBF, maximum bite force; TFM, tongue and/or floor of the mouth

The tongue and/or floor of the mouth (TFM) location was used as reference category, and was therefore zero at every assessment moment. At baseline, six months, and one year after treatment, maxillary and mandibular tumor location decreased the MAI; thus the TFM location performed better at those moments. However, mandibular tumor location and maxillary tumor location increased the MAI at the assessments immediately after treatment and after five years.

The mean MAI before treatment was significantly higher in the healthy controls (11.5 ± 3.7) than in all location groups (maxilla: 5.9 ± 5.9 (P = 0.000), mandible: 6.6 ± 5.0 (P = 0.000) and TFM: 9.0 ± 4.6, P = 0.041). The general course of the mean MAI scores for all primary tumor locations is an initial deterioration after treatment, followed by a recovery over the five years after treatment. The recovery was mainly achieved between one and five years after treatment (Figure 3). No recovery plateau phase was observed for any of the groups.

Five years after treatment, the mean MAI of patients who had a primary maxillary tumor (10.7 ± 1.1) was not significantly different from those who had a tumor in the mandible (9.8 ± 0.9, P = 0.462) or TFM (9.4 ± 0.9, P = 0.252). At five years after treatment, patients who had a mandibular or TFM tumor had worse MAI scores than the healthy controls (P = 0.015 and P = 0.001, respectively); however, patients who had a maxillary tumor showed no significant difference compared to the healthy controls at the end of the five-year follow-up period (P = 0.279; Figure 3).

Although pT-classification was not a significant factor according to our mixed model analysis, subjects who survived for five years after the treatment more often had lower pT-classification outcomes (1 and 2) at the baseline than those who died during the follow-up period (P = 0.044). The proportion of patients who died before the end of the assessment period was not significantly different between the patients with different tumor locations (P = 0.454).

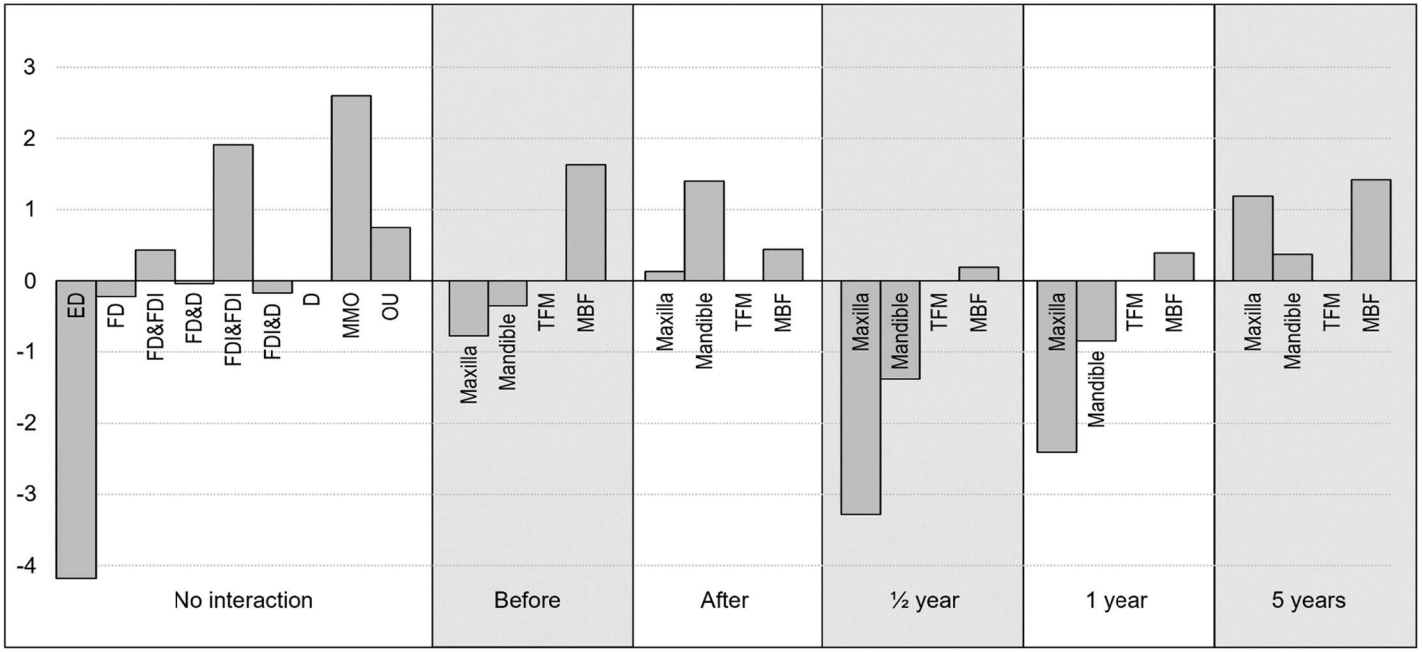

Figure 2. Visual presentation of the significant variables and their coefficients on the estimated Mixing Ability Index (MAI) formula. A distinction is made between variables with and without an interaction with the assessment moment. The continuous variables (MMO, OU, and MBF) are presented as the impact for the mean values of those variables. The mean number of occlusal units was 2.9 and the mean MMO was 52 mm. Mean MBF differs per assessment moment and is respectively, 326 N before intervention, 145 N directly after intervention, 193 N at ½ year, 194 N at 1 year, and 283 N at 5 years. Factors with positive outcomes increase the mixing ability outcome, reflecting an improvement of masticatory performance. ED, edentulous (no functioning dentures); FD, full denture; FDI, full denture with implant retention; D, dentate; MMO, maximum mouth opening; OU, occlusal unit; MBF, maximum bite force; MAI, mixing ability index; TFM, tongue and/or floor of the mouth

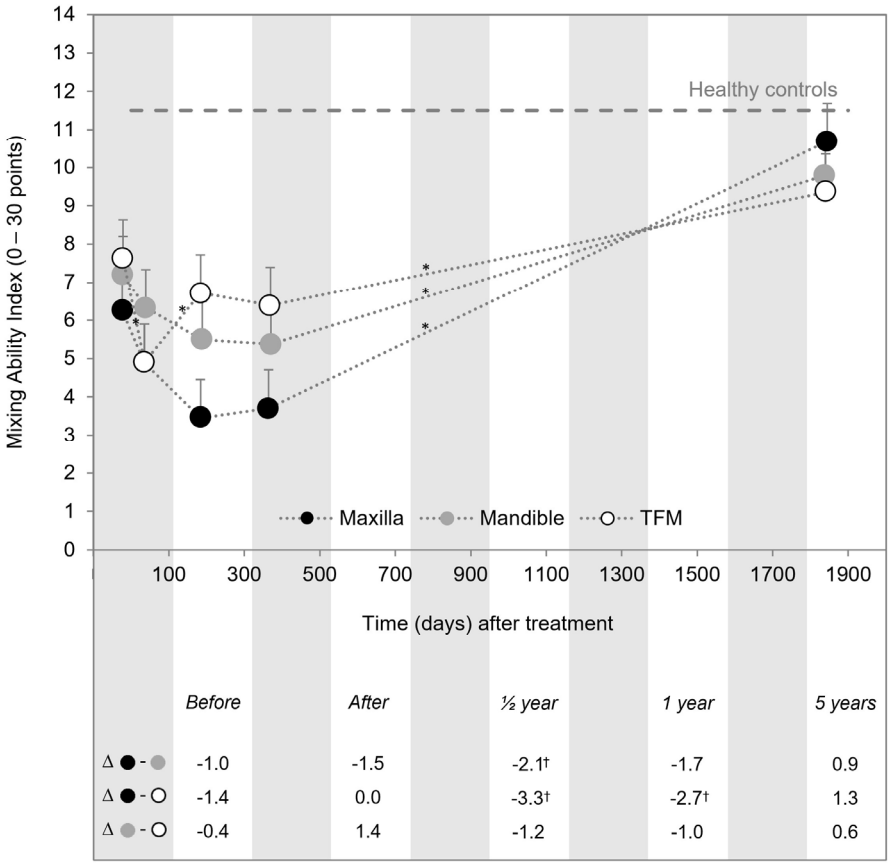

Figure 3. Estimates of the Mixing Ability Index (MAI) with standard errors, rendered using a mixed model analysis. Values entered into the model were that of the mean patient in the cohort, calculated using a least squares method. The outcome presented is divided by the location of the primary tumor over a five-year follow-up. Differences between groups are presented in the table under the figure. MAI ranges from 0 to 30, where 0 represents the worst and 30 the best possible outcome. Only the assessment at five years after treatment of the maxillary tumor group was not significantly different from the control group (P = 0.279). TFM, tongue and/or floor of the mouth

* P < 0.050 between adjacent assessments in one tumor location † P < 0.050 between tumor locations at one assessment

DISCUSSION

In this five-year prospective study, factors with a significant contribution to masticatory performance were identified for patients who underwent a curative oncological intervention because of an oral carcinoma. The relative impacts of these factors on masticatory performance, assessed using the mixing ability test, were also quantified. Increased numbers of occlusal units, MBF, and MMO all had a positive influence on masticatory performance, while the absence of a functioning dentures in edentulous patients had a negative impact.

The mean masticatory performance was higher at five years after treatment than it was before treatment, which might partially be explained by the fact that the tumor itself, especially in advanced stages, may cause pain and discomfort. Furthermore, (partially) edentulous patients generally receive their definitive dentures within 1 or 2 years after treatment[25,26].

Comparison with existing literature

In contrast to the results of our five-year prospective study, two previous cohort studies and one cross-sectional study reported a lower masticatory performance compared to a healthy control group, but study groups were small[11,15,27]. In contrast to our longitudinal results, a negative effect of age on masticatory performance in healthy subjects was reported in two cross-sectional studies[28,29], but in another cross-sectional study no clear relationship was found between these factors in healthy subjects[10].

Using a comminution test in patients treated for all head and neck cancer locations, a significant and clinically relevant increase in bite force and objective masticatory performance was demonstrated after definitive prosthodontic rehabilitation[28]. In the same study, the number of occluding pairs of (pre)molars were found to influence masticatory performance. Bite force has been previously reported to account for up to 60% of the variance in masticatory performance in healthy subjects[30]. Other objective data in both head and neck cancer patients and healthy subjects found beneficial effects of adequate prosthodontic rehabilitation[17,31,32]. In a systematic review, the importance of rehabilitating the dentition, including the use of dental implants to support a fixed prosthesis, to add occlusal units, or to support a removable prosthesis, was confirmed[33]. Studies on patient reported masticatory ability, however, found little[11] to no effect[31,34] of prosthodontic treatment.

Although trismus has previously been identified in a systematic review as a negative influencer of masticatory performance in head and neck oncology, however, from which severity of MMO-restriction this negative impact occurs is unknown[35]. In our model, each millimeter of mouth opening provides a 0.04 improvement in the MAI, so a reduction of MMO from 55 to 30-mm deteriorates the MAI by 1.0 points, which is a clinically relevant impact independent of all other factors. In another prospective study on oral cancer patients, the prognostic factors of trismus development have been presented. Lower pretreatment MMO, maxillary or mandibular tumor location and (postoperative) radiotherapy increased the risk of the development of trismus[13].

Other studies found a one-year postoperative improvement in objective masticatory efficacy, determined using ATP-grains and a mixing ability test respectively, in patients with a tongue and/or floor of the mouth tumor, when compared with pre-operative values. This effect might be due to the effect of primary tumor discomfort on the masticatory performance[15,36]. In a cross-sectional study, patients who underwent a maxillectomy showed better masticatory performance after full oral rehabilitation than those who had a mandibulectomy, but their chewing ability was still inferior to healthy full-denture wearers. The treatment groups in this study were small, however[16].

Clinical implications

Masticatory performance is an important factor in post-treatment quality of life for patients treated for head and neck cancer[37]. In general, functional outcomes are not the sole contributors to quality of life, but they form a significant part of a patient's wellbeing and are therefore important issues to address[4–6]. This study showed a number of factors that impact masticatory performance during the rehabilitation of patients treated for oral malignancies. The clinical significance of the formula can be to be able to calculate the estimated masticatory performance for any oral cavity patient, although information such as bite force is usually not readily available in daily practice. The factors found to significantly affect masticatory performance: occlusal unit count, dental status, bite force and mouth opening are all factors which need to be considered when constructing the initial treatment plan. Primary consideration of reconstructive and rehabilitative options in a multi-disciplinary setting, might ensure adequate management of these factors. This includes the consideration of digital planning for reconstruction and primary implant placement by the head and neck surgeon and maxillofacial prosthodontist. Additionally, beneficial effects of orofacial physiotherapy have been reported in orthognathic surgery[38],

but have yet to be proven in head and neck cancer patients[35]. Finally, thoughtful consideration should be given in maintaining occlusal units when clearing the dentition of potential foci in osteoradionecrosis prevention. However, the presence of natural teeth after radiotherapy necessitates patients to commit to lifelong meticulous oral hygiene and frequent self-application of fluoride, either as neutral sodium fluoride or a 1% gel applied at least every other day, to prevent radiation caries[39]. We found that the initial tumor location has an effect on masticatory performance. This factor cannot be influenced, but can be addressed during the pre-treatment counseling to optimize a patient's expectations regarding masticatory performance.

Strengths and limitations

The strengths of this study are its long follow-up, prospective design, large study population (*n* = 123), meticulous data generation through testing, and thorough statistical analysis. The latter provided us the opportunity to correct for missing values (participants who dropped out or died), and adjust for repeated measures and an unequal distribution of baseline clinical characteristics between groups. In this cohort study, no subgroup analyses were performed on other possible influential factors, such as lingual nerve removal, the extent of surgery, or the specific location of radiotherapy, due to the small subgroup sample sizes.

The mean estimate of the MAI was higher for patients at five years post-treatment than before treatment, regardless of the location of the tumor. A possible explanation for this is that the mixed model outcome is based on the remaining participants at every assessment moment, which in this case could influence the outcome. In addition, those who survived for five years after their treatment had smaller tumors, and thus smaller resections, than patients who died or dropped out of the study prior to the five-year assessment. This could have influenced the mean outcome of masticatory performance. Unfortunately, the healthy controls were only assessed once, so changes in their masticatory performance over the course of the follow-up could not be compared to the treatment groups.

Future research

Future research should focus on possible further recovery, or a secondary decline, of masticatory performance after the five-year post-treatment period. Tongue function is of great importance in mastication[40,41], however, until now the influence of disabled tongue function on masticatory performance was unknown for patients treated for oral cancer.

The clinical effects of standardized post-treatment physical therapy protocols have yet to be evaluated.

Conclusion

In conclusion, oral cancer and its treatment drastically affect masticatory performance, but it recovers to pre-treatment levels in patients who survive for five years. Masticatory performance in oral oncology patients is positively affected by having full dentures or better, a higher number of occlusal units, increased MMO, elevated MBF, and having a maxillary rather than mandibular or TFM tumor location.

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CHAPTER 4

Maximum mouth opening and trismus in 143 patients treated for oral cancer: a 1-year prospective study

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Head & Neck 2014; 36: 1754-1762

ABSTRACT

Background: Oral cancer patients can develop restricted mouth opening (trismus) due to the oncological treatment.

Methods: Maximum mouth opening (MMO) was measured in 143 patients shortly before treatment and 0, 6 and 12 months post-treatment, and the results were analyzed using a linear mixed-effects model.

Results: In every patient, MMO decreased following treatment. The patients who underwent surgery recovered partially by 6 and 12 months following treatment, whereas the patients who received both surgery and radiotherapy or primary radiotherapy did not recover. Tumor location, tumor size and alcohol consumption had independent effects on MMO. Having trismus (MMO < 35 mm) 1 year after treatment was associated most strongly with pre-treatment MMO, receiving both surgery and radiotherapy, and maxillary or mandibular tumor involvement.

Conclusion: Postoperative radiotherapy and maxillary or mandibular tumor involvement are the highest contributing risk factors to decreasing MMO and the subsequent development of trismus following oral cancer treatment.

INTRODUCTION

Oral cancer is a highly prevalent and serious health-care problem. Worldwide, 263,000 new patients are diagnosed with oral cancer each year, accounting for 2.1% of all cancers cases[1]. Over the past two decades, Western Europe has experienced a rise in the incidence of oral cancer[2]. In most countries the 5-year survival is around 50%[2], and survivors often experience functional limitations following treatment, particularly with respect to eating, drinking, swallowing, speaking and appearance[3,4]. The ability to open one's mouth fully is essential for these oral functions.

In healthy adults, maximum mouth opening (MMO) is between 40 and 60 mm[5]. An MMO of less than 35 mm is defined as trismus; this threshold value is based on functional problems experienced by patients with head and neck cancer[6,7]. The prevalence of trismus varies from 39% to 79% among patients who are treated for oral and oropharyngeal cancer[7-10]. This range in prevalence can be explained by the use of different treatment modalities, various tumor locations and/or sizes, and differing follow-up periods between various study groups[11]. Furthermore, trismus is associated with a reduced quality of life due to impaired oral function[6,12].

When a tumor is located at or adjacent to the suprahyoid muscle, masseter muscle, pterygoid muscle and/or the temporomandibular joint, it can physically obstruct the oral opening and/or trigger a reflex that can increase muscle tonus[13]. Surgery and radiotherapy can cause fibrosis of these structures and can reduce the stretching length, thereby decreasing MMO[14-16]. Two prospective studies conducted among patients with head and neck cancer who received surgery with or without radiotherapy measured pre- and post-treatment MMO, including follow-up measurements after 6 months. In both studies, MMO decreased after treatment and did not change over the following 6 months[8,9]. Nevertheless, no prospective studies have been performed regarding oral cancer with respect to MMO and trismus. The aim of this study was to prospectively follow the time-course of MMO in patients who were treated for a malignancy that involved the oral cavity for up to 1 year following treatment. The secondary aim of this study was to identify clinical factors that increase a patient's risk of experiencing a decrease in MMO and/or developing trismus within 1 year of treatment.

MATERIAL AND METHODS

Subjects

This two-center study was conducted from January 2007 through August 2009 at the University Medical Center Utrecht (UMCU) and Radboud University Nijmegen Medical Center (Radboudumc). Patients were eligible for the study if they had a primary malignant tumor that involved the oral cavity and was treated with surgery, with a combination of surgery and radiotherapy, or with primary radiotherapy. Exclusion criteria included a previous and/or current malignancy, cognitive impairment or the inability to understand Dutch. Sixty healthy age-matched controls were also recruited; details regarding this control group have been published previously[17]. The experimental protocol was approved by the respective Ethics Committees of the UMCU and Radboudumc.

Pre-treatment oral screening and dental management was performed for all patients. Where applicable, radiotherapy was applied 4-6 weeks after surgery (based on the histological analysis of the resection specimen) in accordance with the treatment guidelines of the Dutch Head and Neck Oncology Group. The total radiotherapy dose (primary or adjuvant) was 54-70 Gy. Sex, tumor location, tumor size (T of TNM, 6th edition[18]), resection site and reconstruction details were obtained from the medical records. Age, tobacco use and alcohol consumption were recorded at the pre-treatment session. A distinction was made between patients who smoked daily and those who either did not smoke or smoked infrequently. With respect to alcohol consumption, a distinction was made between patients who consumed an average of more than one alcoholic beverage per day and those who consumed less than this amount of daily alcohol. Dental status was examined at the assessment shortly after primary treatment. Patients were marked as edentulous when all of their upper and lower teeth were missing. The other patients were marked as dentate.

In this study, tumor locations included codes C00, C02-C06 and C31 of the World Health Organization International Classification of Diseases Oncology third edition[19]. The patients were assigned to three anatomical groups based on their tumor location (Table 1). Maxillary tumors included the upper alveolar process, maxillary tuber, palate and maxillary sinus (C03.0, C05, C31.0). Mandibular tumors included the lower alveolar process, the retromolar trigone, the cheek and the lower lip (C00.4, C03.1, C06.0, C06.1, C06.2). Tongue and/or floor of the mouth (TFM) tumors included the tongue and the anterior floor of the mouth (C02, C04).

Measurements

The patients were assessed prior to the primary treatment, 4-6 weeks after surgery and/or radiotherapy, and then 6 and 12 months following primary treatment. The healthy control subjects were assessed once[17]. MMO was measured extra-orally using a previously published protocol[20]. This method was chosen to avoid the effects of any possible decline or change in dental status. Patients who routinely used a dental prosthesis were instructed to wear their prosthesis during the measurements. Two fixed points were marked with a pencil; one point was on the lower side of the chin, and the other was on the tip of the nose. With the patient sitting in an upright position, the distance between the two points was measured using a digital slide gauge with the mouth at rest and at its maximum open position. For the resting position measurement, the patients were instructed to close their mouth without their teeth making contact. For the maximum open position measurement, the patients were instructed to open their mouth as wide as possible. Both positions were measured twice at every assessment, and the average of the two resting positions was subtracted from the highest value of the two maximum opening positions; this difference was defined as the "maximum mouth opening" (MMO) and was used in the subsequent analyses.

In addition, patient function was subjectively assessed using a following question: "During the past week, have you experienced problems with opening your mouth wide?" The possible answers were: "1) never", "2) sometimes", "3) often" and "4) always."

Statistical analysis

The Chi-Square Test was used to analyze any differences in patient characteristics with respect to tumor location; one-way Analysis of Variance (ANOVA) was used to examine the age differences among the groups. A linear mixed-effects model for MMO was constructed to assess both the changes over time and the effect of patient characteristics and clinical parameters. To account for within-patient correlations, a random patient factor was added. The assessment period, sex, age, dental status, smoking, alcohol use, tumor location, tumor size, treatment modality and surgical reconstruction as well as all two-way interactions of these factors with the assessment period were added as fixed effects. Next, the fixed effects that were not significant at a 0.050 level were then removed backwardly, beginning with the interactions, to build a parsimonious model with sufficient good fit keeping a hierarchical structure. If an interaction was in the model, then the main effects were also in the model. When an interaction with the assessment period was

found for a specific variable, the differences at each assessment between the levels of the variable and the differences for each level of the variable between assessments were analyzed. For the other variables, the main effect on MMO was calculated. Normalized tests were used to analyze the differences in MMO between the healthy controls and the patient groups. The within-subjects correlation between MMO and the subjective function was calculated using multiple regression analysis[21].

A multiple linear regression model for MMO 1 year post-treatment was constructed using sex, age, smoking, alcohol use, tumor location, tumor size, treatment modality, surgical reconstruction and MMO as the pre-treatment variables. All variables from this model with a significant effect on MMO after 1 year were used in a multivariate binary logistic regression model to calculate the probability of trismus (defined as MMO < 35 mm) after 1 year. A receiver operating characteristic (ROC) curve was constructed for this logistic regression model when it was used to predict trismus in our study group.

No imputation of missing values was performed. No statistical difference was found with respect to MMO after surgery and after postoperative radiotherapy in the surgery-radiotherapy group. Therefore, the measurements obtained shortly after radiotherapy were not used in the statistical analysis of this patient group. All statistical tests were 2-sided, and differences with a P-value less than 0.050 were considered to be statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 143 patients were included in the study. The baseline characteristics of these patients are listed in Tables 1 and 2. Thirty-four patients had a tumor of the maxilla, 54 patients had a tumor of the mandible, and the remaining 55 patients had a tumor of the tongue and/or floor of the mouth (TFM). Fifty-nine patients were treated with primary surgery (surgery group; SG), 64 were treated with a combination of surgery and radiotherapy (surgery-radiotherapy group; SRG), and the remaining 20 patients were treated with primary radiotherapy (radiotherapy group; RG).

Tumor size (the patients with a TFM tumor had more T1 and T2 tumors) and surgical reconstruction (the patients with a mandibular tumor had more bone reconstructions) were not distributed equally with respect to the tumor locations; the other characteristics were similar among the groups. Of the 34 patients with a maxillary tumor, 20 received

an obturator prosthesis after a maxillectomy. Shortly after treatment, 33% of the patients were dentate and 67% were edentulous. After 1 year, 99 of the 143 patients were still enrolled in the study (Figure 1). Eighteen of the patients had died within the follow-up period, 25 patients had stopped participating, and one patient was excluded because of extensive additional surgeries due to a recurrence of the tumor. Five measurements were not collected due to scheduling conflicts or time constraints. Three of the patients did not answer the functional question at one of their assessments. At both medical centers, standard mouth opening exercises were offered to all patients by the head and neck oncologist without the supportive care of a physical therapist.

Table 1. Tumor locations in the study group (*n* = 143), subdivided into three anatomical entities

Maxilla (34 patients)	*n*	%
Upper alveolar process	18	53
Maxillary tuber	5	15
Palate	8	24
Maxillary sinus	3	9
Mandible (54 patients)	***n***	**%**
Lower alveolar process	21	39
Retromolar trigone	13	24
Cheek	16	30
Lower lip	4	7
Tongue and/or floor of the mouth (55 patients)	***n***	**%**
Tongue	33	60
Floor of the mouth	22	40

Table 2. Baseline demographics and clinical characteristics for the patient groups based on tumor location

	Maxilla (*n* = 34)		Mandible (*n* = 54)		TFM (*n* = 55)		
	n	%	*n*	%	*n*	%	P-value
Sex							0.577
Male	17	50	28	52	33	60	
Female	17	50	26	48	22	40	
Smoking (daily)							0.752
Yes	11	32	21	39	22	40	
No	23	68	33	61	33	60	
Alcohol use (> 1 daily)							0.110
Yes	8	24	16	30	24	44	
No	26	76	38	70	31	56	
Tumor size (T of TNM)*							0.014
T1	5	15	17	32	23	42	
T2	11	32	13	24	17	31	
T3	1	3	3	6	6	11	
T4	17	50	21	39	9	16	
Treatment							0.672
Surgery	12	35	24	44	23	42	
Surgery and radiotherapy	18	53	24	44	22	40	
Radiotherapy	4	12	6	11	10	18	
Surgical reconstruction							0.000
No surgery	4	12	6	11	10	18	
Primary closure	17	50	16	30	23	42	
Local flap	2	6	2	4	0	0	
Split-skin or free flap†	11	32	12	22	19	35	
Bone graft/flap	0	0	18	33	3	5	
Mean age, years (SD)	68.4 (12.2)		66.9 (12.6)		62.3 (12.9)		0.051
MMO at baseline, mm (SD)	51.8 (12.7)		45.9 (12.7)		54.5 (9.8)		0.001

*, pT for patients who received surgery, cT for patients who received primary radiotherapy; †, split-thickness skin graft (25), free vascularized flap (17). TFM, tongue and/or floor of the mouth; SD, standard deviation; MMO, maximum mouth opening

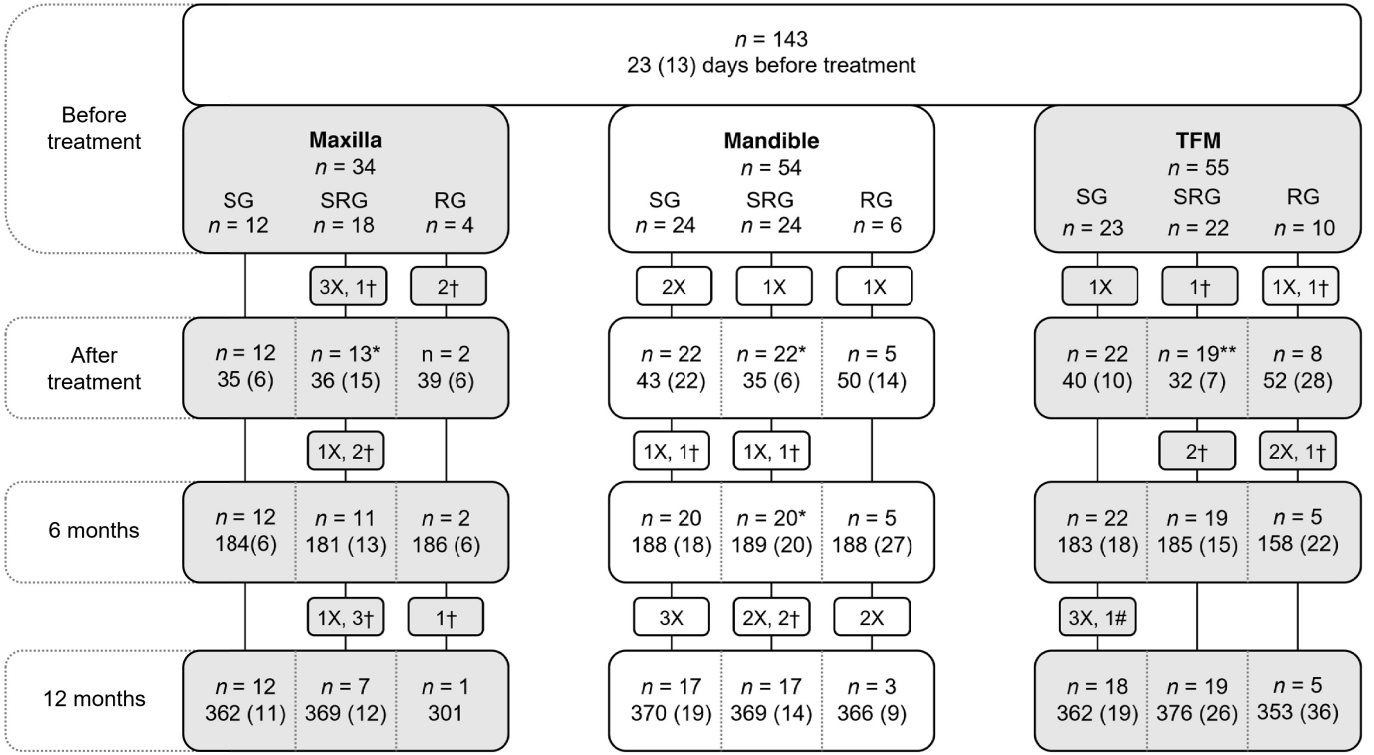

Figure 1. Flowchart showing the number of patients (n) at each assessment and the average time in days (SD) since the primary oncological treatment. TFM, tongue and/or floor of the mouth; SG, surgery group; SRG, surgery-radiotherapy group; RG, radiotherapy group; X, patient(s) stopped participating; †, patient(s) died; *, missing measurement(s); #, patient excluded because of recurrence of the tumor (see Material and methods)

Maximum mouth opening

The assessment period, tumor location, treatment modality, tumor size and alcohol use all had a significant effect on MMO. The average influence of the assessment period in the total patient group accounted for a decrease in MMO shortly following treatment (the mean MMO before and shortly following treatment was 49.5 and 36.3 mm, respectively; Bonferroni adjusted $P < 0.001$), followed by a partial recovery at 6 months post-treatment (40.0 mm, $P < 0.001$) that was stable through the 1–year follow-up period (40.0 mm, Bonferroni adjusted $P < 0.001$). Tumor location had a significant interaction with the assessment period (Figure 2), suggesting that the differences in MMO between tumor locations were different at each assessment. The patients with a TFM tumor had higher MMO values at all post-treatment assessments than the patients with a maxillary or mandibular tumor. Before the oncological treatment, patients with a mandibular tumor had significantly smaller MMO values than the patients with a maxillary or TFM tumor. However, at the three post-treatment assessments the mandibular tumor group was not significantly different from the maxillary tumor group. After 1 year, MMO in the patients with each of the three tumor locations had decreased significantly compared with their respective pre-treatment assessments (Bonferroni adjusted $P < 0.001$). Furthermore, MMO in the patients in each of the tumor location groups was significantly lower than the healthy controls after 1 year; in contrast, MMO in the pre-treatment maxillary and TFM tumor groups did not differ significantly from the healthy control group. When comparing tumor locations of the maxilla and mandible, differences between anterior locations (upper and lower alveolar process, lower lip and hard palate), posterior locations (maxillary tuber, soft palate, maxillary sinus and retromolar trigone) and the cheek were found. Anterior tumor locations had a larger MMO at each assessment compared to posterior tumor locations (6.1 mm, $P = 0.007$) and compared to tumors in the cheek (4.9 mm, $P = 0.082$).

Treatment modality also had a significant interaction with the assessment period (Figure 3). Before treatment and shortly after treatment, there was no significant difference with respect to MMO between any of the treatment modalities. MMO in the surgery-radiotherapy group and the radiotherapy group was similar at all assessments, and MMO decreased significantly in both groups following treatment, with no recovery by either 6 or 12 months.

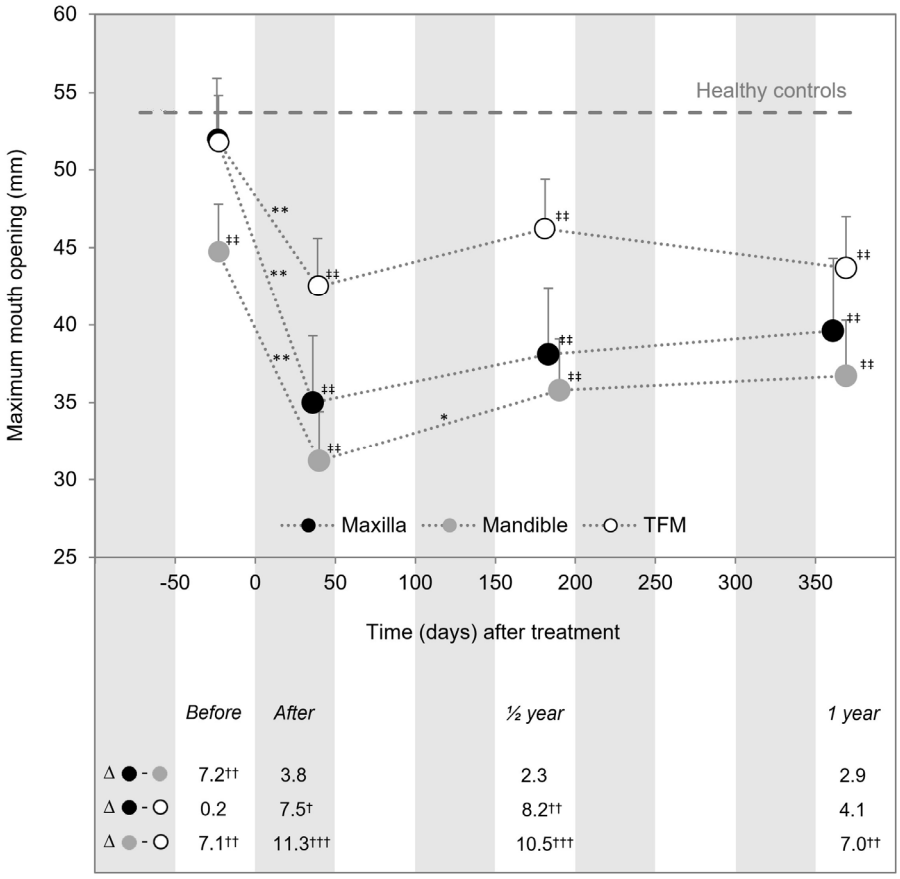

Figure 2. Graph showing mean maximum mouth opening (mm) with 95% confidence intervals for the indicated tumor locations at every assessment plotted against the average time (in days) since the primary oncological treatment. The healthy controls had a mean MMO of 53.7 mm. The table below shows the estimated differences (in mm) in mean maximum mouth opening between tumor locations at each assessment; the statistics reflect differences between tumor locations (†).The means of and differences between the patient groups were calculated with a linear mixed-effects model using the assessment period, tumor location, treatment modality, tumor size and alcohol use as fixed effects. TFM, tongue and/or floor of the mouth.

* $P < 0.050$, ** $P < 0.001$ between adjacent assessments in one tumor location

‡ $P < 0.010$, ‡‡ $P < 0.001$ compared to healthy controls ††† $P < 0.001$ between tumor locations at one assessment

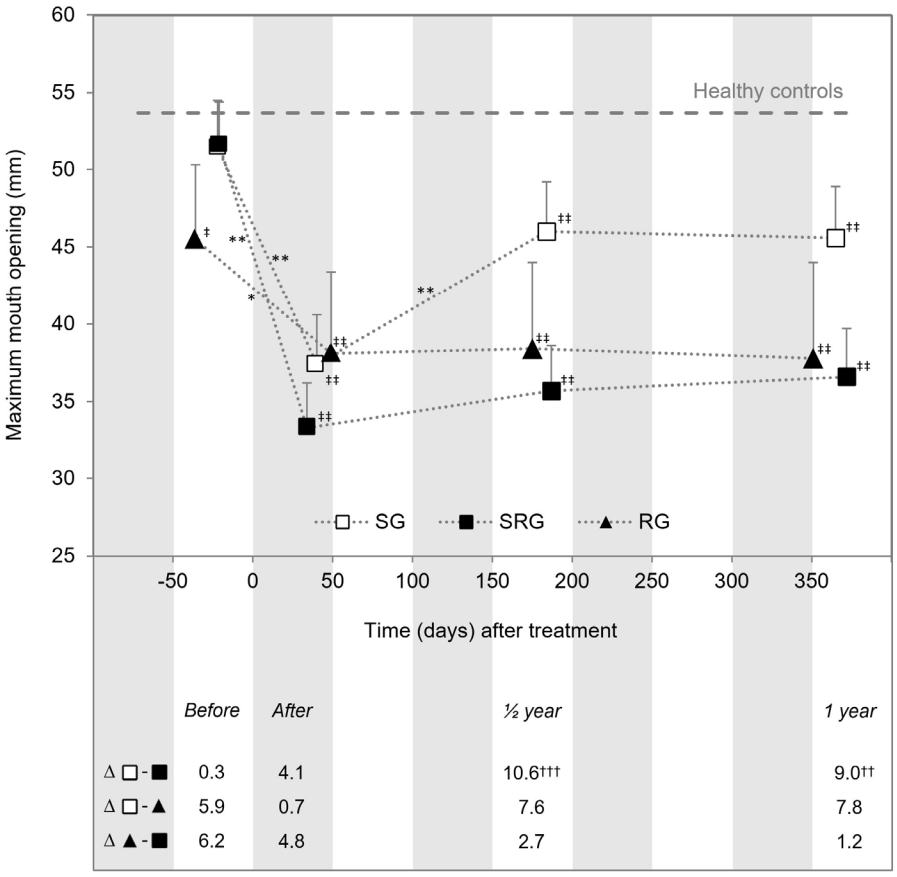

Figure 3. Graph showing mean maximum mouth opening (mm) with 95% confidence intervals for the indicated treatment modalities at every assessment plotted against the average time (in days) since the primary oncological treatment. The healthy controls had a mean MMO of 53.7 mm. The table below shows the estimated differences (in mm) in mean maximum mouth opening between treatment modalities at each assessment; the statistics reflect differences between treatment modalities (†).The means of and differences between the patient groups were calculated with a linear mixed-effects model using the assessment period, tumor location, treatment modality, tumor size and alcohol use as fixed effects. SG, surgery group; SRG, surgery-radiotherapy group; RG, radiotherapy group.

* $P < 0.050$, ** $P < 0.001$ between adjacent assessments in one treatment modality ‡ $P < 0.010$, ‡‡ $P < 0.001$ compared to healthy controls ††† $P < 0.001$ between treatment modalities at one assessment

In contrast, the surgery group recovered partially – but significantly – from their initial post-treatment decrease in MMO by 6 months. As a result of this partial recovery,

MMO was significantly higher in the surgery group than in the surgery-radiotherapy group both 6 and 12 months post-treatment. After 1 year, MMO in both the surgery and surgery-radiotherapy groups had decreased significantly compared to their respective pre-treatment assessments (Bonferroni adjusted $P < 0.001$) and compared to the healthy control group. In the radiotherapy group, MMO was not significantly different after 1 year relative to their pre-treatment values (Bonferroni adjusted $P = 0.062$).

The effect of tumor size (T of TNM) and alcohol use was the same at all assessments, as no interaction with the assessment period was found. Patients with a T4 tumor had a significantly smaller MMO than the patients with a T1 tumor (a mean difference of 8.8 mm) and the patients with a T2 tumor (a mean difference of 5.6 mm) (Table 3). Other differences between groups with different tumor sizes were not significant. With respect to alcohol use, patients who consumed more than 1 alcoholic beverage per day on average had a significantly larger MMO than those who consumed less or no alcohol (a mean difference of 3.8 mm).

Table 3. Differences (Δ) in mean maximum mouth opening (mm) with 95% CI between tumor sizes and between alcohol use

	Δ (mm)	95% CI	P-value
Tumor size			
T1 – T2	3.2	-2.1 – 8.5	0.370
T1 – T3	6.3	-2.2 – 14.7	0.198
T1 – T4	8.8	2.8 – 14.9	0.001
T2 – T3	3.1	-5.2 – 11.3	0.751
T2 – T4	5.6	0.2 – 11.0	0.030
T3 – T4	2.6	-5.7 – 10.8	0.837
Alcohol use (> 1 daily)			
Yes – No	3.8	0.6 – 6.9	0.019

Values calculated with a linear mixed-effects model using tumor location, treatment modality, tumor size and alcohol use as fixed effects. CI, confidence interval

The overall prevalence of trismus (defined as an MMO < 35 mm) in the patient cohort was 4% pre-treatment, 44% shortly after treatment, 31% after 6 months, and 31% 1 year after treatment. When analyzed based on tumor location, the prevalence of trismus at 1 year post-treatment was 41% in the patients with a maxillary tumor, 46% in the patients

with a mandibular tumor and 9% in the patients with a TFM tumor. When analyzed based on treatment modality, the prevalence of trismus at 1 year post-treatment was 8% in the surgery group, 50% in the surgery-radiotherapy group and 35% in the radiotherapy group.

Probability of trismus 1 year after treatment

The combination of three pre-treatment variables yielded the largest correlation coefficient in the multiple linear regression model for MMO 1 year post-treatment: MMO, tumor location and treatment modality. These three variables were then used in a logistic regression to calculate the probability of developing trismus within 1 year of treatment (Table 4). Other pre-treatment variables (including tumor size) were either not significant or gave a smaller correlation coefficient. Pre-treatment MMO was the highest risk factor for developing trismus (1/OR 1.148 per mm); thus, the probability of developing trismus is higher with a smaller pre-treatment MMO.

Table 4. Logistic regression model for trismus 1 year after treatment

	OR	95% CI	P-value
MMO at baseline (per mm)	0.871	0.809 – 0.937	0.000
Tumor location			
Maxilla	7.702	1.169 – 50.758	0.034
Mandible	7.661	1.578 – 37.181	0.012
TFM	1	N/A	N/A
Treatment group			
SG	1	N/A	N/A
SRG	18.318	3.829 – 87.635	0.000
RG	4.624	0.364 – 58.700	0.238

OR, odds ratio; MMO, maximum mouth opening; N/A, not applicable; TFM, tongue and/or floor of the mouth; SG, surgery group; SRG, surgery-radiotherapy group; RG, radiotherapy group. The estimate of the intercept is 16.106

Other risk factors included undergoing both surgery and radiotherapy (OR 18.318) and having a mandibular (OR 7.661) or maxillary (OR 7.702) tumor. In addition, undergoing primary radiotherapy was also a risk factor (OR 4.624); although the effect of primary radiotherapy was not significant. Table 5 summarizes the probability of developing trismus within 1 year for the various patient groups based on a pre-treatment MMO of 40, 50 or

60 mm. Using this model to predict trismus after 1 year yielded an area-under-ROC of 0.921 (Figure 4).

Table 5. Probability of developing trismus 1 year after treatment (based on tumor location, treatment modality and a pre-treatment MMO of 40, 50 or 60 mm) according to the logistic regression model

Pre-treatment MMO	Treatment modality	Tumor location		
		Maxilla	Mandible	TFM
40 mm	SG	33%	33%	6%
	SRG	90%	90%	54%
	RG	69%	69%	23%
50 mm	SG	11%	11%	2%
	SRG	69%	69%	22%
	RG	36%	36%	7%
60 mm	SG	3%	3%	0%
	SRG	36%	36%	7%
	RG	12%	12%	2%

MMO, maximum mouth opening; TFM, tongue and/or floor of the mouth; SG, surgery group; SRG, surgery-radiotherapy group; RG, radiotherapy group

Self-reported mouth opening function

The correlation coefficient (within-subjects effect) for MMO and subjective mouth opening problems was r = -0.55. Hence, a decrease in MMO was correlated with an increase in self-reported mouth opening problems.

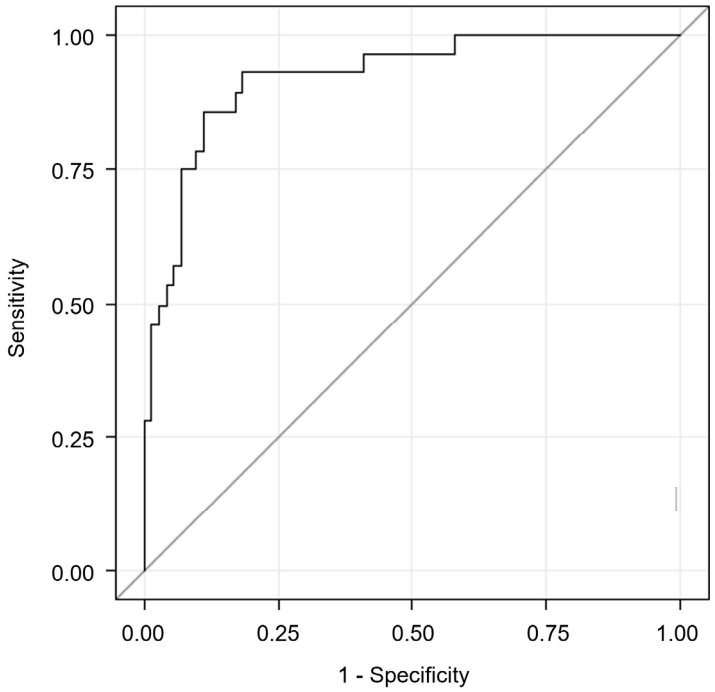

Figure 4. Receiver operating characteristic (ROC) curve for the prediction of trismus 1 year after treatment, using the logistic regression model (based on tumor location, treatment modality and pre-treatment maximum mouth opening). The area under the curve is 0.921. Areas under the curve can vary between 0 and 1; a value of 0.5 indicates that the model is useless, 1 indicates that the model has perfect diagnostic accuracy

DISCUSSION

This study revealed that maximum mouth opening (MMO) decreases following treatment for oral cancer, partially recovers within 6 months and then stabilizes up to 1 year after treatment. Factors that influenced this process included tumor location, treatment modality, tumor size (T of TNM) and alcohol use. Trismus (defined as MMO < 35 mm) within 1 year could be predicted reliably using pre-treatment variables and was most strongly associated with a smaller pre-treatment MMO, undergoing both surgery and radiotherapy, mandibular or maxillary tumor involvement, and receiving primary radiotherapy.

Strengths and limitations

The primary strengths of this study are its 1-year prospective design, the relatively large number of participants (143 patients), our distinction between tumor locations, and our comparison of the results obtained from patients with data collected from age-matched healthy controls. Our use of a linear mixed-effects model allowed us to adjust for repeated observations, loss of participants from the study and an unequal distribution of clinical characteristics (e.g., treatment modality and tumor size). Because three distinct anatomical entities were distinguished, the effect of the tumor's location on MMO could be measured. A previously validated method for measuring MMO extra-orally was used[20], because the inter-incisal method can yield unreliable results due to changing dental status and vertical overbite in the oral cancer patients between assessments. For a more comprehensive analysis, MMO was measured in millimeters rather than a simply binary measurement of the presence or absence of trismus. Each measurement was performed twice at every assessment and then averaged, yielding the smallest detectable MMO difference of 3.5 mm (as opposed to 5.0 mm when a single measurement is performed)[22].

One limitation of this study was the relatively small number of patients who received primary radiotherapy (20 patients). The resulting lack of statistical power made the results obtained from this patient group more difficult to interpret than the patients in the other treatment groups. In addition, no precise data were available regarding whether patients received orofacial physiotherapy for the MMO difficulty, the duration of their physiotherapy, the number of treatments the patient received, and the nature of their physiotherapy. Therefore, this study did not allow us to evaluate the effect of physiotherapy on MMO[23].

Risk factors

Here, we report the clinical risk factors for decreased MMO and for developing trismus (defined as MMO < 35 mm). Both surgery and radiotherapy had a negative effect on MMO, as all patient groups experienced a decrease in MMO after 1 year compared to their pretreatment assessment and compared to healthy controls. However, MMO in patients who received radiotherapy (either primary or postoperative) did not improve after their initial post-treatment decrease in MMO; therefore, these patients had a significantly smaller MMO than patients who received surgery alone. Hence, receiving radiotherapy was one of the strongest risk factors for developing trismus. Previous studies regarding

oral and oropharyngeal cancer have also reported a negative effect of radiotherapy on MMO[6,9].

With respect to tumor location, patients with a tumor of the tongue and/or floor of the mouth (TFM) had a larger MMO at each assessment and had a lower risk of developing trismus than patients with a maxillary or mandibular tumor. Only one other study found a clear distinction in MMO and trismus based on tumor location, and consistent with our results, they also concluded that patients with a TFM tumor had a lower risk of developing trismus[6]. Furthermore, we found that patients with a posterior maxillary or mandibular tumor or a tumor in the cheek had a smaller MMO than patients with an anterior maxillary or mandibular tumor. A plausible explanation for this difference is the proximity of posterior tumors to the masticator space, which results in more tumor- and/or treatment-associated damage to the masticatory muscles or temporomandibular joint. The importance of these anatomical structures in the development of trismus was demonstrated by two previous studies of head and neck cancers, which found a direct linear relationship between the magnitude of MMO reduction and the dose of radiation applied to the medial pterygoid muscle and temporomandibular joint[15,16].

Tumor size (T of TNM) also had an independent effect on MMO in our study; the magnitude of this effect was similar at each assessment, indicating that tumor size does not affect the course of MMO. A possible explanation for this finding is that the negative effect of a larger tumor on MMO (due to the pre-treatment physical obstruction of the masticatory muscles) was similar to the damage caused to these muscles by the larger magnitude of the surgical defect and/or radiation field associated with treating these larger tumors.

A surprising finding that emerged from our study was the apparent positive effect of alcohol on MMO. Patients who consumed an average of more than 1 alcoholic beverage per day had a significantly larger MMO (by 3.8 mm) at each measurement compared with patients who did not consume as much alcohol; this finding is consistent with a previous study of head and neck cancer patients[8]. Interestingly, recent in vivo studies using rats reported a significant increase in vascular endothelial growth factor (VEGF) and angiogenesis in the skeletal muscle of rats that were subjected to alcohol consumption[24,25]. Thus, an increase in the density of blood vessels in the masticatory muscles might protect against tumor- and/or treatment-induced damage.

Neither the course of MMO nor the prevalence of trismus was affected by sex, age or smoking. In addition, neither MMO nor trismus was affected by the patient's dental status, suggesting that dentate and edentulous patients have a similar development and recovery of MMO after oncological treatment (although mouth opening exercises might be easier for a dentate patient to perform). The type of surgical reconstruction had no significant effect on MMO or trismus, perhaps because the effect was already reflected in the tumor size (T of TNM), as larger tumors require more extensive surgical reconstruction. The prevalence of trismus in our study was relatively low compared to other studies[7-10,27]. However, none of these previous studies focused solely on oral cancer; these studies also included patients with oropharyngeal cancer. Thus, oral cancer patients may have a lower risk of developing trismus than oropharyngeal cancer patients.

Our analysis also revealed a linear relationship between subjective mouth opening problems and MMO, indicating that mouth opening problems arise gradually as MMO decreases (as opposed to appearing suddenly when MMO falls below a specific threshold value). This finding suggests that patients might experience mouth opening problems after a substantial decrease in MMO, even if they still have a relatively large post-treatment MMO compared to other oral cancer patients.

Clinical implications and future research

In this study, we identified the clinical characteristics of oral cancer patients who are at high risk for developing trismus. Future research should attempt to determine whether these high-risk patients can actually be identified in practice in order to prevent and treat trismus. By reducing the prevalence of trismus in oral cancer, we might improve oral functions – including chewing, dietary consistency, oral hygiene and a deterioration in quality of life – that are generally associated with trismus[6,12,27,28].

Various physical therapy regimens for patients with trismus have been suggested, but whether they are effective remains unclear. Moreover, the advantage of preventing rather than treating trismus in oral cancer patients has not been established. Only two prospective studies (regarding primary radiotherapy) in head and neck cancer patients have been published, and both studies found no positive effect of early preventive physical therapy[29,30]. Although most researchers suggest that improving MMO after head and neck cancer treatment – particularly following radiotherapy – is rarely effective[31-34], two studies reported significant post-treatment improvement using TheraBite® (Atos Medical, West Allis, WI, USA)[35,36]. Therefore, future prospective randomized clinical trials should

compare various physical therapy regimens before and after treatment in patients who are at high risk for developing trismus (for example, based on the clinical characteristics identified in this study). An alternative strategy for lowering the prevalence of trismus is to modify the radiation fields applied to patients who have a high risk of developing trismus in order to reduce the dose of radiation that is applied to the mastication apparatus.

Conclusion

Based on the results of this study, we conclude that receiving postoperative radiotherapy of an oral carcinoma, in which the maxilla or mandible is involved, results in the highest risk for developing a decrease in maximum mouth opening and subsequently developing trismus following oral cancer treatment. Future research should examine various physical therapy regimens designed to prevent and treat trismus in patients who have the clinical characteristics that place them at high risk for developing trismus.

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CHAPTER 5

Costs and clinical outcomes of implant placement during ablative surgery and postponed implant placement in curative oral oncology: a 5-year retrospective cohort study

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Clinical Oral Implants Research 2017; 28: 1433-1442

ABSTRACT

Background: The aim of this study was to compare costs and clinical outcomes of two protocols for implant placement in edentulous oral cancer patients: implant placement during ablative surgery or optional (postponed) implant placement.

Methods: All edentulous patients who underwent curative tumor surgery between 2007 and 2009 at the Radboud university medical center (Radboudumc) and UMC Utrecht, both in the Netherlands, were included retrospectively. At the Radboudumc, 79 out of 98 patients received implants during ablative surgery. At the UMC Utrecht, 18 out of 95 patients received implants after a disease-free period of at least six months, because satisfying conventional dentures could not be made. Costs, implant details and clinical outcomes were recorded retrospectively up to five years after tumor surgery.

Results: Individual costs of implant placement were lower in the during-ablative-surgery protocol (€2,235 vs. €4,152), while implant failure and loading were comparable to the postponed-placement protocol. In the during-ablative-surgery protocol, more patients received implant-retained overdentures (62% vs. 17%) and more patients had functioning dentures (65% vs. 47%); which were placed at an earlier stage (291 vs. 389 days after surgery). Overall costs of the during-ablative-surgery protocol were higher, as more patients received implants and functioning implant-retained overdentures, which were more costly than conventional dentures.

Conclusion: Placing implants during ablative surgery lowered the individual costs of implant placement and led to more patients with functioning dentures, while implant failure and loading were comparable to postponed placement.

INTRODUCTION

Patients with oral cancer face serious functional challenges after curative treatment. Restoring masticatory function is one of the key components in rehabilitating these patients and has a significant influence on health-related quality of life[1-4]. In the case of edentulous patients, conventional dentures (CDs) can be fabricated to restore this function. However, functioning CDs can only be fabricated in approximately 31% - 69% of the patients treated for oral cancer[5,6], because of the changed anatomy of the upper and lower jaw due to tumor resection, limited mouth opening[7], xerostomia, and atrophy of mucous membranes caused by postoperative radiotherapy[8,9]. Furthermore, the functionality of CDs in patients treated for oral cancer is reported to be less than optimal, restricting many patients to a semi-solid diet[6].

Placing interforaminal implants to fabricate full dentures with a mandibular implant-retained overdenture (IODs) has been shown to increase masticatory function in patients treated for oral cancer[4,10], mainly because of increased stability of the lower denture, which increases maximum bite force and permits the mastication of solid foods more easily[11]. This effect is also well documented in healthy edentulous individuals, in which a larger masticatory function and denture satisfaction compared to CDs is reported[12-16].

Current practice for the rehabilitation of patients treated for oral cancer in most centers is fabrication of CDs, when possible, followed by optional placement of implants after a disease-free period of at least six months (postponed-placement protocol)[17,18]. Recent studies, however, have reported satisfying results of an alternative strategy of rehabilitation: immediate implant placement during ablative surgery. A number of advantages over the postponed-placement protocol were reported. Firstly, a larger number of edentulous patients in the during-ablative-surgery protocol received implants, which results in more patients receiving IODs[19,20]. This difference could, at least partially, be explained by the need for an extra surgical intervention in the postponed-placement protocol, sometimes combined with additional hyperbaric oxygen therapy, for which only few patients were motivated[21]. Clinicians often refrain from implant surgery in irradiated bone, because of increased risk for developing osteoradionecrosis (ORN)[5]. Another advantage of the during-ablative-surgery protocol is that patients receive their IODs, on average, 20 months earlier, which seems to lead to better masticatory function in the long-term[11,19,22,23].

There have also been a number of disadvantages of the during-ablative-surgery protocol reported. Implant survival appears to be lower, mainly because more patients who received implants passed away or suffered a tumor recurrence which led to removal of the implants[19]. Furthermore, positioning of the implants is more difficult at the time of the ablative surgery, mainly because of unfavorable soft-tissue conditions, when the tumor resection is close to the implants[20]. It has also been speculated that backscattering of radiation might increase the risk for ORN and peri-implantitis[24-26]. So far, this effect has not yet been demonstrated, and implant failure rates have been reported to be low and equal among both protocols (3% - 11%)[19,20,27].

One important aspect which has not yet been addressed in literature, is the cost-effectiveness of both protocols. It could be expected, as demonstrated in studies on healthy individuals[28-31], that placing implants and fabricating IODs is more costly than fabricating CDs. However, the exact costs of implant placement and prosthodontics in patients treated for oral cancer are unknown. It is also not well-known, which patients can be rehabilitated with conventional prosthodontics, and which patients benefit the most from implants placed during ablative surgery.

The aim of this study was to analyze the costs and clinical outcomes of two protocols for implant placement in patients treated for oral cancer up to five years after ablative tumor surgery. Differences in implant placement, loading and loss between the two protocols were also analyzed.

MATERIAL AND METHODS

Subjects

All consecutive patients with a primary malignant tumor of the oral cavity that were treated at the Radboud university medical center (Radboudumc) and UMC Utrecht during the years 2007-2009 were analyzed. Patients were included in the study when they received ablative tumor surgery with a curative intent, and were edentulous in upper- and lower jaws prior to surgery, or became edentulous during surgery. Exclusion criteria were the presence of dental implants before surgery and previous or synchronous malignancies. All patients with a remaining natural dentition were screened by the hospital dental services in both medical centers before surgery. Teeth lost due to extensive dental caries, periodontitis, or periapical periodontitis were removed during ablative surgery. Patients with few remaining teeth, in whom prosthodontic problems could be expected, were made

edentulous during the ablative surgery. Reconstruction of a segmental mandibular defect with a reconstruction plate or a free vascularized bone flap was performed immediately in both hospitals. Based on the histological findings of the resected tissues, patients received postoperative radiotherapy within six weeks after surgery, according to the guidelines of the Dutch Head and Neck Society, up to a maximum dosage of 70 Gy. For all patients, treatment plans for prosthodontic rehabilitation and optional implant placement were accepted by their health insurance companies for full coverage. Informed consent was obtained from all patients. The study was authorized by the Ethics Committees of both the Radboudumc and UMC Utrecht, and was conducted in accordance with the guidelines for reporting observational studies from the STROBE statement[32].

During-ablative-surgery protocol

At the Radboudumc, edentulous patients received two to four two-phase implants in the interforaminal area during ablative surgery, when there was sufficient bone height, no mucosal problems were present, and the oral hygiene and compliance of the patient were deemed to be sufficient. When necessary, the alveolar ridge was lowered and the mucosa was corrected. Additionally, two to four two-phase implants were placed in the upper jaw, when retention of a conventional upper denture was deemed to be insufficient. Abutments were placed after a minimum healing period of three months. Irradiated patients received the abutments at least six months after radiotherapy. An individualized treatment plan was developed, with the aim of creating the best possible prosthodontic rehabilitation; depending on the anatomical conditions, presence and location of implants, general condition, and wishes and needs of the patient. As an illustration, two patients from this study are depicted in Figure 1 and Figure 2.

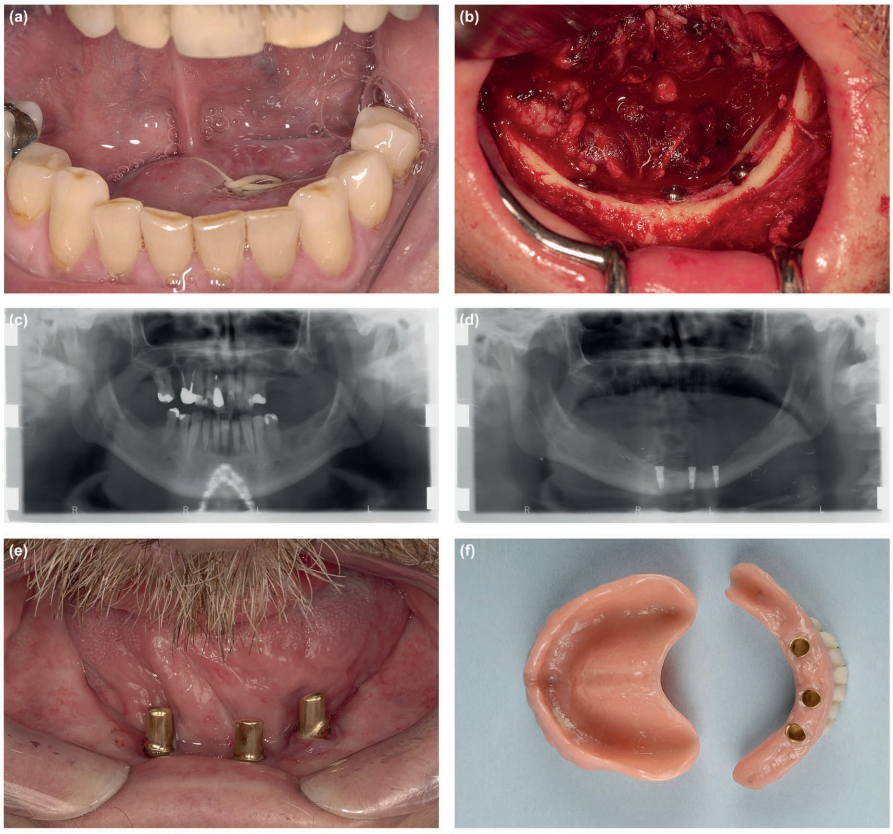

Figure 1. A 61-year old male patient presented with T4N0M0 squamous cell carcinoma of the anterior floor of the mouth (a). Three interforaminal implants were placed after removal of the remaining dentition and tumor resection including a marginal mandibular resection (b). The soft tissue defect was closed with a radial free forearm flap. Postoperative radiotherapy was administered on the tumor site. Pre (c) and postoperative (d) panoramic radiographs. Customized abutments were used for optimal retention of the dentures (e), which were placed 371 days after surgery and were still functional after 5 years (f)

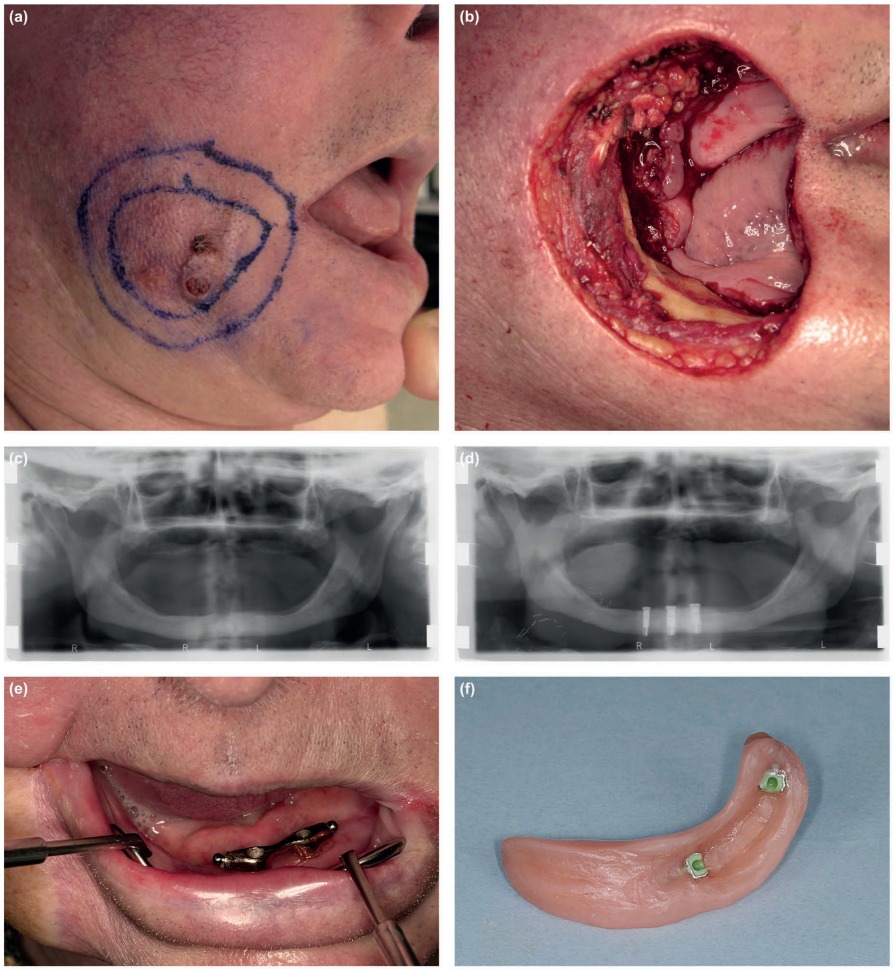

Figure 2. A 74-year old male patient presented with T4N0M0 squamous cell carcinoma of the cheek with involvement of the skin (a). The tumor was removed (b) and the defect was closed with a folded free anterolateral thigh flap. Three interforaminal implants were placed in the same session. Pre- (c) and postoperative radiographs (d) show the position of the implants. The patient received postoperative radiotherapy of the tumor site. Despite severe trismus and fibrosis, functioning implant-retained overdentures could be fabricated after 374 days on two implants using a bar attachment (e). Because of its location in the high-dose radiation field, the implant on the right side was not exposed. The dentures (f) remained functional until the patient died 4 years and 2 months after surgery due to cardiac arrest

Postponed-placement protocol

At the UMC Utrecht, all edentulous patients were invited to a consultation with the maxillofacial prosthodontist postoperatively, and conventional dentures were fabricated when possible. Patients who were not satisfied with their dentures, or patients in whom functioning dentures could not be made, were eligible for placement of two to four two-phase implants in the interforaminal area and upper jaw after a disease-free period of at least six months. Patients who received postoperative radiotherapy underwent 20 sessions of hyperbaric oxygen before implant placement and 10 sessions after implant placement. The pre-implantation surgery, abutment placement and prosthodontic rehabilitation were comparable to the during-ablative-surgery protocol.

Data collection

The electronic databases of the Radboudumc and UMC Utrecht were screened. Details on tumor location, resection, reconstruction, histopathology, postoperative TNM staging (6th edition)[33], radiotherapy and implant placement, were collected. Implants were considered as lost when they were removed due to implant failure (peri-implantitis, failed osseointegration), tumor recurrence or ORN, but also in the case of patient-death. Demographics were recorded as reported at the time of the ablative surgery and included age, sex, smoking, alcohol use and diabetes. The archives of the maxillofacial prosthodontists at the Radboudumc and UMC Utrecht were screened for details on the prosthodontic treatment, the functionality of the prostheses, the costs of the prosthodontic work and costs of the dental technician. Data also included repair, relining, and replacement of the dentures. When patients were treated at an outdoor prosthodontic center for logistic reasons, the treatment details were obtained from this facility.

Cost analysis

Costs were determined from a health-care perspective. Volumes of care were collected retrospectively from case record forms supplemented with input from the inpatient facility's administration system. Direct medical costs were calculated using hospital charges between 2007 and 2014. At both institutions, rates for implant and pre-prosthodontic surgery were determined according to the regulations of The Dutch Healthcare Authority (NZA). These included the bisection rule, which states that during every procedure under local or general anesthesia, only the costliest unit of surgery is charged at 100%. All other units during the same procedure (for instance, implant placement during ablative surgery) are charged at 50% of the rate. When patients were admitted to the hospital

due to implant placement or pre-prosthodontic surgery, costs for each day of admission were calculated using a cost manual[34]. Costs of prosthodontics were composed of in-office treatment costs, charged in quarter-hour rates; and dental laboratory costs, which were based on the fee charged by the in-office laboratories at the Radboudumc and UMC Utrecht. Average costs of different types of dentures were calculated using the average treatment costs, dental laboratory costs, repairs and relines for a particular type of dentures. All costs were adjusted for inflation and expressed in € as at 2008.

Statistical analysis

Differences between the two treatment protocols regarding demographics and oncological details were analyzed with the Chi-Square Test, or Fisher's Exact Test for cell counts lower than 5. Age was analyzed with the Independent Samples T-Test. Possible factors of influence on costs and clinical outcomes were first analyzed univariately. These factors included: treatment protocol (during-ablative-surgery or postponed-placement); age; sex; smoking; diabetes; alcohol use; tumor location; TNM staging; preoperative dental status; mandibular resection; reconstruction of bone defect; implant location (upper or lower jaw); radiotherapy and hyperbaric oxygen therapy. The continuous outcome variables were tested for normality before and after logarithmic transformation. When a normal distribution was assumed, the Independent Samples T-Test and Analysis of Variance (ANOVA) were used. Variables that failed the normality test were analyzed with the Mann-Whitney U and Kruskal-Wallis Test. Dichotomous outcome variables were analyzed with the Chi-Square Test and Fisher's Exact Test. Secondly, multivariate linear and logistic regression models were constructed for all continuous and dichotomous outcome variables, using treatment protocol and all factors of influence that had statistical significance ($P < 0.050$) in the univariate analyses. Bootstrapping was performed for continuous variables without a normal distribution. Kaplan-Meier Survival Analysis including the Log Rank Test was performed for patient survival, implant survival and survival of functioning IODs in both protocols. All tests were two-sided, and differences with a P-value < 0.050 were considered to be statistically significant. All analyses were performed using SPSS version 20.0 (IBM Corp. Armonk, NY, USA).

RESULTS

Ninety-eight patients were enrolled in the during-ablative-surgery protocol and 95 in the postponed-placement protocol. Demographics and tumor characteristics were equally distributed among both protocols (Table 1). Ninety-six patients (98%) in the during-ablative-surgery protocol had a squamous cell carcinoma, compared to 89 patients (94%) in the postponed-placement protocol (P = 0.090). Other tumor types included Merkel cell, salivary gland and odontogenic carcinoma. With regard to oncological treatment, significantly more segmental resections and less rim resections of the mandible were performed in the postponed-placement protocol (Table 2). In addition, significantly more free vascularized bone flaps or reconstruction plates were used for reconstruction of the mandible. Histopathologic examination revealed that, on average, the maximum tumor diameter did not differ significantly between patients in both protocols (P = 0.233). This was also true for the distance of the nearest margin to the tumor (P = 0.410). One-year patient survival was 82% in the during-ablative-surgery protocol and 83% in the postponed-placement protocol. Five-year patient survival was 63% in the during-ablative-surgery protocol and 58% in the postponed-placement protocol. Overall patient survival did not differ significantly between both protocols (P = 0.446). Patients from the during-ablative-surgery protocol who underwent postoperative radiotherapy started earlier (39 vs. 44 days after surgery, P = 0.023) and took less time to complete the radiotherapy (40 vs. 43 days, P = 0.002). Patients from the Radboudumc with and without implants did not differ significantly regarding the onset and duration of radiotherapy.

Implant placement

In the during-ablative-surgery protocol, 79 out of 98 patients (81%) received interforaminal implants during ablative surgery, nine of which also received implants in the upper jaw in the same session (Figure 3). Additionally, a total of 18 implants in six patients were placed post-surgery (all with local anesthesia), at a mean of 864 (SD 516) days after surgery.

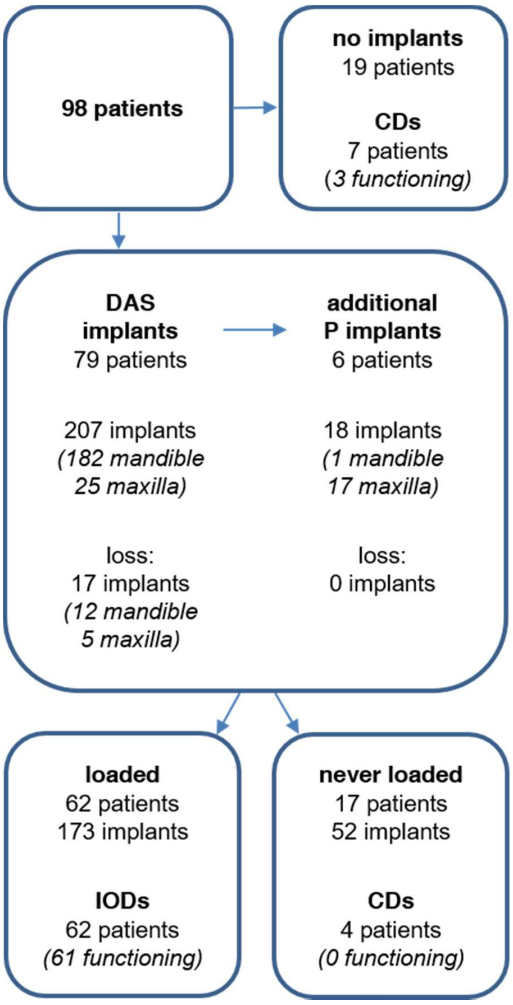

Figure 3. Flowchart on the during-ablative-surgery protocol, which shows the number of patients with implants, the type of dentures received and the number of implants placed, loaded and lost up to five years after tumor surgery. DAS, during-ablative-surgery; P, postponed-placement; IODs, implant-retained overdentures; CDs, conventional dentures

All 225 implants were Brånemark® Mk III [Nobel Biocare AB, Göteborg, Sweden] implants and were placed in native bone. Fifty-two of these implants were never loaded, but were included in the total cost analysis. Two patients required hyperbaric oxygen therapy. Three patients received a palatal keratinized mucosal graft of the anterior floor of the mouth at a later surgical intervention.

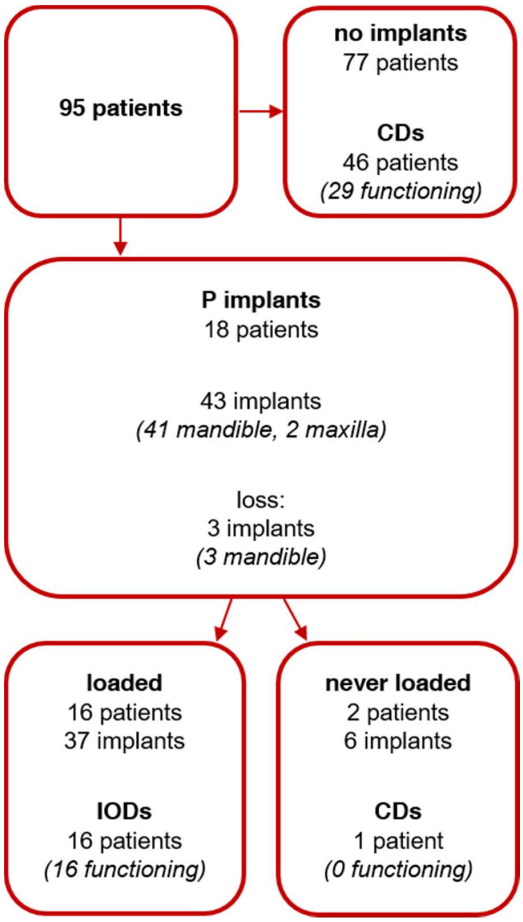

Figure 4. Flowchart on the postponed-placement protocol, which shows the number of patients with implants, the type of dentures received and the number of implants placed, loaded and lost up to five years after tumor surgery. P, postponed-placement; IODs, implant-retained overdentures; CDs, conventional dentures

Fifty-seven patients received full dentures with a mandibular IOD, four of which eventually received maxillary and mandibular IODs. Another five patients initially received maxillary and mandibular IODs. Fifty-four IODs were made with Locator® abutments [Zest Anchors LLC, Escondido, CA, USA], 12 with a bar attachment. Eleven patients wore CDs at some point up to five years after surgery, two of which used their CDs from before surgery. Three of these patients had functioning CDs, the other nine only wore an upper denture for aesthetic or speech purposes.

In the postponed-placement protocol, 18 out of 95 patients (19%) received a total of 39 Astra® Osseospeed [Astra Tech AB, Mölndal, Sweden] implants and four Straumann® [Institut Straumann AG, Basel, Switzerland] implants, at a mean of 528 (SD 406) days after surgery (Figure 4). Seven implants were inserted in free vascularized bone flaps in two separate patients, 36 implants were inserted in native bone. Four patients required general anesthesia for implant placement. Six patients received hyperbaric oxygen therapy, before and after implant placement. Two patients had a bone augmentation procedure of the mandible using iliac crest bone, two other patients received a palatal keratinized mucosal graft in the anterior floor of the mouth. Sixteen patients received full dentures with a mandibular IOD, one of which eventually received maxillary and mandibular IODs. Nine IODs were retained by Locator® abutments, eight used a bar attachment. Fifty-five patients in the postponed-placement protocol received CDs, 35 of which were functioning. In 16 patients in the postponed-placement protocol, previously fabricated CDs were completely or partially used after ablative surgery.

Implant loss

Seventeen implants in the during-ablative-surgery protocol were lost (6.7%), in 10 separate patients. Only five of these implants were lost due to implant-related causes such as peri-implantitis or failed osseointegration. These implants were placed in four separate patients; two in the upper jaw, three in the lower jaw. Four out of 98 patients had a re-resection after ablative surgery, but no implants were removed during this procedure. Five out of 98 patients had local tumor recurrence within 5 years followed by ablative surgery. In two of these patients, a total of 5 implants were removed during surgery. Seven implants were removed during segmental resection of the mandible due to osteoradionecrosis (ORN) in four patients. One other patient in the during-ablative-surgery protocol required extensive surgery due to ORN of the mandible, but this did not involve the implants.

In the postponed-placement protocol implant loss was 7.0%; three implants were removed in one patient due to loss of the fibula flap in which they were inserted. Four out of 95 patients required a re-resection after tumor surgery. Local tumor recurrence followed by ablative surgery occurred in 5 out of 95 patients within 5 years; but this did not involve the implants.

Table 1. Demographics and tumor details of patients in the during-ablative-surgery and postponed-placement protocols

	DAS (*n* = 98)		P (*n* = 95)		
	n	%	*n*	%	P-value
Sex					0.527
Male	55	56	49	52	
Female	43	44	46	48	
Tumor size (pT of TNM)					0.088
T1	20	21	24	25	
T2	43	44	32	34	
T3	14	14	7	7	
T4	21	21	32	34	
Nodes (pN of TNM)					0.997
N0	60	61	58	61	
N1	11	11	11	12	
N2	27	28	26	27	
Stage (pTNM)					0.285
I	14	14	21	22	
II	25	26	17	18	
III	18	18	13	14	
IVA	41	42	44	46	
Tumor location					0.576
Maxilla	6	6	11	12	
Lower alveolar process	24	24	26	27	
Cheek	8	8	9	10	
Tongue	27	28	24	25	
Floor of the mouth	29	30	24	25	
Lip	4	4	1	1	
Mean age, years (SD)	66.3 (11.5)		68.3 (10.8)		0.199

DAS, during-ablative-surgery protocol; P, postponed-placement protocol; SD, standard deviation

Table 2. Details regarding the oncological treatment of patients in the during-ablative-surgery and postponed-placement protocols

	DAS (*n* = 98)		P (*n* = 95)		
	n	%	*n*	%	P-value
Treatment					0.731
Surgery	44	45	45	47	
Surgery and radiotherapy	54	55	50	53	
Mandibular resection					<0.001
No resection	58	59	46	48	
Rim	32	33	14	15	
Segment	8	8	35	37	
Reconstruction of soft tissue					<0.001
Primary closure	34	35	47	50	
Local flap	0	0	2	2	
Split-thickness skin graft	34	35	8	8	
Vascularized flap‡	30	30	38	40	
Reconstruction of bone defect					<0.001
No reconstruction needed	83	85	52	55	
Free vascularized bone flap†	5	5	16	17	
Reconstruction plate	3	3	19	20	
Obturator prosthesis	7	7	8	8	
Radiation dose on tumor area					0.055
< 50 Gy	2	4	9	18	
≥ 50 and < 55 Gy	1	2	0	0	
≥ 55 and < 60 Gy	14	26	9	18	
≥ 60 Gy and ≤ 70 Gy	37	68	32	64	

‡ radial free forearm flap, ulnar free forearm flap, anterolateral thigh flap, latissimus dorsi flap, pectoralis major flap, fibula flap (with skin paddle), deep circumflex iliac artery flap (with skin paddle); † fibula flap, deep circumflex iliac artery flap; DAS, during-ablative-surgery protocol; P, postponed-placement protocol; Gy, gray

The incidence of ORN was equal to the during-ablative-surgery protocol: five patients required extensive surgery of the mandible due to ORN, but these patients did not have implants. In four of these patients, ORN developed around plate material; two patients previously underwent a fibula flap reconstruction, one patient received a reconstruction plate after a segmental resection, and one patient received mandibular plates after a lip-splitting mandibulotomy.

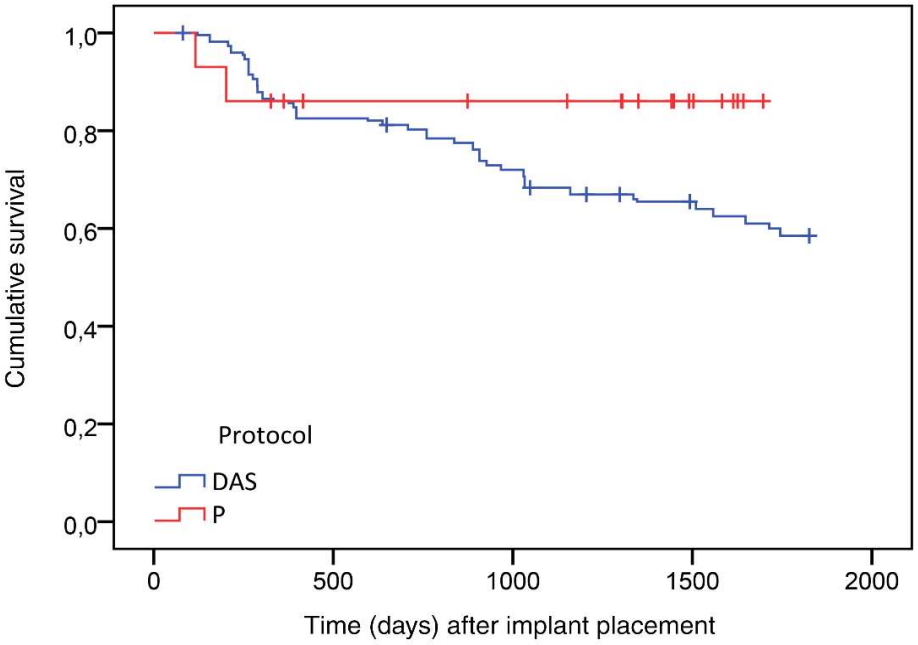

Figure 5. Cumulative survival of 225 implants in the during-ablative-surgery (DAS) protocol and 43 implants in the postponed-placement (P) protocol, with an observational period of five years after tumor surgery. Censored observations are cross-hatched

Seventy-three out of 225 implants (32%) placed in the during-ablative-surgery protocol lost their functionality due to patient-death. In the postponed protocol, 3 out of 43 implants lost their functionality because of patient-death (7%). Total survival of the implants, which includes implant loss and patients' survival, is shown in Figure 5. The cumulative implant survival after five years in the during-ablative-surgery protocol was significantly lower than the postponed-placement protocol (60% vs. 86%, P = 0.039).

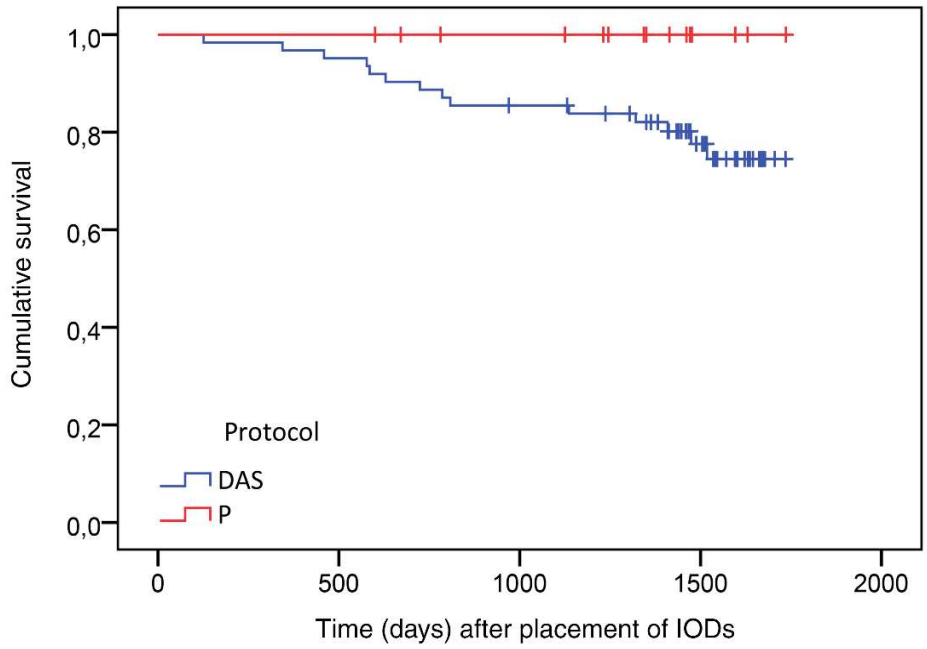

Figure 6. Cumulative survival of 62 implant-retained overdentures (IODs) in the during-ablative-surgery (DAS) protocol and 16 IODs in the postponed-placement (P) protocol, with an observational period of five years after tumor surgery. Censored observations are cross-hatched

Survival of IODs is displayed in Figure 6. In the during-ablative-surgery protocol, 77% of IODs were still functioning five years after ablative surgery, against 100% in the postponed-placement protocol; a difference that was not significant (P = 0.073).

Cost-consequence analysis

Costs of implant placement and prosthodontic rehabilitation are displayed in Tables 3 and 4. Costs of implant placement per patient with implants were 86% higher in the postponed-placement protocol. This was largely caused by more patients received hyperbaric oxygen therapy, which significantly increased costs (P = 0.001). Extra hospital admission days and higher rates for implant placement due to the bisection rule also increased costs in the postponed-placement protocol. Logically, the overall costs of implant placement and prosthodontics were 92% higher in the during-ablative-surgery protocol, since more patients received implants (81% vs. 19%) and more patients received

IODs, which were 81% more expensive compared to CDs (€4,053 vs. €2,239, P < 0.001).

Table 3. Costs per unit health-care resource for implant placement and prosthodontics

Health-care resource (unit)	Unit cost (€ as at 2008)
Implant placement	
Placement of first implant (per jaw)	635
Placement of following implant in the same jaw	160
Implant costs (per implant)	350
X-Ray examination	63
Implant exposure (per jaw)	286
Autologous bone graft	981
Palatal keratinized mucosal graft	852
Hyperbaric oxygen therapy (per session)	166
1 day of hospital admission	575‡
Prosthodontics	
CDs	2,234
CDs with obturator	4,875
Upper CD only	1,347
Full dentures with mandibular IOD	
2 Locator® abutments	3,681
3 or more Locator® abutments	3,915
bar attachment, 2 implants	4,042
bar attachment, 3 or more implants	5,189
Maxillary and mandibular IODs	5,873

Implant placement costs represent the average fees from the years 2007-2014. Prosthodontic costs reflect the average prosthodontist fee and dental laboratory costs of a particular type of dentures from the years 2007-2014. CDs, conventional dentures; IODs, implant-retained overdentures.
Sources: regulations of The Dutch Health-care Authority (NZA) on dental fees and diagnosis treatment combinations (DBCs) for oral and maxillofacial surgery from the years 2007-2014.
‡, Cost manual (Tan, Bouwmans & Hakkaart 2012)

Table 4. Comparison of costs between the during-ablative-surgery and postponed-placement protocols

	DAS (*n* = 98)	P (*n* = 95)	Univariate P-value	Multivariate P-value
Implant placement (individual costs)	2,235	4,152	<0.001	0.540
Implant placement (total costs)	176,535	74,730	<0.001	0.540
IODs (individual costs)	4,115	3,812	0.464	0.310
CDs (individual costs)	1,744	2,365	0.284	0.305
Total costs (implant placement and prosthodontics)	467,329	243,276	<0.001	0.001
Per patient with functioning IODs	6,687	9,422	0.007	0.781
Per patient with functioning dentures (CDs or IODs)	6,453	4,767	0.001	0.001

Costs (€ as at 2008) represent cumulative costs in the period from the tumor surgery up to five years thereafter. DAS, during-ablative-surgery protocol; P, postponed-placement protocol; IODs; implant-retained overdentures; CDs, conventional dentures

In both protocols, the total amount spent on implant placement was markedly lower than the amount spent on prosthodontics. In the during-ablative-surgery protocol, 38% of the total expenditure was on implantology, compared to 31% in the postponed-placement protocol. Prosthodontic costs were higher in patients with an obturator prosthesis, both for IODs and CDs ($P < 0.036$ and $P = 0.028$). When patients became edentulous during ablative surgery, their overall costs were higher than when they were already edentulous before surgery ($P = 0.019$). Furthermore, fabricating IODs was more expensive in patients with larger tumors (pT of TNM; $P = 0.049$).

The clinical outcomes of both protocols are shown in Table 5. The percentage of implants loaded and failed did not differ significantly between protocols. The major contributor to implants not being loaded was if patients died within five years ($P < 0.001$). However, receiving postoperative radiotherapy ($P = 0.010$), larger tumors (pT of TNM; $P = 0.004$), regional metastasis (pN of TNM; $P = 0.033$) and older age ($P < 0.001$) also influenced implant loading negatively. Only one implant in the during-ablative-surgery protocol was not loaded because of its position; since the area in which it was placed suffered greatly from radiation-induced fibrosis (Figure 2). Significantly more patients in the during-ablative-surgery protocol received IODs compared to the postponed-placement protocol (62% vs. 17%). Furthermore, significantly more patients in the during-ablative-surgery

protocol received functioning dentures (65% vs. 47%). However, in the multivariate analysis, this difference was not significant, because significantly less patients with a segmental mandibular resection received functioning dentures (P = 0.002). In the postponed-placement protocol, chances of receiving functioning CDs decreased significantly when patients had a segmental resection (odds ratio (OR) = 0.048), rather than a rim resection (OR = 1.429), or no mandibular resection (OR = 1). Patients in the during-ablative-surgery protocol received their functioning IODs significantly faster than those from the postponed-placement protocol, and had a significantly longer period with functioning dentures up to five years after surgery. Placement of IODs was furthermore delayed by postoperative radiotherapy (P < 0.001), segmental mandibular resection (P = 0.042) and higher tumor stages (pTNM; P = 0.046). Females received their functioning dentures on average 110 days earlier compared to males (P = 0.012).

Table 5. Comparison of clinical outcomes between the during-ablative-surgery and postponed-placement protocols

	DAS	P	Univariate	Multivariate
	(*n* = 98)	(*n* = 95)	P-value	P-value
Implants loaded	173 / 225 (77%)	37 / 43 (86%)	0.182	0.928
Implants failed	5 / 225 (2%)	0 / 43 (0%)	0.138	0.997
Patients with functioning IODs	61 / 98 (62%)	16 / 95 (17%)	<0.001	<0.001
Patients with functioning dentures (CDs or IODs)	64 / 98 (65%)	45 / 95 (47%)	0.012	0.156
Placement of IODs (days after surgery)	296 days	780 days	<0.001	<0.001
Placement of functioning dentures (days after surgery)	291 days	389 days	0.240	0.035
Average period with functioning dentures up to 5 years	899 days	558 days	0.006	0.194

DAS, during-ablative-surgery protocol; P, postponed-placement protocol; IODs; implant-retained overdentures; CDs, conventional dentures

DISCUSSION

This study has demonstrated that individual costs of implant placement were markedly lower when implants were placed during ablative surgery. In contrast, the overall costs of implant placement during ablative surgery and subsequent prosthodontics were higher compared to optional (postponed) implant placement, since more patients received implants and IODs. The percentage of implants loaded and implants failed did not differ significantly between the two protocols.

Individual costs of implant placement were higher in the postponed-placement protocol compared to the during-ablative-surgery protocol (€4,152 vs. €2,235), because more patients received hyperbaric oxygen therapy; but also since implant placement often required general anesthesia with a day of hospital admission, and the charged rate for implant placement was higher. These costs might even be higher when regarding the hospital costs instead of the charged fees, since the postponed-placement protocol requires renting an operating room, medical staff and sometimes general anesthesia, while the during-ablative-surgery protocol only requires extra operating time. To the authors' knowledge, no other study has reported on costs of implant placement or prosthodontics in patients treated for oral cancer; although one study speculated that the costs of four mandibular implants equates to €2,682[5].

In healthy subjects, one-year total costs of interforaminal implant placement and IOD fabrication (on two ball abutments) were €2,801[35]. Another study reported total implant and IOD (two ball abutments) costs of €5,695 up to three years after implant placement[31]. Costs of implant placement in patients treated for oral cancer, therefore, seem to be only slightly higher compared to healthy edentulous individuals. However, no studies that reported on the costs of implant placement separately were available.

Prosthodontic costs found in this study were €4,053 for functioning IODs and €2,239 for CDs. These costs did not differ significantly between both treatment protocols. Greater costs were incurred when patients required an obturator prosthesis and when they became edentulous during ablative surgery; possibly because of resorption of the newly edentulous jaws that required additional relines of the dentures. Results from this study on patients treated for oral cancer seem to be comparable with healthy individuals: for IODs on two ball abutments, initial costs were €2,413[36] and €5,841 after 18 years[30]. Costs for CDs were €1,528 after one year[35], €2,359 after three years[31] and €3,726 after 18 years[30]. However, making a full comparison with these studies is difficult, because of

the different countries and health-care systems they were reported from, and because costs probably have increased in the time leading up to our study due to inflation.

Full comparison between the during-ablative-surgery and postponed-placement protocols might be difficult, because relatively more patients in the latter protocol had a segmental mandibular resection, followed by fibula flap or plate reconstruction, while in the during-ablative-surgery protocol more patients had a rim resection. This finding was not related to the tumor location, maximum diameter, size (pT of TNM) or resection margin. Hence, this difference might be partially explained by personal preferences of the surgeons involved in each protocol. Another possible limitation of this study is that, because of the retrospective nature, some patients might be 'lost' in follow-up and have received additional treatment in an outdoor facility, without the authors' knowledge. Fees were chosen for the cost calculation, because they represent actual health-care costs and are relevant when considering the limited funds for oral rehabilitation. In the Dutch tariff system, treatments are evaluated yearly to determine at what fee they should be charged. Therefore, it was assumed that costs based on fees accurately reflected the costs of labor, time spent by clinicians and overhead costs. Indirect costs, such as patients' traveling expenses and work absenteeism were not included in this analysis, because these costs are mostly based on estimation and are less relevant to the matter of societal funding.

One might further argue that the indication for hyperbaric oxygen therapy when implants are installed in irradiated bone is questionable. Experimental studies have shown a beneficial effect on osseointegration and prevention of ORN, but no proper clinical trials have been performed[37]. Recent systematic reviews have failed to demonstrate a positive effect on implant survival; although the quality of the evidence was suboptimal, since only 3 clinical studies (involving 102 patients) were available[18,38,39]. The effect of hyperbaric oxygen on ORN after implant placement was not analyzed, probably because the incidence of such events is low[40]. Nevertheless, the European Committee for Hyperbaric Medicine and the Dutch Association of Oral Implantology recommend considering hyperbaric oxygen therapy when placing implants in bone that received over 50-55 Gy; although the available evidence is considered weak[41]. To the authors' knowledge, all centers in the Netherlands apply hyperbaric oxygen therapy when implants are installed in heavily irradiated bone, and, therefore, these costs were included in our study.

Although the overall (hospital, society or insurance company-related) costs were higher, the individual functional benefits of the during-ablative-surgery protocol were clearly demonstrated in this study. Firstly, nearly four times more patients received IODs compared to the postponed-placement protocol. It is well known that IODs have better overall masticatory function compared to CDs, mainly because of increased retention of the lower denture, higher bite force and more ease with eating solid food[10,11,42,43].

Secondly, nearly two-thirds of the patients in the during-ablative-surgery protocol received functioning dentures, while in the postponed-placement protocol more than half of patients were left with no functional dentures. Such condition is associated with poor masticatory function, problems with dietary intake and increased psychologic morbidity[2,4]. This was especially true for the patients in this study, who received a segmental resection of the mandible, because in most cases, an adequate conventional lower denture could not be made. Placing mandibular implants directly after a segmental resection or performing a rim resection should, therefore, be considered when possible.

Thirdly, patients in the during-ablative-surgery protocol received their functioning IODs on average 484 days earlier than patients in the postponed-placement protocol. Earlier prosthodontic rehabilitation will speed up recovery of masticatory function, and might even lead to better function in the long-term. This effect was also demonstrated in other domains in oral cancer, such as neck-shoulder function and mouth opening[44,45]. Interestingly, females received their functioning dentures significantly faster than males. No other studies related to this subject were found, and, therefore, future research might explain this finding. The improved oral function from rehabilitation with IODs compared to CDs might lead to improvement of the quality of life, although no studies have examined this properly so far. Because costs of rehabilitation with IODs were markedly higher than CDs in this study, more research into quality of life is needed to fully determine the cost-effectiveness of both rehabilitation protocols.

Implant failure was low and comparable between both treatment protocols, which indicated that the timing of placement does not affect the viability of the implants. Other studies have also demonstrated that the location (maxilla or mandible) and receipt of postoperative radiotherapy are associated with implant failure, rather than the timing of placement[18,39,46,47]. Radiotherapy after implant placement causes backscattering, which might increase the risk of implant failure or ORN[24-26], but these risks are also present when implants are placed in irradiated bone. In this study, no indication of an increased

risk for ORN caused by backscattering was found, since the incidence of ORN was equal among treatment protocols. Furthermore, placing implants during ablative surgery did not delay the onset and course of postoperative radiotherapy.

Implant loading was comparable between protocols, and was largely dependent on the oncological prognosis resulting in tumor recurrence or death within five years. Factors of influence found in the multivariate analysis were postoperative radiotherapy, tumor size (pT of TNM), regional metastasis (pN of TNM) and age. Improper positioning did not have a significant impact on implant loading in this study. These findings have shown that, when anatomical conditions are carefully considered during ablative surgery, the timing of placement does not significantly influence the usefulness of the implants with regard to positioning.

On the contrary, implant and IOD survival rates were both higher in the postponed-placement protocol, although the latter was not significant. This was largely because patients in the postponed-placement protocol received their implants after a disease-free period of at least six months, which resulted in less implants that lost their functionality due to tumor recurrences and tumor-related deaths compared to the during-ablative-surgery protocol. Therefore, when considering placing implants during ablative surgery, factors of influence on implant loading, oncological prognosis and overall life expectancy of patients must be taken into account. In addition, patients' functional needs and the chance of fabricating satisfying conventional dentures must be considered to increase the cost-effectiveness of the during-ablative-surgery protocol.

In conclusion, placing implants during ablative surgery lowered the individual costs of implant placement, while implant failure and loading were comparable to postponed placement. Nevertheless, overall costs of the during-ablative-surgery protocol were higher, because more patients received functioning implant-retained overdentures, which are placed at an earlier stage as compared to patients from the postponed-placement protocol. More research on individualized treatment planning is required to increase the cost-effectiveness of both protocols.

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CHAPTER 6

Immediate implant placement in edentulous oral cancer patients: a long-term retrospective analysis of 207 patients

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ABSTRACT

Background: Although the functional benefits of implants in the rehabilitation of edentulous cancer patients are well-known, most studies report on postponed implant placement. The outcome of immediate implant placement regarding successful rehabilitation, implant loading and survival is unclear.

Methods: Two hundred and seven edentulous oral cancer patients that received implants during ablative surgery at the Radboudumc between 2000 and 2011 were included. Data regarding the oncological treatment, implant placement, follow-up and prosthodontic rehabilitation were recorded retrospectively with a follow-up period of 5 up to 17 years.

Results: Functioning implant-retained overdentures were made in 73.9% of the patients. Of the surviving patients, 81.9% had functioning overdentures after 2 years and 86.3% after 10 years. Patients with ASA score 1 and younger patients were rehabilitated more frequently. The median time of functioning denture placement was 336 days after surgery, with a negative influence of postoperative radiotherapy. Implant survival was 90.7%, and was lower when the implant was placed in a jaw involved in the tumor.

Conclusion: Immediate implant placement during oral cancer surgery lead to a high number of edentulous patients rehabilitated with implant-retained overdentures, which are placed at an early time.

INTRODUCTION

Patients treated for oral cancer often suffer from permanent functional impairments after surgery, especially when postoperative radiotherapy is administered. Important functions at risk include chewing, speech and swallowing, and their deterioration negatively influences quality of life[1-3]. Oral cancer patients who are edentulous, or become edentulous during tumor surgery, are even more at risk of losing oral functions, since fabrication of conventional full dentures is often difficult or impossible. Especially in the lower jaw, ablative surgery may reduce the area of support for the dentures, while radiotherapy-induced xerostomia and atrophy of the mucosa underlying the dentures may hinder denture tolerance even more. Because satisfying conventional dentures can only be made in 30% - 50% of this patient group, a large number of edentulous patients will receive no dentures or wear solely an upper denture for aesthetics or speech[4,5]. Patients without functioning dentures have markedly decreased masticatory performance, which may restrict them to soft foods or fluids permanently[6,7].

When full dentures are retained by implants, they increase the dentures' stability and retention, which has been widely documented in healthy edentulous patients[8,9]. In patients treated for oral cancer, prosthodontic rehabilitation using implants leads to more functioning dentures, improved patient's chewing ability and denture satisfaction compared to conventional dentures[5,10-12]. To date, the timing of implant placement in oral cancer patients remains a matter for discussion.

Most head and neck oncology centers place implants after a disease-free period of at least 6 to 12 months following oncological treatment, on the condition that conventional dentures could not be made or when patients report significant functional problems with their dentures. This protocol of postponed implant placement is reported to have a high rate of successful rehabilitation and high implant survival, ranging between 93% and 96%[13-15]. Even higher implant survival is reported when implants are placed in the mandible versus the maxilla, or in native bone versus autologous bone grafts[16,17]. Although past studies suggested a significant difference in implant survival between irradiated and non-irradiated patients with oral cancer, recent studies that include modern radiation techniques report more similar implant survival[18]. The main disadvantage of the postponed protocol is that, in the end, many patients will not receive implants, because they are unwilling or incapable to undergo an extra surgical and prosthodontic procedure. Furthermore, in patients that received high-dose radiotherapy in the interforaminal area,

the risk of developing osteoradionecrosis either makes implant placement impossible or necessitates additional hyperbaric oxygen therapy[19].

An alternative strategy is immediate placement of implants during the ablative surgery. In this protocol, edentulous patients in whom problems with the prosthodontic rehabilitation are very likely, receive implants in the lower jaw or in both jaws, already in the same session as the tumor removal. This protocol increases the number of patients rehabilitated with implant-retained overdentures and increases the speed of rehabilitation[20]. Because osseointegration takes place before postoperative radiotherapy, implant failure is lower or at least equal to postponed implant placement[21-23]. However, there are also disadvantages to immediate implant placement. Obviously, a number of implants are not utilized due to tumor recurrence, comorbidity, osteoradionecrosis or patient death. Also, the costs of prosthodontic rehabilitation for the total patient group are higher with immediate placement compared to postponed placement, although the individual costs are lower[5]. It is furthermore speculated that immediately placed implants sometimes may not be loaded due to improper placement or soft-tissue problems, and might increase the risk of post-treatment complications such as osteoradionecrosis.

The first aim of this study was to determine implant loss, implant failure, implant loading and prosthodontic rehabilitation in edentulous oral cancer patients that received implants during ablative surgery. The second aim was to identify demographic, oncological and treatment-related factors of influence on these outcome measures.

MATERIAL AND METHODS

Subjects

All consecutive patients who were treated for oral cancer in the Radboud university medical center (Radboudumc; Nijmegen, The Netherlands) in the years 2000 to 2011 were examined retrospectively. When patients had a primary malignancy of the oral cavity for which they underwent ablative surgery with a curative intent, their dental records were also screened. Patients were included when they were edentulous in both jaws before surgery or became edentulous during surgery, and received interforaminal implants during ablative surgery. Exclusion criteria were the presence of dental implants prior to oncological treatment and previous or synchronous head and neck malignancies. Patients received postoperative radiotherapy within six weeks after surgery based on the histopathologic findings, according to the guidelines of the Dutch Head and Neck

Society. The study was conducted in accordance with the World Medical Association Declaration of Helsinki (June 1964) and subsequent amendments, and the rules for reporting observational studies from the STROBE statement.

Implant placement

All oral cancer patients received preoperative dental screening by a multidisciplinary team including a head and neck surgeon, maxillofacial prosthodontist, dentist, and an oral hygienist. Teeth with extensive caries, periodontal disease or periapical periodontitis, were removed during surgery. Teeth were also removed when they had a dubious prognosis and were in a potentially high-dose radiation area. Prior to oncological treatment, a prosthodontic rehabilitation plan was made for dentate patients with a mutilated dentition, and included the fabrication of partial dentures, crowns and bridges; with or without implant retention. When prosthodontic rehabilitation was not possible due to little remaining teeth or an unfavorable occlusal relationship, patients were made edentulous during surgery.

All edentulous patients, pre-existent or new, were eligible for the placement of two to four implants in the interforaminal region of the mandible. Patients did not receive mandibular implants when insufficient bone height was present, when a segmental resection of the entire interforaminal area was conducted, when there was a lack of motivation for rehabilitation with implant-retained overdentures or when there was advanced cognitive impairment. Additionally, implants were placed in the upper jaw in patients who received a maxillectomy and in patients with preexisting retention problems of the upper denture, provided that sufficient bone volume was present and retention problems with a conventional upper denture could be expected. All implants were Brånemark® Mk II/III (Nobel Biocare AB, Göteborg, Sweden) two-phase implants and were placed in native bone. Implants were loaded after a minimum healing period of three months. When patients received postoperative radiotherapy, implants were surgically exposed at least six months after radiotherapy.

Data collection

The databases of the hospital and the department of maxillofacial prosthodontics at the Radboudumc were examined. Hospital data included routine oncology check-ups up to 5 years after treatment, as well as additional appointments regarding implantology, tumor recurrence, or complications with a follow-up period between 5 and 17 years. At the prosthodontics department, data were collected with a follow-up period between 5

and 17 years, regarding both the fabrication and modification of dentures. When dentures were made at an outdoor prosthodontic unit, data from this unit were also acquired. Sex, age, smoking, diabetes and the American Society of Anesthesiologists Physical Status score (ASA score) as reported at the time of surgery were obtained. A distinction was made between patients who smoked daily and those who smoked less frequently or not at all. Data on tumor type, tumor location, preoperative dental status, pre- and postoperative TNM staging (7th edition), tumor resection, reconstruction, histopathology, radiotherapy, chemotherapy, tumor recurrence, osteoradionecrosis and pathological fractures were assessed. There was mandibular tumor involvement when the tumor was primarily located on the lower alveolar process or the retromolar trigone, and in other tumor locations where a rim or segmental mandibular resection was performed. There was maxillary tumor involvement when the tumor was primarily located on the maxilla and in other locations where a maxillectomy was performed. Furthermore, implant placement, loading, survival, failure, date of denture placement and denture functionality were recorded. Dentures were considered functional when patients used them to eat their meals. The Dutch population register was accessed to verify the information on patient survival.

Statistical analysis

Binary outcome measures, which included placement of dentures (yes/no), osteoradionecrosis requiring surgery (yes/no) and implant loading (yes/no) were first analyzed univariately with logistic regression. All possible factors of influence that had statistical significance ($P < 0.050$) in the univariate analyses, were used in multivariate logistic regression models with backward elimination with 0.050 significance level for removal. The other outcome measures were displayed in days after surgery. These included placement of dentures, survival of dentures, implant loading, implant survival and patient survival. These outcome measures were first analyzed univariately with Cox proportional hazard models, using the log-rank test to calculate statistical significance. The factors with a significant influence ($P < 0.050$) in the univariate analyses, were included in multivariate Cox proportional hazard models, using backward elimination with 0.050 significance level for removal. Kaplan-Meier survival curves were constructed for patient survival and implant survival. Patients were censored at the end of the follow-up period, or at the moment of death. Timing of denture placement and survival of dentures were analyzed with a follow-up period of 5 years, the other outcome measures with a minimum of 5 and a maximum of 17 years. All tests were two-sided, and differences

with a P-value < 0.050 were considered to be statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Table 1. Demographics and tumor details of 207 edentulous oral cancer patients with implants placed during ablative surgery

	n	%		*n*	%
Sex			ASA score		
Male	124	60	1	28	13
Female	83	40	2	120	58
Smoking (daily)			3	59	29
Yes	128	62	Diabetes		
No	79	38	Yes	24	12
Tumor location[a]			No	183	88
Floor of the mouth	70	34	Tumor size (cT of TNM)		
Tongue	47	23	T1	39	19
Lower alveolar process / lip	53	25	T2	104	50
Maxilla or cheek	37	18	T3	21	10
Tumor type			T4	43	21
Squamous cell carcinoma	199	96	Nodes (cN of TNM)		
Osteosarcoma	1	1	N0	169	82
Glandular carcinoma	7	3	N1	14	7
Mean age, years (SD)	65.2 (10.5)		N2	24	11

SD, standard deviation; ASA, American Society of Anesthesiologists; [a], tumor location can be further subdivided into anterior floor of the mouth (47), posterior floor of the mouth (23), tongue (47), lower alveolar process (20), retromolar trigone (24), lower lip (9), maxilla (16) and cheek (21)

RESULTS

A total of 602 patients had a primary malignancy of the oral cavity, of which 255 were edentulous before tumor surgery and 76 were made edentulous during surgery. Of these 331 edentulous patients, 207 patients received interforaminal implants during ablative surgery. Details regarding the study group and the oncological treatment are displayed in Tables 1 and 2.

Table 2. Details regarding the oncological treatment of 207 edentulous oral cancer patients with implants placed during ablative surgery

	n	%		*n*	%
Postoperative radiotherapy			Mandibular resection		
No	93	45	No resection	127	61
Yes[a]	114	55	Rim	64	31
Tumor size (pT of TNM)			Segment	16	8
T1	56	27	Reconstruction of soft tissue		
T2	95	46	Primary closure	65	31
T3	16	8	Local flap	5	2
T4	40	19	Split-thickness skin graft	73	36
Nodes (pN of TNM)			Vascularized flap[b]	64	31
N0	140	68	Reconstruction of bone defect		
N1	19	9	No reconstruction needed	174	84
N2	48	23	Fibula flap	4	2
Mean tumor diameter, cm (SD)	2.54 (1.34)		Reconstruction plate	12	6
Edentulous			Obturator prosthesis	17	8
Before ablative surgery	151	73	Radiation dose on tumor area		
During ablative surgery	56	27	< 50 Gy	4	4
Mandibular implants			≥ 50 and < 55 Gy	2	2
2	133	64	≥ 55 and < 60 Gy	22	19
3	66	32	≥ 60 Gy and ≤ 70 Gy	86	75
4	8	4			

SD, standard deviation; Gy, gray; [a], six patients received postoperative chemoradiotherapy; [b], vascularized flap reconstruction can be further subdivided into radial free forearm flap (40), anterolateral thigh flap (16), fibula flap with skin paddle (4), platysma flap (2), pectoralis major flap (2)

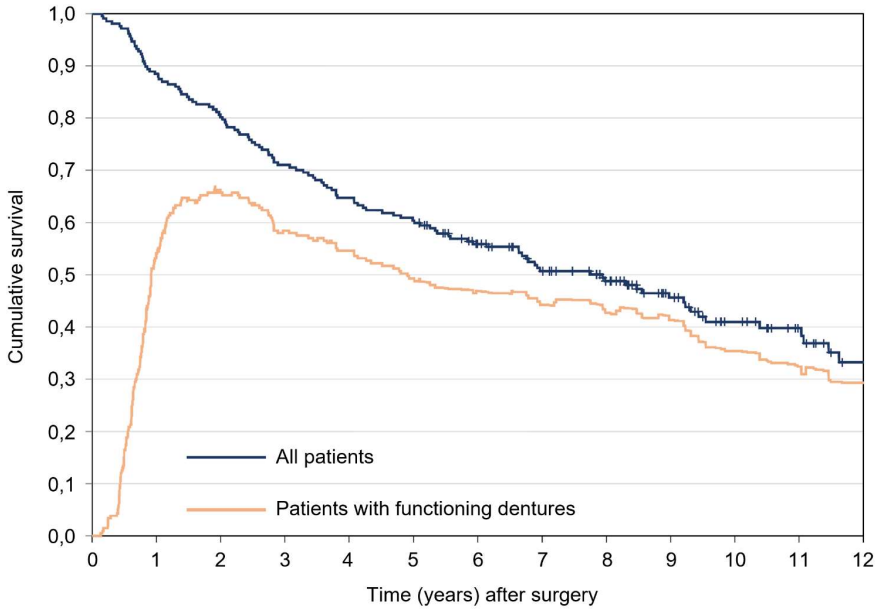

Figure 1. Kaplan-Meier survival curve of 207 patients, with an observational period of 12 years after tumor surgery (upper line). Censored observations, due to the end of the follow-up or patient death, are cross-hatched. The lower line represents the proportion of surviving patients with functioning dentures

The average follow-up period was 9.8 years, with a minimum of 5 and a maximum of 17 years. Out of the 207 patients, 125 were still alive 5 years after surgery (60.4%). Figure 1 shows the survival curve of the study group up to 12 years. Patient survival decreased with higher ASA score (ASA 3 versus 1, hazard ratio (HR) 3.559, P = 0.002) and higher pN stage (N2 versus N1, HR 2.778, P < 0.001). Patients with a tumor of the maxilla or cheek had a lower survival rate compared to those with a tumor of the tongue (HR 2.455, P = 0.003).

Functioning overdentures

Out of 207 patients, 153 patients received functioning overdentures (73.9%), 51 patients did not receive functioning overdentures (24.6%) and 3 patients were lost in follow-up. Thirty patients had died due to tumor-related causes before overdentures could be made. Other reasons that prevented the fabrication of functioning overdentures included trismus (*n* = 8), poor soft tissue conditions (*n* = 7), pathological fracture or osteoradionecrosis

(ORN) of the mandible (*n* = 3), poor general health (*n* = 2) and lack of motivation (*n* = 1). In the multivariate analysis, ASA score was a good predictor for receiving functioning overdentures, since all patients with ASA score 1 had functioning overdentures (Table 3). For patients with ASA score 2 or 3, the odds of receiving functioning overdentures were lower with higher age at baseline (odds ratio (OR) 0.947 per year increase, P = 0.006). The odds were higher in patients with lower pN stage (N0 versus N2, OR 6.275, P < 0.001), less extensive soft tissue reconstruction (primary closure versus vascularized flap, OR 5.546, P = 0.003) and when less mandibular implants were placed (2 versus 3 implants, OR 3.062, P = 0.007).

Table 3. Multivariate logistic regression model for receiving functioning dentures[a]

	OR	95% CI	P-value
Age (per year increase)	0.947	0.910 – 0.983	0.006
Reconstruction of soft tissue			
Primary closure	5.546	1.949 – 17.575	0.003
Local flap	0.601	0.060 – 5.259	0.237
Split-thickness skin graft	1.673	0.703 – 4.032	0.819
Vascularized flap	1	N/A	N/A
Nodes (pN of TNM)			
N0	6.275	2.627 – 15.853	<0.001
N1	1.992	0.536 – 7.962	0.714
N2	1	N/A	N/A
Mandibular implants			
2	3.062	1.356 – 6.912	0.007
3	1	N/A	N/A
4	1.805	0.290 – 15.625	0.138

OR, odds ratio estimates for receiving functioning dentures; CI, confidence interval; N/A, not applicable; [a], patients with ASA score 1 all received functioning dentures. Therefore, only patients with ASA score 2 or 3 were included in this model

The median time of functioning denture placement was 336 days after surgery. In the multivariate analysis, receiving radiotherapy significantly delayed the placement of overdentures (233 versus 420 days, P = 0.005). Placement of overdentures was faster with less advanced pT stage (T1 (289 days) versus T4 (400 days), P = 0.027), pN stage (N0 (290 days) versus N2 (463 days), P = 0.002) and reconstruction of soft tissue (primary

closure (259 days) versus vascularized flap (435 days), P = 0.001). Out of 153 functioning overdentures placed, 103 were still functional 5 years after surgery (67.3%). Reasons why patients lost their functioning overdentures, included patient death (*n* = 37), surgery due to tumor recurrence (*n* = 11), ORN (*n* = 1) and soft tissue problems (*n* = 1). Higher age significantly reduced denture survival (HR 1.051 per year increase of age, P < 0.001). Survival of the functioning overdentures is displayed in Figure 1. The percentage of surviving patients with functioning overdentures was 62.2% 1 year after surgery, 81.9% after 2 years, 81.6% after 5 years and 86.3% after 10 years.

Implant loading and survival

A total of 548 implants were placed, 496 in the mandible and 52 in the maxilla. In one patient, a virtual implant planning and surgical template was used to place the implants in the maxilla. In total, 383 implants were loaded (69.9%), 156 implants were not loaded (28.5%) and 3 patients with a total of 9 implants were lost in follow-up. A total of 64 implants (11.7%) were not loaded because satisfying dentures could not be made, and 83 implants (15.1%) were not loaded because patients had died before possible prosthodontic rehabilitation. In 9 patients functioning overdentures were made, while one of the implants was not loaded; eight implants were not loaded due to improper positioning (7 in the mandible, 1 in the maxilla), and 1 implant was removed due to ORN of the mandible before overdentures could be made. Improper positioning of one mandibular implant occurred more frequently in patients with 3 (7.6%) or 4 mandibular implants (12.5%), compared to patients with 2 mandibular implants (0.8%).

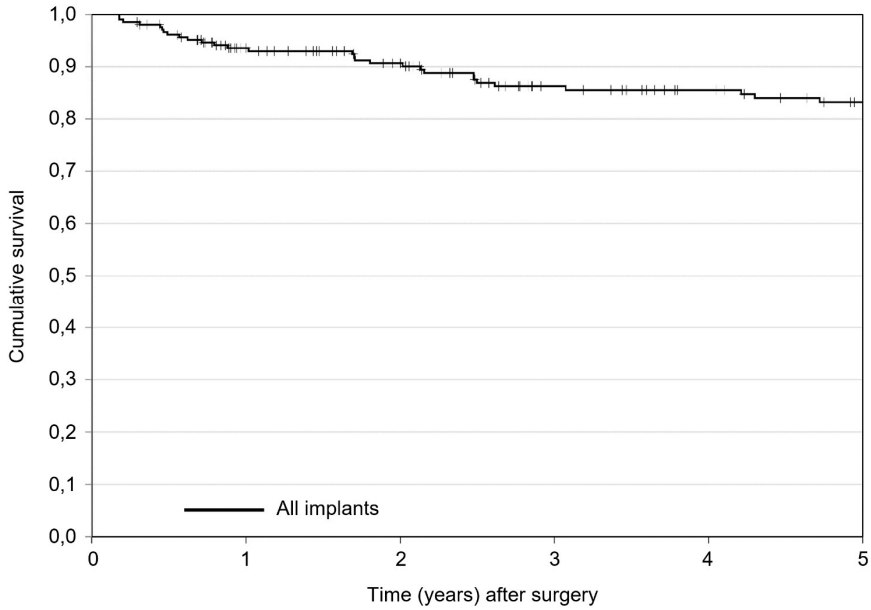

Figure 2. Kaplan-Meier survival curve of 548 implants, with an observational period of 5 years after implant placement. Censored observations due to patient death, are cross-hatched

In the total follow-up period, 51 out of 548 implants were lost (9.3%). Figures 2 and 3 show survival curves of the 548 implants up to 5 years after placement. Reasons for implant loss were tumor recurrence requiring surgery (*n* = 18), ORN of the mandible (*n* = 16), peri-implantitis (*n* = 13), failed osseointegration (*n* = 2) and mandibular fracture (*n* = 2). The only factor with a significant influence on implant loss in the multivariate analysis was tumor involvement of the jaw in which the implant was placed. A total of 251 out of 548 implants were placed in a jaw involved in the tumor. Thirty two of these implants were lost (12.7%), compared to 19 out of 297 implants that were placed in a jaw without tumor involvement (6.4%). The risk of implant loss was higher when there was tumor involvement compared to no tumor involvement (HR 2.760, P = 0.006). Implant placement in the mandible or the maxilla did not influence implant loading, loss or failure significantly.

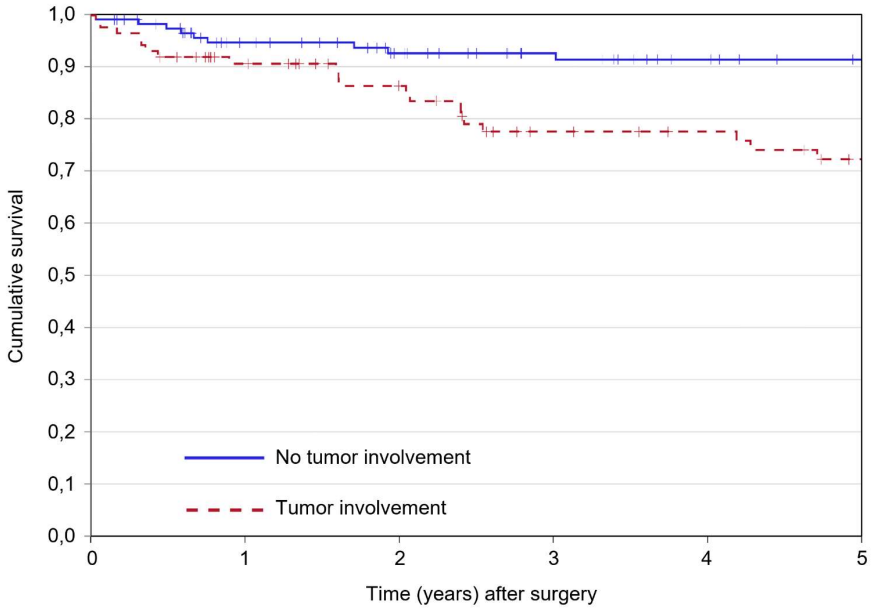

Figure 3. Kaplan-Meier survival curve of 297 implants placed in a jaw without tumor involvement (solid line) and 251 implants placed in a jaw with tumor involvement (dashed line), with an observational period of 5 years after implant placement. Censored observations due to patient death, are cross-hatched

ORN of the mandible requiring surgery under general anesthesia, occurred in 14 out of 114 patients who received radiotherapy (12.3%). Smoking had a significant effect on the occurrence of ORN in the univariate analysis (P = 0.040), since 12 out of 14 patients with ORN were smokers. However, this effect was not significant in the multivariate analysis (P = 0.058). Furthermore, performing a segmental mandibular resection followed by a plate reconstruction significantly increased the occurrence of ORN in the multivariate analysis (P = 0.042).

DISCUSSION

In this study, immediate placement of implants in oral cancer patients who were edentulous or became edentulous during tumor surgery, lead to a high percentage of functioning implant-retained overdentures (73.9%). Two years after tumor surgery, 81.9% of the survivors wore functioning implant-retained overdentures, a number that further increased

after ten years (86.3%). The median time of functioning denture placement was 336 days after surgery, and was faster in patients who did not receive postoperative radiotherapy. In the total follow-up period, implant survival was 90.7%, which is comparable to studies on postponed implant placement[15,18,24].

The number of patients rehabilitated with functioning dentures is higher following the immediate implant placement protocol (73.9%) compared to postponed implant placement, where half of the patients did not receive functioning dentures[5]. It is likely that patients often refrain from postponed implant placement, due to a lack of motivation for an additional surgical procedure or hyperbaric oxygen therapy when necessary. Furthermore, when the site-specific radiation dose was too high, implant placement is sometimes not possible due to the risk of osteoradionecrosis. The percentage of survivors with functioning overdentures in this study further increased at 2-years (81.9%) and 10-years follow-up (86.3%), because patients with a worse oncological prognosis and worse survival received overdentures less frequently. Furthermore, good general health (ASA score 1) and lower age at baseline were predictors for receiving functioning overdentures.

Most patients received functioning dentures within 1 year of surgery, and radiotherapy was one of the main delaying factors (233 versus 420 days after surgery). This is in accordance with another study on immediate implant placement[11]. Studies on postponed implant placement show a markedly slower prosthodontic rehabilitation, ranging from 24 to 60 months after surgery[5,14,25]. Main reason, is that in most head and neck oncology centers, implants are placed after a disease-free period of at least 6 to 12 months. Most systematic reviews indicate that the risk of implant failure is higher when implants are placed within 6 months after finishing radiotherapy[23,26], and some even show higher failure rates within 12 months[27]. However, it seems undesirable to further postpone implant placement, since tissue fibrosis due to ischemia and reduced cell reproduction starts 6 months after radiotherapy and increases over time[28]. Because prosthodontic rehabilitation is faster with immediately placed implants, the recovery of the masticatory function is also quicker[6], which in turn may lead to a better function in the long-term.

Out of 548 implants placed, 383 were loaded (69.9%). Studies on postponed placement report slightly higher implant loading, between 73% and 91%[5,22,25,29,30]. This advantage of postponed placement, can be explained by the fact that patients with a poor oncological prognosis, trismus and bad soft tissue conditions do not receive implants in this protocol.

Only 8 implants in our study were not loaded due to improper positioning, and this was more frequent in patients with 3 or 4 mandibular implants. However, in all of these patients, functioning overdentures could still be made. Implant survival was 90.7% in the total follow-up period, which is comparable to both another study on immediate placement[11] and to studies on postponed placement, which report survival rates between 83% and 96%[14,15,18,24]. Some of these studies report that survival is lower in irradiated bone[20] or in the maxilla compared to the mandible[13,16]; although our study found no significant differences between these groups. This can be explained by the relatively small number of implants lost (51), and it is possible that a future study with more participants will identify a statistically significant effect for both factors. In our current study however, implants placed in a jaw involved in the tumor had significantly lower implant survival (87.3%) than implants in a jaw without tumor involvement (93.6%).

Strengths of this study are the large number of patients (207), the long follow-up (5 up to 17 years), and the use of multivariate Cox proportional hazard models, in which we analyzed many possible factors of influence. A limitation is the retrospective design of this chart study. If the data had been collected prospectively, more accurate estimates of treatment outcome and risk factors could have been calculated. Furthermore, subgroups such as chemotherapy, diabetes, tumor type and fibula flap reconstruction had only a small number of patients, making it more difficult to identify them as factors with statistically significant influence.

Reconstructive protocols after ablative surgery have been optimized in recent decades. Free flap reconstruction has become the standard of care for large surgical defects, including a hemiglossectomy, a segmental mandibular defect or a defect involving 3 or more functional anatomical units[31,32]. It is likely that in future studies, more patients will be rehabilitated with a vascularized flap than the 31% in our study, which in turn will positively affect oral functions such as speech, swallowing and masticatory function. Furthermore, implants can be placed more accurately by using a virtual implant planning and surgical template, allowing the implant positioning to better suit the prosthodontic needs. Such virtual planning can also be used to immediately place implants in vascularized bone at the time of the tumor resection and reconstruction, and appears to be a reliable treatment technique[33]. By carefully planning the positioning of the implants, interference with the fixation screws is avoided and implants are placed in the most optimal bone.

The Dutch healthcare system up to 2019, provides total coverage of costs for the oncological treatment and rehabilitation of oral cancer patients, including placement of implants and overdentures when needed. The authors acknowledge that reimbursements for health-care can be very different in other countries, where patients often have to contribute to the expenses for oral rehabilitation. Due to the current differences between health insurance systems, many oral cancer patients might not be able to profit from the functional benefits of (immediate) implant placement, and end up without functioning dentures. Future research should focus on further individualizing the prosthodontic rehabilitation of these patients, thereby reducing the total costs for rehabilitation, and increasing the number of patients that can receive the best treatment.

In conclusion, this study has demonstrated that implant placement during oral cancer surgery results in a large number of edentulous patients rehabilitated with implant-retained dentures, which are placed at an early stage. Patient age, ASA score and tumor involvement of the jaw might increase the cost-effectiveness when taken into account before implant placement.

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CHAPTER 7

General discussion and future perspectives

Introduction

Oral cancer patients in the Netherlands have a 5-year overall survival of 62%[1,2]. Even when curative treatment is successful, patients often experience permanent impairment of oral functions such as eating[3], drinking[4] and speaking[5] and of facial appearance[6]. The ability to maintain an oral diet after oral cancer treatment, without dependence on a feeding tube, is important for the patient's quality of life[7]. Furthermore, in order to digest solid food, one needs a functioning dentition for chewing (mastication) and an adequate mouth opening to introduce the food particle. In patients without remaining teeth (edentulous patients), masticatory function can be at least partially restored by fabricating conventional full dentures.

Regarding oral cancer patients, more than 50% are edentulous or become so during the oncological treatment[8-10]. Due to the sequelae of the oncological treatment, it is challenging and often impossible to fabricate functioning conventional full dentures. Tumor surgery damages the oral anatomy including its innervation, thereby reducing the support, stability and functionality of the dentures. When postoperative (chemo) radiotherapy is administered, patients frequently suffer from dry mouth due to reduced saliva production, which may lead to further intolerance to wear full dentures.

Edentulous oral cancer patients might benefit from dental implants to support full dentures. In non-oncological patients, implant-retained overdentures are more stable and result in better masticatory function than conventional dentures, especially when implants are placed in the lower jaw[11,12]. This thesis investigated the possible benefits of implants for edentulous oral cancer patients with regard to masticatory function. Also, the number of patients who were successfully rehabilitated with dentures was studied. Furthermore, the optimal timing of implant placement (immediate or postponed), and the cost-effectiveness of the overall rehabilitation were evaluated. To put the subject in wider perspective, possible factors of influence on masticatory function and mouth opening in oral cancer patients were also considered.

Address to the aims

1. What is the masticatory function of edentulous oral cancer patients who are rehabilitated with implant-retained overdentures, with conventional dentures and of those without functioning dentures?

The goal of this 5-year prospective study, was to measure the masticatory function of toothless (edentulous) oral cancer patients with different types of dentures, using both objective and subjective outcome measures (chapter 2). Bite force, which was measured as the maximum amount of force a patient could exert between the upper and lower jaw[13], improved the most after rehabilitation with implant-retained overdentures. Patients who were rehabilitated with conventional dentures showed hardly any improvement of bite force; their bite force was comparable to patients who had received no functioning dentures. Strikingly, the level of bite force in edentulous oral cancer patients with implant-retained overdentures was equal to healthy subjects with conventional dentures. Masticatory performance, measured by the level of mixing of a two-colored wax-tablet after 20 chewing strokes[14,15], was equal for oral cancer patients rehabilitated with conventional dentures and implant-retained overdentures. Furthermore, the masticatory performance of patients with functioning dentures was comparable to healthy subjects with conventional dentures.

Five years after surgery, patients with implant-retained overdentures demonstrated a higher bite force and masticatory performance when implants were placed immediately during ablative surgery, compared to when implants were placed at a later stage. Patients without functioning dentures had the worst overall bite force and masticatory performance. When asked about their subjective masticatory function with questionnaires, patients with implant-retained overdentures reported fewer problems with solid food and less interference with their choice of food. Furthermore, when bite force and masticatory performance improved, fewer problems with dentures, chewing and food choice were reported.

In conclusion, both objective and subjective measures of masticatory function favor implant-retained overdentures over conventional dentures, although no differences regarding the mixing ability test were found. These results are in accordance with studies on healthy subjects, which showed a higher bite force[14,16-19] and a higher masticatory performance[16,20,21] for implant-retained overdentures. Regarding oral oncology patients, a similar effect was found[22-24], although very few studies use objective measures, or

are comparing patients with healthy subjects. Furthermore, this is the first study to describe the functional benefits of implants placed immediately during ablative surgery, as compared to postponed placement.

2. Which factors influence the masticatory function before and after oral oncological treatment?

Chapter 3 describes a 5-year prospective study to measure the masticatory performance of oral cancer patients and to identify possible factors of influence. Masticatory performance was measured by chewing on a two-colored wax-tablet. Dental status was a large contributing factor to the masticatory performance. Edentulous patients without functioning dentures performed worse than patients with functioning dentures (conventional or implant-retained). Patients with a functioning natural dentition (dentate patients) showed the most favorable masticatory function, which further increased when more opposing posterior teeth (occlusal units) were present.

Bite force was another important independent factor of influence on mastication. When patients could exert a higher maximum bite force, their masticatory performance was higher as well. Previous studies on healthy subjects also showed a strong correlation, where up to 60% of the variance in the masticatory performance could be explained by bite force[25,26]. Furthermore, it is known from literature that the bite force in dentate subjects is at least three times higher than in denture wearers[14,27]. Therefore, oral cancer patients who keep a functioning natural dentition with sufficient occlusal units will generally have the highest masticatory function compared to edentulous patients with or without dentures.

On average, masticatory performance decreased after oncological treatment, and then at least partially recovered 6 months, 1 year and 5 years thereafter. This can be attributed mainly to the placement of the functioning dentures, of which more than half were installed within 1 year after surgery. However, there was also an improvement of masticatory performance between 1 and 5 years independent of other factors. This may be explained by adaptation of the patient to their new dentures, or by improvement of the tongue function which benefits denture stability, food transportation and breakdown of the food bolus[28,29]. The location of the tumor also had an independent effect on masticatory performance. Patients with a tumor in the maxilla had the most deterioration of mastication after 6 months and 1 year, but also showed most recovery at 5 years after surgery. A possible explanation is that patients with a maxillary defect

often receive a temporary obturator prosthesis to cover the surgical defect during the first year after oncological treatment, which provides less stability and retention than the definite obturator. An increased maximum mouth opening had a positive influence on the masticatory performance. Previous studies also identified a correlation between reduced mouth opening (trismus) and impaired masticatory performance[30,31].

In conclusion, masticatory performance is mainly influenced by the dental status, bite force, mouth opening following oral cancer treatment and the location of the tumor.

3. Which factors influence the maximum mouth opening, and which risk factors are responsible for developing a reduced mouth opening (trismus)?

Patients may suffer from a reduced mouth opening (trismus) after oral cancer treatment, which negatively impacts their quality of life[32,33]. The following 1-year prospective study was performed to investigate mouth opening in oral cancer patients, and to identify risk factors for trismus (defined as maximum mouth opening < 35 mm[34]) (chapter 4).

Mouth opening decreased after tumor surgery, partially recovered after 6 months and stabilized at 12 months after surgery. When patients received postoperative radiotherapy, far less recovery at 6 and 12 months was observed. Mouth opening for these patients was comparable to patients who received primary radiotherapy. None of the patients reached the level of their pre-treatment mouth opening, or the average of the healthy control subjects.

Patients with a tumor located in the maxilla or mandible tended to have a smaller mouth opening after oncological treatment than those with a tumor of the tongue or the floor of the mouth, which was also reported elsewhere[32]. Mouth opening further decreased when the tumor was located more posteriorly (maxillary tuber, sinus, soft palate or retromolar trigone). When the tumor was locally advanced (T4), mouth opening tended to be smaller compared to less advanced tumors (T1 and T2). Furthermore, an alcohol consumption of more than 1 unit per day had a positive effect on the mouth opening (3.8 mm on average); which is consistent with a previous study on head and neck cancer patients[35]. This interesting finding might be explained by the positive effects of moderate alcohol consumption on blood vessel density in muscle tissue, which leads to better muscle regeneration and has a cardioprotective effect[36,37].

A model for the prediction of trismus 1 year after oral oncological treatment was created, using the type of treatment the patient received, the location of the tumor and the mouth opening before treatment. With these three variables, the occurrence of trismus could be predicted with 87% sensitivity and 89% specificity. The largest risk factors for trismus were having a small mouth opening before treatment, and undergoing surgery followed by postoperative radiotherapy. In previous studies, receiving surgery followed by radiotherapy was also established as a main cause of trismus[32,38].

The prevalence of trismus in this study was 31% among surviving oral cancer patients after 6 and 12 months. Other studies have reported a higher prevalence, ranging from 39% to 79%[34,35,38,39]. However, these studies also included patients with oropharyngeal cancer, who might receive radiotherapy (primary or postoperative) more frequently. Also, the pterygoid muscles might receive a higher radiation dose due to their proximity to the oropharynx, which is directly correlated to the occurrence of trismus[40,41]. Therefore, patients with oral cancer seem to have a lower risk of developing trismus than patients with oropharyngeal cancer.

4. What are the clinical outcomes and costs of immediate implant placement during ablative surgery versus optional (postponed) implant placement?

Previous chapters described the masticatory function of edentulous oral cancer patients, and the functional benefits of implant-retained overdentures compared to conventional dentures. In chapter 5, a two-center study was performed to compare the clinical outcomes and costs of two protocols for implant placement: immediate implant placement during ablative surgery and optional (postponed) implant placement. In one oncology center, implants were placed during ablative surgery, and patients were primarily rehabilitated with implant-retained overdentures. In the other center, patients first received conventional dentures after oncological treatment. When patients were dissatisfied with these dentures, additional implants and implant-retained overdentures were placed when feasible. In both centers, implants were placed in the interforaminal region to support the lower denture, and additional implants were placed in the upper jaw on indication.

Immediate implant placement led to more patients successfully rehabilitated with implant-retained overdentures than postponed placement (62% versus 17%), which is in accordance with other studies[9,42]. More patients received functioning dentures (conventional or implant-retained) after immediate implant placement (65%) than after

optional (postponed) implant placement (47%). Performing a segmental resection of the mandible followed by reconstruction with a free vascularized bone flap or reconstruction plate, led to fewer patients with functioning dentures compared to when a rim or no mandibular resection was performed. This can partly be explained, because both patients and clinicians might refrain from postponed implant placement into a free vascularized bone flap to minimize the risk of late complications, especially when postoperative radiotherapy is administered[43].

On average, edentulous oral cancer patients rehabilitated with immediate implant placement received their functioning dentures 291 days after surgery; which was 98 days earlier than those rehabilitated with optional (postponed) implant placement. When only regarding implant-retained overdentures, the difference between both protocols was even greater (484 days earlier after immediate implant placement). Previous studies also show this difference, and similarly report that the majority of overdentures are placed within 1 year after immediate implant placement[9,42,44].

The percentage of implants loaded was slightly smaller for immediate placement (77%) than postponed placement (86%), which can be attributed to the number of patients that had already died before dentures could be made. Implant failure (due to failed osseointegration or peri-implantitis) was low and comparable between both protocols (2%). Implant survival after 5 years was 93% for both protocols, and reasons implants were lost included implant failure, tumor recurrence, osteoradionecrosis and loss of the fibula flap in which they were inserted. This percentage is comparable to other studies, which reported survival rates between 83 and 93% and also did not find a clear difference between immediate and postponed implant placement[22,45-47]. However, despite comparable outcome in implant loading, failure and survival, a larger percentage of immediately placed implants lost their functionality after 5 years due to tumor recurrence or patient death compared to implants placed at a later stage (23% versus 0%).

Lastly, the costs of both protocols were compared. The individual costs of immediate implant placement were lower than postponed placement (€2,235 versus €4,152 per patient), mainly because hyperbaric oxygen therapy was not needed for immediate placement. Furthermore, implant placement in a separate session was more costly due to higher hospital charges. This is explained by the number of patients requiring general anesthesia with a day of hospital admission (22%), and by the fact that some patients first required bone augmentation to allow implant placement. However, the overall societal

costs for immediate placement were higher (€390,000 versus €199,000), because more patients received implants and implant-retained overdentures, which were more expensive than conventional dentures (€4,053 versus €2,239).

5. What are the long-term results of immediate implant placement?

In chapter 6, the long-term results of rehabilitation with immediately placed implants were evaluated. Success rates, survival and complications were examined with a follow-up period ranging from 5 to 17 years. Functioning implant-retained overdentures were made in 74% of the patients. The main reason overdentures could not be fabricated was patient death (14%). Other reasons included trismus (4%), poor soft tissue conditions (3%), pathological fracture or osteoradionecrosis of the mandible (1%) and poor general health or motivation (1%). In 7 patients, mandibular implant-retained overdentures were fabricated while one of the implants was not used because of poor positioning. This occurred more frequently in patients who received 3 (8%) or 4 mandibular implants (13%), compared to 2 mandibular implants (1%). All patients with ASA score 1 received implant-retained overdentures. Furthermore, overdentures were placed more frequently in younger patients, patients with a lower pN stage, less extensive soft tissue reconstruction and when fewer mandibular implants were placed. Overdentures were placed at a median time of 336 days after surgery. Receiving radiotherapy was one of the main delaying factors (233 versus 420 days), which was also concluded in another study[42]. Placing implants during ablative surgery did not delay the onset of postoperative radiotherapy when compared to optional (postponed) placement (chapter 5).

One year after surgery, 62% of the surviving patients had received implant-retained overdentures. This percentage further increased after 2 and 5 years (82%) and after 10 years (86%). A possible explanation, is that patients with a worse oncological prognosis and overall survival received overdentures less frequently. Overdenture survival was 67% after 5 years, and the main reasons overdentures were lost were patient death (24%) and surgery due to tumor recurrence (7%). Implant survival was 91%, and was comparable to other studies on immediate and postponed placement[45,47-49]. Implants were lost because of tumor recurrence requiring surgery (3%), peri-implantitis or failed osseointegration (3%) and osteoradionecrosis of the mandible (3%). Implant loss occurred more frequently when there was tumor involvement of the jaw in which the implant was placed (13%). Radiotherapy was not a risk factor for implant loss, which was in contrast to another study on immediate implant placement[22]. This can be explained by the fact that the initial phase

of osseointegration, characterized by vascularization around the implant, influx of bone cells and growth of early (woven) callus[50,51], already has taken place before the onset of postoperative radiotherapy.

Osteoradionecrosis of the mandible requiring major surgery occurred in 12% of the patients who received postoperative radiotherapy. The percentage of patients with osteoradionecrosis did not differ between immediate implant placement and optional (postponed) implant placement (chapter 5). Other studies found that the main risk factor for osteoradionecrosis was resection of the mandible followed by postoperative radiotherapy, and reported that the majority of osteoradionecrosis cases appeared at the margins of the mandibular resection[52,53]. Hence, the additional risk of osteoradionecrosis due to radiation backscattering from immediately placed implants, as previous in-vitro and modelling studies suggested[54-56], appears to be low.

Conclusions

Edentulous oral cancer patients rehabilitated with implant-retained overdentures showed a better overall masticatory function compared to those with conventional dentures. When implants were placed immediately during ablative tumor surgery, more patients were rehabilitated with functioning dentures than when implants were placed optionally at a later stage. Furthermore, immediate implant placement resulted in a faster prosthodontic rehabilitation compared to optional (postponed) implant placement. Masticatory performance was highest in dentate patients and lowest in edentulous patients, and was strongly influenced by the maximum bite force a patient could exert. Tumor location and maximum mouth opening also influenced masticatory performance. Having a reduced maximum mouth opening, which is termed trismus when the mouth opening is smaller than 35 mm, was strongly associated with postoperative radiotherapy and tumor involvement of the mandible or maxilla.

Implant survival was comparable for immediate and postponed implant placement. The number of implants that were loaded was lower for immediate implant placement, because a number of patients had already died before implant-retained overdentures could be made. Immediate implant placement did not delay the onset of postoperative radiotherapy, and no additional cases of osteoradionecrosis were observed. Furthermore, only a small number of implants were not loaded due to improper positioning; and in all instances functioning implant-retained overdentures could still be made. Costs per

patient rehabilitated with implant-retained overdentures were lower for immediate implant placement. However, the cumulative costs for all patients were higher compared to optional (postponed) placement, since more patients received implants and implant-retained overdentures.

Future perspectives

The conclusions of this thesis clearly underline the benefits of immediate implant placement: an increased number of edentulous oral cancer patients were rehabilitated with functioning dentures, which were placed at an earlier time, and led to a better overall masticatory function.

Quality of life

Although it is obvious that having a good masticatory function is beneficial to the patient, its exact role in the general quality of life (QoL) after oral cancer treatment is not understood. Current literature on QoL lacks evidence of a beneficial effect of prosthodontic rehabilitation in edentulous oral cancer patients[24,57,58], although a positive effect on the psychological well-being has been described[59].

Factors that negatively influence QoL after oral cancer treatment include the presence of comorbidities, dyspnea, dependence on a feeding tube and a low socio-economic status[7,22,60]. Most studies on the subject, however, lack a sufficient sample size, use non-standardized questionnaires, are retrospective of design, and have a short follow-up period. Therefore, a positive effect of implant-retained overdentures on the overall QoL might be masked by a deterioration in other health domains after oral cancer treatment, such as mobility, self-care, performing daily activities, pain and psychological problems.

To fully address the relationship between mastication, prosthodontic rehabilitation and QoL, future studies should have a prospective design and should include repeated measures at fixed intervals pre- and posttreatment. Studies should use validated questionnaires such as the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ H&N35, the University of Washington (UW)-QOL and the EuroQol (EQ)-5D[61-63], should contain objective measures of masticatory function, and should compare immediate implant placement to optional implant placement at a later stage. Patient-reported outcome measures (PROMs) could also be useful to gain insight

into the prosthodontic rehabilitation of edentulous oral cancer patients[64]. These outcome measures offer more in-depth detail of the patient's experience than traditional QoL questionnaires, which may lead to a better understanding of the benefits of prosthodontic rehabilitation using (immediately placed) implants.

There also seems to be a relationship between masticatory function, weight loss and QoL. A retrospective study showed that one-third of the oral cancer patients lose weight after treatment[65]. Having a normal diet, including the ability to eat solid food, is important to maintain a healthy weight. The QoL of oral cancer patients who are not able to maintain weight, is worse than those of normal weight. A possible explanation is a reduction in physical strength due to weight loss, thereby limiting movement and activity of the patient.

Furthermore, masticatory function is associated with cognitive health. Non-oncological subjects with a good masticatory function, display better cognitive functions and fewer memory problems than those with a poor masticatory function[66]. One possible cause, seems to be an improved cerebral blood flow to areas of the brain responsible for memory and learning, such as the thalamus and frontotemporal cortex, which increases with more chewing intensity[67]. Animal studies have revealed an increase in neurons and neuronal activities in the hippocampus when masticatory function was improved[68-70]. Further research in humans is needed to determine the exact interrelation, and to define which patients are most in need for (early) prosthodontic rehabilitation regarding weight and cognition.

Technical aspects

Although implant placement into native bone is reliable and accurate in the rehabilitation of edentulous oral cancer patients, implant placement into grafted bone is more challenging. After reconstruction of a segmental mandibular defect with a free vascularized bone flap, clinicians mostly wait 4 to 6 months before placing implants into the grafted bone[71]. For patients who do not require postoperative radiotherapy, implant survival is high and comparable to implants installed in native bone[58,72]. However, in the case of postoperative radiotherapy, subsequent implant placement into the irradiated bone flap is far less successful[47]. Implant survival is lower when the site-specific radiation dose exceeds 50 gray, but a critical upper limit is not known[73,74]. Furthermore, the risk of developing osteoradionecrosis might increase after implant placement in irradiated bone[72,75].

Therefore, patients and clinicians often refrain from postponed implant placement into bone flaps to avoid complications, and because patients often lack motivation to undergo another surgical procedure. The risk of implant loss, osteoradionecrosis, flap loss and the relationship to the site-specific radiation dose, as well as the possible benefits of hyperbaric oxygen therapy, need further clarification.

An alternative technique is immediate placement of implants into a vascularized bone flap at the time of the reconstruction. In these cases, implant survival seems to be comparable to postponed implant placement into a vascularized bone flap[76,77], and independent of the timing of radiotherapy (before or after implant placement)[78,79]. The fibula flap is the most ideal bone flap for reconstruction of the body of the edentulous mandible, given its equal anatomic proportions and the superior primary implant stability compared to other bone flaps[71]. Preferably, the implants are placed before segmentation of the fibula, while the vascular pedicle is still attached to the leg. By using a virtual surgical planning and patient specific templates, the implants can be placed in the most optimal position, without interfering with the fixation screws of the fibular segments. The current accuracy of this method of immediate implant placement is acceptable[80,81], but is likely to increase when more experience is gained. Future studies are needed to enhance immediate implant placement techniques.

A number of novel techniques are being developed. With the introduction of virtual surgical planning, it is now feasible to remove the tumor, reconstruct the mandible with a bone flap and perform immediate implant placement and prosthodontic rehabilitation in one treatment session (jaw-in-a-day). A temporary implant-retained overdenture can already be fabricated before operation, and can also serve as a surgical guide to position the proximal and distal mandibular segments. Patients must be restricted to a pureed diet until bony union and osseointegration has been completed. Although the first studies on these new techniques in treating benign tumors are promising[76,82], further research on immediate implant loading in patients with oral cancer is needed.

Treatment time can also be reduced by the use of digital scanning. Not only can the implants be placed during the ablative surgical treatment, they can also be scanned in the same session using specially designed scan abutments; the so-called scan markers. Using an intra-oral scanner, the surrounding soft tissue can also be registered. In advance of implant exposure, the implant-retained overdentures can already be designed and manufactured using 3D-printing or CADCAM-techniques. Although some reports

describe current techniques to be less accurate than the conventional pick-up or transfer impression techniques[83,84], novel scanning techniques are very promising.

Reducing the prevalence of trismus might also improve the prosthodontic rehabilitation of edentulous oral cancer patients. Fabrication of full dentures is challenging in patients with a restricted mouth opening, often requiring modified impression techniques and denture design (partial, two-piece or foldable dentures)[85-88]. Patients with severe trismus may not be able to receive functioning dentures at all, which was the case in 4% of patients in this thesis. Various physical therapy regimens to prevent or treat trismus have been proposed, including TheraBite® and Dynasplint® exercises, which show a moderate increase in mouth opening (6 mm on average)[89,90]. However, the results of mouth opening exercises vary significantly among patients, and no superior technique or regimen has been identified; although a larger increase in mouth opening can be expected when patients start exercising early[91].

To compensate for trismus, the intermaxillary distance can be increased by surgically reducing the height of the edentulous mandible; thereby creating more space for full dentures[92]. In edentulous patients who are at high risk for developing trismus, lowering the mandibular height preventively during ablative surgery might reduce the prevalence of mouth opening problems and problems with denture fabrication; especially when implants are placed simultaneously. However, more research on this topic is needed, which should consider the minimal mandibular height necessary for implant placement and prevention of (pathological) mandibular fractures, as well as the intermaxillary relationship. It has furthermore been suggested that a preventive ipsilateral coronoidectomy and a myotomy of the temporalis, masseter and medial pterygoid muscles might also lower the prevalence of trismus in high-risk patients[93]. Lastly, using proton therapy instead of photon therapy might reduce the radiation dose to the mastication apparatus, and thereby the prevalence of trismus; but further development of this technique is necessary to increase affordability and adoption[94].

The management of peri-implant and denture-bearing soft tissue remains a challenge. Loss of keratinized gingiva due to tumor surgery can (at least partially) be restored by performing a secondary vestibuloplasty with a split-thickness skin graft and/or a palatal keratinized mucosal graft[95,96]. In patients with complete loss of vestibular depth due to free vascularized flap reconstruction, a two-stage vestibuloplasty can be successful to rebuild the vestibule and peri-implant soft tissue[97]. Peri-implant health of implants penetrating

keratinized gingiva seems to be comparable to grafted tissue, although the split-thickness skin and gingival graft perform worse; possibly due to mobility of the graft[98]. However, it is unclear if these techniques can also be used in patients who receive postoperative radiotherapy, and whether the optimal timing of the reconstruction is pre- or postradiation. Future research should also include prosthodontic aspects of soft tissue management in edentulous oral cancer patients to optimize denture fit and peri-implant health.

Costs

Global health-care spending has been rising in the last decades, in most countries faster than the economic growth[99]. Therefore, research into the cost-effectiveness of treatments has become increasingly important. In this thesis, immediate implant placement resulted in a better masticatory function than optional (postponed) implant placement at a later stage, while the total costs of rehabilitation nearly doubled. The cost-effectiveness can be increased by selecting patients who can benefit from immediate implant placement more thoroughly. Quality-adjusted life-years (QALYs) of both treatments can be calculated for each patient, using the expected patient survival and improvement in quality of life[100]. Calculating costs per QALY can help patients and clinicians in the decision making regarding prosthodontic rehabilitation. Furthermore, a comparison with treatments in other health-care domains can be made, so health-care resources can be used more effectively.

Currently in the Netherlands, collective health-care insurance provides (almost) full coverage of costs for prosthodontic rehabilitation of oral cancer patients, including implant placement. The situation in other countries is not well-described in current literature, but it is likely that in many countries implant placement is not widely accessible to patients due to costs, especially in countries outside Europe. For developed countries, the percentage of the gross domestic product (GDP) spent on dental care differs significantly. France, the United Kingdom, Belgium and the Netherlands spent 0.4% on dental care, where the USA, Canada and Germany spent 0.8% on average[101]. In developing countries, the GDP as well as the percentage spent on dental care is smaller, making implant placement only accessible to wealthier patients. Furthermore, the percentage of dental costs paid from public and private insurance differs, where a trend towards more public coverage has been seen in the past years in the USA and France. In the USA, costs for implant placement are roughly double compared to the Netherlands[102,103], making immediate implant placement more lucrative for patients, since it lowers the individual

costs of implant placement. More studies in different countries are needed to assess the insurance systems, the costs of implant placement and prosthodontics and the financial situation of edentulous patients with oral cancer. Furthermore, all edentulous oral cancer patients in developed countries should be able to consult a multi-disciplinary team including a dentist and maxillofacial prosthodontist before oncological treatment, and should be offered the option of immediate implant placement when possible and beneficial.

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CHAPTER 8

Summary

Samenvatting

Summary

Patients treated for oral cancer often suffer from reduced masticatory function. This is especially the case in toothless (edentulous) patients, who account for more than 50% of all oral cancer patients. In these patients, masticatory function can be restored by manufacturing conventional full dentures, but this is often difficult after oncological treatment. Especially in the lower jaw, dentures often lack retention and stability after tumor surgery and subsequent radiotherapy, as a result of which many patients do not have adequately functioning dentures. Masticatory function may be improved by placing dental implants to support implant-retained overdentures, as is well-documented in healthy edentulous subjects. The aim of this thesis was to determine the effect of implant placement on the masticatory function of edentulous oral cancer patients, by using objective outcome measures. Secondly, a comparison was made between immediate implant placement and postponed implant placement.

In **chapter 2**, the masticatory function of 56 edentulous oral cancer patients was measured, and rehabilitation with implant-retained overdentures, conventional dentures and without functioning dentures was compared. Bite force and masticatory performance were assessed before surgery and at 6 months, 1 year and 5 years thereafter. Patients rehabilitated with implant-retained overdentures demonstrated a higher maximum bite force than patients with conventional dentures, who had a similar bite force to those without functioning dentures. In addition, rehabilitation with implant-retained overdentures resulted in fewer problems with consuming solid food and less interference with food choice. Masticatory performance, measured as the ability to mix a two-colored wax-tablet by chewing, was equal for patients with implant-retained overdentures and conventional dentures. This level of masticatory performance was comparable to a group of healthy edentulous subjects with conventional dentures, which were measured once. Patients without functioning dentures had the worst masticatory performance. Immediate implant placement resulted in higher bite force and masticatory performance compared to postponed implant placement.

Masticatory function was studied further in **chapter 3**. A prospective study was conducted in 123 oral cancer patients, including both edentulous patients and those with remaining teeth (dentate patients). Masticatory performance, maximum bite force and maximum mouth opening were measured before oncological treatment and at different time points up to 5 years after treatment. Masticatory performance decreased after oncological

treatment and showed a partial recovery after 6 months, 1 year and 5 years. Dentate patients had the best masticatory performance, which was even greater when more opposing posterior teeth (occlusal units) were present. Edentulous patients without functioning dentures performed worst and scored lower than patients with functioning dentures (conventional or implant-retained). Having a high bite force, which is more prevalent in dentate patients or patients with implant-retained dentures, was associated with a high masticatory performance. In addition, an increase in maximum mouth opening also led to a better masticatory performance. It was concluded that dentate patients perform best, and that edentulous patients require functioning dentures to provide adequate masticatory function.

An adequate mouth opening is necessary for introduction and transportation of food particles in the mouth, as well as for fabrication of dentures. A reduced mouth opening (trismus), defined as a maximum mouth opening less than 35 mm, is a common complication following oral cancer treatment. Hence, a prospective study of maximum mouth opening was conducted in 143 oral cancer patients with a follow-up of 1 year, as outlined in **chapter 4**. Maximum mouth opening decreased shortly after surgery, partially recovered after 6 months and stabilized at 12 months. Mouth opening recovery was considerably less in patients who also received postoperative radiotherapy. Patients with a tumor of the upper or the lower jaw had a smaller mouth opening after treatment, which decreased further when the tumor was located more posteriorly. Alcohol consumption had a positive effect on the mouth opening. Trismus occurred in 31% of patients at 12 months. Based on this study, the main risk factors for trismus in oral cancer patients are postoperative radiotherapy, a tumor of the upper or lower jaw, and a small mouth opening before treatment.

Chapter 5 described two oncology centers, each using a different protocol for implant placement. In one center, implants were placed during ablative surgery if possible, and patients were rehabilitated with implant-retained overdentures. In the other center, patients primarily received conventional dentures after oncological treatment, followed by implant placement on indication. Clinical outcomes and costs were studied retrospectively in 193 patients with a follow-up of 5 years. Immediate placement resulted in more patients with implants (81%) compared to postponed placement (19%), as was the case for implant-retained overdentures (62% versus 17%), and functioning dentures (62% versus 47%). Overdentures were placed more quickly after immediate implant placement (291 versus 484 days after surgery). Implant loading and implant survival were comparable between

protocols. The individual costs for implant placement were lower for immediate implant placement, although the overall societal costs almost doubled. The results showed that immediate implant placement benefits the patient's functionality and lowers individual costs, while the reliability is comparable to postponed implant placement and the total societal costs increase.

The long-term results of immediate implant placement in edentulous oral cancer patients were described in **chapter 6**. A retrospective study examined 207 patients who received immediate implants with a follow-up period up to 17 years. Functioning implant-retained overdentures were placed in 74% of patients. The main reasons why overdentures were not fabricated or were lost included patient death, tumor recurrence, trismus, and poor soft tissue conditions. Overdentures were more frequently placed in patients with low ASA score, low pN stage, less extensive reconstruction and in younger patients. Five years after surgery, 67% of implant-retained overdentures were still functioning, and a high number of patients had overdentures (82%). Implant survival was high and comparable to postponed placement. No additional cases of osteoradionecrosis were observed. Only a small number of implants were not used due to improper positioning. The findings demonstrated that immediate implant placement has a high success rate and leads to rapid prosthodontic rehabilitation. The risks for improper implant positioning, infection and osteoradionecrosis appear to be low.

Chapter 7 discusses the aims, conclusions and future perspectives of this thesis. To conclude, implant-retained overdentures are functionally beneficial for edentulous oral cancer patients, due to the increased masticatory function over conventional dentures. Immediate implant placement is preferable to postponed placement, as it results in a higher number of patients with functioning dentures, and a faster prosthodontic rehabilitation. By including patient and therapy-related factors in further optimization and individualization, the cost-effectiveness of immediate implant placement will increase.

Samenvatting

Patiënten die voor mondkanker zijn behandeld, hebben vaak een verminderde kauwfunctie. Dit is vooral het geval bij tandeloze (edentate) patiënten, die meer dan 50% van alle patiënten met mondkanker uitmaken. Bij edentate patiënten kan de kauwfunctie worden hersteld door een kunstgebit (prothese) te maken, maar dit is vaak moeilijk na de oncologische behandeling. Door de tumoroperatie en aansluitende radiotherapie ontstaan er vaak problemen met de retentie en stabiliteit van de prothese, waardoor bij veel patiënten geen functionerende prothese kan worden gemaakt. Het plaatsen van tandheelkundige implantaten ter ondersteuning van een klikgebit (implantaatprothese) kan leiden tot een verbetering van de kauwfunctie, zoals uitgebreid is onderzocht bij gezonde edentate personen. Het doel van dit proefschrift was om het effect van implantaatplaatsing op de kauwfunctie van edentate patiënten met mondkanker te onderzoeken, door gebruik te maken van objectieve metingen. Daarnaast werd een vergelijking gemaakt tussen directe implantaatplaatsing en uitgestelde implantaatplaatsing.

In **hoofdstuk 2** werd de kauwfunctie van 56 edentate patiënten met mondkanker gemeten. Rehabilitatie met een implantaatprothese, een conventionele prothese en zonder functionerende prothese werden vergeleken. Bijtkracht en kauwvermogen werden gemeten vóór de operatie en vervolgens 6 maanden, 1 jaar en 5 jaar na de operatie. Patiënten met een implantaatprothese hadden een grotere bijtkracht dan patiënten met een conventionele prothese, die een vergelijkbare bijtkracht hadden als patiënten zonder functionerende prothese. Bovendien leidde het maken van een implantaatprothese tot minder problemen met het eten van vast voedsel en minder problemen met voedselkeuze. Kauwvermogen werd gemeten door te kauwen op een tweekleurig wasblokje, waarna de mate van vermenging werd bepaald. Een implantaatprothese en een conventionele prothese resulteerden in een vergelijkbaar kauwvermogen, welke op het niveau lag van gezonde edentate personen met een conventionele prothese. Patiënten zonder functionerende prothese hadden het slechtste kauwvermogen. Directe implantaatplaatsing leverde een grotere bijtkracht en kauwvermogen dan uitgestelde implantaatplaatsing.

Kauwfunctie werd verder onderzocht in **hoofdstuk 3**. Er werd een prospectieve studie uitgevoerd bij 123 patiënten met mondkanker, waaronder zowel edentate patiënten als patiënten met tanden (dentate patiënten). Kauwvermogen, maximale bijtkracht en maximale mondopening werden gemeten vóór oncologische behandeling, en

op verschillende tijdstippen tot 5 jaar na behandeling. Kauwvermogen nam af na oncologische behandeling en herstelde gedeeltelijk na 6 maanden, 1 jaar en 5 jaar. Dentate patiënten hadden het beste kauwvermogen, welke verder toenam bij de aanwezigheid van meer kiezen (occlusale eenheden). Edentate patiënten zonder functionerende prothese presteerden het slechtst en scoorden lager dan patiënten met een functionerende prothese. Het hebben van een grotere bijtkracht zorgde voor een groter kauwvermogen, en kwam vaker voor bij dentate patiënten en patiënten met een implantaatprothese. Bovendien leidde een toename van de maximale mondopening ook tot een beter kauwvermogen. Geconcludeerd werd dat dentate patiënten het beste presteren, en dat edentate patiënten een functionerende prothese nodig hebben om hen een adequate kauwfunctie te bieden.

Patiënten hebben een adequate mondopening nodig om voedsel in de mond te brengen, te kauwen, maar ook voor de vervaardiging van een kunstgebit. Een beperkte mondopening (trismus), gedefinieerd als een maximale mondopening kleiner dan 35 mm, is een veel voorkomende complicatie na de behandeling van mondkanker. Daarom werd een prospectieve studie verricht naar de maximale mondopening van 143 patiënten met mondkanker, beschreven in **hoofdstuk 4**. Maximale mondopening nam kort na de operatie af, herstelde gedeeltelijk na 6 maanden en stabiliseerde na 12 maanden. Het herstel van de mondopening was aanzienlijk minder bij patiënten die ook postoperatieve radiotherapie kregen. Patiënten met een tumor van de boven- of onderkaak hadden na behandeling een kleinere mondopening, vooral bij locaties achter in de mond. Alcoholconsumptie had een positief effect op de mondopening. Trismus kwam voor bij 31% van de patiënten na 12 maanden. Deze studie liet zien dat postoperatieve radiotherapie, een tumor van de boven- of onderkaak en een kleine mondopening vóór de behandeling, de belangrijkste risicofactoren voor trismus zijn.

In **hoofdstuk 5** werden twee oncologiecentra vergeleken, die elke een ander protocol voor implantaatplaatsing gebruikten. In het ene centrum werden implantaten indien mogelijk direct geplaatst tijdens tumorchirurgie, en werden patiënten gerehabiliteerd met een implantaatprothese. In het andere centrum kregen patiënten na herstel van de oncologische behandeling eerst een conventionele prothese, gevolgd door implantaatplaatsing op indicatie. De klinische uitkomsten en kosten werden retrospectief onderzocht bij 193 patiënten met een follow-up van 5 jaar. Directe plaatsing resulteerde in meer patiënten met implantaten (81%) in vergelijking met uitgestelde plaatsing (19%), en ook meer patiënten met een implantaatprothese (62% versus 17%) en een

functionerende prothese (62% versus 47%). Implantaatprotheses werden sneller gemaakt na directe plaatsing dan uitgestelde plaatsing (291 versus 484 dagen na operatie). Implantaatgebruik en –overleving waren vergelijkbaar tussen beide protocollen. De individuele kosten voor implantaatplaatsing waren lager voor directe implantaatplaatsing, hoewel de totale maatschappelijke kosten bijna verdubbelden. De resultaten toonden aan dat directe implantaatplaatsing de functionaliteit van de patiënt ten goede komt en de individuele kosten verlaagt, terwijl de betrouwbaarheid vergelijkbaar is met uitgestelde implantaatplaatsing en de totale maatschappelijke kosten toenemen.

Om de resultaten van directe implantaatplaatsing op lange termijn te bestuderen, werd in **hoofdstuk 6** een retrospectieve studie met een follow-up tot 17 jaar verricht. In totaal werden 207 edentate patiënten onderzocht, die allen directe implantaten hadden gekregen. Bij 74% van de patiënten werd een functionerende implantaatprothese gemaakt. De belangrijkste redenen waarom een prothese niet werd gemaakt of verloren ging waren overlijden van de patiënt, tumor recidief, trismus en ongunstige weke delen. Bij patiënten met een lage ASA-score, laag pN-stadium, minder uitgebreide reconstructie en bij jongere patiënten werd vaker een prothese geplaatst. Vijf jaar na de operatie waren 67% van de protheses nog steeds functioneel, en had een groot aantal patiënten een prothese (82%). Implantaatoverleving was hoog en vergelijkbaar met uitgestelde plaatsing. Er werden geen extra gevallen van osteoradionecrose gezien. Slechts een klein aantal implantaten werd niet gebruikt vanwege een verkeerde positionering. Kortom, directe implantaatplaatsing heeft een hoog slagingspercentage en leidt tot een snelle prothetische rehabilitatie. De risico's van onjuiste positionering van het implantaat, infectie en osteoradionecrose lijken laag te zijn.

In **hoofdstuk 7** werden de doelstellingen en conclusies van dit proefschrift besproken, alsmede de vooruitzichten voor de toekomst. Concluderend, is een implantaatprothese functioneel gunstig voor edentate patiënten met mondkanker, omdat deze een betere kauwfunctie biedt dan een conventionele prothese. Directe implantaatplaatsing heeft de voorkeur boven uitgestelde plaatsing, omdat dit leidt tot een groter aantal patiënten met een functionerende prothese en een snellere prothetische rehabilitatie. Door patiënt- en therapie-gerelateerde factoren op te nemen in verdere optimalisatie en individualisering, zal de kosteneffectiviteit van directe implantaatplaatsing toenemen.

APPENDIX A

Dankwoord

Curriculum Vitae

List of publications

Dankwoord

In het laatste hoofdstuk van dit proefschrift wil ik mijn dank uitspreken voor iedereen die mij de afgelopen jaren, op directe of indirecte wijze heeft geholpen bij het uitvoeren van het onderzoek en het schrijven van dit proefschrift. Zonder jullie was dit nooit gelukt! Ik wil graag van de gelegenheid gebruik maken om een aantal mensen in het bijzonder te bedanken.

Dr. C.M. Speksnijder, beste Caroline, als copromotor en eerste aanspreekpunt hebben wij in de eerste jaren van het onderzoek vele uren samen doorgebracht. Je hebt me begeleid bij het uitvoeren van metingen en het verwerken van data, en ik heb veel van je geleerd over onderzoeksmethodologie en het schrijven van een wetenschappelijk artikel. Ik heb veel respect gekregen voor je grondige manier van werken en je passie voor onderzoek. Ook heb ik het zeer gewaardeerd dat we naast het harde werken ook altijd leuke gesprekken over van alles en nog wat hadden. In de latere fases was je ook nauw betrokken, zij het op afstand vanuit Utrecht. Je wist altijd precies waar ik mee bezig was, en iedere email kon rekenen op je uitgebreide commentaar, ook wanneer je eigen agenda overvol was. Ik ben je dankbaar dat je me de ruimte gaf om zelf invulling aan het onderzoek en het traject te geven. Je bent recht door zee, principieel en eerlijk, waardoor je promovendi altijd op je kunnen bouwen. Bedankt voor alles!

Prof. dr. M.A.W. Merkx, beste Thijs, ik wil je bedanken voor de fijne begeleiding de afgelopen jaren en het vertrouwen dat je in me hebt gesteld. Jouw visie voor het verbeteren van de hoofd-hals oncologische zorg, in het bijzonder de kwaliteit van leven van de patiënt, vormde de basis van dit onderzoek. Jij wist altijd het overzicht te behouden, en ogenschijnlijk complexe situaties tot de kern terug te brengen; hierbij dikwijls gebruik makend van je gevleugelde uitspraken en wijze woorden, zoals “het leven wordt vooruit geleefd, en achteruit begrepen”. Ik sta er altijd van te kijken hoe snel en to-the-point jij kan reageren; ondanks dat je door je vele nevenactiviteiten altijd op meerdere borden tegelijk schaakt. In de laatste fase heeft jouw input mij erg geholpen bij het doorhakken van knopen en vinden van pragmatische oplossingen. Ik ben je dankbaar, en trots dat jij mijn promotor bent.

Prof. dr. R. Koole, beste Ron, naast je vele werkzaamheden als opleider en begeleider van diverse promovendi aan het UMC Utrecht, was je ook voor een groot deel verantwoordelijk voor het opzetten van de prospectieve studie naar mondfunctie van orale oncologie patiënten, waarin Utrecht en Nijmegen hun krachten bundelden. Mijn

promotieonderzoek vloeide hieruit voort, en in het begin heb je me vooral geholpen te kiezen welke richting ik in zou slaan. Ook na jouw emeritaat kon ik rekenen op je kritische kanttekeningen bij mijn artikelen, waarbij je altijd het accent legde op relevantie voor de clinicus. In de korte tijd dat ik met jou heb mogen samenwerken, heb ik je leren kennen als een bevlogen, betrokken, allround MKA-chirurg, en het is een genoegen jou als 2e promotor te hebben.

Prof. dr. G.J. Meijer, beste Gert, jij was direct enthousiast toen ik je op een NVMKA najaarsvergadering aansprak over het doen van onderzoek, en hebt me vervolgens geïntroduceerd aan Thijs en Caroline. Jouw passie voor de implantologie, je wetenschappelijke kennis en manier waarop je met jonge onderzoekers omgaat, hebben mij hierin geweldig geïnspireerd. Naast de vele bemoedigende schouderkloppen en commentaar als “dit leest als een jongensboek”, heb ik vooral veel geleerd van je schrijfstijl en je presentatie-skills. Je weet als geen ander de essentie van een verhaal op te schrijven, om te zetten op het scherm, en over te brengen aan het publiek. Ook waren de donderdagen op OK 11 altijd een feest! Ik wil je bedanken voor je rol als 3e promotor, en het geloof, enthousiasme en energie dat je hierin hebt gestoken!

Prof. dr. H. de Bruyn, Prof. dr. R.P. Takes, Prof. dr. A. Vissink, geachte leden van de beoordelingscommissie, bedankt voor het beoordelen van dit proefschrift, en de tijd en moeite die u hierin heeft gestoken.

Drs. A.F.J. de Haan, beste Ton, jouw statistiek is een onmisbaar onderdeel van dit proefschrift geworden. De uitleg van de ingewikkelde multivariate modellen heeft me enorm geholpen om uit de grote berg van data de relevante gegevens te kunnen halen. De wijze waarop je dit doet, je helderheid, geduld, en portie droge humor, heb ik enorm op prijs gesteld.

Prof. dr. S.J. Bergé, beste Stefaan, ik heb vier jaar lang deel uitgemaakt van jouw opleiding en team. Je hebt me tijdens deze periode altijd gesteund en gestimuleerd in mijn promotieonderzoek, waarvoor ik je dankbaar ben. Wat ik het meest heb gewaardeerd, is dat je de kwaliteit van de zorg en de opleiding voorop stelt, terwijl je jouw assistenten vrijlaat om zelf invulling te geven aan de opleiding, en leert regisseur te zijn binnen en buiten hun vak. Je bent een inspirerend leider, die altijd kritisch nadenkt en grenzen verlegt. Bedankt voor de kansen die je me hebt geboden om me te ontwikkelen, en het warme hart dat je je AIOS toedraagt.

Jan Abbink, mede dankzij jou is een nieuwe meetmethode voor de kauwfunctie ontwikkeld, de kleurenmengtest. Naast toepassing in onze eigen studies, wordt deze methode nu ook gebruikt in diverse andere onderzoekscentra in binnen- en buitenland. In dat kader wil ik ook Andries van der Bilt bedanken voor het opzetten van de prospectieve studie, waar dit proefschrift mede uit voortkomt. Reilly de Groot, ik wil je bedanken voor de fijne samenwerking; eerst tijdens het opzetten van jouw eigen promotieonderzoek, en later met het samen schrijven van het kauwfunctie artikel. Ook wil ik Koen Metsemakers en Anneloes de Jong bedanken voor het verzamelen van data, het was me een genoegen om jullie master-scriptie te begeleiden.

Ik ben de patiënten die hebben deelgenomen aan deze studie erg dankbaar. Jullie hebben op meerdere momenten voor en na oncologische behandeling een deel van je kostbare tijd opgeofferd voor de functiemetingen, welke dikwijls meer dan een uur in beslag namen. Tijdens het uitvoeren van de 5-jaars metingen heb ik veel geleerd van jullie ervaringen en verhalen.

Medewerkers van het secretariaat en de polikliniek van de afdelingen MKA-chirurgie van het UMC Utrecht en Radboudumc, hartelijk dank voor jullie hulp bij het plannen van de afspraken, versturen van brieven, ondersteuning op de poli, en de fijne en de gemoedelijke sfeer op de afdeling!

Beste stafleden Nijmegen: Wilfred, Martien, Tong, Marloes, Rik, Willem, Casper, François, Eric en Thomas, en stafleden Arnhem: Theo, Jeroen, John, Sophie en Marc: bedankt voor de opleidingstijd en het vele wat ik van jullie geleerd heb. Jullie staan altijd klaar voor de afdeling, de patiëntenzorg en de opleiding, waarbij het plezier en enthousiasme waarmee jullie je deskundigheid delen enorm is. Wat me bij zal blijven zijn de vele mooie operaties die we samen hebben gedaan, de memorabele patiënten, treffende uitspraken en gouden tips; maar ook de skivakanties, de borrels en dagjes-uit die altijd erg gezellig waren.

Beste collega AIOS: Jeroen, Bram, Tong, Hossein, Marieke, Stefanie, Sanneke, Tim, Hanneke, Julie, Robbert, David, Reinoud, Henri, Jeroen, Rutger, Neeltje, Julien, Ilse en Dominique. Het was me een genoegen om met jullie samen te werken, en wat hebben we een lol beleefd samen op de AIOS kamer, tijdens KIO cursussen, congressen, skivakanties, in de Aesculaaf en st Anneke. We hebben samen mooie verhalen en onvergetelijke momenten gedeeld, en ik beschouw velen van jullie nu als goede vrienden. Ik vond het een eer om in het begin de kneepjes van het vak van jullie leren, en later een begeleidende rol in jullie opleiding te kunnen vervullen. Met een warm gevoel kijk

ik hierop terug, en ik hoop dat we elkaar in de toekomst nog vaak zien en oude tijden doen herleven.

Medewerkers van de afdeling MKA-chirurgie Radboudumc op de administratie, het secretariaat, de polikliniek, 3d-lab, onco-verpleegkundigen, verpleegafdeling en operatiekamers, bedankt voor de fijne opleidingstijd! Jullie ondersteuning, betrokkenheid, leuke gesprekken, (en vaak engelengeduld) zijn van grote waarde voor iedere AIOS.

Afdeling Mond- Kaak- en Aangezichtschirurgie Doetinchem en Winterswijk, beste Rob, Edo, Marc en Sanneke, assistentes en medewerkers van de poli, bedankt voor het afgelopen jaar waarin ik jullie heb leren kennen, de warme sfeer op de poli, en de mentale ondersteuning bij de laatste loodjes van dit onderzoek. Ik kijk uit naar onze toekomstige samenwerking!

Afdeling Mond- Kaak- en Aangezichtschirurgie Ede, beste Peter, Machiel, Susanne en Laurens, polikliniek assistentes en medewerkers; ik wil jullie bedanken voor de fijne tijd op jullie polikliniek, en de ervaring die ik hier heb opgedaan. Ik hoop in de toekomst nog vaak met jullie samen te werken!

Mattijs, beste Matti, wat hebben we veel meegemaakt de afgelopen jaren. We zaten samen aan de unit in het eerste jaar tandheelkunde, waren huisgenoten op de villa en Borneostraat. Toen ik na mijn opleiding wilde gaan reizen, maakte jij dit mogelijk door me een plek in jouw huis aan te bieden; iets wat ik nooit zal vergeten. Samen op vakantie, naar festivals, een zolder verbouwen. Maar helaas was er ook het plotse overlijden van Janneke, jouw liefde. Dat kwam als een schok voor iedereen, en ik vind het ongelofelijk knap hoe je je er doorheen hebt geslagen de afgelopen jaren, en altijd bent blijven lachen. Je ziet altijd het goede in mensen, hebt een enorm relativeringsvermogen en altijd een luisterend oor. Ik wil je bedanken dat je zo'n goede vriend geweest bent, en dat je m'n paranimf bent.

Rene, my man. Per toeval kwamen we op dezelfde gang op Vossenveld terecht, en nu ben je paranimf bij m'n promotie. Keer op keer geniet ik van onze conversaties, je genialiteit, humor en de verhalen die je weet te vertellen. Ik ben dankbaar voor onze vriendschap, en alle steun die ik van je heb ontvangen met dit onderzoek; vooral tijdens onze co-habitatie aan de Casa de Stieltje. Het is fijn om te weten dat, ongeacht het moment of de complexiteit van het probleem, jij er altijd voor me bent. Veel plezier in jullie nieuwe crib in Bilthoven!

Matthijs, beste Admi. We werden vrienden toen je aan het Graafse Ringpad woonde, waar we vele avonden geberberd hebben. Film kijken op je beamer, muziek luisteren en het voeren van urenlange gesprekken. Onze avonturen in California, Thailand en de weekendjes aan de Mathenesserlaan waren legendarisch, en hebben een band voor het leven geschapen. Tijdens mijn onderzoek kon ik altijd bij je terecht, en met je heldere en rationele blik heb je me vaak op andere gedachtes gebracht. Ik ben je dankbaar, en blij dat we nu weer dicht bij elkaar wonen!

Niels, bru. Toen wij bevriend raakten was ik al bezig met dit onderzoek, en ook vaak in de weekenden druk. Ik vond bij jou altijd een plek om te ontspannen en bij te praten, waarbij je me geïnspireerd hebt om naast al het studeren “ook nog een beetje te leven”. Met je initiatieven, sociale skills en gevoel voor stijl maak je elke ontmoeting tot een feest. Stapavondjes in Roffa, trips naar Thailand, Zuid-Afrika en Ibiza behoren tot m’n dierbaarste herinneringen. Bedankt dat ik deze mooie tijden met je heb beleefd!

Tom Lassing, beste Altec. Samen in het TFV bestuur, samen op de villa; al snel groeide er een band tussen ons. Intens heb ik genoten van onze roadtrip naar Kroatië, de festivals, bezoekjes aan de Arena, maar ook gewoon het op de bank hangen en Will Ferrell films kijken. Ik ben je dankbaar dat, ook in momenten dat ik me afzonderde, je altijd dichtbij was en ik op je terug kon vallen. Ik hoop met jou nog vele setjes back-to-back te gaan draaien! En ik weet dat je dit leest!

Rick, vriend. We kennen elkaar al vanaf de middelbare school, toen we een aantal jaren samen in een band hebben gespeeld. Toen ik in Nijmegen ging studeren spraken we elkaar minder vaak, maar ik ben blij dat we de afgelopen jaren weer close zijn geworden. Ik kan altijd m’n verhaal bij je kwijt, en bij jou en Roos langskomen om even “bij te tanken”. Ik vind het altijd erg waardevol met jullie van gedachten te wisselen, en vind het erg fijn dat we deze bijzondere band hebben opgebouwd. Ik wens jullie heel veel geluk met jullie zoon!

Dennis, beste Deni. Ik wil je bedanken voor de fijne tijd de afgelopen jaren dat we elkaar kennen, de gesprekken die we gevoerd hebben waarin we altijd lekker de diepte in gaan. De last-minute verhuizing die zonder jouw hulp onmogelijk was geweest. Alle feestjes en festivals waarna “de geschiedenis nooit meer hetzelfde was”. Oud en nieuw aan het Keizer Karelplein. Ik wens jou en Moniek veel geluk in jullie nieuwe stek in Weurt!

Tom, beste Driessen. Tijdens tandheelkunde was het altijd gezellig op jouw kamer. Deze lijn heb je na de studie doorgetrokken, en het was me een genoegen om samen te wonen aan de Borneostraat. Het is heerlijk met jou te praten over uiteenlopende thema's, en ik verbaas me iedere keer weer hoe groot je specifieke kennis is. De afgelopen jaren ben ik samen met jou en Elte op vele festivals geweest, en hebben we lief en leed samen gedeeld. Ik wil jullie daarvoor bedanken, en ik hoop nog vele jaren plezier met elkaar te maken.

Suvarna, lieve Suv. Met jou kon ik de afgelopen jaren altijd sparren over medische onderwerpen. Je weet me altijd te prikkelen met je gedachtes en spontaniteit, bent sociaal en attent, en houdt hiermee de groep bij elkaar. Bedankt voor al je warmte, de gezellige feestjes en festivals, en ik weet dat je het met jouw capaciteiten ver gaat schoppen binnen de anesthesiologie!

Khader, we werden buren op de Stieltjesstraat, en hoewel ik er pas kort woonde, nodigde je mij altijd uit bij de feestjes van jou, Ferdy en Sanne, en tijdens jullie kerstdiner. Als ik druk aan het werk was, kwam jij vaak langs om even bij te kletsen, en om te kijken of "alles in orde was". Bedankt voor je gastvrijheid en warmte!

Anneke, bedankt voor de gezellige feestjes en de gesprekken die we hebben gevoerd de afgelopen tijd tijdens wandelingen en lunchafspraken. Ook geniet ik van je enthousiasme tijdens het spelen van cambio met Lasso en de Waard, en ik hoop dat we deze traditie in stand houden!

Timo, tijdens tandheelkunde beleefden we mooie tijden, maar ook na de studie spraken we vaak af om een film te kijken, een pizzaatje te eten of de barbecue aan te steken bij jou in Beuningen. Het is altijd fijn met jou van gedachten te wisselen over het leven, en ik hoop dat we dat nog lang blijven doen.

Hugo, Jan, Johannes, Roderick; we leerden elkaar kennen tijdens de studie, en ik vind het mooi dat we nog steeds bij elkaar komen. De weekendjes weg, etentjes en wintersport vakanties zijn altijd erg leuk, vooral omdat oude verhalen weer worden opgehaald. Bedankt voor jullie support de afgelopen jaren!

Miranda, Eva en Inke, we vonden elkaar snel toen we in dezelfde cogroep terecht kwamen, maakten bijzondere ervaringen mee tijdens de coschappen, en vormen sindsdien een hecht groepje. Het is altijd erg gezellig om samen te dineren, en ik geniet

telkens weer van de verhalen en jullie culinaire skills. We hebben door de jaren heen een speciale band opgebouwd, en ik ben dankbaar dat ik jullie heb leren kennen.

Gui, gozer, bedankt voor de top tijd op de vakanties die we samen hebben gevierd, en bedankt voor de prikkelende conversaties die me altijd aan het denken zetten. Mischa en Evelien, ik heb intens genoten van de vakanties en feestjes, bedankt voor jullie warmte en gezelligheid!

Vincent, Rens, Peter en Thomas, jullie zijn een uniek groepje bij elkaar, en ik wil jullie bedanken voor de gesprekken en gezelligheid tijdens feestjes, Lan-parties en wintersport.

Wibi, Maaike, Reinoud, Stefan, Patrick, Bas, Martin, Tijmen en Sanne; bedankt voor het opbouwen en in stand houden van het festival-groepje, en het meemaken van vele onvergetelijke momenten.

Mannen van Villa Schimmelzicht, Joep, Gijs, Joost, Mattijs, Tom, Maurits, Evert en Sjors; bedankt voor de mooie jaren, waarop ik met een glimlach terugkijk.

Robert, Eric, Erik, Funs, Ger, Johan, Joost, Niels en Robbert, we kennen elkaar al vanaf de introductie tandheelkunde en zijn hierna een hecht groepje geworden, die alle verjaardagen en feesten samen viert. Naast de vele mooie verhalen over vakanties in Rovinj, de Astragalo en het zeilen met Rikst, is het ook altijd fijn met jullie over serieuze zaken te praten. Ik bedank jullie voor de steun die ik gehad heb tijdens dit promotieonderzoek, en ben erg dankbaar voor onze vriendschap.

Lieven, Anne, lieve schoonbroer en schoonzus, wat ben ik blij dat ik jullie in mijn leven heb gekregen. De afgelopen jaren stonden jullie altijd klaar om me te helpen, stonden me bij met advies en moedigden me aan wanneer ik het nodig had. Ook waren de dinertjes en verjaardagen altijd erg gezellig! Elize, Alexander, Casper, Olivia en Matthijs, bedankt dat jullie mijn nichtjes en neefjes zijn! Iedere keer geniet ik er weer van jullie te zien, samen plezier te maken en jullie groter te zien worden.

Charlotte, lieve zus. Van jongs af aan hebben we een hechte band gehad, gingen we samen fietsen, op gitaarles en beleefden we avonturen tijdens vakantie. Toen je in Leuven ging studeren kwam ik vaak logeren, en hadden we het altijd leuk. Ik heb bewondering voor hoe gedegen je te werk gaat, je oprechtheid, en het vele dat je hebt bereikt. Tijdens dit onderzoek kwam ik met veel plezier bij jullie op bezoek in de Smaragdstraat en later

in Nuenen om bij te kletsen, of om op te passen op de kids. Ik wil je bedanken dat je altijd begripvol bent, voor me klaarstaat en om me bekommert. Ik ben dankbaar dat ik zo'n fijne zus heb!

Leonard, beste Leo. Als grote broer ben je altijd m'n voorbeeld geweest, en heb je me geïnspireerd om net als jij tandheelkunde te gaan studeren. Ik vind het leuk dat we nog steeds allebei in Nijmegen wonen, en geniet van onze etentjes, stapavonden bij de zomerfeesten en de wintersportvakanties die altijd garant staan voor vuurwerk. Je was de afgelopen jaren een van m'n steunpilaren, was altijd betrokken en bereid om me te helpen. Je scherpe analyses en uiteenlopende interesses zijn enorm waardevol, maar wat ik het meeste waardeer is dat je altijd probeert het juiste te doen en nooit opgeeft. Bedankt dat jij m'n broer bent!

Marjan, lieve mama, tot slot wil jou bedanken. Je hebt me altijd gestimuleerd me verder te ontwikkelen, voor mezelf te denken en m'n eigen keuzes te maken. De kansen die ik heb gehad in dit leven heb ik voor een groot deel te danken aan jou en papa, omdat jullie je leven lang hard hebben gewerkt en jullie gezin boven alles hebben gesteld. Het dankbaarste ben ik voor de liefde die je me hebt gegeven en de warme herinneringen aan m'n jeugd, te veel om op te noemen. Ook bij het maken van dit proefschrift was jouw steun, luisterend oor en wijze raad onmisbaar. Ik heb ontzettend veel respect voor hoe je na het overlijden van papa de zaken hebt aangepakt, je draai in Nuenen hebt gevonden, en ik geniet ervan hoe mooi je met je kleinkinderen omgaat. Bedankt voor je onvoorwaardelijke liefde!

Curriculum Vitae

Jan-Willem Wetzels was born on May 26th, 1986 in Roermond, the Netherlands. After completing secondary school (gymnasium) at BC Broekhin Roermond, he started his dentistry studies at the Radboud University Nijmegen in 2004. His interest in doing scientific research started with his bachelor's thesis, for which he won the national NT-GSK bachelor thesis award in 2008.

After obtaining his master's degree in dentistry in 2010, he started his medical studies at the Radboud University Nijmegen, and received his master's degree in 2015. While studying medicine, he also worked as a general dentist in a private practice in Sint Anthonis (de Vicarie), with a special interest in oral surgery and endodontology. He started his PhD research in 2012 at the departments of Oral and Maxillofacial Surgery at the UMC Utrecht and Radboud University, under the supervision of prof. dr. M.A.W. Merkx, prof. dr. R. Koole, prof. dr. G.J. Meijer and dr. C.M.S. Speksnijder. He measured the oral functioning of seventy three 5-year survivors of oral cancer, for which he made many home visits throughout the country. During the years of his research, he gave various scientific presentations at national and international conferences.

In 2015, he started his residency in Oral and Maxillofacial Surgery at the Radboudumc Nijmegen, under the supervision of prof. dr. S.J. Bergé. He spent eight months at the Rijnstate hospital in Arnhem as part of his residency, under the supervision of dr. Th.J.M. Hoppenreijs. After completing his residency in 2019, he started working as an oral and maxillofacial surgeon at the departments of OMF surgery in Doetinchem and Ede, where he currently works.

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