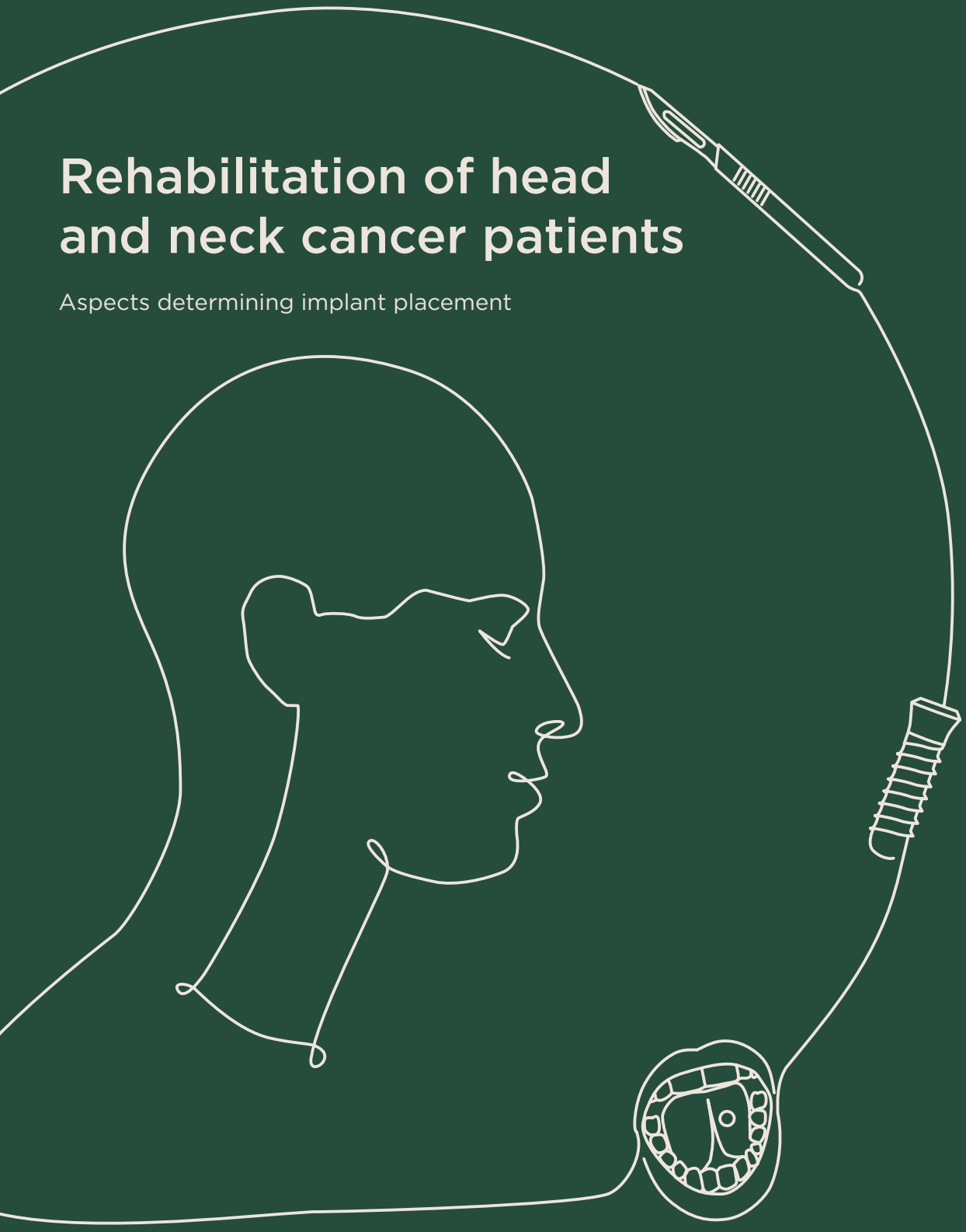
Rehabilitation of head and neck cancer patients

Aspects determining implant placement



Jamie M. Alberga

Rehabilitation of head and neck cancer patients: aspects determining implant placement

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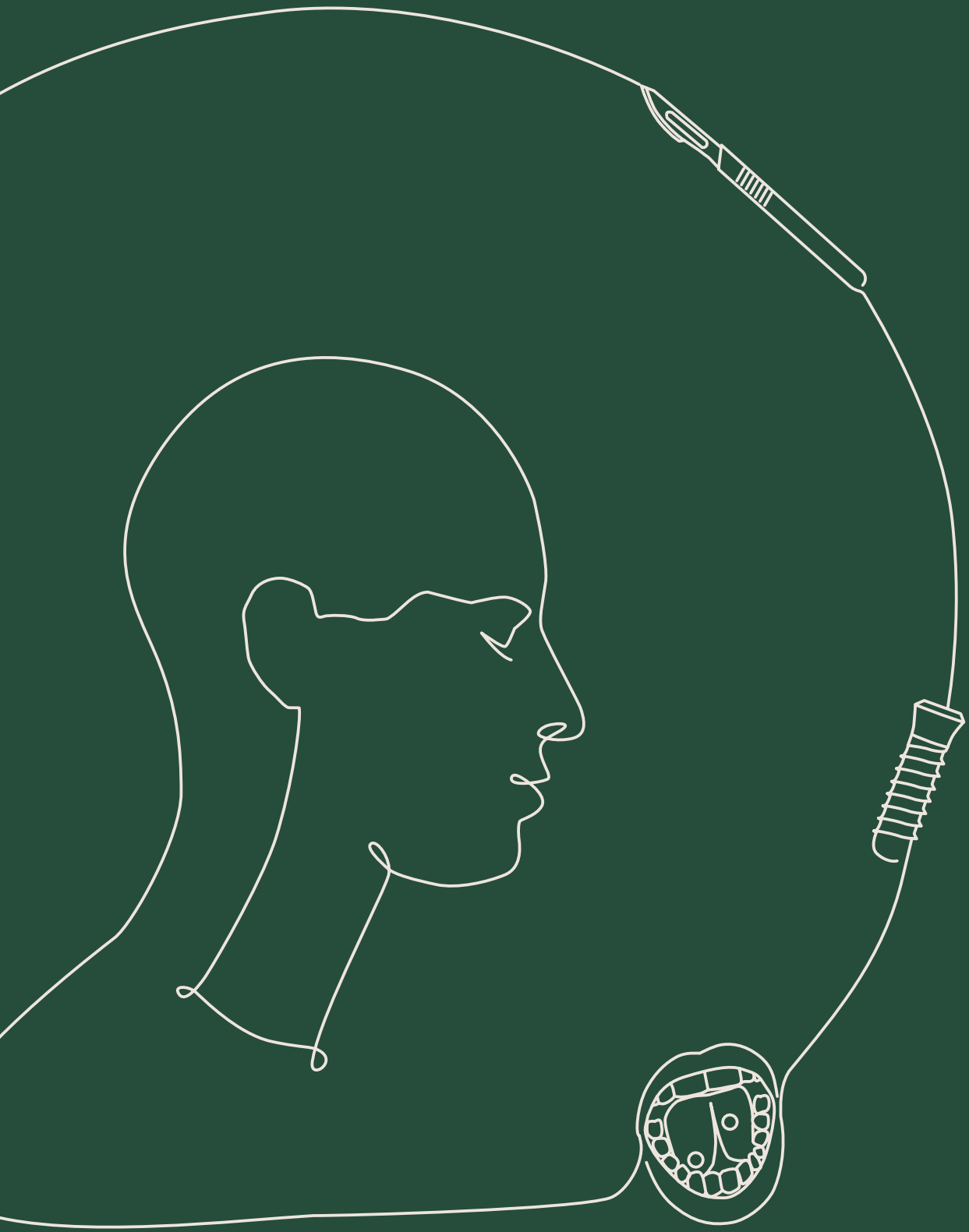

Chapter 1

General introduction

HISTORICAL PERSPECTIVE AND CURRENT TREATMENT

Some of the earliest evidence of head and neck cancer is found in Egyptian skulls dating back to 3000 BC[1]. The first reports of surgical treatment for intraoral tumours originate from the early 1700s when Marchetti, Professor of Surgery at Padua, removed a lingual tumour with cautery. In those days surgical developments for treating tumours in the oral cavity were limited because of the absence of appropriate anaesthesia[2]. As surgery at that time was accompanied with exorbitant mortality rates, the discovery of x-rays in 1895 and the subsequent development of radiation therapy (1900-1920) was a welcome addition to the treatment arsenal[3]. Because of the development of adequate anaesthesia, surgical treatment had a comeback around the 1930s. Hayes Martin, a radiotherapist and surgeon, was one of the first to propose radical surgery for head and neck cancer and reconstructive surgery techniques were further developed during the Second World War[2,3].

Initially, the treatment goal was eradicating the tumour and no emphasis was placed on postoperative function or prosthetic rehabilitation. In the post-World War Two era, prosthetic rehabilitation in head and neck cancer patients began to play a bigger role and led to the founding of the American Academy of Maxillofacial Prosthodontics in 1953 and the International Anaplastology Association in 1980[4]. A breakthrough in prosthodontic rehabilitation came with the discovery that titanium implants could achieve anchorage in bone with direct bone-to-implant contact, a process described as osseointegration[5]. In 1965, the first endosseous implant in an edentulous patient for retention of a fixed prosthesis was placed by professor Brånemark[6,7]. Previously, head and neck cancer treatment was considered a contraindication for implant placement, but in 1979, the first implant for an ear prosthesis was placed in a cancer patient[7]. In the years that followed, implants in cancer patients were also placed in other craniofacial regions and intraorally[8].

Currently, head and neck cancer is the seventh most common type of cancer worldwide. In The Netherlands, approximately 3000 patients are diagnosed annually[9,10]. Nowadays, treatment consists of surgery, radiotherapy, systemic therapy or a combination of these modalities[10]. Treatment often takes place in multidisciplinary teams in tertiary centres due to the complexity of the disease[11]. After diagnosis, patients are seen by a team of head and neck oncologists, dentists, prosthodontists and radiation oncologists. In this pre-treatment phase, plans are made for the actual treatment (CT-scans, MRI, dental screening and when necessary pre-radiation dental extractions). Also, prosthetic rehabilitation and implant placement are considered as the consequences of surgery (changed

anatomy, compromised soft tissue conditions, sensitivity disorders, loss of lip competence, loss of teeth, and changes in facial appearance) and the consequences of radiotherapy (hyposalivation, trismus and an increased risk of developing osteoradionecrosis) can have an enormous impact on aesthetics and oral function[12,13]. Regaining oral function is of great importance for patients' quality of life after oncologic treatment[14-16].

TECHNIQUES AND BENEFITS OF EXTRAORAL AND INTRAORAL IMPLANT PLACEMENT

Endosseous implants in head and neck cancer patients can be used in intraoral and extraoral regions to support prosthetic constructions. For intraoral prostheses, implants are mainly placed in the edentulous mandible as conventional mandibular prostheses are most likely to fail after surgery and/or radiotherapy. Previously, a minimum of 4 implants was advised, but nowadays 2 implants in the mandible to support an overdenture are considered sufficient to restore function[17]. For the maxilla, the type of prosthodontic rehabilitation depends on the shape and location of the surgical defect. Treatment options for the maxilla include surgical reconstruction with soft tissue flaps, fabrication of a conventional obturator prosthesis, or placement of endosseous implants for additional retention of an obturator prosthesis[18-20]. In craniofacial regions, implant-supported craniofacial prostheses are a durable solution, mimicking the contour of the missing facial region and blending into the surrounding regions[21,22]. When compared with autologous surgical reconstruction of these defects, which usually require several extensive procedures, implant-retained prostheses lead to a more acceptable combination of a relatively limited surgical procedure and satisfactory aesthetic results[23,24]. For auricular prostheses 2 or 3 implants are placed in the mastoid bone, approximately 18mm from the external auditory canal with a minimum distance of 11mm between the implants[23]. In the nasal region, implants can be placed in the maxillary bone of the nasal floor, glabella or zygoma[25,26]. Implants in the orbital region are placed in the supraorbital (2 or 3 implants) and infraorbital rim (1 or 2 implants)[27]. Implants in craniofacial regions of head and neck cancer patients are usually covered with skin and subcutaneous tissues while osseointegration occurs. After osseointegration, second-stage surgery takes place and a prosthesis attached to a suprastructure can be made.

CHOOSING THE RIGHT TIMING OF IMPLANT PLACEMENT

Implants in head and neck cancer patients were initially placed after finishing oncologic treatment (secondary implant placement)[28]. This implies an additional surgery, for irradiated patients under antibiotic prophylaxis, and with an additional treatment burden in, not seldom, frail patients with multiple comorbidities[29]. Patients are also less likely to accept or undergo additional procedures, even when they could benefit from an implant-supported prosthesis[30]. Therefore, when feasible, the implants are already placed during tumour surgery (primary implant placement). The advantages of primary implant placement have been described previously and include saving the patient the burden of additional surgery with a faster time to oral rehabilitation[31,32]. Potential risks in primary implant placement are mispositioning of implants due to the changed anatomy during surgery and loss of resources due to implants not being used when tumours recur of patients pass away before a prosthesis is made. These limitations might outweigh the beneficial impact of immediate implant placement for the patient. Guidelines on when to ideally start oral rehabilitation with dental implants in oral cancer patients are lacking and treatment decisions are often based on the available resources in the treatment centre (for example the participation and availability of a prosthodontist and oral and maxillofacial surgeon with expertise in implant placement).

RADIOTHERAPY: IMPLANT PLACEMENT AND NEW DEVELOPMENTS

Radiotherapy for head and neck cancer can be administered after surgery or as a primary treatment. Indications for postoperative radiotherapy are positive or close (<5mm) surgical margins and extranodal extension, perineural invasion, bone invasion, and 2 or more positive lymph nodes[33].

Usually, postoperative radiotherapy with a cumulative dose of 60 to 70 Gy is administered in daily fractions of 2 Gy[33,34]. Ionizing radiation has several biologic effects on the exposed tissues including hyperaemia, endarteritis, thrombosis, cellular loss, loss of microvascular content, and fibrosis[35]. Several studies show that radiotherapy has a negative influence on the survival of dental implants, for implants placed both before and after radiotherapy and implant loss seems associated with increasing radiations dose on the implant area[36-39]. However, in the majority of published literature, exact radiation dose levels on the implant areas are not reported.

Newer developments in radiation techniques, such as intensity modulated radiotherapy (IMRT) and volumetric modulated arch therapy (VMAT), offer the possibility to limit the radiation dose on multiple organs at risk (e.g., salivary glands, swallowing muscles, mandibular bone), resulting in a decrease in treatment-associated toxicities such as hyposalivation, xerostomia, dysphagia and possibly osteoradionecrosis[40-42]. In more recent years, proton therapy is also being administered in head and neck cancer patients. The superior physical beam properties of protons compared to photons offer the possibility of depositing their energy at a specific depth known as the Bragg peak. The cumulative dose to the tissues lying superficially is reduced and beyond the peak, there is a rapid loss of energy, sparing the tissue behind the tumour without affecting target dose coverage[43-45]. How the recent introduction of proton therapy influences the radiation dose on the tooth-bearing regions of the jaw, and, therefore, the decision-making process regarding pre-radiation extractions in cancer patients, in comparison to VMAT has not been studied widely.

AIM AND OUTLINE OF THE THESIS

This thesis aims to give insight into the factors determining implant placement for the rehabilitation with implant-supported prostheses in head and neck cancer patients. The specific aims were:

- To assess the current knowledge regarding the timing of implant placement (**Chapter 2**) as well as to describe challenges and new developments in prosthodontic rehabilitation of head and neck cancer patients (**Chapter 3**).
- To describe the outcome of implants placed in the edentulous mandible during ablative surgery and immediately after teeth removal (**Chapter 4**).
- To assess the outcome of implants placed to retain prostheses in craniofacial regions (**Chapter 5**).
- To compare the radiation dose on tooth-bearing regions of volumetric modulated arch therapy (VMAT) and intensity modulated proton beam therapy (IMPT) in a cohort of head and neck cancer patients in order to assess whether IMPT leads to less irradiation to the teeth (**Chapter 6**).
- To determine the influence of implant-specific radiation dose on the survival of implants placed in the edentulous mandible (**Chapter 7**).

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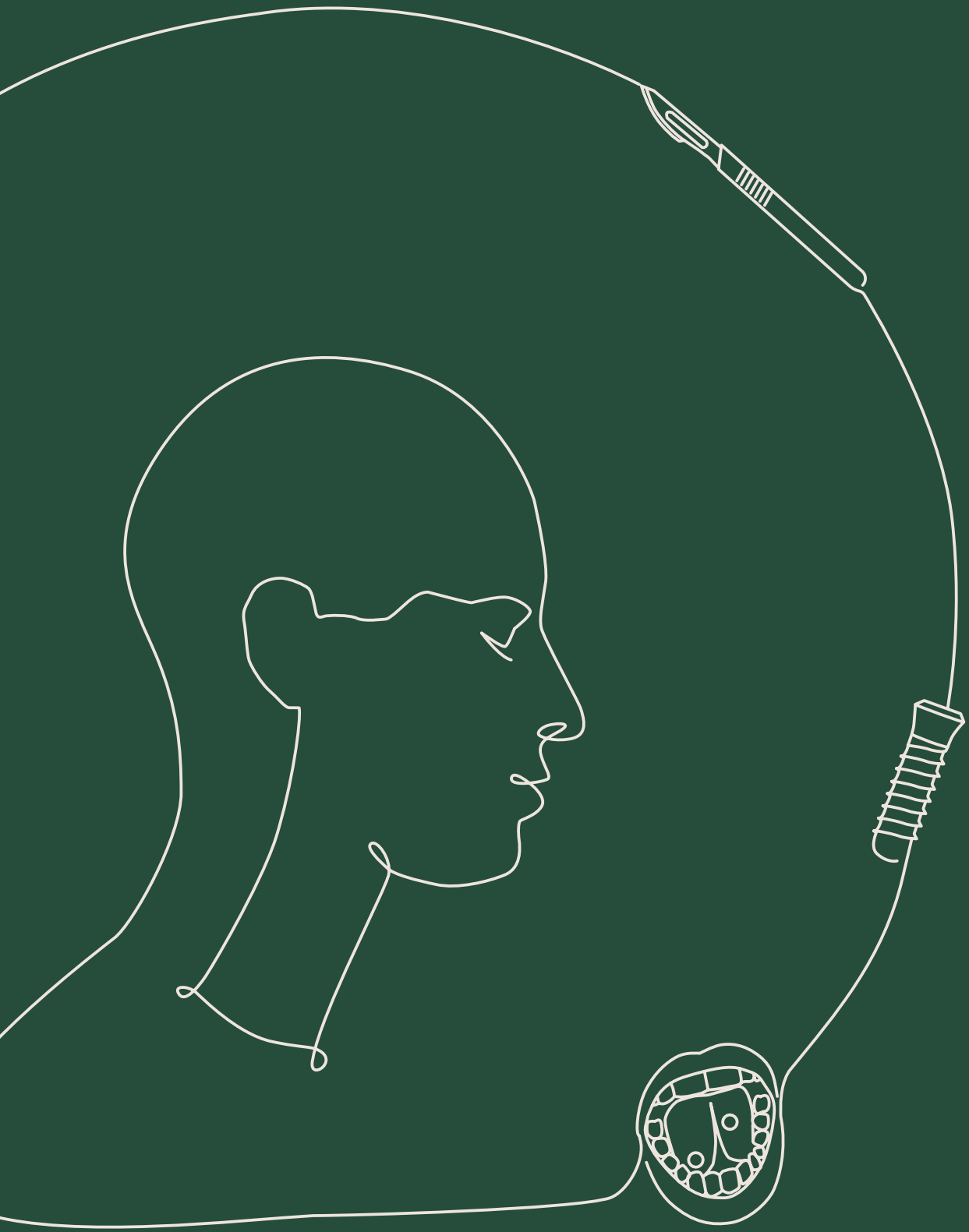


Chapter 2

What is the optimal timing for implant placement in oral cancer patients? A scoping literature review

J.M. Alberga, N. Vosselman, A. Korfage, K. Delli, M.J.H. Witjes, G.M. Raghoebar, A. Vissink

This chapter is an edited version of the manuscript:
What is the optimal timing for implant placement in oral cancer patients? A scoping literature review.

Oral Diseases 2021;27(1):94-110.

ABSTRACT

Background

Oral cancer patients can benefit from dental implant placement. Traditionally implants are placed after completing oncologic treatment (secondary implant placement). Implant placement during ablative surgery (primary placement) in oral cancer patients seems beneficial in terms of early start of oral rehabilitation and limiting additional surgical interventions. Guidelines on the ideal timing of implant placement in oral cancer patients are missing.

Objective

To perform a scoping literature review on studies examining the timing of dental implant placement in oral cancer patients and propose a clinical practice recommendations guideline.

Methods

A literature search for studies dealing with primary and/or secondary implant placement in Medline was conducted (last search December 27th, 2019). The primary outcome was 5-year implant survival.

Results

16 out of 808 studies were considered eligible. Both primary and secondary implant placement showed acceptable overall implant survival ratios with a higher pooled 5-year implant survival rate for primary implant placement 92.8% (95% CI: 87.1%-98.5%) than secondary placed implants (86.4%, 95% CI: 77.0%-95.8%). Primary implant placement is accompanied by earlier prosthetic rehabilitation after tumour surgery.

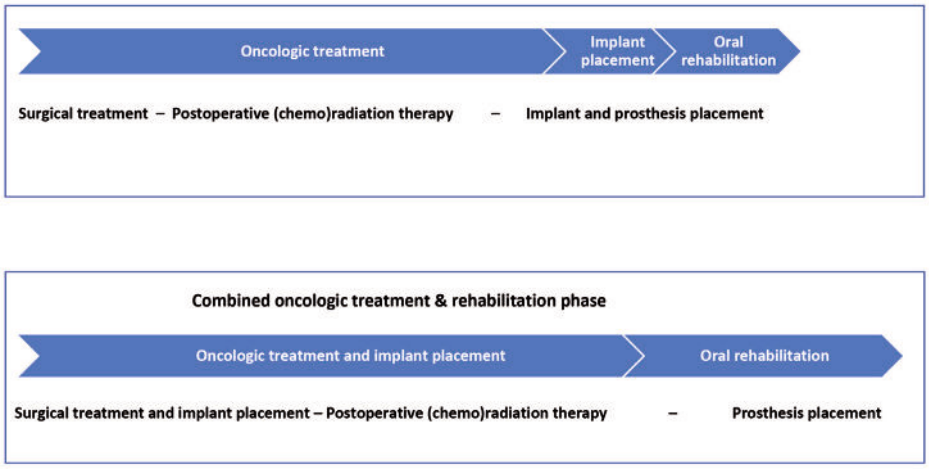
Conclusion

Patients with oral cancer greatly benefit from, preferably primary placed, dental implants in their prosthetic rehabilitation. The combination of tumour surgery with implant placement in native mandibular bone should be provided as standard care.

INTRODUCTION

The general treatment timeline for oral cancer patients consists of diagnostics, surgical treatment followed by postoperative (chemo)radiation therapy depending on the surgical margins and specific tumour properties, or solely (chemo)radiation therapy. Traditionally, oral rehabilitation comes last, i.e., after the oncologic treatment when the oral mucosa is completely healed (figure 2.1). Oral function after treatment for a malignancy in the oral cavity is often compromised due to changed anatomy after surgery and/or the oral sequelae of radiotherapy like xerostomia and trismus[1,2]. Sometimes teeth need to be extracted during ablative surgery because of their location in proximity to the tumour or as part of a pre-radiation screening examination[3]. This compromised oral condition also leads to a decrease in oral function and possible a negative effect on nutritional status and quality of life[4]. Fabrication of functional prostheses, frames and conventional partial dentures is often difficult to achieve after oncologic treatment and in some cases even impossible[5,6].

Figure 2.1 Timing of oncologic treatment and oral rehabilitation



Dental implants have shown to be a great asset in oral cancer patients and provide good results[7,8]. When dental rehabilitation based on implants first was introduced in oral cancer patients, they were often placed after oncologic treatment (secondary implant placement)[9]. This implies an additional surgery, for irradiated patients under antibiotic prophylaxis, and an additional treatment burden in older patients with often multiple comorbidities. When pre-treatment hyperbaric oxygen treatment is advised, the treatment burden increases even more[10]. When offering implant treatment in a secondary phase, patients are less likely to accept or undergo additional procedures, even when they could benefit from an implant-supported prosthesis[7,11].

Implants can also be placed during tumour surgery (primary implant placement)[12]. An advantage of this treatment sequence is that most of the osseointegration takes place during the recovery phase, saving the burden of additional surgery and a considerable amount of time. The patient can function with an implant-supported prosthesis much earlier after completion of oncologic treatment[6]. Disadvantages are possibly improper placement of implants due to the changed anatomy during surgery or the risk of implants not being used because of tumour recurrence or patients passing away before a prosthesis can be made (loss of resources). The effects of radiotherapy on the osseointegration process and implant survival rates are also subject of debate and primary implant placement is not always available in the hospital setting[13-15].

Guidelines when to ideally start oral rehabilitation with dental implants in oral cancer patients are lacking. Several systematic reviews have been published, mainly dealing with timing of secondary implant placement after radiotherapy[16-20]. Claudy et al. (2013) reported that dental implant placement between 6 and 12 months after radiotherapy was associated with a 34% higher risk of failure and therefore suggest waiting periods over 1 year after radiotherapy[17]. On the contrary, it has been suggested that implant placement just becomes more critical over time because of the ongoing progressive decrease in healing capacity of bone after radiotherapy[21]. Other studies showed no significant relationship between time interval and dental implant survival rates[18-20]. The implant survival rate in patients with a history of radiotherapy seems to be more associated with the location of the implants (more implant loss in the maxilla than in the mandible) than with the length of time after radiotherapy[22]. Far less studies on primary implant placement have been published. A systematic review by Barber et al. (2011) on primary implant placement provides an extensive literature overview, but no clear conclusions or recommendations were made[23]. The latter systematic review also included case reports and studies

on patients with benign lesions, which could have influenced the outcome. The authors of another systematic review highlighted the importance of timing of implant placement and concluded that they could not extract scientific evidence for the optimal timing of implant placement[24].

Before being able to propose guidelines for optimal timing of implant placement in head and neck cancer patients needing radiotherapy, the following questions have to be answered: (1) what is the optimal timing of dental implant placement in oral cancer patients with regard to implant survival and functional outcomes, and (2) can all oral cancer patients benefit from primary placement or is this method of treatment only suitable for specific patient groups. As implant treatment and techniques have evolved during the last decade, we comprehensively reviewed the literature on the timing of implant placement in oral cancer patients to compose recommendations for clinical practice with regard to optimal timing of implant placement in this category of patients.

METHODS

A search was conducted in MEDLINE (from 1995 through October 16th 2019) on October 16th 2019 according to the syntax rules of the database. Key words and their combinations were used to identify relevant studies (table 2.1). The titles and abstracts from all searches were reviewed.

Inclusion criteria were studies published in English regarding primary or secondary implant placement in oral cancer patients, cohort studies, case-control studies, (randomized) controlled trials. Review articles, animal studies, case reports, case series with less than 10 patients and studies regarding extraoral craniofacial implants were excluded. When it was not clear from the title and abstract if the paper dealt with implant placement in the upcoming irradiated (primary implant placement) or already irradiated (secondary implant placement) mandible or maxilla, the full text was reviewed and the article was included or excluded. 41 full-text articles were assessed followed by exclusion of 26 articles due to various reasons (figure 2.2). Furthermore, hand searches of the references of retrieved articles were carried out. The search was updated on December 27th 2019 and one additional article was included. Eventually 16 studies were included.

Table 2.1 Search strategy

Database	Search Terms
Medline	("Head and Neck Neoplasms"[Mesh] OR Head and Neck Neoplasm*[tiab] OR Head and Neck cancer*[tiab] OR cancer of head and neck[tiab] OR head and neck oncol*[tiab] OR Head and Neck malignan*[tiab] OR head and neck tum*[tiab] OR Upper Aerodigestive Tract Neoplasm*[tiab] OR mouth neoplasm*[tiab] OR oral cancer*[tiab] OR oral neoplasm*[tiab] OR oropharynx malignan*[tiab] OR oropharynx tum*[tiab]) AND ("Dental Implants"[Mesh] OR "Dental Implantation, Endosseous"[Mesh] OR "Dental Prosthesis, Implant-Supported"[Mesh] OR implant*[tiab] OR denture*[tiab]) AND (Primary placement*[tiab] OR primary insert*[tiab] OR ablation surg*[tiab] OR ablative surg*[tiab] OR "Time"[Mesh] OR time*[tiab] OR timing[tiab] OR delay*[tiab] OR sequence*[tiab])

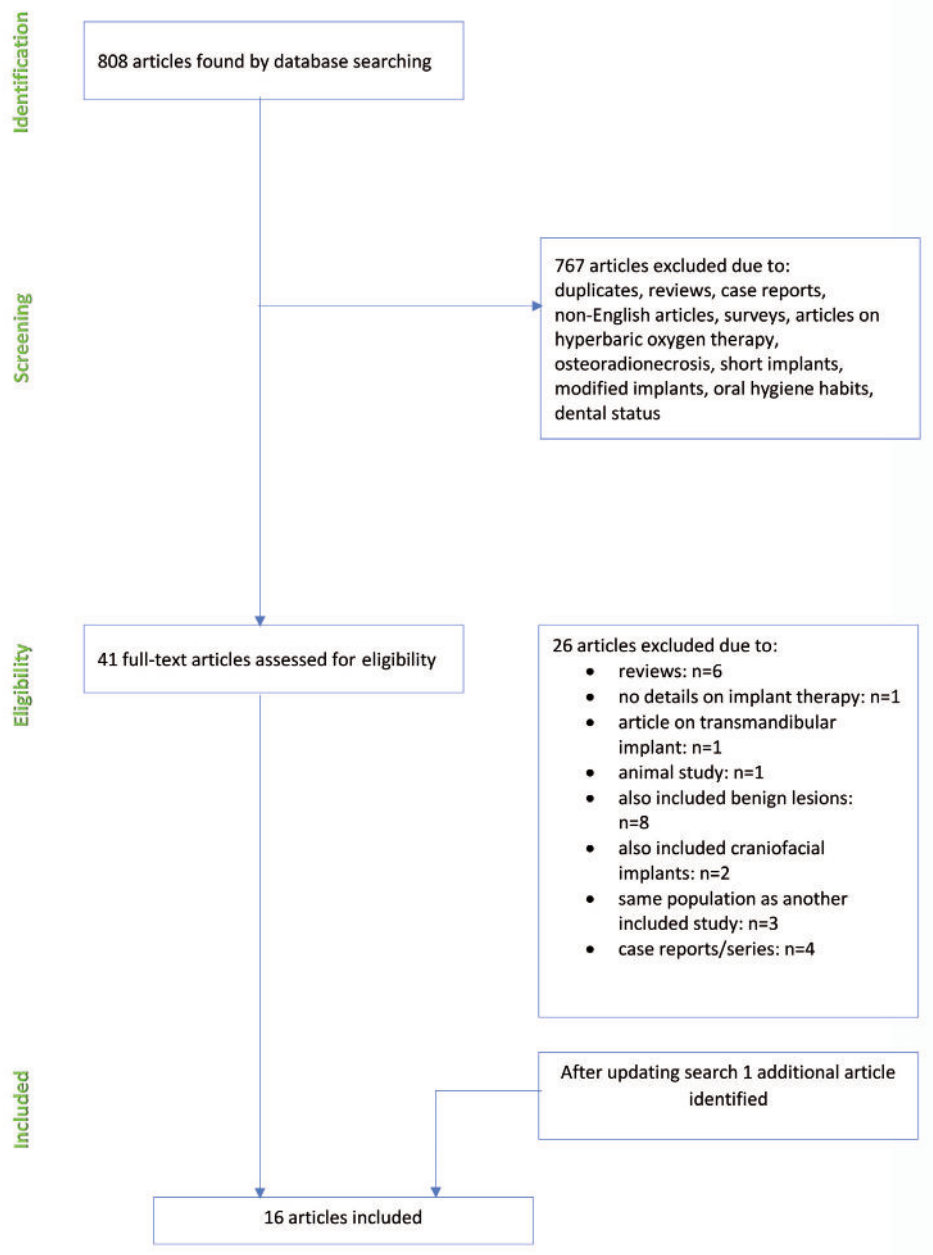
Data extraction

The following data were collected from the studies: patient demographics (age, oncologic diagnosis, patients' dental status before treatment), type of oncological treatment, timing of endosseous or zygomatic implant placement (primary, secondary), implant system, site of implant placement, type of tissue implants were inserted into (native or augmented bone), time until loading, implant loss, implant survival ratios, complications, perioperative measurements, type of prosthesis and follow-up period (table 2.2 to 2.4). When available, the time span between (implant) surgery and prosthesis placement, and the time between radiotherapy and secondary implant placement was recorded.

Statistical analysis

Quantitative data-synthesis was performed for the studies reporting 5-year dental implant survival rates of primary placed implants and secondary placed implants. Studies which did not report on the 5-year implant survival rate were not included in the quantitative analysis. The pooled 5-year implant survival rates were analyzed using a random effects model. Analyses were performed with Comprehensive Meta-Analysis software, Version 3 (CMA, Biostat, Englewood, NJ 07631, USA).

Figure 2.2 Flowchart of study selection procedure



RESULTS

16 out of 808 papers were considered eligible for our study and one additional article was included after updating the search (figure 2.2). These 16 studies provided data on a total of 4449 implants, of which 753 implants were placed in grafted bone (osseous free flaps). The majority of studies (68.8%) had a retrospective design. Preoperative dental status (edentulous or dentate) was not always reported. Patients received an implant-supported removable or fixed prosthesis. A variety of malignancies in the head and neck region was reported. Oncologic treatment consisted of tumour surgery in addition to radiotherapy. Three articles reported on including patients who were treated with chemotherapy[25-27]. Eight articles reported solely on secondary implant placement[25,27-33], two studies described patients with only primary placed implants[34-35] and six articles described both primary and secondary implant placement[26,36-40]. In all studies implants were placed in a 2-stage manner. When mentioned, the number of implants per patient ranged between 2 to 4 in the interforaminal region of the mandible[34-36,38]. Only one study reported the number of implants placed in the maxilla (3 to 5)[31]. From the available data, a total of 987 implants were placed in the maxilla and 131 zygomatic implants were placed in the zygomatic bone.

Implant survival

The pooled 5-year survival rate for primary placed implants was 92.8% (95% CI: 87.1%-98.5%) (figure 2.3), while the pooled implant survival rate for secondary placed implants was 86.4% (95% CI: 77.0%-95.8%) (figure 2.4). The 5-year implant survival rate of primary placed implants tended to be higher compared to secondary placed implants. Survival ratios for dental implants placed in vascularized bone grafts varied between 54 and 93.8% (table 2.3). The implants in vascularized bone grafts were placed in a secondary procedure. Implant survival ratios in native maxillary bone ranged between 57.1 and 95.3%. One study focused mainly on zygomatic implants and reported a 5-year implant survival rate of 92%[39].

Figure 2.3 Forest plot for cumulative weighted 5-year implant survival rate for primary implant placement

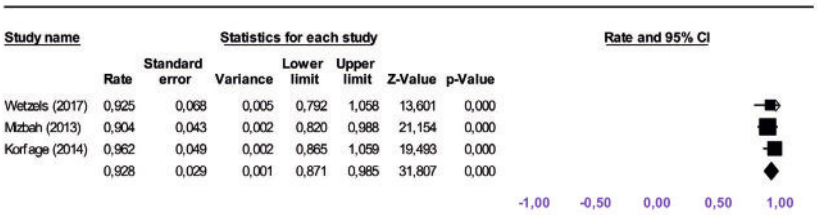
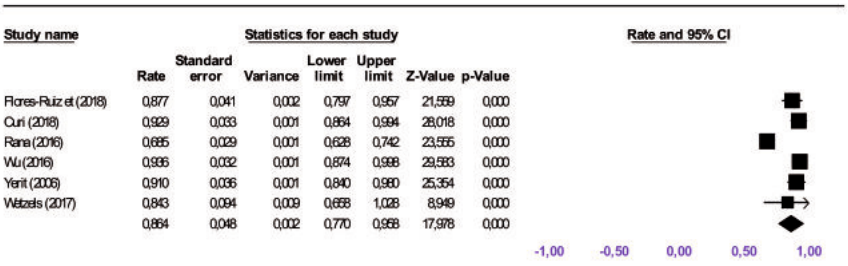


Figure 2.4 Forest plot for cumulative weighted 5-year implant survival rate for secondary implant placement



Time between ablative surgery, implant placement, radiotherapy and prosthesis placement

In two studies on primary implant placement, a healing period of 6 months after radiotherapy was applied before second stage surgery[35,40]. In another study a waiting period of 9 months was applied[34]. Time from tumour surgery and implant placement until prosthesis placement from 3 studies varied from 6.3 to 21.4 months[35,38, 40].

In the secondary setting there was a preference for waiting at least six months after completing radiotherapy before starting implant treatment. Some studies even preferred to wait at least 1 year[36,38]. Generally, patients had to wait more than one year after oncologic treatment before the oral rehabilitation was started. In the article by Flores-Ruiz et al. (2018) 70% of the patients started with implant therapy even later than 2 years after oncologic therapy[27]. The study of Seikaly et al. (2019) reported a mean time to prosthetic rehabilitation of 73.1 months[40]. For zygomatic implants there was also a difference between primary and secondary placed implants (median time until loading 1.7 months versus 9.3 months)[39].

Functional outcomes

Korfage et al. (2014) described that irradiated patients experience more limitations in oral function than those who were not[35]. Chewing ability decreased over time in irradiated patients, but there was still a better oral function in patients with a prosthesis than in patients without a prosthesis[35]. A more objective method for measuring oral function was applied in the study by Wetzels et al. (2016) by determining masticatory performance[36]. The authors showed an increased masticatory performance in all patients with implant-supported prostheses, supporting the assumption that implants are beneficial for improved oral function in oral cancer patients.

Complications

Intra- and postoperative complications of dental implant placement were uncommon. The most common reported complication was osteoradionecrosis (ORN) in irradiated patients[26,35-37]. The ORN rate varied between 1.8 and 7.7%. One study reported a pathologic fracture, but it was unclear if the fracture occurred because of implant placement[26]. In the study with zygomatic implants, infection of the overlying skin in secondary placed implants occurred in 2 patients[39]. There were no complications in the group with primary placed zygomatic implants. Other complications like wound infections, wound breakdown and partial fibular skin graft loss were described for implants placed in fibula free flaps[40]. Technical complications in primary and secondary placed implants included incorrect implant positioning. In the study of Korfage et al (2014), 6 out of 164 patients (3.7%) with primary placed implants did not receive an implant-supported prosthesis due to incorrect implant positioning[35]. Another study reported 17.7% unused implants after primary placement (17.7%) due to incorrect positioned implants and tumour related factors[38].

DISCUSSION

Timing of dental implant placement in oral cancer patients is a subject of continuing debate. Although most of the studies that were considered to be eligible for the review had retrospective study designs and studied implant placement in heterogeneous patient populations, it can be concluded that dental implant placement, irrespective of the timing of implant placement, is a reliable treatment option for head and neck cancer patients. Both primary and secondary implant placement show an acceptable overall implant survival. Comparison between both groups showed a tendency for a higher 5-year implant survival rate in primary

implant placement. This trend, however, did not reach statistical significance. Implants placed in the maxilla tended to have lower survival ratios than implants placed in the mandible. The lower implant survival ratios in maxillary bone might be related to the thinner cortical bone of the maxilla. For zygomatic implants however, 5-year implant survival rates of 92% were reported[39]. An explanation for these favourable outcomes could be that zygomatic implants are inserted in highly cortical bone of the zygoma, leading to a high initial stability. Because of their length, these implants may also be situated outside of the radiated field, therefore avoiding toxic radiation dosages. At this moment, functional results for zygomatic implants seem good and complication rates low, but guidelines on the optimal workflow are not yet available[41].

A great advantage of primary implant placement is the earlier prosthetic rehabilitation after tumour surgery. The latter is a great asset, also because it is not uncommon that head and neck cancer patients refuse the burden of undergoing the secondary implant placement, notwithstanding the great advantage they could experience from an implant-supported oral rehabilitation[42].

The costs and potential 'loss of resources' from implants not being used is an important issue in primary implant placement. The percentage of incorrect placed implants varied between the studies. We believe that with the help of 3D-technology, implant positioning (especially in difficult cases) can be further improved as has already been demonstrated in small groups for primary implant placement[43]. Placing implants during ablative surgery slightly lengthens the operating time, but the extra costs and burden to the patient of an additional secondary implant procedure under local anaesthesia are prevented.

As stated earlier, precision of implant placement can be improved further with 3D-technologies or surgical design and simulation (SDS). In both primary and secondary implant placement 3D-planning software can be used to assess the amount of available bone height and width for dental implants after resection and to assess the ideal location for the implants from a prosthetic point of view[44]. The use of SDS has resulted in a high percentage of implant utilization (96%) for mandibular defects constructed with fibula free flaps[40]. We therefore consider the availability of 3D-planning techniques a necessity in the reconstruction of oral cancer patients with complex (continuity) defects.

Only one study on primary implant placement in osseous free flaps for larger defects was considered eligible for our review[40]. In this prospectively conducted

study, dental implants were placed in bone grafts (mainly fibula grafts) during the ablative procedure. This resulted in a significant reduction of time to rehabilitation and percentage of patients rehabilitated. Most reports on implant placement in osseous free flaps include heterogeneous patient populations and show successful treatment outcomes with implant survival ratios between 80 to 100%[45,46]. Jackson et al. (2016) compared primary to secondary implant placement in fibula free flaps and found no difference in implant survival between primary and secondary implantation, and between non-irradiated and irradiated patients[47]. The 1-year results of Sandoval et al. (2019) in 10 patients with primary placed implants in fibula free flaps show that the presence of dental implants in fibula free flaps does not lead to more postoperative complications or an increase of radiotherapy related toxicities[48]. Despite these promising results, correct placement of dental implants in osseous free flaps during ablative surgery is technically challenging as reviewed by Bodard et al. (2011)[49]. One way of partially reducing these challenges is through the use of occlusion-driven reconstructions aided by 3D-planning, as is demonstrated in the article of Seikaly et al. (2019)[40]. However, the essential difference in tissues covering the grafted bone of the fibula and native mandibular bone remains. The presence of subcutaneous tissue and the absence of keratinized gingiva could affect implant survival and peri-implant health. The patients should be strictly monitored to see whether complications might occur on the long run. Additional thinning or correction of the overlying skin paddle is sometimes necessary during second stage surgery[45]. Regarding functional outcomes, Wijbenga et al. (2016) concluded from their systematic review that despite high implant survival ratios, it is not possible to state what the effect of implant-supported dental prostheses is after reconstruction with a fibula free flap, again mainly due to the diversity of methods used to assess functional outcomes[50]. Awad et al. (2019), however, concluded in their systematic review that 61% of patients with a vascularized fibula flap receiving dental rehabilitation reported good oral function and was able to consume a normal diet[51]. The latter authors, however, did not make a statement on the timing of implant placement in vascularized fibula flaps. With respect to timing of implant placement in osseous free flaps, it is generally advised to insert implants primarily only in patients with benign lesions[52,53]. In our clinic we prefer to place dental implants as much as possible in the remaining native mandibular bone (during ablative surgery) in order not to jeopardize the vitality of the vascularized fibula flap. As mechanical stability comes from the more anterior region of the mandible, this approach is successful in lateral and antero-lateral defects.

Limitations of this scoping review include, as stated earlier, the retrospective study designs, heterogeneous patient populations, exclusion of non-English papers, the

use of one database and the fact that screening by carried out by one assessor. These factors could result in bias. Due to the unavailability of large prospective studies on the timing of implant placement in oral cancer patients, the treatment of choice will mainly depend on surgeon experience and preference. However, based on the findings in the current study and our own experience in treating these patients, we composed treatment recommendations on the timing of implant placement in patients with malignant intraoral tumours (table 2.5). We realize that these recommendations may not be applicable to all hospital settings as 3D-planning software and the financial resources for primary implant placement may not be available in every centre.

Table 2.5 Recommendations for dental implant placement to support implant-retained overdentures in head and neck cancer patients

		Dental status		
		Edentulous mandible	**Edentulous maxilla**	**Suggestions / points of concern**
Extensiveness of oncologic treatment	**Surgery with or without local flap, and with or without (chemo) radiotherapy**	· primary implant placement. · 2 implants in the interforaminal region.	· primary implant placement. · number and type of implants* depends on size of defect, type of reconstruction and prosthetic rehabilitation.	· as an alternative, second stage surgery can be considered after the short-term adverse effects of radiotherapy have subsided.
	Surgery with osseous free flap (e.g., free fibula flap) with or without (chemo) radiotherapy	· primary or secondary implant placement, preferably in remaining native bone or otherwise in osseous free flap. · 2 – 4 implants	· primary or secondary implant placement, preferably in remaining native bone or otherwise in osseous free flap. · number and type of implants* depends on size of defect and type of reconstruction and prosthetic rehabilitation.	· thinning of the overlying soft tissues might be needed as a secondary treatment during second stage surgery. · apply 3D-planning techniques when available for both primary and secondary implant placement. · consider hyperbaric oxygen therapy in cases of treatment in irradiated tissues.

*Includes zygoma implants

CONCLUSION

Based on the studies included in this review, as far as the timing of implant placement is regarded, we propose to routinely combine tumour surgery with implant placement in native mandibular bone as standard care (primary implant placement). The functional benefits of primary implant placement outweigh the risk of leaving (some) implants unused. For more complex reconstructive cases, a personalized treatment approach (aided by 3D-technologies) is necessary and is more often in need of a secondary implant placement. It seems that primary placement of zygomatic implants is accompanied by a high implant survival and good oral rehabilitation although more research is needed on this particular topic.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Table 2.2 General characteristics of eligible studies

	First author	Year	Study type	N	Patient age (mean, range)	Oncologic diagnosis	Patients' dental status	Site of implant placement	Implant system	Tissue implants inserted to	RT	Radiation dose in region of implant	Timing of implant placement
1	**Flores-Ruiz**	2018	Retrospective	17	30-60	Epidermoid carcinoma, osteosarcoma, lymphoepithelioma	Edentulous and partially edentulous	Mandible and maxilla	Unknown	Native and grafted bone	Yes (47%)	Not reported	Secondary
2	**Curi**	2018	Retrospective cohort study	35	46-94	SCC	Not reported	Mandible and maxilla	Replace Select Tapered; Nobel biocare	Native bone	>50Gy	>50Gy	Secondary
3	**Rana**	2016	Retrospective	46	60	Oral cancer	Not reported	Mandible and maxilla	Biomet 3i	Native bone	Yes	Not reported	Secondary
4	**Wu**	2016	Retrospective	34	52.1	SCC, ACC, mucoepidemoid carcinoma, malignant ameloblastoma, nasopharynx tumour, acinic cell carcinoma	Not reported	Mandible and maxilla	Straumann, Nobelbiocare	Native and grafted bone (4 ilium bone, 18 fibula grafts)	Yes <50Gy	Not reported	Secondary
5	**Sammartino**	2011	Prospective	77	55.8, 28-63	Head and neck cancer	Edentulous and partially edentulous	Mandible and maxilla	Solid screw with microstructured surface	Native bone	Yes all	Not reported	Secondary
6	**Nelson**	2007	Retrospective	93	59, 26-89	Malignant intraoral tumour	Edentulous and partially edentulous	Mandible and maxilla	CAMLOG, Steri-oss (nobel biocare), Straumann	Native and grafted bone (ilium and fibula bone)	Yes (29/93) patients with up to 72Gy)	Not reported	Secondary
7	**Yerit**	2006	Retrospective	71	57.8, 16-84.1	Oral cancer (majority SCC T2-T4)	Not reported	Mandible	IMZ (Friadent), Frialit II (Friadent), Xive (Friadent)	Native and grafted bone (iliac bone)	Up to 50Gy	Not reported	Secondary
8	**Visch**	2002	Prospective	130	62, 34-87	Head and neck cancer	Not reported	Mandible and maxilla	Hydroxy-appatite coated titanium. Dyna, Screw-Vent implants	Native bone	Yes (50-72Gy)	Not reported	Secondary

Table 2.2 General characteristics of eligible studies *(continued)*

	First author	Year	Study type	N	Patient age (mean, range)	Oncologic diagnosis	Patients' dental status	Site of implant placement	Implant system	Tissue implants inserted to	RT	Radiation dose in region of implant	Timing of implant placement
9	**Seikaly**	2019	Prospective	30	57	Malignant disease not further specified	Not reported	Mandible and maxilla	Not reported	Grafted bone (fibula free flap)	7/15 primary; 9/15 secondary	Not reported	Primary and Secondary
10	**Butterworth**	2019	Prospective	49	70, 13-92	SCC, ACC, sarcoma, adenocarcinoma, melanoma, rhabdomyosarcoma, ameloblastoma, pleomorphic adenoma, ORN	Edentulous and dentate	Upper jaw / zygoma	Not reported	Native bone	Yes 16/49	Not reported	Primary and Secondary (2 groups)
11	**Wetzels**	2017	Retrospective cohort study	97 (79 prim. 18 sec.)	66.25 (prim.), 68.32 (sec.)	SCC, merkel cell carcinoma, salivary gland carcinoma	Edentulous	Mandible and maxilla	Branemark Nobel Biocare (primary), Astra/ Straumann (secondary)	Native bone (both primary and secondary	55% (prim.), 53% (sec.)	Not reported	Primary and Secondary (2 groups)
12	**Ch'ng**	2016	Retrospective	246	59.0	ACC, adenocarcinoma, ameloblastic carcinoma, desmoid tumour, fibrosarcoma, melanoma, osteosarcoma, SCC, hemangioendothelioma	Unknown	Mandible and maxilla	Astra Tech	Native and grafted bone (67 fibula free flaps)	165/246 (60-72Gy)	Not reported	Primary and secondary

Table 2.2 General characteristics of eligible studies *(continued)*

	First author	Year	Study type	N	Patient age (mean, range)	Oncologic diagnosis	Patients' dental status	Site of implant placement	Implant system	Tissue implants inserted to	RT	Radiation dose in region of implant	Timing of implant placement
13	**Wetzels**	2016	Prospective	56	67 - 70	Intraoral malignancies not further specified	Edentulous	Mandible	Branemark (primary), Astra+ Straumann (secondary)	Native and grafted bone. Primary: 2 free vascularized bone flaps.. Secondary: 4 free vascularized bone flaps.	Yes	Not reported	Primary and secondary
14	**Mizbah**	2013	Retrospective	99	Not reported	Primary SCC	Edentulous	Mandible	Branemark (primary), Frialit (delayed)	Native bone	Primary 47/99. Secondary 17/29.	Not reported	Primary and secondary
15	**Korfage**	2014	Prospective cohort	164	64.8, 39-88	SCC	Edentulous	Mandible	Branemark (Nobelbiocare)	Native bone	Yes (64)	Not reported	Primary
16	**Schepers**	2006	Retrospective	48	64.8 (men), 68.1 women)	Primary SCC in oral cavity	Edentulous	Mandible	Branemark	Native bone	Yes (21/48)	10-68Gy	Primary

RT: radiotherapy; SCC: squamous cell carcinoma; ACC: adenoid cystic carcinoma; ORN: osteoradionecrosis, FFF: fibula free flaps; Gy: Gray; prim: primary; sec: secondary,
Studies number 1 – 8: Studies on secondary implant placement
Studies number 9 – 14: Studies on both primary and secondary placed implants
Studies number 15 – 16: Studies on primary implant placement

Table 2.3 Data on implant treatments and implant survival of included studies

First author	Primary implant placement (N)	Secondary implant placement (N)	Total no. of implants	Time after RT until implant placement	Time until loading	Number of implants per patient	Implant loss	Implant survival rate	Follow-up period
Flores-Ruiz	0	17	106 (15 implants in grafted bone; 43 in the maxilla)	70% >2 years after radiotherapy	Not reported	Not reported	13 failed (9 maxilla, 4 mandible; 9 native bone, 4 grafted bone).	90.1% native bone. 73.3% grafted bone. 79.2% maxilla. 87.7% mandible. Overall 87.7% .	5 yrs
Curi	0	0	169 (79 implants in the maxilla, 90 implants in the mandible)	1-92 mo	6 mo	Not reported	12 implants (3 during healing period and 9 lost after loading)	92.9% 5 yrs	7.43 yrs
Rana	0	46	162 (70 implants in the maxilla)	6-24 mo	Not reported	Not reported	52	65% maxilla 71% mandible	5 yrs
Wu	0	34	187 (63 implants in maxilla; 68 implants in native bone)	6-12 mo	0.8 yrs	Not reported	27	93.2% native bone. 93.8% grafted bone. 87.3% maxilla. 97.5% mandible Overall 93.6%	5 yrs
Sammartino	0	77	188 (42 implants in the maxilla, 146 in the mandible)	At least 6 months. Mean time: 9.4 months.	6 mo (mandible), 8 mo(maxilla)	2 mandible; 3-5 maxilla	2 implants lost in mandible; 18 implants lost in maxilla.	98.4% in mandible; 57.1% in maxilla. 90.5% in <12 mo after RT. 82.2% in >12 mo after RT.	3 yrs
Nelson	0	93	435 (281 implants in the maxilla; 95 implants in grafted bone).	Minimum 6 mo	3 mo mandible, 6 mo maxilla	3 to 8	43 implants	Maxilla 70% after 4 yrs. Overall implant survival 92%, 84%, and 69% after 3.5, 8.5, and 13 years. Implant survival rates for implants in grafted bone unknown.	13 yrs

Table 2.3 Data on implant treatments and implant survival of included studies *(continued)*

First author	Primary implant placement (N)	Secondary implant placement (N)	Total no. of implants	Time after RT until implant placement	Time until loading	Number of implants per patient	Implant loss	Implant survival rate	Follow-up period
Yerit	0	71	316 (171 in iliac bone)	1.41 yrs after surgery	>6mo	Not reported	44 implants	Overall: 95%, 94%, 91% and 75% after 2,3,5,8 yrs. Irradiated: 93%,90%,84% and 72% after 2,3,5,8 yrs. Grafted bone: 96%,96%,96% and 54% after 2,3,5,8 yrs.	5.4 yrs
Visch	0	130	446 (108 implants in the maxilla, 338 implants in the mandible)	6 mo – 22 yrs	6mo	Not reported	64 implants	Overall: 78% 10yr. Maxilla 60%, mandible 85%. 10 yrs.	10 yrs
Seikaly	15	15	110 (57 implants primary; 53 implants secondary). Number of implants in maxilla / mandible not reported.	Not reported	6mo	Not reported	2 implants lost in both groups	Overall: 96%	1 year
Butterworth	27 patients and 75 zygoma implants + 14 standard	22 patients and 56 implants + 16 standard	131 zygomatic implants. Additionally 30 dental implants in the maxilla.	Not reported	primary 1.7mo, secondary 9.3 mo	NA	9 zygoma implants	12 mo estimated 94%, 60 mo estimated 92%	2-110 mo

Table 2.3 Data on implant treatments and implant survival of included studies *(continued)*

First author	Primary implant placement (N)	Secondary implant placement (N)	Total no. of implants	Time after RT until implant placement	Time until loading	Number of implants per patient	Implant loss	Implant survival rate	Follow-up period
Wetzels (2017)	79 patients and 207 implants. 52 implants never loaded.	18 patients and 43 implants placed 528 days after surgery	268 (in primary group 18 additional implants were placed post-surgery)	At least 6mo disease free	3 mo (non-irradidated), 6 mo (irradiated)	2 to 4	17 primary implants failed (6.7%), 12 mandible, 5 maxilla. 5/17 due to implant related cause. Secondary group 3 implants lost (7%) due to loss of flap in which implants were placed. In primary group 32% implants failed due to patient death, versus 7% in secondary group due to patient death.	Higher cumulative implant survival rates in secondary group. Primary 60%. Secondary 86%.	5yrs
Ch'ng	115 during ablative surgery. 41 primary RT.	90	1132 (243 implants in fibula free flaps; 618 implants in native mandible, 271 in native maxilla)	Not reported	Not reported	2-9 in fibula free flap.	Overall 42/1132 lost	Mandible 97.4%. Maxilla 95.3%. Fibula free flap 92.6% Overall 96.3% at follow-up. 5 yrs 94.9%.	5 yrs
Wetzels (2016)	18 patients and 40 implants	9 patients and 19 implants placed 568 days after surgery	59	Unknown. (Secondary implants were placed at least 1 year after ablative surgery)	Not reported	2 or 3	In primary group 3/40 implants lost. In secondary group 3/19 implants lost.	Primary 92.5%. Secondary 84.2%.	5 yrs

Table 2.3 Data on implant treatments and implant survival of included studies *(continued)*

First author	Primary implant placement (N)	Secondary implant placement (N)	Total no. of implants	Time after RT until implant placement	Time until loading	Number of implants per patient	Implant loss	Implant survival rate	Follow-up period
Mizbah	99	29	163	At least 1 year no recurrence	3 mo (non-irradiated), 6 mo (irradiated)	2 to 4	24 (primary) = 9.6%,. 6 (secondary) = 9.2%.	Primary 90.4%; Secondary 90.8%	5 yrs
Korfage	164	0	524	-	3 mo (non-irradiated), 9 mo (irradiated)	2 to 4	31 (irradiated patients), 5 (non-irradiated patients)	93.1%	Up to 14 yrs
Schepers	48	0	139	-	9 mo (irradiated), 4.7 mo (nonirradiated)	2 to 4	2/61 (irradiated) , 0/78 (non-irradiated)	96.7% (irradiated), 100% non-irradiated	29.6mo

RT: radiotherapy; mo: months; yrs: years

Table 2.4 Data on type of prosthetic rehabilitation, functional outcomes and perioperative measurements

First author	Reported clinical measurements	Peri-implant bone loss	Type of prosthesis	Functional outcomes	Prophylaxis	Complications	Overall conclusion
Flores-Ruiz	None	Not reported	Overdenture, fixed prostheses	None	None	Not reported	There is no consensus as to the time needed to achieve successful survival after placement of implants
Curi	None	Not reported	Overdentures	Patient satisfaction, mastication, speech, aesthetics	Clindamycin 4x300mg 1 week starting 1 day before treatment; HBO (37.1%)	Not reported	Dental implants in head and neck cancer patients with RT is a viable treatment alternative with a high degree of satisfaction. The type of RT may require special consideration. IMRT has less implant failure than conformal RT.
Rana	Not reported	Not reported	Cemented and removable overdentures	None	None	Not reported	Further research is required in this field to improve aesthetics and quality of life.
Wu	BI,GI,PI	1.2 ± 0.4 to 1.6 ± 0.6 mm.	Fixed and removable dentures	None	HBO (14 patients)	65 prosthetic maintenance procedure (abutment/screw loosening). No surgical complications reported.	Dental implants are more successful in the mandible than in the maxilla. No difference in survival rates between patients who received HBO and who did not. The restoration of oral function in radiotherapy patients with tumour resection using implant-supported prostheses is a viable treatment option.
Sammartino	None	Panoramic and periapical	Overdentures, maxillary obturators	None	No HBO	Not reported	Implant therapy can be considered in irradiated patients when from an oncologic standpoint the tumour prognosis is benign and the risk of recurrence is poor. Higher implant success rates in the mandible and in irradiated implant sites with a dosage no more than 40-50Gy.

Table 2.4 Data on type of prosthetic rehabilitation, functional outcomes and perioperative measurements *(continued)*

First author	Reported clinical measurements	Peri-implant bone loss	Type of prosthesis	Functional outcomes	Prophylaxis	Complications	Overall conclusion
Nelson	None	Not reported	Fixed and removable dentures	None	Irradiated patients clindamycin 300mg 1 day pre- and 3 days postoperatively	Technical complications: Replacement of 11 bar-retained dentures. 2 patients with mucosa ulcers after loss of retention of the removable denture. 3 patients with dehiscence and disturbed wound healing.	The mean 10.3-year survival rate was low, and there was no statistically significant difference in implant survival between irradiated and nonirradiated patients. The increased failure rate was caused by the higher mortality rate of the patients; it was not the result of lack of osseointegration. There was no difference between implant survival in grafted and nongrafted patients.
Yerit	None	Not reported	Removable denture	None	No HBO	1 patient with a pathological fracture of the mandible leading to loss of 3 implants.	Shorter implant survival in irradiated and grafted bone. No difference in survival between implant placed < or > 12mo after RT. Surgical and prosthetic implant rehabilitation of tumour patients offer long-term results with favourable implant survival rates.
Visch	None	Not reported	Not reported	None	AB prophylaxis. No HBO.	Not reported	After a post-irradiation interval of six months, the influence of time on implant survival is not significant. Bone-resection surgery in the jaw where the implant is placed has a significantly negative influence on implant survival. Implant location is the most dominant variable influencing implant survival (more implant loss in maxilla than in the mandible).

Table 2.4 Data on type of prosthetic rehabilitation, functional outcomes and perioperative measurements *(continued)*

First author	Reported clinical measurements	Peri-implant bone loss	Type of prosthesis	Functional outcomes	Prophylaxis	Complications	Overall conclusion
Seikaly	None	Not reported	Not reported	Not reported	HBO	Primary placement: 2 major complications (hematoma, pulmonary embolism) and 7 minor complications (tachycardia, atelectasis, wound infection/breakdown, partial fibular skin graft loss). Secondary placement: 2 major complications (flap venous congestion and pneumonia) and 5 minor complications (wound infection/breakdown)	Primary implant placement in fibula free flaps reduced the duration of time to complete treatment from 6.1 yrs to 1.8 yrs. The reduction in treatment time was not associated with a statistically significant increase in complications.
Butterworth	None	Not reported	Oral (fixed and removable) and facial prostheses	QOL. No significant problems with swallowing	NA	No significant complications in primary implant group. Secondary implant group: 2 patients with an infection of the skin overlying the zygomatic body. 2 patients with peri-implant bone loss. Small number of patients with screw loosening and screw fracture.	Primary implant placement should be the gold standard. Access for zygomatic implant placement is much improved at primary resective surgery. There is a trend towards worse survival rates in secondary placement.
Wetzels (2017)	None	Not reported	Overdenture	None	6 patients HBO in secondary group	Primary implant group: 52 implants were never loaded. 5 patients with ORN. Secondary implant group: 5 patients with ORN.	1. More functional overdentures in primary group. 2. Prosthetic rehabilitation 484 days earlier in primary implants. 3. Timing of placement does not affect viability of implants.

Table 2.4 Data on type of prosthetic rehabilitation, functional outcomes and perioperative measurements *(continued)*

First author	Reported clinical measurements	Peri-implant bone loss	Type of prosthesis	Functional outcomes	Prophylaxis	Complications	Overall conclusion
Ch'ng	None	Not reported	Removable denture	None	Not reported		More implant losses in fibula free flaps. RT adversely affects implant survival in FFF but not in the native mandible or maxilla. The sequence of RT in relation to implant placement did not significantly affect the implant survival rate, except in fibula free flaps. Irradiation might be considered a relative contraindication to implant placement in osseous free flaps. No conclusion on timing.
Wetzels (2016)	None	Not reported	Overdenture	Bite force, masticatory performance	HBO in irradiated patients in secondary group	1 patient with ORN (not adjacent to the still functional implants).	There is a strong indication of superior bite force and masticatory performance after 5 years in primary group when compared to postponed placement. It seems that primary placement is superior to secondary placement.
Mizbah	None	Not reported	Overdenture	None	HBO in irradiated patients in secondary group	Not reported	Using primary placement, more patients benefit and receive their overdentures at an earlier stages (20months earlier) compared to secondary placement.
Korfage	Periodontal indices	Panoramic	Overdenture	EORTC QLQ, OHIP.	HBO in 3 patients who developed ORN	5 patients with ORN in proximity to the implants. Pathological mandible fracture in 1 patient with a recurrent tumour and ORN.	More limitations in oral function and less satisfaction in irradiated patients. Better oral function with than without prosthesis. A large number of patients with oral cancer in whom implants are inserted during resection may benefit at an early stage from an overdenture and develop good function, satisfaction. Primary insertion should be routinely incorporated into surgical planning. More implant loss in irradiated patients.

Table 2.4 Data on type of prosthetic rehabilitation, functional outcomes and perioperative measurements *(continued)*

First author	Reported clinical measurements	Peri-implant bone loss	Type of prosthesis	Functional outcomes	Prophylaxis	Complications	Overall conclusion
Schepers	None	Not reported	Removable denture	None	Not reported	No patients developed ORN. No other complications reported.	Success of prosthetic rehabilitation on implants inserted during ablative surgery is independent of whether postoperative RT is applied. Primary implant placement in edentulous mandibles appears to have advantages over secondary implant placement in patients with oral SCC.

RT: radiotherapy; SCC: squamous cell carcinoma; ACC: adenoid cystic carcinoma; ORN: osteoradionecrosis, FFF: fibula free flaps. PORT: postoperative radiotherapy; IMRT: intensity-modulated radiation therapy, HBO: hyperbaric oxygen; BI: bleeding index; GI: gingiva index; PI: plaque index, Gy: Gray; AB: antibiotic; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; OHIP: Oral Health Impact Profile.

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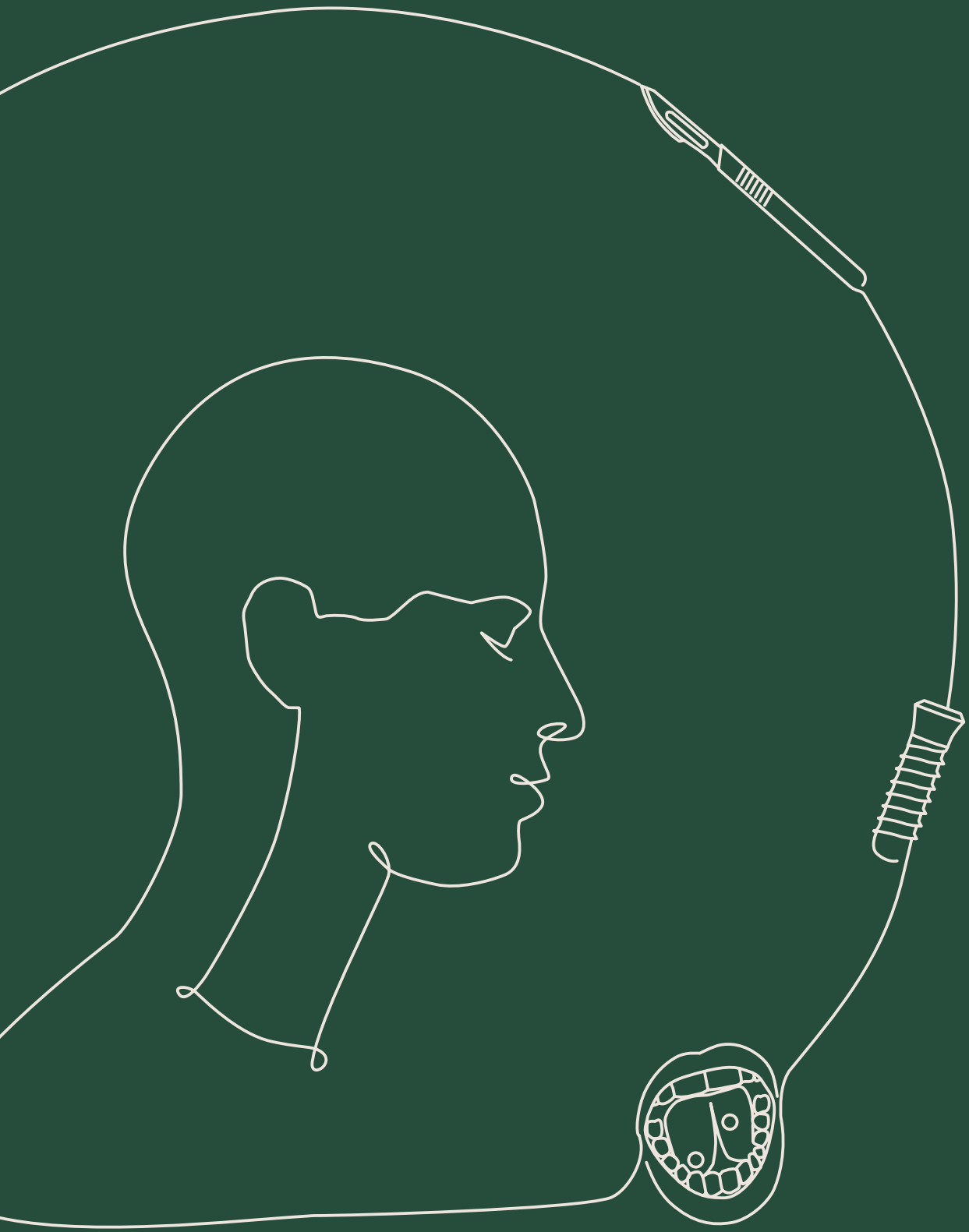

Chapter 3

Prosthodontic rehabilitation of head and neck cancer patients: Challenges and new developments

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ABSTRACT

Head and neck cancer treatment can severely alter oral function and aesthetics, and reduce quality of life. The role of maxillofacial prosthodontists in multidisciplinary treatment of head and neck cancer patients is essential when it comes to oral rehabilitation and its planning. This role should preferably start on the day of first intake. Maxillofacial prosthodontists should be involved in the care pathway to shape and outline the prosthetic and dental rehabilitation in line with the reconstructive surgical options. With the progress of three-dimensional technology, the pre-treatment insight in overall prognosis and possibilities of surgical and/or prosthetic rehabilitation has tremendously increased. This increased insight has helped to improve quality of cancer care. This expert review addresses the involvement of maxillofacial prosthodontists in treatment planning, highlighting prosthodontic rehabilitation of head and neck cancer patients from start to finish.

INTRODUCTION

Head and neck cancer is the fifth most common cancer worldwide[1]. The course of the disease and its treatment have major effects on psychological well-being and functioning of the patients[2]. The treatment of head and neck cancers consists of different treatment modalities, typically being surgery, radiotherapy, chemotherapy or a combination of these modalities. Besides curing cancer, another important aim is to regain the oral function and aesthetics that got lost or altered due to the treatment.

Effects of primary oncology surgery can impede rehabilitation goals[3]. These effects include an altered oral anatomy, compromised soft tissue conditions like missing or scarred tissues and bulky flaps, altered muscle attachments and muscle balance, sensitivity disorders, loss of lip competence and trismus, loss of anatomical structures, loss of bony structures and/or teeth, and alterations in facial appearance. Regaining oral function and aesthetics is a challenge because of limitations in the restorative treatment options due to, e.g., poor support and lack of space for a prosthesis, impeded resilience of soft tissues, impaired tongue function, and loss of integrity and competence of the velopharyngeal complex[4].

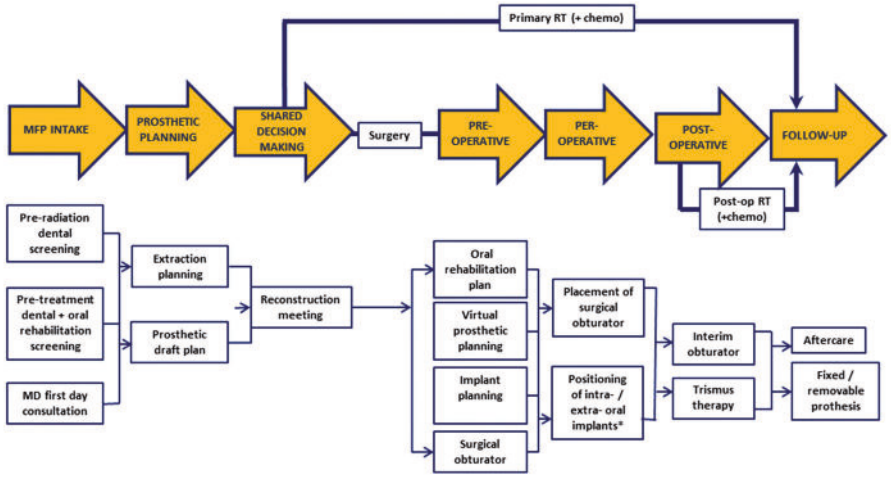
Posteriorly situated tumours, tumour size, adjuvant radiotherapy and extensive soft-palate and tongue resections have been shown to be predictors for deterioration of oral functioning[5-7]. Studies that looked into the quality of life of head and neck cancer patients after completion of oncologic treatment reported that regaining oral function, including prosthetic rehabilitation, is of great importance[8-10]. Therefore, the oncological team is in need of specially trained, experienced dental professionals, preferably maxillofacial prosthodontists, to support the team with planning of the oral rehabilitating head and neck patients. This planning and treatment may include the use of osseointegrated intra- and extraoral implants to retain oral and/or craniofacial prostheses.

As mentioned, to achieve rehabilitation goals, a close and open collaboration between ablative surgeons, reconstructive surgeons, radiation oncologists, maxillofacial prosthodontists and medical engineers is of utmost importance to move towards an optimal rehabilitation of the head and neck cancer patient. The purpose of this expert review is to emphasize the role of the maxillofacial prosthodontist in the treatment planning and oral rehabilitation of head and neck cancer patients as well as to discuss challenges and new developments in the prosthodontic rehabilitation of these patients.

Pre-treatment screening

Multidisciplinary first-day consultation intents to shorten time between diagnosis and treatment of oral cancer[11]. Maxillofacial prosthodontics should be included in the multidisciplinary first-day consultation. This first-day consultation aims to provide a preliminary plan stating the required diagnostic procedures and prosthetic involvement (figure 3.1) so that treatment can start as soon as and as effective as possible. The involvement of the maxillofacial prosthodontist includes a pre-radiation dental screening, and a pre-treatment dental and oral rehabilitation screening[12]. During this screening, all available information is gathered with regard to self-care, oral hygiene, dental situation, mouth opening, location of the suspected or confirmed tumour, presumed need for ablative surgery and/or radiotherapy, estimation of retention and bearing of a future (obturator, dental) prosthesis, and estimation of the pre-existent level of oral function[13,14]. This information is needed to design the best prosthetic treatment plan. This plan should be designed taking the patients' wishes, the tumour characteristics, extent of acquired resection for clean margins, possible types of reconstruction, need for (chemo)radiation, and dental and/or prosthetic possibilities into account.

Figure 3.1 Involvement of the maxillofacial prosthodontist in treatment planning and rehabilitation of head and neck cancer patients focused on ablative surgery. MD: Multidisciplinary, MFP: maxillofacial prosthodontics; Post-op: Post-operative, RT: radiotherapy;



**Preferably, implants are placed during ablative tumour surgery. When not feasible, implants can also be placed during follow-up. For details see Alberga et al. (2020).*

Pre-radiation dental screening

In case radiotherapy might become involved, head and neck cancer patients in whom the oral cavity is within the radiation treatment portal are in need of a thorough dental examination. These patients have to complete any required dental treatment before the onset of radiotherapy[15]. Pre-radiation dental screening aims to locate and eliminate oral foci of infection, such as unrestorable caries, periodontal disease with pockets ≥6mm, periapical problems and (partially) impacted teeth[12].

Pre-treatment dental and oral rehabilitation screening

Although at the first day consultation the extent of the final oncologic treatment plan is uncertain, at this stage the maxillofacial prosthodontists should already estimate whether patients are in need of a prosthetic rehabilitation simultaneously with reconstructive surgery or after completion of cancer therapy, and what the patients' desires are. Implementing the results of pre-treatment screening into the prosthetic workflow ensures that all information is gathered and all needed care is provided to design a patient specific prosthetic rehabilitation draft plan. In some cases, prosthetic retentive considerations are critical to achieve successful prosthetic rehabilitation. The size of the defect and number of critical remaining teeth that may serve as anchorage for a conventional clasp-retained removable partial denture challenges the maxillofacial prosthodontists to obtain insight into the intended therapeutic isodosis fields in relation to the strategic important teeth. This sometimes results in a well-considered decision to leave teeth which are considered an oral focus of infection in situ (including a thorough discussion of the risk on development of osteoradionecrosis).

With regard to the future prosthodontic rehabilitation, an early decision whether there is a need to place implants is important. This allows for the preferred prosthodontic rehabilitation of head and neck patients. For example, choices in planning, positioning and number of endosseous oral implants or oncology zygomatic implants are key factors for retention of the prosthetic construction[16,17]. Literature emphasizes the importance of an immediate implant procedure as it has been shown that placement of mandibular implants in edentulous patients during ablative surgery results in a higher number of patients with functioning mandibular dentures after completion of oncologic therapy[2,18,19]. Furthermore, an increasing trend is observed to complete the prosthodontic rehabilitation early, for which an immediate implant procedure is often a prerequisite[16,20]. When implants are placed after radiation treatment, the anatomical site where the implants are placed seems to effect implant survival; the implant survival rate is higher in the mandible than in

the maxilla and in grafted bone[21,22]. Therefore, implant placement during ablative surgery is preferred, at least in selected cases[16].

When there is a need for per-operative prosthetics, the maxillofacial prosthodontist has to record the actual intraoral situation through impression taking, intraoral scanning and/or cone beam computer tomography (CBCT) imaging, all to capture the intraoral pre-treatment situation and occlusal plane for fabrication of a surgical obturator, surgical guides and models, or an implant-supported prosthesis. A huge advantage of working with three-dimensional (3D) intraoral scanning is the ease to combine the data of the intraoral situation, like the position of teeth and occlusion, with (CB)CT and magnetic resonance imaging (MRI) data of the surrounding tissues in an augmented model. This 3D virtual model provides more insight into the implications and complexity of surgical and prosthetic rehabilitation. This insight allows the surgical team to analyse the surgical and rehabilitation outcome and plan the treatment[23,24]. Although intraoral scan techniques are widely used nowadays, some limitations can occur mostly due to poor intraoral access caused by, e.g., the tumour, trismus or pain. In those situations analogue impressions are the only feasible option. The produced plaster model can then in a second stage be digitalized in order to create the 3D virtual model.

When mutilating extraoral defects are expected as a result of ablative surgery, extraoral dimensions have to be recorded as well as to prepare for future extraoral prostheses. Although analogue workflows still meet the quality standards of prosthetic care, digital technology has demonstrated ease and utility in design and construction workflows in prosthodontics[25]. The prosthodontic documentation can be completed by taking clinical photographs. In this way skin-, prosthetic- and facial characteristics are captured and aid with communication within the head and neck team. With all gathered information a prosthetic draft plan can be worked out in preparation of the necessary input of maxillofacial prosthodontists in choice of rehabilitation treatment.

Multidisciplinary approach

In the past, prosthodontic rehabilitation in the oncological treatment path was a stand-alone final procedure after completion oncological therapy. Nowadays, planning of surgical reconstruction starting with occlusion of teeth also safeguards a proper dental rehabilitation. This approach supports a thorough adjustment of the surgical and prosthetic planning and treatment before the oncologic treatment is started[23,26]. In a reconstruction meeting, the head and neck team can go through the available options of surgical, prosthetic or combined reconstruction. The input of

maxillofacial prosthodontists in such a reconstruction meeting guards the feasibility from a prosthetic point of view, guided by a prosthetic draft plan, and includes the eventual need for implant placement. With the introduction of 3D planning and computer aided design (CAD) assistance, preoperative virtual augmented models provided by medical engineers at these meetings are a great asset to the surgical team and support shared decision-making regarding favourable reconstruction option after oncology treatment.

Virtual planning

Once the final oncological treatment plan is agreed upon, having access to a preoperative virtual surgical planning (VSP) can be of importance for the surgical team[24]. Three-dimensional planning enables a high accuracy of guided resection surgery and prosthetic-driven reconstruction planning[27,28]. Besides a reliable intended outcome, the concept of backwards planning from occlusion maximizes the chances of completing oral rehabilitation of the patient. A 3D VSP can be very precisely executed, with the use of 3D printed guides creating the possibility of completing a full ablative and reconstructive plan in one surgery[23,26]. However, soft tissues are not very reliable reproduced yet by digital techniques. This is still an uncertain factor to be taken into account when it comes to planning prosthetic treatment. The risk of losing prosthetic retention options due to compromised soft tissues means critically assessing choices such as preservation of a functional dental arch (shortened), planning a fixed or removable prosthesis, and indication of peroperative insertion of endosseous oral implants or oncology zygomatic implants. Tools to better reproduce soft tissues are in development.

Rehabilitation of mandibular defects

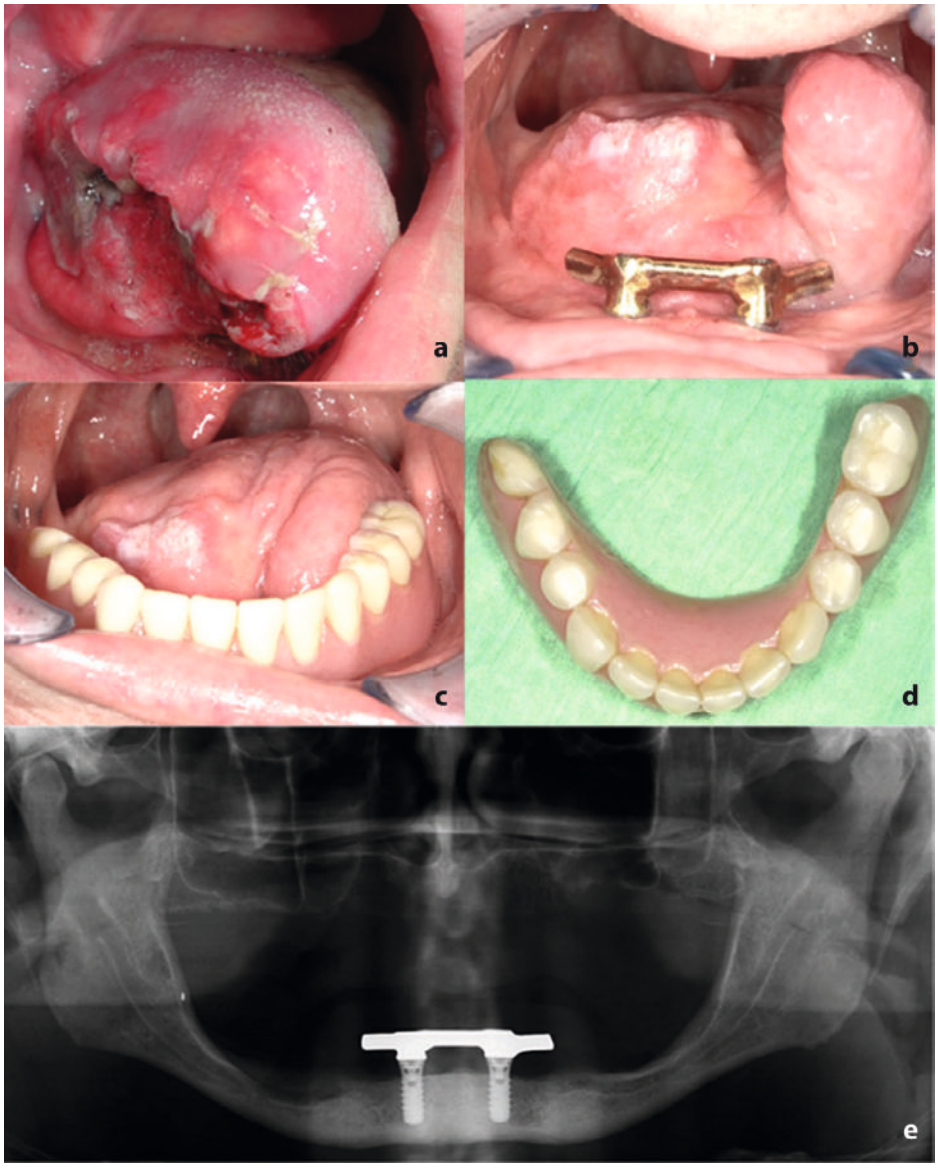
Smaller head and neck tumours can require resection of soft tissue only and can surgically be managed by primary closure. To overcome possible absence of vestibule or compromised neutral zone provision of individualized adapted prostheses is required. With such an approach oral function might reach a near normal level after ablative surgery and prosthetic rehabilitation[8].

Advanced tumours can result in large defects, requiring surgical reconstruction[29]. The resulting altered anatomy can be unfavourable because of flap positioning and presence of scar tissue. Such unfavourable conditions may impair the ability to speak, masticate and swallow. Loss of sensibility, a shallow or absent buccal vestibule, radiation-induced hyposalivation and trismus may further compromise oral function. Advanced tumour surgery requiring bone resection may further compromise oral function due to loss of the continuity of the mandible, loss of teeth

and severe deformities. Most of all, an impaired motility of the tongue challenges the fabrication of a functional mandibular resection prosthesis as it compromises stability of this prosthesis during speech and mastication[30].

Many of the aforementioned problems can, at least in part, be reduced by the use of endosseous oral implants to retain prostheses (figure 3.2). These implants contribute to stabilization of prostheses and reduce loading of the compromised soft tissues and underlying bone[31]. In many patients, an almost normal masticatory function can be achieved with a rehabilitation of the reconstructed side with implant-supported removable partial dental prostheses or implant-retained mandibular overdentures[32]. Maximization of dental rehabilitation significantly improves oral functioning, oral diet achievements and oral health related quality of life[2,33]. Several authors reported that a relatively low percentage of reconstructed patients complete prosthetic rehabilitation[34]. Causes of not completing the prosthetic treatment after implant placement are, vertical discrepancy between the graft and the remaining mandible, which leads to an unfavourable implant-crown ratio, poor quality of soft tissues (hypertrophy often appears after the placement of the abutments), and the type of the prosthesis (fixed or removable)[35]. As implant placement during primary reconstruction shortens the interval between surgery and dental rehabilitation, the number of orally rehabilitated patients will increase[16,36].

Figure 3.2



Patient diagnosed with squamous cell carcinoma of the tongue after hemiglossectomy and radial forearm free flap reconstruction.

a. Pre-operative image of tumour **b**. Intraoral view after ablative surgery and postoperative radiotherapy. Bar suprastructure with distal extensions fixed on two endosseous implants **c,d**. Implant-supported prosthesis with patient specific design to optimize tongue function during speech and mastication **e**. Orthopantomogram two years after reconstructive surgery showing good integration of endosseous implants.

Rehabilitation of maxillary defects

Management of maxillary, midface and skull-base tumours is challenging and complex when it comes to ablative surgery with a need for oral and facial reconstruction, and oral rehabilitation. Maxillary resections lead to a variety of oronasal defects, with a diversity of approaches for restoring oral functioning. Manifold maxillectomy classification schemes are mentioned in literature, all originating from the Brown classification published in 2000[37]. These schemes categorize the range of maxillary defects by location, extension like the vertical and horizontal components, and biomechanical forces, and provide guidelines for surgical and prosthetic rehabilitation choices**.**

Restorative decision making

When tumour resection causes a minor oronasal fistula and primary closure is not feasible, surgical reconstruction with soft tissue flaps alone can lead to excellent functional and aesthetic results, as long as prosthetic retention of teeth replacement is guaranteed. For larger maxillary defects, the option of prosthetic rehabilitation with an obturator prosthesis is the standard of care in many institutions since decades[38,39]. This approach includes maxillary obturators for defects of the hard palate, pharyngeal obturators for defects of the soft palate, and maxillopharyngeal obturators for defects that include both structures. However, the discomfort of wearing, removing, and cleaning such a prosthesis, its poor retention in large defects, and the frequent need for readjustments often limit the value of this cost-effective method of restoring speech and mastication[40].

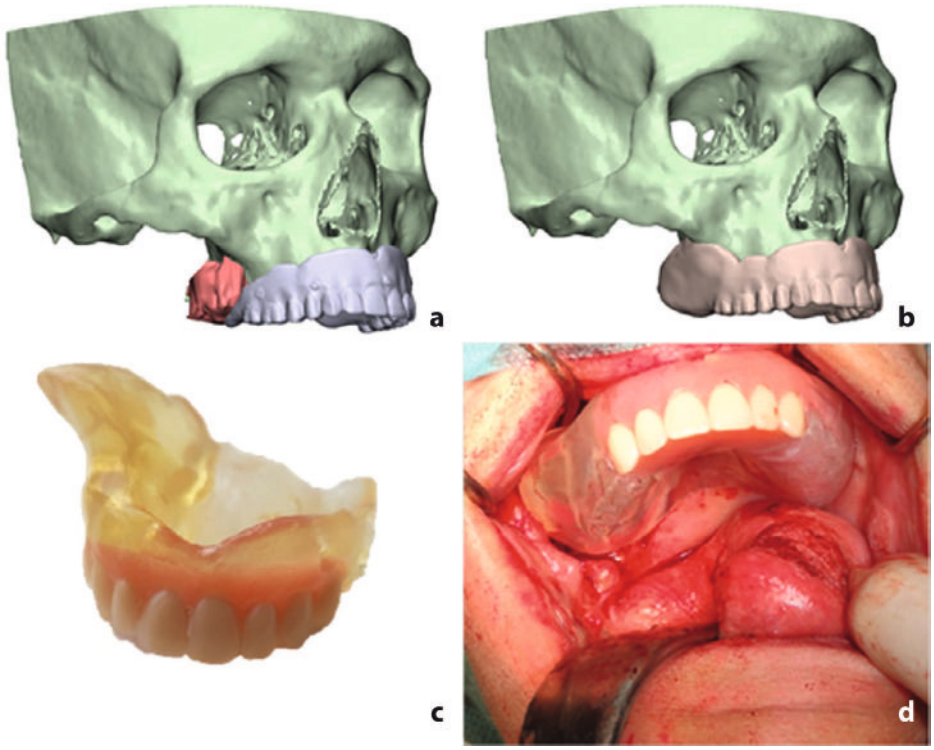
In case of even larger tumours, the defect size increases and the remaining dentition and supporting palatal bone will be more limited. Due to lack of retention and stability of a prosthesis, the interplay of forces further compromises functional rehabilitation and thereby overall success of treatment[41]. Placing endosseous implants in the native bone of the maxilla will allow to improve retention of the obturator prosthesis and thereby increase the success of prosthetic rehabilitation. Patients with implant-supported obturator prostheses have significantly better masticatory and oral function, and less discomfort during food intake than patients with a conventional obturator[42]. Studies which compared prosthetic obturation with reconstruction of a palatomaxillary defect demonstrated that there are some advantages to reconstruct the defects above obturation of these defects, in particular with regard to quality-of-life issues such as comfort, convenience, and feelings of self-consciousness[9]. However, especially in medically compromised and older patients, implant-supported obturator treatment is a viable alternative to surgical reconstruction after maxillectomy[42], although an obturator prosthesis is

not obsolete and is still standard care in low-income and middle-income countries. With the benefits of digital techniques and surgical reconstruction options the obturator prosthesis has increasingly gained a temporary function by bridging time to secondary surgical reconstruction of the defect.

New workflows are rising in processing surgical obturators. Several case reports describe production of 3D obturator prostheses[43,44]. 3D knowledge of resection planes provides a better knowledge of the dimensions of the post-resection defect, giving the option of preoperative production of a surgical obturator. With proper tumour visualisation and insight in the remaining anatomic structures, a surgical obturator prosthesis can be digitally designed and printed prior to ablative surgery. A nearby fit can be achieved and only minor per-operative adjustments are needed (figure 3.3).

If the defect overextends in size and vertical dimension, obturation of the defect cannot be adequately addressed with prosthetic management alone[45]. Surgical reconstruction combined with dental rehabilitation is then preferred. Zygomatic implants can, for example, provide a predictable in-defect support for prosthetic rehabilitation of the maxilla if placed at the time of primary surgery[46]. The zygomatic implant perforated flap procedure combines autogenous soft tissue reconstruction with zygomatic implant-supported fixed dental rehabilitation[17,47]. Furthermore, using the Rohner technique in combination with VSP it is possible to reconstruct high level maxillectomy cases with a reliable single-stage approach (figure 3.4) in a secondary stage procedure[26,48-50].

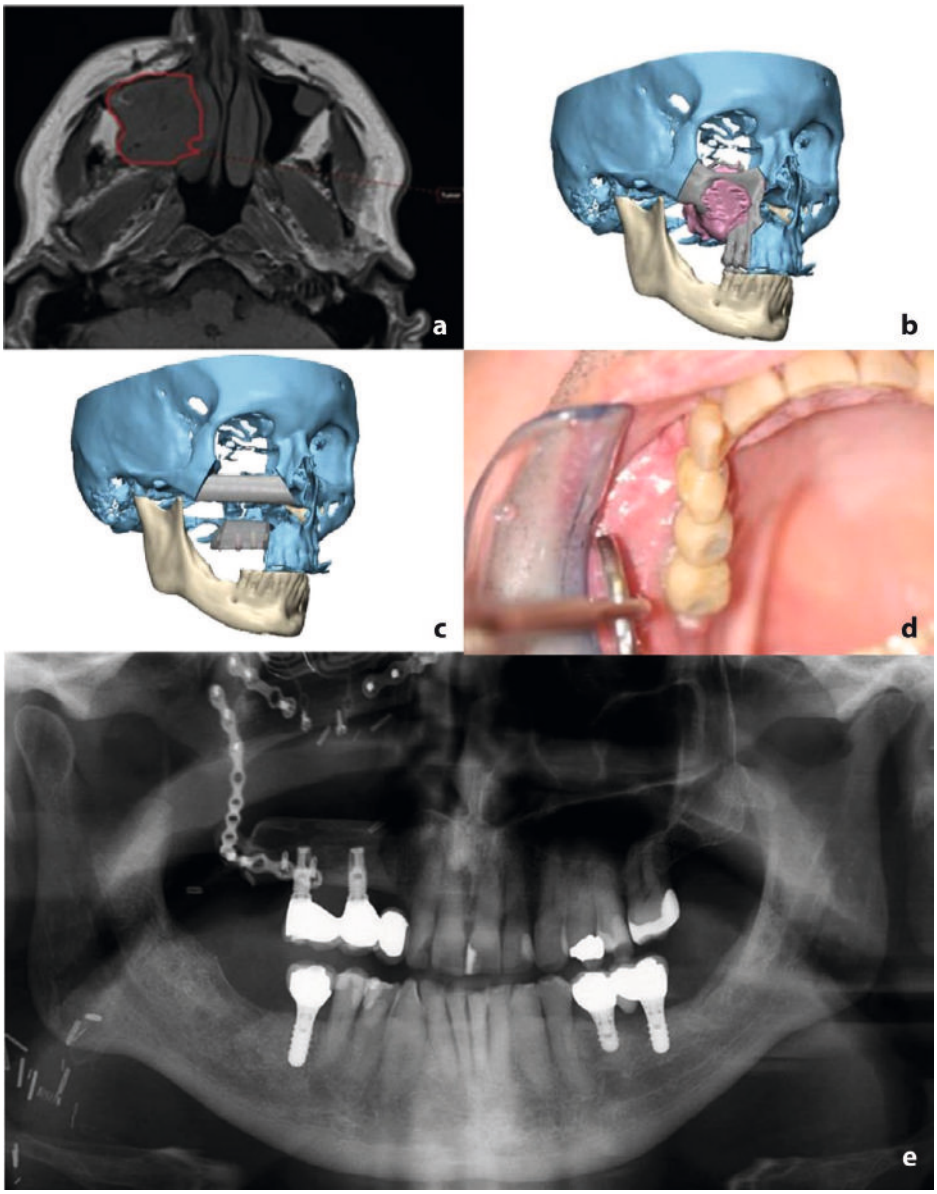
Figure 3.3



Patient diagnosed with mucoepidermoid carcinoma of the maxilla with prosthetic rehabilitation using a 3D printed obturator prosthesis based on a 3D VSP workflow.

a. Tumour visualization based on CT and MRI data fusion related to position of digitalised conventional prosthesis **b**. Virtual design of surgical obturator **c**. Image showing pre-operative printed surgical obturator **d**. Digital designed and printed obturator prosthesis with nearby fit during ablative surgery.

Figure 3.4



Jaw reconstruction of patient diagnosed with ameloblastoma treated with maxillectomy and reconstruction with fibula free flap.

a. The tumour was delineated on the MRI using radiotherapeutic planning software **b.** 3D VSP for tumour ablation surgery **c.** Virtual surgical planning of the maxilla and orbital floor reconstruction with fibula bone and implant planning. **d.** Suprastructure fixed on 2 endosseous implants placed in the fibula bone segment. **e.** Orthopantomogram four years after reconstructive surgery showing good integration of fibula bone segment and implants.

CONCLUSION

Oral rehabilitation is an encompassing component of the treatment of head and neck cancer patients and is a major contributor to enhance the quality of life of cancer survivors. Involvement in a multidisciplinary team to prepare and execute the rehabilitation treatment is of utmost importance. Maxillofacial prosthodontists should be involved from the beginning, their role in this process is essential and guiding. The rise of 3D techniques in diagnostics, planning and oral rehabilitation is enormous, and is expected to evolve to the standard of care.

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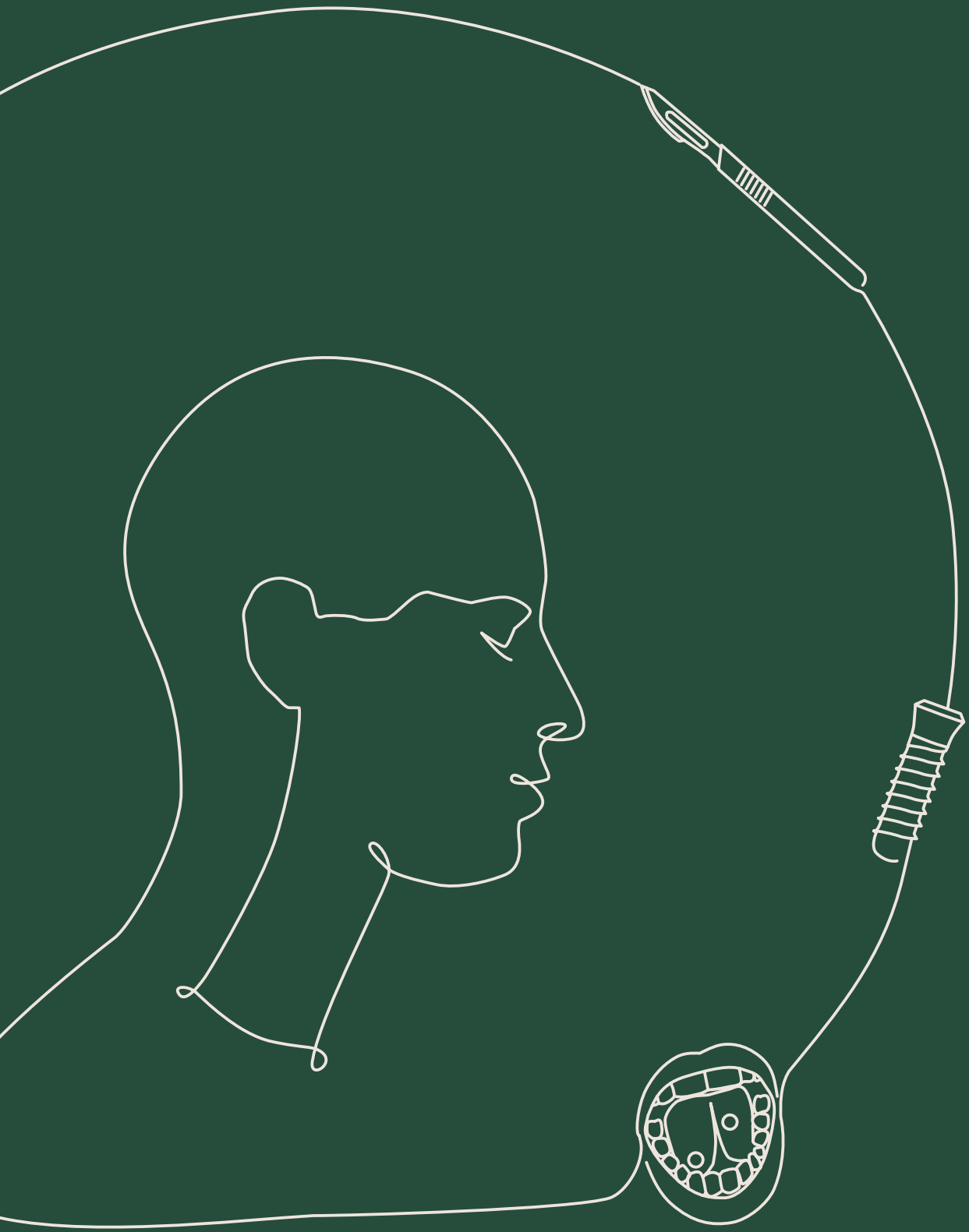


Chapter 4

Mandibular dental implant placement immediately after teeth removal in head and neck cancer patients

J.M. Alberga, A. Korfage, I. Bonnema, M.J.H. Witjes, A. Vissink, G.M. Raghoebar

This chapter is an edited version of the manuscript:
Mandibular dental implant placement immediately after teeth removal in head and neck cancer patients.

Supportive Care in Cancer 2020;28(12):5911-5918

ABSTRACT

Background

Little is known about immediate implant placement in head and neck cancer patients. We studied implant survival and functional outcomes of overdentures fabricated on implants placed immediately after removal of the lower dentition during ablative surgery or preceding primary radiotherapy.

Methods

Inclusion criteria were primary head and neck cancer, dentate lower jaw and indication for removal of remaining teeth. Two implants to support a mandibular overdenture were placed immediately after extraction of the dentition during ablative surgery, or prior to starting primary radiotherapy. Standardized questionnaires and clinical assessments were conducted (median follow-up 18.5 months, IQR 13.3).

Results

58 implants were placed in 29 patients. Four implants were lost (implant survival rate 93.1%). In 9 patients, no functional overdenture could be made. All patients were satisfied with their dentures.

Conclusion

Combining dental implant placement with removal of remaining teeth preceding head neck oncology treatment results in a favourable treatment outcome.

INTRODUCTION

In patients with malignancies in the oral cavity, oral foci (caries profunda, periodontal disease, presence of periapical pathology) are frequently encountered during pre-radiation dental screening[1-3]. Detection and elimination of these oral foci before starting treatment is needed for patients in need of radiation therapy to prevent post-radiation oral sequelae. For some patients, elimination of oral foci implies removal of all remaining teeth during tumour resection. In patients who will undergo primary radiotherapy the teeth are usually removed 2-3 weeks before starting radiotherapy[4]. Patients are often left with a strongly reduced oral function due to the changed anatomical situation after surgery. When ablative surgery is followed by radiotherapy, oral function is additionally compromised due to reduced salivary secretion, reduced chewing, swallowing and radiotherapy-induced trismus.

Fabricating a functional conventional denture in the lower jaw is challenging and sometimes even impossible[5,6]. Dental implant placement in patients with oral cancer results in improvement of oral function after oncological treatment[7-9]. Lower implant survival rates have been associated with radiotherapy, however, with appropriate perioperative measurements and strict monitoring, irradiated patients can also benefit from dental implant placement[10-15].

Several options exist regarding timing of implant placement in oncology patients. Implants can be inserted after oncologic treatment is completed. When necessary, extraction of the remaining dentition is carried out during ablative surgery and implants are placed in a second surgery when the surgical defect is fully healed and patients have completed post-operative radiotherapy. A possible benefit of this method is that proper implant planning and positioning can be achieved to facilitate the implant-supported overdenture. Also, when postponing the decision to start implant treatment until after oncologic surgery or radiotherapy, the clinician has the opportunity to only select those patients with severe functional problems who are presumed to benefit from an implant-supported overdenture. In this manner no implants are placed in patient who will not use them or who will be deceased before starting the prosthetic rehabilitation process. This could be of value from a cost-effectiveness point of view. A major disadvantage is the need for additional surgical procedures. Oral cancer patients have shown to decline additional implant surgery after finishing the oncologic treatment, even when significant benefits were to be gained from the treatment. This issue is probably related to treatment exhaustion[16]. Another disadvantage when treating patients after oncologic therapy is that patients who have received radiotherapy may need antibiotic prophylaxis

and/or a course of pre-treatment hyperbaric oxygen therapy in order to prevent osteoradionecrosis.

Alternatively, implants can be placed during ablative surgery. Combining implant placement and tumour surgery has certain benefits: implants are not placed in irradiated bone, patients do not need additional surgery with antibiotics or long-term hyperbaric oxygen therapy and oral rehabilitation starts earlier, resulting in an increased quality of life[17]. Possible disadvantages of implant insertion during ablative surgery are: improper implant positioning especially in patients with large defects, difficulties in acquiring sufficient keratinized mucosa around the implants, not using placed implants due to tumour recurrence, and patients refusing abutment connection surgery. In a longitudinal, prospective clinical trial on implant placement during ablative surgery refusal of abutment connection surgery occurred in 3 out of 50 included patients[17].

Current research on implant insertion during ablative surgery has mainly focused on patients who were edentulous at the time of diagnosis or had their teeth extracted before tumour surgery in a separate procedure[8,18-21]. These patients show high overall implant survival rates (>90%) and are generally satisfied with the function of their implant-supported overdenture[8,18-22]. For patients with a remaining dentition which needs to be removed, there are three options regarding dental rehabilitation: 1) removal of the dentition and fabrication of a conventional denture, 2) removal of the dentition during ablative surgery followed by delayed dental implant placement in healed sites or 3) immediate implant placement after tooth extraction in fresh extraction sockets (figure 4.1 - 4.4). In healthy patients, a systematic review showed that implants placed immediately after tooth extraction are accompanied by a survival rate comparable to implants placement in healed sites[23,24]. Even though there are studies claiming that immediate implant placement leads to a decrease in survival rates, the use of immediate implant therapy in specific populations, as in this study, requires consideration because of the potential benefits like a decrease in prosthetic rehabilitation time and fewer surgical procedures, to be gained from the therapy[25]. In addition, dental loss has a negative impact on patients' quality of life which further emphasizes the importance of adequate dental rehabilitation[26-28]. Therefore, the aim of this study was to assess performance of implants placed immediately after teeth extraction in the mandible during ablative surgery or preceding primary radiotherapy. Also, the study aims to describe oral function and denture satisfaction after immediate implant placement in patients with head and neck cancer.

Figure 4.1 Panoramic radiograph of a patient with a squamous cell carcinoma located in the floor of the mouth

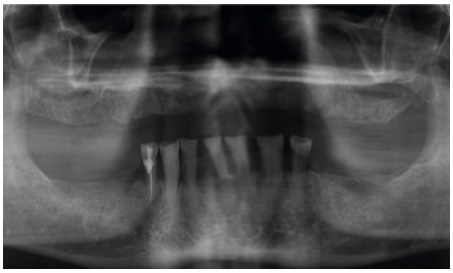


Figure 4.2 Clinical situation after preparation of the implant sites

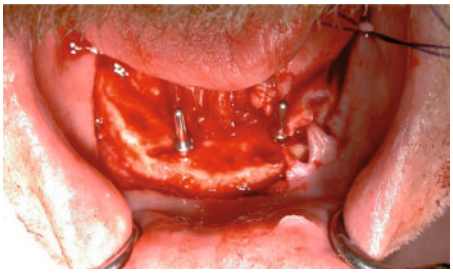


Figure 4.3 Panoramic radiograph immediately after teeth extraction and implant placement

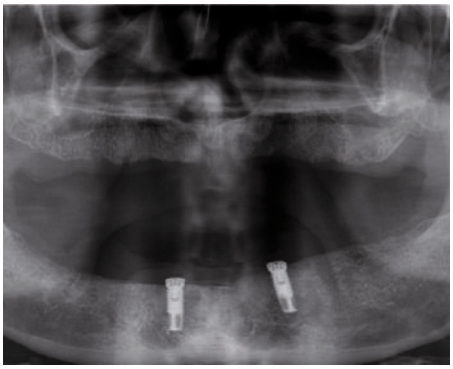
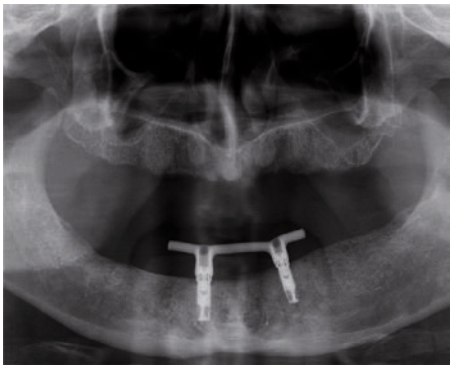


Figure 4.4 Panoramic radiograph 1.5 year after implant placement. There are no signs of peri-implant bone loss



MATERIAL AND METHODS

Patients

All consecutive patients with a malignancy in the head and neck region referred to the head and neck centre of the University Medical Center Groningen between 2014 and 2017 were screened to be included in this study. The inclusion criteria were: primary tumour in the head and neck region, dentate lower jaw and an indication for removal of the remaining dentition due to the presence of dental foci.

The oncologic treatment consisted of ablative surgery (when needed followed by postoperative radiotherapy) or primary radiotherapy (RT). Patients eligible for surgical removal of the tumour had their teeth removed during ablative surgery. These patients were offered either primary immediate mandibular implant placement (during ablative surgery), delayed mandibular implant placement (after completion of oncologic treatment) or no implant placement. For patients planned to receive primary radiotherapy, extraction of the remaining dentition followed by immediate mandibular implant placement at least 2 weeks before starting radiotherapy, delayed implant placement after radiotherapy or no implant placement was offered. All patients preferred primary immediate implant mandibular placement and informed consent was obtained. It was concluded by the Medical Ethical committee of the University Medical Center Groningen that this study was not subject to the Medical Research Involving Human Subjects Act (Number M19.234574).

After extraction of the remaining dentition, the extraction sockets were thoroughly cleaned, the height of the lower alveolar ridge was reduced and care was taken to round off the sharp bone edges. The implant regions were prepared and implants were placed in the native bone during ablative surgery with good primary stability of 45Ncm (figure 4.1 - 4.4). Two dental implants (Brånemark Mk III TiUnite RP, Nobel Biocare, Gothenburg, Sweden) were placed in the interforaminal area in a two-stage procedure by the same surgeon (GMR). All implants were placed with antibiotic prophylaxis (amoxicillin/clavulanic acid 1000/200mg i.v.). An osseointegration period of 3 months was considered for patients receiving only surgery and patients receiving only radiotherapy. In patients subjected to surgery followed by postoperative radiotherapy (starting 6 weeks after surgery), abutment connection surgery was postponed until after finishing the radiotherapy treatment and the short-term side-effects of radiotherapy had subsided. Abutment connection surgery was carried out under local anaesthesia. Two weeks after abutment connection surgery, prosthodontic rehabilitation was started. An implant

supported overdenture was made by a maxillofacial prosthodontist. The mandibular overdentures were supported by a bar-clip construction. For all patients receiving radiotherapy the cumulative dose at the implant locations was attained from the radiation plan provided by the radiotherapist.

Clinical assessments

All patients were on a standardized recall schedule. After placement of the overdenture, patients were examined half-yearly by a prosthodontist. Clinical parameters, implant loss and postoperative complications (inflammation, wound dehiscence, sequestration) were prospectively collected from the time of implant placement until final assessment in 2018.

During intraoral examination the following clinical parameters were assessed:

- Plaque-index assessed at four sites per implant (mesial, buccal, distal, lingual) using the modified plaque index[29].
- Bleeding-index: assessed at four sites per implant (mesial, buccal, distal and lingual) using the modified sulcus bleeding index[29].
- Gingiva index: Measured on a 4-point scale from 0-3: 0=no visible inflammation, 1=mild inflammation (moderate redness, mild swelling), 2=moderate inflammation (moderate redness), 3=severe inflammation (severe redness, swelling ulceration)[30].
- Probing pocket depth: measured to the nearest 1 mm using a manual periodontal probe (Williams Color-Coded Probe; Hu-Friedy, Chicago, IL USA) at the mesial, buccal, distal and lingual aspects of the implants. Subsequently, the largest pocket depth for each implant was included for analysis.

Radiographic analysis

At least 2 panoramic radiographs of each patient were made, one directly after implant insertion and one during final assessment. The change in marginal bone loss (in millimetres) in relation to the implant shoulder was calculated (figure 4.1-4.4).

Oral health impact, functional assessment and patient satisfaction

Oral function and patient satisfaction were assessed when the denture had been in situ for a period of at least 6 months. Overall patient satisfaction was expressed on a 10-point rating scale ranging from very dissatisfied (1) to very satisfied (10). Denture satisfaction was specifically measured by a validated questionnaire on denture satisfaction consisting of 8 items focusing on upper and lower dentures, and on specific features such as aesthetics, retention, and functional comfort[31].

Answers are given on a 5-point rating scale ranging from very satisfied (0) to very dissatisfied (4). Regarding the oral function, patients were asked to fill in a 9-item questionnaire on their ability to chew different kinds of food[32]. The Oral Health Impact Profile in short-form (OHIP-14) was used to assess the physical, psychological and social impact of oral disease[33]. Patients were asked to answer questions about the frequency of pain, functional limitations, psychological discomfort and social disability. Responses are made on a 5-point scale coded from never (0) to very often (4).

Data analysis

Data analysis was performed using the Statistical Package for Social Sciences (version 23, SPSS Inc., Chicago, IL, USA). Depending on the distribution of the data, results are either expressed as mean ± standard deviation (s.d.) or median (interquartile range; IQR). When comparing data of ratio level between radiated and irradiated patients the independent-samples *t*-test was used. Between-group comparisons for ordinal data were calculated with the Mann–Whitney U-test. P-values less than 0.05 were considered statistically significant.

RESULTS

Patients and implants

Twenty-nine patients, 15 men and 14 women, participated in this study (mean age 63.4±11.1 years; range 31-81 years). Patient demographics and treatment intervals of irradiated and non-irradiated patients are presented in table 4.1 and 4.2. 79.3% of the patients smoked at the time of the intake. The reasons for removal of the dentition were severe periodontal disease, non-restorable caries profunda and periapical infections.

Eight patients (27.6%) were subjected to primary radiotherapy with a dose of 70Gy at the tumour site. The average radiation dose at the implant site for these patients was 32.9±4.8Gy (range 27 – 40Gy). Thirteen patients (65.5%) were treated with postoperative radiotherapy with a mean radiation dose at the tumour site of 62.4±7.4Gy (range 46 - 70Gy) and 41.1±21.5Gy (range 2.1 - 64.6Gy) at the implant region. Eight patients were treated by surgery only. One patient treated with postoperative radiotherapy developed osteoradionecrosis near the implant region which healed after a sequestrectomy under local anaesthesia.

During the first two weeks post-operatively there were no problems with wound healing related to the implant procedure. Four implants in three patients were lost during follow-up which results in an overall implant survival rate of 93.1%. Implant loss was not associated with smoking. The implants that were lost had been in situ for a mean period of 17.3±15.4 months (range 7 – 35 months). All implant losses occurred in irradiated patients (primary RT n=2; postoperative RT n=1) who received a radiation dose above 40Gy at the implant site. This leads to implant survival rates of 90.5% and 100%, respectively, in irradiated and non-irradiated patients. The primary tumour in the patients with implant loss was located in the oropharynx (n=2; T2-T3 tumours) or floor of mouth (n=1; T4 tumour). One patient received a new implant 3 months after the old implant was removed. The new implant was placed under local anaesthesia with antibiotic prophylaxis. The second patient lost both implants and continued to wear a conventional denture. The third patient lost one implant and continued to wear an implant-supported overdenture.

In 9 patients no functional implant-retained overdenture could be made because of tumour recurrence in the implant region or metastatic tumour growth (n=5), implant loss (n=2) or severe pain in the implant area (n=1). One patient did not show up for further follow-up (figure 4.5). The remaining 20 patients received implant-retained mandibular overdentures of which 13 had undergone radiotherapy. After overdenture placement, seven patients had to be excluded for further assessment, due to refusing further follow-up at the prosthodontist and oncologic surgeon after receiving the overdenture (n=3), tumour recurrence or death (n=2), dehiscence occurrence around the reconstruction plate in such manner that the patient was not allowed to wear the fabricated overdenture (n=1) and implant loss (n=1). Ultimately, 13 patients received oral function questionnaires. Of these 13 patients, 8 patients had received radiotherapy.

Clinical and radiographic analysis

The plaque and bleeding scores around the implants were considered low for all patients in the study group. Mean probing pocket depth was 2.3±0.4mm with a mean marginal bone loss around the implants of 1±0.7mm. Peri-implant bone loss was greater (but not statistically significant) in irradiated patients than in patients who were treated by surgery only (respectively, 1.5mm and 0.9mm). There were no clinically and statistically significant differences between irradiated and non-irradiated patient with the exception of the bleeding index (table 4.3).

Oral health impact, functional assessment and patient satisfaction

Results of the OHIP-14, total chewing ability, and denture satisfaction are presented in table 4.1. A higher score for denture satisfaction and chew function indicates a less satisfied patient and worse chew function. A higher OHIP-14 score indicates a higher physical, psychological and social impact of the oral disease. The results show reasonably satisfied patients and good oral function for all three types of food. No statistically significant differences could be found in chewing ability and satisfaction rates between irradiated and non-irradiated patients (table 4.5).

Table 4.1 Patient characteristics regarding age at implant placement, gender, diagnosis and type of reconstruction of the soft tissues and bone defect

Patient	Age at implant placement	Gender	Tumour	Stage	Type of reconstruction
1	65	male	Maxillary sinus	T3N0	Primary closure
2	81	female	Tongue	T1N1	Split thickness skin graft
3	62	male	Oropharynx	T3N2c	N/A (primary RT)
4	61	male	Mandibular gingiva	T4N2b	Free vascularized flap
5	63	male	Oropharyngeal	T4aN2b	N/A (primary RT)
6	73	female	Buccal mucosa	T2N0	Free vascularized flap
7	31	male	Lower lip	T2N0	Free vascularized flap (after multiple re-excisions)
8	51	male	Supraglottic Larynx	T4N3	N/A (primary RT)
9	66	female	Floor of Mouth	T4N1	Split thickness skin graft
10	76	female	Mandibular gingiva	T1N0	Primary closure
11	57	female	Mandibular gingiva	T4N0	Regional flap
12	56	male	Oropharynx	T4apN3	N/A (primary RT)
13	62	female	Floor of Mouth	T4N2c	Split thickness skin graft
14	71	female	Floor of Mouth	T1N0	Local flap
15	47	male	Mandibular gingiva	T4aN0	Free vascularized flap
16	58	male	Oropharynx	T2cN2b	N/A (primary RT)
17	74	female	Mandibular gingiva	T4N0	Free vascularized flap
18	62	female	Tongue	T2N0	Primary closure
19	56	male	Tongue	T3N2c	Split thickness skin graft
20	66	male	Floor of Mouth	T1N0	Split thickness skin graft
21	80	male	Supraglottic Larynx	T3cN2b	N/A (primary RT)
22	69	female	Mandibular gingiva	T1N0	Regional flap
23	49	female	Oropharynx	T4N2c	N/A (primary RT)
24	59	male	Floor of Mouth	T1N0	Local flap
25	60	female	Carcinoma ex pleiomorphic adenoma of the submandibular gland	T3N0	N/A (removal of the gland)
26	71	male	Floor of Mouth	T1N0	Split thickness skin graft
27	60	female	Maxilla	T4N0	Free vascularized flap
28	83	male	Tongue	T1N0	Primary closure
29	68	female	Oropharynx	T4bN2c	N/A (primary RT)

N/A: not applicable; RT: radiotherapy.

Table 4.2 Treatment intervals of irradiated and non-irradiated patients (months)

	Irradiated Mean (s.d.)	Non-irradiated Mean (s.d.)
Time between implant placement and second stage surgery	5.5 (2.7)	3.9 (1.3)
Time between implant placement and prosthesis placement	8.3 (3.1)	7.4 (3.9)
Time between implant placement and data collection	16.3 (9.4)	21.7 (8.9)

Figure 4.5 Algorithm showing the selection of patients

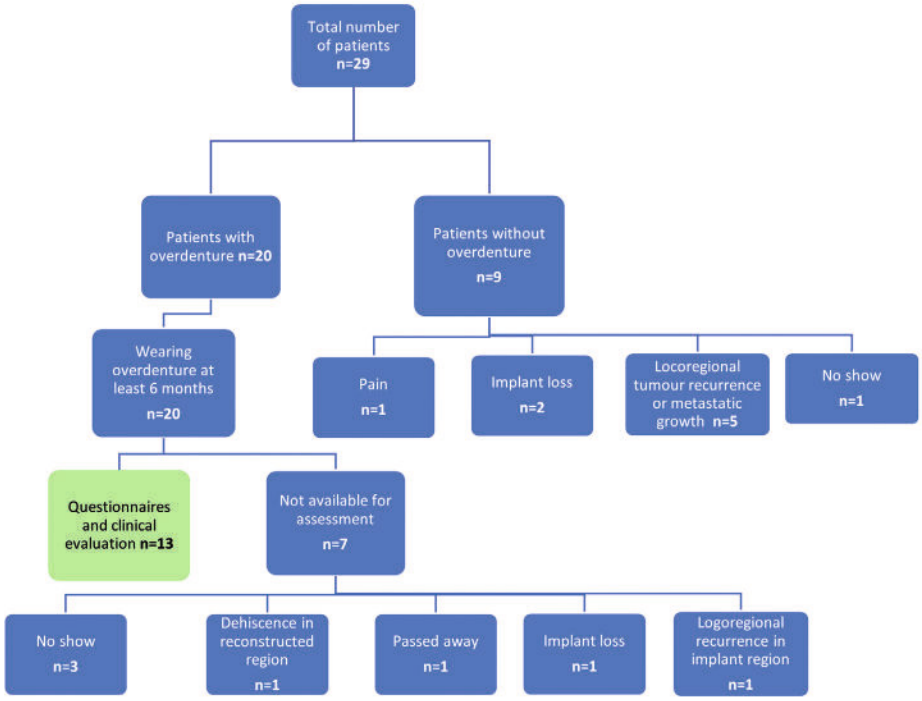


Table 4.3 Results of periodontal indices around the implants between irradiated patients and non-irradiated patients

	Surgery and Postoperative RT			Only surgery			
	Median	Mean	s.d.	Median	Mean	s.d.	p-value
Bleeding index (0-3)	0	0.4	0.7	1	1.2	0.8	0.04
Plaque index (0-3)	1	0.8	0.7	1	0.8	0.4	0.80
Pocket depth (mm)	NA	2.2	0.4	NA	2.5	0.3	0.18
Marginal bone loss (mm)	NA	2	0.6	NA	1	0.9	0.17

Table 4.4 Patient satisfaction, functional assessment and oral health impact

	Mean (s.d.)
Overall satisfaction [0-10]*	8.6 (0.9)
Total denture satisfaction score [8-40]	12.6 (3.6)
Chew function score [0-18][a]	
- Soft food	0.0 (0.1)
- Tough food	0.2 (0.3)
- Hard food	0.9 (0.9)
OHIP-14 Total	5.8 (5.7)

*Range 0-10: 0=very dissatisfied, 10=very satisfied
[a]Range 0-2: Scale 0=good, 1=moderate, 2=bad

Table 4.5 Differences in oral function between patients with and without radiotherapy

	Irradiated Mean (s.d.)	Non-irradiated Mean (s.d.)	p-value
Overall satisfaction [0-10]	9 (0.9)	8 (0.7)	0.08
Denture satisfaction [8-40]	10.8 (3.4)	14.8 (2.8)	0.10
Chew function [0-18]	3.2 (3.0)	3.2 (3.9)	0.93
OHIP-14 Total	3.8 (3.8)	8.2 (6.9)	0.27

DISCUSSION

This study aimed to assess the treatment outcomes of mandibular implants placed immediately after removal of the dentition in head and neck cancer patients. The results showed a high implant survival rate for non-irradiated patients and a reduced survival rate in irradiated patients. The implant survival rates are comparable to the edentulous patients in previous studies [17,19,20].

A history of radiation therapy is not considered a contraindication for implant placement as long as strict monitoring is provided to prevent complications[12]. Previous studies on implant placement in irradiated patients do not regard immediate implant placement, making a comparison between our study and previously published studies not entirely reliable[10-15.] But as all implant losses in our study occurred in irradiated patients, it can be stated that radiotherapy also has a negative effect on survival of immediately placed implants. Due to the small sample size in the current study, no reliable conclusion could be drawn on implant survival rates or the proportion of unused implants in relation to tumour stage or tumour location. The optimal time between implant placement and start of radiotherapy is still in need of further research. One could argue that the osseointegration of implants placed pre-radiation therapy has already largely taken place before the bone is compromised by radiotherapy, but it is known that

late effects of radiotherapy continue years after the initial treatment is finished[34]. The implants in our study were on average inserted 5.3 weeks before starting postoperative radiotherapy and 2.9 weeks before starting primary radiotherapy. Thus, the implants were not in the process of osseointegration when radiotherapy was started and this could have played a role in the implant loss in the irradiated patients. It is, however, from an oncologic treatment perspective not preferable to further delay the start of radiation therapy. All irradiated patients in the current study received intensity modulated radiation therapy (IMRT). A tendency towards more bone loss in irradiated patients than in those without radiotherapy was seen. This finding is comparable to the findings of Ernst et al.[35]. In a recent study of Papi et al. the type of radiotherapy (3D conform radiotherapy versus IMRT) does not seem to effect the amount of peri-implant bone loss[36].

One of the advantages of primary implant placement is the early prosthodontic rehabilitation in head and neck oncology patients as confirmed by the studies of Wetzels et al. and Mizbah et al.[8,21]. In an earlier study of Korfage et al., non-irradiated patients received their overdenture after 6 months and irradiated patients received their overdenture after 11 months[37]. This difference in loading time is due to the minimal time-span of 6 months applied for irradiated patients between the end of radiotherapy and abutment connection surgery. The rationale behind this additional healing period is that implants are given some extra time for osseointegration and that the radiation effects on the soft-tissue will have subsided. Schoen et al. have already questioned whether the additional 6 months is really necessary because most of the osseointegration takes place during the first 6 weeks after placement[16]. In our study, abutment connection surgery in irradiated patients took place as soon as the treatments at the department of radiotherapy were completed and the short-term side-effects of radiotherapy had subsided. This probably resulted in a shortening of the time until overdenture placement (8.3 months).

A possible disadvantage of implant placement during ablative surgery is improper positioning of implants, due to an altered anatomical situation or intermaxillary relationship, e.g., after mandibular continuity resections. In our study, all primary implants could be placed in a proper position, even in patients with a tumour located more ventral in the floor of the mouth. In those cases it is often difficult to acquire enough keratinized mucosa around the implants and sometimes a secondary mucosa graft might be necessary. This was not needed in the current study.

Satisfaction rates and oral function do not seem to be influenced by radiotherapy in the current study. Overall it could be stated that the results are comparable to previously edentulous patients[20]. The results in our study are to be considered as short-term results but it is expected that the oral function will be rather stable, as this is also the case in an earlier study from our group[7]. From the results of the OHIP-14 questionnaire (table 4.5), non-irradiated patients seem to experience more physical, psychological and social impact of their oral functioning than the irradiated patients. This is striking because irradiated patients are expected to experience a larger oral health-related impact due to the effects of radiotherapy. When examining the individual results of the patients it was revealed that the higher OHIP-14 score in non-irradiated patients in our study is caused by one patient being particularly dissatisfied, therefore causing a distortion in the results because of the low number of included patients.

Another known disadvantage of implant placement during ablative surgery is the risk of unused implants due to tumour recurrence. In our study this was the case for 5 patients. Four of these patients presented with large (T4 stage) tumours with regional metastases in combination with other co-morbidities like diabetes mellitus, COPD and hypertension. The other patient had multiple tumour recurrences which resulted in the implants eventually not being used. Furthermore, 4 patients (13.7%) refused further follow-up, 3 of these 4 patients after having received the implant-supported denture. These patients also declined further oncological follow-up despite efforts with regard to the need for regular follow-up. Numbers on head and neck cancer patients declining follow-up for their implant-supported overdenture are unknown, but a study by Toljanic et al. on dental follow-up of irradiated head and neck cancer patients stated that dental follow-up compliance is an issue in this population[38].

The question raises whether placing implants prior to radiotherapy or during ablative surgery is cost-effective. In The Netherlands, the costs of implant rehabilitation in head and neck cancer patients are covered by the insurance which makes primary immediate implant placement an actual treatment option. A study of Wetzels et al. on cost-effectiveness stated that individual costs of implant placement during ablative surgery have shown to be lower when compared to postponed placement, but that factors as oncological prognosis, and overall life expectancy must be taken into account when considering placing implants during ablative surgery[39]. The same conditions should apply for immediate implant placement.

Although this is the first study to report solely on immediate implant placement in head and neck cancer patients, there are certain limitations. A drawback is the low number of patients and the rather high fall-out rate. Regarding the method of measuring the marginal bone loss, it would be preferable to use standardized intraoral dental radiographs. However, clinical experience with oral cancer teaches that in anatomically altered patients there is often no possibility for taking standardized intraoral radiographs with individual devices and panoramic radiographs are the only option for routine follow-up. Moreover, for evaluation of bone around implants panoramic radiographs are widely used and accepted, despite that they distort images, superimpose bony structures of the spine and lack sharpness[40]. This should be taken into account when interpreting these results. Recommendations for further research in this field of work include: identifying possible predictive factors for implant survival and setting up a treatment algorithm for clinicians.

Despite the limitations of the study, immediate primary implant placement is a viable treatment option and should be offered to head and neck cancer patients because of the earlier mentioned benefits to be gained.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that they have no conflict of interest.

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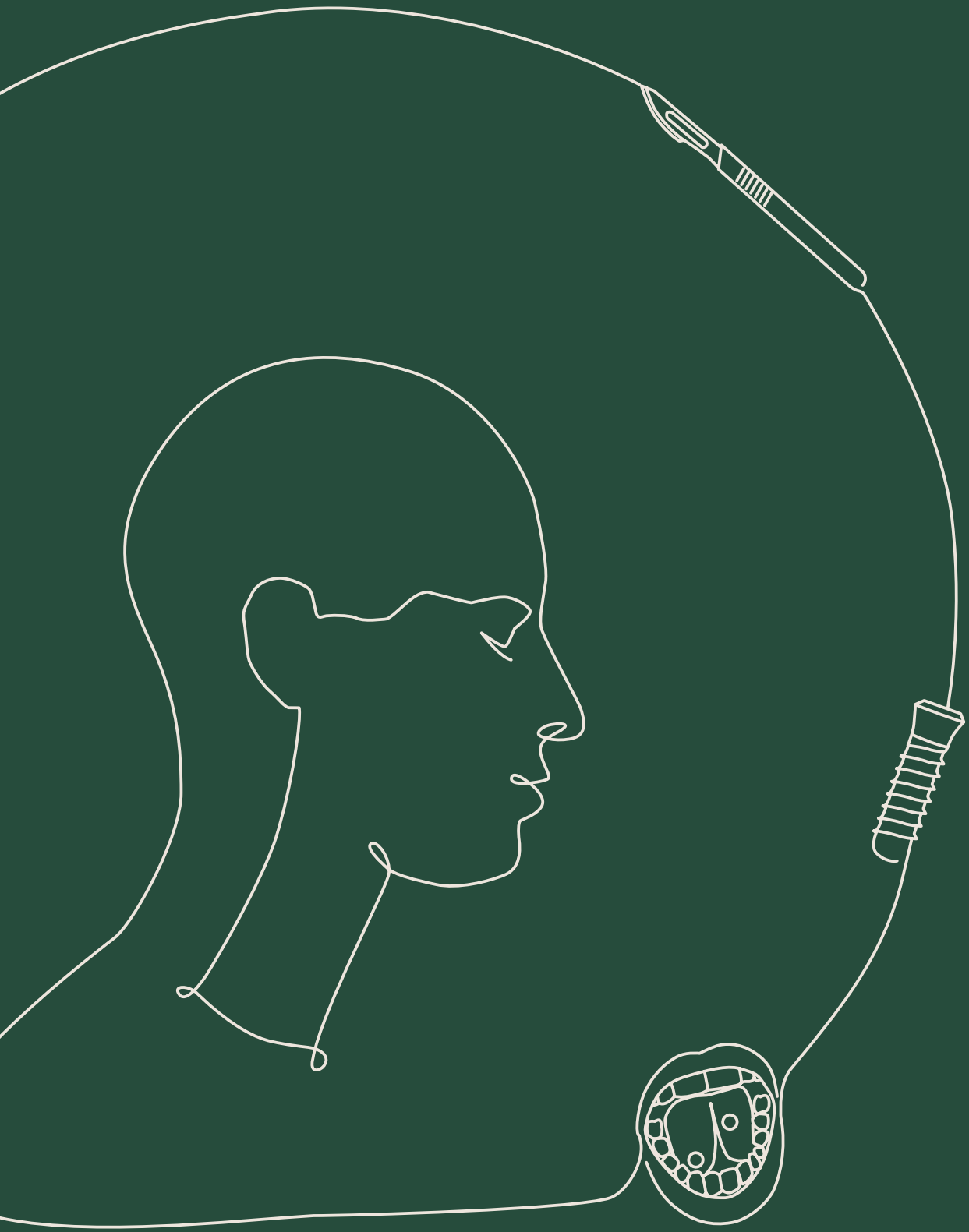

Chapter 5

Outcome of implants placed to retain craniofacial prostheses: A retrospective cohort study with a follow-up of up to 30 years

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This chapter is an edited version of the manuscript:
Outcome of implants placed to retain craniofacial prostheses – A retrospective cohort study with a follow-up of up to 30 years.

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ABSTRACT

Objectives

To retrospectively assess the treatment outcomes of endosseous implants placed to retain craniofacial prostheses.

Methods

Patients with craniofacial defects resulting from congenital disease, trauma or oncologic treatment had implant-retained prostheses placed in the mastoid, orbital or nasal region and were then assessed over a period of up to 30 years. Implant survival rates were calculated with the Kaplan-Meier method. Clinical assessments consisted of scoring skin reactions under the prosthesis and the peri-implant skin reactions. Possible risk factors for implant loss were identified. Patient satisfaction was evaluated using a 10-point VAS-scale.

Results

A total of 525 implants placed in 201 patients were included. The median follow-up was 71 months (IQR 28-174 months). Implants placed in the mastoid and nasal region showed the highest overall implant survival rates (10-year implant survival rates of 93.7% and 92.5%, respectively) while the orbital implants had the lowest overall survival rate (84.2%). Radiotherapy was a significant risk factor for implant loss (HR 3.14, $p<0.001$). No differences in implant loss were found between pre- and postoperative radiotherapy ($p=0.89$). Soft tissue problems were not frequently encountered and the patients were highly satisfied with their implant-retained prosthesis.

Conclusion

Implants used to retain craniofacial prostheses have high survival and patient satisfaction rates and can thus be considered as a predictable treatment option. Radiation is the most important risk factor for implant loss.

INTRODUCTION

Implant placement to retain a prothesis in patients with defects in the craniofacial region due to oncologic treatment, congenital disease, or trauma is a predictable treatment option, with high implant survival and patient satisfaction scores[1]. Craniofacial prostheses are a durable solution that mimic the contour of the missing facial region, blend into the surrounding regions, and can be worn and placed with relative ease and comfort[2,3]. When compared with autologous surgical reconstructions, which usually require several extensive procedures, implant-retained prostheses lead to a more acceptable combination of a relatively limited surgical procedure and satisfactory aesthetic results[4,5].

An optimal treatment outcome (from a prosthetic as well as a surgical point of view) crucially requires careful pre-operative implant placement planning[6,7]. Poor bone quality, as well as low bone volume, are important risk factors for craniofacial implant loss, with the highest reported implant loss occurring from the orbital regions[8–10]. Also, radiotherapy is negatively associated with implant survival as radiation has a high impact on bone quality[11,12]. However, the timing of craniofacial implant placement in oncology patients, e.g., before or after radiotherapy, is still an issue of debate[13–15]. Some studies recommend placing implants before starting radiation therapy (during ablative surgery) while others recommend implant treatment after radiotherapy[16,17] .

Although implant survival and patient satisfaction rates are high, most studies in the literature present short-term results on small patient groups. This is in line with the conclusion of the Chrcanovic et al. review on craniofacial implant survival and complications[11]. Our aim, therefore, was to assess the treatment outcome of endosseous implants placed to retain craniofacial prostheses in a large group of patients with a craniofacial defect.

MATERIAL AND METHODS

Patients and treatment protocols

All consecutive patients treated with implants in the mastoid, auricular or nasal region to retain a craniofacial prosthesis between May 1988 and December 2018 at the University Medical Center Groningen (UMCG) were included in this retrospective study. All the implants were placed by two experienced oral and maxillofacial surgeons in the native bone under general anaesthesia using a 2-stage

method; each patient received antibiotic prophylaxis at general anaesthesia induction (Augmentin 1200mg i.v.). The irradiated patients then continued with a broad-spectrum antibiotic for a further 2 weeks. The oncology patients' implants were placed during or after ablative surgery and, when applicable, before or after radiotherapy.

Auricular prostheses involved placing 2 or 3 implants in the mastoid bone, approximately 18mm from the external auditory canal. A minimum distance of 11mm was maintained between the implants. In the nasal region, two implants were placed in the maxillary bone of the nasal floor after trimming the sharp edges from the caudal site of the piriform aperture. Implants in the orbital region were placed in the supraorbital (2 or 3 implants) and infraorbital rim (1 or 2 implants). The Nobel Biocare (Zurich, Switzerland) and Entific Medical Systems Inc (Gothenburg, Sweden) implant systems were used. Second stage surgery in the non-irradiated patients involved retrieving the implants under local anaesthesia and thinning the subcutaneous tissue surrounding the implants after 3 months of osseointegration. Regarding the irradiated patients, the second stage surgery took place 3 months after the last radiotherapy session. Gauze dressings with antibiotic ointment (Terra-Cortril, Pfizer Inc., New York, NY) were draped around the abutments to guarantee good skin positioning and to prevent abutment overgrowth. The gauze dressings were changed weekly and removed completely after three weeks. Prosthetic rehabilitation was carried out after the second stage surgery by a team of experienced maxillofacial prosthodontists. The patients were seen at the regular yearly follow-ups.

A waiver of exemption regarding the Medical Research Involving Human Subjects Act (WMO) was granted by the Medical Ethics Committee of the University Medical Center Groningen (reference number M19.235062).

Data collection and treatment outcome assessment

The patients' demographics, implant treatment variables, and data on implant survival and complications were collected retrospectively from the patient records. With respect to the radiotherapy patients, the data on the timing of the implant placement (before or after radiotherapy) and radiation dose on the tumour area were also recorded. In the survival analysis, implant loss was defined as the loss of an implant for any reason during the follow-up period. Implant survival was defined as the time from implant placement until the date of implant loss (event) or the last known follow-up. Death was censored and did not count as an event. Implants which were never retrieved after being placed were excluded from the survival

analysis. The subgroup analysis was based on implant location, implant indication, the presence of radiotherapy, and the timing of the implant placement.

Clinical assessment

The patients who were still attending the follow-ups were clinically assessed by an oral and maxillofacial surgeon (JA) and maxillofacial prosthodontist (IE) who had not been involved in their treatment. A minimal follow-up period of one year after the prosthesis placement was required. The clinical assessment included scoring the skin reactions around the implants and underneath the prosthesis. The peri-implant tissues were scored according to the Tolman and Taylor criteria[18]: 0, no irritation; 1, slight redness; 2, red and moist tissue; 3, granulation, red and moist tissue; 4, active infection. Skin reactions under the prosthesis were scored as being present or not present. The patients were also asked to score their overall satisfaction with the prosthesis using a 10-point VAS-scale (1, absolutely not satisfied; 10, very satisfied). The clinical outcomes of the irradiated and non-irradiated patients were compared.

Statistical analysis

The categorical data from the calculated descriptive statistics were presented as number and percentages. In case of normality, the groups were compared using one-way ANOVA. The Mann-Whitney U-test was used to compare the groups with a categorical variable. Implant survival rates were determined with the Kaplan-Meier method and reported as a percentage of survival. The survival curves were compared with the log-rank test. In order to identify possible risk factors for implant loss, a multivariate analysis using a Cox-proportional-hazards model was performed. The following covariates were added to the analysis: age at implant placement, gender, implant location (mastoid, nasal, orbit), and radiotherapy (yes or no). A p-value <0.05 was regarded as statistically significant. Graphpad Prism 8 for Windows was used for the survival analyses and curve comparison. All the remaining statistical analyses were carried out with IBM SPSS statistics 23 (SPSS, Chicago, IL, USA).

RESULTS

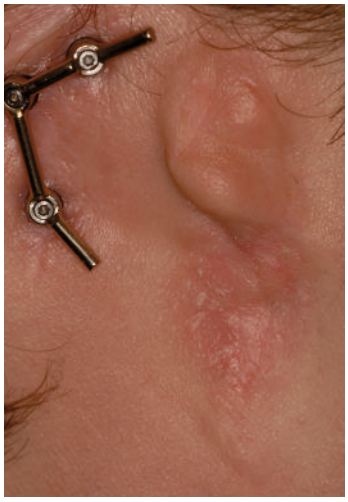
A total of 220 patients with 575 craniofacial implants were initially evaluated. Fifty implants in 19 oncology patients (11.2%) were never retrieved before the second stage surgery due to tumour recurrence (11 patients) or death (8 patients) and so were excluded. The remaining 525 implants placed in 201 patients were included in this retrospective study. The patient characteristics are presented in table 5.1.

Patient characteristics, and the clinical aspects from baseline to long-term follow-up are shown in figure 5.1 to 5.4. More males than females were involved. The traumatology patients and those with congenital deformities were significantly younger at the time of implant placement compared to the oncology patients ($p<0.001$).

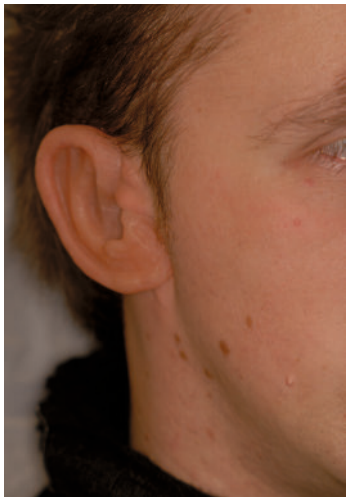
Table 5.1 Patient characteristics

		Indication for implant placement		
		Oncology	**Traumatology**	**Congenital**
Number of patients per group		150 (74.6)	18 (9.0)	33 (16.4)
Mean age at implant placement	Years (s.d.)	67.0 (14.5)	42.1 (14.8)	31.4 (17.9)
Gender	Male (%)	101 (67.3)	11 (61.1)	20 (60.6)
	Female (%)	49 (32.7)	7 (38.9)	13 (39.4)
Number of patients per implant location	Mastoid	50	14	33
	Nasal aperture	44	1	0
	Orbit	56	3	0
Number of implants per patient	Mastoid	2 or 3		
	Nasal aperture	2		
	Orbit	3 or 4		
Timing of implant placement	During ablative surgery, no radiotherapy (%)	52 (34.7)	Not applicable	Not applicable
	During ablative surgery, before radiotherapy (%)	40 (26.7)		
	During ablative surgery, after radiotherapy (%)	32 (21.3)		
	After ablative surgery, no radiotherapy (%)	19 (12.7)		
	After ablative surgery, before radiotherapy (%)	1 (0.7)		
	After ablative surgery, after radiotherapy (%)	6 (4.0)		
Radiotherapy dose on tumour area (Gray)	Median (min-max)	64 (30-70)		

Figure 5.1 Clinical aspect of a patient with a congenital ear deformity shortly after prosthesis placement (A and B) and 15 years later (C and D)



A



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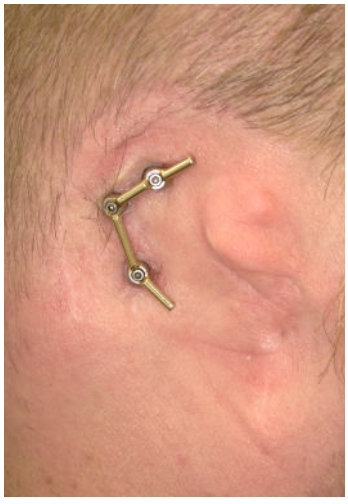
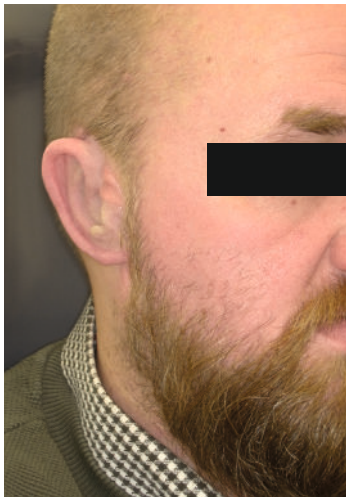
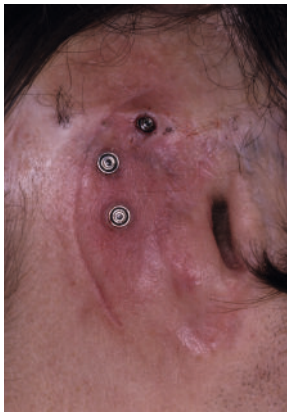


C

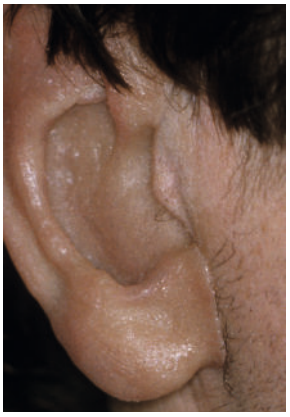


D

Figure 5.2 Clinical aspect of a trauma patient shortly after prosthesis placement (A,B,C) and 29 years after implant placement (D and E)



A



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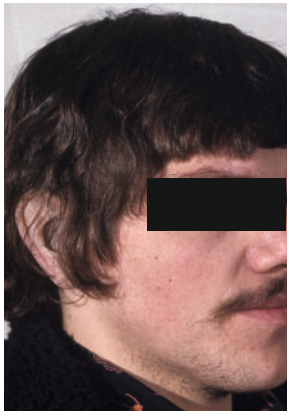

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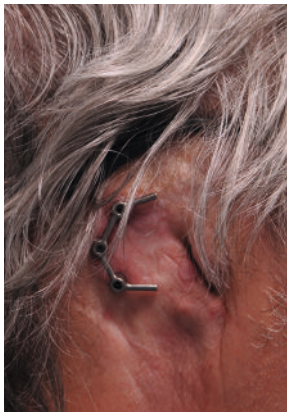
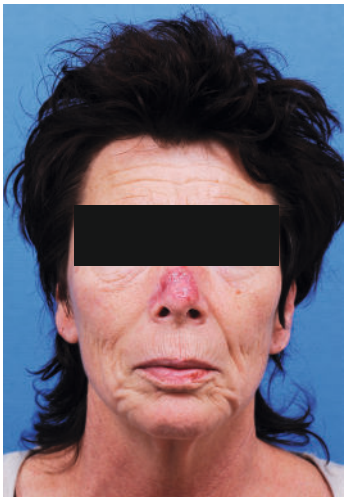


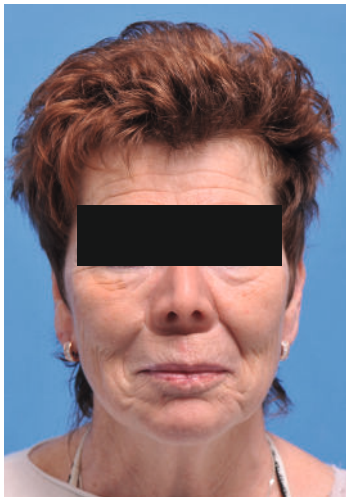
D

E

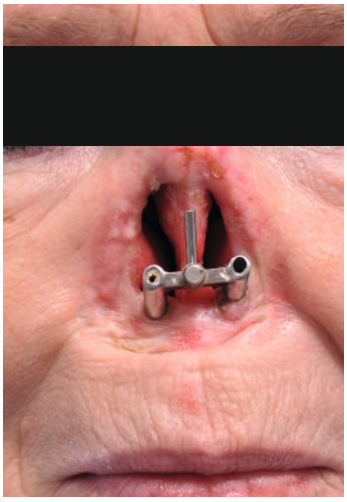
Figure 5.3 Clinical aspect of a patient with a squamous cell carcinoma of the nose (A) and 11 years after implant placement (B and C)



A

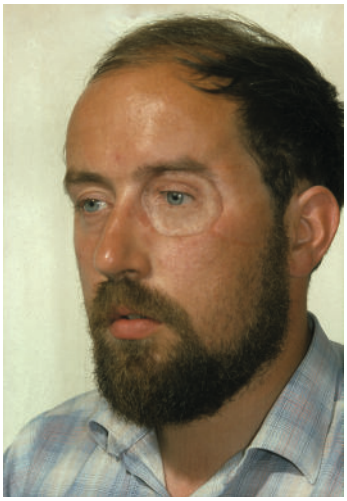


B



C

Figure 5.4 Clinical aspect of an oncologic patient with an orbital defect. (A) With the implant-retained prosthesis shortly after implant placement. (B) 15 years after implant placement. (C and D) 24 years after placement 2 implants were lost but the prosthesis could still be worn successfully



A

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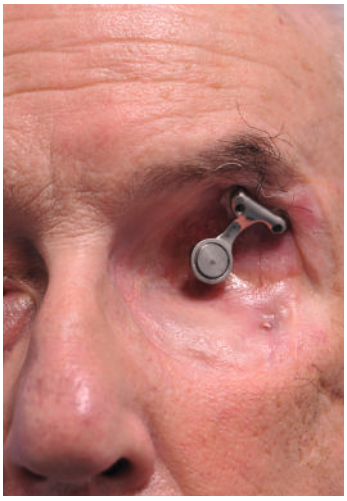


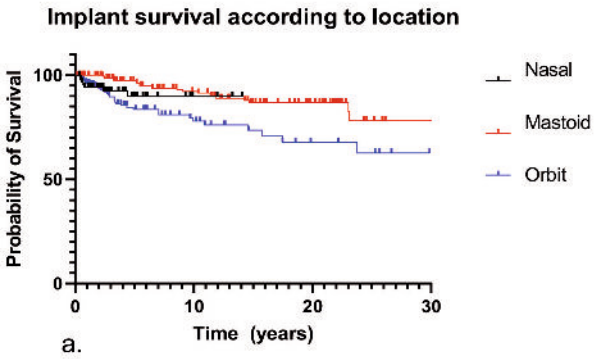
C

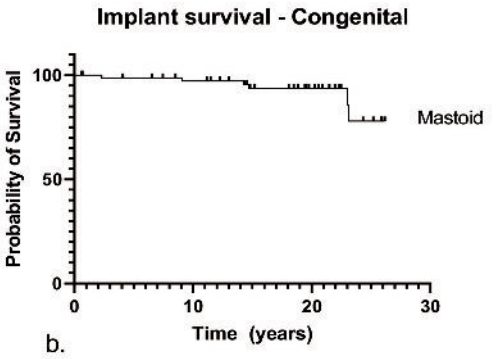
D

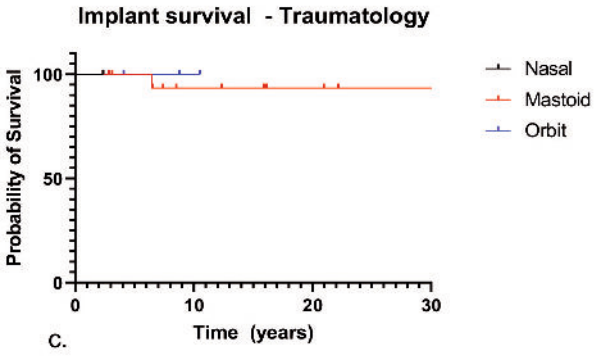
The mean time between implant placement and second stage surgery was 6 months (IQR 4 - 8) for the irradiated patients and 4 months (IQR 3 – 6) for the non-irradiated patients. The median time between implant placement and radiotherapy commencement was 6 weeks (IQR 4 - 8.75). Regarding the patients treated after radiotherapy (secondary implant placement), the median time between the end of radiotherapy and implant placement was 108.5 weeks (IQR 34 – 232.5).

The Kaplan-Meier survival curves per patient group (oncology, traumatology, and congenital disease) and location (mastoid, orbit, nasal aperture) are presented in figure 5.5a to d. The implant survival rates differed per patient group and implant location. The percentage of implants lost per location did not vary greatly: the mastoid region 21/231 implants (10-year implant survival rate 93.7%); the nasal region 7/90 implants (10-year implant survival rate 92.5%); and the orbital region 33/204 implants (10-year implant survival rate 84.2%) table 5.2 to 5.4 show the implant loss per subgroup. Implant survival in the various implant locations differed significantly ($p<0.001$). Radiotherapy had a negative effect on implant survival ($p<0.001$) (figure 5.6). A comparison of the survival curves in figure 5.7 did not result in a statistically significant implant survival difference between the implants placed before or after radiotherapy ($p=0.89$).

Figure 5.5 Kaplan-Meier survival analyses of implants according to location (a) and treatment indications (b-d)







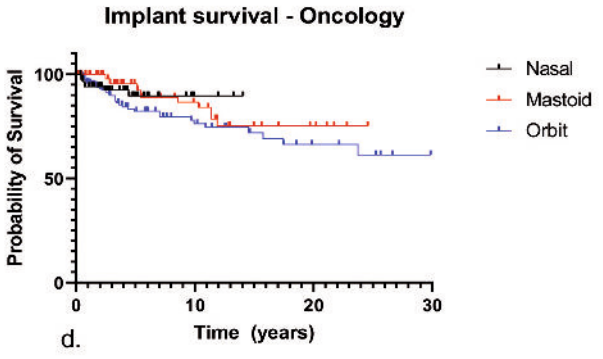


Table 5.2 Distribution of implants placed in and lost by oncology patients

	Implant region			
	Mastoid	**Nasal**	**Orbit**	**Total**
Number of placed implants (number of lost implants)	108 (13)	88 (7)	194 (33)	390 (53)
During ablative surgery, no RT	47 (3)	26 (3)	49 (4)	122 (10)
During ablative surgery, pre RT	26 (6)	16 (0)	78 (11)	120 (17)
During ablative surgery, post RT	5 (0)	40 (4)	28 (6)	73 (10)
After ablative surgery, no RT	23 (4)	4 (0)	23 (6)	50 (10)
After ablative surgery, pre RT	0 (0)	0 (0)	5 (1)	5 (1)
After ablative surgery, post RT	7 (0)	2 (0)	11 (5)	20 (5)
Median follow-up in months (IQR)	51.5 (23-124)			

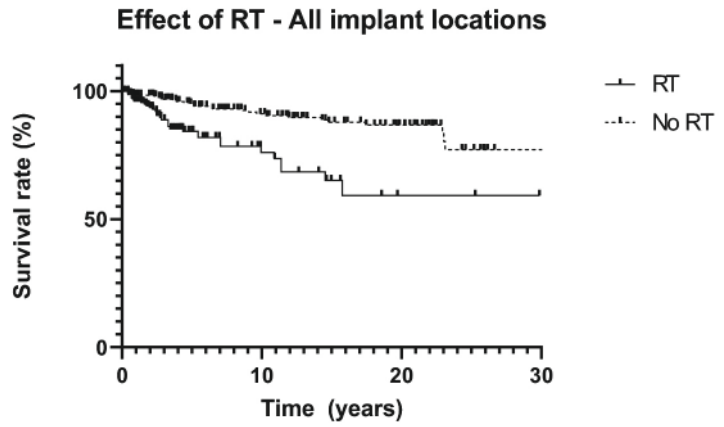
Table 5.3 Implants placed in and lost by traumatology patients

	Implant region			
	Mastoid	**Nasal**	**Orbit**	**Total**
Number of placed implants (Number of lost implants)	41 (2)	2 (0)	10 (0)	53 (2)
Median follow-up in months (IQR)	102 (43-193)			

Table 5.4 Implants placed in and lost by patients with congenital defects

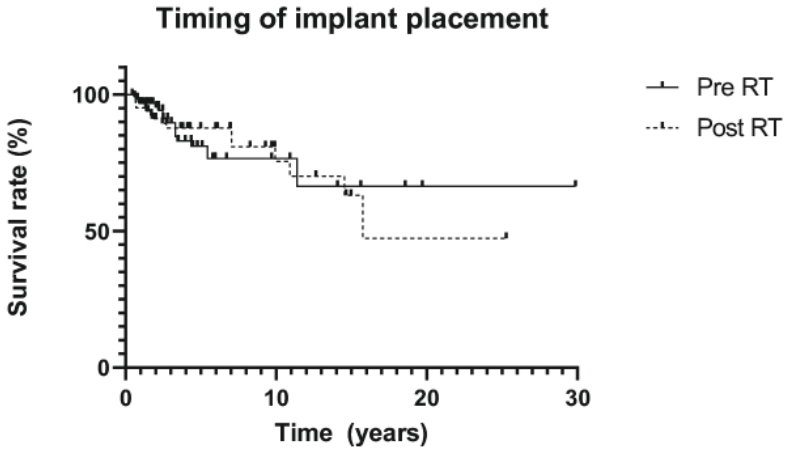
	Implant region			
	Mastoid	**Nasal**	**Orbit**	**Total**
Number of placed implants (Number of lost implants)	82 (6)	0 (Not applicable)	0 (Not applicable)	82 (6)
Median follow-up in months (IQR)	234 (153.8-264.3)			

Figure 5.6 Kaplan-Meier survival analyses of implants in non-irradiated and irradiated sites



RT=radiotherapy

Figure 5.7 Kaplan–Meier survival analyses of implants according to implant placement timing: before or after radiotherapy



RT=radiotherapy

Multiple variables (age at implant placement, gender, implant location and the presence of radiotherapy) were included in the Cox proportional-hazard model. Within the study population, two variables (gender and the presence of radiotherapy) remained statistically significant in the multivariate analysis (table 5.5).

Table 5.5 Results of univariate and multivariate Cox regression analyses

Variable	Univariate model hazard ratio (95% CI)	p-value	Multivariate model hazard ratio (95% CI)	p-value
Age at implant placement	1.02 (1.00 – 1.03)	0.011	1.01 (0.99 – 1.03)	0.227
Gender (female)	0.51 (0.28 – 0.92)	0.018	0.47 (0.26 – 0.86)	0.015
Implant location				
Nasal	Reference			
Mastoid	0.51 (0.21 – 1.23)	0.135		
Orbit	1.42 (0.62 – 3.25)	0.402		
Radiotherapy	3.4 (2.03 – 5.76)	<0.001	3.14 (1.80 – 5.47)	<0.001

Forty-five out of the 61 implants which were lost (73.8%) were not replaced because the patients could still wear a functioning prosthesis on the remaining implants. The 24 implants lost by ten patients were replaced to increase prosthesis retention but three were lost again. At follow-up, 96.9% of the auricular prostheses, 93.4% of the nasal prostheses, and 89.8% of the orbital implant-retained prostheses were still functional. A new craniofacial prosthesis was made every 2 to 2.5 years.

During the follow-up, seven patients (two patients with nasal implants and five patients with orbital implants) developed osteoradionecrosis. In the majority of these patients (n=5), the exposed bone developed outside the implanted region and the implants were not affected. Two patients experienced loss of an orbital implant as a result of progressive osteoradionecrosis. Osteoradionecrosis was usually treated with a combination of hyperbaric oxygen, antibiotics and debridement therapy.

Clinical assessment

Of the initial 220 patients, 126 patients died during the follow-up period. Unfortunately, 28 out of the remaining 94 patients were lost to further follow-up (due to moving to another part of the country or multiple no-shows). Sixty-two patients (20 irradiated and 42 non-irradiated patients) were available for the clinical assessment (tables 5.6 to 5.8). The mean follow-up period in this group was 164.4 months (s.d. 100.8). There was no statistically significant difference in skin reactions under the prosthesis between the irradiated and non-irradiated patients (p=0.76). Peri-implant soft tissue reactions were more frequent in the irradiated patients (p=0.02). The presence of soft tissue problems did not vary between the various implant locations (p=0.34 for the presence or absence of skin reactions; p=0.06 for peri-implant reactions).

Table 5.6 Clinical assessment and patient-reported outcome results

Clinical assessment		**N (%)**
Skin reaction under the prosthesis	Present	17 (27.4)
	Not present	45 (72.6)
Reaction around the abutments	No irritation	39 (62.9)
	Slight redness	11 (17.7)
	Red and moist tissue	7 (11.3)
	Granulation, red and moist tissue	3 (4.8)
	Active infection	2 (3.2)
Patient-reported outcomes		
Overall satisfaction with implant-retained prosthesis	Mean score (s.d.)	8.4 (1.7)

Table 5.7 Peri-implant skin reactions according to implant location

		No irritation	**Slight redness**	**Red and moist tissue**	**Granulation, red and moist tissue**	**Active infection**	**Total**
Implant location	Mastoid	26	5	4	0	0	35
	Nasal	8	2	2	3	0	15
	Orbit	5	4	1	0	2	12
	Total	39	11	7	3	2	62

Table 5.8 Peri-implant skin reactions according to implant placement indication

		No irritation	**Slight redness**	**Red and moist tissue**	**Granulation, red and moist tissue**	**Active infection**	**Total**
Indication for implant placement	Oncology	21	9	3	3	2	38
	Traumatology	8	0	2	0	0	8
	Congenital	12	2	2	0	0	16
	Total	39	11	7	3	2	62

DISCUSSION

This study presents the treatment outcomes for implants used to retain craniofacial prostheses in maxillofacial defects. The overall survival rates of the endosseous implants placed in patients with craniofacial defects due to trauma (96.2%) and congenital diseases (92.7%) were higher compared to the implants placed in patients with oncological defects (86.4%). The lower survival rates in the latter might be because the oncology group consisted of more patients with orbital

implants and patients who had to undergo radiotherapy. These findings are in accordance with earlier studies on craniofacial implant placement[8,10,12,19,20].

When treating patients with orbital defects, various challenges need to be addressed, for example the poor bone quality in the orbit region and potential issues with cleaning the peri-implant skin due to the local anatomy and the visual handicaps that patients with monocular vision encounter[21]. Although older age (frailty) and a decline in visual capacities during aging can also be mentioned as factors affecting peri implant hygiene, age was not identified from the current study's multivariate regression analysis data as a significant risk factor for implant survival. Adding radiotherapy, however, to areas comprised of bone and soft tissues increased the susceptibility of implant failure, such as in the orbital region, even more, resulting in lower implant survival rates.

The effect of ionizing radiation on peri-implant bone was confirmed by animal studies and it seems that radiation therapy negatively influences the microarchitecture and biomechanical properties of bone tissue, especially near the surface of the implant[22,23]. Earlier research concluded, though, that the survival of nasal implants is not influenced by radiotherapy[5, 12]. Our study confirms this observation as an equal proportion of nasal implants were lost by irradiated and non-irradiated patients.

The radiation dosages on the tumour varied between 30 and 70 Gray but, because radiation techniques have evolved greatly, it cannot be concluded that the radiation dose on the tumour was equal to the radiation dose on the implant area. Thus, firm conclusions on the effect of implant-specific radiation dosages on implant survival cannot be drawn. Literature on site-specific radiation dosages, and the effect of ionizing radiation on basic bone biology in the craniofacial region, is not available yet.

The results of the multivariate analysis show that female gender has a positive effect on implant survival (hazard ratio 0.47, p=0.015). Even though Toso et al. reported a similar finding[20], ours could also have been a result of the skewed gender ratio in the studied population. The male predominance, which was also mentioned in a recent systematic review, can be due to the higher incidence of congenital aural atresia and craniofacial tumours in males[12,24].

Besides the timing of implant placement in relation to radiation therapy, placing implants during or after ablative surgery is also a common issue of debate. The few available studies that treated patients during and after ablative surgery infer that

placing endosseous implants during ablative surgery does not lead to worse or better function than implants placed in a secondary setting[15,16,25]. We could confirm this observation. It is sometimes argued that secondary placement offers better implant positioning but, with the current advances in digital planning techniques and early involvement of a maxillofacial prosthodontist, we believe that optimal implant positioning can also be achieved during ablative surgery[5,26].

An additional phenomenon when treating head and neck cancer patients during ablative surgery is the issue of some implants possibly not being used due to various disease- or patient-related factors. In our study, 50 implants in 19 oncology patients (11.2%) had to be excluded from the analysis because it was not possible to perform second-stage surgery due to the earlier mentioned reasons. This seems to be an inevitable risk when treating oncology patients during ablative surgery. However, we still advise implant placement during ablative surgery because of the clear functional benefits in the majority of patients (earlier prosthetic rehabilitation, implant placement before radiotherapy, and no need for an additional operation (patients are often tired and do not feel up to the treatment at a later stage, even though they can really benefit from it)).

Performing regular clinical examination on implants placed in craniofacial regions is important in the aftercare period. Contrary to implants placed in the oral cavity, radiographic evaluation of the peri-implant bone level is not common is extraoral regions for a number of reasons: 1) Because of local anatomy, perpendicular placement of the x-ray tube to the sensor is not possible in extraoral regions. 2) 3-dimensional imaging modalities such as (conebeam) computed tomography ((CB) CT) tend to show a lot of scattering (especially when extraoral implants with a wider flange are use) resulting in unreliable measurements. Also, taking multiple, repeated radiographs and exposing patients to these levels of radiation when applying a (CB)CT does not adhere to the ALARA (‘as low as reasonably possible’) concept of radiation. 3) Implants used for extraoral application are generally short (maximum length of 7mm, often shorter). When peri-implant bone loss occurs, the implants will presumably already show mobility due to the shortness of the implants.

Further studies on the influence of aftercare and soft tissue reactions on implant survival are needed. These issues should, preferably, be studied prospectively in larger groups. This is challenging because each treatment centre carries its own treatment protocol according to the specialties available. No statistically significant differences were found in the presence of skin reactions under the prosthesis between the irradiated and non-irradiated patients. An earlier study

on the aftercare of craniofacial prostheses, however, reported that skin reactions were significantly milder in irradiated patients than in non-irradiated patients[27]. The authors hypothesized that irradiated skin is thinner and drier than healthy skin and thus less susceptible to peri-implant problems. We could not confirm this finding but concluded from our study that although severe peri-implant skin reactions are not common, some redness is present around the abutments in 17.7% of patients. There is a tendency for healthier peri-implant skin in the mastoid region but to what extent this is related to anatomic factors such as thinner skin in the mastoid region and a less moist environment, self-care, or other patient-related factors such as frailty, could be a subject for further research. Some researchers[17] stated that the main reasons for implant loss are soft tissue problems while other authors claimed the opposite: implant loss is not related to adverse skin reactions but to loss of integration[28]. We could not draw any conclusions on a potential causal relationship between peri-implant skin reactions and implant loss.

Few studies on craniofacial implant placement mentioned the development of osteoradionecrosis and, when reported, the incidence was low[5,13,15,28–30]. This could imply that osteoradionecrosis is not a significant issue in craniofacial implant therapy. In all the current study's patients with osteoradionecrosis, the exposed bone did not originate from the region with the implants and the implants were not affected in most of the patients (5 out of 7). It can be stated that all the patients with osteoradionecrosis had extensive mid-face defects due to large tumours (a T4 adenoid cystic carcinoma of the maxillary sinus, and a large basal cell carcinoma). This indicates that the development of osteoradionecrosis probably depends more on the extent of the surgical reconstruction than on the presence or placement of implants.

The finding that the majority of the lost implants were not replaced indicates that the loss of a craniofacial implant does not necessarily lead to the loss of the prosthesis in the long term. Even one implant can, in some patients, be enough for prosthesis retention, resulting in a high percentage of functional prostheses despite implant loss. This is in accordance with the Subramaniam et al. findings[17]. The patients also seemed to be highly satisfied with their prosthesis. Nevertheless, more insight can be gained from the patient's specific wishes.

Strengths and limitations

The current study presents implant survival data with a follow-up of up to 30 years in a large group of patients. The Kaplan-Meier survival method was used to indicate the probability of implant loss or implant survival after a particular

point in time. The patients who did not experience implant loss were censored and could have been either lost to follow-up, continued in the follow-up without experiencing implant loss, or died after implant treatment. With the Kaplan-Meier method, an assumption is made that when patients are censored, they are still at risk of experiencing implant loss after the censoring date. This is not a viable assumption for patients who have died. As our study had a large oncology group, death is a competing risk in our analysis and thus a limitation of our study as it can lead to an overestimation of experiencing the event (implant loss) in the long term[31]. Another issue in our survival analysis is that each implant was considered an independent sample instead of counting multiple measurements in each patient. Also, because of the long follow-up period, few patients remained (especially in the oncology group), which makes interpretation of the survival rates after 20 years difficult. This is also reflected in the number of patients remaining for the clinical assessment; an unfortunate and inevitable consequence of providing long-term patient care.

CONCLUSION

Within the limitations of this study, we can conclude that the outcome of craniofacial implants to retain craniofacial prosthesis is favourable. Congenitally deformed patients and traumatology patients have higher implant survival rates than oncology patients. Orbital implants score worse than nasal and mastoid implants. Radiotherapy has a negative effect on implant survival irrespective of whether the implants are placed before or after radiotherapy.

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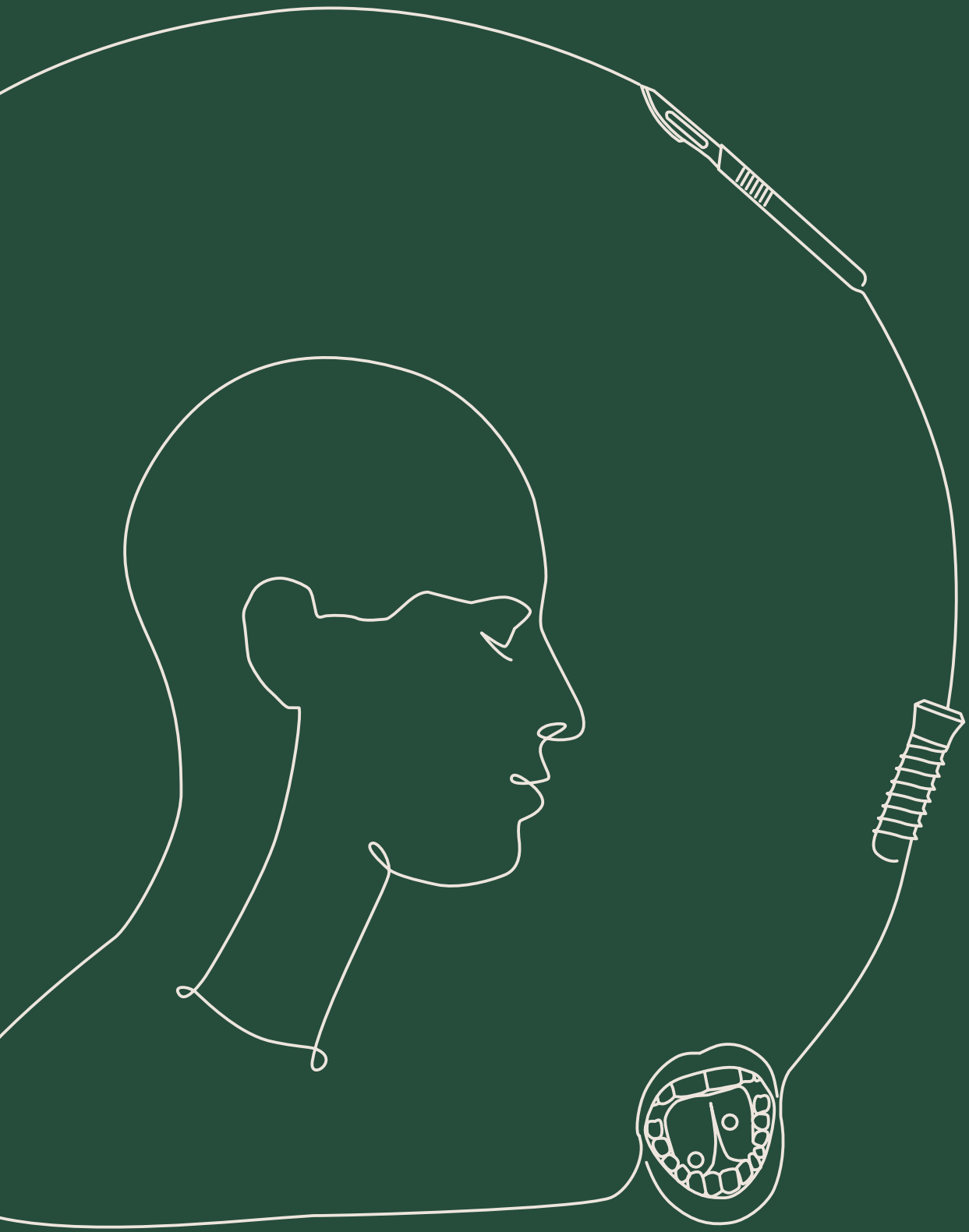

Chapter 6

Planned dose of intensity modulated proton beam therapy versus volumetric modulated arch therapy to tooth-bearing regions

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This chapter is an edited version of the manuscript:
Planned dose of intensity modulated proton beam therapy versus volumetric modulated arch therapy to tooth-bearing regions.

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ABSTRACT

Background

Intensity modulated proton beam therapy (IMPT) for head and neck cancer offers dosimetric benefits for the organs at risk when compared to photon-based volumetric modulated arch therapy (VMAT). However, limited data exists about the potential benefits of IMPT for tooth-bearing regions.

The aim of this study was to compare the IMPT and VMAT radiation dosimetrics of the tooth-bearing regions in head and neck cancer patients. Also, we aimed to identify prognostic factors for a cumulative radiation dose of ≥40 Gy on the tooth-bearing areas, which is considered the threshold dose for prophylactic dental extractions.

Methods

A total of 121 head and neck cancer patients were included in this retrospective analysis of prospectively collected data. We compared the average D_{mean} values of IMPT versus VMAT of multiple tooth-bearing regions in the same patients. Multivariate logistic regression analysis was performed for receiving a cumulative radiation dose of ≥40 Gy to the tooth-bearing regions (primary endpoint) in both VMAT and IMPT.

Results

A lower D_{mean} was seen after applying IMPT to the tooth-bearing tumour regions ($p<0.001$). Regarding VMAT, oral cavity tumours, T3-T4 tumours, molar regions in the mandible, and regions ipsilateral to the tumour were risk factors for receiving a cumulative radiation dose of ≥40 Gy.

Conclusion

IMPT significantly reduces the radiation dose to the tooth-bearing regions.

INTRODUCTION

Pre-radiation dental screening of patients with head and neck cancer is carried out early in the diagnostic phase before commencing treatment. The treatment of dental foci has evolved from a strict approach where all the foci are eliminated to a more targeted approach where infectious foci are grouped into low-risk and high-risk areas, according to the localized radiation dose[1,2,3,]. Generally, when the area of interest is due to receive a cumulative dose of ≥40 Gy, tooth extraction is advised [3]. If oral foci receive a cumulative dose of <40 Gy, more conservative treatment options, such as restoration, endodontic treatment and periodontal therapy, can be applied[4]. The goal of dental screening is to reduce the risk of post-radiation dental extractions, thereby reducing the risk of developing osteoradionecrosis (ORN)[3,5]. The incidence of ORN has declined in the last few years, most likely due to advances in radiotherapy techniques[6-11].

The risk of ORN increases with radiation exposures beyond 40 Gy, with a clear increase in risk when the dose delivered to the mandible is more than 60 Gy[7,8]. However, it is generally assumed that the development of ORN is a multifaceted process which also includes issues like tumour staging and localization, radiation dose and volume, patient-related factors such as tobacco/alcohol use, and post-radiation invasive bone procedures[9]. Multiple studies identified tooth extraction (pre- and post-radiotherapy) and periodontal decay as risk factors for osteoradionecrosis[3,15–14].

New radiation techniques, such as intensity modulated radiotherapy (IMRT) and volumetric modulated arch therapy (VMAT), offer the possibility to limit the radiation dose on multiple organs at risk (e.g., salivary glands, swallowing muscles, mandibular bone), resulting in a decrease in treatment-associated toxicities such as hyposalivation, xerostomia and dysphagia[15–17]. Tooth-bearing regions can also be considered to be organs at risk which can be helped by, for example, constraining the radiation dose to the anterior mandible in oropharynx tumours[18]. In January 2018, intensity modulated proton therapy (IMPT) was introduced in our treatment centre as an option for head and neck cancer patients[19]. The superior physical beam properties of protons compared to photons offer the possibility of depositing their energy at a specific depth known as the Bragg peak. Distally from this peak, there is a rapid loss of energy, sparing the tissue behind the tumour without affecting target dose coverage[20–23]. Hence, for patients with oropharyngeal cancer, the use of IMPT results in a further dose reduction to organs at risk, potentially leading to a reduction in treatment-related toxicities[24–26]. However, as to how proton therapy can influence

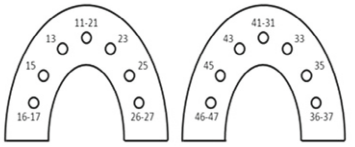
the decision-making processes still has to be determined for dental professionals undertaking pre-radiation dental screening, as the dosimetric differences between VMAT and IMPT for dental structures have not been studied widely. Therefore, the aim of this study was to compare the radiation dosimetrics of IMPT and VMAT on the tooth-bearing regions in head and neck cancer patients. Secondly, we aimed to identify the prognostic factors after applying a cumulative radiation dose of ≥40 Gy to the tooth-bearing areas, which is considered the threshold dose to reduce the risk of prophylactic dental extractions.

MATERIALS AND METHODS

All the patients treated with radiotherapy for a head and neck malignancy between January 2018 and January 2020 were evaluated. At the time of the diagnosis, all the patients underwent the standard pre-radiation dental screening, including a panoramic x-ray and a periodontal pocket status. Intraoral periapical radiographs were made of all the endodontically treated teeth to enable a proper evaluation of the periapical region by an oral and maxillofacial surgeon, a dental hygienist and a maxillofacial prosthodontist. Pre-radiotherapy treatment consisted of extractions or apicoectomies. As the definite type of radiation therapy, i.e., VMAT or IMPT, had not been determined yet at the time of the pre-radiotherapy treatment, the patients receiving IMPT underwent similar preventive measures as the patients treated with VMAT. Patients were deemed eligible for IMPT through model-based selection[19,27,28]. This method utilises multivariable prediction models to determine the risk of radiation-induced side-effects (xerostomia, dysphagia, tube feeding dependence) as a function of radiation dose deliverance to organs at risk (OAR) and other risk factors[20,28]. A VMAT plan and an IMPT plan was composed for each patient (RayStation treatment planning system v6.1 and v8, RaySearch Laboratories AB, Stockholm, Sweden). Subsequently, the difference in dose between the VMAT and IMPT (DDose) was translated into an expected difference in the risk of a radiation-induced side effect (ΔNTCP), using the above mentioned prediction models. The patients who were expected to benefit significantly from IMPT in terms of the expected risk profiles, and who met the criteria of the National Indication Protocol for Proton therapy, would then receive IMPT, while the remaining patients were treated with VMAT. The patients received definitive radiation therapy or postoperative radiotherapy, with or without systemic treatment. When indicated, chemotherapy was given concurrently with the radiotherapy, consisting of cisplatin, carboplatin/5-fluorouracil (5-FU), or cetuximab intravenously.

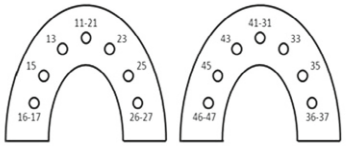
The VMAT and IMPT plans from the planning software were translated by the radiation oncologist to dental maps, a symbolic representation of the radiation dose on the dental arch (figure 6.1), and were included in the patient file. Each number in the dental map is the result of a dose calculation for a cylindrical sample of 5 mm in diameter and 6 mm in height, and represents the localized radiation dose for two adjacent teeth in the upper or lower jaw.

Figure 6.1 Examples of dental maps provided by the department of radiotherapy for a patient with a T3N1M0 oropharyngeal tumour. Each point corresponds to a location in the upper and lower jaw



Type of treatment: Photon / ~~Proton~~

Dose point	Dose (Mean Gy)
11-21	9.99
13	15.77
15	25.27
16-17	31.7
23	18.45
25	31.5
26-27	55.08
31-41	13.27
33	19.7
35	47.69
36-37	56.85
43	16.33
45	33.34
46-47	37.54



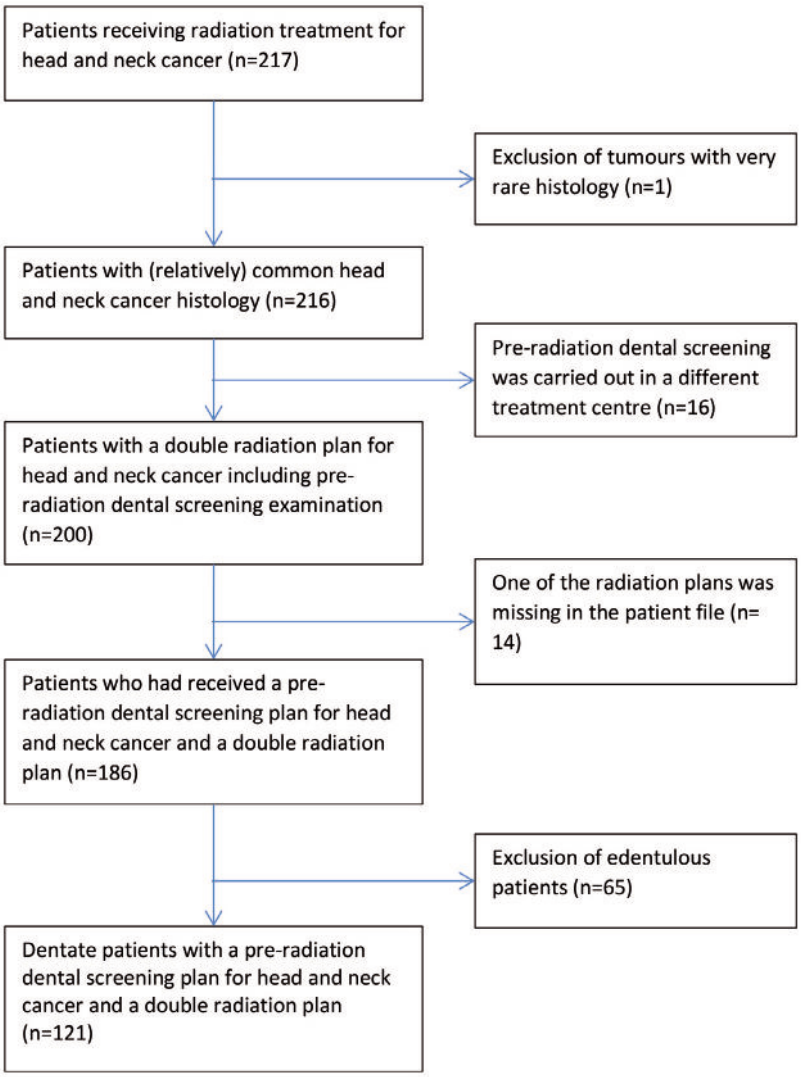
Type of treatment: ~~Photon~~ / Proton

Dose point	Dose (Mean Gy)
11-21	0.1
13	0.2
15	0.2
16-17	0.2
23	0.2
25	0.2
26-27	1.4
31-41	0.2
33	0.2
35	0.5
36-37	26.2
43	0.2
45	1.0
46-47	2.9

Inclusion and exclusion criteria

The inclusion criteria were dentate patients with a malignancy in the head and neck region who had undergone a pre-radiation dental screening and were eligible for VMAT and IMPT plan comparisons (figure 6.2). Edentulous patients, patients who had undergone pre-radiation dental screening at a different treatment centre, and patients with a missing radiation plan, were excluded. The patient characteristics, tumour characteristics, and radiotherapy data were retrieved from the patient files.

Figure 6.2 Algorithm for the inclusion and exclusion of patients



Plan comparison of the tooth-bearing regions

The cumulative VMAT and IMPT radiation doses were retrieved from the dental maps. The mean radiation dose levels (average D_{mean}), according to tumour location (nasopharynx, oral cavity, oropharynx, hypopharynx, larynx), tumour size and location relative to the tumour (contra- or ipsilateral), were calculated. The average subgroup D_{mean} values were analysed for the anterior (canine to canine) and posterior (premolar and molar) regions in the maxilla and mandible. The number of high-risk regions in the jaw, defined as regions in the jaw receiving a VMAT or IMPT radiation dose of ≥40 Gy, were identified.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the study population. To compare the radiation dose parameters between the VMAT and IMPT plans, a paired samples T-test or Wilcoxon Signed Rank Test was applied whenever appropriate, depending on the distribution (normal or non-normal) of the data. A p-value of ≤0.05 was considered statistically significant. The potential risk factors of receiving a radiation dose of ≥40 Gy, and thus becoming a high-risk region, were identified through multivariate logistic regression analysis with forward selection. The following covariates were included in the analysis: tumour location, T-status, N-status, tooth location in the jaw, tooth location in relation to the tumour (contralateral or ipsilateral) and applied radiation technique (VMAT or IMPT). The odds ratios, regression coefficients and predicted probabilities were calculated. Risk scores were reported by multiplying the regression coefficient by 5 and rounding off to the first integer. IBM SPSS statistics version 23 was used to execute the statistical analyses. Graphs were constructed with GraphPad Prism version 9.1.0.

RESULTS

Clinical data

The original study population consisted of 216 patients whereupon 95 patients were excluded due to various reasons, resulting in 121 eligible patients (figure 6.2). The patient demographics are given in table 6.1. Among the 121 included patients, 2525 teeth were still in situ at the time of the dental screening (mean 21 teeth per patient, SD 7.9). Forty-eight patients (39.7%) were treated with definitive radiotherapy, while 52 patients (42.9%) received concurrent chemoradiotherapy (chemotherapy types: cisplatin (5-FU), carboplatin (5-FU)) and six patients (5%) were treated with radiotherapy and cetuximab. Fifteen patients (12.4%) initially underwent surgery

followed by radiotherapy (with or without chemotherapy). After the model-based selection, 55 patients (45.5%) were ultimately treated with VMAT and 66 patients (54.5%) with IMPT.

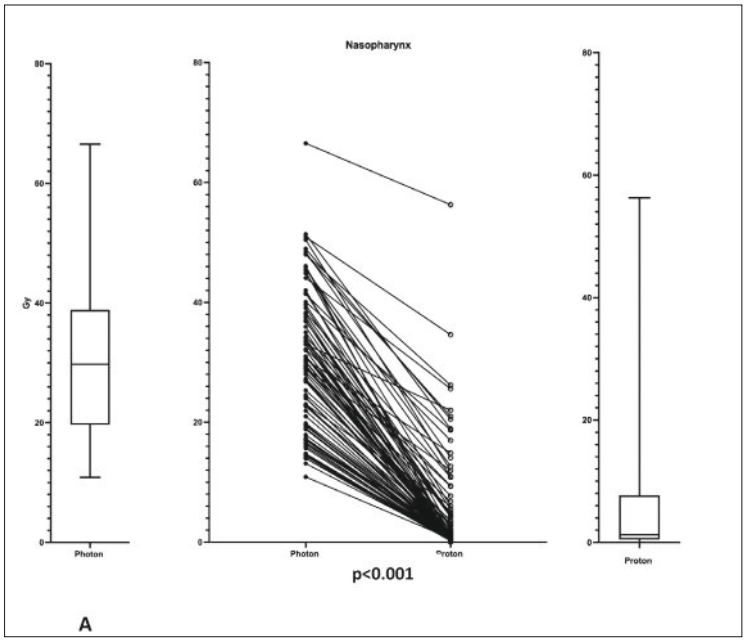
Table 6.1 Patient demographics. (s.d. = standard deviation)

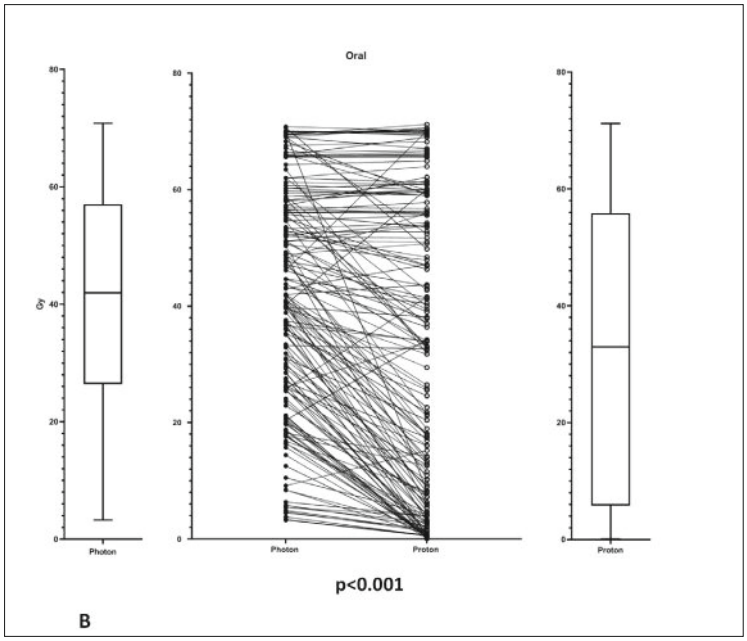
	N=121
Mean age in years (s.d.)	60.5 (11.1)
Gender (%)	
Male	90 (74.4)
Female	31 (25.6)
Smoking (%)	
Current smoker	36 (29.8)
Never smoked	24 (19.8)
Previous smoker	54 (44.6)
Not reported	7 (5.8)
Tumour site (%)	
Oropharynx	62 (51.2)
Tonsillar region	44 (36.3)
Uvula	1 (0.8)
Base of tongue	17 (14)
Larynx	20 (16.5)
Oral cavity	13 (10.8)
Tongue	5 (4.1)
Floor of mouth	2 (1.7)
Maxillary gingiva or palate	2 (1.7)
Mandibular gingiva or retromolar region	4 (3.3)
Hypopharynx, piriform sinus	9 (7.4)
Nasopharynx	7 (5.8)
Lymph node metastasis of unknown primary	5 (4.1)
Sinonasal cavity	4 (3.3)
Parotid gland	1 (0.8)
Histology	
Squamous cell carcinoma	113 (93.4)
Other	8 (6.6)
T-classification	
T1	21 (17.4)
T2	25 (20.6)
T3	22 (18.2)
T4	48 (39.6)
Tx	5 (4.2)
N-classification	
N0	25 (20.7)
N1	30 (32)
N2	44 (36.3)
N3	20 (16.5)
Nx	2 (1.7)

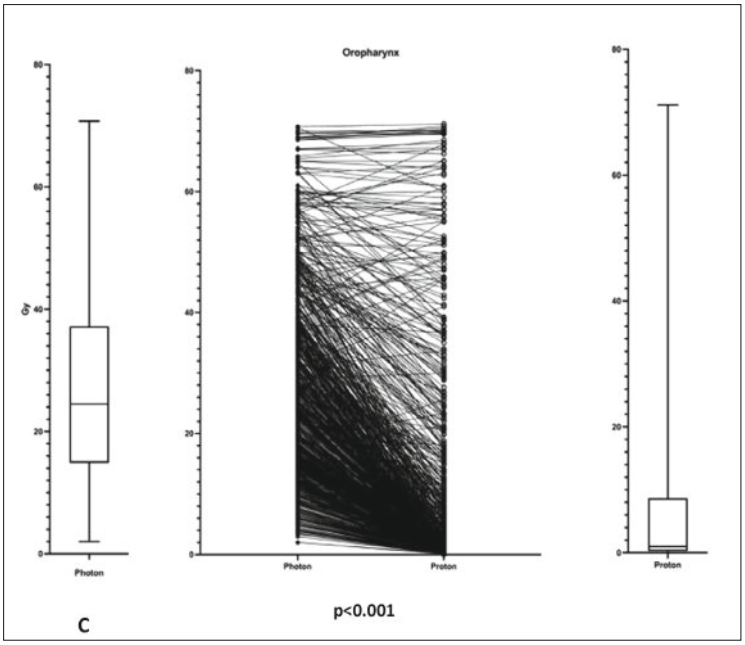
Radiation dose comparison

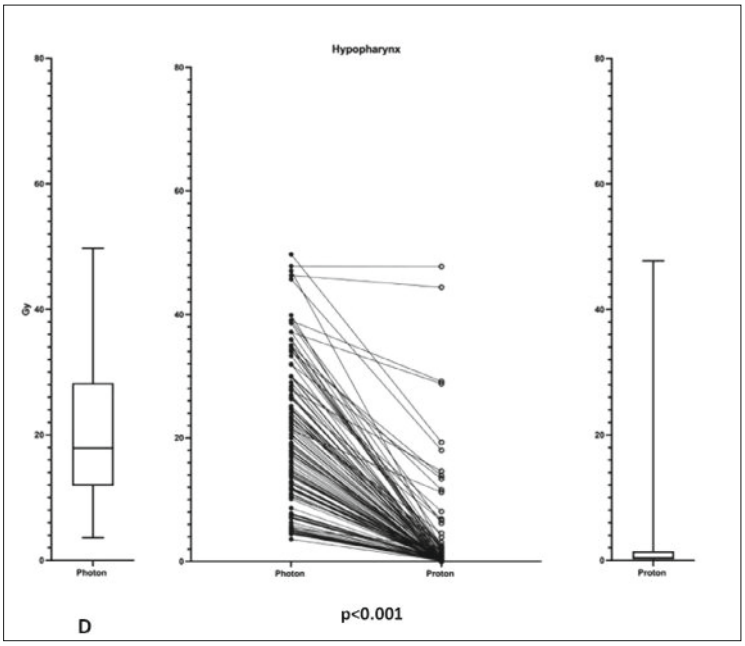
The median prescribed radiation dose to the target was similar for both VMAT and IMPT (70 Gy for definitive radiotherapy; 66 Gy for postoperative radiotherapy). Figure 6.3A-E compares the value of the individual VMAT dose points (left side of the graph) with the corresponding IMPT dose points in various tumour locations. Each point in the graph represents a specific tooth-bearing area in the jaw. The average D_{mean} of the specific tooth-bearing tumour areas was significantly lower for IMPT than for VMAT ($p<0.001$). The intraoral tumour values show the highest average D_{mean} for the tooth-bearing areas (VMAT: 41.5 Gy, SD 19.3; IMPT 31.3 Gy, SD 24.7; $p<0.001$). When analysing the influence of tumour size on radiation dose, the average D_{mean} for the VMAT of the larger (T3 and T4) tumours (26.8 Gy; SD 18.8) was not significantly different from the average D_{mean} of the smaller (T1 and T2) tumours (25.8 Gy; SD 14.8). However, the patients with larger tumours received a significantly higher average D_{mean} to the tooth-bearing areas with IMPT (12.9 Gy; SD 21.2) when compared to smaller tumours (8.0 Gy; SD 14.6; $p=0.042$). The distributions of the average D_{mean} in the various anterior, premolar and molar tumour locations are presented in tables 6.2 (maxillary regions) and 6.3 (mandibular regions), respectively. As depicted in figure 6.4, the high-risk areas for VMAT and IMPT were mostly located in the posterior regions of the lower jaw.

Figure 6.3 Display of individual dose points in the upper and lower jaw for photon therapy (VMAT) on the left side of the graph. The points on the right side of the graph depict the corresponding dose points for proton therapy (IMPT). Each graph represents a certain tumour location






Oropharynx
Gy
Photon
Photon
Proton
Proton
p<0.001
C


Hypopharynx
Gy
Photon
Photon
Proton
Proton
p<0.001
D

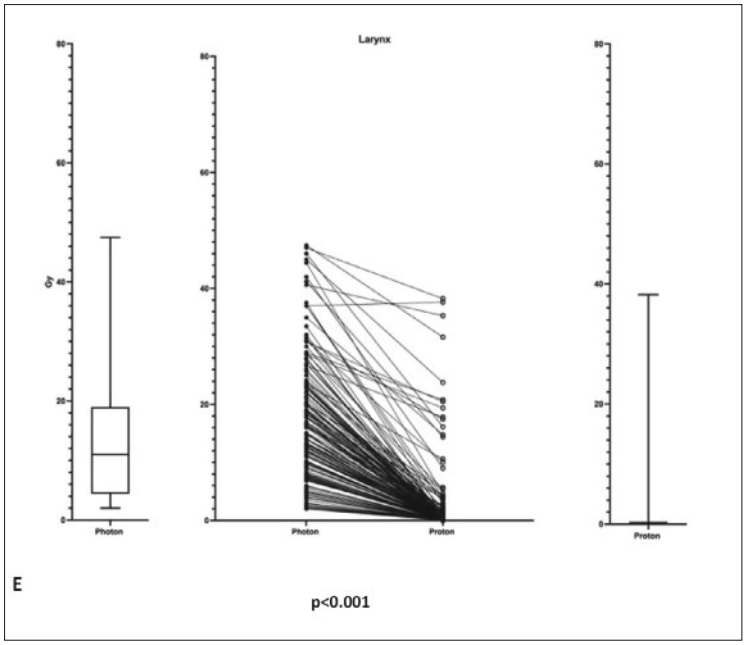

Larynx
Gy
Photon
Photon
Proton
Proton
E
p<0.001

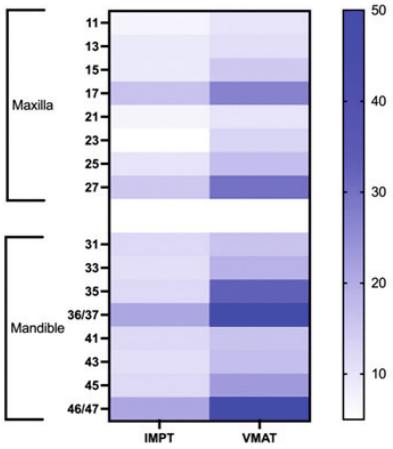
Table 6.2 Dosimetry (average D_{mean}) of maxillary teeth in the anterior region, ipsilateral and contralateral to the tumour (VMAT=volumetric modulated arch therapy, IMPT=intensity modulated proton beam therapy)

	VMAT	IMPT		VMAT	IMPT		VMAT	IMPT		VMAT	IMPT		VMAT	IMPT	
	Ipsilateral molar	Ipsilateral molar	p	Ipsilateral premolar	Ipsilateral premolar	p	Anterior	Anterior	p	Contralateral premolar	Contralateral premolar	p	Contralateral molar	Contralateral molar	p
Nasopharynx															
Mean (s.d.)	52.1 (9.1)	27.2 (18.5)	0.01	41.6 (8.1)	5.6 (6.1)	0.07	27.5 (10.6)	0.6 (0.8)	<0.01	33.9 (3.8)	4.4 (3.7)	0.06	40.5 (8.5)	13.8 (5.9)	0.01
Min-max	44.8-66.5	11.0-56.3		30.2-48.4	1.0-14.1		13.9-37.5	0-2.2.0		31.0-39.6	0.6-9.3		29.0-51.4	5.5-18.9	
Oral															
Mean (s.d.)	45.1(18.6)	42.4 (20.7)	0.27	38.9 (20.7)	31.8 (20.8)	0.02	32.3(20.8)	23.6 (23.2)	<0.01	25.9 (17.2)	13.0 (19.8)	<0.01	26.1 (13.2)	8.8 (12.5)	<0.01
Min-max	5.8-68.3	0.9-69.0		4.7-69.1	0.5-63.9		3.3-69.9	0.1-70.5		3.4-67.6	0.3-68.2		3.8-53.5	0.62-46.9	
Oropharynx															
Mean (s.d.)	33.2(16.8)	17.4 (20.5)	<0.01	25.3 (14.1)	6.7 (12.6)	<0.01	16.5 (10.6)	2.7 (8.9)	<0.01	17.3 (10.9)	2.9 (10.8)	<0.01	20.9 (11.8)	4.7 (12.5)	<0.01
Min-max	5.0-70.7	0.1-71.2		3.0-63.2	0.0-60.9		2.0-50.0	0.0-55.1		3.0-57.0	0.0-65.1		4.0-60.0	0.0-67.8	
Hypopharynx															
Mean (s.d.)	26.9(11.9)	1.06 (1.1)	<0.01	18.4 (9.4)	0.3 (0.2)	<0.01	11.8 (6.4)	0.2 (1.3)	<0.01	13.1 (6.9)	0.2 (0.1)	<0.01	15.8 (9.7)	0.5 (0.8)	<0.01
Min-max	7.0-39.9	0.2-3.9		5.0-29.0	0.0-0.6		3.6-21.2	0.0-0.4		5.2-24.0	0.0-0.5		5.2-32.0	0.1-2.3	
Larynx															
Mean (s.d.)	6.6 (6.3.)	0.1 (0.1)	<0.01	5.6 (5.7)	0.1 (0.1)	<0.01	4.2 (3.0)	0.1 (0.1)	<0.01	5.1 (3.8)	0.1 (0.1)	<0.01	6.0 (4.6)	0.1 (0.2)	<0.01
Min-max	2.0-25.0	0.0-0.4		2.0-21.0	0.0-0.4		2.0-15.0	0.0-0.4		2.0-16.0	0.0-0.4		2.0-20.0	0.0-0.6	

Table 6.3 Dosimetry (average D_{mean}) of mandibular teeth in the anterior region, ipsilateral and contralateral to the tumour (VMAT=volumetric modulated arch therapy, IMPT=intensity modulated proton beam therapy)

	VMAT	IMPT		VMAT	IMPT		VMAT	IMPT		VMAT	IMPT		VMAT	IMPT	
	Ipsilateral molar	**Ipsilateral molar**	**p**	**Ipsilateral premolar**	**Ipsilateral premolar**	**p**	**Anterior**	**Anterior**	**p**	**Contralateral premolar**	**Contralateral premolar**	**p**	**Contralateral molar**	**Contralateral molar**	**p**
Nasopharynx															
Mean (s.d.)	38.4 (6.4)	15.1 (9.8)	0.01	29.1 (1.6)	3.5 (2.9)	0.06	22.2 (8.7)	0.3 (0.23)	<0.01	23.4 (5.3)	1.4 (1.1)	0.07	26.9 (3.4)	6.2 (5.8)	0.01
Min-max	33.0-47.9	4.5-26.2		27.2-31.0	0.4-6.8		10.9-34.0	0.0-0.6		16.5-28.0	0.3-2.8		23.0-30.5	0.7-14.9	
Oral															
Mean (s.d.)	60.7 (9.7)	54.4 (19.1)	0.30	57.5(12.7)	50.7(24.5)	0.84	52.1 (16.4)	35.8 (23.7)	<0.01	42.2(11.8)	27.1(19.2)	<0.01	43 (7.1)	25.1(15.8)	<0.01
Min-max	36.0-69.8	8.3-70.2		29.3-70.1	9.3-70.6		18.6-70.8	0.1-69.9		20.7-62.0	0.2-56.3		35.2-57.0	3.2-56.7	
Oropharynx															
Mean (s.d.)	48.7 (13.5)	32.8 (21.6)	<0.01	37.4(12.8)	13.1(17.3)	<0.01	25.6(13.2)	4.5(13.7)	<0.01	27.6(12.2)	5.8(14.0)	<0.01	31.7(12.6)	9.8 (16.6)	<0.01
Min-max	18.0-70.5	1.7-69.9		14.1-68.8	0.0-69.7		5.3-69.6	0.0-70.2		10.2-68.9	0.0-70.8		11.0-68.5	0.0-70.1	
Hypopharynx															
Mean (s.d.)	35.7 (8.1)	14.1 (9.9)	<0.01	25.3(6.7)	3 (2.6)	<0.01	18.4(8.4)	1.4(2.6)	<0.01	23.5(12.1)	6.3(14.5)	<0.01	27.1(13.6)	9.0 (15.5)	<0.01
Min-max	20.6-47.1	0.4-29.1		14.9-34.7	0.3-6.8		7.5-35.9	0.1-11.2		10.9-46.3	0.1-44.3		14.0-49.7	0.3-47.7	
Larynx															
Mean (s.d.)	23.6 (10.2)	4.1 (9.5)	<0.01	18.9 (8.0)	1.9 (4.6)	<0.01	13.8(5.4)	0.9(2.0)	<0.01	21.3(10.1)	2.9 (5.8)	<0.01	26.6(12.2)	9.1(13.9)	<0.01
Min-max	12.0 -46.0	0.1-37.6		8.0-37.0	0.0-19.3		7.0-26.1	0.0-10.0		8.0-44.4	0.0-20.4		11.3-47.4	0.0-38.2	

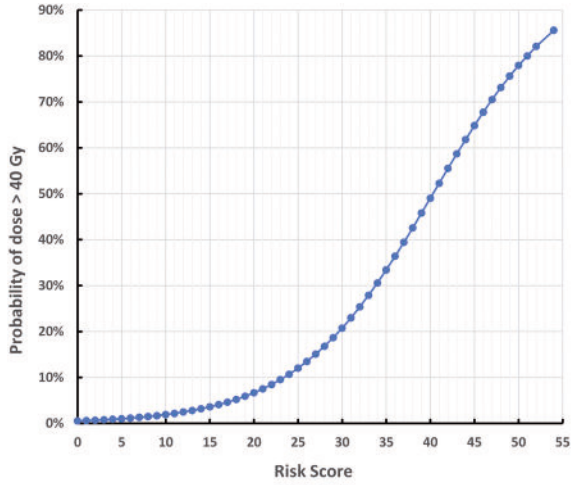
Figure 6.4 Heatmap of the number of high-risk regions defined as teeth receiving ≥40 Gy during IMPT and VMAT



Logistic regression analysis and risk scores

From the multivariate logistic regression analysis, treatment with VMAT molars in the lower jaw, teeth ipsilateral to the tumour, patients with larger tumours, and patients with a tumour in the oral cavity were significantly associated with a higher risk of receiving a D_{mean} ≥ 40 Gy (table 6.4). Adding up the risk scores from table 6.4 on the basis of clinical risk factors gives an estimate of the probability of a certain tooth receiving a radiation dose ≥ 40 Gy (figure 6.5).

Figure 6.5 The probability of a dose of ≥ 40 Gy to tooth elements was estimated from the Risk Scores derived from table 6.4



OR=odds ratio

Table 6.4 Factors associated with a D_{mean} of 40Gy or higher based on a multivariate regression analysis. The risk score was derived from the regression coefficient multiplied by 5 and rounded off at the first integer. The risk score varies from -4 to 54. The probability of a dose > 40 Gy per element was derived from figure 6.5

Predictors	Multivariate analysis				Risk score
	Regression coefficient	OR (95% CI)	95% of OR	p-value	
Radiation technique					
IMPT reference	1.00				0
VMAT	1.08	2.94	2.48 – 3.49	<0.001	5
Tumour location					
Larynx reference	1.00				0
Hypopharynx	1.14	3.14	1.61 – 6.13	<0.001	6
Oropharynx	2.95	19.07	11.92 – 30.51	<0.001	15
Nasopharynx	3.01	20.26	10.96 – 37.44	<0.001	15
Oral	5.14	171.23	103.5 – 283.2	<0.001	25
T-classification					
T1-T2 reference	1.00				0
T3-T4	0.79	2.21	1.85 - 2.64	<0.001	4
N-classification					
N0 reference	1.00				0
N1	-0.77	0.47	0.36 – 0.61	<0.001	-4
N2	-0.47	0.62	0.49 – 0.79	<0.001	-2
N3	-0.36	0.70	0.51 – 0.95	0.02	-2
Tooth location					
Upper incisor or cuspid reference	1.00				0
Lower incisor or cuspid	1.19	3.29	2.37 – 4.58	<0.001	6
Upper premolar	0.59	1.81	1.23 – 2.65	<0.001	3
Lower premolar	1.85	6.34	4.51 – 8.92	<0.001	9
Upper molar	1.33	3.77	2.72 – 5.23	<0.001	7
Lower molar	2.54	12.65	9.21 – 17.36	<0.001	13
Laterality					
Contralateral reference	1.00				0
Ipsilateral	1.35	3.85 (3.23 – 4.59)	3.23 – 4.59	<0.001	7

OR=odds ratio

DISCUSSION

The results from this study illustrate a significant reduction in the D_{mean} regarding IMPT and VMAT of the tooth-bearing regions in head and neck cancer patients. The reduction in D_{mean} occurred for all the tumour locations. The difference in dosimetry between VMAT and IMPT was significant for all the tooth locations, except for the premolars and molars in the mandible and the molars in the maxilla of patients with intraoral tumours.

The dosimetric benefits of IMPT for organs at risk were published by an earlier study focusing on oropharyngeal cancer patients[20]. That study illustrated a D_{mean} of more than 40 Gy for VMAT of the oral cavity to less than 30 Gy for IMPT, which is comparable to our study's results where the average D_{mean} of the dentition in oropharyngeal tumours also dropped significantly for IMPT. Although it appears that IMPT has a significant dose-sparing effect on the dentition, we see that the single dose values are more relevant to the individual patient. Single radiation dosages exceeding 40 Gy were still observed in the mandibular regions of both groups' patients with nasopharyngeal, oral, oropharyngeal and hypopharyngeal tumours. An IMPT regimen can also result in high radiation dosages in the maxilla of patients with nasopharyngeal, oral, and oropharyngeal tumours. This is a finding clinicians need to be aware of when screening their patients before radiotherapy.

Undergoing VMAT instead of IMPT leads to a risk of the dentition being exposed to a radiation dose exceeding 40 Gy. Also, larger tumour sizes are risk factors for receiving radiation doses ≥40 Gy. The role of tumour size on the tooth-bearing regions was illustrated by one other study reviewing the radiation dose metrics in patients with a tongue tumour [29]. They also concluded that a larger tumour size is an important predictor of high radiation doses to the tooth-bearing regions. Tumour location also plays a role in the radiation dose on tooth-bearing regions. Patients with tumours located further away from the tooth-bearing regions benefit the most from the dose-sparing effect of IMPT; when the distance between the tumour location and the oral cavity is shorter, the tooth-bearing regions will receive more radiation [30]. Consequently, the difference between VMAT and IMPT is less striking for patients with oral tumours. The relationship between tumour location and radiation dose was also clearly observable in our study population where the maxillary molars in the nasopharyngeal tumour patients and the mandibular molars in the oropharyngeal tumour patients were most likely to become high-risk regions, which is also in line with the findings of others[31–34].

Possible consequences for the clinician

When performing a pre-radiation dental screening, the definitive irradiated volumes and radiation technique (VMAT or IMPT) are often still unknown. This puts clinicians in a difficult situation regarding the decision of whether or not a dental focus of infection needs to be extracted as the data is still unknown. The risk scores and probability curve from table 6.4 and figure 6.5, respectively, can be used as a tool to make a rough estimate of whether or not a tooth will be exposed to high radiation doses. However, communication between the dental clinician and radiation oncologist in this stage of the treatment process is of utmost importance and can prevent dental foci of infection being unnecessarily or unjustifiably extracted before radiation treatment. Previously, when patients were treated with conformal radiotherapy, a more aggressive approach, whereupon all the dental foci were removed before the radiotherapy, was preferred. When considering VMAT, a more tailored approach is advised because more dental foci will be located outside irradiated volumes. As the irradiated volumes are even smaller for IMPT, we expect that fewer pre-radiation extractions will be carried out in the future. This is an important consequence as pre-radiating tooth extractions can have a significantly negative impact on the quality of life and is considered a risk factor for weight loss in oropharyngeal cancer patients[35,36]. It needs to be stated that these dental foci still have to be attended to after radiation treatment in order to achieve a healthy dental status. A recent study on the value of radiotherapy dose mapping for tooth-bearing regions illustrated that the teeth which were exposed to ≥40 Gy were significantly more at risk of being extracted in the future than teeth located outside the irradiated volumes or receiving <40 Gy[37] . This illustrates that tooth loss is not only the result of the indirect effect of radiation-induced hyposalivation caused by salivary gland damage, but is also directly caused by the individual dose values on the teeth. Nonetheless, further prospective studies are needed in order to demonstrate the effects of IMPT on salivary gland function and the development of late radiation-induced toxicities such as radiation-induced caries.

Strengths and limitations

This is the first study comparing radiation dose levels to tooth-bearing regions for VMAT and IMPT within the same patient. The availability of both radiation plans clearly illustrates the dosimetric benefits of IMPT for the dentition. The potential tissue-sparing abilities of IMPT on the tooth-bearing regions were illustrated by another study[5]. However, the latter study was relatively small and they did not compare VMAT and IMPT plans from the same patient[5]. Our study also has several limitations. First, when calculating our results, certain radiation dosage assumptions had to be made for the tooth-bearing regions: the dental maps provided the exact

dose for 2 adjacent teeth (e.g., 11, 13, 15, 16-17). Thus, the exact radiation dose for the teeth in the 12 and 14 locations were unknown. Regarding these locations, we assumed the same radiation dose as the highest adjacent value. Second, the threshold of 40 Gy for high-risk regions was rather 'conservative' as some studies applied a threshold of 50-60 Gy[12,38]. This could have led to an overestimation of the number of high-risk regions.

CONCLUSION

Compared to VMAT, applying IMPT to head and neck cancer patients leads to less cumulative radiation doses on the tooth-bearing regions of the upper and lower jaw. Treating a patient with IMPT can lead to a reduction in the number of pre-radiation dental extractions.

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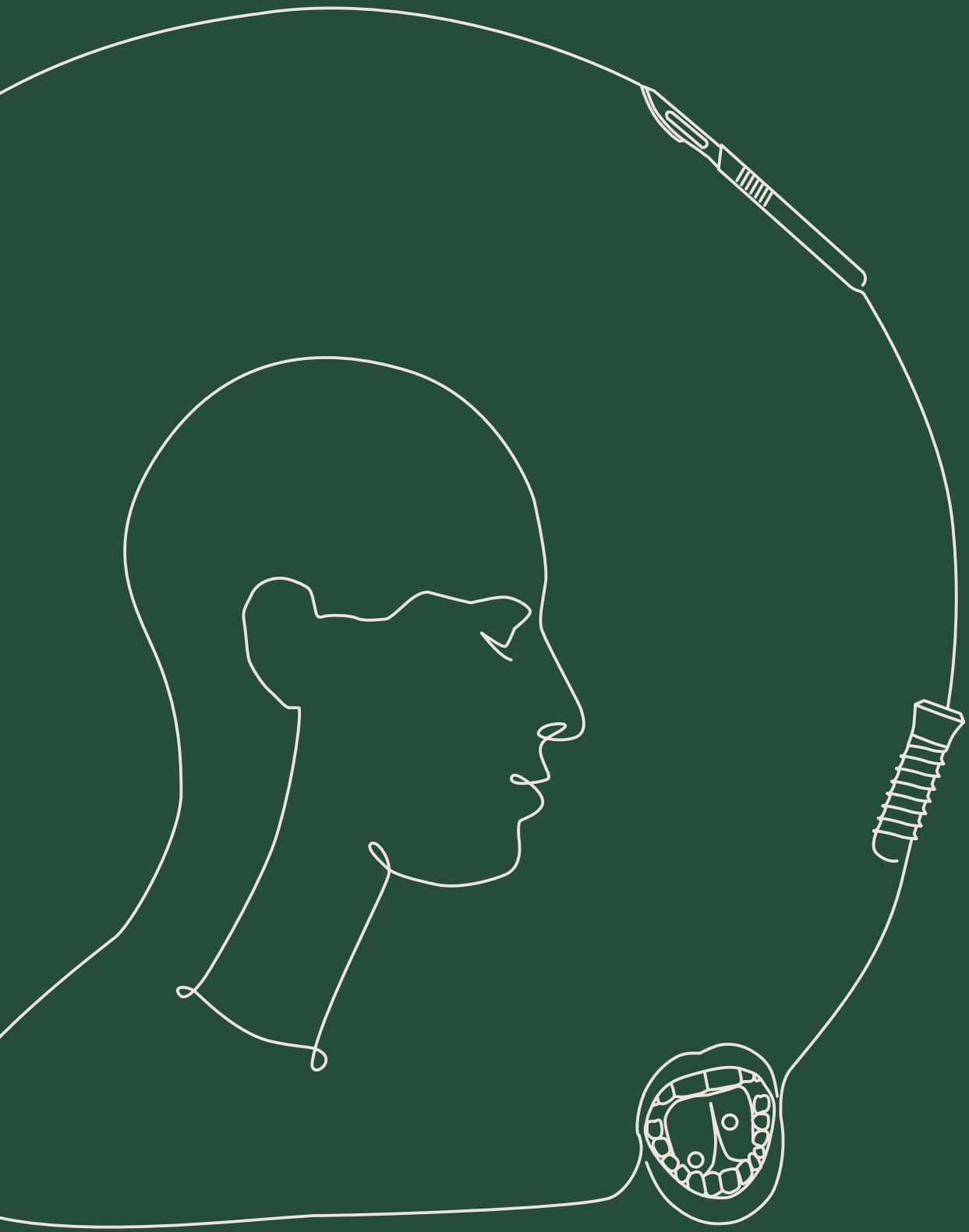

Chapter 7

The influence of site-specific radiation dosage on dental implant survival in patients with an intraoral malignancy: A cohort study

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The influence of site-specific radiation dosage on dental implant survival in patients with an intraoral malignancy: a cohort study

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ABSTRACT

Background

Data on implant-specific radiation dosages are often not reported or unknown. We assessed the radiation dosages (D_{mean}) on implant regions to identify the threshold for implant loss in patients with an intraoral malignancy treated with dental implants to support a mandibular denture during ablative surgery before volumetric modulated arc therapy (VMAT).

Methods

The data was collected prospectively from 28 patients treated surgically for an intraoral malignancy, followed by postoperative radiotherapy (VMAT), and thus analysed retrospectively. The patients received 2 implants in the native mandible during ablative surgery for an implant-supported mandibular prosthesis. Implant-specific D_{mean} values were retrieved from the patients' files. Radiographic bone loss was measured one year after implant placement and during the last follow-up appointment. Implant survival was analysed with the Kaplan-Meier method. Univariate logistic regression and Cox-regression analyses were performed to investigate the effect of increasing implant-specific radiation dosages on implant loss.

Results

Five out of the 56 placed implants were lost during the follow-up (median 36.0 months, IQR 39.0). Radiographically, peri-implant bone loss occurred in implants with a D_{mean} >40 Gy. Implant loss occurred only in implants with a D_{mean} >50 Gy. During the follow-up, there was an increasing tendency of bone loss levels.

Conclusion

An implant-specific D_{mean} higher than 50 Gy is related to more peri-implant bone loss and, eventually, implant loss.

INTRODUCTION

Mandibular implant treatment in edentulous head and neck cancer patients has shifted from secondary treatment (after completing oncologic treatment) to placing implants during ablative surgery. This treatment approach has several advantages, including initial osseointegration before starting radiotherapy, increased oral function after oncologic treatment, faster prosthodontic rehabilitation, and prevention of an additional surgical procedure[1–4]. In dentate patients with an indication for pre-treatment extractions, implants placed immediately after extractions also result in good clinical and radiographic outcomes[5].

Several studies showed that radiotherapy has a negative influence on the survival of dental implants placed both before and after radiotherapy[6–9]. Ionizing radiation has several biological effects on the exposed tissues including hyperaemia, endarteritis, thrombosis, cellular loss, loss of microvascular content, and fibrosis[10]. It is assumed that these underlying processes are responsible for the observed increase in implant loss in irradiated patients. Also, an increase in implant loss is seen with increasing radiation dosages[8,11,12]. Unfortunately, most studies have not reported the exact radiation dose levels on the implant areas. When mentioned, radiation dose levels are often reported as the prescribed radiation dose on the target or tumour area, which mostly does not correspond with the dose on the implant. Consequently, the threshold dose in relation to problems arising with dental implants exposed to radiation has not been established. A threshold of 40-60 Gy is assumed to result in a higher risk of developing osteoradionecrosis. Based on these results, this is often also the threshold for performing extractions and other types of dentoalveolar surgery under antibiotic prophylaxis in order to prevent the development of osteoradionecrosis[13,14].

Over the last few years, radiation techniques have evolved from 3D-conformal radiation (3D-CRT) to more precise techniques like intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and intensity modulated proton therapy (IMPT), leading to significant dose reductions for organs-at-risk[15]. Also, restraining the radiation dose on the anterior mandible in order to facilitate implant placement is advised, and radiation dose-mapping, illustrating the wide variety of radiation doses on tooth-bearing regions, has become a useful tool for clinicians[16–18].

A recent study confirmed that one major risk factor for implant loss in patients receiving implants after radiotherapy is an implant-specific radiation dose of >50 Gy[19]. Regarding implants placed during ablative surgery before radiotherapy,

the threshold for decreased radiologic implant success was >40 Gy[20]. However, studies reporting on implant-specific radiation dosages remain scarce. Therefore, in the current study we aimed to analyse the influence of site-specific radiation dose levels on implant survival in patients with intraoral malignancies who had mandibular dental implants inserted during ablative surgery before commencing VMAT radiation treatment.

MATERIALS AND METHODS

Study population

All consecutive patients with a malignancy in the oral cavity referred to the head and neck centre of the University Medical Center Groningen, The Netherlands, between January 2015 and January 2020 were screened for this retrospective study based on prospectively collected data. Inclusion criteria were the placement of 2 dental mandibular implants during ablative surgery followed by post-operative radiotherapy (VMAT) or post-operative chemoradiation, the availability of implant-specific radiation dosages, and the presence of an implant-supported mandibular prosthesis. Patients were excluded when data on the implant-specific radiation dose were not available, when second-stage surgery did not take place, or when the implants were placed in a fibula free flap, in maxillary bone, or in zygomatic bone. Implant placement involved a two-stage procedure. First, during ablative surgery, 2 dental implants (Brånemark Mk III TiUnite RP, Nobel Biocare, Gothenburg, Sweden) were placed in the native bone of the edentulous mandible. Postoperative radiotherapy or chemoradiation commenced within 6 weeks after the surgery. Second-stage surgery took place under local anaesthesia with antibiotic prophylaxis (amoxicillin 500 mg 3 times a day for 2 weeks starting 1 day prior to the surgery) after finishing radiotherapy and the acute side effects of radiotherapy had subsided.

Data collection and treatment outcome assessment

Patient characteristics (age, gender, tumour site, T-status, N-status) and treatment characteristics (type of surgical reconstruction, dental implant characteristics, implant location, and implant-specific radiation dose) were collected from the patients' files. The implant-specific radiation dosages were translated from the planning software by the radiation oncologist to dental maps, a symbolic representation of the radiation dose on the dental arch. On these dental maps, each dose point corresponds to a specific tooth-bearing region or implant position. Marginal peri-implant bone loss was measured by one observer (JMA) by comparing the panoramic radiograph taken directly after implant placement (baseline) with

those obtained after 1 year and the last clinical assessment. Implant length was used as a reference when assessing bone loss on the radiographs and was measured between the tip and outer border of the neck of the implant. A waiver of exemption was granted for the Medical Research Involving Human Subjects Act (WMO) by the Medical Ethics Committee of the University Medical Center Groningen (reference number M21.276032).

Statistical analysis

The descriptive statistics, baseline variables, and implant survival rates using the Kaplan-Meier method were calculated in IBM SPSS version 23. Loss of an implant was considered an event. Group differences were assessed with the Kruskal-Wallis-test and Mann-Whitney U test. Bone loss and implant survival rates were analysed for each implant. A univariate Cox-regression analysis and logistic regression analysis were carried out with implant-specific radiation dose as the predictor variable and implant loss the event. The hazard ratio (HR) and odds ratio (OR) were reported with 95% confidence intervals. A p-value ≤0.05 was considered statistically significant. A dose response curve was constructed using the regression model illustrating the effect of an increasing D_{mean} on the probability of implant loss.

RESULTS

Forty patients with an intraoral malignancy, who had received 2 mandibular implants during ablative surgery and treated postoperatively with VMAT, were identified. Twelve patients were excluded: 6 patients had passed away before second stage surgery could take place and in the 6 other patients, an implant-supported prosthesis could not be fabricated due to pain or tumour recurrence. Consequently, 28 patients could be included in this study. The patients' characteristics are presented in table 7.1 and in table 7.2. The median time between implant placement and radiotherapy commencement was 6 weeks (Q1 4.25; Q3 8.0). The median time between implant placement and second stage surgery was 6 months for the patients who had only undergone postoperative radiotherapy (Q1 5.0; Q3 7.0) and 6.5 months for the patients treated postoperatively with chemoradiation (Q1 5.0; Q3 10.0). The patients received their implant-supported mandibular prostheses after a median period of 9.0 months (Q1 8.0; Q3 14.0). The mean clinical follow-up was 46.0 months (s.d. 26.7). The radiation dose on the tumour site was 66 Gy for all the patients. The implant-specific D_{mean} values are shown in figures 7.1 and 7.2.

Table 7.1 Patient characteristics (n=28)

	Mean (s.d.) or number (%)
Age, years	68.2 (9.3)
Gender	
Male	12 (42.9)
Female	16 (57.1)
Smoking status at time of diagnosis	
Never smoked	7 (25.0)
Former smoker	15 (53.6)
Current smoker	6 (21.4)
Tumour location	
Tongue	12 (42.9)
Floor of mouth	10 (35.7)
Mandibular gingiva	6 (21.4)
T stage	
T1	5 (17.9)
T2	8 (28.6)
T3	3 (10.7)
T4	12 (42.9)
N stage	
Positive lymph nodes (N+)	14 (50.0)
Negative lymph nodes (N-)	14 (50.0)
Treatment	
Postoperative radiotherapy	22 (78.6)
Postoperative chemoradiation	6 (21.4)

Table 7.2 Summary of the patient characteristics and implant-specific D_{means}

Patient	Age at implant placement	Gender	Smoking status at time of diagnosis	Tumour location	Tumour side	T-stage	N-stage	Peri-implant specific radiation dose left of implant	Peri-implant specific radiation dose right of implant
1	66	Female	Current	Floor of mouth	Right	4	+	54.0	55.0
2	73	Female	Current	Floor of mouth	Right	2	+	64.0	67.0
3	64	Male	Former	Floor of mouth	Left	1	-	52.6	52.9
4	62	Female	Former	Floor of mouth	Left	4	+	65.6	63.0
5	71	Female	Current	Floor of mouth	Left	1	+	32.5	35.5
6	65	Male	Former	Floor of mouth	Midline	4	-	31.0	16.0
7	52	Male	Never	Floor of mouth	Left	2	-	31.5	34.6
8	62	Female	Current	Floor of mouth	Midline	1	-	63.4	48.5
9	59	Male	Current	Floor of mouth	Left	2	-	35.0	27.0
10	61	Female	Former	Floor of mouth	Right	1	-	61.0	64.0
11	82	Male	Former	Tongue	Left	4	+	53.0	54.0
12	56	Female	Current	Tongue	Right	1	+	40.3	47.2
13	76	Male	Former	Tongue	Right	2	+	43.5	55.3
14	76	Female	Never	Tongue	Left	2	-	55.3	53.7
15	65	Male	Never	Tongue	Right	4	+	55.0	55.0
16	84	Male	Former	Tongue	Left	3	-	34.6	39.9
17	66	Male	Former	Tongue	Left	3	+	59.3	48.9
18	64	Female	Former	Tongue	Left	4	-	29.5	30.0
19	65	Female	Former	Tongue	Midline	3	-	26.1	32.0
20	77	Male	Former	Tongue	Right	2	-	18.1	50.9
21	72	Male	Never	Tongue	Left	2	+	31.0	9.0
22	82	Female	Former	Tongue	Left	2	+	24.4	8.0
23	73	Female	Never	Mandibular gingiva	Right	4	-	23.0	55.0

Table 7.2 Summary of the patient characteristics and implant-specific D_{means} *(continued)*

Patient	Age at implant placement	Gender	Smoking status at time of diagnosis	Tumour location	Tumour side	T-stage	N-stage	Peri-implant specific radiation dose left of implant	Peri-implant specific radiation dose right of implant
24	67	Female	Never	Mandibular gingiva	Right	4	+	52.0	57.0
25	78	Female	Never	Mandibular gingiva	Right	4	-	52.0	65.0
26	65	Female	Former	Mandibular gingiva	Left	4	+	66.5	56.7
27	66	Female	Former	Mandibular gingiva	Midline	4	+	60.0	59.0
28	52	male	Current	Mandibular gingiva	Left	4	-	54.9	50.8

Figure 7.1 Implant-specific radiation dosages (D_{mean}) for each implant site in the mandible

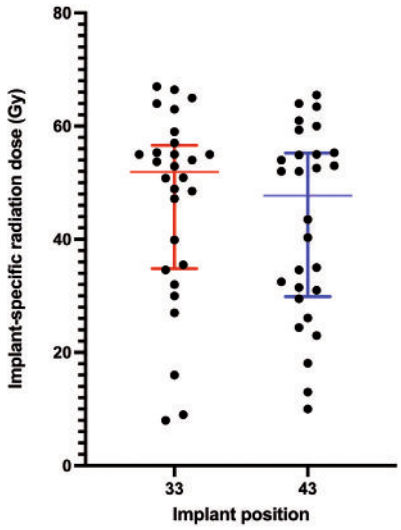
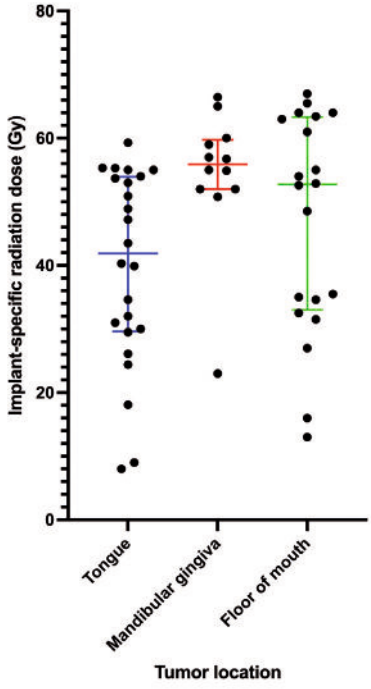


Figure 7.2 Implant-specific radiation dosages (D_{mean}) for each implant per tumour location



A total of 5 implants were lost by 4 patients during the follow-up, resulting in an overall implant survival rate of 91% (figure 7.3). A summary of the 5 lost implants is given in table 7.3. Two patients lost one each and continued to wear their prosthesis on the remaining implant. One patient passed away shortly after the implant loss. A conventional prosthesis was made for the fourth patient who had lost both implants. All the implant loss sites healed uneventfully.

Figure 7.3 Kaplan-Meier analysis of implant survival

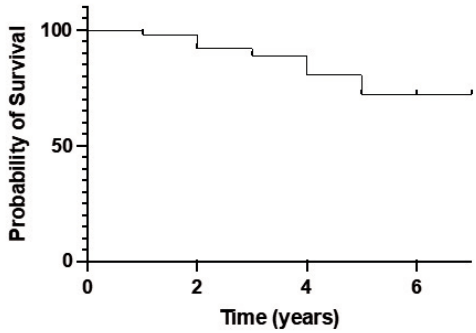
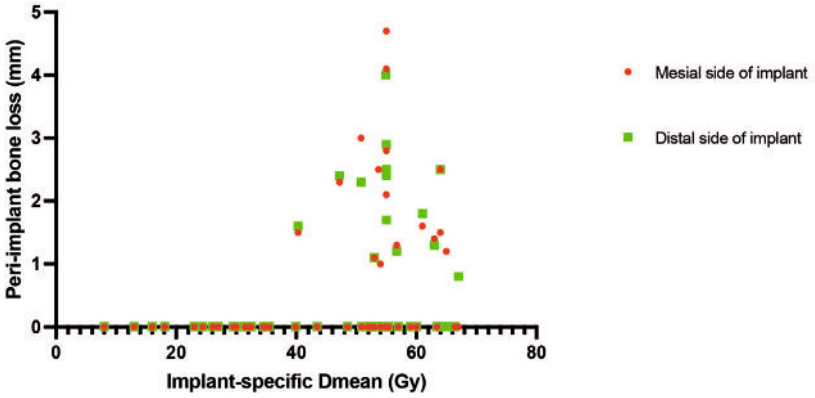


Table 7.3 Summary of implants lost during follow-up

Patient number	Tumour location	T stage	N stage	Implant position in relation to tumour side	Implant-specific D_{mean} (Gy)	Time from implant placement to implant loss (weeks)	Was the implant replaced?
1	Tongue	4	+	Ipsilateral	53.0	43.0	no
2	Tongue	4	+	Ipsilateral	55.0	53.0	no
3	Floor of mouth*	4	+	Contralateral	63.0	26.0	no
3	Floor of mouth*	4	+	Ipsilateral	65.6	13.0	no
4	Mandibular gingiva	4	-	Ipsilateral	54.9	54.0	no

Figure 7.4 depicts the bone loss at the mesial and distal side of the implants in relation to implant-specific radiation dose. The mean peri-implant bone loss after 1 year was 0.7 mm on the mesial side (range 0 – 4.7) and 0.6 mm on the distal side of the implant (range 0 – 4.0). The peri-implant bone loss, calculated from the last available panoramic radiographs, had increased to 1.3 mm (range 0 – 5.8) mesially and 1.5 mm (range 0 – 5.5) distally of the implants. In this study group, no patients showed signs of osteoradionecrosis during the follow-up.

Figure 7.4 Peri-implant bone loss on the mesial and distal side of the implants, 1 year after implant placement, according to the implant-specific radiation dose (D_{mean})

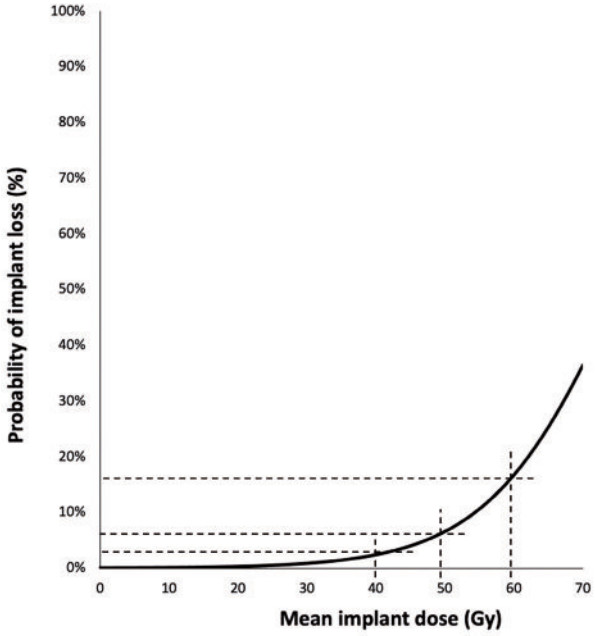


The results of the univariate logistic regression analysis and the Cox-regression analysis are presented in table 7.4 and show a tendency towards an increased, although not significant, risk of implant loss with increasing implant-specific D_{mean} (OR 1.11; 95% CI 0.98 – 1.23; p-value 0.09; HR 1.67; 95% CI 0.89 – 3.13; p-value 0.11). The dose response curve (figure 7.5) shows the increased probability of implant loss with increasing implant specific D_{mean}.

Table 7.4 Results of the univariate logistic regression analysis (OR) and Cox regression analysis (HR) of implant loss using patient and treatment-specific variables

	Univariate logistic regression			**Univariate Cox regression**		
	OR	95% CI	p-value	HR	95% CI	p-value
Implant-specific D_{mean}	1.11	0.98 – 1.23	0.09	1.67	0.89 – 3.13	0.11

Figure 7.5 Dose response curve showing the increasing probability of implant loss with increasing implant-specific D_{mean}



DISCUSSION

This study analysed the influence of implant-specific radiation dosage on implant survival. The results show a dose-effect relationship between implant loss and increasing D_{mean} values. This relationship was not considered statistically significant, most likely because of our study's small sample size. Radiographic peri-implant bone loss occurred when the implants were exposed to a D_{mean} above 40 Gy. None of the lost implants were replaced because of a high risk of the loss recurring and the associated risk of inducing osteoradionecrosis with an additional surgical procedure. Three other studies also evaluated the effect of implant-specific radiation dosages on implant survival[20–22]. One of them focused on patients who received implants before radiotherapy, and observed an increase in peri-implant bone loss when the implants were exposed to >40 Gy[20]. The other two studies, which focused on implants placed in the upper and lower jaw after radiotherapy was finished (secondary implant placement), had similar results[21,22]. Neckel et al. found a higher bone resorption rate, measured on cone beam CT-scans, around implants that had received higher implant-specific radiation dosages, especially in women. Wolf et al. concluded that a radiation dose of >50 Gy is a significant risk factor for implant loss[21,22].

The results of our study illustrate how widely the implant-specific radiation dose in the interforaminal region varies depending on tumour characteristics (location, T- and N-status). This is due to variations in radiation techniques, like VMAT and IMRT, with smaller radiation fields sparing certain organs-at-risk. The dosimetric benefits of IMRT on the oral cavity and/or mandible have been described by multiple studies, and newer radiation techniques like proton beam therapy (IMPT) have an even more dose-sparing effect on the dentition[17,18,23,24]. However, the effect of proton therapy on implant survival needs further research.

The overall implant survival rate in our study is comparable to the survival rates in two other studies of implants placed during ablative surgery, 91.5% and 90.4% respectively [25,26]. However, the follow-up period of the Korfage et al. study was significantly longer (up to 14 years) than in our study. An often debated but underreported issue in the literature is the time between implant placement and starting radiotherapy. The question whether the negative effect of radiotherapy is greater on implants which are still in the process of osseointegration compared to implants which have been fully osseointegrated is still unanswered.

The time from implant placement to prosthesis placement in our study was 9 months, which was somewhat shorter than in the Korfage et al. study (11.3 months for irradiated patients)[25]. This difference can be explained by a change in treatment protocol; initially, a period of 6 months was applied between the end of radiotherapy and second-stage surgery whereas now, second-stage surgery is planned as soon as the short-term side-effects of radiotherapy have subsided.

An advantage of our study is that the population consisted of a homogenous cohort of patients with oral cancer who had all received the same type of radiotherapy (VMAT) and implant treatment (insertion of 2 implants in the native mandible), giving a better insight into the specific risk factors for implant loss in this patient category. Our study's limitations are the relatively small sample size, short radiographical follow-up period and the absence of a matched, (non-irradiated) control group.

CONCLUSION

This study illustrates the negative influence of high radiation dosages on implant survival. Patients with implants exposed to a cumulative radiation dose >50 Gy are more prone to peri-implant bone loss and eventual implant loss. Minimizing the radiation dose to the implant regions is important to maximize prosthetic rehabilitation in the patient.

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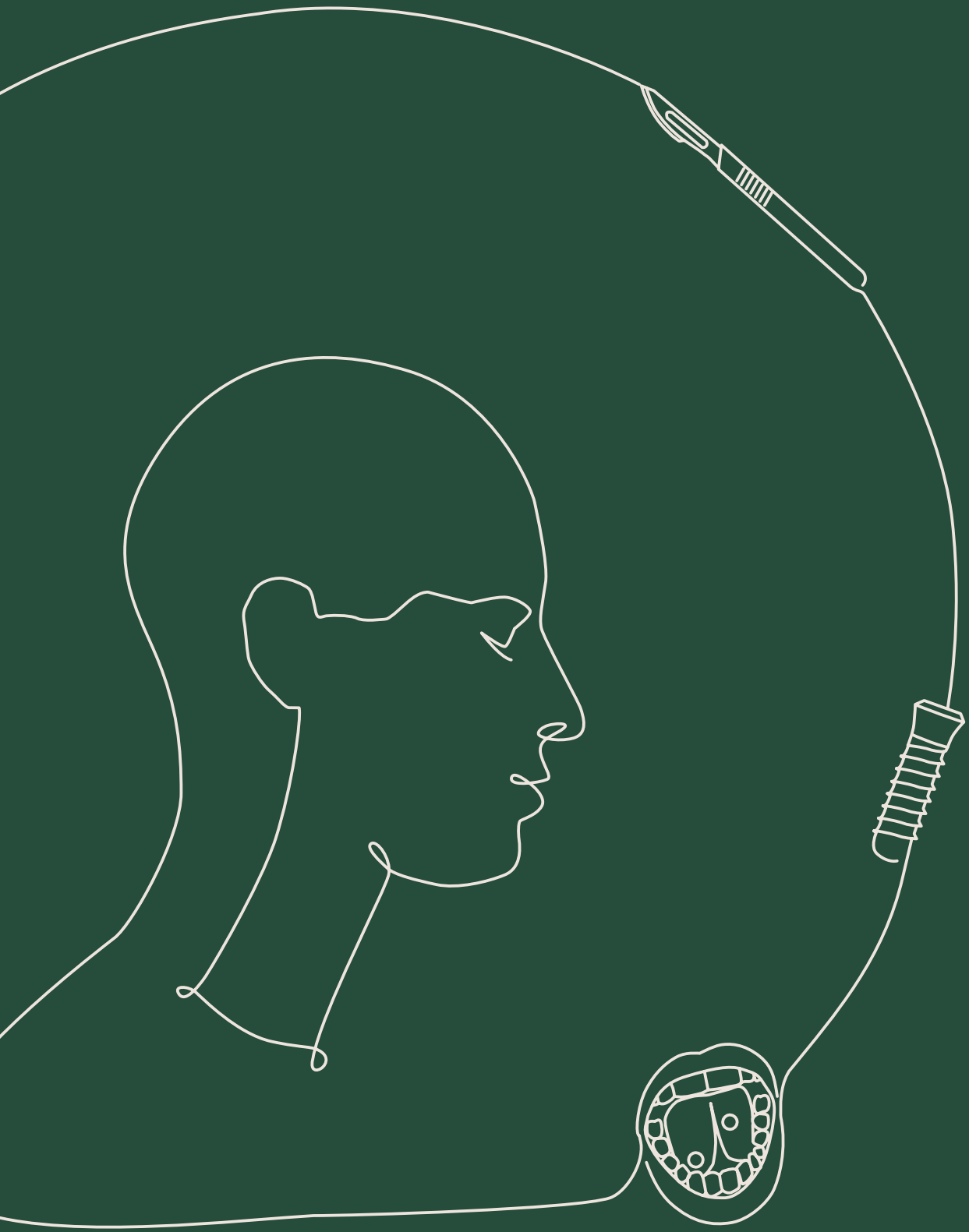

Chapter 8

Reply to the editor: Potential contributors to implant losses following radiotherapy or chemoradiotherapy

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We would like to thank Somay et al. for their comments on our study on the influence of site-specific radiation dosages on implant survival in oral cancer patients[1]. In the latter study, we concluded that an implant-specific D_{mean} higher than 50 Gy is related to more peri-implant bone loss and, eventually, implant loss[2]. We agree with the authors that it would be interesting to see whether a distinct, statistically significant threshold dosage can be found to predict an increased upon implant loss. Therefore, we applied the method described by Budzcies et al., using a dichotomized variable for different threshold dosages and the survival variable to determine a cut-off point[3]. We did not use receiver operating characteristic curve analysis as this method is only suitable for sensitivity and specificity analyses. Using the Budzcies et al. method, a cut-off dosage of 60 Gy yielded a hazard ratio of 5.9 (95% confidence interval 0.8 – 42.8, p-value 0.08) and a cut-off dosage of 55 Gy resulted in a hazard ratio of 1.4 (95% confidence interval 0.4 – 5.2, p-value 0.64). Thus, no statistically significant cut-off dosages were found, but the results further illustrate the increasing risk of implant failure with higher site-specific radiation dosages. However, the larger confidence interval for 60 Gy also indicates less precision or greater variability in the estimate. Additionally, the implant survival rate for the group with an implant-specific D_{mean} >50 Gy was 83.9% compared to the 100% implant survival in the group with a D_{mean} <50 Gy.

Regarding clinical relevance, we like to conclude that the D_{mean} on the implant regions should, when possible, not exceed 50 Gy. The radiation dose on a particular region in the oral cavity depends on the location of the tumour and the treatment plan of the radiation oncologist, thus whenever possible the D_{mean} should be <50 Gy in the regions planned for insertion of an implant. In another study, in which we analyzed the radiation dose on tooth-bearing regions, we already showed that when treating nasopharynx, oropharynx, hypopharynx and larynx tumours, the anterior mandible is already exposed to low radiation dosages, both for photon and proton treatment[4]. Thus, clinicians should especially be aware of the site-specific radiation dose in patients with an oral cavity tumour, particularly in the (planned) implant regions. Therefore, close collaboration between the prosthodontist and radiation oncologist is one of the most important factors to maximize treatment results of implant-supported prostheses in irradiated patients.

Regarding the second comment of the authors on the influence of chemoradiation, we can report that one out of the four patients with implant loss in our study had received chemoradiotherapy for a T4N2b squamous cell carcinoma in the floor of the mouth. There was an indication for weekly treatment with cisplatin (50mg/m2) for seven weeks because of a lymph node metastasis with extranodal growth. From

our data in the chemoradiation group, two out of 12 implants were lost (cumulative dose in the implant region was 63.0 Gy and 65.6 Gy), resulting in an implant survival rate of 83.3% in this group. Because of the small study group, we unfortunately cannot make any firm statements on the specific role of chemotherapy in dental implant survival. In a broader context, the possible effect of chemoradiation on bone remodeling and the osseointegration of dentalimplants has been described in animal studies[5,6]. However, as with any animal study, the limited generalizability of the results remains a problem. From a systematic review by Zen Filho et al. which included patients with chemoradiation, no clear conclusions on the influence of chemotherapy on dental implants can be made[7].

As for the comment on the probable additional dosage impact of 6-9 Gy for patients treated with chemoradiation, the question arises whether this theoretical additional dosage impact is of any clinical relevance to the patient. Patients with an indication for chemoradiation (inadequate resection margins, extranodal growth, or multiple involved lymph nodes) already receive high radiation dosages (in our study group up to 66 Gy) and implants placed in these patients will therefore automatically fall in the high-risk category with an increased risk for implant loss.

In conclusion, the risk for implant loss increases significantly when the site-specific implant dose is more than 50 Gy and more implant studies on the influence of chemoradiation are needed.

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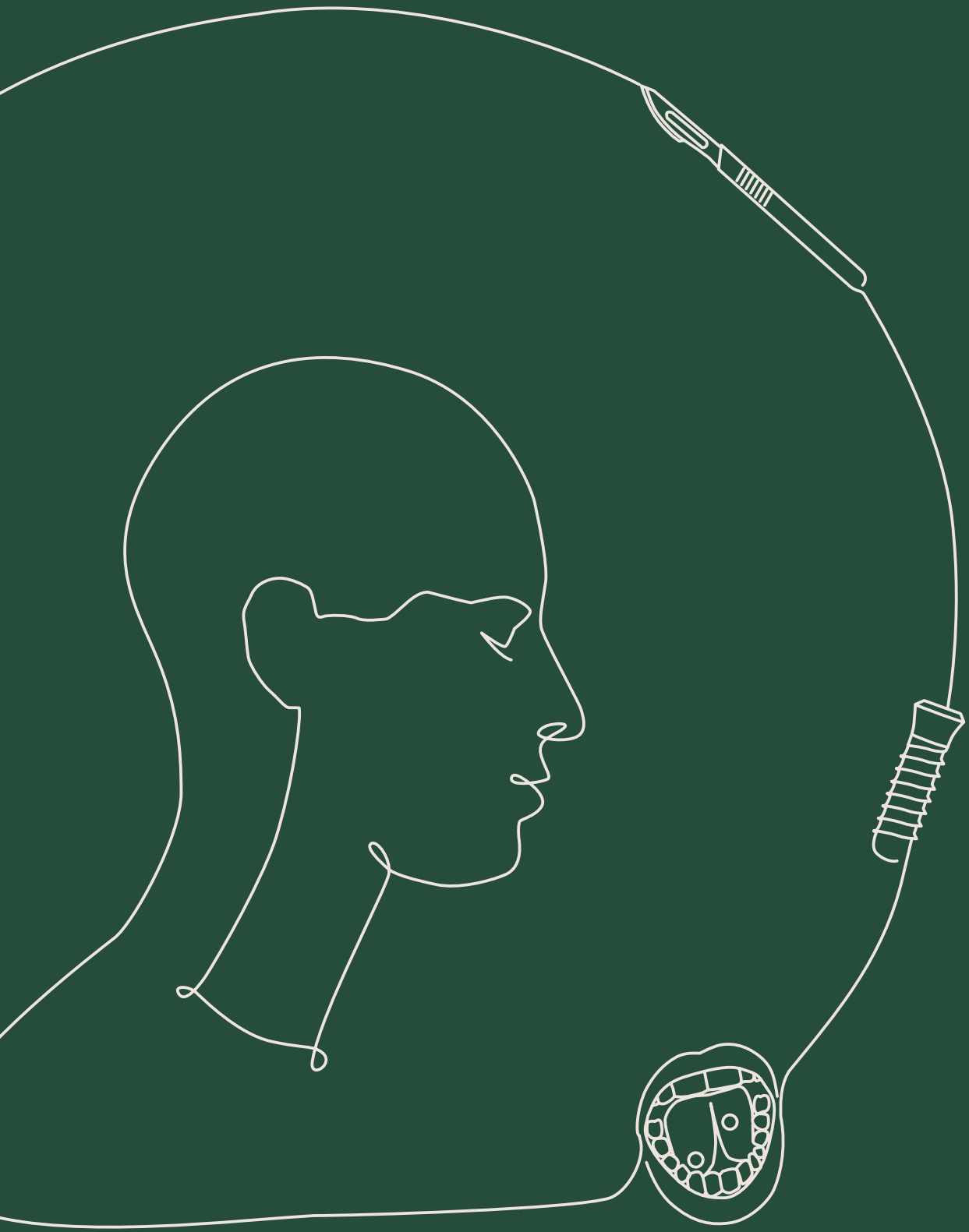


Chapter 9

General discussion

Alongside oncologic treatment, head and neck cancer patients require adequate prosthodontic rehabilitation. In order to achieve this, endosseous implants are often inserted to improve the retention of intraoral or craniofacial prostheses. The outcome of implant placement in these patients depends on several patient and treatment related factors. The research in this PhD thesis aimed to provide insight into factors involved in rehabilitation of head and neck cancer patients with implant-supported prostheses.

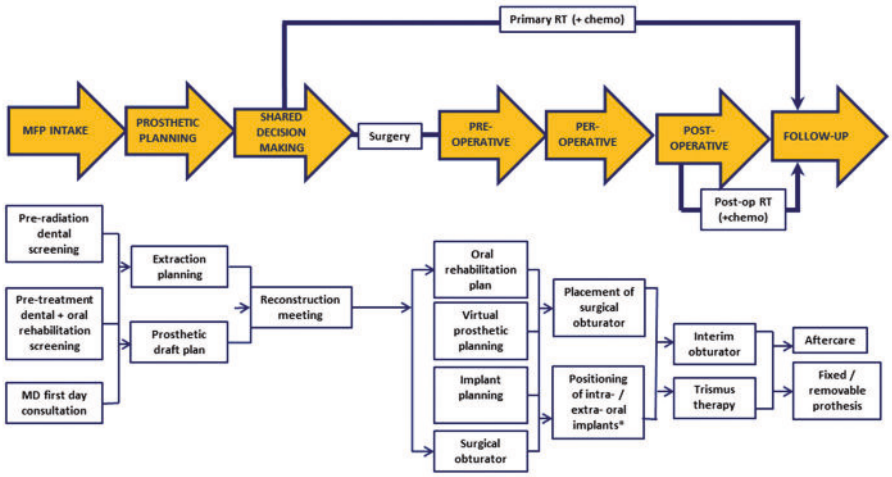
One of these factors is the timing of implant placement (during or after ablative surgery). In our treatment centre, implant placement in the edentulous mandible during the ablative surgery, aimed to ease the prosthetic rehabilitation after oncologic treatment, is the current standard care for patients with an intraoral malignancy. Also, many patients are not willing to have implants inserted after oncologic treatment although their prosthodontic rehabilitation would greatly benefit from implant placement[1]. With respect to implant survival, the choice for this treatment approach is supported by the outcomes of the review described in chapter 2 where pooled implant survival rates for primary implant placement showed a slightly higher pooled 5-year implant survival rate (92.8% (95% CI: 87.1-98.5%)) than secondary placed implants (86.4% (95% CI: 77.0-95.8%)).

When considering primary implant placement, there are some differences between implant placement immediately after extraction (immediate placement) and implants placed in an already healed edentulous mandible: 1) The alveolar ridge in immediate placement is extensively reduced in order to create sufficient intermaxillary space, thus there is less cortical bone at the cranial side of the implants contrary to already healed sites. 2) the implants in immediate placement are placed in the alveolus of the previous canines, thus there can be initially less bone to implant contact compared with implants placed in healed bone. These factors could play a role in the osseointegration and loss of immediately placed implants. As there are no other studies on immediate primary implant placement in head and neck cancer patients, a comparison with the literature cannot be made.

Even of more importance than implant survival rates, irrespective of implants placed during ablative surgery, is the involvement of a maxillofacial prosthodontist early in the treatment process in order to safeguard patients' final oral function. The review in chapter 3 focusses on the role of the prosthodontist in every treatment phase (figure 9.1). This involves informing patients of their dental status, the need for pre-radiation extractions, the expected limitations after cancer treatment, and treatment options regarding prosthodontic rehabilitation. Besides informing

the patient, maxillofacial prosthodontists need to be involved in the planning of future implant positions, especially in complex reconstructions. 3D-technologies are a useful tool in enabling a high accuracy of guided surgery and reconstruction planning[2].

Figure 9.1 Involvement of the maxillofacial prosthodontist in treatment planning and rehabilitation of head and neck cancer patients



In chapter 4 the outcome of implants placed in the mandible immediately after removal of all teeth is described. Head and neck cancer patients frequently present with dental foci. When there are no possibilities to safeguard teeth with dental foci on the short run, extraction of the remaining dentition is often advised[3–5]. In the study described in this chapter, the extractions and implant placement took place during ablative surgery or, in case that the patients will be treated with primary radiotherapy, extractions and implant placement took place at least two weeks before starting radiotherapy treatment. Despite the short follow-up period in this study (median follow-up 18.5 months), a tendency towards lower implant survival rates in irradiated patients was observed when compared to non-irradiated patients, a finding also found in other studies on implant placement during ablative surgery and before radiotherapy[1,6–11]. Also, the implants placed in patients who received primary radiotherapy in this study were in the early phase of osseointegration when radiotherapy started (on average 2.9 weeks after insertion), and this could have played a role in the observed implant loss. However, the study population is too small to draw any definitive conclusions on this theory.

Previous studies have suggested that backscattering of radiation could increase the risk of implant loss when implants are placed (shortly) before starting radiotherapy, as was in our study, due to higher irradiation doses in the bone adjacent to the implants[12–14]. This presumption comes from in vitro studies in which it was shown that single direct photo beams cause a dose disturbance in the area around metal surfaces[12,15–17]. The disturbance is caused by a collision of irradiation and metal and is presumed to be the highest in the area close to the metal implant[18,19]. Binger et al. studied the dose disturbances in different types of implants (titanium implants with polished surface, hydroxyapatite coated titanium implants and implants of aluminium oxide ceramics) and found that the scattering effect is the least in implants made of aluminium oxide ceramics[20]. Based on these findings, the authors suggest the use of ceramic implants in head and neck cancer patients. Not only the type of implant material, but also radiation technique can influence the backscattering effect around metal implants. Nowadays, radiation with single direct photon beams has been replaced by modern radiation techniques as VMAT which uses multiple beams and rotation angles. Several in vitro studies (Li, Kamomae and Maerz et al.) have illustrated that VMAT leads to less scattering around metal objects when compared to single photon beams and is also superior to IMRT[21–23]. Whether or not the use of different types of implants (e.g. ceramic implants) leads to better implant survival in patients with oral cancer treated with VMAT or IMPT after implant placement could be a subject of future studies.

Based on the scoping review on optimal timing of implant placement in oral cancer patients (Chapter 2) and supported by one recent systematic review, we and others consider primary implant placement as a viable treatment option for head and neck cancer patients [24]. However, the number of studies on primary implant placement remain scarce and the majority of the studies were performed in The Netherlands[1,6,8,10,11,25]. A possible explanation for the fact that to date most studies were performed in The Netherlands is that the costs of implant placement in head and neck cancer patients is covered by the insurance system in The Netherlands, which is not always the case in other countries. The authors of the only study from outside The Netherlands on primary implant placement stated that implant placement during ablative surgery could only be provided at their institution after a change in the funding system, illustrating how funding effects the treatment being offered to patients[26]. It has to be mentioned, however, that a consequence of our system, where we provide all patients with an intraoral malignancy with endosseous implants in the interforaminal area of the mandible, is the loss of resources because not all patients will be provided with a functioning prosthesis and some implants will never be used. In our study (chapter 4), no functional implant-retained prosthesis

could be made in 9 out of 29 patients due to tumour recurrence in the implant region or metastatic tumour growth, implant loss, or severe pain in the implant area. From a cost-effectiveness point of view, opponents of primary implant placement can state that implant placement in all edentulous mandibles is ineffective patient care. Nevertheless, we believe that as long as patients are being treated with curative intent for their oncologic disease, adequate and early treatment with dental implants should be part of the treatment plan, because of earlier rehabilitation of oral function and a possible increase in (oral health related) quality of life[8,11,27].

In chapter 5, the outcomes of a large cohort of patients with implants in craniofacial regions are presented. The main results indicate that on the long-term, patients can benefit greatly from the implants to retain craniofacial prostheses. The craniofacial defects (mastoid, nasal and orbital regions) resulted from congenital disease, trauma, or oncologic treatment. The implant survival rate was the lowest in patients with oncological defects, especially radiotherapy has a negative effect as is in line with the literature[28–32]. Because exact radiation dosages on the implant region could not be retrieved for several patients, no statement can be made on the specific radiation dose in relation to implant survival in the various implant locations. Implants placed in orbital regions show the worst implant survival rates, also a well-known fact reported in other studies, most probably a result from the poorer bone quality and limited bone volume in the orbital region[28,29,33]. Not only bone quality and volume, but also factors as decreased hygiene due to monocular vision, and the inability to create only axial loading of the fixtures due to the positioning of implants might play a role in the poorer prognosis of orbital implants. Implant placement in the nasal region at our treatment center was introduced several years after implants were inserted in the orbital and mastoid regions, and these implants also show stable and high survival rates. It has been suggested in two earlier studies that the nasal aperture seems less likely to be effected by ionizing radiation, a finding we also observed in our study[33,34]. However, the results of nasal implants in literature are conflicting and the systematic review of Chrcanovic et al. concluded that nasal implants perform worse than implants in other locations, because of difficult surgical access in combination with the loose trabecular bone of the nasal floor[29]. In our treatment center the available bone height and angulation of the implants is assessed preoperatively in order to guarantee correct placement[34]. The preoperative planning and insertion of implants during ablative surgery, which usually provides plenty of surgical access, could explain the favourable survival rates of nasal implants found in our study.

Regarding the timing of implant placement, no difference in implant survival was found between implants placed during ablative surgery and after completion of oncologic treatment. As implant placement during ablative surgery is standard care at our institution, the majority of implants were placed in this fashion and secondary placement is only performed when patients were treated elsewhere without implants, or when loss of (a) previous implant(s) lead(s) to insufficient retention of the prosthesis. The latter was only necessary in 26.2% of lost implants. The choice whether or not an implant is replaced is made on an individual level, taking into consideration the need for additional retention in combination with the quality and volume of the available bone, the prognosis of the patient, and the received radiation dose on the implant area. Careful deliberation within the multidisciplinary team is especially required in these cases.

The 62 out of the initial 220 patients who were still in clinical follow-up (chapter 5) showed no signs of active infection in the implant region in the majority of patients. From earlier studies it is known that skin reactions are often mild provided that a daily cleaning regimen is followed. Active infection around implants occurred most frequently in the orbit and nasal regions, possibly due to local anatomy which makes cleaning in those regions more challenging. Irradiated patients showed more peri-implant skin reactions in contrast to findings in the study of Visser et al.[35]. To what extent these conflicting results are influenced by other factors such as selfcare and/or the manufactured retention system, is unclear. In a study on selfcare in patients with craniofacial prostheses, no statistically significant differences were seen in the prevalence of soft tissue reactions in groups with different retention systems[36]. However, in that study the skin reactions were reported by patients themselves and not assessed clinically. The patients may need help from others with cleaning the skin around the implants, especially in older age groups[36-38]. As patient populations continue to grow older, it can be interesting to see how age or frailty influences the selfcare routine and the development of skin reactions around implants. Although patients in several studies seem satisfied with their prostheses, more studies are needed to identify patients' challenges when using their prosthesis in order to further improve prostheses materials.

In chapter 6, a study is described in which the dosimetric differences between volumetric modulated arch therapy (VMAT) and intensity modulated proton beam therapy (IMPT) on the tooth-bearing regions was assessed in a cohort of head and neck cancer patients. This study illustrates how IMPT significantly can reduce the cumulative radiation dose on the upper and lower jaw when compared to VMAT. The reduction in radiation dose is most striking for nasopharynx, hypopharynx, and

larynx tumours and least impressive for tumours located in the oropharynx and oral cavity. This is not surprising as oropharynx and oral cavity tumours are in closer proximity to the teeth and thus will result in more ionizing radiation to the teeth. The study also shows how the various radiation dosages (for VMAT and IMPT) are spread across the jaw for different tooth locations (ipsi- and contralateral molars and premolars, and teeth in the anterior region). Earlier studies have reported on the dosimetry of VMAT and the dosimetric benefits of IMPT for the dentition, but the current study is the only article to perform the dose comparison within the same patient[40–44].

Also the calculated risk scores and probability curve for an expected radiation dose can aid the dental clinician in determining whether a particular dental focus needs to be extracted before starting radiotherapy, or whether treatment of the focus can take place at a later stage. To our knowledge, the study of Tsai et al. is the only other study generating a risk model for expected radiation dose on the teeth, but the authors only included patients with carcinomas of the tonsil[44]. Since the exact dose points on the teeth are provided by the radiation oncologist, the dentists at our treatment center performing the pre-radiation dental screening, have made a shift in treatment approach of dental foci. Previously, all dental foci were removed before radiotherapy because the exact dose on the teeth was not yet known at the time of the screening. Now an earlier risk assessment can be performed resulting in a more tailored approach and thus preventing unnecessary pre-radiation dental extractions[45–48]. Whether or not the increased deliberation between the dentists and radiation oncologist also leads to a better dental status or a decreased risk of developing osteoradionecrosis needs to be assessed in the future.

In chapter 7, a study is described analysing how the exact dosimetrics on the implant region influences survival of implants placed in the edentulous mandible during ablative surgery. From earlier studies on the development of osteoradionecrosis, we know that the risk of developing problems with bone healing or osteoradionecrosis increases with higher radiation dosages[49,50]. For osseointegration of dental implants the same presumption exists. Despite the relatively short follow-up period in this study, a threshold of 50 Gy was found for increased peri-implant bone loss. The dose response relationship between implant loss and increasing radiation dose levels was not yet statistically significant, which is probably due to the small study population. In other studies also using site-specific radiation dosages, radiation dosages of 40-50 Gy were found as a significant risk factor for implant loss[51-53]. Several animal studies have shown that radiotherapy has a negative effect on peri-implant bone regeneration, although sufficient osseointegration can be

achieved[54-56]. More recently, spectroscopic and quantitative studies of irradiated bone samples of human mandibles in humans have been published[57-60]. These studies show decreased vascularity, early death of osteocytes and osteoblasts leading to a decrease in bone turnover with a critical threshold of 50 Gy leading to more detrimental effects. However, in these studies the bone biopsies were taken from previously irradiated patients with different intervals from radiotherapy to biopsy and some patient were treated with a regimen of hyperbaric oxygen therapy, making it difficult to extrapolate the findings to our study population. Based on the results described in this chapter, we conclude that in order to maximize patients' possibilities for prosthodontic rehabilitation, the radiation dose on the implant regions needs to be <50 Gy.

LIMITATIONS AND SUGGESTIONS FOR FURTHER RESEARCH

Although the application of endosseous implants in head and neck cancer patients is regularly practiced and well-documented, the majority of available evidence in this patient category is characterized by small and heterogeneous study populations, retrospective study designs, and short-term follow-up periods, an issue addressed in several systematic reviews[24,33,61]. These variables make the relevance of literature findings difficult to interpret. Partly, this is a consequence of the characteristics of the study population which often consists of frail patients with a reduced life expectancy due to their disease, comorbidity or lifestyle leading to losing patients in follow-up. In the literature there is also inconsistent use of terminology describing the timing of implant placement.

In order to overcome these challenges and to allow for better quality future studies, we propose the following implementations in reporting the implant and prosthodontic treatment of head and neck cancer patients:

- The use of consistent terminology regarding implant placement in head and neck cancer patients:
    - Immediate implant placement: Placement of implants immediate after tooth extraction[62]
    - Primary implant placement: Placement of implants during ablative surgery
    - Secondary implant placement: Placement of implants after oncologic treatment (surgery and/or radiotherapy).
- Routinely (yearly) collection of data on patient-reported outcomes with standardized questionnaires.

- Routinely (yearly) x-rays and collection of clinical data such as plaque and bleeding indices around placed implants.
- Providing implant-specific radiation dosages for all patients.

When the abovementioned limitations are solved, the following topics of interest can be addressed in retrospective and the future prospective studies:

- Bone biology experiments in animals, and when possible in human, to get a better understanding of how radiation therapy influences implant osseointegration for implants placed several weeks before irradiation starts.
- Studies assessing the effect of backscattering around titanium implants for VMAT and IMPT.
- Long-term results (at least 5 years) on implant survival in relation to site-specific radiation dose.
- The insertion of implants in a single stage, thereby reducing the need for an additional procedure.
- A study assessing patients' wishes regarding the use and aesthetics of craniofacial prostheses.
- A study assessing whether increased deliberation between dentists and radiation oncologists and patient-specific choices made after pre-irradiation dental screening lead to an increased dental status in head and neck cancer patient and a decreased risk of developing osteoradionecrosis.

CONCLUSIONS

Based on the studies in this thesis, the following conclusions can be drawn:

- Patients with oral cancer greatly benefit from primary placed dental implants and this should be provided as standard care for the edentulous mandible or immediately after removal of all teeth in the mandible.
- Involvement of maxillofacial prosthodontists in a multidisciplinary team is crucial to maximize patients' prosthodontic rehabilitation.
- Implants used to retain craniofacial prosthesis are a predictable treatment option on the long term.
- IMPT can significantly reduce the radiation dose to tooth-bearing regions.
- Primary placed implants in the mandible which are exposed to >50 Gy of radiation, may be more prone to implant loss.

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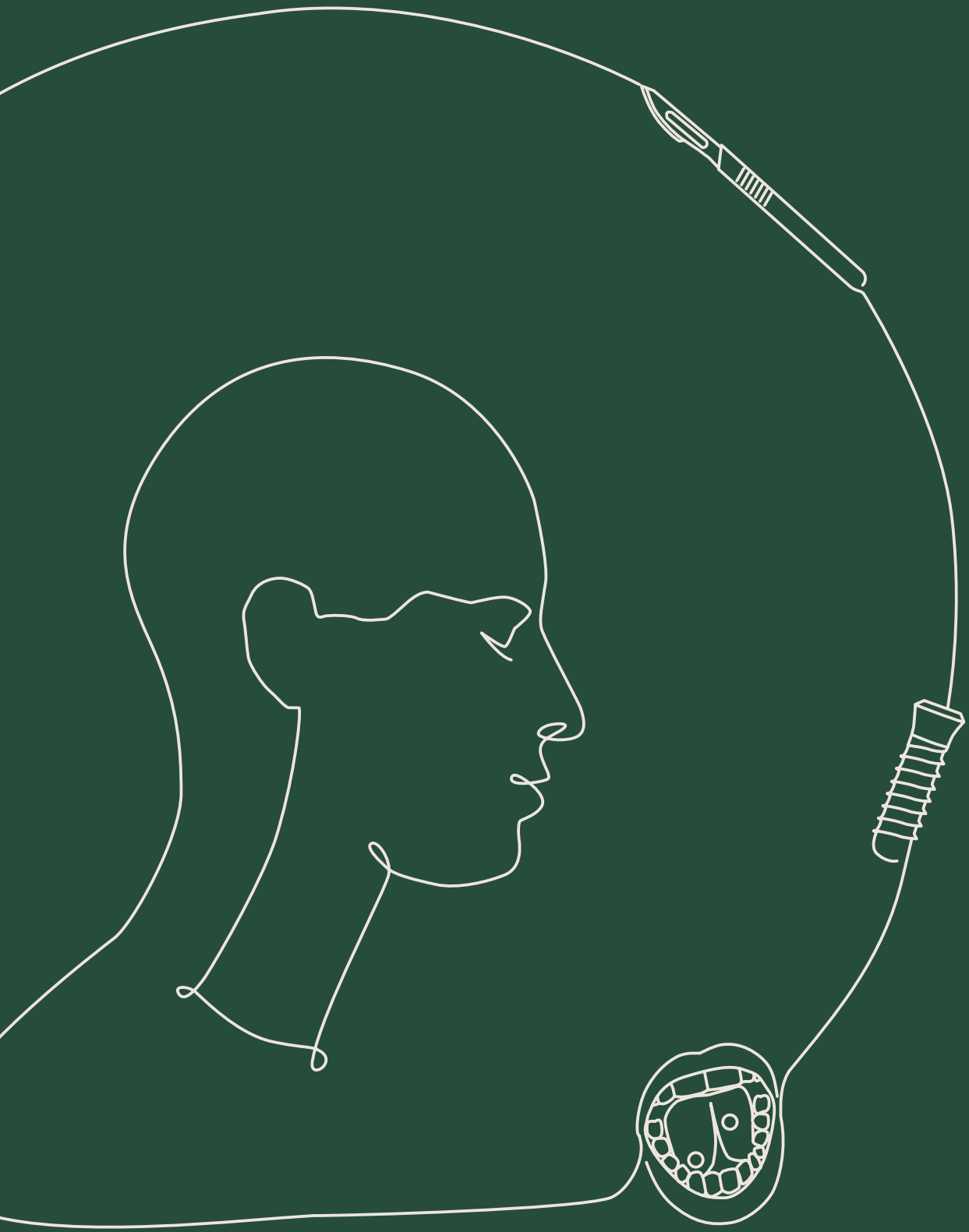

Appendices

SUMMARY

Implant placement for the retention of a prosthesis has proven to be a valuable treatment option in the rehabilitation of patients treated for head and neck cancer (**Chapter 1**). Implants for intraoral prostheses can be placed in the upper and lower jaw. The most common locations for craniofacial prostheses are the temporal bone (mastoid), the orbital rim, and the nasal floor. Implants can be placed during ablative surgery (primary placement) or after completion of oncological treatment (secondary placement). The general aim of this thesis was to gain insight into factors that may determine the rehabilitation of head and neck oncology patients with implant-supported prostheses.

In **Chapter 2**, current knowledge on the optimal timing of implant placement in oral cancer patients is described in a scoping review. A literature search was conducted in MEDLINE. Inclusion criteria were studies published in English regarding primary or secondary implant placement in oral cancer patients, cohort studies, case-control studies, and (randomized) controlled trials. The primary outcome was 5-year implant survival rate. 16 studies providing data on 4449 implants were included. Quantitative data-synthesis was performed for the studies reporting 5-year dental implant survival rates of primary placed implants and secondary placed implants. Studies which did not report on the 5-year implant survival rate were not included in the quantitative analysis. The pooled 5-year survival rate for primary placed implants was 92.8% (95% CI: 87.1%–98.5%), while the pooled implant survival rate for secondary placed implants was 86.4% (95% CI: 77.0%–95.8%). In conclusion, based on the findings in this review, we propose to combine tumour surgery with implant placement in native mandibular bone as standard care (primary implant placement).

Chapter 3 highlights the role of the maxillofacial prosthodontist in the rehabilitation of head and neck cancer patients and addresses challenges and new developments in the treatment of these patients. Early involvement of the maxillofacial prosthodontists in the care pathway is essential in order to outline and coordinate the prosthetic and dental rehabilitation with the oncologic treatment. Although at the first-day consultation the extent of the final oncologic treatment plan is uncertain, at this stage the maxillofacial prosthodontist should already estimate whether patients are in need of a prosthetic rehabilitation simultaneously with reconstructive surgery or after completion of cancer therapy, and what the patients' desires are. An early decision on the need to place implants to support the prosthodontic rehabilitation is important. Furthermore, with the introduction

of 3D planning and computer-aided design (CAD) assistance, preoperative virtual augmentation models are an asset to the surgical team and support shared decision-making regarding favourable reconstruction. It is expected that 3D technology can help improve the quality of cancer care and can contribute to enhance the quality of life of cancer survivors.

Subsequently, in **Chapter 4** a study is described in which implants were placed in the mandible immediately after tooth extraction (immediate implant placement) during ablative surgery or before radiotherapy. Implant survival and functional outcomes of implant-supported overdentures were assessed. Inclusion criteria were primary head and neck cancer, dentate lower jaw and indication for removal of remaining teeth. For this study, 29 patients received 2 implants in the interforaminal area. Median follow-up was 18.5 months, (Q1 13.5; Q3 26.8 months). Four implants were lost (implant survival rate 93.1%). In 9 patients, no functional overdenture could be made. All patients with an overdenture were satisfied with their dentures. It was concluded that combining dental implant placement with removal of remaining teeth preceding head and neck oncology treatment results in a favourable treatment outcome.

In **Chapter 5**, a cohort of patients with implants to retain a craniofacial prosthesis in the mastoid, nasal or orbital region is described. Patients had craniofacial defects resulting from congenital disease, trauma, or oncologic treatment and were assessed over a period of up to 30 years (median follow-up was 71 months (Q1 28; Q3 174 months)). Implant survival rates were calculated with the Kaplan–Meier method and possible risk factors for implant loss were identified. Clinical assessments consisted of scoring skin reactions under the prosthesis and the peri-implant skin reactions. Patient satisfaction was evaluated using a 10-point VAS-scale. 201 patients with 525 implants were included. Implants placed in the mastoid and nasal region showed the highest overall implant survival rates (10-year implant survival rates of 93.7% and 92.5%, respectively), while the orbital implants had the lowest overall survival rate (84.2%). Radiotherapy was a significant risk factor for implant loss (hazard ratio 3.14, $p < 0.001$). No differences in implant loss were found between implants placed before and after radiotherapy ($p = 0.89$). Soft tissue problems were not frequently encountered, and the patients were very satisfied with their implant-retained prosthesis.

The dosimetric differences on the tooth-bearing regions between volumetric modulated arch therapy (VMAT) and intensity modulated proton beam therapy (IMPT) are described in **Chapter 6**. A second goal of the study was to identify

prognostic factors for receiving a cumulative radiation dose of ³40 Gy on the tooth-bearing areas, which is considered the threshold dose for prophylactic dental extractions. 121 head and neck cancer patients were included. Average D_{mean} values of IMPT versus VMAT were compared within the same patients. Multivariate logistic regression analysis was performed for receiving a cumulative radiation dose of ≥40 Gy to the tooth-bearing regions (primary endpoint). A lower D_{mean} was seen after applying IMPT to the tooth-bearing tumour regions ($p<0.001$). The difference between VMAT and IMPT was less impressive for patients with a tumour in the oral cavity. VMAT, oral cavity tumours, T3-T4 tumours, molar regions in the mandible, and regions ipsilateral to the tumour were risk factors for receiving a cumulative radiation dose of ≥40 Gy. It was concluded that IMPT significantly reduces the radiation dose to the tooth-bearing regions in the upper and lower jaw.

The study described in **Chapter 7** assessed the radiation dosages (D_{mean}) on the implant regions and aimed to identify the threshold for implant loss in patients with an intraoral malignancy treated with dental implants to support a mandibular denture during ablative surgery before volumetric modulated arc therapy (VMAT). 28 patients with an intraoral malignancy treated with surgery followed by postoperative radiotherapy (VMAT) were included. Patients received 2 implants in the native mandible during ablative surgery for an implant-supported mandibular prosthesis. Implant-specific D_{mean} values were retrieved from patient files. Radiographically, bone loss was measured one year after implant placement and during the last follow-up appointment. Implant survival was analysed with the Kaplan-Meier method. A univariate logistic regression analysis and Cox-regression analysis was performed to investigate the effect of increasing implant-specific radiation dosages on implant loss. Five out of the 56 placed implants were lost during follow-up (median 36.0 months, Q1 26.0; Q3 65.0 months). Radiographically, peri-implant bone loss occurred in implants with a D_{mean} >40 Gy. Implant loss occurred only in implants with a D_{mean} >50 Gy. A tendency towards increasing bone loss levels during follow-up was observed. Based on the results of this study it was concluded that an implant-specific D_{mean} higher than 50 Gy is related to more peri-implant bone loss and eventually implant loss.

In **Chapter 8,** the studies are discussed in broader context. Based on the chapters in this thesis the following conclusions can be drawn:

- Patients with a tumour in the oral cavity can greatly benefit from primary placed implants in the lower jaw. This treatment option should be routinely offered to patients who are edentulous or will become edentulous in the lower jaw.
- Early involvement of the maxillofacial prosthodontist is crucial to guarantee the prosthetic and prosthodontic rehabilitation of head and neck cancer patients.
- Implants for the retention of a craniofacial prosthesis are a reliable treatment option, also on the long term.
- IMPT reduces the radiation dose to the tooth-bearing regions in the upper and lower jaw.
- Primary placed implants in the lower jaw which receive an implant-specific radiation dose of >50 Gy after placement are more at risk for implant loss.

SAMENVATTING

Het plaatsen van enossale implantaten ten behoeve van de prothetiek is een waardevolle behandeling gebleken in de rehabilitatie van patiënten die zijn behandeld vanwege een hoofd-hals tumor (**hoofdstuk 1**). Implantaten voor intraorale implantaatgedragen prothesen kunnen zowel in de boven- als onderkaak worden geplaatst. Voor craniofaciale prothesen zijn de meest voorkomende locaties het rotsbeen (mastoïd), de oogkas (orbita) en de neusbodem. Het plaatsen van implantaten kan tijdens de ablatieve chirurgie plaatsvinden (primaire behandeling) of na afronden van de oncologische behandeling (secundaire behandeling). Het algemene doel van het onderzoek van het onderzoek beschreven in dit proefschrift was het verkrijgen van inzicht in factoren die de rehabilitatie van hoofd-hals oncologie patiënten met implantaatgedragen prothesen kunnen bepalen.

Een van de factoren die van invloed is op de rehabilitatie van hoofd-hals oncologie patiënten is de timing van het plaatsen van implantaten. In **hoofdstuk 2** wordt de uitkomst van een literatuuroverzicht gepresenteerd over primair en secundair geplaatste implantaten beschreven. De primaire uitkomstmaat was 5-jaars implantaatoverleving. 16 studies werden geïncludeerd. Op basis van de kwantitatieve analyse werd een hogere 5-jaars implantaatoverleving gevonden voor primair geplaatste implantaten (92.8% (95% CI: 87.1%–98.5%)) dan voor secundair geplaatste implantaten (86.4% (95% CI: 77.0%–95.8%)). Niet alleen vanwege de verhoogde implantaatoverleving, maar ook vanwege de andere voordelen van primaire implantaat plaatsing (snellere prothetische rehabilitatie, mogelijk toegenomen kwaliteit van leven) wordt geadviseerd om ablatieve chirurgie standaard te combineren met het plaatsen van implantaten in de edentate onderkaak.

Behalve de implantaatoverleving, onafhankelijk of de implantaten primair of secundair worden geplaatst, is de rol van de tandarts maxillofaciale prothetiek (tandarts MFP) erg belangrijk voor het resultaat van de prothetische behandeling. Vroege betrokkenheid van de tandarts MFP zorgt ervoor dat de patiënt al vroeg in het behandeltraject een beeld krijgt van de prothetische (on)mogelijkheden en de diverse behandelingen die daarvoor nodig zijn. Het belang van de tandarts MFP en de voordelen van 3D technologie voor de planning en prothetische behandeling worden beschreven (**hoofdstuk 3**). De verwachting is dat met behulp van 3D technologie de prothetische uitkomst en daarmee de kwaliteit van leven van hoofd-hals oncologie patiënten kan verbeteren.

In **hoofdstuk 4** wordt de uitkomst van implantaten die werden geplaatst in de onderkaak direct na het uitvoeren van een totaalextractie in het te implanteren gebied (immediate plaatsing van implantaten) beschreven. De behandeling vond plaats tijdens ablatieve chirurgie en/of voor behandeling met radiotherapie. 29 patiënten werden geïncludeerd en deze ontvingen elk 2 implantaten in het interforaminale gebied ten behoeve van een overkappingsprothese in de onderkaak. Mediane follow-up was 18.5 maanden (Q1 13.5; Q3 26.8 maanden). 4 implantaten gingen verloren tijdens de follow-up periode. De implantaatoverleving was 93.1%. Een functionele overkappingsprothese kon niet worden vervaardigd in 9 patiënten. Alle patiënten met een functionele overkappingsprothese waren tevreden over de functie van hun prothese. De conclusie van het onderzoek was dat het combineren van een totaalextractie met het plaatsen van 2 implantaten in de edentate onderkaak een geschikte behandeloptie is.

Doel van het in **hoofdstuk 5** beschreven onderzoek was het bepalen van de (lange termijn) uitkomsten van implantaten geplaatst in craniofaciale gebieden ten behoeve van de retentie van een craniofaciale prothese, alsmede het identificeren van risicofactoren voor implantaatverlies. Tevens werd de peri-implantaire huid klinisch gescoord bij een subgroep van patiënten die beschikbaar was voor follow-up. De tevredenheid over de implantaatgedragen prothese werd gescoord met behulp van een 10-punts VAS score. 201 patiënten met in totaal 525 implantaten werden geïncludeerd voor de analyse naar implantaatoverleving. De mediane follow-up was 71 maanden (Q1 128; Q3 174 maanden). Implantaten geplaatst ten behoeve van een implantaatgedragen oorprothese en neusprothese toonden de hoogste overleving (10-jaars implantaatoverleving van respectievelijk 93.7% en 92.5%). Implantaten geplaatst voor retentie van een orbitaprothese bleken de laagste overleving te hebben (84.2%). Radiotherapie was een duidelijke risicofactor voor implantaatverlies (HR 3.14, p>0.001) en er werd geen verschil gevonden in overleving van implantaten die voor of na radiotherapie werden geplaatst. Problemen met de huid deden zich weinig voor en patiënten waren over het algemeen tevreden met hun prothese. Uit het onderzoek werd geconcludeerd dat het plaatsen van implantaten voor craniofaciale prothesen ook op de lange termijn een goede behandeloptie is.

Tegenwoordig wordt naast bestraling met fotonen ook bestraling met protonen toegepast bij hoofd-hals oncologie patiënten. De dosisverschillen tussen fotonen en protonentherapie op de tanden van de boven- en onderkaak worden beschreven in **hoofdstuk 6**. Daarnaast werd gepoogd om factoren te identificeren voor het ontvangen van een cumulatieve stralingsdosis ≥40 Gy; een grenswaarde die

wordt gehanteerd voor het uitvoeren van extracties voor start van de bestraling en een waarde waarbij wordt aangenomen dat het risico op het ontwikkelen van osteoradionecrose verhoogd is. 121 patiënten werden geïncludeerd in de studie. Gemiddelde dosiswaarden voor fotonen- en protonentherapie werden met elkaar vergeleken binnen dezelfde patiënt. De dosisvergelijking liet zien dat sprake was van een lagere stralingsdosis op de tanden als patiënten behandeld zouden worden met protonen. Het verschil tussen fotonen en protonen was het minst uitgesproken voor patiënten met een tumor in de mondholte. De regressieanalyse liet zien dat behandeling met fotonen, mondholte tumoren, T3-T4 tumoren, elementen in de molaarstreek van de onderkaak en gebieden ipsilateraal aan de tumor risicofactoren zijn voor het ontvangen van een stralingsdosis van 40 Gy of meer. De conclusie van het onderzoek was dat behandeling met protonentherapie leidt tot een significante reductie in straling op de tanden en kiezen van de boven- en onderkaak.

In **hoofdstuk 7** wordt een onderzoek beschreven over de invloed van de implantaat-specifieke stralingsdosis op de overleving van implantaten geplaatst in de edentate onderkaak tijdens de ablatieve chirurgie. Doel van het onderzoek was het identificeren van een grenswaarde voor een verhoogd risico op implantaatverlies. 28 patiënten werden geïncludeerd en 2 implantaten werden geplaatst in de edentate onderkaak ten behoeve van een implantaatgedragen overkappingsprothese. De implantaat-specifeke stralingsdosis, het peri-implantaire botniveau 1 jaar na het plaatsen van de implantaten en de implantaatoverleving werden geanalyseerd. 5 van de 56 geplaatste implantaten gingen verloren tijdens de follow-up periode (mediane follow-up 36.0 maanden, Q1 26.0; Q3 65.0 maanden). Implantaatverlies werd in deze studie alleen gezien voor implantaten met een stralingsdosis van meer dan 50 Gy.

In **hoofdstuk 8** worden de resultaten van voorgaande studies verder bediscussieerd. Op basis van de bevindingen uit de onderzoeken kunnen de volgende conclusies worden getrokken:

- Patiënten met een tumor in de mondholte kunnen veel baat hebben bij primair geplaatste implantaten in de onderkaak. De behandeloptie zou standaard aangeboden moeten worden voor patiënten die edentaat zijn of edentaat worden in de onderkaak.
- De rol van de tandarts MFP in het behandelteam is van cruciaal belang om de kans op een goede prothetische rehabilitatie te waarborgen.
- Implantaten voor de retentie van een craniofaciale prothese zijn een betrouwbare behandeloptie, ook op de lange termijn.

- Bestraling met protonen zorgt voor een dosisreductie op de tanddragende gebieden van de boven- en onderkaak.
- Primair geplaatste implantaten in de onderkaak die een stralingsdosis >50 Gy ontvingen hebben een grotere kans om verloren te gaan.

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Jamie lives together with Nick Tjon A Tjieuw and their son Oliver in Eelderwolde.

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