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Dental implants in maxillofacial prosthodontics

An asset in head and neck cancer and Sjögren's syndrome patients

Anke Korfage

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Contents

Chapter 1

Introduction and aim of the study

Introduction

Maxillofacial prosthodontics is the discipline that concerns the prosthetic rehabilitation of patients with acquired and congenital defects of the head and neck (Beumer 3rd et al. 2011). Examples of such patients are head and neck cancer patients, patients with defects as a result of trauma and cleft patients. The prosthetic rehabilitation of these patients is challenging, particularly when aiming for optimal facial aesthetics and oral functioning (speech, chewing, swallowing). Furthermore, maxillofacial prosthodontists are involved in the dental care of patients with a compromised immune status, such as Sjögren's patients. Currently, dental implants play an important role in the multidisciplinary rehabilitation of patients with a compromised intraoral and/or extraoral condition (Beumer 3rd et al. 2011). Implants are used for retention of a large variety of prostheses, such as full dentures, single tooth replacements and craniofacial prostheses. Treatment planning of compromised patients, particularly when including implant-retained prostheses, should be performed in a multidisciplinary team, aiming for optimal rehabilitation of the patient, with the prosthodontist being involved from the intake of the patient until the final prosthetic rehabilitation. Next, prosthodontists play an important role in the aftercare of these patients (Visser 2009).

With regard to head neck cancer patients, conventional prosthetic rehabilitation is often challenging (Hayter & Cawood 1996, Marker et al. 1997, Misiek & Chang 1998, Schoen et al. 2007, Tang et al. 2008). Yet, adequate prosthetic rehabilitation is a crucial factor for these patients to regain oral functions that are lost due to the intra- or extraoral defect and/or compromised oral condition (Kamstra et al. 2011). E.g., when a tumour is located in the oral cavity, its surgical resection has a profound effect on oral functions such as chewing, swallowing and speech intelligibility. In addition, when postoperative radiotherapy is needed, oral functioning is usually further compromised due to the resulting xerostomia and intolerance of the denture-bearing mucosa to mechanical loading (Beumer 3rd et al. 1995, Kwakman et al. 1997, Visch et al. 2002, Vissink et al. 2003).

When being provided with implant-retained prostheses, it is presumed that many head and neck cancer patients will experience an improved level of oral functioning (Schoen et al. 2008, Tang et al. 2008). It has to be mentioned, however, that many patients postpone or simply decline an offered implant-based treatment after tumour surgery and postoperative radiotherapy notwithstanding the great benefits patients can expect from implant-retained prostheses (Kwakman et al. 1997, Schoen et al. 2008, Mizbah et al. 2013). To let more patients benefit from implant-retained prostheses, it is therefore advocated to insert the implants already during ablative surgery (primary implant insertion; Urken et al. 1989, Sclaroff et al. 1994, Schepers et al. 2006, Schoen et al. 2008, Mizbah et al. 2013). Although the early results of primary implant insertion, as mentioned in these studies, are very promising (Barber et al. 2011), systematic reviews show that to date most publications on dental implants in oral cancer patients are still on implants inserted after the surgery and/or radiotherapy has been completed. Besides that, studies reporting on primary

implant insertion are often of retrospective design (Colella et al. 2007, Barber et al. 2011, Chrcanovic et al. 2014). Thus, it remains unclear whether the benefits of primary implant insertion outweigh the risk that implants will not be used for prosthetic rehabilitation, which indeed is the case in about 10-25% of the patients with primary mandibular implants (Schoen et al. 2008, Schepers et al. 2006, Mizbah et al. 2013).
Therefore, further study is needed to estimate which head and neck cancer patients can benefit from primary implants. Does it, e.g., depend on the primary location of the tumour, the tumour size, if the patient is irradiated and/or the type of reconstructive surgery? Furthermore, insight is needed whether oral functioning, patients' satisfaction and quality of life related to implant-retained prostheses is also beneficial in the long term in head and neck cancer patients with primary mandibular implants.
Besides for intra-oral prosthetic rehabilitation in head and neck cancer patients, implants are also used in the rehabilitation of patients with extraoral defects (ear, nose, orbit). Surgical reconstruction of such defects is difficult or even impossible to perform (orbit) and the outcome of such reconstructions has not been described for large patient numbers. Furthermore, treatment of a local tumour recurrence may necessitate removal of the surgical reconstruction. A major advantage of rehabilitation with extra-oral prostheses is that the defect resulting from ablative tumour surgery can be observed in total, allowing for thorough oncological inspections (Ariani et al. 2013). While there is ample evidence that implant-retained prostheses serve very well for replacing missing ears and eyes, there is still a lot of concern how to optimally restore a nasal defect with implant-retained prostheses (Parel et al. 1986, Lundgren et al. 1993, Granström et al. 1994, Roumanas et al. 1994, Nishimura et al. 1996, Tolman & Taylor 1996, Flood & Russell 1998, Roumanas et al. 2002, Visser et al. 2008, Karayazgan-Saracoglu et al. 2010, Ethunandan et al. 2010, Dings et al. 2011, Curi et al. 2012). E.g., treatment protocols how to insert implants for implant-retained nasal prostheses vary largely. There is no consensus with regard to implant location, type and length of implants and how to treat irradiated and non-irradiated patients and edentulous and dentate patients. Also the need for aftercare and the satisfaction experienced by the patients are hardly established (Nishimura et al. 1996, Flood & Russell 1998, Ethunandan et al. 2010).
Besides head and neck cancer patients and patients with facial defects, the prosthetic rehabilitation of patients with a compromised immune status can be challenging as well. Particularly Sjögren's patients can suffer from severe problems with oral functioning, as well as that wearing conventional dentures on their dry and tender mucosal surfaces is very uncomfortable. Currently, there is some evidence that systemic conditions and their therapy, e.g., rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), osteoporosis and corticosteroid therapy, are no longer considered as risk factors for successful osseointegration of dental implants (Slagter et al. 2008, Diz et al. 2013, Clementini et al. 2014). With regard to Sjögren's syndrome the sparse evidence for insertion of dental implants is mainly from case-reports and small case-series (Payne et al. 1997, Isidor et al. 1999, Binon 2005, Spinato et al. 2010, Krenmair et al. 2010).

Aim of the study

The overall aim of this PhD study was to assess the treatment outcome of implant therapy in patients with a compromised intra- or extraoral condition.

The specific aims were:

- to assess the long term results of prospective studies on mandibular implants in oral cancer patients installed during ablative tumour surgery, focussing on oral functioning, quality of life, denture satisfaction, peri-implant health and implant survival (Chapter 2);
- to describe the use of implants in patients treated for rhabdomyosarcoma during childhood (Chapter 3);
- to assess the clinical outcome, the need for surgical and prosthetic aftercare, and satisfaction of patients provided with implant-retained nasal prostheses (Chapter 4);
- to assess the clinical outcome of implant therapy in a cohort of well-classified patients with Sjögren's syndrome compared with healthy controls (Chapter 5).

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Chapter 2

Long-term results of mandibular implants installed in oral cancer patients during ablative tumour surgery

This chapter is an edited version of:
Anke Korfage, Pieter J. Schoen, Gerry M. Raghoebar, Jelte Bouma, Fred R. Burlage, Jan L.N. Roodenburg, Arjan Vissink, Harry Reintsema. A 5-year follow-up of oral functioning and quality of life in oral cancer patients with implant-retained mandibular overdentures. Head and Neck 2011; 33(6): 831-839

Chapter 2.1

A 5-year follow-up of oral functioning and quality of life in oral cancer patients with implant-retained mandibular overdentures

Abstract

Background

This prospective study assessed the quality of life (QoL) and oral functioning of oral cancer patients up to 5 years after prosthodontic rehabilitation with mandibular implant-retained overdentures.

Methods

Fifty patients who had received implants during ablative surgery were evaluated by standardized questionnaires before and after oncological and prosthetic treatment.

Results

In 20 of the 24 surviving patients, the dentures were in function after 5 years. In these survivors, oral function remained unchanged during this period. In the 6 patients with concurrent comorbidity, global health and QoL had deteriorated, while in the patients without comorbidity global health and QoL were very high. Five-year survivors had a higher global health and better oral functioning at the 1-year evaluation than non-survivors.

Conclusion

Oral function and denture satisfaction were high and did not change over time for survivors. Deterioration in overall global health and QoL was associated with concurrent comorbidity.

Introduction

Prosthodontic rehabilitation in oral cancer patients is challenging as oral functioning is hampered due to the surgical treatment and the subsequent radiotherapy. As a consequence of this combined treatment, wearing a mandibular prosthesis is severely impeded due to the changed anatomical conditions and the intolerance of the denture-bearing mucosa to mechanical loading.[1-4] A solution for this problem might be to provide the patients an implant-retained mandibular overdenture. Implant survival in irradiated mandibles, although in general lower than in healthy patients, has been shown to be still relatively high in most articles shown in the literature, and patients have reported an improved level of oral functioning when being provided with such a denture.[5-13] Also, assessment of the effect of such a treatment on patients' functioning and overall quality of life (QoL) is of the utmost importance.[14-20]

In healthy subjects, no clinically relevant changes in oral functioning and patient satisfaction are to be expected after the first year of prosthodontic rehabilitation with an implant-retained overdenture.[21-22] In oral cancer patients, it is questionable whether this is also applicable, or whether the remaining side effects of the oncological treatment and the impact of having had cancer are more prominent and veil the beneficial effect of an adequate prosthodontic rehabilitation on oral function and QoL. Thus, the purpose of this prospective study was to assess oral functioning and QoL in patients with oral cancer in whom implants had been installed during ablative tumour surgery, up to 5 years after prosthodontic rehabilitation with implant-retained mandibular overdentures.

Materials and methods

Patients and treatment

All consecutive edentulous patients with oral cancer referred to the Head and Neck Oncology group of the University Medical Center Groningen between May 1998 and April 2002 were screened to be included in this study. Inclusion criteria were edentulous upper and lower jaw, history of prosthetic problems related to lack of stability and retention of the lower denture or expected denture-related problems after oncology treatment, first malignancy in head and neck region (squamous cell carcinoma of tongue, floor of the mouth, mandibular gingiva, buccal mucosa, or oropharynx) and the need for primary ablative surgery. The patients were screened by an experienced maxillofacial surgeon (G.M.R.) and prosthodontist (H.R.). It was required that little or no improvement was to be expected from making new dentures after oncological treatment. Patients were offered conventional or implant-based treatment. Fifty-three patients fulfilled the inclusion criteria and 50 patients accepted the option of implant installation during ablative surgery. Two patients refused to have implants installed and 1 patient had never worn a prosthesis. Informed consent was provided from all patients before treatment.

Tumour surgery and implant insertion were performed at the University Medical Center Groningen. All implants (3.75 mm Brånemark screw implants with a machined surface, Nobelbiocare, Gothenburg, Sweden) were inserted during the ablative tumour surgery procedure. All implants were placed in the interforaminal region of the native bone of the mandible in a 2-stage surgical procedure. A 3-month osseointegration period before abutment connection was considered in patients not having radiotherapy after tumour surgery (18 patients). If postoperative radiotherapy was scheduled (32 patients), in general, starting within 6 weeks after surgery, the osseointegration time before abutment connection was increased to 9 months after surgery. All patients were treated by 1 maxillofacial surgeon (G.M.R.) and 1 prosthodontist (H.R.). Details are described in the article by Schoen et al.[10]

Functional assessments and QoL

Preoperatively, on the day of hospital admission (T_0), patients were asked to complete questionnaires regarding oral functioning and QoL. The questionnaires were administered by an investigator not involved in treatment of the patients (P.S.). Similar questionnaires and questionnaires regarding denture satisfaction and the impact of denture-related problems on social activities had to be completed 6 weeks (T_1), 1 year (T_2) and 5 years (T_3) after placing the new dentures.

QoL was assessed using the core questionnaire (Quality of Life Questionnaire-Core 30-questions [QLQ-C30]) and head and neck module (Quality of Life Questionnaire-Core 30 Head and Neck 35-questions [QLQ-H&N35]) of the European Organization for Research and Treatment of Cancer (EORTC).[23] Psychological, physical and social impact of oral disorders was assessed using the Oral Health Impact Profile (OHIP).[24] General QoL was assessed with the Linear Analogue Self Assessment method (LASA, 1-item version).[25] Denture satisfaction was assessed using a validated questionnaire consisting of 8 separate items focusing on the function of upper and lower dentures, and on specific features such as aesthetics, retention and functional comfort.[26] Overall denture satisfaction was expressed on a 10-point rating scale (0–10); '0' being completely dissatisfied, '10' being completely satisfied. Subjective chewing ability was assessed using a 9-item questionnaire on which the patient could rate on a 3-point scale their ability to chew different kinds of food.[27] Impact of denture problems on social activities, such as going out, and contacting and visiting people, was assessed with the Groningen Activity Restriction Scale Dentistry.[28]

Data analysis

The obtained data were evaluated using SPSS (version 16.0 for Windows, SPSS Inc., Chicago, IL, USA). Data are shown as means ± standard deviation (SD). Changes were stated as significant if $p<0.05$. When comparing different groups of patients at the same time, the Mann-Whitney test was used. When comparing results within groups at different times, the Wilcoxon signed-rank test was applied.

Table 1. Patient characteristics

Age at diagnosis (years)	Sex	Primary tumour	Stage	Total intraforaminal dose (Gy)	Status
57	F	Mandibular gingiva	T4N1	–	1 (NTR)
59	M	Floor of mouth	T4N2b	–	1 (NTR)
77	F	Tongue	T3N2b	64	1 (TR)
79	M	Floor of mouth	T4N0	60	1 (TR)
52	F	Tongue/floor of mouth	T2N1	64	1 (TR)
53	M	Floor of mouth	T4N0	65	1 (TR)
69	M	Oropharynx	T2N2b	64	1 (TR)
81	M	Oropharynx	T3N1	30	2 (NTR)
52	F	Tongue	T2N1	58	2 (NTR)
61	M	Mandibular gingiva	T2N0	64	2 (TR)
81	F	Tongue/floor of mouth	T2N0	–	2 (TR)
50	M	Mandibular gingiva	T4N2b	61	2 (TR)
75	M	Tonsil	T2N0	–	3 (NTR)
64	M	Floor of mouth	T2N2c	59	3 (NTR)
59	M	Tonsil	T3N0	60	3 (NTR)
68	F	Floor of mouth	T2N0	–	3 (NTR)
65	M	Mandibular gingiva	T2N0	–	3 (NTR)
49	F	Base of tongue	T3N1	58	3 (NTR)
66	M	Mandibular gingiva	T4N2b	67	3 (NTR)
48	M	Floor of mouth	T4N1	55	3 (NTR)
78	F	Mandibular gingiva	T1N0	–	3 (NTR)
54	M	Mandibular gingiva	T4N1	62	3 (NTR)
70	M	Mandibular gingiva	T4N2b	50	3,4 (NTR)
50	M	Floor of mouth	T2N1	65	3 (TR)
66	M	Mandibular gingiva	T4N2b	64	3 (TR)
59	M	Oropharynx	T4N2b	61	3 (TR)
49	F	Floor of mouth	T2N0	57	4
76	F	Mandibular gingiva	T4N0	64	4
49	M	Floor of mouth	T2N0	50	4 (after 1 y)
71	M	Tonsil	T3N1	67	4 (after 1 y)
43	M	Tongue/floor of mouth	T2N0	–	5
65	M	Floor of mouth	T2N1	70	5
43	F	Tongue	T1N0	–	5
55	F	Tongue	T2N0	–	5
77	M	Tongue	T1N0	–	5
56	F	Floor of mouth	T1N0	–	5
41	M	Base of tongue	T3N0	63	
54	M	Tongue	T2N1	46	
51	F	Floor of mouth	T1N0	61	
64	M	Mandibular gingiva	T4N0	62	
52	M	Oropharynx	T3N0	12	
65	M	Floor of mouth	T2N0	–	
63	F	Tongue	T3N2c	62	
46	M	Tongue	T3N0	64	
54	M	Mandibular gingiva	T1N0	–	

69	M	Tongue	T2N0	–
71	M	Tongue	T2N0	–
72	M	Tongue	T2N0	–
66	M	Tongue	T3N2b	66
80	M	Tongue	T2N0	–

Abbreviations: F, female; M, male; NTR, not tumour-related; TR, tumour-related.
Notes: Patient characteristics regarding age, sex, primary tumour, staging, total interforaminal dose of radiotherapy, and status: 1: died in first year, before prothesis could be made; 2: died in the first year after delivery of prosthesis; 3: died after first year, but before 5-year evaluation; 4: wears no prosthesis; 5: comorbidity notified at T3

Results

Patients and implants

Patient characteristics are presented in Table 1.

In total 50 patients, 35 men and 15 women (mean age 61.5±11.2 years; range 41–81 years) were included at T_0. In total, 195 implants were placed in the initial group of 50 patients; of them, 18 patients were treated by surgery only (72 implants) and 32 patients were treated with radiotherapy in addition (123 implants). During the 5-year follow-up, a total of 14 implants was lost; 13 implants in 6 patients that received radiotherapy (implant survival rate 89.4%) and 1 implant in a non-irradiated patient (implant survival rate 98.6%).
At T_2, 1 year after denture placement, 35 overdentures were in function. Twelve patients had died (48 implants), 7 before abutment connection. Two patients had refused abutment connection (6 implants), because they did not want any additional, nontumour-related, surgery; and 1 patient had already lost three implants before abutment connection. The results of T_2 have been published previously.[10] At T_3, 5 years after denture placement, 26 patients were deceased. Another 4 patients who survived T_3 had to be excluded from follow-up, due to removal of the superstructures related to local irritation (n=2), loss of 3 implants (n=1), and the impossibility of making a denture after ablation because of derived anatomical limitations (n=1). Of the remaining 20 patients with functional dentures at T_3, 9 patients were irradiated (45%).

QoL and functional assessments

EORTC QLQ-C30 and QLC-H&N35

The results of the EORTC QLQ-C30 and QLQ-H&N35 questionnaires are presented in Table 2. The results of the evaluations after 1 and 5 years are presented for patients that survived T_3 (n=20), divided into irradiated (RTX, n=9) and non- irradiated patients (non-RTX, n=11). Hardly any differences between and within the groups were found. In the total group, the reported global health and general health after 5 years was lower than after 1 year ($p<0.05$) and general QoL tended to decrease ($p=0.070$). Weight loss had increased in 4 years. In irradiated patients, the mouth opening was reported more restricted and dry mouth was more severe (only significant after 1 year; $p<0.05$).

Table 2. EORTC QLQ-C30 and EORTC QLQ-H&N 35 questionnaires

EORTC QLC-C30	After 1 year		After 5 years	
	RTX n=9	non-RTX n=11	RTX n=9	non-RTX n=11
Global health status/ quality of life	93.5 ± 8.1	74.2 ± 24.6 *	83.3 ± 12.5	64.4 ± 30.5 †
Physical functioning	85.9 ± 17.5	73,3 ± 23.5	88.9 ± 10.0	68.5 ± 33.3
Role functioning	90.7 ± 14.7	77.3 ± 31.0	88.9 ± 18.6	72.7 ± 38.2
Emotional functioning	94.4 ± 16.7	87.9 ± 22.5	91.7 ± 15.0	79.5 ± 28.0
Cognitive functioning	90.7 ± 12.1	86.4 ± 19.5	88.9 ± 8.3	75.8 ± 27.2
Social functioning	94.4 ± 11.8	86.4 ± 30.6	88.9 ± 16.7	83.3 ± 25.8
Fatigue	13.6 ± 16.5	20.2 ± 30.2	12.3 ± 14.1	24.2 ± 26.7
Nausea and vomiting	0.0 ± 0.0	3.0 ± 6.7	5.6 ± 16.7	1.5 ± 5.0
Pain	13.0 ± 16.2	10.6 ± 25.0	13.0 ± 23.2	9.1 ± 15.6
Dyspnoea	0.0 ± 0.0	24.2 ± 36.8	11.1 ± 23.6	27.3 ± 46,7
Insomnia	3.7 ± 11.1	9.1 ± 15.6	3.7 ± 11.1	9,1 ± 15.6
Appetite loss	0.0 ± 0.0	9.1 ± 30.2	7.4 ± 14.7	16.7 ± 28.3
Constipation	3.7 ± 11.1	0.0 ± 0.0	3.7 ± 11.1	3.0 ± 10.1
Diarrhoea	0.0 ± 0.0	6.1 ± 13.5	11.1 ± 23.6	6.1 ± 13.5
Financial difficulties	14.8 ± 17.6	6.1 ± 20.1	22.2 ± 37.3	10.0 ± 16.1
EORTC QLQ-H&N35				
Pain	15.7 ± 22.6	6.1 ± 9.9	19.4 ± 11.8	9.1 ± 17.3
Swallowing	19.4 ± 15.6	6.8 ± 9.0 *	12.7 ± 14.2	15.8 ± 23.4
Sensory problems	18.5 ± 17.6	15.2 ± 32.0	13.0 ± 23.2	22.7 ± 31.0
Speech problems	13.6 ± 18.2	9.1 ± 14.8	18.5 ± 22.9	14.1 ± 21.1
Trouble with social eating	22.2 ± 19.5	12.1 ± 25.6	21.3 ± 28.0	20.0 ± 28.7
Trouble with social contact	4.4 ± 11.1	5.5 ± 12.9	5.2 ± 15.6	4.2 ± 8.0
Less sexuality	16.7 ± 28.9	14.8 ± 32.7	18.8 ± 30.1	25.0 ± 34.5
Teeth	14.8 ± 33.8	9.1 ± 15.6	25.9 ± 32.4	6.7 ± 21.1
Opening mouth	44.4 ± 28.9	9.1 ± 21.6 ‡	25.9 ± 32.4	6.7 ± 14.1
Dry mouth	55.6 ± 28.9	21.2 ± 22.5 *	51.9 ± 29.4	26.7 ± 34.4
Sticky saliva	33.3 ± 28.9	12.1 ± 16.8	37.0 ± 35.1	30.3 ± 34.8
Coughing	14.8 ± 17.6	27.3 ± 25.0	14.8 ± 17.6	15.2 ± 22.9
Felt ill	3.7 ± 11.1	6.1 ± 20.1	14.8 ± 33.8	15.2 ± 22.9
Pain killers	22.2 ± 44.1	45.5 ± 52.2	22.2 ± 44.1	18.2 ± 40.5
Nutritional supplements	22.2 ± 44.1	9.1 ± 30.2	22.2 ± 44.1	18.2 ± 40.5
Feeding tube	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	18.2 ± 40.5
Weight loss	0.0 ± 0.0	9.1 ± 30.2	22.2 ± 44.1	36.4 ± 50.5
Weight gain	11.1 ± 33.3	27.3 ± 46.7	0.0 ± 0.0	9.1 ± 30.2

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-questions; EORTC QLQ-H&N-35, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Head and Neck 35-questions.
* Significant difference between irradiated and non-irradiated patients at the same point in time $p < 0.05$.
† Significant difference between five years after placement and one year after placement $p<0.05$.
‡ Significant difference between irradiated and non-irradiated patients at the same point in time $p < 0.01$.
Notes: Results of the functional scales, symptom scales and single items of the EORTC QLQ-C30 and multi-item scales and single items of the EORTC QLQ-H&N 35 questionnaires for the 5 years surviving patients with a functional implant-retained overdenture, at 1 year and 5 years after placement of the dentures (for irradiated (*RTX*) and non irradiated patients (*non-RTX*) patients). For the 1-year results (n=35 patients) see Schoen et al.[10]

Table 3. Comorbidity versus no comorbidity

EORTC QLQ-C30	Comorbidity n=6	No comorbidity n=14
Global health status/ quality of life	48.6 ± 27.6	83.3 ± 16.3 *
Physical functioning	50.0 ± 35.5	89.5 ± 9.3 *
Role functioning	55.6 ± 44.3	90.5 ± 16.9
Emotional functioning	69.4 ± 33.6	91.7 ± 14.2
Cognitive functioning	63.9 ± 30.6	89.3 ± 10.5
Social functioning	69.4 ± 28.7	92.9 ± 14.2
Fatigue	40.7 ± 26.0	9.5 ± 12.2 *
Nausea and vomiting	2.8 ± 6.8	3.6 ± 13.4
Pain	16.7 ± 18.3	8.3 ± 19.3
Dyspnoea	61.1 ± 49.1	2.4 ± 8.9 †
Insomnia	11.1 ± 17.2	4.8 ± 12.1
Appetite loss	33.3 ± 33.3	4.8 ± 12.1
Constipation	5.6 ± 13.6	2.4 ± 8.9
Diarrhoea	11.1 ± 17.2	7.1 ± 19.3
Financial difficulties	16.7 ± 18.3	15.4 ± 32,2

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-questions
* Significant difference between patients with and without comorbidity after five years $p<0.01$.
† Significant difference between patients with and without comorbidity after five years $p<0.05$.
Notes: Results of the functional scales, symptom scales and single items of the EORTC QLQ-C30 for patients with and without comorbidity, 5 years after placement of the dentures.

Comorbidity

Based on the data in the patients' medical histories, patients were subdivided into 2 groups based on the comorbidity noticed at T_3 (Table 3). Six patients were identified with comorbidity, including secondary radiotherapy (after T_2) in the head and neck region (n=2), an established stroke, lung metastases, severe lung emphysema and a transient ischemic attack (Table 1). When looking into detail in these patients, global health, physical function, fatigue and dyspnoea were significantly worse in these patients with comorbidity. QoL and global health were very high in patients without comorbidity and remained at the same level between T_2 and T_3. When comparing the T_1-data and T_2-data, there was a progressive decrease in general health, global health, and cognitive function over time in patients with comorbidity. A tendency towards a decrease in cognitive function ($p=0.078$) and an increase in weight loss ($p=0.083$) with time was also seen in patients with comorbidity.

Radiotherapy

The global health status in irradiated patients was higher than non-irradiated patients. However, 5 patients with comorbidity were among the 11 non-irradiated patients, whereas there was only 1 patient with comorbidity among the 9 irradiated patients. When excluding

Table 4. OHIP questionnaire

	After 1 year		After 5 years	
	RTX n=9	non-RTX n=11	RTX n=9	non-RTX n=11
OHIP14	12.4 ± 10.9	6.3 ± 8.9 *	12.8 ± 12.1	6.7 ± 6.5
Functional limitation	12.0 ± 6.5	6.6 ± 5.4 †	11.1 ± 5.9	7.3 ± 4.8
Physical pain	7.0 ± 9.5	4.0 ± 6.3	11.0 ± 9.6	4.3 ± 6.1 ‡
Physical disability	13.0 ± 10.7	5.9 ± 8.1 §	10.4 ± 10.5	6.2 ± 6.3
Psychological discomfort	2.1 ± 5.3	0.8 ± 1.9	3.4 ± 5.8	1.0 ± 2.0
Psychological disability	2.0 ± 4.3	0.9 ± 2.4	1.9 ± 3.6	0.9 ± 1.0
Social disability	1.3 ± 2.5	0.8 ± 1.8	1.3 ± 2.7	0.9 ± 1.3

Abbreviations: OHIP, Oral Health Impact Profile
* Significant difference between irradiated and not irradiated patients at the same point in time; $p < 0.05$.
† Tendency towards difference between irradiated and non-irradiated patients at the same point in time; $p = 0.056$.
‡ Tendency towards difference between irradiated and non-irradiated patients at the same point in time; $p = 0.067$.
§ Tendency towards difference between irradiated and not irradiated patients at the same point in time; $p = 0.056$.
Notes: Results of the Oral Health Impact Profile (OHIP) questionnaire, at 1 year and 5 years after placement of the dentures, for irradiated (RTX) and non-irradiated (non-RTX) 5-years survivors with a functional implant-retained overdenture. For the 1-year results (n=35 patients) see Schoen et al[10].

the patients with comorbidity, the differences in the EORTC QLQ-C30 disappeared. At T_2, the irradiated patients reported a dryer mouth, less opening of the mouth and more difficulties with swallowing in the QLC-H&N35 questionnaires (Table 2). At T_3, the differences between irradiated and non-irradiated patients did not reach significance, although trends were seen towards a dryer mouth ($p = 0.095$) and more pain ($p = 0.056$) in irradiated patients. When taking comorbidity into account, we saw several differences in the QLC-H&N35; the irradiated patients reported a dryer mouth, more pain ($p < 0.05$), less opening of the mouth, more problems in speech and more problems related to the dentures ($p = 0.059$).
When comparing the irradiated patients with the non-irradiated patients, over time, global health and global health related QoL tended to decrease for the irradiated patients ($p = 0.059$ and $p = 0.066$).

Survivors versus non-survivors

When looking retrospectively into the 35 patients with functional dentures at T_2, there were some differences between the 5-year survivors with functional dentures (n=20) and those patients that did not make it to T_3 (n=12); the results are not depicted in a table. At T_2, the 5-year survivors had reported a higher global health and fewer problems with swallowing ($p < 0.05$) than the nonsurvivors. Nonsurvivors tended to report more pain and a lower general QoL than the survivors ($p = 0.068$).

OHIP, functional assessments, social restrictions and denture satisfaction

The OHIP results are presented in Table 4, and the results of questionnaires regarding oral functioning and denture satisfaction are presented in Table 5. Over time, there were no changes in results for the total group, neither were differences seen between patients with or without comorbidity.

Table 5. Oral functioning and denture satisfaction

	After 1 year		After 5 years	
	RTX n=9	non-RTX n=11	RTX n=9	non-RTX n=11
GARS-D	2.6 ± 4.6	1.9 ± 3.9	3.5 ± 5.0	2.8 ± 5.1
Denture satisfaction	12.9 ± 4.8	11.6 ± 4.4	13.9 ± 4.8	11.8 ± 3.1
Overall denturesatisfaction	8.4 ± 1.2	8.5 ± 1.4	8.5 ± 1.3	8.9 ± 1.1
Chewing/eating	7.4 ± 7.0	3.8 ± 4.3	6.0 ± 6.7	4.6 ± 4.9
LASA quality of life	81.8 ± 18.5	69.3 ± 24.9	87.4 ± 9.5	65.3 ± 28.7 *

Abbreviations: GARS-D, Groningen Activity Restriction Scale Dentistry; LASA, Linear Analogue Self Assessment.
* Tendency towards difference between irradiated and non-irradiated patients at the same point in time p= 0.055.
Notes: Results of questionnaires regarding oral functioning and denture satisfaction, at 1 year and 5 years after placement of the dentures, for irradiated (RTX) and non-irradiated (non-RTX) patients with a functional implant-retained overdenture. For the 1-year results (n=35 patients) see Schoen et al.[10]

Radiotherapy

A tendency toward more pain was reported in the OHIP in the irradiated group (p=0.067) between T_2 and T_3. When excluding patients with comorbidity, more differences were found between irradiated patients and non-irradiated patients: at T_3 irradiated patients reported more functional limitations and physical pain ($p<0.05$) than non-irradiated patients and a tendency was seen towards more physical disability (p=0.081) and a higher score in the handicap domain (p=0.081) in irradiated patients. Previously, we reported that overall denture satisfaction was higher in non-irradiated than in irradiated patients at T_2,[10] but in the irradiated patients denture satisfaction was also rather high. On the other scales of functional assessment the non-irradiated patients showed better results than the irradiated patients at T_2.[10] At T_3, denture satisfaction again scored high, but denture satisfaction and functional assessment showed no differences between irradiated and non-irradiated patients. Overall QoL, as measured with the LASA, showed, as did the EORTC QLQ-C30, a higher QoL for the irradiated patients after five years (p=0.055), but this difference disappeared when taking comorbidity into account.

Survivors versus non-survivors

At T_1, nonsurvivors reported to be more concerned with the future functioning of their dentures than the 5-year survivors ($p<0.05$). There tended to be more social restrictions

and chewing problems (p=0.095 and p=0.074) for the nonsurvivors than for the survivors. At T_2, survivors reported less social restrictions than nonsurvivors (p=0.059). Also, survivors tended to be more satisfied with their dentures than the nonsurvivors (p=0.087).

Discussion

The surviving 20 patients with functional dentures did not report a difference in oral function between 1 and 5 years after prosthetic rehabilitation. The observed deterioration in overall global health and QoL was strongly associated with concurrent comorbidity in 6 patients. For patients without known comorbidity general QoL and global health were very high.

No difference in oral function was reported at the 1 year and 5 year follow after placement of the prostheses. This observation is comparable to results of studies in healthy subjects.[21-22] The oral function of the patients in this study was reasonable, but lower than in healthy subjects.[27] Still, the denture satisfaction was very high. However, there was a difference in global health, oral and social functioning and denture satisfaction between the 5-year survivors and the nonsurvivors, indicating a 'natural' selection of patients. This is in agreement with the findings of other studies [30-31], where high scores of functioning scales and low scores on symptom items at 1-year follow up seemed to predict a high survival at 5 years. In our study, survivors reported fewer problems with swallowing and less restrictions in social activities. The nonsurvivors were more concerned with the future functioning of their dentures than the survivors. An explanation can be that the 20 patients with a functional denture had a lower percentage of large tumours compared to the nonsurvivors (Table 1), thus needing less extensive surgery with less morbidity. Also, among the deceased and excluded patients at T_3, a larger percentage had received radiotherapy in comparison to the survivors, probably giving less favourable oral conditions.

The scores of the EORTC QLC-C30 and QLC-H&N35 questionnaires at T_3 are comparable to the results of other QoL studies in patients with head and neck cancer.[30-34] The patients without known comorbidity reported high scores comparable to those of healthy subjects. This observation indicates that even after oncological treatment patients still can reach 'normal' health levels. Furthermore, in previous studies, the question was raised whether patients do value oral rehabilitation as essential in their life after head and neck cancer. In one study reporting on general QoL in patients without an implant-borne overdenture, no difference in general QoL was found between patients that wore their mandibular dentures and patients that did not.[35] A review relating QoL to functional outcome also showed no difference in QoL between patients with a conventional dental/tissue-supported denture, an implant-retained overdenture and patients without dentures.[17] Most patients reported satisfactory outcomes regardless of the type or presence of prosthetic rehabilitation. This finding is in agreement with the findings of Murphy et al[18], as data correlated QoL with functional outcome and symptom burden often fails to demonstrate a consistent

relationship. The latter authors suggested that this may be attributed to methodological issues in the study design or the patient's ability to adapt to functional and symptom control problems.

It is obvious that certain stages of disease and cancer treatment will lead to disastrous anatomical or physiological conditions in which oral rehabilitation cannot be restored to a level comparable to the level before onset of the disease. However, the patients' ability to adapt to functional problems and to accept the loss of some oral functions should not be underestimated. Another conclusion could be that validated sensitive instruments to rate the influences of oral rehabilitation on QoL are still not available for general application. Regarding general health-related QoL, such validated instruments are commonly available.[15] However, these general health-related QoL questionnaires seem to lack the discriminating ability to measure the effects of prosthodontic treatment on QoL in oral cancer patients. Efforts have been done to develop instruments that might solve this problem such as Liverpool Oral Rehabilitation Questionnaire (LORQ), which was developed in 2004 and has been used on since. [36-39] Also more specific questionnaires that focus on head and neck function, such as speech and swallowing are currently available. [40] Unfortunately we were not able to use such questionnaires as these questionnaires were not available at the time of inclusion of our patients into our study.

It seems that other factors such as comorbidity are far more important in determining the patients' QoL being an important caution that has to be considered when interpreting the results of the questionnaires regarding general health. With a closer look, the decrease in QoL we observed appeared to be caused by a small group of patients with severe comorbidity. Most patients with comorbidity were not irradiated. When taking this comorbidity into account, the specific head and neck module reveals differences between the irradiated and non-irradiated patients even after 5 years, which can be related to the late effects of the radiotherapy, such as dry mouth, less opening of the mouth and problems with swallowing and speech. Terrell et al[41] ranked comorbidity to be the second greatest predictor of decreased QoL in head and neck cancer patients. In our study, we did not apply standard comorbidity measures as the Adult Comorbidity Evaluation (ACE27), that are currently used in studies to code and quantify comorbidity[42-44] Nevertheless, we were able to indicate that comorbidity apparently played a larger role in decreased QoL scores than radiotherapy. However, 2 patients received radiotherapy between T_2 and T_3 due to recurrent disease. In the analysis these patients were scored as non-irradiated (intention-to-treat procedure) and were considered as having comorbidity. This could also explain why differences are only found in the head and neck module when excluding patients with comorbidity.

Implant loss was higher in patients that received radiotherapy post-tumour surgery. This is in agreement with other studies.[5,7,8,11] A review reports that the increase in the risk of implant loss in irradiated patient may be up to 12 times greater; however, the magnitude of this difference should be accepted with caution since studies making these comparisons

are of poor to moderate quality.[12] The failure rate of 10.6% in irradiated bone over a period of 5 years found in our study is considered good. However, 26 patients had died and the percentage of patients that had received postoperative radiotherapy decreased over time amongst the survivors (73% at baseline vs. 54% 5 years after placement of the dentures). This could have contributed to the relatively low failure rate of implants in irradiated bone. The percentage of patients rehabilitated with the help of dental implants placed after ablative surgery and postoperative radiotherapy varies in the literature. Reported percentage are between 22-91%,[9,14,45-50] depending largely on the type of patients included, the type of reconstruction, the survival rate of patients and implants and the length of the follow-up. In our study where the implants were placed during ablative surgery, a relatively large number of the living patients was rehabilitated with dentures (at T_2: 92%, at T_3: 83%). No delay or complications in oncological treatment were seen due to the placement of the implants at that time. Still, 2 patients refused abutment connection because of the expected extra burden of abutment connection surgery. Also, from previous data, it was concluded that many patients refrain from further surgery, including implant installation, after they survived head and neck oncology treatment, despite an improvement of oral functioning was to be expected postsurgery[35]. When placing the implants during ablation, a significant time reduction of (pre)prosthetic rehabilitation can be achieved. Consequently, a large percentage of patients and even patients with a worse general prognosis can benefit for some time from the improvements in aesthetics and oral function. Future study might identify patients who are less likely to benefit from implant placement per ablation. Our study indicates that implant installation during ablative surgery results in a high percentage of rehabilitated patients, also after 5 years. From a health economics point of view, however, the loss of resources needs further consideration by performing a cost-effectiveness analysis.

Based on this study we conclude that the overall global health and QoL deteriorated in the total group between 1 and 5 years after placement of the dentures, which was due to concurrent comorbidity in a small number of patients. The global health and QoL for patients without comorbidity was very high. A large number of surviving patients could benefit from an implant-retained mandibular overdenture (83%) after 5 years. The oral function and denture satisfaction was high and did not change over time for the 5-year survivors.

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Chapter 2.2

Benefits of dental implants installed during ablative tumour surgery in oral cancer patients: a prospective 5-year clinical trial

Abstract

Objective

This prospective study assessed treatment outcome and patient satisfaction of oral cancer patients with a mandibular overdenture on implants up to 5 years after treatment.

Materials and methods

At baseline, 50 consecutive edentulous oral cancer patients, in whom prosthetic problems were expected after oncological treatment, were evaluated by standardized questionnaires and clinical assessments. All implants were installed during ablative tumour surgery in native bone in the interforaminal area. About two-thirds of the patients (n=31) had radiotherapy post-surgery (dose >40 Gy in the interforaminal area).

Results

At the 5-year evaluation, 26 patients had passed away and four patients had to be excluded from the analyses, because superstructures were not present, due to persistent local irritation (n=2), loss of three implants (n=1) and the impossibility of making an overdenture related to tumour and oncological surgery-driven anatomical limitations (n=1). In the remaining 20 patients, the prosthesis was still in function (76 implants). During the 5-year follow-up, in total 14 implants were lost, 13 in irradiated bone (survival rate 89.4%, dose >40 Gy) and one in non-irradiated bone (survival rate 98.6%). Peri-implant tissues had a healthy appearance and remained healthy over time. Patients were satisfied with their dentures.

Conclusions

It was concluded that oral cancer patients can benefit from implants installed during ablative surgery, with a high survival rate of the implants, a high percentage of rehabilitated patients and a high denture satisfaction up to 5 years after treatment.

Introduction

Prosthodontic rehabilitation of oral cancer patients is challenging. Often, oral functioning declines after surgical treatment and is even more impaired if combined with radiotherapy, due to the adverse biological changes resulting from exposure of the oral tissues and salivary glands to ionizing radiation (Vissink et al. 2003). In edentulous cancer patients, in addition, the possibility of making a well-functioning lower denture is often also severely impeded because of changed anatomical conditions (restricted neutral zone) and intolerance of the denture-bearing mucosa to mechanical loading (Buchbinder et al. 1989; Hayter & Cawood 1996; Marker et al. 1997; Misiek & Chang 1998). A solution for this problem can be the fabrication of an implant-retained mandibular overdenture, as implant survival in irradiated mandibles has been shown to be relatively high and patients report an improved level of oral functioning when being provided with such a denture (Granström et al. 1994; Granström 2003, 2005; Müller et al. 2004; Yerit et al. 2006; Colella et al. 2007; Schoen et al. 2007, 2008; Idhe et al. 2009). When considering patients to be treated for oral cancer, timing of implant installation is still subject of discussion. So far, no difference is found in implant loss between the installation of implants before or after radiotherapy (Colella et al. 2007); however, the far majority of studies report on implants installed after radiotherapy.
Named advantages of implant installation during ablative tumour surgery include (Schoen et al. 2004): 1. implant surgery in an area compromised by radiotherapy can be avoided, thus reducing the risk of late complications, such as development of osteoradionecrosis; 2. initial implant healing (osseointegration) will take place before irradiation; 3. the patient can benefit from the support of the implants at an earlier stage after treatment, e.g. concerning the rehabilitation of speech and swallowing; 4. there is no need for adjunctive prophylaxis such as the long-term use of antibiotics or hyperbaric oxygen therapy. Furthermore, it has been shown that many patients were unwilling to undergo another surgical intervention when installation of implants was proposed, even when an improvement in oral function was predicted (Kwakman et al. 1997; Schoen et al. 2007).
Besides these benefits, the risks of installing implants during ablative surgery have to be named as well: 1. improper implant positioning, especially when ablative surgery will result in gross alterations in the anatomical situation and/or intermaxillary relationship; 2. interference with or delay of oncological therapy including radiotherapy; 3. development of post-treatment complications caused by installation of implants during ablative surgery; and 4. lack of use of implants, due to early tumour recurrence or patients refusing abutment connection surgery.
In healthy subjects, no further change in oral functioning and patients' satisfaction is to be expected after the first year of prosthodontic rehabilitation with an implant- retained overdenture (Raghoebar et al. 2003; Meijer et al. 2009). In oral cancer patients, it is questionable whether this is also applicable, or the remaining side effects of the oncological treatment and the impact of having had cancer are more prominent and veil the beneficial effects of an adequate prosthodontic rehabilitation on oral function.

The objective of this prospective study was to assess the treatment outcomes (condition of peri-implant tissues, implant survival, reported denture satisfaction and subjective chewing ability) of oral cancer patients with implant-retained mandibular overdentures, in whom the implants were installed during ablative tumour surgery, up to 5 years after placement of the overdenture.

Material and methods

Patients and treatment

All consecutive edentulous patients with cancer in the mandibular region referred to the Head and Neck Oncology Group of the University Medical Center Groningen between May 1998 and April 2002 were screened to be included in this study. The criteria for inclusion were an edentulous upper and lower jaw, existing prosthetic problems related to lack of stability and retention of the lower denture or to be expected denture-related problems after oncology treatment, first malignancy in the head and neck region (squamous cell carcinoma of tongue, floor of the mouth, mandibular gingiva, buccal mucosa or oropharynx) and need for primary ablative surgery (for patients' characteristics see Table 1). The patients were screened by an experienced maxillofacial surgeon (G.M.R.) and prosthodontist (H.R.). All patients were offered conventional or implant-based treatment. They accepted the option of implant installation during ablative surgery, and informed consent was obtained from all patients as requested by the human ethics committee of the University Medical Center Groningen.

Tumour surgery and implant insertion were performed at the Groningen University Medical Center. All implants (3.75 mm Brånemark screw implants with a machined surface, Nobelbiocare, Gothenburg, Sweden) were inserted immediately after ablation of the tumour. All implants were installed in the interforaminal region of the native bone of the mandible in a two-stage surgical procedure. An osseointegration period of 3 months before abutment connection was considered in patients not needing radiation therapy after tumour surgery. If postoperative radiation therapy was scheduled, starting within 6 weeks after surgery, the osseointegration time before abutment connection was increased to 9 months after surgery. In patients receiving radiotherapy, the cumulative absorbed dose at the implant locations was calculated using the computed tomography data available for the treatment planning (Wang et al. 1998).

All patients received a Dolderbar superstructure with a clip-retained mandibular overdenture and a conventional upper denture. Thus, the overdentures were mainly implant borne but also tissue borne, providing a mixed support. A bilateral balanced occlusal scheme was applied to create a steady occlusal loading of the prostheses. All patients were treated by one experienced maxillofacial surgeon (G.M.R.) and one experienced prosthodontist (H.R.). Home care instructions with regard to maintenance of the dentures and peri-implant tissues were given (for details see Schoen et al. 2008).

Clinical assessments and radiographic analysis

The clinical assessments included a survey of the dental status, the oral condition and the prosthetic rehabilitation. Postoperative complications and implant survival were recorded from the time of surgery until 5 years after placement of the dentures. Periodontal indices were assessed 6 weeks (T1), 1 year (T2) and 5 years (T3) after placing the new dentures. The periodontal indices included plaque index (Mombelli et al. 1987), bleeding index (Mombelli et al. 1987), gingival index (Loë & Silness 1963), probing depth and implant mobility (Teerlinck et al. 1991). Probing depth was measured at four sites of each implant (mesially, labially, distally and lingually) using a periodontal probe (Merit B, Hu Friedy, Chicago, IL, USA) after removal of the bar; the distance between the marginal border of the mucosa and the tip of the periodontal probe was scored as the probing depth. Mobility of the implants was determined quantitatively by perio test values after removal of the bar and (re)tightening of all the abutments. The clinical assessments at T1, T2 and T3 were performed by two investigators (P.J.S. and H.R.).

At the start of prosthetic loading (T1) and every subsequent year until T3, rotational panoramic radiographs were made to evaluate the implant-surrounding bone height. The bone loss measurements were executed by two researchers (A.K. and H.R.). Possible bone loss around the implants was classified according to the scale proposed by Geertman et al. (1996):

0: no apparent bone loss;
1: reduction of bone level not exceeding one-third of the length of the implant;
2: reduction of bone level exceeding one- third of the length of the implant but not exceeding one-half of the length of the implant;
3: reduction of bone level exceeding one-half of the length of the implant; and
4: total reduction of bone along the implant.

Functional assessments and denture satisfaction

Preoperatively, i.e. on the day of hospital admission (T0), patients were asked to complete questionnaires regarding oral functioning and quality of life. The questionnaires were administered by the investigator (P.J.S.) who was not involved in the oncological and prosthodontic treatment of the patients. Similar questionnaires had to be completed 6 weeks (T1), 12 months (T2) and 5 years (T3) after placing the new dentures, as well as questionnaires regarding denture satisfaction and the impact of denture-related problems on social activities. Denture satisfaction was assessed using a validated questionnaire consisting of eight separate items focusing on the function of upper and lower dentures, and on specific features such as aesthetics, retention and functional comfort (Vervoorn et al. 1988). Overall denture satisfaction was expressed on a 10-point rating scale (0– 10); "0" being completely dissatisfied and "10" being completely satisfied. Subjective chewing ability was assessed using a nine-item questionnaire on which the patient could rate on a three-point scale their ability to chew different kinds of food (Stellingsma et al. 2005).

Data analysis

The data of this longitudinal prospective clinical trial were evaluated using SPSS (version 16.0 for Windows, SPSS Inc., Chicago, IL, USA). Data are shown as means ± standard deviation (SD). Changes were stated as significant if $P<0.05$. For the continuous data, when comparing irradiated with non-irradiated patients at the same time point, the independent t-test was used, and when comparing results within groups at different time points, the t-test for dependent samples was applied. For ordinal data, when comparing irradiated with non-irradiated patients at the same time point, the Mann–Whitney U- test was used, when comparing within groups at different time points, the Wilcoxon signed ranks test was used. Implant survival in radiated versus non-radiated patients was tested using a chi square test.

Results

Patients

In total, 50 patients (35 men and 15 women; mean age 61.5 ± 11.2 years; range 41–81 years) were included (Table 1).

At T2 12 patients and at T3 in total 26 patients had passed away (Fig. 1). Regarding the deaths, 11 were tumour related and 15 were non-tumour related. After ablative surgery, 31 of the initial 50 patients (62%) were treated with radiotherapy (dose >40Gy). In the group of survivors after 5 years, 13 of the remaining 24 patients (54%) had been treated with radiotherapy (dose >40 Gy) after surgery. Four patients did not wear their prosthesis (for reasons see below). Of the 20 patients with functional prostheses after 5 years, nine patients (45%) had been irradiated.

One year after placement, 35 overdentures were in function (12 patients had passed away; three patients had no abutment connection). Five years after placement, 20 overdentures remained in function (Fig. 1).

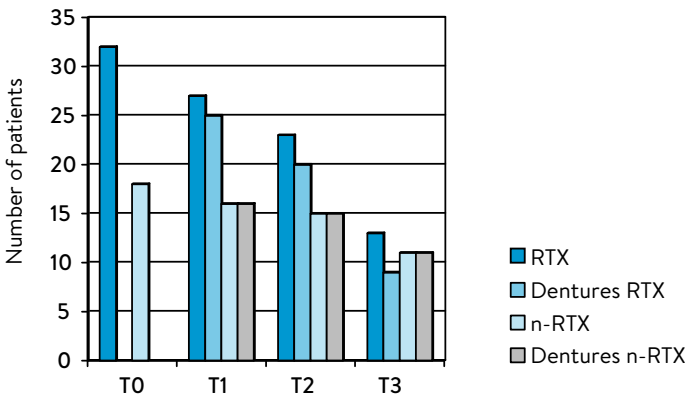
Table 1. Patients' characteristics

Patient characteristics regarding age, sex, primary tumour, staging, total interforaminal dose of radiotherapy and status: 1, died in first year, before prosthesis could be made; 2, died in the first year after delivery of prosthesis; 3, died after first year, but before 5 year evaluation; 4, wears no prosthesis (NTR: death not related to the primary tumour; TR: death related to the primary tumour).

Age at diagnosis (years)	Sex	Primary tumour	Stage	Total intraforaminal dose (Gy)	Status
57	F	Mandibular gingiva	T4N1	–	1 (NTR)
59	M	Floor of mouth	T4N2b	–	1 (NTR)
77	F	Tongue	T3N2b	64	1 (TR)
79	M	Floor of mouth	T4N0	60	1 (TR)
52	F	Tongue/floor of mouth	T2N1	64	1 (TR)
53	M	Floor of mouth	T4N0	65	1 (TR)
69	M	Oropharynx	T2N2b	64	1 (TR)
81	M	Oropharynx	T3N1	30	2 (NTR)
52	F	Tongue	T2N1	58	2 (NTR)
61	M	Mandibular gingiva	T2N0	64	2 (TR)
81	F	Tongue/floor of mouth	T2N0	–	2 (TR)
50	M	Mandibular gingiva	T4N2b	61	2 (TR)
75	M	Tonsil	T2N0	–	3 (NTR)
64	M	Floor of mouth	T2N2c	59	3 (NTR)
59	M	Tonsil	T3N0	60	3 (NTR)
68	F	Floor of mouth	T2N0	–	3 (NTR)
65	M	Mandibular gingiva	T2N0	–	3 (NTR)
49	F	Base of tongue	T3N1	58	3 (NTR)
66	M	Mandibular gingiva	T4N2b	67	3 (NTR)
48	M	Floor of mouth	T4N1	55	3 (NTR)
78	F	Mandibular gingiva	T1N0	–	3 (NTR)
54	M	Mandibular gingiva	T4N1	62	3 (NTR)
70	M	Mandibular gingiva	T4N2b	50	3,4 (NTR)
50	M	Floor of mouth	T2N1	65	3 (TR)
66	M	Mandibular gingiva	T4N2b	64	3 (TR)
59	M	Oropharynx	T4N2b	61	3 (TR)
49	F	Floor of mouth	T2N0	57	4
76	F	Mandibular gingiva	T4N0	64	4
49	M	Floor of mouth	T2N0	50	4 (after 1 y)
71	M	Tonsil	T3N1	67	4 (after 1 y)
43	M	Tongue/floor of mouth	T2N0	–	
65	M	Floor of mouth	T2N1	70	
43	F	Tongue	T1N0	–	
55	F	Tongue	T2N0	–	
77	M	Tongue	T1N0	–	
56	F	Floor of mouth	T1N0	–	
41	M	Base of tongue	T3N0	63	
54	M	Tongue	T2N1	46	
51	F	Floor of mouth	T1N0	61	
64	M	Mandibular gingiva	T4N0	62	
52	M	Oropharynx	T3N0	12	

65	M	Floor of mouth	T2N0	–
63	F	Tongue	T3N2c	62
46	M	Tongue	T3N0	64
54	M	Mandibular gingiva	T1N0	–
69	M	Tongue	T2N0	–
71	M	Tongue	T2N0	–
72	M	Tongue	T2N0	–
66	M	Tongue	T3N2b	66
80	M	Tongue	T2N0	–

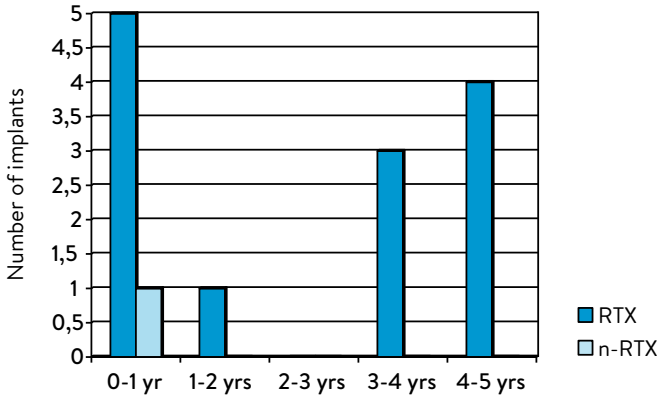
Figure 1. Number of patients alive and dentures worn at baseline (T0), after delivering the dentures (T1), after 1 year (T2) and after 5 years (T3). RTX: irradiated patients; n-RTX: non-irradiated patients



The other four surviving patients had to be excluded due to removal of the superstructures before T3 because of persistent local irritation of the soft tissue near the superstructure (n=2), the impossibility of making a denture due to anatomical limitations resulting from ablative surgery (n=1) and loss of three implants (n=1). In the latter patient, new implants were installed after bone healing and a new prosthesis was made, which was still in function after 5 years. However, this patient was excluded from the 5-year evaluation data as the new implants had been installed after surgery and radiotherapy.

In total, 195 implants were installed in the initial group of 50 patients. In one patient, three implants were installed because of lack of space in the interforaminal area to install four implants with an appropriate distance between the implants (no radiotherapy), and in two patients, two implants were installed instead of four due to anatomical limitations resulting from ablative surgery (resections of the mandible; both patients were irradiated). In total, 14 implants were lost during follow-up, mainly in irradiated patient (chi square test, $P<0.05$); viz. 13 implants in seven patients who received radiotherapy (n=123) (implant survival rate 89.4%) and one implant in a patient treated without radiotherapy (n=72) (implant survival rate 98.6%) (Fig. 2).

Figure 2. Number of implants lost during follow-up. RTX: implants in irradiated patients; n-RTX: implants in non-irradiated patients



Six of these 14 implants were lost before the overdenture could be made. Eight implants were lost after prosthetic loading; all installed in irradiated bone.
In the 20 patients with a functional overdenture at T3, in total 79 implants (19 x 4 implants, 1 x 3 implants) were installed during ablation. In this group, three implants had been lost meanwhile (two in irradiated patients after placement of the overdenture and one in a non-irradiated patient before placement of the overdenture) giving an implant survival rate of 96.2% in this group.

Clinical and radiographic assessments

No postoperative complications or delay in oncological treatment occurred related to implant surgery. The mean scores on the indices for peri-implant parameters were low at all evaluations (Table 2). There were no clinically relevant differences in clinical peri-implant parameters between the irradiated patients and the non- irradiated patients (independent t-test, $P>0.05$). Also over time, there were no differences in clinical parameters between the evaluation time points for the irradiated patients and the non-irradiated patients (independent t-test, $P>0.05$). Regarding the radiographic scores, there was a significant increase between T1 and T3 for both irradiated patients and non-irradiated patients (Table 2, Wilcoxon signed ranks test, $z=-2.366$ and -2.670, $P=0.018$ and 0.008, respectively).

Table 2. Mean and median scores of the peri-implant parameters at T1, T2 and T3 for the 20 patients wearing an implant-retained mandibular overdenture at T3

	T1						T2						T3					
	RTX (n = 9) *			N-RTX (n = 11) *			RTX (n = 9)			N-RTX (n = 11)			RTX (n = 9)			N-RTX (n = 11)		
	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD
Plaque index (score 0 to 3)	1	0.9	0.8	1	0.7	0.6	1	1.0	0.6	1	0.9	0.7	1	0.8	0.5	1	0.9	0.8
Calculus (score 0 to 1)	0	0.1	0.3	0	0.1	0.3	0	0.0	0.0	0	0.0	0.1	0	0.1	0.2	0	0.2	0.3
Bleeding index (score 0 to 3)	1	1.2	0.6	1	0.8	0.7	1	1.4	0.4	1	1.0	0.5	1	1.4	0.4	1	0.5	0.9
Gingiva index (score 0 to 3)	0	0.5	0.6	0	0.3	0.4	0	0.2	0.3	0	0.0	0.0	0	0.4	0.4	0	0.4	0.7
Pocket depth (mm)	n.a.	2.0	0.6	n.a.	2.4	0.4	n.a.	3.0	0.5	n.a.	2.9	0.7	n.a.	2.3	0.4	n.a.	2.1	1.8
Width of attached gingiva (score 0 to 3)	2	1.5	0.7	2	1.8	0.5	2	1.3	0.7	2	1.5	0.7	2	1.7	0.7	2	2.1	0.6
Periotest (scoring range: −8 to 50)	n.a.	-4.4	0.9	n.a.	-4.3	1.2	n.a.	-2.4	2.9	n.a.	-4.5	1.5	n.a.	-3.2	2.5	n.a.	-4.7	0.9
Radiographic analysis (scoring 0-4)	0	0.3	0.4	0	0.2	0.3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1	1.0	0.4	1	0.9	0.7

A higher score indicates more plaque, calculus, bleeding, pocket depth, width of attached gingiva and less stability of the implant (periotest).

* RTX: irradiated patients; N-RTX: non-irradiated patients; n.a.: not applicable; n.d.: not done

Denture satisfaction and chewing ability

The denture satisfaction of the patients with a functional prosthesis is presented in Table 3, the overall denture satisfaction data are given in Table 4 and the results of the chewing ability questionnaire are shown in Table 5. The results are presented for the patients who survived T2 (n=35) and patients who survived T3 (n=20), respectively, divided into irradiated patients and non-irradiated patients, in order to depict the T1, T2 and T3 data for the same subgroup of patients (i.e. survivors).

Table 3. Denture satisfaction

Satisfaction Range (1-5)*	Survivors at T2 (n=35)					
	T1			T2		
	total	RTX	n-RTX	total	RTX	n-RTX
	n=35	n=20	n=15	n=35	n=20	n=15
General	1.59 (n=34)	1.58 (n=19)	1.60	1.54	1.70	1.33
Upper denture	1.50 (n=34)	1.60	1.36 (n=14)	1.60	1.65	1.53
Lower denture	1.54	1.60	1.47	1.57	1.80	1.27
Appearance	1.37	1.45	1.27	1.46	1.60	1.27
Retention	1.43	1.45	1.40	1.43	1.60	1.20
Functional comfort	1.60	1.70	1.47	1.51	1.70	1.27
Eating	2.54	3.05	1.87 **c**	2.12 (n=32)	2.47 (n=17)	1.73 **d**
Speaking	2.14	2.25	2.00	1.91 (n=34)	2.05 (n=19)	1.73

	Survivors at T3 (n=20)								
	T1			T2			T3		
	total	RTX	n-RTX	total	RTX	n-RTX	total	RTX	n-RTX
	n=20	n=9	n=11	n=20	n=9	n=11	n=20	n=9	n=11
General	1.65	1.44	1.82	1.40	1.44	1.36	1.50	1.44	1.55
Upper denture	1.45	1.44	1.45	1.45	1.33	1.55	1.40	1.33	1.45
Lower denture	1.55	1.44	1.64	1.35	1.33	1.36	1.55	1.67	1.45
Appearance	1.30	1.22	1.36	1.35	1.33	1.36	1.20	1.22	1.18
Retention	1.50	1.44	1.55	1.30	1.33	1.27	1.50	1.78 **a**	1.27
Functional comfort	1.55	1.44	1.64	1.35	1.44	1.27 **b**	1.50	1.56	1.45
Eating	2.20	2.56	1.91	1.95	2.22	1.73	1.70 **e**	1.78 **e**	1.64
Speaking	2.05	2.00	2.09	1.65	1.56	1.73	1.75	2.00	1.55

Data are depicted for the survivors at T2 and T3, respectively.
*1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied
a Significant difference between five years and one year after placement $p<0.05$
b Significant difference between one year and 6 weeks after placement $p<0.05$
c Significant difference between irradiated and non-irradiated patients at the same point in time $p< 0.01$
d Significant difference between irradiated and non-irradiated patients at the same point in time $p< 0.05$
e Significant difference between five years and 6 weeks after placement $p<0.05$
RTX: irradiated patients, n-RTX: non-irradiated patients

Table 4. Overall denture satisfaction rate (range 0–10; 0 = completely dissatisfied and 10 = completely satisfied). Data are depicted for the survivors at T2 and T3, respectively

	T1	T2	T3
Survivors at T2			
Total n=35	8.0 ± 1.6	7.9 ± 1.8	deceased
RTX n=20	7.5 ± 1.6	7.5 ± 1.9	deceased
n-RTX n=15	8.6 ± 1.5	8.5 ± 1.4	deceased
Survivors at T3			
Total n=20	8.3 ± 1.5	8.5 ± 1.3	8.7 ± 1.2
RTX n= 9	8.1 ± 1.4	8.4 ± 1.2	8.6 ± 1.3
n-RTX n=11	8.5 ± 1.6	8.5 ± 1.4	8.9 ± 1.1

RTX: irradiated patients, n-RTX: non-irradiated patients

Table 5. Chewing Ability (range 0-2; 0 = good, 1 = moderate, 2 = bad)

	Survivors at T2 (n=35)					
	T1			T2		
	total n=35	RTX n=20	n-RTX n=15	total n=31	RTX n=16	n-RTX n=15
Soft food	0.50	0.72	0.20 ***1***	0.38	0.57	0.18
Tough food	0.90	1.25	0.44 ***2***	0.72	0.98	0.44 ***1***
Hard food	1.32	1.43	1.18	1.04 ***a***	1.23	0.84 ***b***

	Survivors at T3 (n=20)								
	T1			T2			T3		
	total n=20	RTX n=9	n-RTX n=11	total n=20	RTX n=9	n-RTX n=11	total n=18	RTX n=8	n-RTX n=10
Soft food	0.33	0.52	0.18	0.35	0.63	0.12	0.36 (n=19)	0.57 (n=9)	0.17
Tough food	0.67	1.00	0.39	0.60	0.85 ***a***	0.39	0.62	0.67	0.60
Hard food	1.13	1.07	1.18	0.87 ***a***	1.00	0.76 ***a***	0.81	0.88	0.77

Data are depicted for the survivors at T2 and T3, respectively.
a Significant difference between one year and 6 weeks after placement $p<0.05$
b Significant difference between one year and 6 weeks after placement $p=0.01$
1 Significant difference between irradiated and non-irradiated patients at the same point in time $p< 0.05$
2 Significant difference between irradiated and non-irradiated patients at the same point in time $p< 0.01$
RTX: irradiated patients, n-RTX: non-irradiated patients

Denture satisfaction was considered as good, with the least favourable scores on eating and speaking at all evaluations (Table 3). Irradiated patients were more satisfied concerning eating with their dentures at T3 than at T1 (Wilcoxon signed ranks test, z=-2.332, P=0.02). However, between T2 and T3, the reported retention of their dentures had decreased. The non-irradiated patients were more satisfied with the functional comfort of their dentures at T2 than at T1. For the 1-year survivors at 6 weeks and 1 year after placement of the dentures, the irradiated patients reported more difficulty with eating than the non-irradiated patients (data not shown, for details see Schoen et al. 2008).

The overall denture satisfaction was high and did not differ between different evaluation points for the irradiated and non-irradiated patients (independent t-test, P>0.05). Also, there was no difference in overall denture satisfaction between irradiated and non-irradiated patients (Table 4, independent t-test, P>0.05). The reported chewing ability of hard food improved for the non-irradiated patients and irradiated patients who survived T3 between T1 and T2 (Table 5).

Discussion

This study showed a high percentage of rehabilitated patients with a functioning implant-retained mandibular overdenture 5 years after placement of the overdenture. One year after placement of the dentures 92% and after 5 years 83% of the surviving patients were functioning with their overdentures. In addition, we found a high overall survival rate of 92.8% of the implants in these patients and healthy peri-implant tissues. Patients were satisfied with their prosthesis, even though the chewing ability was impaired.
A wide variety in the percentages (22–91%) of patients who completed prosthetic treatment after head and neck oncology treatment has been reported in the literature (Rogers et al. 2005; Garrett et al. 2006; Schepers et al. 2006; Nelson et al. 2007; Schoen et al. 2007; Hundepool et al. 2008; Adell et al. 2008; Smolka et al. 2008). This variation in percentages was heavily depending on the type of patients included, the type of reconstruction, the survival rate of patients and implants and the follow-up. A main advantage of installing implants during ablative surgery seemed to be the high percentage of rehabilitated patients and the time reduction for (pre)prosthetic rehabilitation. Regarding implant installation after oncological treatment, for many patients, the anticipated benefits of an implant-retained overdenture often did not outweigh the burden of another surgical intervention. An additional disadvantage of implantation during ablative surgery, which has to be mentioned, is the risk that implants will not be used due to patients refusing the abutment connection operation and thus refrain from prosthetic rehabilitation (n=3 in this study), or tumour-related death or death because of other reasons (n=7 in this study). Patients with severe comorbidity or higher tumour stages might show less long-time survival. However, this group is also thought to have less favourable anatomic conditions after treatment and therefore was supposed to benefit the most and as early as possible from implant support to be able to function with their prostheses. From a health economics point of view, the loss of resources needs more detailed analyses. Funding of care seems an important decisive factor as funding might be related to survival of the patients. Some jurisdictions will fund care irrespective of expected duration of survival of the patients, while others do not fund care until after 2 years of survival or even delay funding to 5-year survival. In the Dutch health care funding system, the cost of rehabilitation is taken care of irrespective of the prognosis of the patient. These various jurisdictions create a tremendous ethical dilemma and particularly so for clinicians

providing care where managed or public funding is applied. We feel that funding should be made available irrespective of the predicted survival of the patients. Which care the patients should be provided with, should be dependent on professionals' opinion aiming for early restoration of oral functioning where judged feasible for a particular patient. In other words, whether implant treatment is indicated in a particular patient should be based on the complex of expected benefits in that patient taking the expected survival of the patient in consideration too (the patient should be able to benefit of the treatment) and not be predominantly directed by funding jurisdictions.

Implant survival was higher in patients who did not receive radiotherapy after tumour surgery. This is in agreement with other studies (Granström 2003, 2005; Yerit et al. 2006; Colella et al. 2007; Idhe et al. 2009). In addition, we observed more late loss of implants in our study (Fig. 2). However, a failure rate of 10.6% in irradiated bone over a period of 5 years is considered good. After 5 years, 26 patients had died; these patients were excluded from the survival analyses for those evaluation time points that were not complete (in none of these patients additional implants had been lost between the last evaluation and the date they passed away). Also, the percentage of patients who had received postoperative radiotherapy decreased over time among the survivors (73% at baseline versus 54% 5 years after placement of the dentures). This could have contributed to the relatively low failure rate of implants in irradiated bone.

The clinical variables assessed in our study were low at all evaluations, showing a good peri-implant health. These findings were comparable with findings in healthy subjects (Meijer et al. 2004, 2009; Visser et al. 2005). This can be the result of the strict oral hygiene regime to which patients were subjected. However, in a few patients with the tumour located in the ventral part of the floor of the mouth, and who received soft tissue flaps adjacent to the implant site, lasting soft tissue problems were seen, due to mobility and thickness of the skin (n=3 in this study). In this type of patients, soft tissue problems have to be anticipated on beforehand.

Rotational panoramic radiographs are widely used in the evaluation of bone around the implants, although they lack sharpness, distort images and superimpose bony structures of the spine (Meijer et al. 1992). Reproducibility is difficult to achieve. The score used in this study (Geertman et al. 1996) can be seen as a rough estimation of the bone level, suitable for comparison of relatively large differences. Bone loss is to be expected after implant installation, as defined by Adell et al. (1981) and Albrektsson et al. (1986), but no statistical significant differences were observed in bone levels around irradiated implants and non-irradiated implants. It is possible that this is the result of the measuring method. Late implant loss was higher in irradiated patients, which may point to a more severe bone loss in irradiated patients. As the peri-implant tissues remained healthy and the implants were still in use for the implant-retained overdenture, there were no clinical consequences. In the future, however, it is imaginable that implants with higher levels of bone loss are yet suspect to being lost.

Denture satisfaction was considered very high, comparable with the level reported for healthy subjects (Stellingsma et al. 2003), which is surprising, because the oral condition in these oral cancer patients was compromised. However, denture satisfaction was measured of the 20 patients with a functioning prosthesis after 5 years, which might be a more favourable result than would apply for the total group of living patients at T3 (n=24).
The subjective chewing ability did not reach the same level as seen in healthy subjects (Stellingsma et al. 2005). The oral function is compromised in oral cancer patients, as a result of the oncological surgery and, when necessary, additional radiotherapy. Irradiated patients seemed to have more difficulty chewing tough food, perhaps due to hyposalivation and its related complaints resulting from radiotherapy. This difference, however, was not present 5 years after placement of the dentures, which might be due to recovery of the early (mainly mucosal) effects of radiotherapy and patients becoming adjusted to their oral condition. However, patients with a feeding tube or patients who did not wear their dentures while eating (n=2 at T3) did not complete this questionnaire, which might have resulted in more favourable results as well. Tang et al. (2008) indicated in their review that implant-retained prosthetic rehabilitation resulted in the most favourable masticatory outcomes, when compared with no prosthetic treatment or conventional prosthetic treatment. It is probable that, without implant-retained overdentures, the patients in our study would have reported even worse scores on chewing ability.
From this study, it is concluded that the percentage of patients with successful prosthetic treatment with an implant-retained overdenture was high with the implants installed during ablative surgery. In addition, survival rate of implants installed during ablative surgery is high, although the survival rate in irradiated bone is less than in non-irradiated bone. When oral rehabilitation can be established with an implant-retained overdenture in the mandible, satisfaction levels remained high during the 5-year follow-up.

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Chapter 2.3

Overdentures on primary mandibular implants in patients with oral cancer: a follow up study over 14 years

Abstract

Objectives

We aimed to assess oral functioning, patients' satisfaction, condition of peri-implant tissues, and survival of implants up to 14 years after their insertion in patients with oral cancer who had had mandibular overdentures placed over primary implants.

Materials and methods

Endosseous dental implants were inserted prospectively in the interforaminal region of the mandible during resection of the tumour in 164/180 patients with oral cancer. All 58 patients were evaluated by questionnaires and clinical assessments during a final assessment in 2012.

Results

In 84% of the patients an implant-retained mandibular overdenture was inserted. Completion of prosthetic rehabilitation and oral functioning was not associated with primary site or stage of the tumour, number or type of implants inserted, or the type of reconstruction. Over time the peri-implant mucosa was usually free of inflammation. More implants were lost in irradiated patients (8.5%) than in non-irradiated patients (0.5%). Irradiated patients reported more problems in oral functioning and less satisfaction than non-irradiated patients. Patients with an implant-retained mandibular overdenture reported fewer problems in oral functioning than patients without an overdenture.

Conclusion

Primary implant insertion in oral cancer patients should be routinely incorporated in the surgical planning as oral functioning in patients wearing mandibular overdentures improves considerably and peri-implant health is at least reasonable.

Introduction

Surgical tumour resection in the oral cavity can have a profound effect on oral functions such as chewing, swallowing and intelligible speech[1]. Postoperative radiotherapy usually further compromises oral functioning. Changes in oral anatomy due to surgery and sequelae from radiotherapy such as xerostomia and intolerance of the denture-bearing mucosa to mechanical loading limit prosthetic rehabilitation of these patients[2]. As a result, prosthetic rehabilitation of edentulous oral cancer patients is difficult and therefore often omitted. However, adequate prosthetic rehabilitation is a pivoting factor for patients to regain oral functions[3].

In healthy patients oral function can be improved using implant-retained mandibular overdentures [4,5]. This treatment has evolved into an important asset in the rehabilitation of oral cancer patients as well[6]. Insertion of implants may be best during the ablative surgery (primary implant insertion) [7-11] as it has been shown that many patients postpone or simply decline an offered implant-based treatment after tumour surgery and postoperative radiotherapy[12-14].

Primary implant insertion appreciably reduces time between tumour surgery and prosthetic rehabilitation. This may allow patients to better and earlier regain their oral function after completion of the oncologic treatment. Another advantage is the presumed higher survival rate of the implants when implants are inserted before the radiotherapy instead of after radiotherapy, as initial osseointegration will have taken place before implants and mandibular bone are exposed to ionising radiation. Systematic reviews showed that most publications on dental implants in oral cancer patients referred to implants inserted after the surgery and/or radiotherapy had been completed, while only a very limited number of studies reported on primary implants [15,16.] We presume that the benefits of primary insertion outweigh the risk the implants will not be used for prosthetic rehabilitation. However, further study is needed to estimate which oral cancer patients can benefit from primary implants. Does it depend on the primary location of the tumour, its size, if the patient is irradiated or the type of reconstructive surgery?

In this study, we have assessed treatment outcomes (which patients benefit, their quality of life, their oral functioning and satisfaction, the condition of peri-implant tissues and implant survival) in a prospective cohort of 164 oral cancer patients with primary mandibular implants to support an implant-retained mandibular overdenture up to 14 years after insertion of the implants.

Patients and methods

Patient inclusion criteria and treatment

All consecutive edentulous patients with oral cancer referred to the Head and Neck Oncology group of the University Medical Center Groningen between May 1998 and November 2010 were screened to be included in this study. Inclusion criteria were:

- edentulous upper and lower jaw;
- history of prosthetic problems related to lack of stability and retention of the lower denture or expected lower denture-related problems after oncologic treatment;
- malignancy in lower oral cavity region or oropharynx (squamous cell carcinoma of tongue, floor of the mouth, mandibular gingiva, buccal mucosa, lower lip, or tonsil) with the need for primary curative ablative surgery;
- little or no improvement expected from making new dentures after oncological treatment.

At the inclusion, all patients were offered a choice of conventional or implant-based treatment. Tumour surgery, implant insertion and prosthetic treatment were performed at the University Medical Center Groningen. The implants were 3.75 mm Brånemark implants (Nobelbiocare, Gothenburg, Sweden), either with a machined surface (before September 2003) or a Ti-Unite® surface (from September 2003). All implants were inserted in the interforaminal region of the native bone of the mandible immediately after the ablative tumour surgery procedure. Implant insertion and abutment placement were planned as a two-stage surgical procedure. Depending on the available bone and prosthetic demands 2, 3 or 4 implants were inserted.

A 3-months osseointegration period before abutment placement was considered in patients not subjected to radiotherapy after tumour surgery. In patients that were subjected to postoperative radiotherapy or chemoradiation, radiotherapy started in general within 6 weeks after surgery. The osseointegration time before abutment placement in irradiated patients was increased to at least 9 months after surgery, i.e. 6 months after completion of radiotherapy, according to Schoen et al[9]. After abutment placement, an implant-retained overdenture was made.

Clinical assessments

Postoperative complications and implant survival were recorded from the time of surgery until March 2012. Periodontal indices were assessed during a final assessment in 2012 according to Schoen et al[9]. Patients in whom prosthetic rehabilitation was completed less than one year before assessment were excluded from this analysis.

Radiographic evaluation

Marginal bone resorption for the implants was assessed using panoramic radiographs, where the bone level was calculated in relation to the implant shoulder.

Quality of life, functional assessments and denture satisfaction

During a final assessment in 2012, quality of life, oral function and denture satisfaction were assessed using validated questionnaires. Again, patients in whom prosthetic rehabilitation was completed less than one year before assessment were excluded from this analysis. Quality of life (QoL) was assessed using the core questionnaire (QLQ-C30) and head and neck module (QLQ-H&N35) of the European Organization for Research and Treatment of Cancer (EORTC)[17].

Denture satisfaction was assessed using a validated questionnaire consisting of 8 separate items focusing on the function of upper and lower dentures, and on specific features such as aesthetics, retention and functional comfort[18]. Overall denture satisfaction was expressed on a 10-point rating scale. Subjective chewing ability was assessed using a 9-item questionnaire on which the patient could rate on a 3-point scale their ability to chew different kinds of food [5]. Psychological, physical and social impact of oral disorders was assessed using the Oral Health Impact Profile (OHIP)[19].

Data analysis

The data were evaluated using SPSS (IBM SPSS Statistics, version 20, Armonk, NY). For non-parametric data (4 items of the EORTC QLQ-C30: emotional functioning, cognitive functioning, social functioning and pain) Mann-Whitney and Kruskal- Wallis tests were used. For parametric data (all other variables) independent t-tests and one way ANOVA were used.

For testing the distribution among groups the Fisher's exact test was used for comparing two different groups and the chi square test was used for several different groups. Generalized Estimating Equation models were made using Stata IC version 11.0 (StataCorp,Texas USA). For all statistical analyses α was set at 0.05.

Results

Patients and implants

One hundred and eighty patients fulfilled the inclusion criteria. In 15 patients no implants were inserted due to anatomical limitations of the mandible that appeared or were created during ablative surgery, such as lack of bone volume for implant insertion. One patient had chosen conventional treatment instead of implant insertion. Thus, a total of 16 patients were excluded for analyses. Patient selection is depicted in Figure 1. The characteristics of the study group are presented in Table 1.

Figure 1. Algorithm showing selection of patients. The light blue boxes represent the patients' status during the final recall in 2012

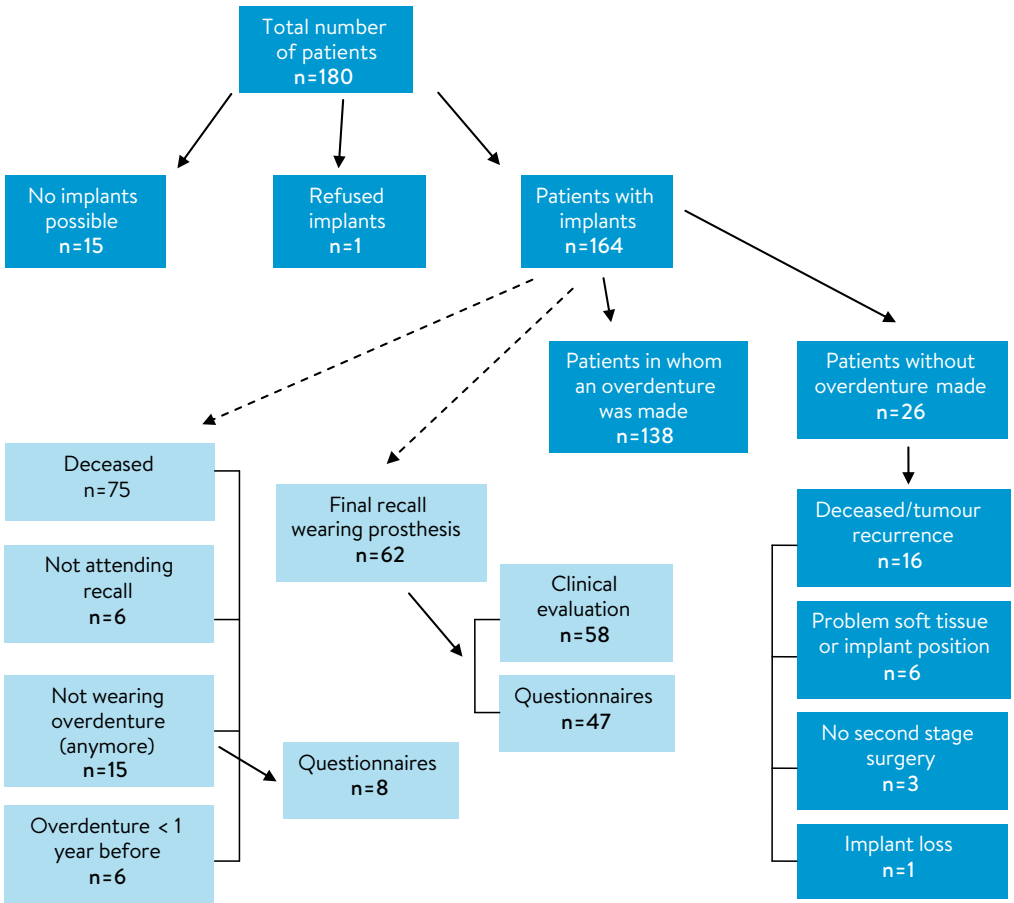


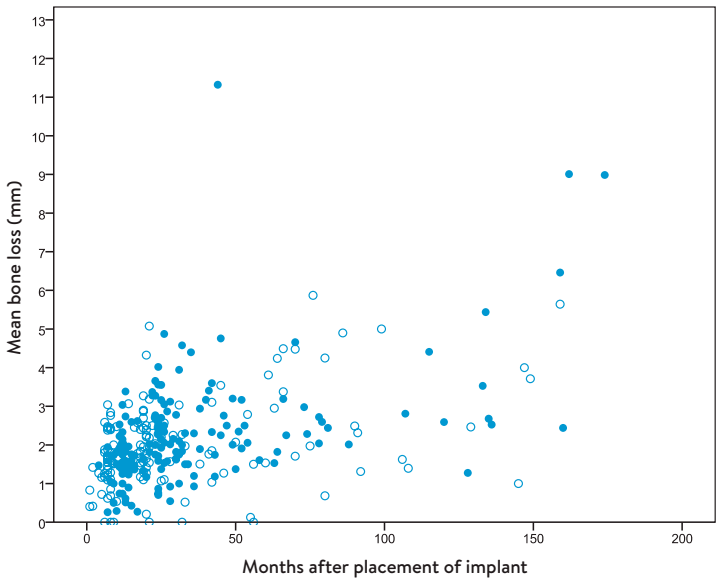
Table 1. Characteristics of the study group (RTX= in irradiated patients, n-RTX= in non- irradiated patients)

Patients	
Total number	164
Gender (number male/ female)	98/ 66
Mean age at time of surgery in years (SD, range)	64.8 (10.9, 39-88)
Tumour UICC stage I (number of patients)	35
Tumour UICC stage II (number of patients)	40
Tumour UICC stage III (number of patients)	40
Tumour UICC stage IV (number of patients)	49
Smoking/non-smoking/unknown (number of patients)	91/ 65/ 8
Radiotherapy (number irradiated/ non-irradiated)	100/ 64
Median follow-up in years (range)	3.8 (0-14.5)
Patients with 2/3/4 implants	62/ 8/ 94
Patients with overdenture (percentage)	138 (84.2%)
Median time between surgery- prosthesis placement in months RTX (range), n=81	11.3 (5.1-64.2)
Median time between surgery- prosthesis placement in months n-RTX (range), n=57	6.3 (4.2-18.7)
Median time prosthesis was worn in years (range)	3.1 (0-13.4)
Implants	
Total number	524
Radiotherapy (number irradiated/ non-irradiated)	318/ 206
Number of lost implants RTX/n-RTX (percentages)	31/ 5 (9.4%/ 2.4%)
Implants lost without implants lost due to resection of recurrent tumour RTX/n-RTX (percentages)	27/ 1 (8.5%/ 0.5%)

Loss of implants in this cohort was higher in irradiated patients than in non-irradiated patients, when excluding implants lost due to resection of recurrent tumour 8.5% versus 0.5% of the implants respectively (Fisher's exact p< 0.001). Implant loss was not associated with smoking at the time of the intake. Furthermore, implant loss in irradiated patients was not dependent on the implant surfaces applied, viz. a Ti-unite surface (16 out of 153 implants) or a machined surface (11 out of 165 implants; Fisher's exact p=0.318). Osteoradionecrosis (ORN) located in proximity of the implants was observed in 5 patients. Ten implants were removed combined with a sequestrectomy. Three patients received additional hyperbaric oxygen (HBO). In 4 patients treatment of ORN was successful; 1 patient appeared to have a tumour recurrence with pathological fracture of the mandible in the area of the ORN. Smoking at time of intake was not associated with the occurrence of ORN. No valid data were available whether or not the patiets continued their smoking habits after treatment.

Bone loss around the implants increased significantly over time, both in irradiated as in non-irradiated patients (Fig 2). There was no significant bone loss in irradiated patients compared to in non-irradiated patients (Longitudinal data analysis, GEE model, p=0.649).

Figure 2. Mean bone loss (difference between bone level and the implant shoulder) in mm for irradiated patients (filled dots) and non-irradiated patients (outlined dots) over time



In 26 patients (16%) prosthetic rehabilitation was not completed for a number of reasons (Fig 1). Completion of prosthetic rehabilitation was not associated with radiotherapy (p=0.388) or type of implants inserted (p=0,828, both Fisher's exact), tumour location (p=0.199), the number of implants (p=0.965), type of surgical reconstruction used during tumour surgery (p=0.063) and tumour stage (p=0.119, all chi square test).

Clinical assessments

The median periodontal indices showed reasonably healthy peri-implant mucosa (Table 2).

Table 2. Periodontal indices of the patients during final recall in 2012

	N	Median (25%-75%)
Plaque index (score 0 to 3)	58	1.00 (0.31-1.54)
Calculus (score 0 or 1)	58	0.00 (0.00-0,54)
Bleeding index (score 0 to 3)	58	1.29 (0.75-1.50)
Gingiva index (score 0 to 3)	58	0.29 (0.00-1.00)
Pocket depth (mm)	57	2.81 (2.37-3.25)
With of attached gingiva (score 0-3)	58	2.25 (1.63-2.78)

Quality of life, functional assessments and denture satisfaction

Irradiated patients reported more insomnia, more problems with social eating, more problems with mouth opening, more limitations of oral function, and less satisfaction than non-irradiated patients (Table 3).

Table 3. Results of EORTC QLQ-C30, EORTC QLQ-H&N 35, Oral Health Impact Profile (OHIP), denture satisfaction and subjective chewing ability questionnaires during final recall in 2012, 1.5-14.5 years postoperatively. (RTX= irradiated, n-RTX= non-irradiated, MW= Mann-Whitney test)

	RTX (n=35) Mean±SD	nRTX (n=23) Mean±SD	Statistic test	95 % confidence Lower	interval Upper	t	df	p-value
EORTC QLQ-C30								
Global health status/QoL	80.5±16.3	75.4±21.1	T-test	-14.97	4.75	-1,04	56	0.30
Physical function	79.8±19.9	70.4±23.2	T-test	-13.44	52.35	1,76	57	0.085
Role function	79.0±26.6	75.4±32.1	T-test	-11.86	19.23	0.48	56	0.64
Emotional function	88.3±17.6	77.5±29.7	MW					0.16
Cognitive function	87.6±16.8	85.5±23.7	MW					0.98
Social function	85.3±21.2	86.2±31.2	MW					0.24
Fatigue	22.1±23.3	26.1±25.6	T-test	-8.94	16.98	0.62	57	0.54
Nausea / vomiting	1.4±8.3	6.5±14.0	T-test	-1.44	11.71	1.59	32.08	0.12
Pain	15.7±23.6	17.4±29.5	MW					0.89
Dyspnoea	15.7±25.8	30.4±31.6	T-test	-29.77	0.38	-1.95	57	0.056
Insomnia	10.2±19.2*	29.0±35.3*	T-test	-35.17	-2.43	-2.35	30.46	0.026
Appetite loss	12.0±27.8	11.6±25.8	T-test	-14.01	14.90	0.061	57	0.95
Constipation	7.6±21.5	14.5±28.1	T-test	-19.95	6.21	-1.05	56	0.30
Diarrhoea	2.9±12.4	8.7±18.0	T-test	-14.58	2.90	-1.36	35.68	0.18
Financial problems	4.9±14.5	8.7±25.1	T-test	-14.31	6.72	-0.72	55	0.47
EORTC QLQ-H&N35								
Pain	14.3±16.1	18.6±27.6	T-test	-8.954	17.50	0.66	30.13	0.51
Swallowing	21.6±22.7	15.1±29.8	T-test	-20.65	7.63	-0.92	54	0.36
Senses	19.0±24.3	17.4±27.4	T-test	-15.55	12.31	-0.23	55	0.82
Speech	17.8±20.4	14.7±22.6	T-test	-14.72	8.50	-0.54	54	0.59
Social eating	28.5±31.3*	12.1±22.2*	T-test	-31.91	-0.92	-2.12	53	0.038
Social contact	8.7±16.5	9.0±18.8	T-test	-9.26	9.75	0.052	54	0.96
Sexuality	30.0±37.6	52.2±40.3	T-test	-3.29	47.74	1.763	38	0.086
Teeth	16.7±25.4	14.3±27.0	T-test	-12.30	17.07	0.33	51	0.75
Opening mouth	36.2±35.6*	18.2±28.6*	T-test	-0.03	36.05	2.00	55	0.050
Dry mouth	45.7±33.4	31.8±36.3	T-test	-4.95	32.74	1.48	55	0.15
Sticky saliva	28.6±36.3	21.2±35.0	T-test	-12.15	26.87	0.76	55	0.45
Coughed	17.1±23.4	18.2±26.7	T-test	-14.51	12.43	-0.16	55	0.88
Felt ill	9.5±17.3	15.2±32.1	T-test	-20.85	9.59	-0.76	28.77	0.46
Pain killers	28.1±45.7	47.8±51.1	T-test	-46.63	7.23	-1.47	44.20	0.15
Nutritional support	30.3±46.7	17.4±38.8	T-test	-10.08	35.90	1.13	52.25	0.27
Feeding tube	6.1±24.2	4.3±20.9	T-test	-10.77	14.19	0.28	54	0.78
Weight loss	15.2±36.4	21.7±42.2	T-test	-27.75	14.58	-0.62	54	0.54
Weight gain	24.2±43.5	30.4±47.0	T-test	-30.69	18.31	-0.51	54	0.61
OHIP								
OHIP14	17.4±12.6	14.4±15.2	T-test	-0.80	2.96	1.31	57	0.19
Functional limitation	13.3±6.8*	8.7±6.6*	T-test	0.88	8.15	2.49	56	0.016
Physical pain	8.3±5.9	7.5±7.5	T-test	-2.61	4.35	0.50	58	0.62
Physical disability	13.3±8.5	8.8±9.4	T-test	-0.26	9.20	1.89	57	0.063

Psychological discomfort	4.4±4.4	4.0±5.6	T-test	-2.21	2.93	0.28	58	0.78
Psychological disability	3.7±4.1	4.3±6.6	T-test	-3.73	2.38	-0.45	35.07	0.66
Social disability	2.6±3.3	3.2±5.4	T-test	-2.83	1.76	-0.46	56	0.65
Denture satisfaction								
Denture satisfaction (range 8-40)	15.4±5.7	13.0±4.2	T-test	-0.55	5.38	1.64	49	0.11
Overall denture satisfaction (range 0-10)	7.4±1.4*	8.1±0.9*	T-test	-1.38	-0.095	-2.30	50.76	0.025
Chewing/ eating (range 0-18)	8.9±6.1	6.6±6.2	T-test	-1.08	5.76	1.37	54	0.18

* p<0.05

Chewing ability and several items reflecting oral functioning of the EORTC QLQ-C30 and QLC-H&N35 and OHIP were significantly worse for patients not wearing an implant-retained mandibular overdenture on the implants (Table 4).

Table 4. Results of EORTC QLQ-C30. EORTC QLQ-H&N 35. Oral Health Impact Profile (OHIP). denture satisfaction and subjective chewing ability questionnaires during final recall in 2012, 1.5-14.5 years postoperatively. (Proth= patient wearing an implant-retained mandibular overdenture. nproth= patient not wearing an implant-retained mandibular overdenture)

	proth (n=51) Mean±SD	nproth (n=8) Mean±SD	Statistic test	95 % confidence Lower	interval Upper	t	df	p-value
EORTC QLQ-C30								
Global health status/QoL	79.6±18.2	70.2±18.5	T-test	-24.07	5.39	-1.27	56	0.21
Physical function	77.6±19.6	66.7±31.3	T-test	-31.79	56.75	1.05	57	0.30
Role function	79.7±26.4	64.6±40.3	T-test	-18.87	49.04	1.03	8.00	0.34
Emotional function	84.6±24.0	79.8±20.9	MW					0.39
Cognitive function	87.3±19.9	83.3±19.2	MW					0.53
Social function	88.3±23.4*	66.7±33.3*	MW					0.04
Fatigue	22.7±24.2	29.9±23.9	T-test	-11.22	25.63	0.78	57	0.44
Nausea / vomiting	3.9±11.8*	0.0±0.0*	T-test	-7.248	-0.60	-2.37	50.00	0.02
Pain	18.0±27.0	6.3±12.4	MW					0.27
Dyspnoea	20.9±27.5	25.0±38.8	T-test	-26.24	18.07	-0.37	57	0.71
Insomnia	19.0±29.3	8.3±15.4	T-test	-10.65	31.89	1.00	57	0.32
Appetite loss	9.8±25.2	25.0±34.5	T-test	-35.39	5.00	-1.51	57	0.14
Constipation	11.1±25.5	4.8±12.6	T-test	-13.41	26.11	0.644	56	0.52
Diarrhoea	3.9±12.7	14.3±26.2	T-test	-34.65	13.92	-1.03	6.39	0.34
Financial problems	6.0±18.7	9.5±25.2	T-test	-19.29	12.24	-0.45	55	0.66
EORTC QLQ-H&N35								
Pain	16.7±22.0	10.7±13.4	T-test	-23.13	11.23	-.69	55	0.49
Swallowing	18.0±25.9	28.7±21.7	T-test	-11.41	32.81	0.97	54	0.34
Senses	18.0±26.5	21.4±15.9	T-test	-17.22	24.08	0.33	55	0.74

Speech	13.9±20.1*	34.9±20.7*	T-test	4.64	37.31	2.57	54	0.013
Social eating	18.1±26.6†	48.8±32.4†	T-test	8.59	52.92	2.78	53	0.007
Social contact	5.9±12.3	29.8±30.8	T-test	-4.59	52.41	2.03	6.28	0.086
Sexuality	38.7±38.9	33.3±57.7	T-test	-54.15	43.34	-0.22	38	0.82
Teeth	16.0±26.3	11.1±19.2	T-test	-26.20	35.97	0.32	51	0.75
Opening mouth	26.0±31.8‡	52.4±42.4‡	T-test	-53.17	0.40	-1.97	55	0.053
Dry mouth	40.0±35.0	42.9±37.1	T-test	-31.35	25.63	-0.20	55	0.84
Sticky saliva	22.7±33.3	47.6±46.6	T-test	-53.25	3.34	-1.77	55	0.083
Coughed	15.3±23.5	33.3±27.2	T-test	-37.38	1.38	-1.86	55	0.068
Felt ill	11.3±24.8	14.3±17.8	T-test	-22.51	16.60	-0.30	55	0.76
Pain killers	37.5±48.9	28.6±48.8	T-test	-30.76	48.62	0.45	53	0.65
Nutritional support	22.4±42.2	42.9±53.5	T-test	-55.69	14.88	-1.16	54	0.25
Feeding tube	4.1±20.0	14.3±37.8	T-test	-45.21	24.80	-0.70	6.49	0.51
Weight loss	16.3±37.3	28.6±48.8	T-test	-43.66	19.17	-0.78	54	0.44
Weight gain	28.6±45.6	14.3±37.8	T-test	-22.04	50.61	0.79	54	0.43
OHIP								
OHIP14	14.2±12.8†	29.3±12.6†	T-test	-0.59	-0.18	-4.00	17.80	0.001
Functional limitation	10.5±6.9†	19.5±1.6†	T-test	-11.33	-6.59	-7.70	32.45	0.000
Physical pain	7.7±6.6	9.7±6.0	T-test	-7.01	3.00	-.81	58	0.42
Physical disability	9.9±8.3†	22.0±6.4†	T-test	-18.31	-6.00	-3.96	57	0.000
Psychological discomfort	3.4±3.9*	9.8±7.0*	T-test	-12.24	-0.53	-2.53	7.67	0.036
Psychological disability	3.4±4.9*	7.5±6.1*	T-test	-7.95	-0.30	-2.16	57	0.035
Social disability	2.3±3.7†	6.6±5.6†	T-test	-7.36	-1.25	-2.82	56	0.007
Denture satisfaction								
Denture satisfaction (range 8-40)	14.2±5.2							
Overall denture satisfaction (range 0-10)	7.7±1.3							
Chewing/eating (range 0-18)	7.0±5.9	15.3±2.7	T-test	-11.08	-5.49	-6.28	16.11	0.000

* $p<0.05$
† $p<0.01$
‡ $p=0.053$

No differences were seen in oral function, chewing ability and satisfaction between the different tumour stages and tumour locations, between the different types of reconstruction used during tumour surgery, or between the number of implants inserted during the ablative surgery (ANOVA, $p>0.05$ and Kruskal- Wallis, $p>0.05$, results not shown).

Discussion

Many edentulous oral cancer patients may benefit from insertion of endosseous dental implants during ablative surgery at an early stage after ablative tumour surgery. Completion of prosthetic rehabilitation and oral functioning, chewing ability and satisfaction were independent of tumour location, tumour stage, type of reconstruction used during ablative surgery and the number of implants inserted. Patients wearing an implant-retained mandibular overdenture had significantly better chewing ability, less social disability and better oral functioning than patients not wearing an overdenture. Furthermore, patients that did not undergo postoperative radiotherapy had higher scores for satisfaction and oral functioning than irradiated patients. Implant loss was higher in irradiated patients than in non-irradiated patients.

Mizbah et al.[14] compared patients with implants inserted during ablative surgery with patients that received implants postponed. They showed that patients with primary implants had their implant-retained overdenture on average after 7.4 months, while patients that received implants postponed received their overdenture after 27.4 months. In this study the median time between implant insertion and prosthesis placement was 11.3 months for irradiated patients and 6.3 months for non-irradiated patients. We used a minimal time-span of 6 months between the end of the radiotherapy and abutment placement, depending on the oral situation of the individual patient. The time between implant insertion and prosthetic rehabilitation can be reduced further, with shortening the time between completion of radiotherapy and abutment placement or by using one stage implants. However, it seems advisable to wait with abutment placement for the short-term side-effects of the radiotherapy such as mucositis to improve, e.g. 3 months at least. To our knowledge, no publications exist on one-stage implant insertion during ablative surgery. We hypothesize that this will yield similar results, also in patients that will be irradiated postoperatively, thus in most cases omitting the need of a second surgical intervention.

Completing prosthetic rehabilitation and its outcome was not associated with tumour location. In 6 patients no implant-retained mandibular overdenture could be made due to improper implant positioning or because of problems with the peri-implant tissue related to the surgical treatment of the tumour. Noticeable was that in 5 out of these 6 patients the primary tumour was located in the ventral area of the floor of the mouth-the same area in which the implants were inserted. This can impede proper implant positioning as the anatomical situation and intermaxillary relationship are altered during surgery. Also it is more difficult to gain proper attached mucosa around the implants and retain a proper buccal and/or lingual vestibule to accommodate an overdenture (neutral zone).

Oral functioning and patients' satisfaction was not associated with the number of implants inserted (2, 3 or 4 implants), as is comparable to previous studies in healthy subjects[20, 21]. From a health- economics point of view, and from a patients' perspective of being able to perform proper oral hygiene in a compromised oral condition, inserting 2 implants during resection of the tumour seems advisable. A disadvantage of inserting 2 implants can be

that implant loss results in the patient not being able to wear an overdenture. In the 3 patients in our study in whom only one implant was left, it was still possible to provide an implant retained overdenture only attached to this one implant.

In this cohort study both short-term and long-term results were presented. Previous studies have shown that the outcome of quality of life and oral functioning questionnaires and patients' satisfaction remained stable between 1 and 5 years after prosthetic rehabilitation[10, 11].
Implant loss is inevitable, especially in irradiated patients, in whom survival rates reported in the literature vary largely[15-16, 22]. In this study all implants were inserted in native mandibular bone by several consultants as well as residents. We therefore consider these results to be a reflection of what is achievable in routine care. ORN leading to implant loss was observed in 5 cases (5% of irradiated patients). This risk on developing ORN and implant loss is presumed to be higher when implants are inserted post radiotherapy. Comparison, however, is difficult since most studies have reported on implants placed after radiotherapy[15]. Primary implants can cause backscattering of radiation, resulting in an increased radiation dose in the surrounding bone in front of and next to the implants of 10-21%[23, 24]. Whether this locally increased radiation dose can be the explanation for the observed higher implant loss in irradiated patients or a higher risk on developing ORN is not yet known, but presumably, even when this risk is increased, this risk will still be lower than for implants placed after radiotherapy.
Implant loss and ORN were not associated with smoking at the time of inclusion of the patients in this study. From the patients' records no reliable information could be retrieved whether patients continued their smoking habit after the oncological treatment or not. However, although it is probable that smoking has contributed to implant loss and occurrence of ORN, their contribution to these phenomena in the current study is considered to be low. Presumably, the leading factor in both implant loss and occurrence of ORN is radiotherapy.

From this study it is concluded that a large number of oral cancer patients in whom implants are inserted during the ablative surgery may benefit at an early stage from an implant-retained mandibular overdenture, with a good oral function, high prosthesis satisfaction and a low risk of implant loss. Implant insertion during ablative surgery in oral cancer patients should be routinely incorporated in the surgical planning.

Conflict of Interest
None declared

Ethics statement/confirmation of patient permission
None required

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Chapter 2.4

Mandibular implants placed during ablative tumour surgery—which patients can benefit?

Dear Editor,

We read the retrospective study of Mizbah et al.[1] on the comparison between oral cancer patients who received endosseous dental implants in the mandibular interforaminal area, either during ablative surgery or delayed, with great interest. We underline their conclusion that patients with the implants placed during ablative surgery will benefit earlier from an implant-retained mandibular overdenture than patients for whom implant placement is delayed, but feel that such a firm conclusion cannot be drawn on the basis of their study design and the analysis provided. In fact, their primary outcome measure, that patients provided with implants during ablative surgery will be subjected to earlier prosthetic rehabilitation without an increased complication rate, is a non issue. As patients for whom implant insertion was postponed had to show a recurrence-free interval of at least 1 year and next had to be subjected to hyperbaric oxygen treatment (HBO) and a longer osseointegration interval, one could expect that most of them would not have started with implant treatment at a date the other patients, with implants placed during the ablation, had already been provided with implant-retained overdentures. Furthermore, from a radio-biological perspective, the risk of developing a higher complication rate is unlikely, as the risk of developing, for example, osteoradionecrosis, will increase with the time elapsed after radiotherapy.

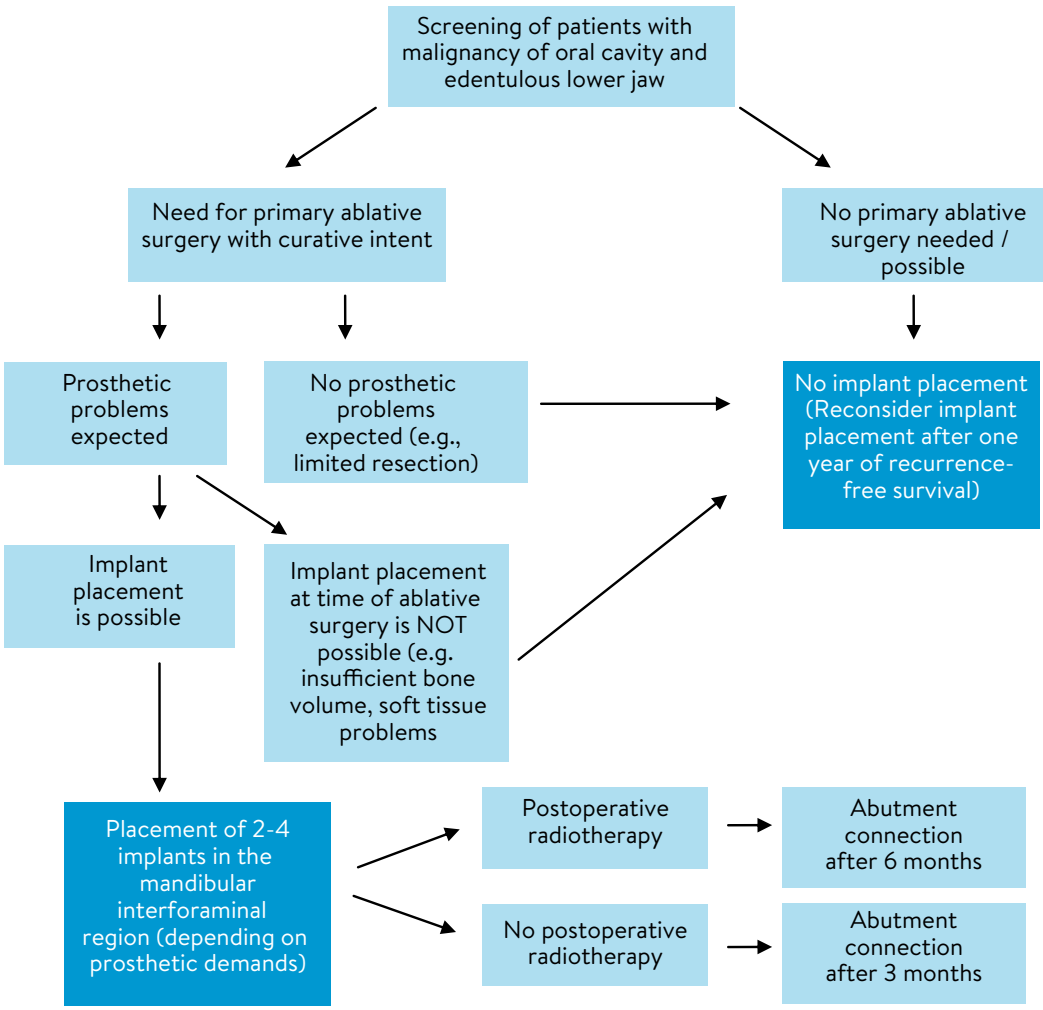
In contrast to what was reported in the prospective studies of, for example, Schoen et al.[2] and Korfage et al.[3, 4], no attempt was made to rate the functional outcome and quality of life using the different treatment protocols, although much attention was paid to this issue in the discussion.

In fact two different protocols applied at different centres were compared, which makes a comparison of the results impossible. What would have been the outcome had the treatments at the two centres been reversed? The same? Or would, for example, implant survival and the number of patients wanting implants later after tumour therapy be higher or lower? Furthermore, the need for HBO is not discussed; it is just standard care at the participating centre. However, in a small prospective, randomized trial[5] it was shown that implant survival and the rate of post-treatment complications were comparable between patients who had received hyperbaric oxygen treatment and those who had not, questioning its need.

Instead of focusing on implant survival and numbers of patients benefitting from implant-retained mandibular overdentures, this paper would gain considerably in strength if the authors analyzed on which indication it was decided to place implants during ablative surgery or not, as well as which subgroup of patients would benefit most from, and would be willing to be subjected to, delayed implant therapy. On the basis of such analyses, including data from other relevant studies, the authors could have proposed an algorithm for determining which patients should be treated during ablative surgery or should have delayed implant placement. Taking the data from their study and our studies [1-6] into account, we would propose the following algorithm (Fig. 1): only patients without the

need or possibility for primary ablative tumour surgery, patients for whom no prosthetic problems are expected, and patients for whom implant placement during surgery is not possible should not receive primary implants. In these patients, delayed implant placement might be considered when indicated and possible. Thus, more patients will benefit from implant-retained overdentures at an earlier stage after oncological treatment, allowing them to improve their oral function as soon as possible. It would be a great asset to the literature if the authors could add to the proposed algorithm on the basis of the data they gathered for their study.

Fig. 1. Decision-making process for mandibular implant placement during ablative surgery



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Oral rehabilitation with implant-based prostheses of two adult patients treated for childhood rhabdomyosarcoma.
Supportive Care in Cancer 2011;19:1477-1480.

Chapter 3

Oral rehabilitation with maxillary implants in childhood rhabdomyosarcoma patients: 2 case-reports

Abstract

Background

Rhabdomyosarcoma is the most common malignant tumour in the nasal and paranasal sinus area at childhood. Multimodal treatment for this disorder has severe side effects due to normal tissue damage. As a result of this treatment, facial growth retardation and oral abnormalities such as malformation of teeth and microstomia can cause esthetic and functional problems.

Case-reports

Two cases are presented of patients with severe midfacial hypoplasia and reduced oral function as a result of treatment of rhabdomyosarcoma of the nasopharyngeal and nasal-tonsil region. With a combined surgical (osteotomy, distraction osteogenesis, implants) and prosthetic (implant-based overdenture) treatment, esthetics and function were improved.

Introduction

Nasopharyngeal rhabdomyosarcoma is usually treated with a combination of chemotherapy, radiotherapy and surgery [1]. Surgical resection of rhabdomyosarcoma is challenging and can result in large maxillofacial defects with loss of function and esthetics of the surrounding tissues. Radiotherapy may result in facial growth retardation, neuroendocrine dysfunction due to radiation injury of the pituitary gland, visual problems and hearing loss [2,3]. In addition, both chemotherapy and radiotherapy have widespread effects on oral tissues. These effects include delayed eruption of the teeth, root stunting, microdontia, hypodontia, discoloration, incomplete calcification of the teeth, microstomia, trismus, velopharyngeal insufficiency and xerostomia [4-9].

As a result of the above-mentioned sequelae, it is not uncommon in childhood cancer survivors that teeth are lost at a later age [5]. Furthermore, the risk of developing dental caries among others can be increased due to reduced salivary flow, changes in the morphology of enamel and dentine and restricted possibilities for oral hygiene (microstomia, trismus). Loss of teeth in these patients will aggravate the already existing loss of oral function and poor esthetics. Moreover, with the loss of teeth, prosthetic treatment becomes even more challenging. Among others, the retention and stability of prostheses are likely to be impaired because the bone volume for good support and tolerance of the denture-bearing mucosa to mechanical loading are reduced. Implant-based prosthodontics might resolve many of the limitations of conventional prosthodontics in a compromised oral situation [6].

In this paper we present two cases of adult patients that were treated for rhabdomyosarcoma during childhood. Both patients had compromised oral function and esthetics due to severe side-effects of their therapy. For both patients a multidisciplinary treatment plan was made.

Case-reports

Patient 1

A 24-year-old male was treated for a nasopharyngeal rhabdomyosarcoma at the age of four. Treatment consisted of surgical debulking of the tumour, followed by chemotherapy and interstitial radiotherapy (cumulative dose 44 Gy). This therapy resulted in complete remission of the tumour. No recurrences occurred and neither did the patient develop metastases during a 20-year follow up period. The late effects of the cancer treatment were delayed growth of the patient, hypoplasia of the midface (Figure 1a), microdontia with root malformation (Figure 1c), velopharyngeal insufficiency, and frequent ear infections with impaired hearing.

At the age of 12, a partial prosthesis (both dental and mucosal supported) with a velopharyngeal obturator was made to improve speech. The retention of this prosthesis was impaired due to the conical shape of the teeth and insufficient bone volume to support the prosthesis. The partial prosthesis had to be renewed after 4 years because of growth of the maxillary complex resulting in a reduced fit of the prosthesis. Orthodontic therapy to correct the midfacial hypoplasia was contraindicated because of the already shortened roots of the teeth.

At the age of 18, i.e., after completion of facial growth, a combined surgical and prosthetic treatment plan was made to improve esthetics by correcting the midface hypoplasia and restoring the oral function. The treatment plan consisted of

- Hyperbaric oxygen (HBO; 20 dives before and 10 dives after orthognatic surgery);
- Le Fort III osteotomy with placement of a rigid external distraction frame (RED) (KLS-Martin L.P., Jacksonville, FL, USA) with rigid plates secured to the infraorbital rim with transcuteneous wires to gradually distract the bones of the midface ventrally (Figure 1a);
- Reconstruction of the hard and soft palate with a temporalis muscle flap;
- Removal of the remaining upper teeth because of dental caries and mobility of the teeth due to the very short, underdeveloped roots;
- Dental implant placement;
- Prosthetic rehabilitation.

The patient agreed with this treatment and the surgical procedure started at the age of 19. Ten days after placement of the RED-frame, the distraction started at a rate of 0.5 mm once daily (Figure 1a). The vector of distraction osteogenesis (DO) was parallel to the Frankfort horizontal plane. Because of little progression, the rate of DO was increased to 0.5 mm twice a day from day 11. After 25 days, active DO was stopped because a satisfying esthetic result was achieved according to the patient and the surgeon (Figure 1b). The total advancement measured on lateral radiographs at the central incisors was 15 mm.

After a 3-month consolidation period, the frame was removed. As a result of forward movement of the maxilla, speech had deteriorated due to worsening of the velopharyngeal insufficiency. Thereupon, the hard and soft palate were reconstructed using a temporalis muscle flap. During that procedure, both coronoid processus were removed to improve

mouth opening and the remaining upper teeth and the maxillary osteosynthesis plates were removed. Because of several nose bleedings that occurred post surgery, a tracheostoma had to be placed for one and a half month.
Fifteen months after the reconstruction of the palate, four dental implants (Brånemark TiUnite regular platform, 13 mm) were placed in the maxilla. Six months later, a maxillary overdenture on a milled titanium superstructure on four implants (Figure 1d) was made. The patient was very satisfied with the final result and no problems occurred during the 3-year follow-up.

Patient 2

A 25-year old female had been treated for a rhabdomyosarcoma in her nasal-tonsil region at the age of three. She was first treated with chemotherapy and subsequently with external beam radiotherapy (cumulative dose 59.4 Gy). This treatment resulted in complete remission of the tumour. No recurrences or metastases were observed during a 22-year follow up period. The late effects of the oncologic treatment were thin hair, development of cataract, impaired hearing at both sides, trismus, maxillary hypoplasia (Figure 2a, b), hypodontia, microstomia and malformation of teeth.
At the age of 20 years, the same combined surgical and prosthetic treatment plan was proposed to this patient as in patient 1 to correct the midface hypoplasia and to restore oral function. The patient, however, did not want to change her facial appearance, needing an alternative surgical treatment plan. This alternative plan consisted of a Le Fort-I osteotomy with ventralization and down grafting of the maxilla to improve esthetics and jaw relationship for prosthetic rehabilitation instead of midface distraction with the RED-frame. The patient also refused this treatment and asked for dental rehabilitation only. Notwithstanding this suboptimal approach, it was assumed the patient would greatly benefit from an implant-based prosthetic rehabilitation.
After 20 treatments with HBO, the remaining maxillary teeth were removed. As the bone volume of the maxilla was insufficient for implant placement, 3 months after teeth extraction, bone from the iliac crest was used to lift the nasal floor and to broaden the maxilla to create bone volume allowing for reliable placement of dental implants at the sites preferred by the prosthodontist. Three months later, 4 dental implants (Brånemark TiUnite regular platform, 10 and 13 mm) were placed in the anterior maxilla with the help of a template, followed by ten treatments with HBO. After 5 months of osseointegration time, abutment connection was done and an impression was made. During this procedure one implant appeared not to be osseointegrated and had to be removed. A milled titanium bar superstructure (Figure 2c) and an overdenture (Figure 2d) were made on the remaining three implants. The patient was very satisfied with her prosthesis and experienced no problems with her prosthetic rehabilitation during a two and a half year follow-up.

Discussion

Radiotherapy in the head and neck region at young age, either solely or combined with chemotherapy, can have severe side effects due to normal tissue damage as is obvious from both cases. When radiotherapy is delivered to the midface, facial growth retardation can cause esthetic and functional problems. Often, teeth are lost in spite of thorough oral hygiene care. Our first case shows that DO to correct midfacial hypoplasia can result in improved esthetics and can be beneficial to oral rehabilitation. Dental implant placement facilitates prosthetic treatment. The second case illustrates that, if the patient refuses optimal treatment, a satisfactory result can occasionally also be obtained by implant-based prosthodontics.

The main advantage of applying DO is simultaneous soft tissue histogenesis that accompanies distraction of the bone [10]. DO in patients after tumour resection has been described for the mandible with varying results [11-14]. However, DO of the midface in irradiated patients is rarely reported [10]. The parameters of DO are empirically used in this case. Our patient showed satisfactory and stable bone formation and had improved facial esthetics.

Prosthetic rehabilitation of patients with a compromised oral situation can greatly benefit from placement of dental implants. In both patients described in this paper, a planning of a prosthetic rehabilitation with four implants was made in a multidisciplinary setting in cooperation with the surgeon and prosthodontist. When planning prosthetic rehabilitation, the most optimal position of the teeth should be the starting position. As both patients were able to maintain the teeth in the lower jaw, the dental configuration of the lower jaw was leading for the position of the teeth and the implants in the upper jaw.

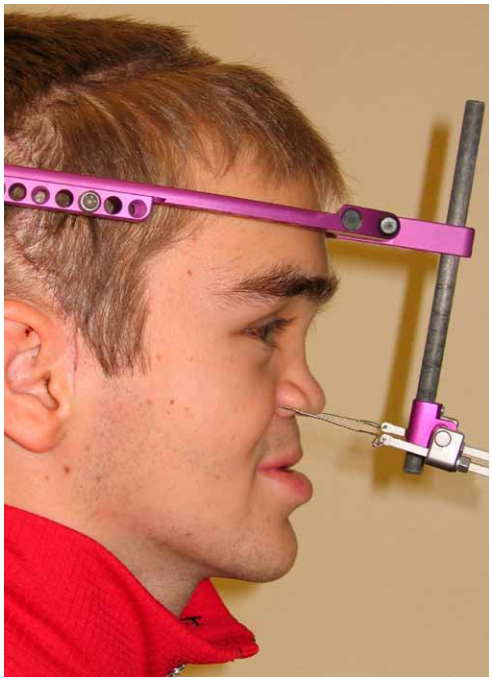
A removable implant-based prosthesis was chosen in both of our patients because of more flexibility in positioning the teeth and fewer implants are needed compared to a fixed bridge. Also, in case of velopharyngeal insufficiency, a removable prosthesis allows for closing the defect, e.g., by combining the implant-retained removable prosthesis with an obturator. Good satisfaction levels can be achieved with removable implant-based prostheses as shown in our cases.

Both patients were treated with HBO before and after surgery. We used HBO treatment according to the Marx protocol, consisting of 20 dives before surgery and 10 dives after surgery [15]. In the literature there is no consensus on the use of HBO to prevent osteoradionecrosis and to improve the success of implant treatment [16-19]. Most studies on these topics suggest a beneficial role for HBO, but these results need to be interpreted with caution. In the presented cases, we used HBO mainly to improve soft tissue healing after surgery [20].

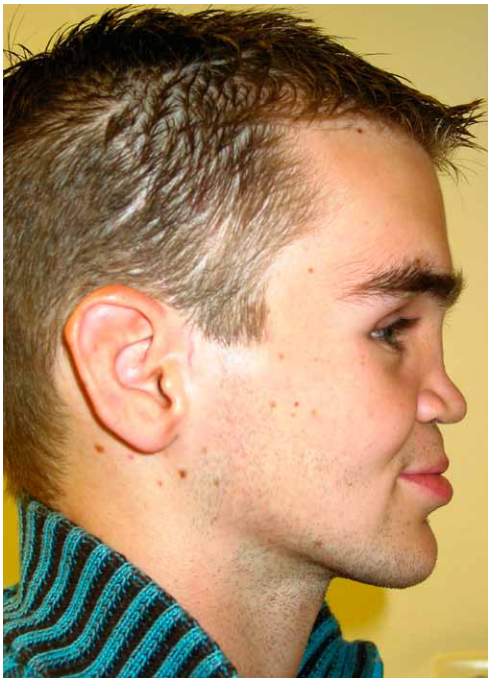
Conclusion

Midfacial hypoplasia and loss of oral function resulting from treatment of childhood maxillofacial rhabdomyosarcoma can be rehabilitated by a combination of orthognatic surgery, distraction osteogenesis and implant-based prosthetics. A satisfying esthetical and functional result can be achieved with this treatment.

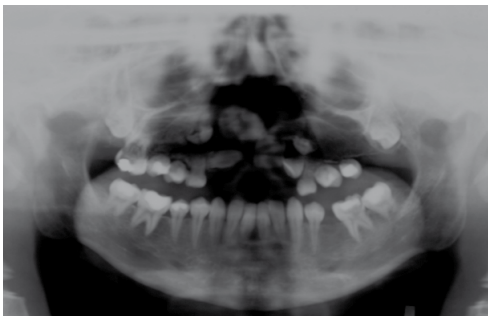
Figure 1



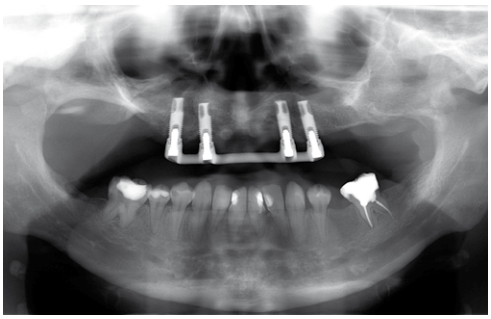
A. Patient at the age of 19 with hypoplasia of the midface due to delayed growth. A rigid external distraction frame (RED) was placed to correct this hypoplasia.



B. Patient at the age of 23 after correction of the midfacial hypoplasia and completion of prosthetic treatment showing a more ventral position of the midface and improved esthetics.

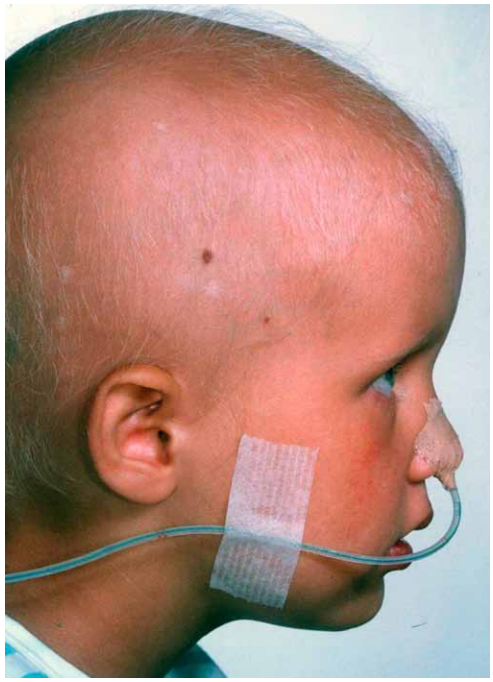


C. Rotational panoramic radiograph of the patient at the age of 13 showing hypodontia, conical shape of the crowns and nearly complete absence of roots of the maxillary teeth.

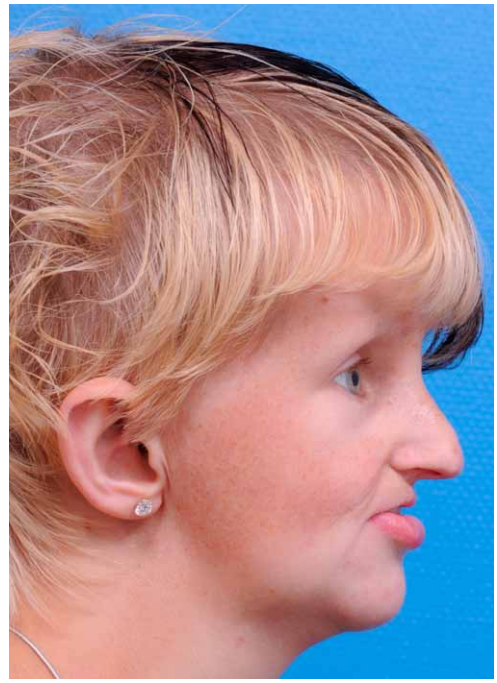


D. Rotational panoramic radiograph at the age of 23 after treatment showing four maxillary implants and a milled titanium superstructure.

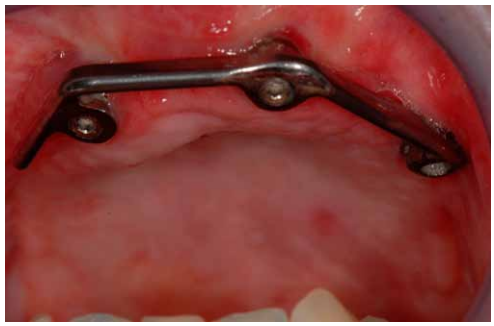
Figure 2



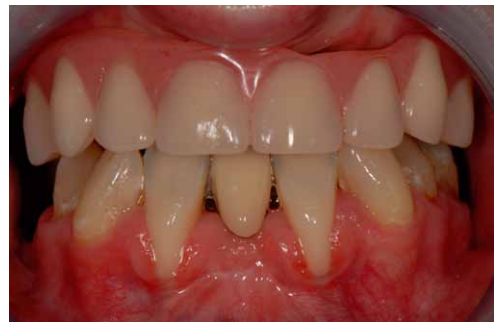
A. En profile image of the patient during treatment of the rhabdomyosarcoma at the age of 36 months.



B. En profile image of the patient at the age of 21 after oral rehabilitation, still showing midfacial hypoplasia.



C. The milled titanium superstructure on three implants.



D. The implant-based maxillary overdenture in situ.

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Chapter 4

Recommendations for implant-retained nasal prostheses after ablative tumour surgery: minimal surgical aftercare, high implant survival and satisfied patients

Abstract

Background

Nasal defects resulting from tumour resection are preferably rehabilitated with implant-retained nasal prostheses. Aftercare, clinical outcome of the implants and patients' satisfaction with implant-retained nasal prostheses were assessed.

Methods

Twenty-eight consecutive patients needing total rhinectomy due to tumour resection between 1998 and 2013 were treated according to a standardized protocol with two implants in the nasal floor. Surgical and prosthetic aftercare was scored using patient records. Finally in 2014 skin reaction, peri-implant bone loss and patients' satisfaction were assessed in all 13 still living patients.

Results

In total 56 implants were inserted (median follow-up 35.1 months, IQR 8.9-63.3). Implant survival was 96.4%, was independent of radiotherapy. Peri-implant skin was healthy and patients' satisfaction high. Longevity of the prostheses was limited.

Conclusions

Rehabilitation of nasal defects resulting from total rhinectomy with implant-retained nasal prostheses according to our protocol resulted in high patient satisfaction and favourable treatment outcome.

Introduction

Nasal defects can occur as a result of ablative oncologic surgery, trauma and congenital disorders, with ablative oncologic surgery being the most common[1,2]. Congenital absent noses are extremely rare[2]. For emotional and cosmetic reasons, nasal defects can be very distressing to patients. These defects can impair the patients' social life [3].
Currently, nasal defects are reconstructed with surgical techniques (e.g., forehead flap)[4-6], prosthetic techniques[3,7,8], or a combination of these two. Surgical reconstruction is difficult to perform and its outcome has not been described in large patient numbers. Furthermore, treatment of a local tumour recurrence may necessitate removal of the surgical reconstruction. An advantage of rehabilitation with nasal prostheses above surgical reconstruction is that the defect resulting from ablative tumour surgery can be observed in total, allowing for thorough oncological inspections. Furthermore, nasal prostheses match a natural cosmetic situation[3]. Therefore, total rhinectomy defects resulting from tumour surgery are preferably rehabilitated with nasal prostheses.
Retention of nasal prostheses include fixation on glasses and gluing to the skin with silicone-based adhesives[7]. None of these fixation methods are optimal because they limit the patients' activities. Especially in warm climates or in a moist environment such as the nasal cavity, the skin glue can dissolve or fail to attach to the skin. In addition, it is difficult to correctly position the prosthesis with skin adhesives. Adhesives can cause skin irritation, allergic reactions, and discolouration and deterioration of the edges of the silicone prostheses.
In 1979 the use of extra oral endosseous implants for retention of craniofacial prostheses was introduced by Brånemark et al.[9] Since then, endosseous implants have acquired an important position in the prosthetic rehabilitation of patients with craniofacial defects, both in irradiated and non-irradiated patients[3,9-12]. Advantages of fixating craniofacial prostheses (especially nasal prostheses) on endosseous implants include easier maintenance of these prostheses (no glue remnants), easier mounting of prostheses in the right position and improved retention compared to adhesive prostheses. Therefore patients' satisfaction with implant-retained craniofacial prostheses is higher compared with adhesive prostheses[9,13,14].
In the literature overall implant survival of implants used for implant-retained nasal prostheses varies largely between 50%-100% with a median survival of 85.5% for non-irradiated patients and 80.0% for irradiated patients[1,15-26]. However, treatment protocols of inserting implants for implant-retained nasal prostheses in these studies were all different. Amongst others, there is no consensus with regard to implant location, type and length of implants, treatment of irradiated and non-irradiated patients and dentate patients. Furthermore, aftercare and patients' satisfaction are hardly discussed. The number of patients is usually low and follow-up periods vary. Currently, only a few studies report on the results of nasal implants with a long follow-up[19,21,24].
Therefore, the aim of this study was to assess aftercare, clinical outcome of the implants

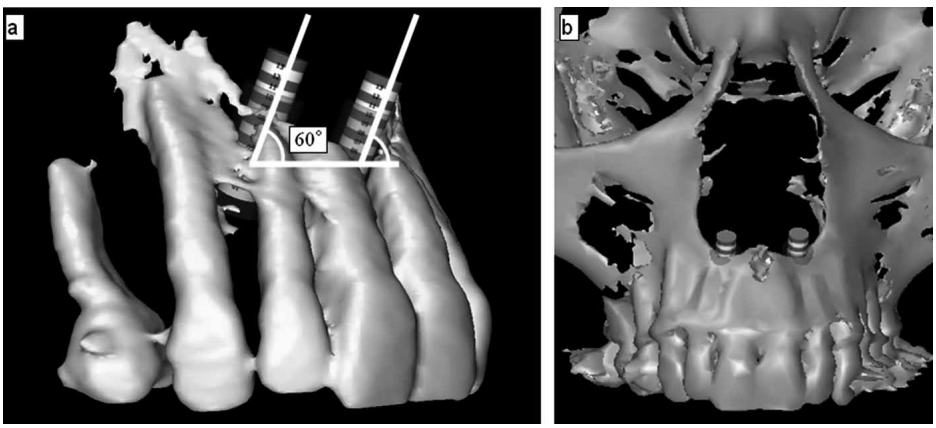
and patients' satisfaction in a relatively large group of patients rehabilitated with an implant-retained nasal prosthesis after total rhinectomy due to tumour ablation. All patients were treated according to a standardized protocol with two endosseous implants in the nasal floor. Both dentate and edentulous patients were included in this study.

Materials and Methods

Patients and implants

All consecutive patients (n=28) treated between 1998 and 2013 with implant-retained nasal prostheses after total rhinectomy due to tumour resection in the Department of Oral and Maxillofacial Surgery and the Department of Otorhinolaryngology/ Head and Neck Surgery of the University Medical Center Groningen (UMCG) were included in this analysis. All patients underwent both tumour surgery and implant insertion in the UMCG. Treatment planning and implant insertion were carried out by one experienced oral and maxillofacial surgeon within the setting of a multidisciplinary team specialized in the treatment and rehabilitation of patients with extra oral defects. This multidisciplinary team was composed of maxillofacial surgeons, maxillofacial prosthodontists, ear, nose and throat surgeons and plastic surgeons.

Figure 1. Planning of implant angulations (approximately 60°) with the horizontal plane (a) and position in nasal floor (b) in a dentate patient



Treatment protocol

Preoperative available bone height was measured on lateral radiographs in edentulous patients or computed tomographic (CT) scans or conebeam CTs (CBCTs) in dentate patients. From 2010, implant planning in dentate patients was fully digitalized from 2010 as described in detail by Van der Meer et al.[27]

In all 28 patients, two implants (Brånemark dental implants with diameter 3.75 mm, length

7 or 10 mm, Nobel Biocare, Gothenburg, Sweden) were inserted according to a 2-stage procedure. Before implant insertion, the prominent bony lip of the piriform aperture was trimmed and the anterior part of the nasal septum and the inferior turbinates were removed. Next, the two implants were inserted via the nasal floor into the maxillary bone at an angle of 60° with the horizontal transversal plane (Figure 1). The implants were covered with a split skin graft.

Figure 2. Superstructure with bar combined with magnet on two implants inserted in nasal floor in a 73-years old man after total rhinectomy: angulation of the implants (a), and inside of the prosthesis (b)

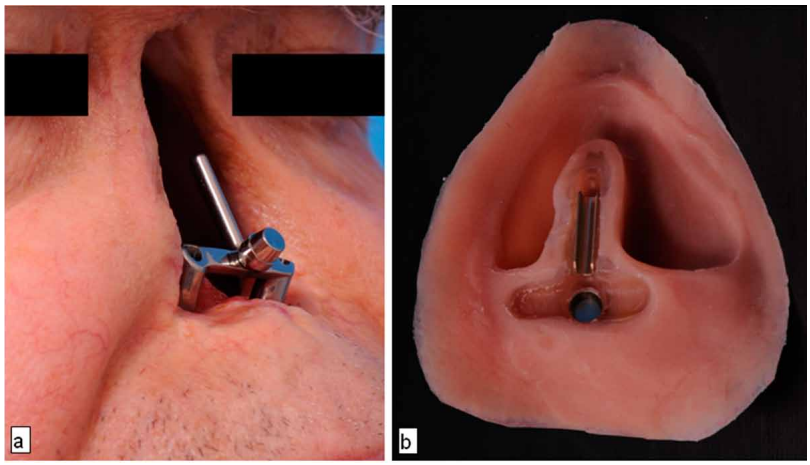
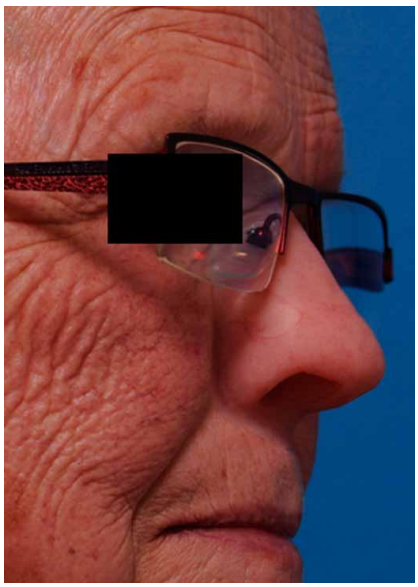


Figure 3. Implant-retained nasal prosthesis in situ in an 84-years old woman after total rhinectomy



To ensure adequate osseointegration, a healing time of at least three months was considered before uncovering. In cases where postoperative radiotherapy was performed, the osseointegration period was increased with three months[9]. Patients could wear an adhesive nasal prosthesis in the meantime.
During the second stage, i.e. the procedure for uncovering the implants and abutment connection, the implants were uncovered under local anaesthesia. The skin around the implants was, when applicable, thinned subcutaneously to prevent pocket formation and inflammation around the implants. Thereafter, the abutments were connected on the implants. To keep the soft peri-implant tissues in place, gauze soaked in ointment was wrapped around the abutments. After one week, the sutures were removed and new gauze was wrapped around the abutments.
Three weeks after abutment connection, the maxillofacial prosthodontist started fabricating the superstructures and nasal prostheses. The implant-retained nasal prostheses were made of intrinsically pigmented silicone elastomers. Retention was achieved with a bar-clip retention system (Haderclips or Friatec clips (former Friadent, now Dentsply IH GmbH, Mannheim, Germany). Since 2011 the bars were milled from titanium (with a macro-dolder clip, Cendres+Métaux, Biel-Bienne, Switserland) and combined with a Steco magnet (Steco-System-Technik, Hamburg, Germany) (Figure 2 and 3).

Surgical and prosthetic aftercare

Surgical and prosthetic aftercare from implant insertion to last available follow-up was retrospectively scored in all patients by assessing patient records according to Visser et al.[1] Surgical aftercare included subcutaneous tissue reduction, split skin grafts and the need for ointment application in case of peri-implant skin infections. Prosthetic aftercare was scored as need for clip repairs, fabrication of new prostheses, repair of superstructure, fabrication of new superstructure, consultation for activation or repair of clips, hygiene instructions, and tightening of loose abutments or superstructure.

Clinical and radiographic assessments

All living patients were recalled for a final clinical assessment in 2014 to score skin reaction and peri-implant bone loss. Skin reactions were scored according to the skin reaction scale of Tolman and Taylor[20] as: (0), no irritation, (1) slight redness, (2) tissue redness and moist but no granulation tissue present, (3) tissue redness and moist with granulation tissue present, or (4) active infection present requiring removal of abutment.
Rotational radiographs (orthopantomograms) were made at the time of abutment connection surgery and during the last follow-up to evaluate the implant-surrounding bone height. Peri-implant bone loss was classified according to Geertman et al.[28]: (0), no apparent bone loss, (1) reduction of bone level not exceeding one-third of the length of the implant, (2) reduction of bone level exceeding one-third of the length of the implant but not exceeding one-half of the length of the implant, (3) reduction of bone level exceeding one-half of the length of the implant, (4) total reduction of bone along the implant.

Patients' satisfaction

In all living patients in 2014, patients' satisfaction with the implant-retained nasal prosthesis was scored. Patients' satisfaction was expressed on a 10-point rating scale (1–10); "1" being completely dissatisfied and "10" being completely satisfied as was also done in the study of Schoen et al[9].

Statistical analysis

The data were analysed using non-parametric tests. A Mann-Whitney *U* test was used to assess differences between irradiated and non-irradiated patients and a Wilcoxon signed-rank test was used to assess differences in bone level in time (IBM SPSS Statistics 22). In all tests a p-value < 0.05 was considered statistically significant.

Results

Patients and implants

Table 1 shows patient and implant characteristics. In total 56 implants were inserted in 28 patients with a median follow-up of 35.1 months (IQR 8.9-63.3). Thirty-six implants were inserted in previously irradiated bone (71.4%). No cases of osteoradionecrosis occurred.

Table 1. Patient and implant characteristics, total group

Patients		
Number of patients	28	
Age at insertion (mean ± SD, range in years)	68.0 (± 9.4)	(51.6-84.3)
Gender (n, %):		
female	10	(35.7%)
male	18	(64.3%)
Oncologic disease (n, %):		
Squamous cell carcinoma	20	(71.4%)
Melanoma	3	(10.7%)
Basal cell carcinoma	2	(7.1%)
Adenoid cystic carcinoma	2	(7.1%)
Adenocarcinoma	1	(3.6%)
Follow-up* (median, IQR)	35.1	(8.9-63.3)
Edentulous (n, %)	21	(75.0%)
Dentate (n, %)	7	(25%)
Patients with implants lost (n, %)	2	(7.1%)
Radiotherapy (n, %):	20	(71.4%)
Before implant insertion	18	(64.3%)
After implant insertion	2	(7.1%)
Rehabilitated patients (n, %)	23	(82.1%)
Implants		
Number of implants:	56	
7 mm	16	(28.6%)
10 mm	40	(71.4%)

Lost implants (n, %)	2	(3.6%)
Insertion during ablative tumour surgery (n, %)	42	(75.0%)
Implants used for prostheses (n, %)	46	(82.1%)

* Follow-up is defined as time between implant insertion and last follow-up or time between implant insertion and patient deceased.

Two implants failed after 13 and 53 months (1x 10 mm, 1x 7 mm, respectively) in two patients, one irradiated and one non-irradiated, resulting in an overall implant survival rate of 96.4%. In one patient the lost implant was successfully replaced by a new implant. In the other patient general anaesthesia in case of implant re-insertion was a high risk procedure due to comorbidity. This patient functioned well with a magnet-retained nasal prosthesis on the remaining implant.
In total 10 implants (in 5 patients) were not used for prosthetic rehabilitation, due to death of 4 patients (3 tumour-related, 1 non-tumour-related) before the rehabilitation could start and due to residual tumour, delaying prosthetic rehabilitation (1 patient).

Surgical and prosthetic aftercare

With regard to surgical aftercare, subcutaneous tissue reduction was performed in 2 out of 28 patients (Table 2). No other surgical interventions were needed.

Table 2. Surgical and prosthetic aftercare given and main reasons for replacing implant-retained nasal prostheses in all patients until last follow-up

Surgical aftercare (n patients, %)	**28**	
Thinning skin	2	(7.1%)
Application ointment	0	(0%)
Skin graft	0	(0%)
Prosthetic aftercare (n patients, %):	**23**	
Hygiene instruction	15	(65.2%)
Repair clips	7	(30.4%)
Retightening of loose abutments/suprastructure	6	(26.1%)
Activating clips	5	(21.7%)
Fabrication new bar	1	(4.3%)
Number of replaced prostheses (n, %):	**47**	
Reasons:		
Discoloration	35	(74.4%)
Fit	7	(14.9%)
Attachment problems of acrylic carrier to silicone	2	(4.3%)
Rupture of silicone	2	(4.3%)
Fractured clip carrier	1	(2.1%)

Surgical and prosthetic aftercare

With regard to surgical aftercare, subcutaneous tissue reduction was performed in 2 out of 28 patients (Table 2). No other surgical interventions were needed.

With regard to prosthetic aftercare in 23 patients with an implant-retained prosthesis, 65.2% of the patients were in need for (repeated) hygiene instructions and 30.4% of the patients needed (repeated) repair of clips (Table 2).
Median time between implant insertion and implant-retained nasal prosthesis placement in 23 patients was 6.8 months (IQR 5.5-8.9). In 7 patients only one implant-retained prosthesis was made because the patient deceased before a new prosthesis could be made (n=3) or because the first prosthesis was still acceptable at time of last follow-up (n=4). In total, 47 replacing prostheses were made in the other 16 patients with a median life span of these prostheses of 11.6 months (IQR 6.8-15.2) (Figure 4). Main reason for prosthesis replacement was discolouration (Table 2).

Clinical and radiographic assessments

Thirteen patients were available for clinical measurements in 2014 (Table 3).

Table 3. Implant characteristics of the 13 patients that could be recalled during last follow-up in 2014

Patients		
Age at insertion (mean ± SD, range in years)	65.8 ± 9.5	(51.6-83.8)
Gender (n, %):		
female	5	
male	8	
Oncologic disease (n, %):		
Squamous cell carcinoma	8	(61.5%)
Melanoma	2	(15.4%)
Basal cell carcinoma	1	(7.7%)
Adenoid cystic carcinoma	1	(7.7%)
Adenocarcinoma	1	(7.7%)
Follow-up (median, IQR)	39.7	(13.0-62.2)
Edentulous (n, %)	6	(46.2%)
Dentate (n, %)	7	(53.8%)
Patients with implants lost (n, %)	0	(0%)
Radiotherapy (n, %):	10	(76.9%)
Before implant insertion	9	(69.2%)
After implant insertion	1	(7.7%)
Rehabilitated patients (n, %)	13	(100%)
Implants		
Number of implants:	26	
7 mm	8	(30.8%)
10 mm	18	(69.2%)
Lost implants (n, %)	0	(0%)
Insertion during ablative tumour surgery (n, %)	10	(38.5%)
Implants used for prostheses (n, %)	26	(100%)

In total 11 patients had died (5 due to tumour-related disease, 6 non-tumour-related), three patients had been lost for follow-up and one patient had residual tumour, without involvement of the peri-implant skin, delaying prosthetic rehabilitation. Median follow-up of

these 13 patients from implant insertion until final assessment was 39.7 months (IQR 13.0-62.2). Peri-implant tissues around the implants were healthy in most patients (Table 4).

Figure 4. Kaplan-Meijer of survival of implant-retained prostheses

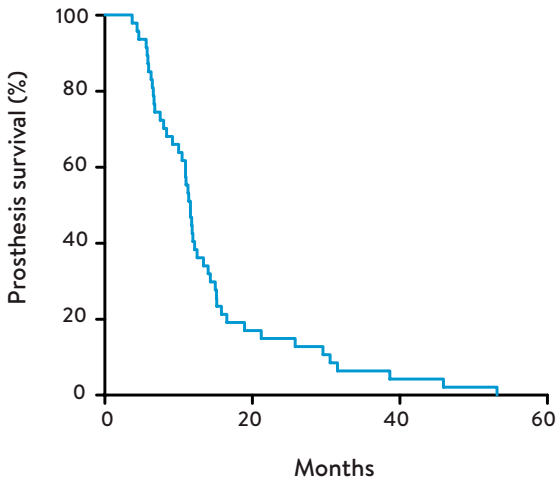


Table 4. Results of clinical and radiographic assessments of 13 patients during last follow-up in 2014

Skin reaction around implants (26 implants, 100%)		
0	16	(61.5%)
1	2	(7.7%)
2	7	(26.9%)
3	1	(3.8%)
4	0	(0%)
Peri-implant bone loss (0-4)		
Median time in months between implant insertion- first radiograph (IQR)	3.0	(2.4-4.5)
Median time in months between implant insertion- radiograph final assessment (IQR)	37.3	(8.5-71.0)
Median score bone loss first radiograph (IQR)	0.13	(0.00-0.56)
Median score bone loss final radiograph (IQR)	0.38	(0.19-0.81)

No difference was seen in skin reaction between irradiated and non-irradiated patients (Mann-Whitney *U* test p=0.161). Median time between first radiograph and radiograph during final assessment was 37.3 months (IQR 8.5-71.0). No significant difference in bone level was observed between first and final radiograph (Wilcoxon signed-rank test p=0.084, Table 4). There was no difference in bone level at first and final radiographs between irradiated and non-irradiated patients (Mann-Whitney *U* test p=0.60 and p=0.60, respectively, Table 4). The level of peri-implant bone was comparable to the peri-implant bone level in patients that deceased before 2014, but of whom sequential radiographs after implant insertion were available (n=5; data not shown).

Patients' satisfaction

Patients' satisfaction with the implant-retained nasal prosthesis was high (median of 8.0, IQR 8.0-9.0).

Discussion

Insertion of two endosseous implants in the nasal floor to support nasal prostheses according to our protocol is accompanied by a high implant survival rate, hardly any surgical aftercare, good peri-implant skin health, negligible peri-implant bone loss and high patient's satisfaction. The average life span of silicone nasal prostheses is limited, however, mainly due to discoloration.

In literature, several factors that might influence survival of implants used for implant-retained nasal prostheses are mentioned. E.g., a lower implant survival rate was reported in the glabella region compared to the nasal floor[18,19,22], but comparable survival rates between these regions were reported too[21,24]. Therefore, it is suggested to use intraoral implants with a length of at least 7 mm since these implants showed a higher survival rate compared with the shorter, craniofacial type implants[22,24]. Also, the timing of implant insertion in the nasal floor, either during the ablative tumour surgery or at a second stage, has been reported to affect the implant survival rate. Dings et al. [25] reported an improved success rate for implants inserted during the ablative surgery, thus before radiotherapy, while others reported that implants placed in irradiated bone are accompanied by a lower survival rate[18,19,22]. In most of the above mentioned studies, patient and implant numbers are limited. In the present study, reporting the results of a rather large patient group treated according to a standardized protocol of inserting intraoral implants with a length of 7 or 10 mm in the nasal floor, very promising results are reported when applying this protocol. Implant survival (96.4%) was amongst the highest reported, both in irradiated and non-irradiated patients, and this survival rate was also irrespective whether the implants were inserted during ablative surgery or thereafter. Since inserting implants during ablative surgery saves a considerable amount of time for patients in being rehabilitated with an implant-retained prosthesis and our favourable results, we recommend this approach[9].

Planning and insertion of implants in the nasal floor is a complicated procedure when the patient has natural teeth in the anterior portion of the maxilla because of the risk of damaging the roots of the natural teeth during the surgical procedure for inserting the implants. When digitally planning the implants according to the technique of Van der Meer et al.[27], the implants can be safely inserted in the nasal floor of dentate subjects.

The median life-span of approximately 1 year for silicone nasal prostheses as observed in our study is comparable to the lifespan reported in the (limited) literature on this subject[1,14,29]. In all studies reported thus far, discolouration is the main reason for replacing the prosthesis. However, the issue of frequent remakes is clinically less relevant as a remake of an implant-retained nasal prosthesis is relatively easy and fast with the use of a mould.

Discolouration might be related to ingrowth of skin flora[30] and pigments in the silicone[31]. Further research on this subject is needed. It also has to be mentioned that we did not observe any clip replacements since we started using the macro-dolder clip system in 2011. No peri-implant skin reactions were seen in the majority of the implants, and when present they are usually mild, which is in agreement with the literature that severe soft tissue reactions around implants used for implant-retained nasal prostheses are rare[1,20,23,24,26]. Possibly the easy access to implants in the nasal floor, facilitating peri-implant hygiene, and thin(ned) skin around the implants contribute to this.

Peri-implant bone loss was negligible and independent of irradiation. These favourable results need to be interpreted with caution, however. In the present study rotational panoramic radiographs were used for evaluation of peri-implant bone loss. Although rotational panoramic radiographs are widely used in the evaluation of bone around intraoral implants; they lack sharpness, distort images and superimpose bony structures of the spine and reproducibility is difficult to achieve[32]. For implants in the nasal floor, no validated radiographic evaluation is available to evaluate peri-implant bone loss. The score for bone loss used in this study[28] can be seen as a rough estimation of the bone level, suitable for comparison of relatively large differences. In this study, no large differences in bone loss between first and last radiograph and between irradiated and non-irradiated patients were seen.

Patients' satisfaction was very high, as confirmed by several studies regarding patients with implant-retained craniofacial prostheses[9,13,14]. Whether satisfaction of patients supplied with an implant-retained nasal prosthesis differs from satisfaction of surgically reconstructed patients is unknown.

In conclusion, insertion of two intraoral implants in the nasal floor according to our protocol provides a predictable and reliable treatment option for prosthodontic rehabilitation of patients after rhinectomy, given the high implant survival rate, healthy condition of the peri-implant tissues and high patients' satisfaction.

Conflict of interest

None declared.

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This chapter is an edited version of:
Anke Korfage, Gerry M. Raghoebar, Suzanne Arends, Petra M. Meiners, Anita Visser, Frans G.M. Kroese, Hendrika Bootsma, Arjan Vissink. Dental implants: a good treatment option in patients with Sjögren's syndrome. (submitted)

Chapter 5

Dental implants: a good treatment option in patients with Sjögren's syndrome

Abstract

Background
Limited evidence is yet available for applying dental implants in SS patients.

Purpose
To retrospectively assess clinical outcome of dental implant therapy in a cohort of well-classified patients with Sjögren's syndrome (SS).

Materials and Methods
All SS patients attending the University Medical Center Groningen for follow-up (n=406) were asked whether they had dental implants. In SS patients with implants peri-implant health and implant survival was recorded and compared with data from matched healthy controls. Patients' symptoms, health-related quality of life, oral functioning and satisfaction were assessed using validated questionnaires.

Results
Of the responding SS patients (n= 335), 21% was provided with dental implants. In 50 SS patients peri-implant health was good with minor marginal bone loss and was comparable to those of healthy controls. Implant survival was 97% (median follow-up 46 months (IQR 26-73) and patients' satisfaction was high in most SS patients. Peri-implantitis was observed in 14% of the SS patients. Oral functioning correlated negatively with dryness, patients' satisfaction and chewing ability in SS patients.

Conclusions
Implant therapy is common in our cohort of SS patients. Considering the good peri-implant health, limited prevalence of peri-implantitis, high implant survival and patients' satisfaction, dental implants are a good treatment option.

Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates in the affected glands. Involvement of the salivary glands results in progressive dryness of the mouth, difficulties with chewing, swallowing and speech, reduced oral clearance and a shift in oral flora[1]. As a result of the reduced saliva production, patients with SS are likely to have progressive caries and erosion of the teeth, and are prone to develop oral infections[2]. SS has a large impact on health-related quality of life (HR-QoL)[3] and the oral condition contributes to this[4,5]. E.g., early loss of teeth results in a need of treatment with (partial) dentures, but patients with SS often experience functional problems and pain when wearing (partial) dentures because of the dry, sensitive oral mucosa.

Dental implants to retain prostheses are known to improve oral function in edentulous healthy subjects[6-10]. Dental implants can also be used in dentate patients as support for crowns or bridges to replace missing teeth. Implant survival rates are up to 98% with 10 years follow-up[8-12].

Currently, systemic conditions and their therapy, e.g., rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), osteoporosis and corticosteroid therapy, are no longer considered as risk factors for successful osseointegration of the implants[13,14]. Despite the severe oral complaints, limited evidence is yet available for applying dental implants in SS patients. The available support for using dental implants in SS patients is mainly from case-reports and small case-series[15-19]. While most reports show favorable results, one small study showed that marginal peri-implant bone loss and bleeding was higher in secondary SS (sSS) patients compared with patients with RA without sSS[19]. Therefore, the aim of this retrospective study was to assess clinical outcome of dental implant therapy in our cohort of well-classified SS patients. Results were compared to data from matched healthy controls obtained from other dental implant studies at our department.

Patients and methods

Patients

All patients with SS (n=406) attending the Department of Rheumatology and Clinical Immunology and the Department of Oral and Maxillofacial Surgery of the University Medical Center Groningen (UMCG) for standardized routine follow-up in a multidisciplinary setting were sent a questionnaire by regular mail regarding their dental status and whether or not they had dental implants inserted. All patients were over 18 years of age and were classified according to the revised American European Consensus Group criteria for primary SS (pSS) or sSS[20]. All patients who reported to have been treated with dental implants were invited by a prosthodontist (AK) for assessing peri-implant health at their next scheduled follow-up visit between February 2012 and September 2013. Implant survival was recorded from patient recordings and by patient interview.
Data from previous studies[8,9,11,21-27] was used to randomly select healthy controls that matched our SS patients with regard to sex, age, position and follow-up of the implants and number of implants and implant system used.
The study was extinct of ethical approval according to the local institutional review board (Medisch Ethische Toetsingscommissie of the UMCG, the Netherlands, letter M11.110548).

Peri-implant indices

During the next follow-up visit, clinical screening was performed to assess peri-implant mucosal health. Peri-implant indices included plaque index and bleeding index[28], gingival index[29], calculus score and probing depth. Probing depth was measured at four sites of each implant (mesially, labially, distally and lingually) using a periodontal probe (Merit B, Hu Friedy, Chicago, IL, USA) with a standardized pressure. The distance between the marginal border of the mucosa and the tip of the periodontal probe was scored as the probing depth. The highest peri-implant scores per patient (plaque-index, gingiva-index and calculus) and the highest probing depth per implant were used for analysis.

Radiographic assessments

Marginal bone resorption around the implants was assessed radiographically using panoramic radiographs made during the current visit and, when available, from previous recordings. On these radiographs, the mesial and distal marginal bone levels were determined in relation to the implant shoulder. Marginal bone loss was calculated as the difference in peri-implant bone level between the first (i.e., the radiograph at the time the suprastructure was placed) and the last radiograph (i.e., the radiograph made during the recall visit). The highest scores per implant were used for analysis. In patients in whom no radiographs were available from the period the suprastructure was made, the marginal bone level was compared to the expected bone level at implant insertion.

Peri-implant mucositis and peri-implantitis

Peri-implant mucositis and peri-implantitis were defined according to the criteria proposed by Linde & Meyle[30]. Acceptable bone loss was set at 1.0 mm the first year and not exceeding further annual loss of 0.2 mm[31,32] combined with a threshold of detectable bone loss of 1.0 mm according to Sanz et al.[33] In patients without previous radiographic records, a threshold vertical distance of 2 mm from the expected marginal bone level following remodelling post-implant placement was applied[33] .

Questionnaires

All patients completed a set of validated questionnaires regarding their Sjögren-related symptoms, HR-QoL, oral functioning and patients' satisfaction with the prosthetic device.
The European League Against Rheumatism Sjögren's Syndrome Patient Reported Index (ESSPRI), a patient administered questionnaire, was used to assess patients' symptoms[34].
ESSPRI total score is the mean of three sub scores: dryness, fatigue and pain, 0 being no symptoms, 10 being the worst possible symptoms. Oral dryness specifically was assessed using the sub score for oral dryness that was part of the early version of ESSPRI.
HR-QoL was assessed using the Short Form-36 (SF-36)[35]. The SF-36 is a questionnaire consisting of 36 items, with eight scales assessing two dimensions, viz. physical and mental health functioning. Scales and summary scores vary from 0 to 100, with 0 being the worst possible health status and 100 representing the best possible health status.
Social impact of oral disorders on well being was assessed using the short version of the Oral Health Impact Profile (OHIP14) [36]. OHIP 14 consists of 14 items, with a 5-point scale from 'very often' (score of 4) to 'never' (score of 0). Total score ranged from 0-56.
Subjective chewing ability was assessed using a nine-item questionnaire on which patients could rate their ability to chew different kinds of food on a three-point scale[7] from 0 (good) to 2 (bad). Total score ranged from 0-18.
Overall satisfaction with the implant-retained prosthetic device (e.g., crown or prosthesis) was expressed on a 10-point rating scale (0– 10); "0" being completely dissatisfied and "10" being completely satisfied.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 22 (SPSS, Chicago, IL, USA). Results were expressed as mean ± SD or median (interquartile range; IQR) for normally distributed and non-normally distributed data, respectively. Independent samples t test, Mann-Whitney U test, and Chi-Square or Fisher's exact test were used to compare differences in patient characteristics between subgroups. Wilcoxon signed rank test and McNemar test were used to compare differences in clinical outcome of dental implant therapy between SS patients and matched healthy controls. Correlations between questionnaires were analyzed using the Spearman's correlation coefficient. P values <0.05 were considered statistically significant.

Results

Patients

In total, 335 of the 406 SS patients responded to the mail survey regarding dental implants (response rate 83%). In 21% of these respondents (n= 69) dental implants were inserted. These 69 SS patients were invited to the hospital for clinical assessments and completion of questionnaires. In 19 patients implant indices could not be assessed as they were currently visiting other hospitals because of travelling distance (n=6), they were too ill (n=5) or refused to participate (n=8). From 50 patients clinical data could be collected.
The 50 included patients were a representative sample of the 69 SS patients with implants inserted considering no significant differences were found in sex, age and disease duration between these 50 patients and the 19 patients without clinical data. Patients' characteristics of the 50 SS patients with dental implants and the 50 matched healthy controls are presented in Table 1.

Peri-implant indices

In total 140 implants were available for clinical assessments in the 50 SS patients (Table 1). Peri-implant indices are shown in Table 2. Bleeding index, gingival index and probing depth were slightly, though significantly higher in SS patients compared with healthy controls. Furthermore, plaque-index and gingiva-index were slightly higher and probing depth was slightly lower in edentulous SS patients compared with dentate SS patients, although again statistically significant. Peri-implant indices did not differ between patients with pSS or sSS and were independent of the use of NSAIDs, corticosteroids, hydroxychloroquine or other immunosuppressives.

Table 1. Characteristics of Sjögren's patients with dental implants and matched healthy controls included in this study

	Sjögren's patients	Healthy controls
Number of patients	50	50
Age (mean±SD, years)	67± 8	66 ± 9
Gender (n, %):		
female	46 (92%)	46 (92%)
male	4 (8%)	4 (8%)
SS (n, %):		
primary SS (n, %)	41 (82%)	NA
secondary SS (n. %)	9 (18%)	NA
Disease duration (years, range)	9 (4-14)	NA
ESSPRI	6.3 (4.7-7.3)	NA
Serological characteristics:		
ESR (mm/hour)	22.0 (14.0-40.5)	NA
IgG (g/l)	14.4 (11.9-16.3)	NA
rheumatoid factor (kIU/L)	26.0 (14.5-116.0)	NA
C3 (g/l)	1.1 (1.0-1.2)	NA
C4 (g/l)	0.2 (0.1-0.3)	NA
anti-Ro/SSA positive (n, %)	41 (82%)	NA
anti-La/SSB positive (n, %)	27 (54%)	NA
Medication:		
NSAIDs (n, %)	13 (26%)	0 (0%)
corticosteroids (n, %)	8 (16%)	0 (0%)
hydroxychloroquine (n, %)	14 (28%)	0 (0%)
other immunosuppressives (n, %)	5 (10%)	0 (0%)
Smoking (n,%)	1 (2%)	0 (0%)
Dental implants:		
maxillary implants (n, %)	20 (14%)	24 (19%)
mandibular implants (n, %)	120 (86%)	101 (81%)
follow-up of implants (years)	3.8 (2.2-6.1)	5.0 (1.0-.0.5)
Implant-retained prosthodontics:		
single crown (n)	27	14
overdenture (n)	36	37
fixed partial denture (n)	2	7
fixed full-arch denture (n)	1	0

Variables are presented as medians (IQR) unless stated otherwise; NSAIDs= non-steroidal anti-inflammatory drugs; ESSPRI= EULAR Sjögren's Syndrome Reported Index; NA: not applicable/not assessed

Table 2. Implant loss, peri-implant indices (highest scores per patient) and peri-implant bone loss (highest scores per implants) in patients with Sjögren's syndrome (SS) for the total group, for edentulous patients and for dentate patients compared with matched healthy controls

	Total group Sjögren's patients	Healthy controls	Edentulous Sjögren's patients	Edentulous controls	Dentate Sjögren's patients	Dentate controls
Patients	n=50	n=50	n=35	n=35	n=15	n=15
Implants	n=140	n=125	n=109	n=96	n=31	n=29
Lost implants	4 (3%)	0 (0%)	4 (4%)	0	0	0
(in patients, %)	2 (4%)	0 (0%)	2 (6%)	0	0	0
Peri-implant indices						
Plaque index (0-3)	1.0 (0.0-1.0)	1.0 (0.0-1.0)	1.0 (0.0-2.0)	1.0 (0,0-1.0)	0.0 (0.0-1.0)[a]	0.0 (0.0-1.0)
Calculus (0-1)	0.0 (0.0-0.0)	0.0 (0.0-1.0)*	0.0 (0.0-0.0)	0.0 (0.0-1.0)*	0.0 (0.0-1.0)	0.0 (0.0-0.0)[c]
Bleeding index (0-3)	1.5 (1.0-2.0)	1.0 (0.0-1.0)***	1.0 (0.0-2.0)	1.0 (0.0-1.0)***	2.0 (1.0-2.0)	1.0 (0.0-1.0)**
Gingival index (0-3)	0.5 (0.0-1.0)	0.0 (0.0-1.0)**	1.0 (0.0-1.0)	0.0 (0.0-1.0)**	0.0 (0.0-1.0)[a]	0.0 (0.0-0.0)
Probing depth (mm)	3.5 (3.0-4.0)	3.0 (2.5-3.1)**	3.3 (3.0-3.5)	3.0 (2.5-3.0)**	4.0 (3.2-5.0)[b]	3.0 (2.5-4.0)
Marginal bone loss	0.89 (0.25-1.56)	0.66 (0.25-1.03)	0.90 (0.50-1.55)	0.85 (0.36-1.27)	0.69 (0.0-2.44)	0.28 (0.0-0.90)
Peri-mucositis						
(patients, %)	47 (94%)	31 (62%)[#]	32 (91%)	22 (63%)[##]	15 (100%)	9 (60%)
(implants, %)	102 (73%)	NA	75 (69%)	NA	27 (87%)	16 (55%)
Peri-implantitis						
(patients, %)	7 (14%)	6 (12%)	4 (11%)	5 (14%)	3 (20%)	1 (7%)
(implants, %)	16 (11%)	11 (9%)	10 (9%)	10 (11%)	6 (19%)	1 (3%)
Prosthesis satisfaction						
General	NA	NA	2.0 (2.0-2.5)	1.1 (1.0-1.3)***	NA	NA
Upper denture	NA	NA	2.0 (2.0-2.5)	1.1 (1.0-1.3)***	NA	NA
Lower denture	NA	NA	2.0 (1.0-2.0)	1.2 (1.1-1.5)**	NA	NA
Satisfaction (0-10)	8.0 (7.0-9.0)	NA	8.0 (7.0-9.0)	NA	8.0 (6.5-9.0)	9.5 (8.0-10.0)*

NA= data not available, *p<0.05, **p<0.01, ***p<0.001 (Wilcoxon signed ranks tests) compared with Sjögren's patients, [a] p<0.05, [b] p<0.01 compared with edentulous Sjögren's patients (Mann-Whitney tests), [c] p<0.01 compared with edentulous controls (Mann-Whitney test), [#] p<0.001, [##] p<0.05 compared with Sjögren's patients (McNemar test)

Radiographic assessments

Rotational radiographs (orthopantomograms) at baseline (i.e., around the period the suprastructure was made) were available for 26 patients (71 implants), either because the implants were inserted in our hospital or radiographs could be obtained from the dentist who inserted the implants or made the prosthetic device. Median bone loss around the implants in SS patients was 0.89 (0.25-1.56) with a median time between the baseline and radiograph made at the recall visit of 42 months (IQR 22-69) (Table 2). There was no significant difference in bone loss between SS patients and healthy controls.

Peri-implant mucositis and peri-implantitis

Peri-implant mucositis, defined as bleeding on probing at one or more sites around one or more implants, was seen in 94% of the SS patients and in 62% of the healthy controls. Peri-implantitis around one or more implants was seen in 14% of the SS patients (11% of the implants) and 12% of the healthy controls (Table 2).
There was no significant difference in the prevalence of peri-implant mucositis and peri-implantitis between patients with pSS an sSS. Prevalence of peri-implantitis and peri-implant mucositis were also independent of disease duration and the use of NSAIDs, corticosteroids, hydroxychloroquine and other immunosuppressives when in SS patients.

Implant survival

Based on patients' interview and patients' records, four out of 142 inserted implants had been lost in two patients during the first three months after insertion, resulting in an overall survival rate of 97% (median follow up after implant insertion 46 months (IQR 26-73); Table 2). All four implants had been inserted in the edentulous mandible. Two of these four failing implants had been replaced in these patients. These two replaced implants were in function for 66 and 36 months at last follow-up, respectively.
In total 125 implants were inserted in the 50 matched healthy controls. No implants were lost during a comparable follow-up period (Table 2).

Oral functioning and patients' symptoms

No significant differences were found in HR-QoL, oral functioning, satisfaction and chewing between patients with a fixed superstructure on the implants and patients with a prosthesis. Patients' satisfaction with the prosthetic device was high (Table 2).
OHIP14 scores correlated positively with ESSPRI dryness ($\rho = 0.393$), ESSPRI oral dryness ($\rho = 0.407$) and chewing scores ($\rho = 0.521$), and negatively with VAS satisfaction ($\rho = -0.452$). Worse oral functioning was thus associated with more dryness complaints, lower patient satisfaction and worse subjective chewing ability. In addition, ESSPRI oral dryness correlated positively with chewing score ($\rho = 0.403$) indicating that the dryer the mouth, the worse the subjective chewing ability.

Discussion

To the best of our knowledge, this is the first study on the prevalence of the use of dental implants, peri-implant health, prevalence of peri-implant mucositis and peri-implantitis, implant survival as well as HR-QoL and oral functioning in a large cohort of well-classified patients with SS. Major findings are the high percentage of patients with implants installed, the rather good peri-implant health not withstanding the high prevalence of peri-implant mucositis, the limited prevalence of peri-implantitis, the high implant survival (97%) and the high satisfaction of patients with their implant-retained prosthetic rehabilitation.
In 21% of the respondents implants had been inserted. In the Netherlands in 2009, 8.0% of the population between 60-70 and 7.0% of the population of 70 years and older had implants inserted (Statistics Netherlands, www.cbs.nl). Apparently, there is a large demand for inserting implants in patients with SS, but not much is known whether this treatment is successful or not. This large demand can be explained by the early loss of teeth in patients with SS and the inability to wear (partial) dentures because of the dry, sensitive oral mucosa. Moreover, to our experience, SS patients have a rather high dental awareness and are thus more demanding regarding optimal dental care including insertion of dental implants to solve dental problems.
SS patients had more signs of soft tissue infection compared with the healthy controls. Care must be undertaken when interpreting these results. The healthy controls were obtained from previous prospective randomized trials, with long follow-up. In SS patients the implants had been inserted in routine dental care settings by several dentists and oral surgeons reflecting common dental care in the Netherlands. As a result, not all SS patients had been subjected to strict, standardized follow-up and oral hygiene measures as usually is the case in well controlled clinical studies. Furthermore, salivary secretion is reduced in SS patients as well as the related self- clearance of the oral cavity. As a result, debris will collect more quickly and remain on the implant surfaces in SS subjects than in healthy controls. This is reflected by the slightly higher gingival health indices and pocket probing depth values in our SS subjects than in their matched controls. As a result the marginal peri-implant tissue is more prone to continuous inflammatory insults than the peri-implant tissue in healthy controls. This will probably have resulted in more gingival swelling, bleeding and increased pocket probing depths in SS patients.
Although probably not clinically relevant as the observed differences were on the healthy end of the peri-implant health spectrum, peri-implant mucosa was healthier for dentate SS patients compared with edentulous SS patients. Dentate SS patients need to have better oral hygiene compared with edentulous patients as their natural teeth are prone to decay as they are exposed to an oral environment with a high risk of dental caries and oral infections. This better oral hygiene need is reflected in a lower gingiva-index and plaque-index. Remarkably, a comparable difference has also been observed in healthy patients supplied with removable or fixed implant-based prosthodontics[37].

Some marginal bone loss was observed in our cross-sectional cohort. The median marginal bone loss seems to be well within the range that is considered as normal in healthy subjects[8,9,11,31,32]. It has to be mentioned, however, that in our study rotational radiographs were used in the evaluation of bone around the implants. This is not optimal, as preferably standardized intra-oral dental radiographs are used for evaluation of peri-impant bone loss as was used for assessing peri-implant bone loss in our healthy controls. Contrary to our results, in one small study it was suggested that marginal peri-implant bone loss was higher in sSS patients compared with patients with RA without sSS[19]. This topic needs further study, but it seems that the difference between healthy patients and SS patients has limited clinical relevance as the prevalence of peri-implantitis showed no difference between the two groups.

Overall implant survival in this cohort was 97% with a median follow-up of 46 months, which is comparable to the implant survival in our matched healthy controls and the previously reported implant survival in healthy patients[8-11]. All 4 lost implants were lost within 3 months after insertion, comparable with the timing of implant loss in healthy patients[8-11]. In two other studies on implant survival in SS patients reported in literature, implant survival in SS patients was 84% and 100%, respectively[16,19].

The findings of the oral functioning questionnaires in our study are consistent with the results from previous studies in SS patients[2,4,5,38]. Oral functioning is impaired in patients with SS and continues to be impaired in patients with implant-retained prosthetics. Subjective chewing ability with implant-based prosthetics did not reach the same level as reported for healthy subjects[7]. SS patients with implant-retained prosthetics report difficulty chewing tough and hard food, although there is a large variety in results. These problems can be due to the sicca component of SS, as shown by the direct correlation between severity of reported oral dryness (ESSPRI dryness) and chewing ability. This could also explain why SS patients were less satisfied with their implant-retained prosthetics than non-SS patients.

Based on the present analysis, we conclude that dental implants are a good treatment option in the prosthetic treatment of patients with SS, although there are more signs of peri-implant mucositis in SS subjects than in healthy controls. Implant survival is high, prevalence of peri-implantitis is comparable to healthy patients, no excessive bone loss was seen and patients were satisfied with their implant-retained prosthetic devices. Dentist, implantologists, rheumatologist and other health care workers should encourage SS patients with dental problems to discuss the possibilities to treat dental problems with implant-retained prosthetics.

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Chapter 6

General discussion

Implant insertion in head and neck cancer patients

Oral cancer patients

Primary mandibular implant insertion in edentulous patients has become a standard treatment in our institute in patients with a malignancy of the lower oral cavity in whom is foreseen that they can benefit from implant-retained prostheses.

From chapter 2 we learned that implant survival is high, although still lower in irradiated patients compared with non-irradiated patients (91.5% compared with 99.5%). This is not surprising as, amongst others, radiotherapy may result in progressive fibrosis of blood vessels and soft tissues, in xerostomia, in a reduced bone-healing capacity, and may even sometimes lead to osteoradionecrosis. Because of the cumulative effects of radiation on vascularisation and cellularity of bone, the regenerative capacity of these tissues is limited, which may exert a negative impact on subsequent implant osseointegration. These concerns are in line with the reported survival rates of implants inserted in irradiated patients, which vary largely, but are usually lower than survival rates of implants inserted in non-irradiated patients (Colella et al. 2007, Ihde et al. 2009, Javed et al. 2010, Chrcanovic et al. 2014). So far, no difference in implant survival in implants inserted pre-radiotherapy and implants inserted post-radiotherapy has been reported, but the reported number of implants inserted pre-radiotherapy is still low (Colella et al. 2007, Barber et al. 2011, Chrcanovic et al. 2014). A concern mentioned of implants inserted pre-radiotherapy is the backscattering that occurs from the metal of the implants in the radiation beam. This backscattering can result in an increased radiation dose in the surrounding bone in front of and next to implants of 10-21% (Ozen et al. 2005, Friedrich et al. 2010). Also shielding of the radiation beam by the implants within the radiation beam, which may result in a lower cumulative radiation dose to the tumour, is mentioned as an unwanted effect. Both side effects can be reduced by multi-beam radiotherapy strategies nowadays. Osteoradionecrosis linked to implant loss was observed in 5% of irradiated patients in our study (chapter 2).

When implants are inserted during ablative surgery, the number of prosthetically rehabilitated patients is much higher than when the need for implant-retained prosthetics is only established after oncologic therapy (Kwakman et al. 1997, Schoen et al. 2007a, Mizbah et al. 2013). Thus, many patients will benefit from their implant-retained prosthesis at an early stage. Although the number of rehabilitated patients is high with primary inserted mandibular implants, a concern of inserting implants during the ablative surgery is loss of resources. Our study (chapter 2) revealed that 16-17% of the patients with primary mandibular implants were not rehabilitated with an implant-retained prosthesis after completion of their oncologic treatment. The main reason for this was that the patient deceased or that recurrent disease occurred before prosthetic rehabilitation was started or could be finished. Although this seems to be an economic disadvantage, it has to be recalled that if implant insertion is postponed until after the oncologic treatment is completed, patients are often psychologically and physically weakened by the therapy. As

a result many of them postpone or even cancel their prosthetic rehabilitation, despite the expected significant improvement of oral functioning with implant-retained prosthetics (Kwakman et al. 1997, Schoen et al. 2007b, Mizbah et al. 2013). Therefore, a large percentage of patients and even patients with a worse general prognosis can benefit for some time from the early improvements in aesthetics and oral function when implants are inserted during ablative surgery.
It has to be mentioned that, although no patients could be identified who were less likely to benefit from primary implant insertion (chapter 2), there is a hazard of incorporation bias regarding the very favourable results we reported in our study. The patients included in our study were in fact a selection of oral cancer patients. All patients were edentulous, had tumours in the lower oral cavity and all implants were inserted in native mandibular bone. So, do primary mandibular implants in oral cancer patients improve oral functioning and quality of life? In healthy patients, implant-retained prostheses improve oral function and chewing ability, both subjectively and objectively (Boerrigter et al. 1995, Stellingsma et al. 2005, Meijer et al. 2009). The results of our studies show that a large number of oral cancer patients is rehabilitated with implant-retained prostheses, when the implants are installed during ablative surgery. However, as expected, the beneficial effects are lower than usually observed in healthy subjects (chapter 2). Amongst others the improvement in chewing ability is not as high as in healthy subjects (Stellingsma et al. 2005). Whether general quality of life improves as a result of implant-retained prostheses could not be shown in our study (Chapter 2). Other factors, such as concurrent comorbidity both as a result of the oncological treatment and other, were shown to be far more important determining patients' quality of life.

Patients with nasal defects after total rhinectomy

Implant-retained nasal prostheses have been shown to be a very valid option for rehabilitation of a patient after total rhinectomy (chapter 4). In line with intraoral implant insertion in oral cancer patients, timing of implant insertion in the nasal floor, either during the ablative tumour surgery or at a second stage, is still subject of discussion. Studies report that implants inserted in irradiated nasal bone are accompanied by a lower survival rate (Roumanas et al. 1994, Nishimura et al. 1996, Roumanas et al. 2002) compared with implants inserted in non-irradiated nasal bone. In addition, Dings et al. (2011) reported an improved success rate for implants inserted during the ablative surgery. In our study we noticed no difference in implant survival in irradiated patients and non-irradiated patients. Also we did not see a difference in implant survival between primary inserted implants and implants inserted in a second procedure. The good quality of bone in the nasal floor, and the fact that intraoral implants were used, might have contributed to the high survival rate in our study. Since inserting implants during ablative surgery saves a considerable amount of time for patients in being rehabilitated with an implant-retained prosthesis and our favourable results, we recommend this approach for patients needing total rhinectomy too.

Implant insertion in patients with Sjögren's syndrome

To the best of our knowledge, in chapter 5 the first study on the prevalence and treatment outcome of dental implants in a large cohort of well-classified patients with Sjögren's syndrome compared with matched healthy controls is described. Apparently, there is a large demand for the use of implants in Sjögren's patients, but not much is known whether this treatment is successful or not. This large demand can be explained by the hazard of early loss of teeth in because of the hostile oral environment for preserving the patients' teeth. Also Sjögren's patients often report difficulty wearing (partial) dentures because of the dry, sensitive oral mucosa. Moreover, to our experience, Sjögren's patients have a rather high dental awareness and might thus be more demanding regarding optimal dental care including insertion of dental implants to solve dental problems.

While implant survival in Sjögren's patients is comparable to that in healthy subjects, as shown in chapter 5, Sjögren's patients had more signs of soft tissue infection compared with healthy controls. Care must be taken in interpreting these results, however. The matched healthy controls were obtained from previous well-designed, prospective randomized trials, with long follow-ups. In our group of Sjögren's patients, the implants had been inserted in routine dental care settings by several dentists and oral and maxillofacial surgeons reflecting common dental care in the Netherlands. As a result, not all Sjögren's patients had been subjected to strict, standardized follow-up and oral hygiene measures as usual in the well controlled clinical studies we performed. Furthermore, salivary secretion is reduced in Sjögren's patients and as a result the related self-clearance of the oral tissues is reduced too. Debris will collect and remain on the implant surfaces more quickly in Sjögren's subjects than in healthy controls. As a result the marginal peri-implant tissue is thought to be more prone to continuous inflammatory insults than the peri-implant tissue in healthy controls. This continuous attack has probably resulted in more gingival swelling, bleeding and increased pocket probing depths in Sjögren's patients.

As we only had access to pre- and post-implant insertion radiographs in a subset of our Sjögren's patients, no firm conclusions can be drawn on the observed level of bone loss around the implants and thus peri-implantitis. However, it seems that there is no difference in peri-implantitis in our study between Sjögren's patients and healthy controls. Probably, the patients clean their implants well: as a result the chronic irritation of the peri-implant mucosa is mild due to the fact that the rapid accumulation of debris around implants due to the reduced oral self-cleansing is compensated by the frequent proper cleansing of the implants by the patients themselves.

Oral functioning is impaired in patients with Sjögren's syndrome and continues to be impaired in patients with implant-retained prosthetics. The findings of the oral functioning questionnaires in our study were consistent with the results from previous studies in Sjögren's patients (Fox et al. 2008, Stewart et al. 2008, Enger et al. 2011, Lopez-Jornet et al. 2008). Sjögren's patients with implant-retained prosthetics still reported difficulty chewing tough and hard food, although there was a large variety in results. These problems

could be due to the sicca component that is present in Sjögren's patients, as shown by the direct correlation between severity of reported oral dryness (ESSPRI dryness) and chewing ability. This could also explain why Sjögren's patients were less satisfied with their implant-retained prosthetics than healthy subjects.

Conclusions and suggestions for future research

Based on the studies described in the previous chapters and discussion, implants can be of great help in the prosthetic rehabilitation of patients with a compromised intraoral condition or a nasal defect. In this respect, the role of the (maxillofacial) prosthodontist is of crucial importance. Treatment planning should take place in a multi-disciplinary setting as well as that prosthodontists should be involved in the full trajectory of treatment planning as they are involved in all stages of care and aftercare.
For edentulous patients with a malignancy in the lower oral cavity, inserting at least 2 mandibular implants during ablative surgery contributes to an early and reliable rehabilitation of oral function, irrespective of radiotherapy, location and size of the tumour and the type of reconstruction. Thus, involvement of maxillofacial prosthodontists should routinely be incorporated in the process of surgical planning in order to judge whether and which implant-based prosthetics is feasible for a particular patient. The latter, however, does not imply that all patients will end with a functional prosthesis. Although, when inserting primary mandibular implants, most patients will end with a functional implant-based prosthetic solution, still not all patients will benefit from the implants.
As mentioned before, the main reason of not using the implants was that the patient deceased or that recurrent disease occurred before prosthetic rehabilitation was started or could be finished. Soft tissue problems resulting from ablative tumour surgery were a second reason, making a proper functioning prosthesis difficult or even impossible as no functional suprastructure and/or overdenture could be made on the implants. Soft tissue problems mainly occurred in patients in whom the primary tumour was in the same area in which the implants were inserted. When indicating primary insertion of implants in these patients, specific attention must be paid whether it is feasible to get a peri-implant mucosal condition that allows for proper attached mucosa around the implants and a proper buccal and/or lingual vestibule to accommodate an overdenture (neutral zone).
While primary insertion of implants should be considered the standard treatment in the edentulous mandible, primary implant insertion can be considered for the maxilla, and in areas in which the mandible or maxilla is reconstructed with, e.g., a fibula, at time of tumour surgery too. Whether this approach is as feasible as in the mandible has to be proven in the future. Latter two treatments are in need of a very meticulous implant planning. To facilitate implant planning in (to be) reconstructed mandibular and maxillary defects, methods for 3D computerized planning of both the surgical reconstruction and the most ideal position of the implants are currently developed. The first results using 3D technology in secondary reconstructions are promising (Schepers et al. 2013)

Other patients that potentially might benefit from primary implant insertion are pre-edentulous patients. Oral cancer patients require dental evaluations as part of their oncological work-up. A common result is that teeth have to be removed due to periodontal infection, periapical infection and/or profound caries. One might consider providing pre-edentulous patients with primary implants so that also these patients, as now is common in our clinic for longstanding edentulous patients, might benefit from an early implant-retained prosthesis. However, it seems advisable to limit primary implant insertion to pre-edentulous patients with just remaining teeth in the mandible and no active periodontal disease as periodontal disease is accompanied by high implant loss in healthy subjects and a high risk of developing osteoradionecrosis (Schuurhuis et al. 2011).
In our study second stage implants were used for primary implant insertion. Another possibility is to insert single stage implants in oral cancer patients, or to insert two-stage implants as single stage implants. With this, the time between implant insertion and completion of prosthetic rehabilitation could be shortened further and no second procedure is needed to use the implants for prosthetic rehabilitation.
In patients with nasal defects resulting from total rhinectomy prosthetic rehabilitation with implant-retained nasal prostheses is accompanied by a favourable treatment outcome, with minor need for surgical aftercare. Prosthetic aftercare is limited to the remake of implant-retained nasal prostheses because the limited average life span of these prostheses. A remake, however, is relatively simple and fast using the existing mould of that patient for a new nasal prosthesis.
In patients with Sjögren's syndrome, insertion of implants is a good treatment option, considering the reasonably good peri-implant health, limited prevalence of peri-implantitis, high implant survival and high patients' satisfaction. In our study implant therapy in patients with Sjögren's syndrome was assessed retrospectively. Prospective assessment of implants in patients with Sjögren's syndrome and healthy controls should be performed to rate the true value of implant-based prosthetics, focussing on implant survival, prevalence peri-implant mucositis and peri-implantitis, oral function and patients' satisfaction.

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Chapter 7

Summary

Prosthetic rehabilitation of patients with a compromised intraoral and extraoral condition is challenging. Examples of those patients are head and neck cancer patients and patients with Sjögren's syndrome. While rehabilitation of these patients with conventional prostheses frequently results in an unsatisfactory or suboptimal treatment outcome, rehabilitation with implant-retained prostheses is in favour of a better treatment outcome (chapter 1). The research described in this thesis assessed the treatment outcome of implant therapy in head and neck cancer patients and patients with Sjögren's syndrome.

In **chapter 2** the long-term treatment outcome of implant-retained overdentures on mandibular implants inserted during ablative surgery (so called primary inserted implants) is described.

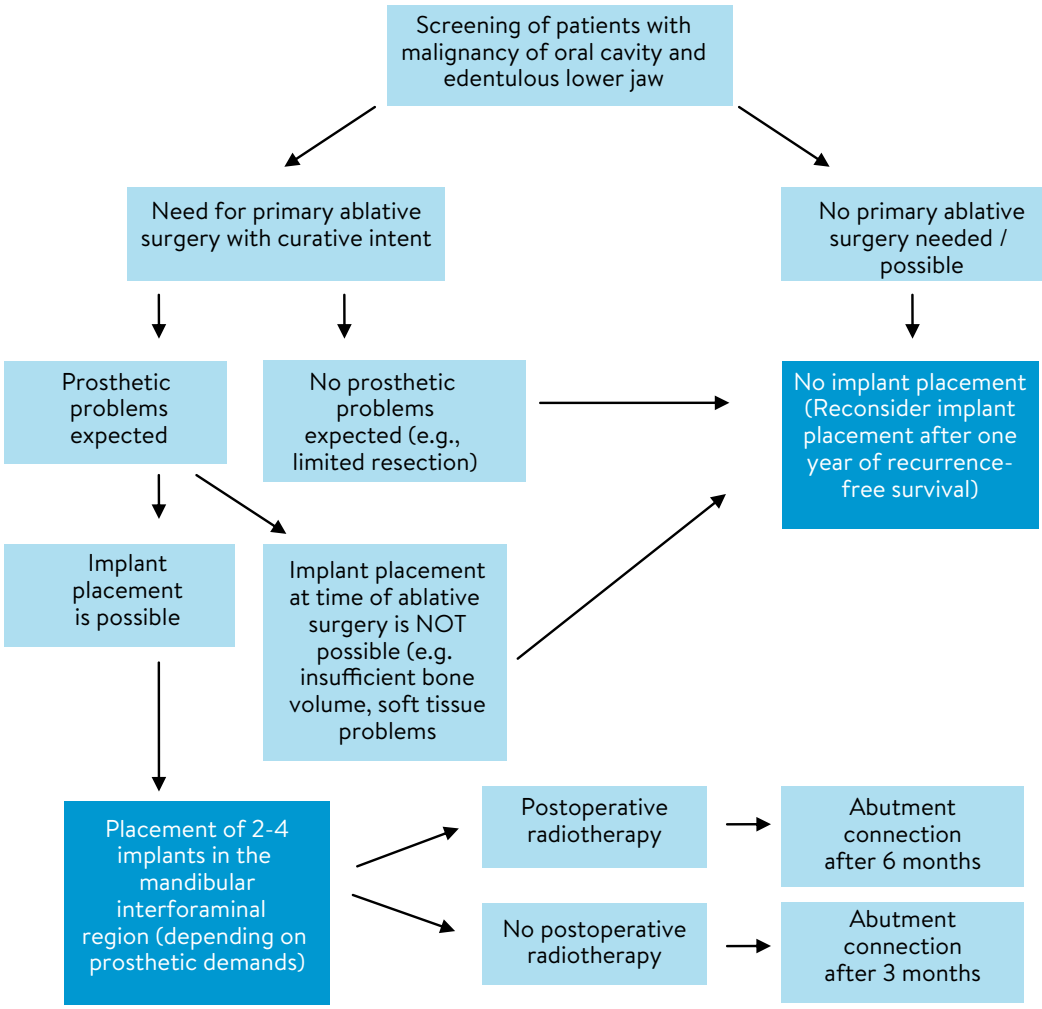
In **chapters 2.1** and **2.2** the results of a prospective 5 year follow-up study on primary inserted mandibular implants in oral cancer patients are described. In this study 50 edentulous oral cancer patients received 4 implants in the mandible during their ablative tumour surgery between 1998 and 2002. Inclusion criteria were: (1) edentulous upper and lower jaw, (2) history of prosthetic problems related to lack of stability and retention of the lower denture, or expected problems with the lower denture after oncological treatment, (3) malignancy in the lower oral cavity or oropharynx which required primary curative resection, and (4) little or no improvement to be expected from making new dentures after oncological treatment. In this study oral functioning, quality of life, condition of peri-implant tissues, implant survival, patients' satisfaction and subjective chewing ability up to 5 years after prosthetic rehabilitation of these 50 patients was assessed. The results 1 year after the prosthetic treatment of these patients had been described previously (Schoen et al. Int J Oral Maxillofac Surg 2008;37:8-16).
Preoperatively, patients had completed validated questionnaires regarding quality of life, oral functioning and patients' satisfaction. The same questionnaires were completed 6 weeks, 1 year and 5 years after completing prosthetic treatment. Also peri-implant indices were assessed at these time points. About two-third of the patients was irradiated postoperatively.
Five years after denture placement, 26 patients were deceased. Four surviving patients did not wear the implant-retained mandibular overdenture for various reasons; meaning 83% of the patients had a functional implant-retained overdenture (n=20). Of these 20 patients, 9 patients had been irradiated postoperatively (45%). Quality of life (QoL) had deteriorated in these 20 patients between 1 and 5 years after placement of the dentures, which was due to the concurrent comorbidity that had occurred in a small number of patients, while global health and QoL for patients without comorbidity was very high. The oral function and denture satisfaction were high too, and did not change over time, comparable to what commonly is observed in healthy patients. At the 5-year follow-up, implant survival rate was 89.4% in irradiated patients and 98.6% in non-irradiated patients (implants as unit).

The mean scores of the peri-implant indices were low at all evaluations, but there was significant bone loss over time in all patients. There were no differences in peri-implant health between the irradiated patients and the non-irradiated patients at all evaluations. Furthermore, overall denture satisfaction was high and did not change over time, both for irradiated and non-irradiated patients. On basis of these results it was concluded that primary implant insertion in this group of patients led to a large number of rehabilitated patients (83%) with favourable long-term treatment outcome.
Based on the favourable results of primary implant insertion as described in chapters 2.1 and 2.2, further study was needed to estimate which patients with oral cancer can benefit from primary implants and how the results of primary implants insertion will be in the long term (see chapter 2.3).

In **chapter 2.3** a study is described assessing the treatment outcomes (which patients benefit, their quality of life, their oral functioning and satisfaction, the condition of the peri-implant tissues, and survival of the implants) of a prospective cohort of 164 patients with oral cancer in the lower oral cavity, who were supplied with primary mandibular implants to support an implant-retained mandibular overdenture up to 14 years after insertion of their implants. The same inclusion criteria and assessments were used as in chapters 2.1 and 2.2, with a few exceptions: the patients were included between 1998 and 2010, and were all reassessed during a final assessment in 2012. Depending on the available bone and the prosthetic demands, 2, 3 or 4 implants were inserted. Also patients not wearing an implant-retained overdenture were asked to complete the questionnaires. Patients in whom prosthetic rehabilitation was completed less than 1 year before assessment were excluded from analysis.
Implant survival in this cohort was lower in irradiated patients compared with non-irradiated patients, viz., 91.5% vs. 99.5%. Five out of 100 irradiated patients developed osteoradionecrosis in proximity to the implants, which could be treated successfully in four out of these five patients. In the fifth patient, a recurrence of the tumour had developed in the same area where the osteoradionecrosis had occurred. Comparable to the results of the study described in chapter 2.2, bone loss around the implants increased significantly over time, both in irradiated and in non-irradiated bone. Again there was no significant difference between irradiated and radiated patients. In 84% of the patients an implant-retained overdenture was made. Completion of prosthetic rehabilitation and oral functioning, chewing ability, and patients' satisfaction were independent of site or stage of tumour, type of reconstruction and the number of implants inserted. Patients wearing an implant-retained mandibular overdenture were able to chew significantly better, had better social function, and had better oral functioning than patients who did not wear an overdenture. Non-irradiated patients had higher scores for satisfaction and oral functioning than irradiated patients.

On basis of the favourable results as reported in chapters 2.1, 2.2 and 2.3, it was concluded that insertion of implants during resection in edentulous patients with oral cancer in the lower oral cavity should be routinely incorporated into surgical planning. To facilitate decision making for implant placement in head neck cancer patients, the algorithm shown in figure 1 is proposed (**chapter 2.4**).

Figure 1. Decision-making process for mandibular implant placement during ablative surgery



Chapter 3 describes the multidisciplinary prosthetic rehabilitation of adult patients after treatment for rhabdomyosarcoma in their childhood. Rhabdomyosarcoma is the most common malignant tumor in the nasal and paranasal sinus area at childhood. The multimodal treatment needed for this disorder (chemotherapy, radiotherapy and

surgery) has severe side effects due to its damaging effects on normal tissue. As a result of this treatment, retardation of facial growth and existence of oral abnormalities such as malformation of teeth and microstomia can cause esthetic and functional problems. Two cases were presented of patients with severe midfacial hypoplasia and reduced oral function as a result of treatment of rhabdomyosarcoma of the nasopharyngeal and nasal–tonsil region. With a combined surgical (osteotomy, distraction osteogenesis, implants) and prosthetic (implant-based overdenture) treatment, esthetics and function were improved.

The use of implants is not restricted to the intraoral rehabilitation of compromised patients. In **chapter 4** aftercare, clinical outcomes of the implants and patients' satisfaction of implant-retained *nasal* prostheses were assessed. This study describes 28 consecutive patients in need of total rhinectomy who were treated according to a standardized protocol with two implants in the nasal floor between 1998 and 2013. Surgical and prosthetic aftercare was scored using patient records. All patients that were alive in 2014 were recalled to assess skin reaction, peri-implant bone loss, and patients' satisfaction. In total 56 implants had been inserted (median follow-up 35.1 months, IQR 8.9-63.3). Implant survival was 96.4%, independent of radiotherapy. Subcutaneous tissue reduction, being the only surgical intervention related to the implants, was performed in 2 out of the 28 patients. With respect to prosthetic aftercare, many patients (65.2%) were in need for (repeated) hygiene instructions and 30.4% of the patients needed (repeated) repair of clips. Median life span of the implant-retained nasal prostheses was 11.6 months (IQR 6.8-15.2). Main reason for prosthesis replacement was discolouration. Peri-implant skin was healthy and patients' satisfaction high with a median of 8.0 out of 10. From the results, it was concluded that rehabilitation of nasal defects resulting from total rhinectomy with implant-retained nasal prostheses according to our protocol resulted in high patient satisfaction and favourable treatment outcome. The average life span of nasal prostheses is limited, mainly due to discoloration of the silicone material.

Not much was known yet about the use of implants in patients with Sjögren's syndrome. In **Chapter 5** clinical outcomes of implant therapy in a cohort of well-classified patients with Sjögren's syndrome is described. The treatment outcome was compared to that observed in matched healthy controls. All Sjögren's patients regularly attending the University Medical Center Groningen for standardized follow-up (n=406) were questioned for earlier oral implant therapy. Patients with implants were recalled to record peri-implant health (using the same indices as described in chapter 2) and implant survival and were compared with data from matched healthy controls. Patients' symptoms, health-related quality of life, oral functioning and satisfaction were assessed using validated questionnaires. Of the responding Sjögren's patients (n= 335), 21% was provided with implants. Data of 50 patients (140 implants) could be collected. Peri-implant health was reasonable, marginal bone loss minor, implant survival was 97% (median follow-up 46 months, IQR 26-73) and

patients' satisfaction was high in most Sjögren's patients. Peri-implant mucositis, defined as bleeding on probing at one or more sites around one or more implants, was higher in Sjögren's patients (94%) than in the healthy controls (71%). There was no difference in prevalence of peri-implantitis between Sjögren's patients and the healthy controls, and also peri-implant health and marginal bone loss were comparable. Furthermore, oral functioning correlated negatively with dryness, patients' satisfaction, and chewing ability in Sjögren's patients. It was concluded that implants are a good treatment option in Sjögren's patients, considering the good peri-implant health, limited prevalence of peri-implantitis, high implant survival and patients' satisfaction.

In the general discussion **(chapter 6)** the results of the previous chapters are placed in a broader context. Based on the results of the various studies described in this thesis it is concluded that patients with a compromised intraoral or extraoral condition benefit largely from rehabilitation with implant-retained prostheses. Implant survival is in general high, peri-implant tissues healthy and patients' satisfaction high.

Chapter 8

Samenvatting

De prothetische rehabilitatie van patiënten met een gecompromitteerde intraorale en extraorale conditie is zeer uitdagend. Voorbeelden zijn patiënten bij wie een tumor in het hoofd-halsgebied is behandeld en patiënten met het syndroom van Sjögren. Aangezien de prothetische rehabilitatie van deze patiënten vaak een suboptimaal of zelfs onbevredigend behandelresultaat heeft, wordt tegenwoordig de voorkeur gegeven aan de behandeling met implantaatgedragen prothetische voorzieningen. Hiermee kan beter houvast en steun voor de protheses worden verkregen en worden de onderliggende slijmvliezen of huid minder belast en geïrriteerd. (hoofdstuk 1). Het in dit proefschrift beschreven onderzoek richt zich op de uitkomsten van een prothetische reconstructie met implantaten bij patiënten die behandeld zijn of worden voor een tumor in het hoofd-halsgebied en patiënten met het syndroom van Sjögren.

In **hoofdstuk 2** worden de langetermijnresultaten van implantaatgedragen overkappingsprothesen in de onderkaak beschreven, waarbij de implantaten tijdens de ablatieve chirurgische ingreep zijn geplaatst, d.w.z. implantaten die worden geplaatst tijdens de chirurgische procedure waarbij de tumor wordt verwijderd (primair geplaatste implantaten).

In de **hoofdstukken 2.1** and **2.2** worden de 5-jaars-resultaten van een prospectieve studie naar primair geplaatste implantaten in patiënten waarbij een tumor in de het onderste gedeelte van de mondholte (tong, mondbodem, oropharynx) is verwijderd. In deze studie kregen 50 patiënten zonder tanden en kiezen die een behandeling ondergingen voor een tumor in de mondholte (tussen 1998 en 2002) 4 implantaten in de onderkaak als steun voor de later te vervaardigen prothese. De implantaten werden tijdens de tumoroperatie geplaatst. De inclusiecriteria waren: (1) onbetande boven- en onderkaak, (2) prothetische problemen gerelateerd aan een gebrek aan stabiliteit en retentie van de onderprothese, of verwachte problemen met de onderprothese na de oncologische behandeling, (3) kwaadaardige tumor in het onderste deel van de mondholte, die kan worden behandeld middels het chirurgisch verwijderen van de tumor, en (4) de verwachting dat het vervaardigen van nieuwe, conventionele prothesen na de chirurgische verwijdering van de tumor en de eventueel radiotherapeutische nabehandeling weinig tot geen verbetering geeft van functie.
In de in de hoofdstukken 2.1 en 2.2 beschreven studies werden het oraal functioneren, de kwaliteit van leven, de conditie van de peri-implantaire weefsels, de implantaatoverleving, de patiënttevredenheid en het subjectief kauwvermogen tot 5 jaar na de prothetische rehabilitatie onderzocht. De resultaten na 1 jaar zijn in een eerdere studie beschreven (zie Schoen et al. Int J Oral Maxillofac Surg 2008;37:8-16). Voorafgaand aan de operatie (chirurgische verwijdering van de tumor en plaatsen van de implantaten) hadden de patiënten gevalideerde vragenlijsten ingevuld, waarin gevraagd werd naar de kwaliteit van leven, het oraal functioneren en de tevredenheid van de patiënt. Dezelfde vragenlijsten

werden 6 weken, 1 jaar en 5 jaar na het voltooien van de prothetische behandeling nogmaals ingevuld. Tevens werden op al deze tijdstippen de uitkomsten van een aantal peri-implantaire indices gescoord. Ongeveer tweederde van de patiënten was postoperatief bestraald.
Vijf jaar na plaatsen van de prothesen waren in totaal 26 patiënten overleden. Vier overlevende patiënten droegen, vanwege verschillende redenen, geen implantaatgedragen prothese, wat inhoudt dat 83% van de patiënten een functionerende prothese droeg (n=20). Van deze 20 patiënten waren 9 patiënten postoperatief bestraald (45%). De kwaliteit van leven van deze 20 patiënten was gemiddeld gezien verslechterd in de periode tussen 1 en 5 jaar na het plaatsen van de prothesen. Deze gemiddelde achteruitgang van de kwaliteit van leven bleek terug te voeren op de bestaande comorbiditeit in een kleine subgroep van de 20 geëvalueerde patiënten; de algehele gezondheid en kwaliteit van leven in patiënten zonder comorbiditeit was hoog. De orale functie en tevredenheid van de patiënt met de prothese waren en bleven hoog gedurende de gehele 5-jaars studieperiode, vergelijkbaar met wat wordt waargenomen bij gezonde patiënten.
De 5-jaars implantaatoverleving varieerde wel tussen bestraalde en niet-bestraalde patiënten, namelijk 89,4% in bestraalde patiënten en 98,6% in niet-bestraalde patiënten (implantaten als eenheid). De gemiddelde scores van de peri-implantaire indices (plaque-index, gingiva-index etc.) waren laag tijdens elk evaluatiemoment, wel was er sprake van significant botverlies als functie van de tijd in alle patiënten. Er waren geen verschillen in peri-implantaire gezondheid tussen bestraalde en niet-bestraalde patiënten tijdens elk evaluatiemoment. Daarnaast was de patiënttevredenheid met de prothese hoog en veranderde deze niet in de tijd, zowel in bestraalde als niet-bestraalde patiënten. Op basis van deze resultaten werd geconcludeerd dat primaire plaatsing van implantaten in deze patiëntenpopulatie leidt tot een groot aantal gerehabiliteerde patiënten (83%) met een gunstig behandelresultaat op de lange termijn.
Gebaseerd op de resultaten van de studie naar primair geplaatste implantaten, zoals beschreven in de hoofdstukken 2.1 en 2.2, was verdere studie nodig om te bepalen *welke* patiënten met een tumor in het hoofd-halsgebied het meest voordeel hebben bij primaire plaatsing van implantaten en wat de resultaten zijn op de lange termijn (zie hoofdstuk 2.3).

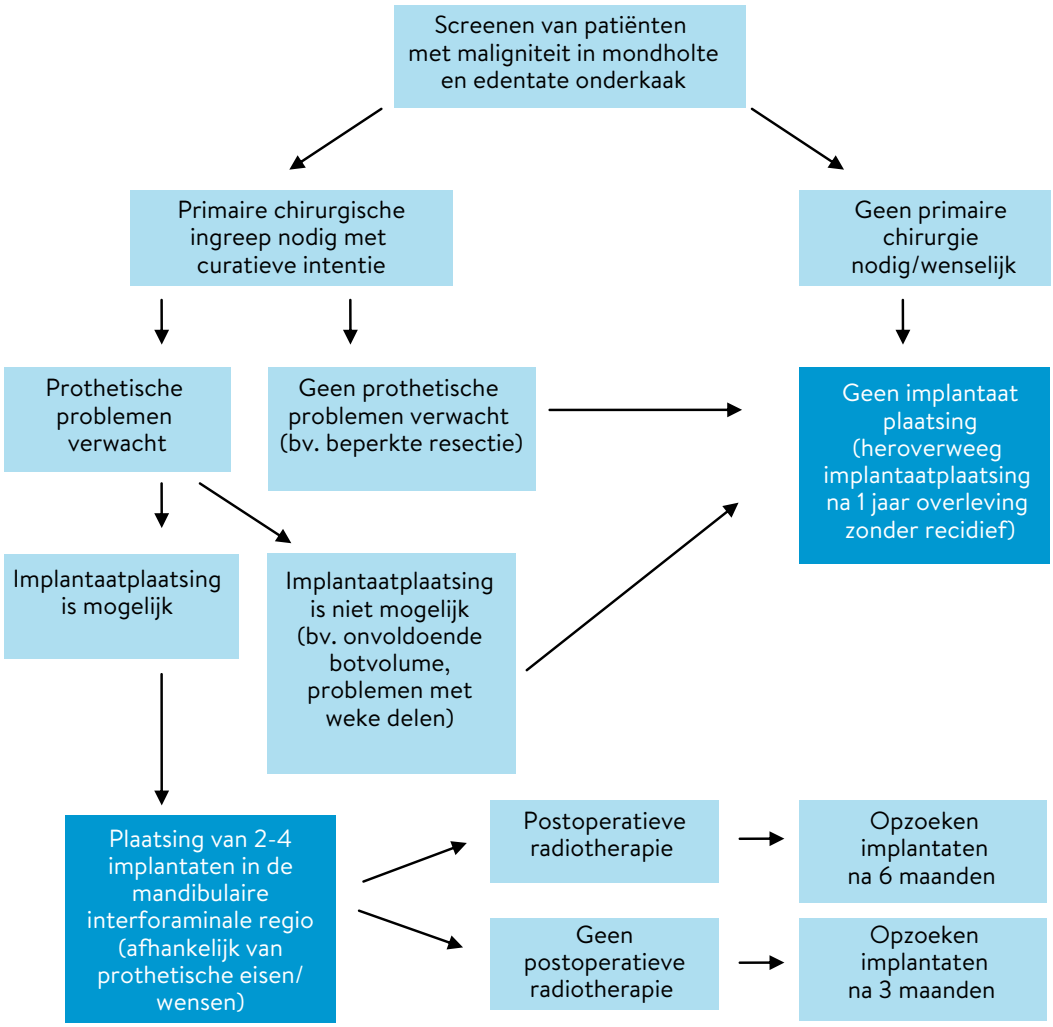
In **hoofdstuk 2.3** is een studie beschreven die de behandeluitkomsten (welke patiënten hebben baat bij een implantaatgedragen prothese in de onderkaak, wat is hun kwaliteit van leven, oraal functioneren en tevredenheid, wat is de conditie van de peri-implantaire weefsels en de implantaatoverleving) beschrijft van een prospectief cohort van 164 patiënten met een tumor in het hoofd-halsgebied, die primair geplaatste implantaten in de onderkaak hebben gekregen ter ondersteuning van een implantaatgedragen overkappingsprothese tot 14 jaar na plaatsen van de implantaten. Dezelfde inclusie- en exclusiecriteria werden gebruikt als in hoofdstuk 2.1 en 2.2, met een paar uitzonderingen: de patiënten waren behandeld tussen 1998 en 2010, en werden opgeroepen voor een

laatste onderzoek in 2012. Afhankelijk van het aanwezige bot en de vooraf bepaalde prothetische eisen waren 2, 3 of 4 implantaten in de mandibula geplaatst. Ook patiënten die hun implantaatgedragen overkappingsprothese in de onderkaak niet droegen werden gevraagd de vragenlijsten in te vullen. Patiënten die minder dan een jaar geleden de prothetische behandeling hadden voltooid, werden buiten de analyse gehouden.
De overleving van implantaten in dit cohort was, conform de uitkomsten van de hoofdstukken 2.1 en 2.2. beschreven studies, opnieuw lager in bestraalde dan in niet-bestraalde patiënten, namelijk 91,5% tegenover 99,5%. Vijf van de 100 bestraalde patiënten ontwikkelden osteoradionecrose in nabijheid van de implantaten; in 4 patiënten kon de osteoradionecrose succesvol worden behandeld. In 1 patiënt bleek sprake te zijn van een nieuwe tumor in het gebied waar zich de osteoradionecrose had ontwikkeld. Conform de uitkomsten van de in de beide vorige hoofdstukken beschreven studies, nam ook in deze studie het botverlies significant toe met de tijd en werd ook geen verschil in botverlies gezien tussen bestraalde en niet-bestraalde patiënten. In 84% van de patiënten kon een implantaatgedragen overkappingsprothese worden vervaardigd. Het al dan niet voltooien van de prothetische behandeling, het oraal functioneren, het kauwvermogen en de patiënttevredenheid hingen niet samen met de plaats en stadiëring van de tumor, het type reconstructie en het aantal geplaatste implantaten. Patiënten die een overkappingsprothese droegen hadden subjectief gezien een beter subjectief kauwvermogen, functioneerden sociaal beter en hadden een beter oraal functioneren dan patiënten die geen overkappingsprothese droegen. Tenslotte bleken niet-bestraalde patiënten hogere scores te rapporteren voor tevredenheid en oraal functioneren dan bestraalde patiënten.

Op basis van de in de hoofdstukken 2.1, 2.2 en 2.3 beschreven gunstige resultaten werd geconcludeerd dat plaatsing van implantaten tijdens de ablatieve chirurgische ingreep in patiënten die worden behandeld voor een tumor in de mondholte een routineonderdeel dient te zijn in de chirurgische planning van deze patiënten. Om de besluitvorming rondom implantaatplaatsing in patiënten met een tumor in het hoofd-halsgebied te vergemakkelijken, werd het in figuur 1 getoonde algoritme opgesteld (**hoofdstuk 2.4**).

Hoofdstuk 3 beschrijft de multidisciplinaire prothetische rehabilitatie van volwassen patiënten die op kinderleeftijd zijn behandeld voor een rhabdomyosarcoom. Rhabdomyosarcomen zijn de meest voorkomende maligne tumoren in het gebied van de nasale en paranasale sinussen bij kinderen. De multimodulaire behandeling van deze aandoening (chemotherapie, radiotherapie, chirurgie) heeft ernstige bijwerkingen tot gevolg door schade aan de gezonde weefsels. Als resultaat van deze behandelingen, in het bijzonder de chemotherapie en radiotherapie, ontwikkelen zich o.a. een groeiachterstand van het gezicht en afwijkingen van de mondweefsels, zoals misvorming van tanden en kiezen, en microstomie. Deze groeiachterstand en afwijkingen van de mondweefsels kunnen leiden tot esthetische en functionele problemen. In hoofdstuk 3 worden twee

Figuur 1. Besluitvorming voor plaatsen mandibulaire implantaten tijdens tumoroperatie



casus gepresenteerd, waarbij sprake is van een ernstige onderontwikkeling van het middengezicht en een verminderde orale functie. Met een gecombineerde chirurgische (osteotomie, distractie osteogenesis, implantaten) en prothetische (implantaatgedragen overkappingsprothese) behandeling werden de esthetiek en de orale functie verbeterd.

Het gebruik van implantaten beperkt zich niet tot de intraorale rehabilitatie van gecompromitteerde patiënten. In **hoofdstuk 4** worden de nazorg, de klinische uitkomsten van de implantaten en de patiënttevredenheid van implantaatgedragen neusprothesen onderzocht. Deze studie beschrijft 28 opvolgende patiënten die een totale neusamputatie

ondergingen, waarbij volgens een gestandaardiseerd protocol twee implantaten in de neusbodem werden geplaatst tussen 1998 en 2013. De geleverde chirurgische en prothetische nazorg werd afgeleid uit de statussen van de patiënten. Alle nog in leven zijnde patiënten werden in 2014 opgeroepen om de conditie van de huid rond de implantaten, het peri-implantaire botverlies en de patiënttevredenheid te onderzoeken. In totaal werden 56 implantaten geplaatst (mediane follow-up 35,1 maanden, interkwartiel spreiding 8,9-63,3 maanden). Implantaatoverleving was 96,4%; dit overlevingspercentage was onafhankelijk of de patiënt radiotherapie had ondergaan of niet. Het uitdunnen van de huid, de enige chirurgische interventie die soms moest worden uitgevoerd in directe relatie tot de implantaten, was in 2 van de 28 patiënten noodzakelijk. Met betrekking tot de prothetische nazorg, hadden veel patiënten herhaalde hygiëne-instructies nodig (65,2%) en kwam 30,4% van de patiënten terug voor clipreparaties. De mediane overleving van de implantaatgedragen neusprotheses was 11,6 maanden (interkwartiel spreiding 6,8-15,2). De meest voorkomende reden om een neusprothese te vervangen was verkleuring van die prothese. De peri-implantaire huid was over het algemeen gezond en de patiënttevredenheid was hoog met een mediane score van 8,0 (interkwartiel spreiding 8,0-10). Uit deze resultaten werd geconcludeerd dat de protocollaire rehabilitatie van patiënten met een totale neusamputatie met implantaatgedragen neusprotheses leidt tot een gunstige behandeluitkomst en hoge patiënttevredenheid. De gemiddelde levensduur van de prothesen is echter beperkt, voornamelijk vanwege verkleuring van de protheses.

Nog weinig is bekend over het gebruik van implantaten bij patiënten met het syndroom van Sjögren. In **hoofdstuk 5** worden de klinische resultaten van implantaten in een cohort van goed omschreven patiënten met het syndroom van Sjögren beschreven en vergeleken met de uitkomsten van een soortgelijke behandeling in gepaarde gezonde controlepatiënten. Alle patiënten met het syndroom van Sjögren die periodiek in het Universitair Medisch Centrum Groningen gezien worden voor standaard controles (n=406) werden gevraagd of zij eerder implantaten hadden gekregen. Patiënten met implantaten werden opgeroepen om peri-implantaire gezondheid en implantaatoverleving te meten (dezelfde indices werden gebruikt als omschreven in hoofdstuk 2). De uitkomsten van deze metingen werden vergeleken met gegevens van gepaarde gezonde patiënten. Symptomen, gezondheidsgerelateerde kwaliteit van leven, oraal functioneren en kauwvermogen werden onderzocht met behulp van gevalideerde vragenlijsten.
Van de patiënten die mee wilden werken aan dit onderzoek (n=335) had 21% een prothetische voorziening op implantaten. Vijftig van de 69 patiënten met implantaten waren bereid of in de mogelijkheid aan het onderzoek mee te werken. Bij deze patiënten werd de peri-implantaire gezondheid gemeten worden en werden vragenlijsten ingevuld. De peri-implantaire gezondheid was redelijk tot goed, het marginaal botverlies was minimaal en de implantaatoverleving was 97% (mediane follow-up 46 maanden, interkwartiel spreiding 26-73 maanden); deze uitkomsten stemden overeen met die van

een groep leeftijd en geslacht gematchte controlepatiënten bij wie een vergelijkbare prothetische constructie op implantaten was vervaardigd.
De meeste Sjögrenpatiënten bleken tevreden met hun implantaatgedragen constructie, maar de tevredenheid was lager dan die in de controlepatiënten. Peri-implantaire mucositis, gedefinieerd als bloeding bij sonderen bij een of meerdere plaatsen rond een of meer implantaten, was hoger in Sjögrenpatiënten (94%) dan in de gezonde controlepatiënten. De prevalentie van peri-implantitis tussen Sjögrenpatiënten en controlepatiënten was vergelijkbaar. Daarnaast was het oraal functioneren negatief gecorreleerd aan de mate van monddroogheid, de patiënttevredenheid en het kauwvermogen in Sjögrenpatiënten. Concluderend kan worden gesteld dat implantaten een goede behandelmodaliteit zijn in patiënten met het syndroom van Sjögren, gezien het niveau van de peri-implantaire gezondheid, de beperkte prevalentie van peri-implantitis, de hoge implantaatoverleving en de hoge patiënttevredenheid.

In de overkoepelende discussie (**hoofdstuk 6)** worden de resultaten van de vorige hoofdstukken in een bredere context geplaatst. Gebaseerd op de resultaten van de verschillende in dit proefschrift beschreven studies wordt geconcludeerd dat patiënten met een gecompromitteerde intra- of extraorale conditie naar verwachting groot voordeel hebben van rehabilitatie met implantaatgedragen protheses. De implantaatoverleving is in het algemeen hoog.

Curriculum Vitae

Anke Korfage was born on March 17 1978 in Delfzijl, the Netherlands. In 1996 she completed pre-university secondary education (VWO) at the Ommelander College in Appingedam. That year she started dental school at the 'Rijksuniversiteit Groningen', which she completed in April 2002.
Between 2002-2005 she worked as a general practitioner in several general dental practices. From 2003 until 2009 she worked at the dental school at the Rijksuniversiteit Groningen (later University Medical Center Groningen, UMCG) as a teacher of (pre)clinical education for dental students. Here she also treated patients in traineeships focusing on implantology and prosthodontics.
In 2005 she started a 4-year part-time differentiation maxillofacial prosthodontics (as recognized by the Nederlandse Vereniging voor Gnathologie en Prothetische Tandheelkunde, NVGPT) at the Center of Special Dental Care at the department of Oral and Maxillofacial Surgery of the UMCG, which she completed in 2009. She returned to this department as a staff member of the Center for Special Dental Care in 2010 after travelling for 6 months in Southeast Asia. In 2010 she started her PhD research which focused on implantology in maxillofacial prosthodontics. She has participated in the organization of several (inter)national conferences.
Anke Korfage lives together with Jeroen Verstraaten and they have two daughters, Cato (2011) and Fien (2013).