Free flap reconstruction and implant-based dental rehabilitation in oral cancer patients

Lodders, Johannes Nicolaas

2023

DOI (link to publisher)
10.5463/thesis.414

document version
Publisher's PDF, also known as Version of record

Free flap reconstruction and implant-based dental rehabilitation in oral cancer patients

Johannes Nicolaas Lodders

The following institutions financially supported the printing of this thesis:

ISBN/EAN: 978-94-6419-951-2
DOI: http://doi.org/10.5463/thesis.414

Lay-out: Tiny Wouters
Cover design: Mitchel de Val
Printed by: Gildeprint Drukkerijen

VRIJE UNIVERSITEIT

FREE FLAP RECONSTRUCTION AND IMPLANT-BASED DENTAL REHABILITATION IN ORAL CANCER PATIENTS

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. J.J.G. Geurts,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Tandheelkunde
op woensdag 29 november 2023 om 11.45 uur
in een bijeenkomst van de universiteit,
De Boelelaan 1105

door

Johannes Nicolaas Lodders

geboren te Rotterdam

promotoren:	prof.dr. T. Forouzanfar prof.dr. E.A.J.M. Schulten
copromotor:	dr. F.K.J. Leusink
promotiecommissie:	prof.dr. J.G.A.M. de Visscher prof.dr. L.E. Smeele prof.dr. C.R. Leemans dr. E.M. van Cann prof.dr. M.J.H. Witjes prof.dr. J.C. Jansen

Table of contents

Chapter 1

General introduction and outline of the thesis

General introduction

Head and neck cancer

Head and neck cancer is a relatively uncommon form of cancer in the Netherlands accounting for approximately 3% of all malignant tumours diagnosed in 2019, with a total of 2839 patients affected. Of these cases, oral cancer was diagnosed in 853 patients, with males being slightly more affected than females. Most oral cancers are classified as oral squamous cell carcinoma, which originates from the mucosal epithelium. Other rarer forms of oral cancer include salivary gland tumours, hematologic tumours, bone tumours, mesenchymal tumours and odontogenic tumours. Sub sites of oral cancer consist of the anterior two-third of the tongue (usually lateral border), floor of mouth, gingiva, buccal mucosa, lip and the hard palate. Patients with oral cancer are typically over 60 years of age (>70%), and nearly half have locally advanced tumours (stage III and IV).[1] Locally advanced tumours are characterized by large tumour size (>4 cm) or infiltration into nearby structures, and/or the presence of cancer cells in regional lymph nodes.

The use of tobacco and excessive alcohol consumption are strongly associated with the development of oral squamous cell carcinoma.[2] Other potential risk factors such as ethnicity, nutrition (raw meat), and dental hygiene are controversial due to potential confounding factors.[1]

Treatment of oral cancer

Treatment options for head and neck cancer include surgery, radiotherapy, chemotherapy, or a combination of these modalities. Surgery is the cornerstone of the oncological treatment for oral cancer and, if indicated, concomitant (chemo)radiotherapy. In the Netherlands, over 90% of oral cancer patients underwent surgery in 2019. Complete tumour resection is crucial, as failure to do so may increase the risk of loco-regional recurrence and possibly poorer overall survival.[3,4] Therefore, surgeons aim to completely remove tumours with clear margins, per-operatively determined mainly by inspection and palpation and assisted by imaging modalities like ultrasonography, MRI, and CT.[5]

Unfortunately, achieving oncological resection with tumour-free margins often means sacrificing important anatomical structures like muscles, nerves, and bone (with or without teeth), which conflicts with preserving oral function. The types of tissues removed during surgery are mostly determined by tumour size and location. For example, small tongue or buccal mucosa tumours may only require resecting mucosa

and muscle fibers, while tumours closely to the maxillary or mandibular bone may necessitate resection of bone, teeth, and muscle including their attachments.

A surgical procedure that involves removing bone from the upper jaw is referred to as a maxillectomy, and the extent of the resection determines its classification.[6] If bone is resected from the mandible, the procedure is known as a mandibulectomy, and can be categorized as either a marginal or segmental mandibulectomy depending on the type of resection. A marginal mandibulectomy maintains mandibular continuity and often spares vital structures like muscle attachments and the inferior alveolar nerve. On the other hand, a segmental mandibulectomy disrupts mandibular continuity and can involve any part of the mandible (with or without teeth).[7,8] In contrast to a marginal mandibulectomy, muscle attachments and sensory nerves are usually included in a segmental mandibular resection.

Free flap reconstruction in head and neck cancer patients

Surgical resection of a tumour in and around the oral cavity may lead to a substantial defect of the soft and hard tissues and consequently impaired oral functioning, including speech, mastication and swallowing. Additionally, surgery may negatively impact aesthetics and result in changes of the patient's physical and emotional wellbeing.[9] To address these issues, reconstruction may be necessary after ablative surgery. This can be done either simultaneously with the tumour surgery (primary reconstruction) or in a second procedure (secondary reconstruction). Most oral and maxillofacial defects are primarily reconstructed due to functional and cosmetic considerations.[10-12]

A wide range of options are available for the reconstructions of tissue defects in the oral and maxillofacial region, with microvascular free tissue transfer or free flap surgery being the final and most complex option in the "reconstructive ladder." [13] A free flap is a section of tissue that is harvested from one site of the body (donor site), and, after it is completely detached from its blood supply, transferred to the desired location (recipient site) with reconnection of the blood vessels and thereby restoring the blood circulation in the transferred tissue. Nowadays, depending on the donor site, a free flap can comprise different types of tissues including skin, fat, muscle and/or bone. This reconstructive option is generally used for large composite head and neck defects and sometimes for smaller critical defects in the oral cavity.

In 1959, the first free flap transfer in a human was carried out for reconstruction of a pharyngeal defect after resection of a squamous cell carcinoma. Eight days after reconstruction the patient probably died of a cerebrovascular accident.[14] Free flap

surgery, as we know today, started at the beginning of 1970s, with the first clinical report of a temporal skin flap in 1972.[15] During the mid and late 1970s different free flaps were reported with success. Despite their development, pedicled myocutaneous flaps were widely used in head and neck surgery at that time due to their reliability, tissue volume and ease of use compared to free flaps.[16,17]

However, free flap surgery became more popular after ablative oncological surgery in the 1990s. Compared to pedicled flaps, free flaps were more versatile as there are no arc limitations of the pedicle with a reliable blood supply to distal portions of the flap and it seemed that functional outcomes were better with free flap reconstruction.[18] Over the next decades flap harvesting and anastomosis techniques were refined, and free flap failure became rare, making it an indispensable treatment option for defects in the oral and maxillofacial region.

Although a wide variety of free flaps have been described since the 1970s, only a few are commonly used for reconstruction of oral and maxillofacial defects nowadays.[16] For soft tissue defects, the radial forearm free flap and anterolateral thigh free flap are the main options. For osseous defects, the fibula free flap, deep circumflex iliac artery free flap and scapula free flap are the most frequently used.[10,11,16]

Mandibular and maxillary reconstruction in head and neck cancer patients

The use of vascularized bone-containing free flaps has brought about significant changes in the reconstruction of osseous defects in the maxillofacial region, in particular mandibular reconstructions. Prior to the 1950s, mandibular and maxillary defects resulting from cancer resection were left untreated, resulting in facial deformities that adversely affected oral function and aesthetics. In patients with segmental mandibular defects, soft tissue closure was the primary approach, without restoration of mandibular continuity. If such a defect included the anterior mandible, this often led to the development of a typical deformity that is called "Andy Gump deformity," which was named after a popular cartoon character in the early 1900s who had an extremely retrognathic or even absent mandible. Interestingly, this character was based on a real person who underwent a lower lip tumour resection in the early 1900s.[19] Maxillary defects were typically addressed with an obturator prostheses, which restored soft tissue projection of the midface and provided acceptable function. This latter prosthetic treatment concept is still widely used today for maxillary defects.[20,21]

In the pre-free flap era around the 1960s, non-vascularized bone grafts from the rib and tibia and later the iliac crest were used to reconstruct osseous maxillofacial defects.[16,17]

However, these grafts had a major disadvantage, as they posed a higher risk for complications and failure of the bone graft if postoperative radiotherapy was given.[22] Additionally, they did not offer the possibility to augment soft tissue after tumour resection. To address these shortcomings, the first vascularized osseous free flap in head and neck surgery was performed in 1970 by Mckee, who used a rib segment for mandibular reconstruction.[23] It wasn't until eight years later that the first larger series on mandibular reconstruction with iliac free flaps was published by Daniel.[24] Taylor published the use of a fibula free flap for a tibia reconstruction in 1975,[25] and 13 years after that Hidalgo published 12 successful mandibular reconstructions with fibula free flaps in 1989.[26] The first series on midface reconstruction with the fibula free flap were published in 1993 by Schusterman.[27]

Since these publications, the use of a fibula free flap has become the standard of care for mandibular reconstruction in most head and neck cancer centres and a good option for reconstruction of maxillary defects. This is due to its favourable properties including sufficient length of cortical bone and vascular pedicle, high bone quality, the possibility of harvesting a thin vascularized skin island, and the possibility for a two-team approach. Furthermore, the combined endosteal and periosteal blood supply of the fibula free flap allows osteotomies to create desirable configurations.[26]

Dental rehabilitation after mandibular and maxillary reconstruction in head and neck cancer patients

The reconstruction of mandibular and maxillary defects with osseous free flaps proved to be highly predictable in preserving facial contour and achieving good aesthetics results. As a result, the goals of reconstructed oncological patients shifted towards improving oral function, such as mastication, speech and deglutition. To achieve these functional goals, dental rehabilitation was proposed as a valuable asset.[28] However, despite restoring the mandibular or maxillary arch, fabricating tissue-borne prosthesis in patients who have undergone mandibular and maxillary reconstruction was, and still is, challenging and sometimes impossible due to changes in oral anatomy.[29]

The challenges faced by maxillofacial prosthodontists and maxillofacial surgeons are often caused by a thick and mobile soft tissue lining in the oral cavity and the lack of a buccal and lingual sulcus, causing reduced stability and retention capacity for a tissue-borne prosthesis.[28-30] The concept of using osseo-integrated dental implants in vascularized free flaps to overcome these problems was explored 16 years after the first report of a osseous free flap by Mckee.[23]

In 1987, Lukash reported the first successful insertion of dental implants in an iliac free flap.[31] The following year, Riediger published the first series of 38 dental implants successfully inserted in iliac free flaps.[32] After these reports, dental implantation in other osseous free flaps, including the fibula free flap seemed feasible.[33,34] Several authors subsequently reported successful dental implantation in fibula free flaps.[35-39]

One of the advantages of using the fibula free flap was its sufficient height to receive dental implants and its bicortical anatomy that provided good primary stability. Even when the fibula flap was irradiated, dental implants could be successfully placed.[37,40] It became clear that dental implantation in fibula free flaps would become mainstay for patients who desired dental rehabilitation. However, it's worth noting that the majority of reconstructed oncological patients did not receive dental implants mainly due to recurrent / metastatic disease or lack of motivation, as reported by some authors.[41,42]
Since the 1990s most surgeons inserted dental implants in a second procedure after the ablative surgery (secondary dental implant placement), allowing for the osseous free flap to heal and form continuity with the native bone. It was mentioned that insertion of dental implants during ablative surgery (primary dental implant placement) could compromise the vascularization of the osseous free flap.[38] Consequently, dental rehabilitation was generally started 6 to 12 months after the ablative surgery to allow the surgeon to evaluate disease recurrence, tissue healing and the intermaxillary relation.[28,32] However, this approach also resulted in additional treatment burdens for the patient.

Some authors have successfully explored primary dental implant placement in osseous free flaps, which allowed for a shorter dental rehabilitation time.[28,38] However, this method had other disadvantages, such as improper implant positioning for a prosthetic device and the loss of resources if dental rehabilitation was not initiated.

Most dental implants have been placed secondarily in patients who underwent reconstruction using fibula free flaps.[37] While the majority of these studies focused on dental implant survival, very few studied dental implant success or outcomes related to dental prostheses, which may hold greater significance. Furthermore, the effects of implant-based dental rehabilitation in reconstructed head and neck patients in terms of quality of life remains an underexposed topic.[43]

Complications after free flap reconstruction and implant-based dental rehabilitation in oral cancer patients

Complications have been associated with surgical procedures in the oral cavity since the mid-1600s, when the first reports on the surgical removal of oral cancers were

documented.[44] Surgeons at that time were particularly concerned about severe uncontrollable bleeding and infections, as adequate treatments were not available. Over the centuries, resection of head and neck cancer, including tumours in the oral cavity, has evolved dramatically due to significant medical and surgical developments. Despite this progress, patients who receive free flap reconstruction after head and neck cancer resection are still at risk for developing complications intra- and postoperatively. The intricacy of ablative and reconstructive surgery is undoubtedly a contributing factor, particularly since most patients are elderly and have a history of smoking and alcohol use.

Previous research has explored complications in free flap reconstructed head and neck cancer patients, identifying various factors that can predict clinical outcomes.[10,11,45-47] Most of these studies included patients with different anatomical head and neck cancer sites, including the oral cavity, oropharynx and larynx. Additionally, the majority of studies have focused on flap-related complications, failing to account for systemic and surgical complications and their predictors.[48] Similarly, few studies have comprehensively studied the effects and complications of implant-based dental rehabilitation in patients who had undergone maxillofacial reconstruction with a fibula free flap.[42] It is crucial to study intra- and postoperative complications as they can have a significant impact on a patient's physical and psychological health in the short and long-term, as well as consume healthcare and economic resources.[49,50] This issue is increasingly gaining attention in surgical head and neck patients who undergo free flap surgery.[51] Additionally, studying complications can provide valuable insights for improving patient care. It can aid in developing strategies to prevent and manage complications.

Outline of the thesis

The studies in this thesis aim to provide more information on the occurrence and prediction of post-operative complications (POCs) in surgical oral cancer patients undergoing free flap reconstruction. A particular focus was given to the clinical outcomes of patients who were reconstructed with a fibula free flap, including implant-based dental rehabilitation and its effect on quality of life.

In this thesis the following specific objectives/issues were addressed:
In **Chapter 2** the occurrence of complications after ablative oral cancer surgery with primary free flap reconstruction was evaluated. Complications were divided in systemic and surgical complications with details on donor site and flap-related complications.

Potential predictors for both systemic and surgical complications and prolonged hospital stay were analysed.

In **Chapter 3** it was aimed to give an accurate estimation of symptomatic venous thromboembolism in oncological oral and maxillofacial surgical procedures. Patients who had undergone general anaesthesia for over 120 minutes were divided in two groups, those with and without free flap surgery. An attempt was made to stratify these patients who were at risk for developing venous thromboembolism and to identify risk factors for developing venous thromboembolism.

In **Chapter 4** the complications after mandibular reconstructions with fibula free flaps in patients with oral squamous cell carcinoma were studied. All systemic and surgical complications were noted during the first postoperative year. The effect of demographic, histopathological, comorbidity and surgical variables on the occurrence of complications and hospital stay were evaluated.

In **Chapter 5** the long-term outcomes of implant-based dental rehabilitation in head and neck cancer patients after reconstruction with a fibula free flap were described. Dental implant survival and dental implant success were analysed, along with prosthesis-related outcomes. The complications that occurred during dental rehabilitation were described with special attention to the effect of radiotherapy on the outcome measures.

In **Chapter 6** the course of health-related quality of life is described of head and neck cancer patients who had undergone implant-based dental rehabilitation after maxillofacial reconstruction with a fibula free flap. A comparison was made between patients who commenced implant-based dental rehabilitation and those who did not, using two validated questionnaires: the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) and the module specifically designed for head and neck cancer patients (EORTC QLQ-H&N 35). For both groups a detailed within-subject and between-subject analysis was performed.

References

1. Nederlandse Kankerregistratie (NKR), IKNL. Verkregen via iknlnl/nkr-cijfers, op 20-01-2021.
2. Zavras AI, Douglass CW, Joshipura K, Wu T, Laskaris G, Petridou E, et al. Smoking and alcohol in the etiology of oral cancer: gender-specific risk profiles in the south of Greece. Oral Oncol. 2001;37(1): 28-35.
3. Ravasz LA, Slootweg PJ, Hordijk GJ, Smit F, van der Tweel I. The status of the resection margin as a prognostic factor in the treatment of head and neck carcinoma. J Craniomaxillofac Surg. 1991;19(7): 314-8.
4. Fowler J, Campanile Y, Warner A, Laxague F, Fnais N, Fung K, et al. Surgical margins of the oral cavity: is 5 mm really necessary? J Otolaryngol Head Neck Surg. 2022;51(1):38.
5. Richtlijn hoofd-halstumoren. Nederlandse Werkgroep Hoofd-Halstumoren 2014.
6. Brown JS, Rogers SN, McNally DN, Boyle M. A modified classification for the maxillectomy defect. Head Neck. 2000;22(1):17-26.
7. Jewer DD, Boyd JB, Manktelow RT, Zuker RM, Rosen IB, Gullane PJ, et al. Orofacial and mandibular reconstruction with the iliac crest free flap: a review of 60 cases and a new method of classification. Plast Reconstr Surg. 1989;84(3):391-403; discussion 4-5.
8. Brown JS, Barry C, Ho M, Shaw R. A new classification for mandibular defects after oncological resection. Lancet Oncol. 2016;17(1):e23-30.
9. Laraway DC, Lakshmiah R, Lowe D, Roe B, Rogers SN. Quality of life in older people with oral cancer. Br J Oral Maxillofac Surg. 2012;50(8):715-20.
10. Hazari A, Walton P. The UK National Flap Registry (UKNFR): A National Database for all pedicled and free flaps in the UK. J Plast Reconstr Aesthet Surg. 2015;68(12):1633-6.
11. Wu CC, Lin PY, Chew KY, Kuo YR. Free tissue transfers in head and neck reconstruction: complications, outcomes and strategies for management of flap failure: analysis of 2019 flaps in single institute. Microsurgery. 2014;34(5):339-44.
12. Urken ML. Composite free flaps in oromandibular reconstruction. Review of the literature. Arch Otolaryngol Head Neck Surg. 1991;117(7):724-32.
13. Beckler AD, Blackwell KE. 10 - Microvascular Surgery. In: Bell RB, Fernandes RP, Andersen PE, editors. Oral, Head and Neck Oncology and Reconstructive Surgery: Elsevier; 2018. p. 195-207.
14. Seidenberg B, Rosenak SS, Hurwitt ES, Som ML. Immediate reconstruction of the cervical esophagus by a revascularized isolated jejunal segment. Ann Surg. 1959;149(2):162-71.
15. Harii K, Omori K, Omori S. Hair transplantation with free scalp flaps. Plast Reconstr Surg. 1974;53(4):410-3.
16. Steel BJ, Cope MR. A brief history of vascularized free flaps in the oral and maxillofacial region. J Oral Maxillofac Surg. 2015;73(4):786 e1-11.
17. Ming-Huei Cheng K-PC, Huang-Kai Kao. Resection and Reconstruction of Head & Neck Cancers. 2019.
18. Hartig GK. Free flaps in oral cavity reconstruction: when you need them and when you don't. Int J Radiat Oncol Biol Phys. 2007;69(2 Suppl):S19-21.
19. Aziz SR. Andy Gump and his deformity. J Oral Maxillofac Surg. 2010;68(3):651-3.
20. de Groot RJ, Rieger JM, Rosenberg A, Merkx MAW, Speksnijder CM. A pilot study of masticatory function after maxillectomy comparing rehabilitation with an obturator prosthesis and reconstruction with a digitally planned, prefabricated, free, vascularized fibula flap. J Prosthet Dent. 2020;124(5): 616-22.
21. Dos Santos DM, de Caxias FP, Bitencourt SB, Turcio KH, Pesqueira AA, Goiato MC. Oral rehabilitation of patients after maxillectomy. A systematic review. Br J Oral Maxillofac Surg. 2018;56(4):256-66.
22. Moura LB, Carvalho PHA, Xavier CB, Post LK, Torriani MA, Santagata M, et al. Autogenous non-vascularized bone graft in segmental mandibular reconstruction: a systematic review. Int J Oral Maxillofac Surg. 2016;45(11):1388-94.
23. McKee DM. Microvascular rib transposition for reconstruction of the mandible. . Presented at the Annual Meeting of the American Society of Plastic and Reconstructive Surgeons. . Toronto, Ontario.1971.
24. Daniel RK. Mandibular reconstruction with free tissue transfers. Ann Plast Surg. 1978;1(4):346-71.

25. Taylor GI, Miller GD, Ham FJ. The free vascularized bone graft. A clinical extension of microvascular techniques. Plast Reconstr Surg. 1975;55(5):533-44.
26. Hidalgo DA. Fibula free flap: a new method of mandible reconstruction. Plast Reconstr Surg. 1989;84(1):71-9.
27. Schusterman MA, Reece GP, Miller MJ. Osseous free flaps for orbit and midface reconstruction. Am J Surg. 1993;166(4):341-5.
28. Urken ML, Buchbinder D, Weinberg H, Vickery C, Sheiner A, Biller HF. Primary placement of osseointegrated implants in microvascular mandibular reconstruction. Otolaryngol Head Neck Surg. 1989;101(1):56-73.
29. Anne-Gaelle B, Samuel S, Julie B, Renaud L, Pierre B. Dental implant placement after mandibular reconstruction by microvascular free fibula flap: current knowledge and remaining questions. Oral Oncol. 2011;47(12):1099-104.
30. Kumar VV, Jacob PC, Kekatpure V, Hedne N, Koch FP, Kuriakose MA. The Jugaad Technique for Jaw Reconstruction: Denture Based Inverse Planning. J Maxillofac Oral Surg. 2016;15(3):346-8.
31. Lukash FN, Sachs SA, Fischman B, Attie JN. Osseointegrated denture in a vascularized bone transfer: functional jaw reconstruction. Ann Plast Surg. 1987;19(6):538-44.
32. Riediger D. Restoration of masticatory function by microsurgically revascularized iliac crest bone grafts using enosseous implants. Plast Reconstr Surg. 1988;81(6):861-77.
33. Frodel JL, Jr., Funk GF, Capper DT, Fridrich KL, Blumer JR, Haller JR, et al. Osseointegrated implants: a comparative study of bone thickness in four vascularized bone flaps. Plast Reconstr Surg. 1993;92(3):449-55; discussion 56-8.
34. Lyberg T, Olstad OA. The vascularized fibular flap for mandibular reconstruction. J Craniomaxillofac Surg. 1991;19(3):113-8.
35. Roumanas ED, Markowitz BL, Lorant JA, Calcaterra TC, Jones NF, Beumer J, 3rd. Reconstructed mandibular defects: fibula free flaps and osseointegrated implants. Plast Reconstr Surg. 1997;99(2): 356-65.
36. Zlotolow IM, Huryn JM, Piro JD, Lenchewski E, Hidalgo DA. Osseointegrated implants and functional prosthetic rehabilitation in microvascular fibula free flap reconstructed mandibles. Am J Surg. 1992;164(6):677-81.
37. Panchal H, Shamsunder MG, Petrovic I, Rosen EB, Allen RJ, Jr., Hernandez M, et al. Dental Implant Survival in Vascularized Bone Flaps: A Systematic Review and Meta-Analysis. Plast Reconstr Surg. 2020;146(3):637-48.
38. Chang YM, Santamaria E, Wei FC, Chen HC, Chan CP, Shen YF, et al. Primary insertion of osseointegrated dental implants into fibula osteoseptocutaneous free flap for mandible reconstruction. Plast Reconstr Surg. 1998;102(3):680-8.
39. Chiapasco M, Biglioli F, Autelitano L, Romeo E, Brusati R. Clinical outcome of dental implants placed in fibula-free flaps used for the reconstruction of maxillo-mandibular defects following ablation for tumors or osteoradionecrosis. Clin Oral Implants Res. 2006;17(2):220-8.
40. Barber HD, Seckinger RJ, Hayden RE, Weinstein GS. Evaluation of osseointegration of endosseous implants in radiated, vascularized fibula flaps to the mandible: a pilot study. J Oral Maxillofac Surg. 1995;53(6):640-4; discussion 4-5.
41. Garrett N, Roumanas ED, Blackwell KE, Freymiller E, Abemayor E, Wong WK, et al. Efficacy of conventional and implant-supported mandibular resection prostheses: study overview and treatment outcomes. J Prosthet Dent. 2006;96(1):13-24.
42. Smolka K, Kraehenbuehl M, Eggensperger N, Hallermann W, Thoren H, Iizuka T, et al. Fibula free flap reconstruction of the mandible in cancer patients: evaluation of a combined surgical and prosthodontic treatment concept. Oral Oncol. 2008;44(6):571-81.
43. Wijbenga JG, Schepers RH, Werker PM, Witjes MJ, Dijkstra PU. A systematic review of functional outcome and quality of life following reconstruction of maxillofacial defects using vascularized free fibula flaps and dental rehabilitation reveals poor data quality. J Plast Reconstr Aesthet Surg. 2016;69(8):1024-36.
44. Inchingolo F, Santacroce L, Ballini A, Topi S, Dipalma G, Haxhirexha K, et al. Oral Cancer: A Historical Review. Int J Environ Res Public Health. 2020;17(9).

45. Borggreven PA, Kuik DJ, Quak JJ, de Bree R, Snow GB, Leemans CR. Comorbid condition as a prognostic factor for complications in major surgery of the oral cavity and oropharynx with microvascular soft tissue reconstruction. Head Neck. 2003;25(10):808-15.
46. Eskander A, Kang S, Tweel B, Sitapara J, Old M, Ozer E, et al. Predictors of Complications in Patients Receiving Head and Neck Free Flap Reconstructive Procedures. Otolaryngol Head Neck Surg. 2018;158(5):839-47.
47. Pohlenz P, Blessmann M, Blake F, Li L, Schmelzle R, Heiland M. Outcome and complications of 540 microvascular free flaps: the Hamburg experience. Clin Oral Investig. 2007;11(1):89-92.
48. McMahon JD, MacIver C, Smith M, Stathopoulos P, Wales C, McNulty R, et al. Postoperative complications after major head and neck surgery with free flap repair--prevalence, patterns, and determinants: a prospective cohort study. Br J Oral Maxillofac Surg. 2013;51(8):689-95.
49. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos CL. The economic burden of head and neck cancer: a systematic literature review. Pharmacoeconomics. 2014;32(9):865-82.
50. McMahon J, Handley TPB, Bobinskas A, Elsapagh M, Anwar HS, Ricciardo PV, et al. Postoperative complications after head and neck operations that require free tissue transfer - prevalent, morbid, and costly. Br J Oral Maxillofac Surg. 2017;55(8):809-14.
51. Cash H, Abouyared M, Houlton JJ. Optimizing value in head and neck cancer free flap surgery. Curr Opin Otolaryngol Head Neck Surg. 2019;27(5):413-9.

Chapter 2

Incidence and types of complications after ablative oral cancer surgery with primary microvascular free flap reconstruction

J.N. Lodders
S. Parmar
N.L.M. Stienen
T.J. Martin
K.H. Karagozoglu
M.W. Heymans
B. Nandra
T. Forouzanfar

This chapter is based on the publication in:

Medicina Oral Patología Oral y Cirugia Bucal. 2015 Nov;20(6):e744-e750

Introduction

Oral cancer ablation can lead to considerable oro-facial defects, with inadequate aesthetics and function.[1-3] Primary reconstruction of oro-facial defects with autogenous free flaps can improve function and aesthetics and thereby improve the quality of life.[4,5] In experienced hands and with modern day techniques the survival rate of these free tissue grafts often exceed 90%[6-11] and is still improving due to research and innovations.[8] This makes current microvascular reconstruction very reliable, and as emphasised in the last decades, the first choice of option after major ablative cancer surgery.[12,13]

Despite major advantages, free flap surgery is complex and serious postoperative morbidity with even mortality can occur. Postoperative complication rates vary between 9.3% and 64%.[7,9-11,14-18] To minimize postoperative complications, authors have analysed possible prognostic factors such as demographic, anaesthetic, surgical and comorbidity variables. Some of these factors, including age[10,11], smoking[10,11], comorbidity[7,10,11,15,18], donor site[14], operating time[15,17-19] and advanced disease[19] could have a profound influence on postoperative complications. However, robust evidence is lacking that identify key variables for developing postoperative complications.[7]

This study aims to retrospectively evaluate the incidence and types of postoperative complications after ablative oral cancer surgery with primary free flap reconstruction. Additionally we tried to identify variables that could have a prognostic value for postoperative complications and hospital stay.

Material and methods

Data extraction

This retrospective analysis was done at the department of Oral and Maxillofacial Department, Queen Elisabeth hospital Birmingham, United Kingdom. A computer database was used to select all oral cancer surgeries with primary free flap reconstruction, between June 2007 and October 2012. Reconstructions of soft tissue as well as bony tissue or combinations were included. Resection of recurrent or second primary oral cancers were also selected.

Study variables

By reviewing the electronic medical records, patient data was collected such as demographics, co morbidities, histopathological, anaesthetic and surgical data. Patient demographics comprised age, gender, weight, body mass index (BMI), nicotine use, alcohol use, chemotherapy and radiotherapy. The patient's comorbidities were subdivided in different organ systems (i.e. cardiovascular, respiratory, gastrointestinal, hepatic, renal, endocrine, neurologic, autoimmune, connective tissue, prior malignant diseases, nutritional). All patients were classified according to their comorbidities in prospect using the American Society of Anaesthesiologists (ASA) classification and in retrospect using the Charlson Comorbidity index (CCI).[20]

Operating time, anaesthesia time, hospital stay, place of malignancy, donor site, primary implant placement, thromboprophylaxis and perioperative red cell transfusion were collected for anaesthetic and surgical data. The period of admittance to the hospital until discharge was defined as hospital stay.

The histopathological T- and N-scores were used for anatomic staging, according to the American Joint Committee on Cancer (AJCC) staging grouping.

Outcome variables

Postoperative complications were defined as any adverse developments that required intervention, compromised the postoperative course or when readmission to the hospital was required. A distinction was made between surgical and systemic complications. Surgical complications were defined as adverse events considering the flap, recipient site or donor site. Systemic complications were defined as medical adverse events not considering the flap, recipient site or donor site. Patients with multiple surgical or systemic complications were classified as one surgical or one systemic complication for statistical analysis.

Statistical analysis

The SPSS Software package (version 20.0 Inc., Chicago, IL, USA) was used for statistical analysis. Univariate and multivariable relationships between surgical complications, systemic complications, hospital stay>15days and the preoperative variables were studied using binary logistic regression. Variables with a p value of <0.25 were included in the multivariable analyses. A 2 tailed p value of <0.05 was considered statistically significant and the confidence interval was set at 95%. For all missing values, analogue patient notes were retrieved from storage and searched to include missing values. The

overall population average was used for missing continuous variables. Continuous variables were dichotomized if necessary, according to clinical judgement.

Ethical approval was not required for the study protocol from the institutional review board of the Queen Elisabeth hospital Birmingham.

Results

The study population consisted of 184 patients, comprising 189 composite surgical resections with free flap reconstruction. Sixty point three percent was male and 39.7% was female. The mean age was 60.3 (standard deviation (SD) ±12.3) years and the mean BMI 25.5 (SD ±5.3) kg/m^2. Active nicotine use was noted in 65 (34.4%) patients, 61 (32.3%) patients never used nicotine and 63 (33.3%) patients were prior nicotine users. Forty nine (25.9%) patients reported alcohol abuse and 6 (3.2%) patients had a history with alcohol abuse. Preoperative chemotherapy was given in 2.6% of the patients, 14.8% received postoperative chemotherapy and 1.6% received both. Preoperative radiotherapy was given in 2.6% of the patients, 64.6% received postoperative radiotherapy and 7% received both.

In Table 2.1 all patients' pre-operative medical comorbidities and comorbidity indexing are shown.

Ninety radial forearm free flaps (RFFF), 18 antero lateral thigh free flaps (ALTFF), 40 fibula free flaps (FFF), 29 scapula free flaps (SFF), 12 deep circumflex iliac artery free flaps (DCIAFF) and a pectoralis major flap (PMF) were used. In Figure 2.1, all operations are plotted according to free flap donor site by year.

Table 2.1 All patients' preoperative medical comorbidities and comorbidity indexing.

Comorbidities	**n**
Cardiovascular	
Myocardial infarct	9 (4.8%)
Ischemic heart disease	10 (5.3%)
Dysrhythmia	7 (3.7%)
Valvulopathies	1 (0.5%)
Hypertension	68 (38.0%)
Peripheral vascular disease	10 (5.3%)
Respiratory	
COPD	10 (5.3%)
Asthma	16 (8.5%)
Emphysema	3 (1.6%)
Sarcoidosis	1 (0.5%)
Bronchitis	1 (0.5%)
Gastrointestinal	
Inflammatory bowel disease	1 (0.5%)
Reflux	5 (2.6%)
Dyspepsia	2 (1.1%)
Peptic ulcer	4 (2.1%)
Hepatic	2 (1.1%)
Renal failure	1 (0.5%)
Neurologic	
CVA/ TIA	9 (4.7%)
Parkinson	1 (0.5%)
Alzheimer	1 (0.5%)
Epilepsy	2 (1.1%)
Autoimmune	5 (2.6%)
Connective tissue	
Rheumatologic	19 (10.1%)
Prior malignancy	40 (21.2%)
Nutritional	
Hyperlipidaemia	18 (19.5%)
Overweight (BMI >25)	85 (45.0%)
Underweight (BMI <18,5)	16 (18.5%)
Anaemic	4 (2.1%)
ASA	
1	17 (19.0%)
2	137 (72.5%)
3	35 (18.5%)
CCI	
2	63 (33.3%)
3	49 (25.9%)
4	34 (18.0%)
5≥	43 (22.8%)

Abbreviations: n, patients; COPD, Chronic Obstructive Pulmonary disease; CVA, Cerebral Vascular Accident; TIA, Transient Ischemic Attack; BMI, Body Mass Index; ASA, American Society of Anaesthesiologists; CCI, Charlson Comorbidity index.

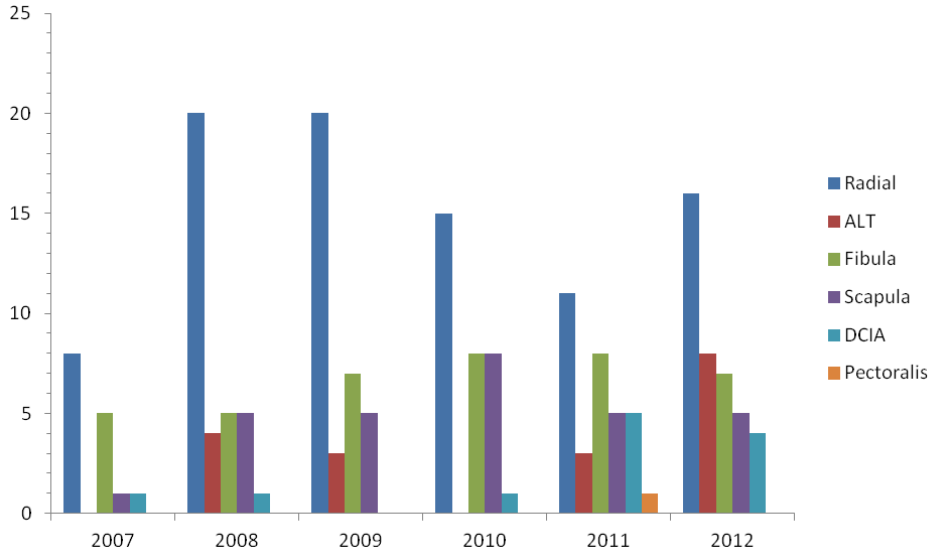

Figure 2.1 Distribution of operations according to free flap donor site by year, from June 2007 to October 2012. In 1 patient a combined reconstruction with a DCIA and pectoralis major flap was performed in 2011.
Abbreviations: ALT, anterolateral thigh free flap; DCIA, deep circumflex iliac artery free flap.

The anaesthesia times ranged from 366 to 959 minutes with a mean of 615.7 minutes and a mean hospital stay of 15.3 (SD ±7.0) days. Hospital stay ranged from 3 days to 52 days. One hundred and five resections could be classified as an anatomic stage IV cancer, with 89.9% of the cancers diagnosed as a squamous cell carcinoma. Table 2.2 shows all patients according to anaesthetic, surgical and histopathological variables.

Postoperative 115 complications (98 surgical complications, 17 systemic complications) developed in 67 patients (35.4%) during hospital stay. Surgical complications occurred in 32.3% and systemic complications occurred in 8% of the patients. No readmissions as a result of complications were noted. Three patients died within 2 weeks (Table 2.3). Twenty one patients had to be brought back to the operating room; debridement of total (n=6), or partial free flap necrosis (n=2), re-exploration of the microvascular anastomosis (n=5), infected/exposed plate or bone (n=3), wound bleeding or haematoma (n=3), abscess evacuation (n=1) and debridement of split skin graft failure (n=1). Donor site problems were registered in 10 patients, caused by wound infection (n=6), wound breakdown (n=1), wound dehiscence (n=1), scar herniation (n=1) and split skin graft failure (n=1).

Table 2.2 All patients' anaesthetic, surgical and histopathological variables.

Variables	n
Operating time (min ±SD)	541.5 ±113.9
Anaesthesia time (min ±SD)	615.7 ±107.5
Hospital stay (days ±SD)	15.3 ±7.0
Place malignancy	
Tongue	47 (24.9%)
Floor of mouth	29 (15.3%)
Buccal mucosa	21 (11.1%)
Mandible	58 (30.7%)
Maxilla	31 (16.4%)
Gland/cutaneous	3 (1.6%)
Primary implant placement	19 (10.1%)
LMWH thromboprophylaxis	181 (95.8%)
Perioperative volume replacement	
Red cell transfusion	60 (31.7%)
Red cell transfusion (ml ±SD)	424.6 ±199.6
Histology	
Squamous cell carcinoma	170 (89.9%)
Sarcoma	7 (3.7%)
Adenoid cystic carcinoma	5 (2.6%)
Spindle cell carcinoma	2 (1.1%)
Basal cell carcinoma	2 (1.1%)
Adenocarcinoma	1 (0.5%)
Melanoma	1 (0.5%)
Ameloblastic carcinoma	1 (0.5%)
T-score*	
1	49 (26.3%)
2	48 (25.8%)
3	13 (7.0%)
4	76 (40.9%)
N-score*	
0	105 (56.5%)
1	22 (11.8%)
2a/2b/2c	59 (31.7%)
Anatomic stage*	
Stage I	31 (16.7%)
Stage II	28 (15.0)
Stage III	22 (11.8%)
Stage IV	105 (56.5%)

Abbreviations: n, patients; SD, standard deviation; LMWH, low molecular weight heparin.
* Anatomic staging according American Joint Committee on Cancer staging grouping.
* For 3 patients the histopathological data were missing.

Total flap failure was diagnosed in 3 RFFFs (3.3%), 1 ALTFF (5.6%), 1 FFF (2,5%) and 1 DCIAFF (8.3%), giving an overall survival rate of 96.8%. In 2 DCIAFF the total skin paddle was loss due to necrosis. Re-exploration of the microvascular anastomosis was necessary in 2.6% of the patients, caused by venous congestion (n=3), anastomosis bleeding (n=1) and an unknown cause (n=1). All anastomosis re-explorations were successful.

Table 2.3 Incidences of post -operative surgical and systemic complications.

Complications	**n**
Surgical	
Wound infection	16 (8.5)
Wound breakdown	5 (2.6)
Wound dehiscence	3 (1.6)
Abscess	3 (1.6)
Fistula	5 (2.6)
Salivary leak	1 (0.5)
Hematoma/Bleeding	7 (3.7)
Fluid collection/Seroma	3 (1.6)
Exposed/Infected plate	6 (3.2)
Exposed/Infected bone	3 (1.6)
Return to operation room	21 (11.1)
Other	2 (1.1)
Donor site	10 (5.3)
Flap	13 (6.9)
Total surgical*	98*
Systemic	
Venous thromboembolism	1 (0.5)
Renal failure	1 (0.5)
Ischemic heart disease	3 (1.6)
Stroke	1 (0.5)
HONK with hypernatremia	1 (0.5)
Severe headaches	1 (0.5)
Confusion	2 (1.1)
Pneumothorax	1 (0.5)
Respiratory infection	3 (1.6)
Death within 2 weeks	
Respiratory/Cardiac arrest	3 (1.6)
Total systemic†	17†

Abbreviations: n, patients HONK, hyperosmolar non-ketotic state.

* Twenty patients had 2 surgical complications, four patients had 3 surgical complications, three patients had 4 surgical complications.

† Two patients had 2 medical complications.

In the univariate analysis surgical complications were not associated with any risk variables. Associations were found between alcohol use, CCI >5, anaesthesia time, T-score ≥3 and systemic complications (*p* value = 0.04, 0.03, 0.01 and 0.01). Hospital stay>15days was related with age, preoperative chemotherapy, anaesthesia time, reconstruction type (bony), perioperative red cell and T-score ≥3 *(p* value =0.04, 0.04, 0.01, 0.00, 0.00 and 0.03)

In the multivariable analysis none of the variables correlated with surgical complications. Associations between anaesthesia time and systemic complications remained significant, however alcohol use, CCI >5, reconstruction type (bony) and T-score ≥3 lost significance. Perioperative red cell transfusion was the only variable that remained significant for hospital stay >15days in the multivariable analysis (Table 2.4).

Table 2.4 Multivariable regression analysis for surgical and systemic complications and hospital stay >15days.

Variable	Odds ratio	*p* value	95% CI
			Lower - Upper
Surgical complications			
Primary implant placement	0.38	0.14	0.11 – 1.38
Perioperative red cell	1.38	0.35	0.71 – 2.71
T score ≥3	1.58	0.16	0.83 – 3.00
Systemic complications			
Alcohol use	0.21	0.25	0.05 – 0.83
CCI >5	1.76	0.64	0.16 – 19.06
Anaesthesia time*	1.01	**0.03**	1.001 – 1.016
Reconstruction type (bony)	0.75	0.75	0.13 – 4.37
T score ≥3	9.77	0.06	2.33 – 235.56
Hospital stay >15days			
Age*	1.01	0.50	0.98 – 1.04
Preoperative chemotherapy	NA	NA	NA
ASA (score ≥3)	2.30	0.86	0.89 – 5.97
Anaesthesia time*	1.00	0.49	0.997 – 1.006
Reconstruction type (bony)	1.37	0.59	0.44 – 4.22
Primary implant placement	0.21	0.08	0.04 – 1.18
Perioperative red cell	2.85	**0.02**	1.18 – 6.85
T-score ≥3	1.67	0.33	0.60 – 4.70

Abbreviations: CCI, Charlson Comorbidity index; CI, Confidence interval; NA, not available.
Significant variables are highlighted in bold.
* Continuous variable.

Discussion

Ablative oral cancer surgery can lead to considerable oro-facial defects, consisting soft tissue (mucosa and skin) and/or hard tissue (bone and teeth). Primary reconstruction of these defects with free flaps is a central part in head and neck surgery nowadays.[12,13] High success rates[6-12,14,15], better disease control[12] and a better quality of life[4,5,12] are the motives for the popularity of free flap reconstructions. On the contrary free flap reconstructions are time and resource consuming, complex and postoperative complications are common. In rare cases mortality occurs after free flap transfers.

This retrospective study evaluated the incidence and types of postoperative complications in a well-defined cohort of 189 patients with oral cancer and primary free flap reconstruction. In total 32.3% of the patients had surgical complications and 8% had systemic complications.

Complication rates following free flap transfers to the head and neck vary between 9.3% and 64%.[7,9-11,14-18] Van Gemert et al. retrospectively analysed 46 FFF, 22 DCIAFF

and 15 RFFF for postoperative complications in patients with malignant and benignant lesions.[14] They found that 29% of the patients developed complications in the first year after surgery. A postoperative complication rate of 53% was found by Clark et al. in 185 free flap reconstructions, however only 40% was considered major.[10] In a prospective study by MacMahon et al. 192 free flap patients were studied over 27 months.[18] They found postoperative complications in 64% of the patients and around one third were serious.

Compared to other studies our complication rates are relatively high. The variety of definitions for postoperative complications is the main reason for that. Furthermore different scoring systems for postoperative complications are used. For example distinction is made between surgical and medical[10], minor and major[15] or mild, moderate and severe[7] complications. The integration of a standardized scoring system for postoperative complications will result in efficient comparison between studies with inherent improvement of practice and quality of care.[21] The Clavien-Dindo grading system for postoperative complications has been adopted in 2 recent head and neck studies.[18,21,22] Despite the fact both studies advocate its use, shortcomings regarding the unique complications in head and neck patients are acknowledged.[21] Therefore future studies are needed for developing a unique classification system for postoperative complications in head and neck patients.

During this study the workhorse for intra oral soft tissue defects was the RFFF, over time the ALTFF gained more popularity. The shift can be explained by the versatility in harvesting fat, fascia or skin, low donor site complications and reliability of the ALTFF.[23] Furthermore the ability to harvest the ALTFF as multiple skin paddles makes it very useful in complicated soft tissue reconstructions in the oral cavity. Other institutions confirm the increase in the use of the ALTFF over the last decade.[8,23]

We found an overall flap failure rate of 3.2%, which is similar to other reports (6.2%[9], 1.6%[10], 4.3%[11], 2.4%[14], 2%[17], 3.4%[24]). Compared to the most robust data currently available published by Wu et al.[8], almost identical results were seen. This recent retrospective single institutionary analysis transferred 2019 ALTFF, FFF, RFF and jejunal flaps to the head and neck region and reported total flap failure of 3.8%.

Predicting postoperative complications is a comprehensive matter, because different variables cannot predict all forms of complications.[10] Therefore key factors are difficult to find, however certain variables seem to have predictive value, such as age[10,11], smoking[10,11], comorbidity[7,10,11,15,18], donor site[14], operating time[15,17-19] and advanced disease.[19]

No risk factors were identified in the univariate or multivariable analysis for surgical complications in these series. We found correlations between anaesthesia time and systemic complications in the multivariable analysis. Other studies[15,17-19] also associated operating time with postoperative complications. Pohlenz et al. even associated increased operating time with postoperative mortality.[19] Therefore aggressive surgery should be indicated with caution in complex head and neck patients with an expected prolonged operating time.

Predictive values for smoking, pre-operative radiotherapy and comorbidity could not be found, despite the negative influence these variables have on the healing process.[25] The ASA classification and CCI were not associated with postoperative complications. Nevertheless medical comorbidities are the most established predictors for postoperative complications[7,10,11,15,18] and therefore extensive preoperative medical screening with optimization of the patients' comorbidities should be a vital part in treatment planning.

Several factors were associated with hospital stay >15days. Only perioperative red cell transfusion (OR 2.85) was significantly correlated in the multivariable analysis. A handful of authors address the importance for optimal fluid management during surgery.[10,11] Haughley et al. correlated, similar to our findings, red cell transfusion to hospital stay in a retrospective analysis of 141 free flap reconstructions.[11]

The retrospective nature of this study can be a flawed method for analysing data, because the data rely on adequate record keeping. Therefore important exposure variables were not retrieved, such as the use of tracheostomy. The importance of record keeping is reflected in the aberrant low incidence of respiratory problems (1.6%), compared to other studies (10-18%)[7,10,11,16] and the main reason why variables did not reach statistical significance in the multivariable analysis.

A significant proportion of the patients with primary free flap reconstructions after oral cancer surgery develops postoperative complications. Prolonged anaesthesia time and red cell transfusion are possible predictors for systemic complications and hospital stay respectively. These and other risk factors are relatively unchangeable, so it seems little influence can be exerted on the patient's outcome. Therefore preoperative screening for risk factors is advocated for patient selection and to have realistic information and expectations.

References

1. Van Cann EM, Dom M, Koole R, Merkx MA, Stoelinga PJ. Health related quality of life after mandibular resection for oral and oropharyngeal squamous cell carcinoma. Oral Oncol. 2005;41(7):687-93.
2. Borggreven PA, Verdonck-de Leeuw I, Langendijk JA, Doornaert P, Koster MN, de Bree R, et al. Speech outcome after surgical treatment for oral and oropharyngeal cancer: a longitudinal assessment of patients reconstructed by a microvascular flap. Head Neck. 2005;27(9):785-93.
3. Borggreven PA, Aaronson NK, Verdonck-de Leeuw IM, Muller MJ, Heiligers ML, Bree R, et al. Quality of life after surgical treatment for oral and oropharyngeal cancer: a prospective longitudinal assessment of patients reconstructed by a microvascular flap. Oral Oncol. 2007;43(10):1034-42.
4. Urken ML, Buchbinder D, Weinberg H, Vickery C, Sheiner A, Parker R, et al. Functional evaluation following microvascular oromandibular reconstruction of the oral cancer patient: a comparative study of reconstructed and nonreconstructed patients. Laryngoscope. 1991;101(9):935-50.
5. Curtis DA, Plesh O, Miller AJ, Curtis TA, Sharma A, Schweitzer R, et al. A comparison of masticatory function in patients with or without reconstruction of the mandible. Head Neck. 1997;19(4):287-96.
6. Pohlenz P, Blessmann M, Blake F, Li L, Schmelzle R, Heiland M. Outcome and complications of 540 microvascular free flaps: the Hamburg experience. Clin Oral Investig. 2007;11(1):89-92.
7. Borggreven PA, Kuik DJ, Quak JJ, de Bree R, Snow GB, Leemans CR. Comorbid condition as a prognostic factor for complications in major surgery of the oral cavity and oropharynx with microvascular soft tissue reconstruction. Head Neck. 2003;25(10):808-15.
8. Wu CC, Lin PY, Chew KY, Kuo YR. Free tissue transfers in head and neck reconstruction: complications, outcomes and strategies for management of flap failure: analysis of 2019 flaps in single institute. Microsurgery. 2014;34(5):339-44.
9. Pohlenz P, Klatt J, Schon G, Blessmann M, Li L, Schmelzle R. Microvascular free flaps in head and neck surgery: complications and outcome of 1000 flaps. Int J Oral Maxillofac Surg. 2012;41(6):739-43.
10. Clark JR, McCluskey SA, Hall F, Lipa J, Neligan P, Brown D, et al. Predictors of morbidity following free flap reconstruction for cancer of the head and neck. Head Neck. 2007;29(12):1090-101.
11. Haughey BH, Wilson E, Kluwe L, Piccirillo J, Fredrickson J, Sessions D, et al. Free flap reconstruction of the head and neck: analysis of 241 cases. Otolaryngol Head Neck Surg. 2001;125(1):10-7.
12. Wong CH, Wei FC. Microsurgical free flap in head and neck reconstruction. Head Neck. 2010;32(9): 1236-45.
13. Gonzalez-Garcia R, Naval-Gias L, Rodriguez-Campo FJ, Munoz-Guerra MF, Sastre-Perez J. Vascularized free fibular flap for the reconstruction of mandibular defects: clinical experience in 42 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(2):191-202.
14. van Gemert JT, van Es RJ, Rosenberg AJ, van der Bilt A, Koole R, Van Cann EM. Free vascularized flaps for reconstruction of the mandible: complications, success, and dental rehabilitation. J Oral Maxillofac Surg. 2012;70(7):1692-8.
15. Ferrier MB, Spuesens EB, Le Cessie S, Baatenburg de Jong RJ. Comorbidity as a major risk factor for mortality and complications in head and neck surgery. Arch Otolaryngol Head Neck Surg. 2005;131(1):27-32.
16. Farwell DG, Reilly DF, Weymuller EA, Jr., Greenberg DL, Staiger TO, Futran NA. Predictors of perioperative complications in head and neck patients. Arch Otolaryngol Head Neck Surg. 2002;128(5):505-11.
17. Singh B, Cordeiro PG, Santamaria E, Shaha AR, Pfister DG, Shah JP. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg. 1999;103(2):403-11.
18. McMahon JD, MacIver C, Smith M, Stathopoulos P, Wales C, McNulty R, et al. Postoperative complications after major head and neck surgery with free flap repair--prevalence, patterns, and determinants: a prospective cohort study. Br J Oral Maxillofac Surg. 2013;51(8):689-95.
19. Pohlenz P, Klatt J, Schmelzle R, Li L. The importance of in-hospital mortality for patients requiring free tissue transfer for head and neck oncology. Br J Oral Maxillofac Surg. 2013;51(6):508-13.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

21. Monteiro E, Sklar MC, Eskander A, de Almeida JR, Shrime M, Gullane P, et al. Assessment of the Clavien-Dindo classification system for complications in head and neck surgery. Laryngoscope. 2014;124(12):2726-31.
22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
23. Park CW, Miles BA. The expanding role of the anterolateral thigh free flap in head and neck reconstruction. Curr Opin Otolaryngol Head Neck Surg. 2011;19(4):263-8.
24. Wei FC, Demirkan F, Chen HC, Chuang DC, Chen SH, Lin CH, et al. The outcome of failed free flaps in head and neck and extremity reconstruction: what is next in the reconstructive ladder? Plast Reconstr Surg. 2001;108(5):1154-60; discussion 61-2.
25. Kroll SS, Robb GL, Reece GP, Miller MJ, Evans GR, Baldwin BJ, et al. Does prior irradiation increase the risk of total or partial free-flap loss? J Reconstr Microsurg. 1998;14(4):263-8.

Chapter 3

Incidence of symptomatic venous thromboembolism in oncological oral and maxillofacial surgery: retrospective analysis

J.N. Lodders
S. Parmar
N.L.M. Stienen
T.J. Martin
K.H. Karagozoglu
M.W. Heymans
T. Forouzanfar

This chapter is based on the publication in:

Br J Oral Maxillofac Surg. 2015 Mar;53(3):244-250

Introduction

Venous thromboembolism (VTE) is a common and serious complication during and after operation that can lead to serious morbidity and even death.[1] Formation of a blood clot (thrombus) causes partial or complete occlusion of a vein and, depending on the location of the embolus, comprises deep venous thrombosis (DVT) and, when dislodged and migrated to the lung, pulmonary embolism (PE).

The incidence of VTE varies among surgical specialties and type of operation. In vascular operations the incidences of DVT and PE is as low as 1% and 0.4%, respectively,[2] but higher rates of VTE are found for abdominal and orthopaedic surgery (between 0.26% and 66%).[3-6] In patients without cancer who have oral and maxillofacial operations, the incidence of VTE ranges from 0.15% to 1.6%.[7-10]

Malignant diseases are considered a serious risk factor for the development of VTE.[11] In a review, Anderson and Spencer[12] verified that active cancer, together with advanced age, prolonged immobilization, type of operation, serious injury, previous VTE, and congestive heart failure, are "convincingly demonstrated" independent risk factors. Obesity, use of nicotine, chemotherapy, red cell transfusion, or coexisting medical conditions, could further increase the risk.

Not all risk factors have the same predictive value for development of a VTE, but they can have a cumulative effect. Assessment tools have been developed to calculate the cumulative risk and identify surgical patients at high risk (Table 3.1).[13]

According to current reports, patients who have oncological oral and maxillofacial operations are categorised as being at high risk of VTE. They often have several serious risk factors, which include prolonged immobilisation, presence of active cancer, and advanced age.[11-13]

We know of few studies that have analysed the risk and incidence of VTE in patients who have oral and maxillofacial operations for cancer. In studies on head and neck cancer surgery, reported incidence ranges from 0% for procedures without free flap reconstruction to 6% for free flap reconstruction.[14-19] They conclude that there is not enough evidence to standardise a protocol for prophylaxis of VTE.[16,17]

Our study was primarily designed to be a retrospective analysis of the incidence of symptomatic VTE in oncological oral and maxillofacial operations. As a secondary outcome, we aimed to identify associated potential risk factors.

Patients and methods

We retrospectively analysed patients treated for cancer of the oral cavity at the department of oral and maxillofacial surgery at the Queen Elizabeth Hospital, Birmingham, United Kingdom, to identify cases of symptomatic DVT and PE. We used a computer database to select patients who had been operated on under general anaesthesia (duration of at least 120 min) between June 2007 and October2012, and had been followed up for more than one month.

Recurrent or second primary diseases were included if operations, like all other procedures, had a curative intention. Patients found to have distant metastases during operation were excluded. Secondary neck dissections were included if the primary tumour was located in the oral cavity.

Data were retrieved from electronic medical records and included discharge and ward notes, external and internal referral letters, and letters to general practitioners; outpatient, clinical examination, operating, and anaesthesia notes, and pathology and imaging reports. We also collected details of patients' characteristics, coexisting medical conditions, and histopathological results. When data were missing we searched the paper notes. If discrete values could not be retrieved, patients were excluded. The overall population mean was used for missing continuous variables.

Operations were categorised into those that included microvascular free tissue reconstruction and those that did not, and patients were assessed for level of risk of VTE according to recommendations by the American College of Chest Physicians (ACCP) (Table 3.1).[13]

We reviewed the medical records to identify symptoms related to DVT and PE such as swelling, redness, or pain in the extremity; shortness of breath, tightness of the chest, or expectoration of blood. All patients at high risk of VTE had Doppler ultrasound imaging, or computed tomographic (CT) pulmonary angiography to confirm diagnosis of DVT or PE, respectively. Additional information on postoperative bleeding was noted.

At the Queen Elizabeth Hospital, the policy on the use of thromboprophylaxis follows the NICE clinical guidelines on VTE, and depends on the clinical condition of the patient(ability to move, risk of VTE), type of operation, and the patient's preference.[20] Patients were given a low molecular weight heparin (LMWH) as pharmacological prophylaxis and wore graduated compression stockings postoperatively as mechanical prophylaxis. Pneumatic compression devices were used in all operations, and patients

were encouraged to get up as soon as possible afterwards and were given physiotherapy.

Table 3.1 Levels of thromboembolism risk in surgical patients without prophylaxis according to the American College of Chest Physicians (ACCP).[13]

Level of risk	DVT, % calf	DVT, % proximal	PE, % Clinical	PE, % Fatal
Low risk	2	0.4	0.2	< 0.01
Minor surgery in patients <40 years with no additional risk factor				
Moderate risk				
Minor surgery in patients with additional risk factor	10-20	2-4	1-2	0.1-0.4
Surgery in patients aged 40–60 years with no additional risk factors				
High risk				
Surgery in patients > 60 years, or age 40–60 years with additional risk factors (cancer, prior VTE)	20-40	4-8	2-4	0.4-1.0
Highest				
Surgery in patients with multiple risk factors (age >40 years, cancer, prior VTE)	40-80	10-20	4-10	0.2-5

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

To calculate the incidence of symptomatic VTE, we used SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, USA). Differences between the groups were analysed using the chi-square test and the independent *t* test. Where possible, we used logistic regression for each risk factor to calculate odds ratios, related 95% CI, and significant risk factors. As an alternative, associations were studied using Fisher's exact test.

Logistic regression analysis was not appropriate for age, sex, BMI, congestive heart failure, previous VTE, classification of operating time, duration of hospital stay, type of operation, donor site, and level of risk of VTE, so the associated odds ratios and confidence intervals could not be calculated.

For statistical analysis, we classified aesthetic time according to duration (Table 3.2), and dichotomised the continuous variables (age over 40, body mass index (BMI) over 25, and hospital stay of more than 20 days). Probabilities of less than 0.05 were considered significant.

Ethics approval was not required.

Table 3.2 Anaesthetic time.

Classification (minutes)	No. of operations
121-240	24
241-360	17
361-480	22
481-600	75
Over 601	106
Total	244

Results

Patients' characteristics and their coexisting medical conditions are shown in Table 3.3. In total, 244 operations were included, comprising 233 patients (139 men and 94 women), mean age 61 years (range 24–94). Both groups had similar characteristics: differences with respect to age (p=0.18,t=1.29, df=242), sex (p=0.31), BMI (p=0.33, t=0.98, df=241), and coexisting conditions were not significant. Differences with respect to radiotherapy and previous malignancy were significant.

The mean (SD) anaesthetic time was 523.5 (186) min (range 121–959) and the mean (SD) duration of hospital stay was 14.1 (8) days. Table 3.4 shows anaesthetic data and surgical variables. The operating time (p<0.001, t=−18.56, df=242), anaesthetic time (p<0.001, t=−23.12, df=242), and duration of hospital stay (p<0.001, t=−4.57, df=242) were significantly longer in patients who had microvascular free tissue reconstruction. There were significant correlations for site of malignancy, histological findings, and red cell transfusions (p<0.001, p=0.03, and p<0.001, respectively). A detailed summary of the anaesthetic time and duration of hospital stay by type of operation is shown in Table 3.5. Table 3.6 shows the levels of risk for VTE by type of operation.

In total, 10 patients (4%) were identified as being at high risk of VTE, 4 of whom had Doppler ultrasound after swelling of an extremity. Two also had pain, and one, redness of the extremity. Six patients had a CT pulmonary angiogram. Three complained of expectoration of blood, 2 of shortness of breath, 3 of tightness of the chest, and one of hyperventilation.

Table 3.3 Patients' details. Data are number (%) unless otherwise stated.

Variable	Type of operation		Total	*p* value
	Microvascular free tissue surgery	Non microvascular free tissue surgery		
No. patients	184	53	233	-
No. procedures	189	55	244	-
Mean (SD) age (years)	60.3 ±12.4	62.8 ±13.5	60.9 ±12.6	0.20
Sex				0.31
Male	114 (60.3%)	29 (52.7%)	143 (58.6%)	
Female	75 (39.7%)	26 (47.3%)	101 (41.4%)	
Mean (SD) BMI (kg/m^2)	25.5 ±5.3	26.3 ±5.0	25.7 ±5.3	0.33
Nicotine				0.21
Never	61 (32.3%)	24 (43.6%)	85 (34.8%)	
Active	65 (34.4%)	13 (23.6%)	78 (32.0%)	
Prior	63 (33.3%)	18 (32.7%)	81 (33.2%)	
Alcohol				0.24
Never	134 (70.9%)	41 (74.5%)	175 (71.7%)	
Active	49 (25.9%)	10 (18.2%)	59 (24.2%)	
Prior	6 (3.2%)	4 (7.3%)	10 (41.0%)	
Chemotherapy				0.15
None	153 (81.0%)	40 (72.7%)	193 (79.1%)	
Preoperative	5 (2.6%)	2 (3.6%)	7 (2.9%)	
Postoperative	28 (14.8%)	9 (16.4%)	37 (15.2%)	
Both	3 (1.6%)	4 (7.3%)	7 (2.9%)	
Radiotherapy				<0.001
None	55 (29.1%)	25 (45.5%)	80 (32.8%)	
Preoperative	5 (2.6%)	6 (10.9%)	11 (4.5%)	
Postoperative	122 (64.6%)	20 (36.4%)	142 (58.2%)	
Both	7 (3.7%)	4 (7.3%)	11 (4.5%)	
Co morbidities				
Diabetes Mellitus	27 (14.3%)	8 (14.5%)	35 (14.3%)	0.96
Atrial fibrillation	6 (3.2%)	1 (1.8%)	7 (2.9%)	0.60
Congestive heart failure	-	2 (3.6%)	2 (0.8%)	0.08
CVA	8 (4.2%)	1 (1.8%)	9 (3.7%)	0.40
TIA	1 (0.5%)	1 (1.8%)	2 (0.8%)	0.35
COPD	10 (5.3%)	-	10 (4.1%)	0.08
Asthma	16 (8.5%)	3 (5.5%)	19 (7.8%)	0.46
Previous malignancy	40 (21.2%)	22 (40%)	62 (25.4%)	0.01
Previous VTE	3 (1.6%)	-	3 (1.2%)	0.35
Varicose veins	2 (1.1%)	2 (3.6%)	4 (1.6%)	0.19
OCP/HRT	2 (1.1%)	-	2 (0.8%)	0.44

Abbreviations: SD, standard deviation; BMI, body mass index; CVA, cerebral vascular attack; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism; OCP, oral contraceptives; HRT, hormone replacement therapy.

Table 3.4 Anaesthetic data and surgical variables for all patients. Data are number (%) unless otherwise stated.

	Type of surgical procedure			
Variable	**Microvascular free tissue surgery**	**Non microvascular free tissue surgery**	**Total**	***p* value**
Mean (SD) operating time (min)	541.5 ±113.9	226.8 ±124.3	462.9 ±179.4	<0.001
Mean (SD) anaesthesia time (min)	615.7 ±107.5	275.3 ±110.9	523.5 ±186.3	<0.001
Mean (SD) hospitalization (days)	15.3 ±7.0	10.1 ±9.1	14.1 ±7.8	<0.001
Site of malignancy				<0.001
Tongue	47 (24.9%)	13 (23.6%)	60 (24.6%)	
Floor of mouth	29 (15.3%)	5 (9.1%)	34 (13.9%)	
Mandible	58 (30.7%)	6 (10.9%)	64 (26.2%)	
Buccal mucosa	21 (11.1%)	5 (9.1%)	26 (10.7%)	
Maxilla	31 (16.4%)	3 (5.5%)	34 (13.9%)	
Neck [±]	-	16 (29.1%)	16 (6.6%)	
Gland/cutanous	3 (1.6%)	7 (12.7%)	10 (4.1%)	
Free tissue donor site				-
Radial forearm	90 (47.6%)	-	-	
Antero lateral thigh	18 (9.5%)	-	-	
Fibula	40 (21.2%)	-	-	
Scapula	29 (15.3%)	-	-	
Deep circumflex Iliac artery	12 (6.3%)	-	-	
Pectoralis major	1 (0.5%)	-	-	
Non free tissue surgery				-
Pectoralis major flap	-	1 (1.8)	-	
Regional advancement flap	-	7 (12.7%)	-	
Split skin graft	-	2 (3.6%)	-	
Buccal fat pat flap	-	1 (1.8%)	-	
Cover plate	-	1 (1.8%)	-	
Primary closure	-	43 (78.2%)	-	
Thromboprophylaxis				0.45
None	2 (1.1%)	2 (3.6%)	4 (1.6%)	
LMWH	46 (24.3%)	11 (20%)	57 (23.4%)	
GCS	6 (3.2%)	3 (5.5%)	9 (3.7%)	
LMWH + GCS	135 (71.4%)	39 (70.9%)	174 (71.3%)	
Histological findings				0.03
Squamous cell carcinoma	170 (89.9%)	46 (83.6%)	216 (88.5%)	
Adenoid cystic carcinoma	5 (2.6%)	3 (5.5%)	8 (3.3%)	
Sarcoma	7 (3.7%)	-	7 (2.9%)	
Adenocarcinoma	4 (2.1%)	1 (1.8%)	5 (2.0%)	
Spindle cell carcinoma	1 (0.5%)	2 (3.6%)	3 (1.2%)	
Basal cell carcinoma	-	2 (3.6%)	2 (0.8%)	
Muco epidermoid carcinoma	1 (0.5%)	-	1 (0.4%)	
Melanoma	-	1 (1.8%)	1 (0.4%)	
Ameloblastic carcinoma	1 (0.5%)	-	1 (0.4%)	
Red cell transfusion	81 (42.9%)	5 (9.1%)	86 (35.2%)	<0.001

Abbreviations: SD, standard deviation; LMWH, low molecular weight heparin; GCS, graduated compression stocking.

[±] secondary neck dissection to oral cancer.

One 65-year-old man (0.4%) in the highest risk group had a confirmed PE. He presented with chest pain, hyperventilation, and heart palpitations 2 days after operation. He had had tracheostomy, left selective neck dissection (levels 1–4), lip split mandibulotomy, left partial glossectomy, and microvascular free tissue transfer of the anterolateral thigh for a T3N2bM0 carcinoma of the tongue. He had been given LMWH and had used graduated compression stockings for thromboprophylaxis. Besides gout, acid reflux, and untreated hypertension, he had previously smoked, and drank 16 units of alcohol/week. According to hospital policy, he was treated with LMWH (enoxaparin 120 mg) and warfarin (5 mg) until his international normalised ratio (INR) was within therapeutic range (INR 2–5), after that, the latter was continued for at least 3 months.

Seven patients had postoperative bleeding and one developed a haematoma. All of them were given LMWH.

Table 3.5 Mean (SD) anaesthesia time and hospitalization according to type of operation.

Donor site	Patients	Anaesthesia time (min ±SD)	Hospitalization (days ±SD)
Free tissue donor site			
Radial forearm	90	711.0 ±70.0	13.5 ±5.9
Antero lateral thigh	18	636.4 ±68.2	17.2 ±8.3
Fibula	40	651.7 ±71.1	16.4 ±7.4
Scapula	29	711.2 ±94.6	17.3 ±6.5
Deep circumflex Iliac artery	12	642.3 ±68.7	20.3 ±8.6
Pectoralis major	1	635.0 ±NA	16.0 ±NA
Non free tissue surgery			
Pectoralis major flap	1	215.0 ±NA	5.0 ±NA
Regional advancement flap	7	221.1 ±80.7	9.6 ±5.4
Split skin graft	2	401.0 ±46.7	20.5 ±26.16
Buccal fat pat flap	1	307.0 ±NA	11.0 ±NA
Cover plate	1	200.0 ±NA	18.0 ±NA
Primary closure	43	280.7 ±111.6	9.6 ±8.8

Abbreviations: NA, not available.

Table 3.6 Level of risk of venous thromboembolism in patients according to the American College of Chest Physicians (ACCP). (13) No patients were considered to have a low or moderate risk. Data are number (%) of operations.

Type of operation	High risk	Highest risk
Total no. of operations	8 (3.3%)	236 (96.7%)
Microvascular free tissue surgery	4 (2.1%)	185 (97.9%)
Non microvascular free tissue surgery	4 (7.3%)	51 (92.7%)

Discussion

Risk factors for the development of VTE are well described. Patients who have ablative oral and maxillofacial operations often have multiple serious risk factors for VTE and can be stratified as being at high risk([11-13]), but we know of no studies that confirm this, because the topic has not been given sufficient attention.

When we compared our rates of VTE with studies from otolaryngology – head and neck cancer surgery, the results were almost identical. Thai et al.[18] found an incidence of 0.72% in 136 patients who had operations for cancer of the head and neck with free tissue reconstruction. Moreano et al. also reported similar rates (DVT: 0.6% and PE: 0.4%) in 3463 operations on the head and neck.[15] It is interesting that all 300 patients who had free tissue reconstructions were given aspirin with dextran for prophylaxis, and none developed asymptomatic VTE.

In a recent prospective study, 47 patients with cancer of the head and neck were routinely examined each postoperative day with venous duplex ultrasonography. A higher incidence of 11% was found for VTE, but 5% of them were clinically asymptomatic, and probably clinically insignificant.[19]

Some of the most convincing data were published by Chen et al.[17] who retrospectively evaluated 1591 oncological operations on the head and neck. They reported an incidence of 0.31% and 0.44% for DVT and PE, respectively. When the procedures were broken down, it seems that those with free tissue reconstruction had 3 times the incidence of DVT (0.31% compared with 0.85%) and PE (0.44% compared with 1.5%).

Despite a wide variation in the rate of VTE in patients who have operations for cancer of the head and neck (DVT: 0%–6%, PE: 0%–0.72%)[14-19], it is relatively low compared with other surgical disciplines. Even for ablative operations with simultaneous reconstruction, rates are as low as 0%[15] –0.85%[17] for DVT and 0%[15] –1.5%[17] for PE, which is in accordance with our findings.

The main reason for the low rates is probably the ability of patients to move around within a short period after operation. However, it should be kept in mind that the true rates could have been underestimated because of the limitations of this study. First, not all patients with VTE become symptomatic. In necropsy studies the true rates of VTE are as high as 50% in patients with cancer, but only 4%–20% are diagnosed.[21] This is partly confirmed with routine diagnostic screening for DVT.[19,22] Secondly, we identified 2 patients who died of a sudden cardiac or respiratory arrest within 2 weeks

of operation. They were not examined post mortem, so fatal PE could not be excluded. Thirdly, the analysis relied, like all retrospective studies, on adequate record keeping.

Correlations between the analysed factors and the risk of VTE could not be found in this population. We found that anaesthetic time and duration of hospital stay were significantly longer in the group who had free tissue reconstruction. If we extrapolate this, it could mean that the type of operation and reconstruction donor site have a profound influence on the risk of VTE. This hypothesis is confirmed by one other study.[17]

To reduce the risk of VTE after operation, pharmacological or mechanical thromboprophylaxis can be used.[13,23] In general surgery, LMWH has been shown to reduce the rates of VTE in at least 60%.[13,24] According to the American College of Chest Physicians[13] and the American Society of Clinical oncology,[25] thromboprophylaxis can be used in patients who have ablative oral and maxillofacial operations. In our study, 75% of the patients used graduated compression stockings and 95% were given LMWH. However, to what extend LMWH reduced the incidence of VTE or contributed to bleeding complications remains unclear, and needs to be clarified with randomised controlled studies.

We report an incidence of 0.41% for symptomatic VTE in oncological oral and maxillofacial operations. These low rates show that it is uncommon, despite patients being stratified as being at high risk. We could not identify any specific risk factors so we cannot make any recommendations on the use of routine thromboprophylaxis. Prospective studies are essential if conclusions are to be reached. Until then, thromboprophylaxis could be advocated in patients who have serious risk factors.

References

1. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med. 1999;341(11):793-800.
2. Ramanan B, Gupta PK, Sundaram A, Lynch TG, MacTaggart JN, Baxter BT, et al. In-hospital and postdischarge venous thromboembolism after vascular surgery. J Vasc Surg. 2013;57(6):1589-96.
3. Gonzalez QH, Tishler DS, Plata-Munoz JJ, Bondora A, Vickers SM, Leath T, et al. Incidence of clinically evident deep venous thrombosis after laparoscopic Roux-en-Y gastric bypass. Surg Endosc. 2004;18(7):1082-4.
4. Sakon M, Maehara Y, Yoshikawa H, Akaza H. Incidence of venous thromboembolism following major abdominal surgery: a multi-center, prospective epidemiological study in Japan. J Thromb Haemost. 2006;4(3):581-6.
5. Bagaria V, Modi N, Panghate A, Vaidya S. Incidence and risk factors for development of venous thromboembolism in Indian patients undergoing major orthopaedic surgery: results of a prospective study. Postgrad Med J. 2006;82(964):136-9.
6. Clarke MT, Green JS, Harper WM, Gregg PJ. Screening for deep-venous thrombosis after hip and knee replacement without prophylaxis. J Bone Joint Surg Br. 1997;79(5):787-91.
7. Van de Perre JP, Stoelinga PJ, Blijdorp PA, Brouns JJ, Hoppenreijs TJ. Perioperative morbidity in maxillofacial orthopaedic surgery: a retrospective study. J Craniomaxillofac Surg. 1996;24(5):263-70.
8. Blackburn TK, Pritchard K, Richardson D. Symptomatic venous thromboembolism after orthognathic operations: an audit. Br J Oral Maxillofac Surg. 2006;44(5):389-92.
9. Forouzanfar T, Heymans MW, van Schuilenburg A, Zweegman S, Schulten EA. Incidence of venous thromboembolism in oral and maxillofacial surgery: a retrospective analysis. Int J Oral Maxillofac Surg. 2010;39(3):256-9.
10. Skorpil N, van den Bergh B, Heymans MW, Forouzanfar T. Is thromboembolism prophylaxis necessary for low and moderate risk patients in maxillofacial trauma? A retrospective analysis. Int J Oral Maxillofac Surg. 2012;41(8):902-5.
11. Williams B, Indresano AT, O'Ryan F. Venous thromboembolism in oral and maxillofacial surgery: a review of the literature. J Oral Maxillofac Surg. 2011;69(3):840-4.
12. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I9-16.
13. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):338S-400S.
14. Gavriel H, Thompson E, Kleid S, Chan S, Sizeland A. Safety of thromboprophylaxis after oncologic head and neck surgery. Study of 1018 patients. Head Neck. 2013;35(10):1410-4.
15. Moreano EH, Hutchison JL, McCulloch TM, Graham SM, Funk GF, Hoffman HT. Incidence of deep venous thrombosis and pulmonary embolism in otolaryngology-head and neck surgery. Otolaryngol Head Neck Surg. 1998;118(6):777-84.
16. Innis WP, Anderson TD. Deep venous thrombosis and pulmonary embolism in otolaryngologic patients. Am J Otolaryngol. 2009;30(4):230-3.
17. Chen CM, Disa JJ, Cordeiro PG, Pusic AL, McCarthy CM, Mehrara BJ. The incidence of venous thromboembolism after oncologic head and neck reconstruction. Ann Plast Surg. 2008;60(5):476-9.
18. Thai L, McCarn K, Stott W, Watts T, Wax MK, Andersen PE, et al. Venous thromboembolism in patients with head and neck cancer after surgery. Head Neck. 2013;35(1):4-9.
19. Clayburgh DR, Stott W, Cordiero T, Park R, Detwiller K, Buniel M, et al. Prospective study of venous thromboembolism in patients with head and neck cancer after surgery. JAMA Otolaryngol Head Neck Surg. 2013;139(11):1143-50.
20. Hill J, Treasure T, Guideline Development G. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital: summary of the NICE guideline. Heart. 2010;96(11):879-82.
21. Gomes MP, Deitcher SR. Diagnosis of venous thromboembolic disease in cancer patients. Oncology (Williston Park). 2003;17(1):126-35, 39; discussion 39-44.

22. Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost. 2005;3(8):1611-7.
23. Urbankova J, Quiroz R, Kucher N, Goldhaber SZ. Intermittent pneumatic compression and deep vein thrombosis prevention. A meta-analysis in postoperative patients. Thromb Haemost. 2005;94(6): 1181-5.
24. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg. 1988;208(2):227-40.
25. Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(17):2189-204.

Chapter 4

Complications and risk after mandibular reconstruction with fibula free flaps in patients with oral squamous cell carcinoma: a retrospective cohort study

J.N. Lodders
E.A.J.M. Schulten
J.G.A.M. de Visscher
T. Forouzanfar
K.H. Karagozoglu

This chapter is based on the publication in:

J Reconstr Microsurg. 2016 Jul;32(6):455-463

Introduction

Ablative oral cancer surgery may lead to large continuity defects of the mandible. Reconstruction of these defects with free vascularised grafts has shown to improve the patient's quality of life with a predictable treatment outcome.[1,2] The fibula free flap (FFF) is considered the flap of first choice for the reconstruction of mandibular continuity defects in oral cavity cancer patients.

Complications after reconstruction of continuity defects of the mandible with FFF's have been extensively studied. The success rates of the FFF varies between 92.9% and 100%.[2-4] However, postoperative complications are described in a substantial number of patients (26.5%-57%).[5-8] It has been reported that, compared to other free flaps, FFF's have an increased risk for postoperative complications, such as flap failure.[2,9]

Although data are available on the use and complications of FFF's in head and neck reconstructions, most studies are descriptive and lack statistical analysis on risk factors for postoperative complications. Several studies have tried to elucidate risk factors for postoperative complications in general free flap surgery. Age, tobacco use and comorbidity,[5,10-12] donor site[8] and operating time have been identified as risk factors for postoperative complications.[12-15] However, these studies comprise a heterogeneous population with different types of malignant and benign tumours and different types of bone and soft tissue free flaps.

The purpose of this retrospective study was to analyse the incidence and types of postoperative complications after mandibular continuity reconstructions with FFF in patients with oral squamous cell carcinoma. Furthermore, potential risk factors for postoperative complications specific for FFF reconstructions were identified.

Materials and methods

This retrospective study was conducted in the Department of Oral and Maxillofacial Surgery/Oral Pathology, VU University Medical Center, Amsterdam, The Netherlands. A computer database was used to identify patients diagnosed with oral squamous cell carcinoma who had undergone segmental mandibular resection and reconstruction with FFF's from April 1995 to September 2013. Patients diagnosed with other types of malignant and benign tumours, such as sarcomas or ameloblastomas, were excluded from this analysis.

Study variables

Patient's characteristics and coexisting medical conditions, surgical and histo-pathological data were collected from the medical records. Patient's characteristics included: age, sex, body mass index (BMI), tobacco and alcohol use, adjuvant treatment (radiotherapy with or without concurrent chemotherapy), follow-up and cause of death. The coexisting medical conditions were scored according different organ systems (cardiovascular, respiratory, gastrointestinal, hepatic, renal, endocrine, neurologic, autoimmune, prior malignancy, nutritional and infectious). All patients were prospectively classified using the American Society of Anaesthesiologists (ASA) score and retrospectively using the Charlson Comorbidity Index (CCI). The CCI classifies patients according to their medical condition(s). Each medical condition is assigned a weight one, two, three or six. The weight depends on the severance of the medical conditions; for example lung disease is one point and severe renal disease two points. All points accumulate and produce a CCI score.[16]

Surgical and histopathological data included site of the primary tumour, type of neck dissection, additional surgery, type of mandibular defect (according to Jewer[17]), number of segmentations of the FFF, performance of a tracheostomy, TNM classification and anatomic staging according to the American Joint Committee on Cancer (AJCC) staging grouping.[18]

Outcome variables

Postoperative complications were defined as any adverse events requiring an intervention or readmission or compromising the postoperative clinical course. A distinction was made between surgical and systemic complications. Surgical complications were defined as adverse events considering the flap, recipient site or donor site. Systemic complications were defined as medical adverse events not considering the flap, recipient site or donor site. Death was not counted as a complication by itself. Patients with multiple complications were scored as a single surgical and/or systemic complication for statistical analysis.

Statistical analysis

The SPSS Software package (version 20.0 Inc., Chicago, IL, USA) was used for statistical analysis. Univariate and multivariable relationships between surgical complications, systemic complications, hospitalization >30 days and risk factors were studied using binary logistic regression.

Variables with a p value of <0.25 were included in the multivariable analyses in a stepwise back manner. A 2 tailed p value of <0.05 was considered statistically

significant and the confidence interval was set at 95%. Continuous variables were dichotomized if necessary, according to clinical judgement.

Results

Patient's characteristics are shown in Table 4.1. Eighty-five patients (39 men, 47 women, mean age 61.2 (range 32-88) years) were included in this study. The mean follow-up was 3.9 years. A total of 86 FFF transfers were performed in this group of 85 patients. Forty-five patients deceased during follow-up (average 2.5 years after surgery).

Table 4.1 Characteristics of 85 patients with oral SCC who underwent mandibular continuity reconstructions with FFFs.

Total patients	85
Total procedures	86
Age (years)	61.2 (SD 11.6)
Gender	
Male	39 (45.3%)
Female	47 (54.7%)
BMI (kg/m^2)	23.4 (SD 5.0)
Tobacco use	
Never	23 (26.7%)
Active	45 (52.3%)
Prior	18 (20.9%)
Alcohol use	
Never	37 (43.0%)
Active	45 (52.3%)
Prior	4 (4.7%)
Chemotherapy	
None	78 (90.7%)
Preoperative	-
Postoperative	7 (8.1%)
Both	1 (1.2%)
Radiotherapy	
None	18 (20.9%)
Preoperative	7 (8.1%)
Postoperative	56 (65.1%)
Both	5 (5.8%)
Follow up (days)	1432.8 (SD 1366.1)
Deceased after operation (days)	917.0 (SD 1033.8)
Cause death	
RRD	31 (68.9%)
UD	6 (13.3%)
OD	2 (4.4%)
Euthanasia	4 (8.9%)
Complication (inpatient)	2 (4.4%)

Abbreviations: SCC, squamous cell carcinoma; FFF, fibula free flap; SD, standard deviation; BMI, body mass index; RRD, residual or recurrent disease; UD, unknown disease; OD, other disease.

The most common coexisting medical conditions were previously diagnosed malignancies, overweight and cardiovascular disease. The majority of patients were classified as ASA 2 and CCI 2. A detailed summary of the patient's coexisting medical conditions are shown in Table 4.2.

Table 4.2 Coexisting medical conditions in 85 patients with oral SCC who underwent mandibular continuity reconstructions with FFFs.

Cardiovascular	35 (40.7%)
Respiratory	7 (8.1%)
Gastrointestinal	1 (1.2%)
Hepatic failure	2 (2.3%)
Renal failure	3 (3.5%)
Endocrine	13 (15.1%)
Neurologic	7 (8.1%)
Auto-immune disease	2 (2.3%)
Connective tissue	3 (3.5%)
Prior malignancy	33 (38.4%)
Nutritional	
Overweight (BMI >25.0)	25 (29.1%)
Underweight (BMI <18.5)	6 (7.0%)
Infectious	1 (1.2%)
Comorbidity indexing	
ASA	
2	66 (76.7%)
3	20 (23.3%)
CCI	
2	77 (89.5%)
3	5 (5.8%)
4	2 (2.3%)
≥5	2 (2.3%)

Abbreviations: SCC, squamous cell carcinoma; FFF, fibula free flap; BMI, body mass index; ASA, American Society of Anaesthesiologists; CCI, Charlson Comorbidity Index.

The surgical and histopathological data are listed in Table 4.3. In all patients a tracheostomy was carried out for respiratory management because of postoperative swelling. A mean operating time of 670.7 minutes (SD 138.1) and a mean anaesthesia time of 770.4 minutes (SD 130.6) was found. Mean hospitalization time was 30.7 days (SD 21.4).

Table 4.3 Surgical and histopathological data of 85 patients with oral SCC who underwent mandibular continuity reconstructions with FFF.

Surgery	
Site tumour	
Tongue	5 (5.8%)
Floor of mouth	27 (31.4%)
Alveolar process	47 (54.7%)
Buccal mucosa	6 (7.0%)
Lower lip	1 (1.2%)
Neck dissection	
Bilateral	44 (51.2%)
Unilateral	39 (45.3%)
Classification	
Selective	29 (33.7%)
Modified radical	49 (57.0%)
Unknown	4 (4.7%)
Additional surgery	
Partial glossectomy	20 (23.3%)
Maxillectomy	4 (4.7%)
Parotidectomy	5 (5.8%)
Laryngectomy	1 (1.2%)
Type mandibular defect[a]	
L	32 (37.2%)
LC	17 (19.8%)
LCL	37 (43.0%)
Segmentations of the FFF, amount (range)	1.8 (0-5)
Histopathology	
T-classification[b]	
1	3 (3.5%)
2	15 (17.4%)
3	5 (5.8%)
4	63 (73.3%)
N- classification[b]	
0	46 (53.5%)
1	15 (17.4%)
2 a/b/c	23 (26.8%)
3	2 (2.3%)
Staging[b]	
I	3 (3.5%)
II	12 (14.0%)
III	7 (8.1%)
IV	64 (74.4%)

Abbreviations: SCC, squamous cell carcinoma; FFF, fibula free flap.

[a] Type mandibular defect according to Jewer et al. (1989).[17]

[b] According to the American Joint Committee on Cancer staging grouping (2010).[18]

One hundred twenty-six postoperative complications (92 surgical and 34 systemic complications) occurred in 47 patients (54.7%). Twenty-eight patients (32.6%) had surgical complications, 10 patients (11.6%) had systemic complications and 9 patients (10.5%) had surgical and systemic complications. The majority of the postoperative complications (83.6%) occurred within the first 90 days. Twenty-four patients (27.9%)

returned to the operating room because of total flap failure (n=3), partial flap failure (n=6), revision surgery of the microvascular anastomosis (n=1), wound necrosis (n=3), wound dehiscence (n=3), bleeding/ haematoma (n=3), fistula (n=1), chyle leakage (n=1), mobile reconstruction plate (n=1), respiratory failure (n=1) and ileus (n=1). Donor site complications occurred in 3 patients (3.5%); wound infection (n=1), wound necrosis (n=1) and wound dehiscence (n=1). Revision of the microvascular anastomosis was necessary in 1 patient (1.2%). Two patients (2.3%) died in the postoperative clinical course. A detailed summary of the postoperative complications is shown in Table 4.4.

Table 4.4 Postoperative complications until 90 days and between 90 and 365 days in 85 patients with oral SCC who underwent mandibular continuity reconstructions with FFF.

Complications	≤90 days	90- 365 days	Total
Surgical			
Wound infection	1 (1.2%)	-	1 (1.2%)
Wound necrosis	6 (7.0%)	4 (4.7%)	10 (11.6%)
Wound dehiscence	5 (5.8%)	4 (4.7%)	9 (10.5%)
Abscess	6 (7.0%)	-	6 (7.0%)
Fistula	3 (3.5%)	6 (7.0%)	9 (10.5%)
Salivary leak	3 (3.5%)	-	3 (3.5%)
Chyle leakage	3 (3.5%)	-	3 (3.5%)
Haematoma/Bleeding	5 (5.8%)	-	5 (5.8%)
Seroma	2 (2.3%)	-	2 (2.3%)
Exposed/Infected plate	4 (4.7%)	2 (2.3%)	6 (7.0%)
Exposed/Infected bone	2 (2.3%)	-	2 (2.3%)
Return to operation room	18 (20.9%)	4 (4.7%)	22 (25.6%)
Total donor site	3 (3.5%)	-	3 (3.5%)
Total flap	10 (11.6%)	1 (1.2%)	11 (12.8%)
Total surgical	71	21	92[a,c]
Systemic			
Myocardial infarction	1 (1.2%)	-	1 (1.2%)
Atrial fibrillation	1 (1.2%)	-	1 (1.2%)
Anaemia	2 (2.4%)	-	2 (2.3%)
Electrolyte disorder	1 (1.2%)	1 (1.2%)	2 (2.3%)
Confusion	7 (8.1%)	-	7 (8.1%)
Respiratory			
Failure	7 (8.1%)	-	7 (8.1%)
Pneumonia	4 (4.7%)	-	4 (4.7%)
Hepatic impairment	2 (2.3%)	-	2 (2.3%)
Ileus	1 (1.2%)	-	1 (1.2%)
Splenomegaly	1 (1.2%)	-	1 (1.2%)
Urinary tract infection	1 (1.2%)	-	1 (1.2%)
Sepsis	1 (1.2%)	-	1 (1.2%)
Deceased during admission	2 (2.3%)	-	2 (2.3%)
Return to operation room	2 (2.3%)	-	2 (2.3%)
Total systemic	33	1	34b[,c]

Abbreviations: SCC, squamous cell carcinoma; FFF, fibula free flap.

[a] Nine patients had 2 surgical complications, seven patients had 3 surgical complications, five patients had 4 surgical complications, three patients had 5 surgical complications and one patient had 6 surgical complications; [b] Five patients had 2 systemic complications, one patient had 3 systemic complications, one patient had 4 systemic complications and one patient had 6 systemic complications; [c] Patients with multiple complications were scored as a single surgical and/or systemic complication for statistical analysis.

In the univariate analysis correlations were found between surgical complications and tobacco use (odds Ratio (OR), 3.02; 95% Confidence Interval (CI), [1.24–7.38]; *p*=0.02), CCI >2 (OR, 5.48; CI, [1.07–28.18]; *p*=0.04), anaesthesia time (OR, 1.01; CI, [1.00–1.00]; *p*=0.009), anaesthesia time >800min (OR, 2.62; CI, [1.06–6.48]; *p*=0.04), (additional surgery) partial glossectomy (OR, 0.25; CI, [0.77–0.83]; *p*=0.02) and type of mandibular defect (OR, 2.75; CI, [1.08–7.03]; *p*=0.03). Correlations were found between systemic complications and age (OR, 1.09; CI, [1.03–1.115]; *p*=0.003), age >60 (OR, 6.58; CI, [1.75–24.72]; *p*=0.005) and ASA-score ≥3 (OR, 3.33; CI, [1.11–10.06]; *p*=0.03), CCI >2 (OR, 18.96; CI, [3.51–102,52]; *p*<0.001). Hospitalization >30 days was associated with anaesthesia time (OR, 1.00; CI, [1.00–1.00]; *p*=0.03), anaesthesia time >800min (OR, 3.29; CI, [1.25–8.67]; *p*=0.02) and type of mandibular defect (OR, 11.13; CI, [2.41-51.38]; *p*=0.002).

Correlations between tobacco use, partial glossectomy, type of mandibular defect, anatomic staging and surgical complications were found in the multivariable analysis, CCI >2 and anaesthesia time >800min did not show significance. Systemic complications remained significant with age >60 and CCI >2, but ASA-score ≥3 did not remain significant. Hospitalization >30days showed associations in the multivariable analysis with type of mandibular defect. However, anaesthesia time lost significance (Table 4.5.).

Table 4.5 Multivariable regression analysis for surgical and systemic complications and hospitalization >30days in 85 patients with oral SCC who underwent mandibular continuity reconstructions with FFFs.

Variable	Odds ratio	*p* value	95% CI
			Lower – Upper
Surgical complications			
Tobacco use	5.97	**0.002**	1.93 – 18.45
Partial glossectomy	0.08	**0.001**	0.02 – 0.36
Classification mandibular defect[a]	4.02	**0.02**	1.31 – 12.28
Anatomic staging III and IV[b]	4.42	**0.04**	1.03 – 18.94
Systemic complications			
Age >60 (years)	8.88	**0.008**	1.77 – 44.57
CCI >2	26.92	**0.001**	3.66 – 198.10
Hospitalization >30days			
Tobacco use	1.97	0.22	0.67 – 5.77
Classification mandibular defect[a]	11.71	**0.002**	2.47 – 55.52
Anatomic staging III and IV[b]	8.57	0.05	1.00 – 73.80

Abbreviations: FFF, fibula free flap; SCC, squamous cell carcinoma; CI, Confidence interval; CCI, Charlson Comorbidity Index.

Significant variables are highlighted in bold.

[a] Mandibular classification according to Jewer et al. (1989) (17) dichotomized in anterior mandibular (C-defects) involvement and lateral defects (L-defects).

[b] Staging according to the American Joint Committee on Cancer staging grouping (2010). (18)

Discussion

Reconstruction of mandibular continuity defects after segmental resection is complex and challenging. The incidence of postoperative complications following free flap reconstructions varies between 26.5% and 57%.[5-8] Studies have shown an increased risk in patients with bony continuity defects or when the FFF was used as donor graft.[2,9] In this retrospective study the complications and possible risk factors were analysed in a well-defined cohort consisting of 85 patients with oral squamous cell carcinoma who underwent segmental mandibular resection and subsequent reconstruction with FFFs. One patient underwent a second surgical procedure because of recurrent disease.

The overall one-year postoperative complication rate in this study was 54.7%. The total flap failure rate is 4.7%. The success rate of the FFF in head and neck patients varies between the 92.9% and 100%.[2-4,7,9] The overall complication rate in our study is relatively high compared to other studies (26,5%-57%).[5-8] This discrepancy is probably explained by the different definitions authors use to describe their complications. Andrade et al.[19] distinguished early and late complications. Sieg et al.[20] did not classify their complications. Other studies distinguished flap-related complications and medical complications.[6,7] In the present study a detailed scoring system is used. In short, different definitions of complications and different time frames are used. A consensus for defining complications in free flap and reconstructive surgery of mandibular defects is lacking. The integration of a standardized scoring system for postoperative complications will result in efficient comparison between studies with inherent improvement of practice and quality of care.[21] The Clavien-Dindo grading system for postoperative complications has been used in two head and neck studies.[12,21] Although both studies advocate its use, shortcomings regarding the unique complications in head and neck patients are acknowledged.[21] Therefore, future studies are needed for developing a unique classification system for postoperative complications in head and neck reconstruction patients.

The mean hospitalization in these series was 30.7 days, which is higher than other studies. This long hospitalization can partly be explained by a quartet of patients, of whom 2 were hospitalized more than 120 days and 2 more than 75 days. Three patients developed flap related problems (2 partial and 1 total flap failure) and two of those patients were reconstructed with a pectoralis major flap. The fourth patient was hospitalized for a delirium, respiratory problems and liver failure. The mean hospitalization decreases to 26,8 days if these 4 patients were excluded.

In the multivariable analysis several variables were associated with an increased risk for postoperative complications. Particularly tobacco use, continuity defects of the anterior mandible and advanced disease (stage III and IV) showed a higher risk for postoperative surgical complications. In patients with age >60 and CCI >2 a higher risk for developing postoperative systemic complications was seen. Patients with defects of the anterior mandible are at risk for prolonged hospitalization. A significant decrease in risk (OR 0.25) for surgical complications was found in patients who had undergone segmental mandibular resection including a partial glossectomy. This could be explained by reduction of mobility in the surgical area. Because the tongue is very mobile structure in the oral cavity, a partial glossectomy will result in lesser tongue movement with a subsequent lower risk for wound dehiscence, bleeding or other flap complications.

Previous studies identified similar factors for predicting postoperative complications. However, these studies comprise heterogeneous populations with the use of various free flap donor sites. Studies analysing risk factors with solely FFF are lacking. Therefore, the findings in the present study were compared with other reported studies describing risk factors in general free flap surgery. Haugley et al.[5] has shown an association between tobacco use and free flap complications and between high age and systemic complications. In the study of Clark et al.[10] an association between tobacco use and an increased risk for medical complications was demonstrated. Other reported studies could not confirm the predictive value of tobacco use regardless of the negative influence tobacco use exerts on the general healing process.[9,22] Both operating time[12-15,23,24] and high age[5,9,10,12,25] are previously correlated with higher complications rates. Operating time partially reflects the complexity and extent of the surgical procedure and could explain the increased complication rates. It remains questionable whether age itself is the primary reason for the increased postoperative complications. High age increases the risk for coexisting medical conditions and could indirectly influence the patient's outcome following surgery. The summarized data above should be interpreted carefully. Most studies dichotomise variables according to clinical judgement, with subsequent different cut off points for high age and prolonged operating time.[14,15]

The negative impact of coexisting medical conditions on the patients quality of life and hospital costs is well demonstrated in head and neck patients.[26] It is by far the strongest predictor for complications in free flap procedures.[9-12,15,25,27,28] Clark et al.[10] studied 185 head and neck free flap patients and compared the ASA classification, CCI and Kaplan-Feinstein Index. These series only showed significant correlation between the ASA classification and postoperative complications. Singh et al.[15] reported in an

analysis of 200 free tissue transfers predictive value for the CCI. McMahon et al.[12] prospectively studied 192 free flap patients in a period over 27 months and demonstrated an association between medical conditions and postoperative complications. Although in most studies the value of the ASA classification is addressed[9,10,25,27], the use of a more detailed and complex index such as the CCI or the Adult Comorbidity Evaluation 27 (ACE-27) is advocated in some other studies.[9,11,15] There is an urge for a classification system that scores relevant medical conditions associated with an increased risk for morbidity in head and neck patients. Most scoring systems are developed for other purposes; for example the CCI was originally created to stratify the patients at risk for long term mortality. In our opinion the simple and subjective ASA classification seems more useful to identify patients at risk for postoperative complications. However, this was not confirmed in the multivariable analysis. The use of a more complex and detailed comorbidity scoring system remains controversial, even though its scientific value and objective character are acknowledged.

This study shows that patients undergoing reconstruction of continuity defects of the anterior mandible with FFF's have a higher risk for developing surgical complications (OR 4.02) and prolonged hospitalization (OR 11.71). This higher complication rate has already been reported.[29,30] Boyd et al.[29] reported a sevenfold higher risk for developing plate related complications in the anterior mandible compared to the lateral mandible. However, in their series reconstructions were performed with reconstruction plates and fasciocutaneous radial forearm flaps. The higher risk for developing complications in the anterior mandible could be explained by the fact that the FFF is often segmented in the reconstructions of the anterior mandible. Forces exerted during function (compression, tension and especially torsion) might lead to significant stress on the segmented graft with increased risk of mobility and flap-related complications. On the other hand the number of segments is not correlated with an increased risk for postoperative complications. Therefore the true reason for the increased complications remains unknown.

An overview of the discussed studies with their key features, surgical and/or medical complications and related risk factors are summarized in Table 4.6. Note that only studies are demonstrated with a surgical and systemic scoring classification (i.e. other classifications for scoring complications are not shown).

Table 4.6 Key features of the included studies with their surgical and/or medical complications and related risk factors.

Study (country)	n	Age (mean)	Donor site(s)	Surgical CMPL	Surgical risk factors	Systemic CMPL	Systemic risk factors
Wu et al.[2] (China)	372	-	FFF	54%	-	-	-
Haugley et al.[5] (U.S.A.)	141	62 years	FFF, SFF, DCIAFF, SeFF, RFFF, ALTFF, LDFF, RAFF, JFF	29%	Tobacco use IV crystalloid fluid >7L Preoperative weight loss >10%	57%	Age >55 years IV crystalloid fluid >7L
Lopez-Arcas et al.[6] (Spain)	117	57 years	FFF	27%	-	-	-
Dowthwaite et al.[7] (Canada)	58	56 years	FFF	24%	-	5%	-
Gemert et al.[8] (Holland)	83	61 years	FFF, DCIA, RFFF	43%	Jaw reconstructions	-	-
Suh et al.[9] (U.S.A.)	400	-	FFF, SFF, DCIAFF, RFFF, RAFF, JFF,	19.0%	Previous surgery	21%	Increased age[a] Increased ASA-score
Clark et al.[10] (Canada)	185	60 years	FFF, SFF, RFFF, ALTFF, LDFF, RAFF	36.8%	Preoperative radiotherapy Tracheostomy	34%	Age >65 years Tobacco use ASA-score >2 IV crystalloid fluid >130ml/kg
McMahon et al.[12] (England)	195	62 years	FFF, SFF, DCIAFF, RFFF, ALTFF, LDFF, RAFF	38%	Occlusive vascular disease Prolonged anaesthesia[a] Perioperative haemoglobin	29%	Increased age[a] Raised CRP preoperative
Singh et al.[15] (U.S.A.)	200	59 years	FFF, SFF, IFF, RFFF, ALTFF, LDFF, RAFF, JFF	28%	Increased CCI Preoperative radiotherapy	14%	Increased CCI Prolonged anaesthesia[a]
Lodders et al.[23] (England)	189	60 years	FFF, SFF, DCIAFF, RFFF, ALTFF, PMFF	32%	-	8%	Prolonged anaesthesia
Farwell et al.[24] (U.S.A.)	93	66 years	FFF, SFF, DCIAFF, RFFF, LDFF, RAFF, JFF	28%	Increased IV fluid[a]	19%	Hepatitis Anaesthesia >8hours
Patel et al.[25] (U.S.A.)	796	62 years	SFF,LDFF, RAFF, TFF	22%	ASA-score >2 Preoperative haemoglobin transfusion	22%	Increased age[a] Body Mass Index[a] ASA-score >2 Kaplan Feinstein Index >1 Tracheostomy
Bozikov et al.[28] (Slovenia)	194	58 years	FFF, SFF, DCIAFF, RFFF, LDFF, RAFF, JFF, CFF	34%	Diabetes mellitus Flap salvage surgery	-	-

Abbreviations: CMPL, complications; FFF, fibula free flap; SFF, scapula free flap; DCIAFF, deep circumflex iliac artery free flap; IFF, ileum free flap; SeFF, serratus free flap; RFFF, radial forearm free flap; ALTFF, antero lateral thigh free flap; LDFF, latissimus dorsi free flap; RAFF, rectus abdominis free flap; JFF, jejunal free flap; CFF, colon free flap; TFF, temporal free flap; PMFF, pectoralis major free flap; U.S.A. United States of America; IV, intravenous; ASA, American Society of Anaethesiologists; CRP, C-reactive protein; CCI, Charlson Comorbidity Index.

[a] Continuous variable.

Unfortunately, there are no reliable alternatives for the reconstruction of mandibular continuity defects other than bony free flaps, especially in anterior defects. Over the last decade virtual surgical planning (VSP) has gained attention in the oncologic head and neck surgery to optimize the patients outcomes. VSP has shown to increase the surgical accuracy by preoperatively planning the resection margins, fabricating cutting templates and pre-bending plate osteosynthesis, leading to a reduction in operating and ischemic time.[31,32] Both factors have shown to be valuable predictors for postoperative complications and thus could be the key to reduce morbidity.[12-15,23,24] During our study no kind of VSP was used, however since 2013 we preoperatively bend the plate osteosynthesis on a 3D printed mandible to facilitate reconstruction and reduce operating time. While the qualitative results are optimistic regarding VSP, robust evidence is lacking regarding quantifiable outcomes such as flap fail, postoperative complications and hospital stay. In our opinion VSP seems very promising and research should be done to further elucidate this topic.

The present study has several shortcomings. As for all retrospective studies, adequate statistical analysis depends on accurate record keeping. The sample size in the present study is relatively small and could lead to underpowered statistics. To overcome such shortcomings in the future a prospective computer database is currently being developed in the department, to keep records of all head and neck patients reconstructed with FFFs. This computer database may be helpful in verifying the present findings and future studies.

The use of FFFs for reconstruction of continuity defects of the mandible in oral cancer patients may have a significant risk for postoperative complications. Especially patients with coexisting medical conditions and anterior mandible defects have a higher risk for postoperative complications, as do patients with age >60 years, tobacco use and anatomic stage III and IV disease. Patients who undergo segmental mandibular resection including a partial glossectomy could have a reduced risk for post-operative complications. Due to the relative unchangeable character, little influence can be exerted on the patient's outcome. Nevertheless a risk assessment could be useful for prognosis and to have realistic information and expectations.

References

1. Curtis DA, Plesh O, Miller AJ, Curtis TA, Sharma A, Schweitzer R, et al. A comparison of masticatory function in patients with or without reconstruction of the mandible. Head Neck. 1997;19(4):287-96.
2. Wu CC, Lin PY, Chew KY, Kuo YR. Free tissue transfers in head and neck reconstruction: complications, outcomes and strategies for management of flap failure: analysis of 2019 flaps in single institute. Microsurgery. 2014;34(5):339-44.
3. Gonzalez-Garcia R, Naval-Gias L, Rodriguez-Campo FJ, Munoz-Guerra MF, Sastre-Perez J. Vascularized free fibular flap for the reconstruction of mandibular defects: clinical experience in 42 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(2):191-202.
4. Cordeiro PG, Disa JJ, Hidalgo DA, Hu QY. Reconstruction of the mandible with osseous free flaps: a 10-year experience with 150 consecutive patients. Plast Reconstr Surg. 1999;104(5):1314-20.
5. Haughey BH, Wilson E, Kluwe L, Piccirillo J, Fredrickson J, Sessions D, et al. Free flap reconstruction of the head and neck: analysis of 241 cases. Otolaryngol Head Neck Surg. 2001;125(1):10-7.
6. Lopez-Arcas JM, Arias J, Del Castillo JL, Burgueno M, Navarro I, Moran MJ, et al. The fibula osteomyocutaneous flap for mandible reconstruction: a 15-year experience. J Oral Maxillofac Surg. 2010;68(10):2377-84.
7. Dowthwaite SA, Theurer J, Belzile M, Fung K, Franklin J, Nichols A, et al. Comparison of fibular and scapular osseous free flaps for oromandibular reconstruction: a patient-centered approach to flap selection. JAMA Otolaryngol Head Neck Surg. 2013;139(3):285-92.
8. van Gemert JT, van Es RJ, Rosenberg AJ, van der Bilt A, Koole R, Van Cann EM. Free vascularized flaps for reconstruction of the mandible: complications, success, and dental rehabilitation. J Oral Maxillofac Surg. 2012;70(7):1692-8.
9. Suh JD, Sercarz JA, Abemayor E, Calcaterra TC, Rawnsley JD, Alam D, et al. Analysis of outcome and complications in 400 cases of microvascular head and neck reconstruction. Arch Otolaryngol Head Neck Surg. 2004;130(8):962-6.
10. Clark JR, McCluskey SA, Hall F, Lipa J, Neligan P, Brown D, et al. Predictors of morbidity following free flap reconstruction for cancer of the head and neck. Head Neck. 2007;29(12):1090-101.
11. Borggreven PA, Kuik DJ, Quak JJ, de Bree R, Snow GB, Leemans CR. Comorbid condition as a prognostic factor for complications in major surgery of the oral cavity and oropharynx with microvascular soft tissue reconstruction. Head Neck. 2003;25(10):808-15.
12. McMahon JD, MacIver C, Smith M, Stathopoulos P, Wales C, McNulty R, et al. Postoperative complications after major head and neck surgery with free flap repair--prevalence, patterns, and determinants: a prospective cohort study. Br J Oral Maxillofac Surg. 2013;51(8):689-95.
13. Pohlenz P, Klatt J, Schmelzle R, Li L. The importance of in-hospital mortality for patients requiring free tissue transfer for head and neck oncology. Br J Oral Maxillofac Surg. 2013;51(6):508-13.
14. Ferrier MB, Spuesens EB, Le Cessie S, Baatenburg de Jong RJ. Comorbidity as a major risk factor for mortality and complications in head and neck surgery. Arch Otolaryngol Head Neck Surg. 2005;131(1):27-32.
15. Singh B, Cordeiro PG, Santamaria E, Shaha AR, Pfister DG, Shah JP. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg. 1999;103(2):403-11.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
17. Jewer DD, Boyd JB, Manktelow RT, Zuker RM, Rosen IB, Gullane PJ, et al. Orofacial and mandibular reconstruction with the iliac crest free flap: a review of 60 cases and a new method of classification. Plast Reconstr Surg. 1989;84(3):391-403; discussion 4-5.
18. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.
19. Andrade WN, Lipa JE, Novak CB, Grover H, Bang C, Gilbert RW, et al. Comparison of reconstructive procedures in primary versus secondary mandibular reconstruction. Head Neck. 2008;30(3):341-5.
20. Sieg P, Zieron JO, Bierwolf S, Hakim SG. Defect-related variations in mandibular reconstruction using fibula grafts. A review of 96 cases. Br J Oral Maxillofac Surg. 2002;40(4):322-9.

21. Monteiro E, Sklar MC, Eskander A, de Almeida JR, Shrime M, Gullane P, et al. Assessment of the Clavien-Dindo classification system for complications in head and neck surgery. Laryngoscope. 2014;124(12):2726-31.
22. Gonzalez-Garcia R, Naval-Gias L, Rodriguez-Campo FJ, Roman-Romero L. Reconstruction of oromandibular defects by vascularized free flaps: the radial forearm free flap and fibular free flap as major donor sites. J Oral Maxillofac Surg. 2009;67(7):1473-7.
23. Lodders JN, Parmar S, Stienen NL, Martin TJ, Karagozoglu KH, Heymans MW, et al. Incidence and types of complications after ablative oral cancer surgery with primary microvascular free flap reconstruction. Med Oral Patol Oral Cir Bucal. 2015;20(6):e744-50.
24. Farwell DG, Reilly DF, Weymuller EA, Jr., Greenberg DL, Staiger TO, Futran NA. Predictors of perioperative complications in head and neck patients. Arch Otolaryngol Head Neck Surg. 2002;128(5):505-11.
25. Patel RS, McCluskey SA, Goldstein DP, Minkovich L, Irish JC, Brown DH, et al. Clinicopathologic and therapeutic risk factors for perioperative complications and prolonged hospital stay in free flap reconstruction of the head and neck. Head Neck. 2010;32(10):1345-53.
26. Paleri V, Wight RG, Silver CE, Haigentz M, Jr., Takes RP, Bradley PJ, et al. Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. Oral Oncol. 2010;46(10):712-9.
27. Serletti JM, Higgins JP, Moran S, Orlando GS. Factors affecting outcome in free-tissue transfer in the elderly. Plast Reconstr Surg. 2000;106(1):66-70.
28. Bozikov K, Arnez ZM. Factors predicting free flap complications in head and neck reconstruction. J Plast Reconstr Aesthet Surg. 2006;59(7):737-42.
29. Boyd JB, Mulholland RS, Davidson J, Gullane PJ, Rotstein LE, Brown DH, et al. The free flap and plate in oromandibular reconstruction: long-term review and indications. Plast Reconstr Surg. 1995;95(6): 1018-28.
30. Kim MR, Donoff RB. Critical analysis of mandibular reconstruction using AO reconstruction plates. J Oral Maxillofac Surg. 1992;50(11):1152-7.
31. Rodby KA, Turin S, Jacobs RJ, Cruz JF, Hassid VJ, Kolokythas A, et al. Advances in oncologic head and neck reconstruction: systematic review and future considerations of virtual surgical planning and computer aided design/computer aided modeling. J Plast Reconstr Aesthet Surg. 2014;67(9):1171-85.
32. Kaariainen M, Kuuskeri M, Gremoutis G, Kuokkanen H, Miettinen A, Laranne J. Utilization of Three-Dimensional Computer-Aided Preoperative Virtual Planning and Manufacturing in Maxillary and Mandibular Reconstruction with a Microvascular Fibula Flap. J Reconstr Microsurg. 2016;32(2):137-41.

Chapter 5

Long-term outcomes of implant-based dental rehabilitation in head and neck cancer patients after reconstruction with the free vascularized fibula flap

J.N. Lodders
F.K.J. Leusink
A. Ridwan-Pramana
H.A.H. Winters
K.H. Karagozoglu
H. Dekker
T. Forouzanfar
E.A.J.M. Schulten

This chapter is based on the publication in:

J Craniomaxillofac Surg. 2021 Sep;49(9):845-854

Introduction

Segmental mandibulectomy or maxillectomy results in the loss of oral soft tissues, bone and teeth. Reconstruction with a free vascularised fibula flap (FFF) has become the standard of care for mandibular defects[1], and is now also the preferred flap reconstruction for maxillary defects.[2]

Although reconstruction with the FFF restores the mandibular or maxillary arch after oncological resection, mastication, speech and swallowing may still be impaired due to the lack of functional dentition. Proper dental rehabilitation is challenging and sometimes impossible, because the oral anatomy often lacks vestibular space, stability and retention for a tissue-borne prosthesis.[3,4] In these cases dental implants can be valuable to achieve dental rehabilitation.[2-16] Prosthetic rehabilitation can be complicated by factors such as coexisting medical conditions and the adverse effects of irradiation.[17]

Studies have shown successful osseointegration of dental implants in FFFs, with implant survival rates, ranging from 38% to 90% for implants placed in irradiated FFFs[3,11-15,18] and from 69% to 100% for implants placed in non-irradiated FFFs.[3,9,11-15,19] Although these survival rates are acceptable, this outcome is of little importance if the implants are not functionally loaded. Most studies of head and neck cancer patients after FFF reconstruction focused on dental implant survival, rather than the success rate of dental implants[9,15] or prosthesis-related functional outcomes.[10]

To determine which patients may benefit from implant-based dental rehabilitation, data are needed on long-term function and reliability of dental implants and, even more important, implant-supported superstructures.

The aim of this study was to evaluate the long-term survival and success of dental implants in head and neck cancer patients after mandibular or maxillary reconstruction with an FFF, and to analyse prosthesis-related outcomes with a particular focus on functional dental rehabilitation.

Materials and methods

Following ethical approval for the study protocol by the Institutional Review Board of Amsterdam UMC (registration number: 2017.446), a computer database was retrospectively reviewed in the Department of Oral and Maxillofacial Surgery/Oral

Pathology, Amsterdam UMC d VU Medical Center in Amsterdam, the Netherlands. A cohort was created of head and neck cancer patients who had undergone implant-based dental rehabilitation after maxillofacial reconstruction with FFF between April 1995 and October 2017. All data were followed up until July 2019. Patients with a history of malignant disease were included and classified according to the original reconstructive indication: (a) tumour resection and immediate FFF reconstruction (primary-FFF); (b) tumour resection and delayed FFF reconstruction (secondary-FFF); (c) resection for osteoradionecrosis (ORN) with immediate FFF reconstruction (ORN-FFF). Benign tumours and free flaps other than FFF were excluded from this study.

Study variables

Demographic characteristics were collected, including age, gender, body mass index (BMI), tobacco and alcohol use, radiotherapy data (with or without concurrent chemotherapy), dental status, follow-up time, and vital status. Histopathological data regarding the tumour site, tumour entity, and TNM-classification were also noted. For statistical analysis, tobacco and alcohol were dichotomized.

Surgical data regarding the FFF reconstruction comprised type of mandibular defect[1], type of maxillary defect[20], and number of segmentations. Data concerning perioperative hyperbaric oxygen therapy (HBO), implant location, implant length, implant diameter, operating time, and hospital stay, as well as information regarding the meso- and superstructure, were assessed.

Outcome variables

Three implant-related outcomes were defined. Firstly, implant survival was defined as any implant that was present in the mouth at the end of follow-up, regardless of the state and/or function of the dental implant. Implant function was defined as any implant that was present in the mouth at the end of follow-up and was loaded with a dental prosthesis. The criteria of Albrektsson et al.[21] were used for implant success: a) immobility of the implant; (b) absence of peri-implant radiolucency; (c) signs of pain, paraesthesia, or infection; (d) <0.2 mm vertical bone loss per annum; and (e) <1.5 mm vertical bone loss the first year after loading. Panoramic radiographs were used to evaluate peri-implant one loss, using imaging software (AGFA Enterprise Imaging XERO Viewer, version 8.0.1). The mesial and distal surfaces were measured from implant shoulder to bone level. The following criteria for functional dental rehabilitation were used: (a) there is one or more functional integrated dental implant(s) present that support a fixed or removable prosthetic construction; (b) the implant-supported prosthetic device is worn for esthetical and/or mastication purposes without pain or discomfort; (c) there is at least a 6-month follow-up after placement of the

superstructure; (d) the patient confirms satisfaction with the oral rehabilitation and/or aesthetics during recall visits.

Statistical analysis

The SPSS software package version 20.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Patient-related outcomes were analysed using the chi-square test. If the observed counts were less than 5, the Fisher's exact test was used. Cohort life tables and Kaplan-Meier plots were used to evaluate implant survival and success. Because implant data were clustered within patients, univariate associations between risk factors and implant failure were analysed using generalized estimating equations. Statistical significance was achieved using a two-tailed *p*-value of <0.05.

Dental implantation: procedures and timeline

To qualify for dental implants, patients needed to have unsatisfactory function and/or aesthetics that could be improved with dental rehabilitation, and to have been free of disease or recurrence for at least 12 months after completion of all adjuvant therapy. A maxillofacial prosthodontist was always involved in the multidisciplinary assessment for dental rehabilitation in order to optimize care and reduce adverse outcomes. Dental implantation was performed in a two-stage procedure. Both surgeries were performed under general anaesthesia. The first stage comprised (partial) removal of the reconstruction plate(s) and screws, evaluation of the consolidation of the FFF and placement of regular-neck, soft-tissue-level Straumann implants, which were left submerged for osseointegration. If the implant area of the FFF reconstruction had received irradiation >50 Gy, HBO was initiated, comprising 20 sessions preoperatively and 10 sessions postoperatively.[22]

The second stage of surgery started at least 3 months after the first procedure. It comprised retrieval of the dental implants, evaluating their clinical stability, and placement of healing abutments. Prior to the latter procedure a panoramic radiograph was taken to evaluate osseointegration and to check for signs of infection. If osseointegration had failed, the implant was removed. Soft tissue management consisted of debulking and/or excision of the overlying skin flap, followed by a vestibuloplasty with split thickness keratinized palatal mucosal grafting to create a more favourable peri-implant soft tissue condition and prosthetic platform. To prevent gingival overgrowth, a resin-bonded stent was used to contour the surrounding soft tissues and to fix the mucosal grafts over a 3 week period. Around 4-5 weeks after completion of the second stage, prosthetic rehabilitation was initiated. All patients were clinically and radiographically evaluated annually by an oral and maxillofacial surgeon (ES) to evaluate patient satisfaction and to identify peri-implant pathology.

Results

A flowchart for the included head and neck cancer patients is shown in Figure 5.1.

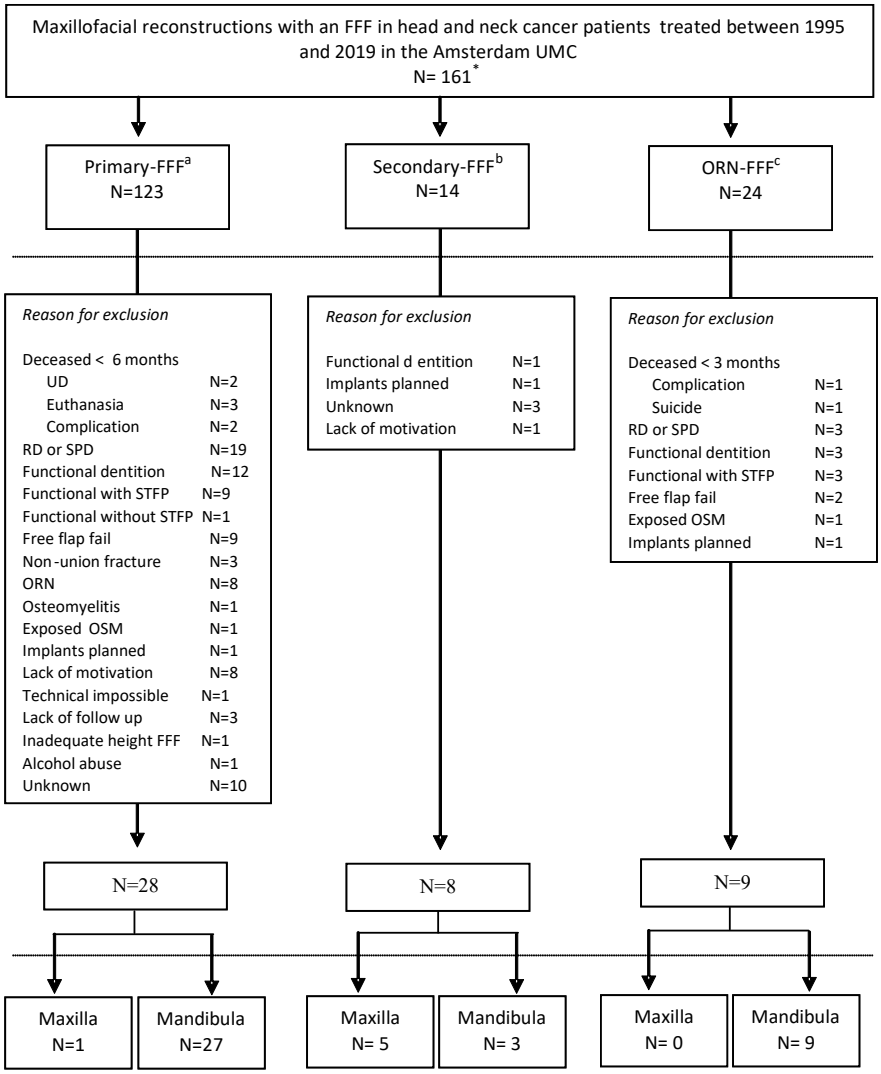

Figure 5.1 Flowchart of the included patients with FFF maxillofacial reconstructions by reconstructive indication.
* two reconstructions were performed for failure of the FFF.
Abbreviations: FFF, free fibula flap; ORN, osteoradionecrosis; OSM, osteosynthesis; RD, local, regional or distant recurrent malignant disease; SPD, second primary malignant disease; STFP, soft tissue supported full prosthesis; UD, unknown disease. [a] tumour resection and immediate FFF reconstruction; [b] tumour resection and delayed FFF reconstruction; [c] resection for ORN and immediate FFF reconstruction.

In total, 161 FFFs were transplanted in 150 patients. Implant-based dental rehabilitation was started 45 times in 42 patients; three patients underwent a second FFF reconstruction after the initial graft was lost. Relatively more patients received dental implants with secondary FFFs (57.1%) than patients with primary FFFs (22.8%) or ORN FFFs (37.5%) (p=0.01). One patient was excluded from further analysis, because the dental implants were placed simultaneously with tumour resection, resulting in 44 reconstructions in 41 patients.

Table 5.1 shows the patient demographics and the histopathological profiles of the patients who received dental implants.

Table 5.1 Patient demographics at the time of implantation and histopathological profile of the included head and neck cancer patients reconstructed with an FFF. Data are numbers.

	Irradiated FFF	Non-irradiated FFF			
Variable	**Primary[a]**	**Primary[a]**	**Secondary[b]**	**ORN[c]**	**Total**
Total patients	13	14	8	9	44
Age (years ±SD)	54.4 (±14.1)	66.6 (±11.1)	57.3 (±16.9)	61.7 (±7.3)	60.3 (±13.2)
Gender					
Male	7	5	7	4	23
Female	6	9	1	5	21
Tobacco					
Never	2	4	4	2	12
Active*	3	3	1	3	10
Prior	8	7	3	4	22
Alcohol					
Never	5	4	4	3	16
Active*	4	7	3	4	18
Prior	4	3	1	2	10
Prior radiotherapy	13	2	7	9	31
Radiation dose	6111.0	6575.0	6133.3	6427.8	6241,7
(Gray, range)	(5500 – 7000)	(6550 – 6600)	(5600 – 7000)	5600-7000	(5500-7000)
Prior chemotherapy	3	-	1	1	5
Dental status					
Reconstructed jaw					
Edentulous	11	11	6	8	36
(Partial) dentate	2	3	2	1	8
Opposing jaw					
Edentulous	9	7	3	4	23
(Partial) dentate	4	7	5	5	21
Tumour site					
Tongue	-	1	-	-	1
Floor of mouth	3	3	1	4	11
Mandibular alveolus	9	10	2	4	25
Maxillary alveolus	1	-	2	-	3
Maxillary sinus	-	-	1	-	1
Tonsil	-	-	-	1	1
Nose	-	-	2	-	2

Table 5.1 (continued)

	Irradiated FFF	Non-irradiated FFF			
Variable	**Primary[a]**	**Primary[a]**	**Secondary[b]**	**ORN[c]**	**Total**
Tumour entity					
SCC	12	13	6	9	40
Sarcoma	1	1	2	-	4
T-classification†					
1	-	2	-	2	4
2	-	5	-	2	7
3	-	1	1	1	3
4	12	4	6	4	26
N-classification†					
0	9	11	7	5	32
1	1	1	-	3	5
2 a/b/c	2	-	-	1	3

Abbreviations: FFF, free fibula flap; SCC, squamous cell carcinoma; SD, standard deviation.
*Active was defined as substance use within one month of dental implantation.
† The TNM classification of 3 patients could not be retrieved from the medical records.
[a] tumour resection and immediate FFF reconstruction.
[b] tumour resection and delayed FFF reconstruction.
[c] resection for ORN and immediate FFF reconstruction.

Of the 44 reconstruction cases, 23 were males and 21 were females. The mean age at the time of dental implantation was 60.3 years (range 20-84). The mean follow-up time was 4.9 years (range 0.2-23.4). Twelve patients died at a median time of 2.9 years after dental implantation (range 0.2-9.9), due to recurrent disease (n=7) or unknown disease (n=5).

In total, 202 dental implants were placed: 161 in the FFF, 26 in the native maxilla, and 15 in the native mandible (Table 5.2). Thirty-three implants failed in 12 patients. At failure, the mean time since implantation was 16.2 months (range 2-91). The implant failure rates were 18.0% (29/161) in the FFF (Figure 5.2), 11.5% (3/26) in the native maxilla, and 6.7% (1/15) in the native mandible. As shown in Figure 5.3, dental implant survival was 55.3% in irradiated FFFs and 96% in non-irradiated FFFs. The effect of smoking on the implant survival rate in irradiated and non-irradiated FFFs is shown in Figure 5.4. In active smokers with an irradiated FFF, 100% dental implant failure was seen.

Reasons for dental implant failure in the FFFs were necrosis of the bony graft (n=19), peri-implant bone loss (n=5), recurrent cancer (n=4), and failed osseointegration (n=1). All failing implants in the native jaws had been placed in irradiated bone and failed due to lack of osseointegration (n=3) and peri-implant bone loss (n=1).

The types and incidence of post-implantation complications are summarized In Table 5.3. Twenty-two patients developed a total of 48 post implantation complications: 47 surgical and one systemic. Patients with irradiated FFFs were more likely to develop complications (p=0.02). Peri-implant mucosal hyperplasia was noted in 13 patients.

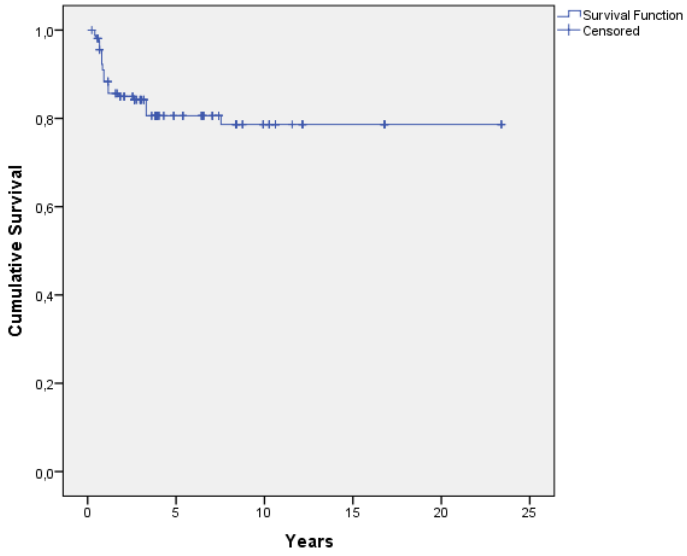

Figure 5.2 Kaplan-Meier plot of the overall survival of 161 dental implants placed in free fibula flaps.

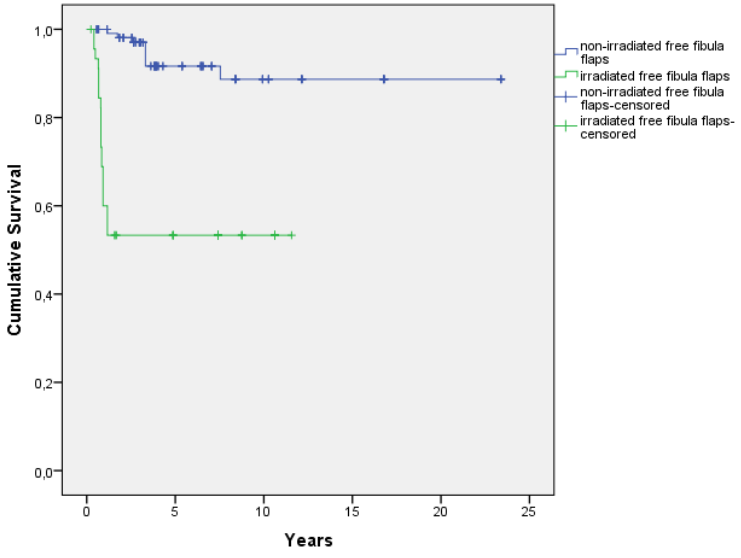

Figure 5.3 Kaplan-Meier plot of the implant survival in non-irradiated free fibula flaps (blue plot) and irradiated free fibula flaps (green plot).

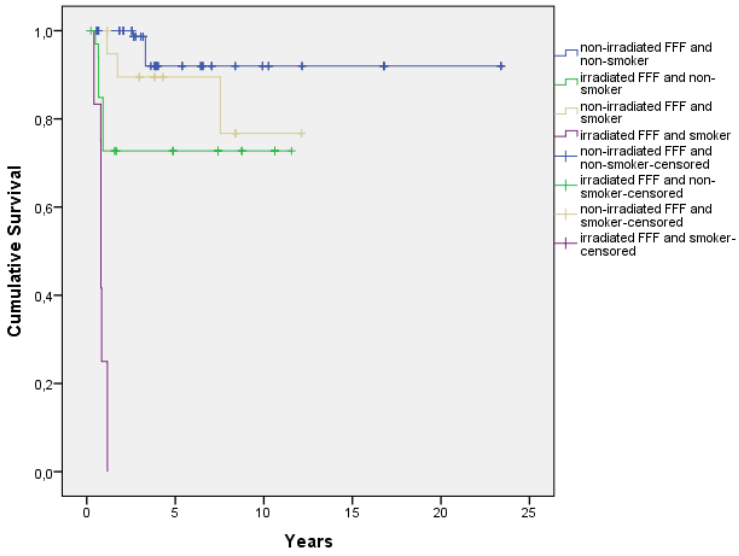

Figure 5.4 Kaplan-Meier plot of the implant survival in patients with non-irradiated FFF who do not smoke tobacco (blue plot), irradiated FFF who do not smoke tobacco (green), non-irradiated FFF who smoke tobacco (yellow) and irradiated FFF who use tobacco (purple).
Abbreviations: FFF, free fibula flap.

Table 5.2 Surgical and implant data of 202 osseointegrated dental implants placed in oncological head and neck patients reconstructed with an FFF. Data are numbers (%) unless stated otherwise.

Variable	Irradiated FFF	Non irradiated FFF			
	Primary[a]	Primary[a]	Secondary[b]	ORN[c]	Total
Total reconstructions	13	14	8	9	44
Type of mandibular defect*					
Class 1	4	1	-	1	6
Class 2	2	5	1	2	10
Class 3	6	8	2	6	22
Type of maxillary defect †					
II b			1		1
II c			2		2
III b			1		1
III d	1				1
IV c			1		1
Segmentations of the FFF (range)	1.85 (0-5)	1.50 (0-3)	1.50 (1-2)	1.56 (0-2)	1.64 (0-5)
Total implants (n)	58	57	42	45	202
Mean implants per patient (range)	4.8 (2-8)	3.8 (2-8)	5.25 (3-8)	5.0 (4-10)	4.7 (2-10)
HBO therapy					
Pre-operative	58 (100)	-	-	-	58 (28.7)
Postoperative	50 (86.2)	-	-	-	50 (24.8)

Table 5.2 (continued)

Variable	Irradiated FFF	Non irradiated FFF			
	Primary[a]	Primary[a]	Secondary[b]	ORN[c]	Total
Implant location					
FFF	47 (81.0)	48 (84.2)	35 (83.3)	31 (68.9)	161 (79.7)
Native maxilla	3 (5.2)	8 (14.0)	5 (11.9)	10 (22.2)	26 (12.9)
Native mandible	8 (13.8)	1 (1.8)	2 (4.8)	4 (8.9)	15 (7.4)
Implant length					
8mm	4 (6.9)	5 (8.8)	13 (31.0)	-	22 (10.9)
10mm	27 (46.6)	12 (21.1)	11 (26.2)	14 (31.1)	64 (31.7)
12mm	27 (46.6)	40 (70.2)	18 (42.9)	31 (68.9)	116 (57.4)
Implant diameter					
3.3mm	1 (1.7)	4 (7.0)	3 (7.1)	10 (22.2)	18 (8.9)
4.1mm	57 (98.3)	53 (93.0)	39 (92.9)	35 (77.8)	184 (91.1)
Implant operating time (min ±SD)	126.4 ±47.0	109.0 ±19.2	110.8 ±36.8	103.7 ±57.0	112.8 ±38.5
Implant hospital stay (days ±SD)	2.85 ±3.1	2.43 ±0.8	2.13 ±0.4	2.11 ±0.6	2.4 ±1.8
Keratinized mucosal graft	6 (46.2)	13 (92.9)	8 (100)	8 (88.9)	35 (79.5)
KMG operating time (min ±SD)	71.8 ±19.3	68.1 ±18.1	98.8 ±32.2	71.8 ±19.3	77.0 ±23.3
KMG hospital stay (days ±SD)	1.8 ±0.4	2.2 ±0.9	2.1 ±0.4	2.0 ±0.8	2.1 ±0.7

Abbreviations: FFF, free fibula flap; HBO, hyperbaric oxygen; KMG, keratinized mucosal graft; SD, standard deviation.

* Type of mandibular defect according to Brown et al (2016).

† Type of maxillary defect according to Brown et al (2010).

[a] tumour resection and immediate FFF reconstruction.

[b] tumour resection and delayed FFF reconstruction.

[c] resection for ORN and immediate FFF reconstruction.

Table 5.3 Post-implantation complications after 44 FFF reconstructions in head and neck cancer patients Data are numbers of patients.

Complications	Irradiated FFFs	Non-irradiated FFFs	Total
Surgical			
Wound breakdown		1	1
Wound dehiscence	6	3	9
Wound infection	1	1	2
Bleeding	1		1
Fistula	3	1	4
Exposed/infected bone	1	1	2
Exposed/infected OSM	2		2
Necrosis of the bony graft	5		5
Facial nerve paralysis		1	1
Peri-implant abscess		1	1
Peri-implantitis		5	5
Implant failure	7	4	11
Non-union fracture	2	1	3
Total local	28[a]	19[b]	47[a,b]
Systemic			
Respiratory failure	1[a]		1

Abbreviations: FFF, free fibula flap.

[a] one patient had one systemic complication, one patients had one surgical complication, five patients had three surgical complications, three patients had four surgical complications.

[b] six patients had one surgical complications, five patients had two surgical complications, one patients had three surgical complications.

Univariate analysis showed significant associations between dental implant failure in the FFFs and tobacco use (OR, 5.67; CI, 1.24-25.88; *p*=0.03); irradiated FFFs (OR, 10.33; CI, 2.23-47.85; *p*=0.00); T-classification >2 (OR, 10.09; CI, 1.26-80.72; *p*=0.03), and HBO (OR, 10.33; CI, 2.23-47.85; *p*=0.00). Variables including age, gender, alcohol use, dental status, bony defect classification, amount of segmentation, implant length, and the use of keratinized tissue grafts did not significantly influence the implant failure rate.

Table 5.4 Cohort life table analysis of 161 osseointegrated dental implants placed in head and neck cancer patients reconstructed with a FFF. Data are given in percentage.

Interval in years	*****	**0-1**	**1-2**	**2-3**	**3-4**	**4-5**	**> 5**
Primary-FFF[a] irradiated							
Total implants at interval	47	26	23	21	21	21	17
Failure within period	38.3	11.5	-	-	-	-	-
Function loss within period		3.8	-	-	-	-	5.9
Cumulative survival rate	61.7	55.3	55.3	55.3	55.3	55.3	55.3
Cumulative function rate	51.1	42.6	42.6	42.6	42.6	42.6	40.4
Cumulative success rate		42.6	42.6	42.6	42.6	42.6	40.4
Primary-FFF[a] non-irradiated							
Total implants at interval	48	43	39	37	28	22	21
Failure within period		-	-	13.5	-	-	4.8
Function loss within period		25.6	-	-	-	-	-
Cumulative survival rate	100	100	100	89.6	89.6	89.6	87.5
Cumulative function rate	89.6	66.7	66.7	58.3	58.3	58.3	56.2
Cumulative success rate		66.7	66.7	58.3	58.3	58.3	50.0
Secondary-FFF[b]							
Total implants at interval	35	35	34	12	10	6	6
Failure within period		2.9	2.9	-	-	-	-
Function loss within period		17.1	5.9	-	-	-	-
Cumulative survival rate	100	97.1	94.3	94.3	94.3	94.3	94.3
Cumulative function rate	88.6	68.6	62.9	62.9	62.9	62.9	62.9
Cumulative success rate		65.7	60.0	60.0	60.0	57.1	57.1
ORN-FFF[c]							
Total implants at interval	31	31	27	19	15	15	15
Failure within period		-	-	-	-	-	-
Function loss within period		-	18.5	-	-	-	-
Cumulative survival rate	100	100	100	100	100	100	100
Cumulative function rate	100	100	83.9	83.9	83.9	83.9	83.9
Cumulative success rate		100	83.9	83.9	83.9	83.9	83.9
Total population							
Total implants at interval	161	135	123	89	74	64	59
Failure within period	11.2	3.0	0.8	5.6	-	-	1.7
Function loss within period		11.2	5.7	-	-	-	-
Cumulative survival rate	88.8	86.3	85.7	82.6	82.6	82.6	82.0
Cumulative function rate	80.1	66.5	62.1	59.6	59.6	59.6	58.4
Cumulative success rate		65.8	61.5	59.0	59.0	58.4	55.3

Abbreviations: FFF, free fibula flap; ORN, osteoradionecrosis.

* Time from dental implantation to loading.

[a] tumour ablation and immediate FFF reconstruction.

[b] tumour ablation and delayed FFF reconstruction.

[c] resection for ORN and immediate FFF reconstruction.

A life table analysis of the cumulative survival, function, and success of the dental implants placed in FFFs is shown in Table 5.4. At the end of follow-up, 55.3% were successful. Implant success was 40.4% for implants placed in irradiated FFFs and 61.4% for implants placed in non-irradiated FFFs. Seventy-two dental implants did not fulfill the success criteria as a result of: non-functional implants (38/72), peri-implant lucency/necrosis of the FFF (19/72), >0.2 mm peri-implant bone loss annually (10/72), and implant mobility/failed osseointegration (1/72). Four implants were resected for tumour recurrence and were scored as unsuccessful. Non-function of implants was caused by inadequate position (n=16), poor oral function/patient request (n=14), recurrent disease (n=5), and oral pain (n=3).

Thirty-seven of 44 implant-based dental rehabilitations were successfully completed. The mean duration from dental implantation to superstructure placement was 36.1 weeks. The superstructures were placed at a mean of 94.3 weeks after FFF reconstruction. Reasons for not completing the rehabilitation were necrosis of the bony graft (n=4) and tumour recurrence (n=3). All patients with secondary FFFs and ORN FFFs received dental superstructures, compared with 20/27 of the patients with primary FFFs (p=0.07). Patients with non-irradiated FFFs (30/31) were more likely to complete the dental rehabilitation than patients with irradiated FFFs (7/13) (p=0.00).

Function was restored using implant-supported bar-retained removable full dentures (n=23), implant-supported locator-retained full dentures (n=8), screw-retained bridges (n=2), screw-retained crowns (n=1), and implant-supported bar-retained partial dentures (n=3). No significant differences were found with regard to prosthesis design between the three FFF subgroups (p=0.58), patients with or without irradiated FFFs (p=1.00), and mandibular or maxillary reconstruction (p=0.42).

Twenty-nine of 37 patients who received a prosthetic construction achieved functional dental rehabilitation during follow-up. Eight superstructures failed: four patients experienced poor oral function; one patient had chronic oral pain; one lost the bony graft; one had recurrent cancer; and one had unfavourable maxillomandibular relation. Functional rehabilitation was achieved in 6/13 of the patients with irradiated FFFs and in 23/31 of the patients with non-irradiated FFFs (p=0.07).

In Figure 5.5 the mean BMI is plotted at different timepoints for patients who achieved functional dental rehabilitation and for those who did not. Of the 44 patients who had undergone dental implantation, 29 patients had a mean weight loss from reconstructive surgery up to dental implantation of 3.3 kg (±6.5). For patients who did not achieve functional dental rehabilitation (n=15) the mean BMI was 25.2 kg/m^2 at the

time of FFF reconstruction and 23.6 kg/m^2 more than 6 months after dental implantation, which was significantly lower (p=0.04). For patients who achieved functional dental rehabilitation (n=29) the mean BMI was 24.6 kg/m^2 at the time of FFF reconstruction and 23.9 kg/m^2 after placing the fixed or removable prosthetic construction, suggesting a regain of their initial weight (p=0.12).

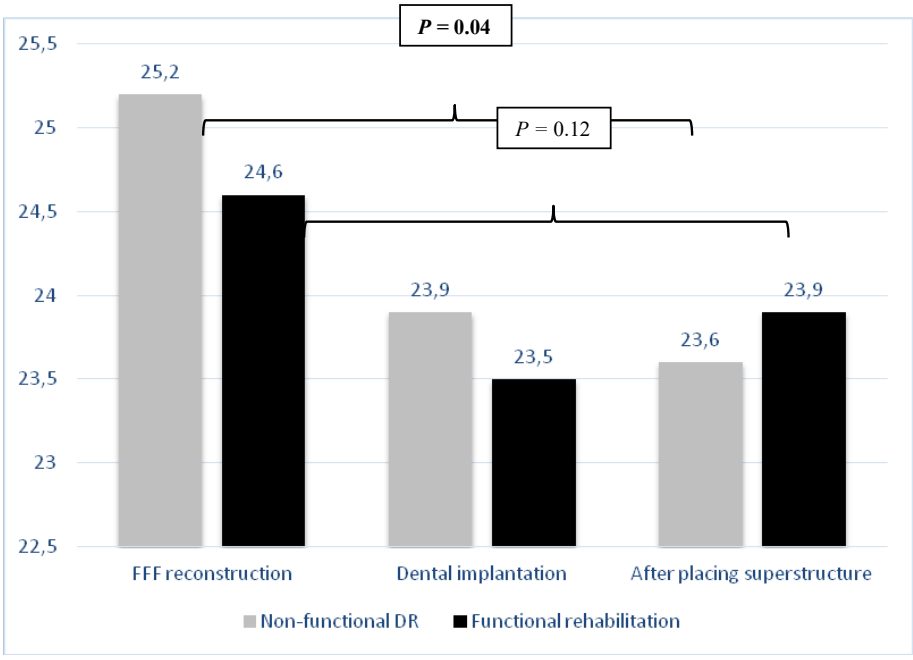

Figure 5.5 Diagram of mean BMI in kg/m^2 at different timepoints for head and neck cancer patients who achieved functional dental rehabilitation after FFF reconstruction (N=26/29) and those who did not achieve functional dental rehabilitation (N=12/15).
Abbreviations: BMI, body-mass index; FFF, free fibula flap; DR, dental rehabilitation.

Discussion

In this long-term retrospective study we present a well-defined cohort of head and neck cancer patients who had undergone implant-based dental rehabilitation after maxillofacial reconstruction with FFFs. Functional implant-based dental rehabilitation was achieved in 24.7% of the reconstructed patients, which is fairly consistent with the literature. Similar findings were reported in a series of 28 reconstructed oncological patients.[8] Following the authors' combined surgical and prosthodontic protocol, 21% of the reconstructed patients achieved functional dental rehabilitation. A similar approach

has been shown to result in functioning superstructures in 42.9% of cases.[10] Two other studies completed dental rehabilitations in 28.6% and 32.6% of patients who had undergone maxillofacial reconstruction with FFF.[9,23] To what extend oral function was restored in these patients was not reported in these studies.

Although the differences in successful rehabilitations can be explained by the surgical/prosthodontic protocol, selection bias should be acknowledged. Inevitably, the use of different selection criteria for dental rehabilitation creates heterogeneity between patient groups.[8-10,23] This made it difficult to compare our results adequately.

The literature provides several reasons for failure of dental rehabilitation, including microstomia, unfavourable maxillomandibular relations, and dental implant failure.[10] The most common reasons in our series for not completing dental rehabilitation were necrosis of the bony graft after dental implantation (57%), followed by recurrent cancer (43%). In total, 11.3% of the 44 FFF reconstructions were lost after dental implantation. Jacobsen et al. described one patient who had lost the bony graft in a series of 23 patients with jaw reconstruction and dental implantation.[12] Smolka et al. reported partial necrosis of the FFF in 20% of the patients with dental implants.[10] Ch'ng et al. described 54 patients, 7.4% of whom had necrosis of the FFF.[3] This devastating outcome has been experienced by only a handful of authors. Unfortunately, there is little information available on the incidence and pathophysiology of FFF necrosis after radiation therapy. During our study, all five bony reconstructions with necrosis were debrided. Four patients underwent revision of the reconstruction with a second FFF.

To prevent necrosis of the FFF in these series, all patients with irradiated FFFs received prophylactic HBO. This made it impossible to analyse the effect of HBO on dental implant loss. Evidence for the prophylactic effect of HBO in irradiated patients receiving dental implants is controversial.[24] Nevertheless, in our institution perioperative HBO is advocated in patients with a history of irradiation of the FFF reconstruction, in particular when the local dose in the dental implant region was 50 Gy or more. The reason for this is not only because FFF necrosis is associated with high morbidity, but also because there is some evidence that it improves healing in irradiated head and neck patients.[25]

An interesting question is whether the placement of dental implants in irradiated FFF reconstructions increases the risk of FFF necrosis.[6] In our irradiated group without dental implants, 23.4% of the reconstructions (15/64) developed full or partial necrosis of the FFF, as did 38.5% of the reconstructions (5/13) in our irradiated group with dental implants. Although our numbers were too small to draw firm conclusions, the

incidence of FFF necrosis in patients seemed to be higher in those who received dental implants. Even so, our results lay within the reported range of other studies[3,10,12] and within the range of ORN in native jaws (0.4-56%).[26]

Identifying functional dental rehabilitation is difficult because an implant-supported prosthetic construction may serve different purposes in head and neck cancer patients for example, cosmetic and/or functional. In our experience, there are reconstructed patients who still cannot masticate properly after completing implant-based dental rehabilitation. On the other hand, these patients are satisfied with their prosthetic device because it fulfills a clear cosmetic function when participating in society.

To the authors' knowledge there are no widely accepted success criteria for functional dental rehabilitation in reconstructed head and neck cancer patients. We evaluated functional dental rehabilitation with criteria that could be retrospectively assessed. Of the 37 patients who completed dental rehabilitation in our study, 29 achieved functional dental rehabilitation according to our criteria. Interestingly, functional dental rehabilitation was achieved by only 46.2% of those with irradiated FFFs and by 79.3% of patients with non-irradiated FFFs. These differences can be explained by the high rate of dental implant failure in irradiated FFFs. Although other studies have associated irradiated FFFs with implant failure[3,12,13] the negative effects on prosthetic rehabilitation have not been previously reported.

The majority of patients in this cohort lost weight after FFF reconstruction. However, patients who achieved functional dental rehabilitation gained weight after placement of the prosthetic construction. In contrast, patients who did not achieve functional dental rehabilitation seemed to lose more weight after dental implantation. Although our study was prone to selection bias, this trend may be explained by improved masticatory performance after functional dental rehabilitation. Attia et al. reported that over 70% of patients who underwent dental implantation after FFF reconstruction could consume a normal diet.[16] To further elucidate this topic, future studies should focus on objective measurements of masticatory performance[27-29] and validated patient-reported outcome measurements.[30]

Four of the eight patients who failed to achieve functional rehabilitation were unable to wear the implant-supported dentures, and reported dysfunction. Despite an attempt to improve function with altered prosthetic design, all patients requested the removal of their superstructures. One study described a patient with poor oral function in a non-reconstructed oncological cohort and emphasized the need for case selection and a multidisciplinary approach.[6] While we comprehensively assessed all patients who

started implant-based rehabilitation in a multidisciplinary team, the number of superstructures that failed (8/37) cannot be overlooked. We could not identify key reasons why patients failed to achieve function rehabilitation. Moreover, most reasons became apparent only after placement of the superstructures and could not have been anticipated at the time of dental implantation. An explanation could be that functional dental rehabilitation does not only need a technically well-fabricated superstructure, but also requires adequate oral motoric and sensory functions, which are often disturbed in reconstructed head and neck cancer patients.

Our overall implant survival in FFFs of 82.0% after 10 years was similar to those reported in other studies.[7,13,15] However, due to the heterogeneity of the study populations and, more importantly, differences in follow-up time, most studies should be compared with caution. The most robust evidence to date reported a 5-year survival rate of 92.6% in FFFs.[3] Interestingly, this number was followed 1 year later by a survival rate of approximately 40%. This increase in implant failure over time has also been reported by others authors, ranging from 16.9% to 20.7% after 10 years.[7,13,15] The authors did not report or speculate on the etiology of these late implant failures.

Late implant failures are most likely caused by soft tissue problems and subsequent peri-implant bone loss. In our series, only minimal implant loss was seen after 5 years. This could be explained by our recall system and strict oral hygiene regime. To identify peri-implant pathology at an early stage and take action to prevent irreversible damage, all patients were clinically and radiographically evaluated annually by an oral and maxillofacial surgeon, and a dental hygienist. In addition, the soft tissue management around the dental implants, as previously described, may explain a better clinical performance of the implants. If necessary, during the retrieval of the dental implants and vestibuloplasty, the overlying skin island of the FFF was replaced by keratinized mucosa from the hard palate, resulting in a better peri-implant soft tissue condition.

Studies on implant success in patients who had undergone jaw reconstruction are rare. Pellegrino et al. investigated 21 patients with reconstructed mandibles.[15] According to Albrektsson's criteria, 64.7% of the dental implants were successful after 10 years. After a mean follow-up of 50.2 months, 93.1% of the implants in a prospective series of 16 patients were successful.[9] Our implant success rate for FFFs was lower: 58.4% after 5 years and 55.3% after 10 years. If loading of the implant was not a prerequisite for implant success, our numbers would be higher after 10 years (78.9%). Challenging factors in these series, such as a high percentage of stage IV disease, extensive bone

defects, and a high number of irradiated patients, could explain why almost a quarter of the dental implants were not functional.

Osseointegration of dental implants is seen in irradiated native and grafted bone. If the FFF had been irradiated, there was a significant increase in implant failures in the FFF (OR, 10.3). Other studies have analysed implant failure in irradiated FFFs[3,11-15,18] and some of these published similar results.[3,12,13] An interesting finding in our study was the extremely high implant failure rate (100%) in patients with irradiated FFFs who smoked during the time of dental implantation. In total, 12 implants failed in three patients because of FFF necrosis.

The overwhelming majority of studies, including ours, have been retrospective in nature, with small sample sizes. Although we tried to eliminate as many confounders as possible, there were large differences in tumour location, disease staging, bone defects, and dental status. These limitations should be acknowledged when interpreting the results, and emphasize the need for prospective studies.

Conclusion

Functional implant-based dental rehabilitation, if started, can be achieved in the majority of head and neck cancer patients after FFF reconstruction. Actively smoking patients with an irradiated FFF should be clearly informed about the increased risk for implant and prosthetic treatment failure.

References

1. Brown JS, Barry C, Ho M, Shaw R. A new classification for mandibular defects after oncological resection. Lancet Oncol. 2016;17(1):e23-30.
2. Urken ML, Roche AM, Kiplagat KJ, Dewey EH, Lazarus C, Likhterov I, et al. Comprehensive approach to functional palatomaxillary reconstruction using regional and free tissue transfer: Report of reconstructive and prosthodontic outcomes of 140 patients. Head Neck. 2018;40(8):1639-66.
3. Ch'ng S, Skoracki RJ, Selber JC, Yu P, Martin JW, Hofstede TM, et al. Osseointegrated implant-based dental rehabilitation in head and neck reconstruction patients. Head Neck. 2016;38 Suppl 1:E321-7.
4. Kumar VV, Ebenezer S, Kammerer PW, Jacob PC, Kuriakose MA, Hedne N, et al. Implants in free fibula flap supporting dental rehabilitation - Implant and peri-implant related outcomes of a randomized clinical trial. J Craniomaxillofac Surg. 2016;44(11):1849-58.
5. Urken ML, Buchbinder D, Weinberg H, Vickery C, Sheiner A, Parker R, et al. Functional evaluation following microvascular oromandibular reconstruction of the oral cancer patient: a comparative study of reconstructed and nonreconstructed patients. Laryngoscope. 1991;101(9):935-50.
6. Shaw RJ, Sutton AF, Cawood JI, Howell RA, Lowe D, Brown JS, et al. Oral rehabilitation after treatment for head and neck malignancy. Head Neck. 2005;27(6):459-70.
7. Teoh KH, Huryn JM, Patel S, Halpern J, Tunick S, Wong HB, et al. Implant prosthodontic rehabilitation of fibula free-flap reconstructed mandibles: a Memorial Sloan-Kettering Cancer Center review of prognostic factors and implant outcomes. Int J Oral Maxillofac Implants. 2005;20(5):738-46.
8. Iizuka T, Hafliger J, Seto I, Rahal A, Mericske-Stern R, Smolka K. Oral rehabilitation after mandibular reconstruction using an osteocutaneous fibula free flap with endosseous implants. Factors affecting the functional outcome in patients with oral cancer. Clin Oral Implants Res. 2005;16(1):69-79.
9. Chiapasco M, Biglioli F, Autelitano L, Romeo E, Brusati R. Clinical outcome of dental implants placed in fibula-free flaps used for the reconstruction of maxillo-mandibular defects following ablation for tumors or osteoradionecrosis. Clin Oral Implants Res. 2006;17(2):220-8.
10. Smolka K, Kraehenbuehl M, Eggensperger N, Hallermann W, Thoren H, Iizuka T, et al. Fibula free flap reconstruction of the mandible in cancer patients: evaluation of a combined surgical and prosthodontic treatment concept. Oral Oncol. 2008;44(6):571-81.
11. Salinas TJ, Desa VP, Katsnelson A, Miloro M. Clinical evaluation of implants in radiated fibula flaps. J Oral Maxillofac Surg. 2010;68(3):524-9.
12. Jacobsen C, Kruse A, Lubbers HT, Zwahlen R, Studer S, Zemann W, et al. Is mandibular reconstruction using vascularized fibula flaps and dental implants a reasonable treatment? Clin Implant Dent Relat Res. 2014;16(3):419-28.
13. Fang W, Liu YP, Ma Q, Liu BL, Zhao Y. Long-term results of mandibular reconstruction of continuity defects with fibula free flap and implant-borne dental rehabilitation. Int J Oral Maxillofac Implants. 2015;30(1):169-78.
14. Hakim SG, Kimmerle H, Trenkle T, Sieg P, Jacobsen HC. Masticatory rehabilitation following upper and lower jaw reconstruction using vascularised free fibula flap and enossal implants-19 years of experience with a comprehensive concept. Clin Oral Investig. 2015;19(2):525-34.
15. Pellegrino G, Tarsitano A, Ferri A, Corinaldesi G, Bianchi A, Marchetti C. Long-term results of osseointegrated implant-based dental rehabilitation in oncology patients reconstructed with a fibula free flap. Clin Implant Dent Relat Res. 2018;20(5):852-9.
16. Attia S, Wiltfang J, Streckbein P, Wilbrand JF, El Khassawna T, Mausbach K, et al. Functional and aesthetic treatment outcomes after immediate jaw reconstruction using a fibula flap and dental implants. J Craniomaxillofac Surg. 2019;47(5):786-91.
17. Shugaa-Addin B, Al-Shamiri HM, Al-Maweri S, Tarakji B. The effect of radiotherapy on survival of dental implants in head and neck cancer patients. J Clin Exp Dent. 2016;8(2):e194-200.
18. Awad ME, Altman A, Elrefai R, Shipman P, Looney S, Elsalanty M. The use of vascularized fibula flap in mandibular reconstruction; A comprehensive systematic review and meta-analysis of the observational studies. J Craniomaxillofac Surg. 2019;47(4):629-41.
19. Attia S, Wiltfang J, Pons-Kuhnemann J, Wilbrand JF, Streckbein P, Kahling C, et al. Survival of dental implants placed in vascularised fibula free flaps after jaw reconstruction. J Craniomaxillofac Surg. 2018;46(8):1205-10.

20. Brown JS, Shaw RJ. Reconstruction of the maxilla and midface: introducing a new classification. Lancet Oncol. 2010;11(10):1001-8.
21. Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: a review and proposed criteria of success. Int J Oral Maxillofac Implants. 1986;1(1):11-25.
22. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. J Am Dent Assoc. 1985;111(1):49-54.
23. Garrett N, Roumanas ED, Blackwell KE, Freymiller E, Abemayor E, Wong WK, et al. Efficacy of conventional and implant-supported mandibular resection prostheses: study overview and treatment outcomes. J Prosthet Dent. 2006;96(1):13-24.
24. Esposito M, Grusovin MG, Patel S, Worthington HV, Coulthard P. Interventions for replacing missing teeth: hyperbaric oxygen therapy for irradiated patients who require dental implants. Cochrane Database Syst Rev. 2008(1):CD003603.
25. Bennett MH, Feldmeier J, Hampson NB, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst Rev. 2016;4(4):CD005005.
26. Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. Int Dent J. 2018;68(1):22-30.
27. Speksnijder CM, Abbink JH, van der Glas HW, Janssen NG, van der Bilt A. Mixing ability test compared with a comminution test in persons with normal and compromised masticatory performance. Eur J Oral Sci. 2009;117(5):580-6.
28. Kumar VV, Srinivasan M. Masticatory efficiency of implant-supported removable partial dental prostheses in patients with free fibula flap reconstructed mandibles: A split-mouth, observational study. Clin Oral Implants Res. 2018;29(8):855-63.
29. de Groot RJ, Rosenberg A, van der Bilt A, Aalto D, Merkx MAW, Speksnijder CM. The association between a mixing ability test and patient reported chewing ability in patients treated for oral malignancies. J Oral Rehabil. 2019;46(2):140-50.
30. Kumar VV, Jacob PC, Ebenezer S, Kuriakose MA, Kekatpure V, Baliarsing AS, et al. Implant supported dental rehabilitation following segmental mandibular reconstruction- quality of life outcomes of a prospective randomized trial. J Craniomaxillofac Surg. 2016;44(7):800-10.

Chapter 6

Implant-based dental rehabilitation in head and neck cancer patients after maxillofacial reconstruction with a free vascularized fibula flap: the effect on health related quality of life

J.N. Lodders
G.J.C. van Baar
M.R. Vergeer
F. Jansen
E.A.J.M. Schulten
B. I. Lissenberg-Witte
I.M. Verdonck-de Leeuw
T. Forouzanfar
F.K.J. Leusink

This chapter is based on the publication in:

Support Care Cancer. 2022 Jun;30(6):5411-5420

Introduction

Surgical treatment of oral cavity tumours may lead to complex segmental mandibular or maxillary defects[1,2] resulting in functional impairment with regard to mastication, speech and swallowing. The vascularised fibula free flap (FFF) has become the standard of care for reconstruction of mandibular defects[1,3], and is also the preferred flap for reconstruction of maxillary defects.[4]

Maxillofacial reconstruction with an FFF after ablative oncological surgery optimizes function and aesthetics, with acceptable results regarding flap survival, donor site morbidity and perioperative complications.[5,6] However, patients who have undergone FFF reconstruction expect restoration of oral function close to their pre-surgical state.[7] To fulfill this wish, implant-based dental rehabilitation (IDR) can contribute to improve functional and aesthetic outcomes[8], and may become a standard part of the total rehabilitation plan.[9]

In the literature it is shown that, although a minority of head and neck cancer (HNC) patients commence IDR after FFF reconstruction[10,11], good results can be achieved regarding dental implant survival, dental implant success and percentage of functional prosthetic rehabilitations.[8,10,11] However, evidence on the effect of IDR on health related quality of life (HRQoL) in this patient group is limited.[8] Four studies showed minor improvements in HRQoL using validated questionnaires in patients who underwent IDR after FFF reconstruction.[12-15] One prospective trial reported a clear benefit of IDR on HRQoL with validated questionnaires.[16] Limitations of these studies were the lack of a control group[13,16] and that HRQoL was measured at one timepoint.[12,14] In addition, most studies on HRQoL included benign pathology.[12-14,16]

Therefore, the purpose of this study was to evaluate the effect of IDR on HRQoL in HNC patients after FFF reconstruction, measured at different timepoints and using a control group.

Materials and methods

Study design and study population

In this retrospective cohort study, two databases were searched to identify patients eligible for the study: a clinical database of the Department of Oral and Maxillofacial Surgery/Oral Pathology, Amsterdam UMC - VU Medical Center (VUmc) in Amsterdam,

The Netherlands, and a database with patient-reported outcome measures (OncoQuest) of the Department of Otolaryngology – Head and Neck Surgery and the Department of Radiation Oncology of Amsterdam UMC - VUmc, Amsterdam, The Netherlands. OncoQuest comprises patient-reported outcomes measures (PROMs) that are gathered as part of routine patient care before the start of oncological treatment and during follow-up visits via a touch screen computer.[17]

Patients were included in this study if they were (1) diagnosed with HNC; (2) had undergone maxillofacial reconstruction with an FFF between January 2006 to October 2017; (3) aged 18 years or older; and 4) data regarding HRQOL was available, of which (5) the patient provided informed consent to use these data for research purposes. Patients with benign diseases and free flaps other than FFF were excluded from this study.

All included patients were allocated in two groups: a) FFF reconstruction without implant-based dental rehabilitation (without IDR) and b) FFF reconstruction followed by implant-based dental rehabilitation (IDR).

To qualify for IDR, patients needed to have unsatisfactory oral function and/or aesthetics that could be improved with dental rehabilitation, and to have been free of disease or recurrence for at least 12 months after completion of all adjuvant therapy.

Demographic and clinical variables

Demographic and clinical characteristics such as age, gender, tobacco and alcohol use, ASA classification, radiotherapy data (with or without concurrent chemotherapy), dental status, number of FFF segmentations, type of mandibular defect[1] and type of maxillary defect[2] were collected from the medical information system. Disease stage and tumour entity were gathered as histopathological data. The amount of dental implants and information regarding the dental superstructures were assessed.

HRQoL measurements

HRQoL was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30)[18] and the module specifically designed for HNC patients (EORTC QLQ-H&N 35).[19]

The EORTC QLQ-C30 contains one global QoL scale, five functional scales, three symptom scales and six single items. The EORTC QLQ-H&N 35 module contains seven symptom scales and 11 single items. A higher score for global QoL scale and functional

scales reflects a better level of functioning. A higher score for symptom scales reflects a higher level of symptoms. All scales and single items are converted to a score from 0 to 100.

Statistical analysis

The SPSS Software package (version 20.0 IBM, Armonk, NY, USA) was used for statistical analysis.

To identify differences in demographic parameters between the defined groups, Independent *t*-test and chi-square test were used. If the expected counts were less than five, Fishers' exact test was used.

Two timepoints were defined, T_0: HRQoL data for the period from six months before FFF reconstruction until the FFF reconstruction, and T_1: HRQoL data in the period after completing IDR (i.e. after placement of the dental superstructure). For patients who did not undergo IDR T_1 was defined as the period after FFF reconstruction. If HRQoL data was available for multiple timepoints after T_1, HRQoL data closest to two years after completing oncological treatment was used. This specific timepoint was used as T_1 because global QoL seems to gradually improve until one year after finishing oncological treatment in HNC patients.[20]

For cross-sectional analysis at T_0, Chi-square test was used for dichotomous variables and Independent samples T-test for continuous variables.

Longitudinal Linear Mixed models (LMM) were used for within-subject analysis to analyse the course of HRQoL in patients who had undergone IDR after FFF reconstruction versus those who did not, as well as to analyse differences in the course of HRQoL between these patients. The within-subject model included a fixed effect for time and a random effect for subject, and the between-subject model additionally included a fixed effect for group and the interaction between time and group.

Results

Out of 96 patients who had undergone maxillofacial FFF reconstruction between January 2006 to October 2017, 84 patients had HRQoL data, of which 57 patients at both T_0 and T_1. These 57 patients were included in this study, of which 18 patients had undergone IDR after FFF reconstruction and 39 did not (Figure 6.1).

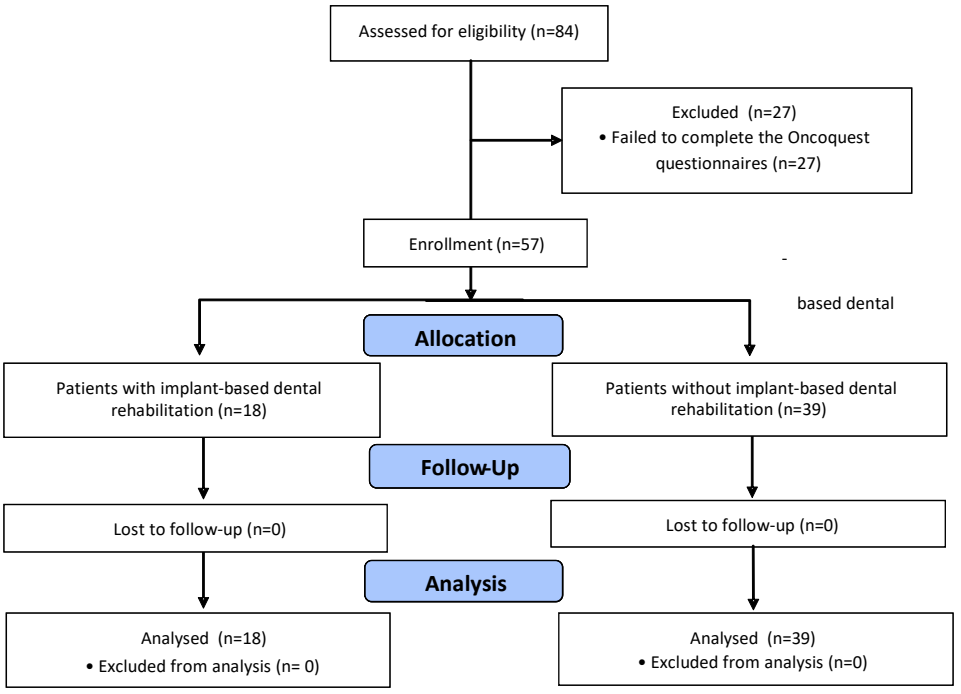

Figure 6.1 Flow diagram of the included head and neck cancer patients who had undergone maxillofacial reconstruction with a fibula free flap between January 2006 and October 2017.

In Table 6.1 the demographic and clinical characteristics of the included patients are shown. Significantly more patients in the IDR group (16/18) were edentulous in the reconstructed jaw, compared to the group without IDR (23/39; $p<0.01$). Significantly more maxillary reconstructions were located in the group with IDR (4/18), compared to the group without IDR ($p=0.03$).

Among the 18 patients who received IDR, in total 55 dental implants were placed in the FFFs, with an average of 4.6 dental implants per patient (range: 3-7). Most patients (n=17) received a removable prosthetic construction (bar-retained, n=12; locator-retained, n=4) and achieved a functional dental rehabilitation. One patient received a fixed prosthesis (solitary crowns, n=1). Data regarding the dental implantation procedure and rehabilitation timeline have been previously published.[11]

Table 6.1 Demographic, clinical characteristics and histopathological profile of the included patients at the time of maxillofacial reconstruction with a free vascularized fibula flap (data are percentages unless stated otherwise).

	Without IDR	With IDR	Total	*P*-value
Number of patients	39	18	57	
Age (years ±SD)	63.2 ±9.9	61.9 ±11.8	62.8 ±10.4	*0.67*
Gender				
Male	23	11	34	*1.00*
Female	16	7	23	
Tobacco				
Never	10	5	15	*0.40*
Active	21	7	28	
Prior	8	6	14	
Alcohol				
Never	13	6	19	*1.00*
Active	23	10	33	
Prior	3	2	5	
ASA				
II	31	13	44	*0.74*
III	8	5	13	
Radiotherapy				
No	3	5	8	*0.18*
Pre-operative	5	6	11	
Post-operative	29	7	36	
Both	2	0	2	
Radiation dose (cGy ±SD)	6381.4 ±461.1	6162.5 ±562.9	6325.5 ±492.2	*0.19*
Reconstructed jaw				
Mandible	39	14	53	***<0.01***
Maxilla	0	4	4	
Post-operative dental state				
Reconstructed jaw				
Edentulous	23	16	39	***0.03***
(Partial) dentate	16	2	18	
Opposing jaw				
Edentulous	21	11	32	*0.78*
(Partial) dentate	18	7	25	
Number of osteotomy (min-max)	1.5 (0-3)	1.8 (1-3)	1.6 (0-3)	*0.08*
Type of mandibular defect*				
Class I	10	1	11	-
Class II	11	4	15	
Class III	14	9	23	
Class IV	4	0	4	
Type of maxillary defect †				
IIc		1	1	-
IIIb		1	1	
IIId		1	1	
IVc		1	1	
Disease stage				
I / II	6	2	8	*1.00*
III/IV	33	15	48	
Cancer type				
Squamous cell carcinoma	39	17	56	*0.32*
Sarcoma	0	1	1	

Abbreviations: IDR, implant-based dental rehabilitation. Note: for statistical analysis radiotherapy was dichotomized to radiotherapy and no radiotherapy, tobacco and alcohol use was dichotomized to yes and no. For one patient the disease stage could not be found. * Type of mandibular defect according to Brown et al. (2016) (1); † Type of maxillary defect according to Brown et al. (2010) (2)

In Table 6.2 results on the EORTC QLQ-C30 scales are summarized per time assessment. The scales emotional functioning (*p=0.01*), cognitive functioning (*p=0.01*) and diarrhoea (*p=0.01*) were significantly better at T_0 for patients in the group with IDR, compared to the group without IDR. In Table 6.3 results on the EORTC QLQ-H&N35 scales are summarized per time assessment. Pain killers were less frequently used at T_0 for patients in the group with IDR, compared to the group without IDR (*p=0.04*).

Table 6.2 Within-subject analysis, cross-sectional analysis at T_0 and comparison of the mean changes in EORTC QLQ-C30 scales for patients who had undergone implant-based dental rehabilitation after FFF reconstruction and those who did not at T_0 and T_1.

		Without IDR (n=39) Mean ±SD	**Within-subject *P*-value**	**With IDR (n=18) Mean ±SD**	**Within-subject *P*-value**	**Cross-sectional analysis *P*-value**	**Between-subject *P*-value**
Global health status[a]	T_0	58.0 ±21.2	0.6	64.3 ± 25.8	0.71	0.42	0.99
	T_1	61.5 ±26.8		67.9 ± 25.0			
Functional scales[a]							
Physical functioning	T_0	76.0 ±23.4	0.5	85.7 ±22.5	0.77	0.25	0.82
	T_1	71.3 ±25.6		83.6 ±12.7			
Role Functioning	T_0	58.0 ±23.5	0.83	69.0 ±35.1	0.16	0.4	0.41
	T_1	60.1 ±34.8		84.6 ±15.9			
Emotional	T_0	55.0 ±27.6	**0.01**	76.8 ±21.5	0.71	**0.01**	0.20
functioning	T_1	73.7 ±26.1		80.1 ±24.4			
Cognitive	T_0	76.7 ±21.5	0.75	92.9 ±10.8	0.37	**0.01**	0.41
functioning	T_1	78.8 ±24.0		85.9 ±26.2			
Social Functioning	T_0	72.7 ±29.2	0.95	75.0 ±35.5	0.79	0.82	0.79
	T_1	72.2 ±29.1		78.2 ±28.4			
Symptom scales[b]							
Fatique	T_0	42.6 ±32.2	0.42	28.6 ±29.5	0.52	0.19	0.97
	T_1	35.8 ±30.6		22.2 ±20.3			
Nausea and	T_0	5.3 ±14.2	0.43	3.6 ±7.1	0.94	0.67	0.64
vomiting	T_1	8.6 ±16.2		3.8 ±10.0			
Pain	T_0	38.0 ±25.7	0.30	29.8 ±35.9	0.32	0.41	0.83
	T_1	29.3 ±34.9		17.9 ±23.0			
Dyspnoea	T_0	14.7 ±23.7	0.94	11.9 ±28.1	0.92	0.76	0.97
	T_1	15.2 ±23.7		12.8 ±16.9			
Insomnia	T_0	42.7 ±24.6	**0.03**	26.2 ±37.4	0.88	0.11	0.19
	T_1	25.3 ±33.4		28.2 ±32.9			
Appetite loss	T_0	25.0 ±29.9	0.93	14.3 ±31.3	0.89	0.3	0.96
	T_1	24.2 ±32.6		12.8 ±21.7			
Constipation	T_0	6.7 ±19.2	0.50	7.1 ±19.3	0.69	0.94	0.95
	T_1	10.4 ±21.5		10.3 ±21.0			
Diarrhoea	T_0	20.0 ±30.4	0.32	2.4 ±8.9	0.16	**0.01**	0.11
	T_1	12.1 ±28.6		15.4 ±32.2			
Financial difficulties	T_0	10.7 ±24.9	0.82	11.9 ±24.8	0.39	0.88	0.44
	T_1	12.1 ±23.3		5.1 ±12.5			

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; FFF, free fibula flap; SD, standard deviation; IDR, implant-based dental rehabilitation. Note: bold printing indicates $P < 0.05$. T_0 was defined as the period from 6 months before FFF reconstruction until the FFF reconstruction. T_1 was defined as the period after completing implant-based dental rehabilitation (i.e. after placement of the dental superstructure). For patients who did not undergo implant-based dental rehabilitation T_1 was defined as the period after FFF reconstruction. [a] High scores reflect better functioning; [b] High scores reflect more severe symptoms.

Table 6.3 Within-subject analysis, cross-sectional analysis at T_0 and comparison of the mean changes in EORTC QLQ-H&N35 scales for patients who had undergone implant-based dental rehabilitation after FFF reconstruction and those who did not at T_0 and T_1.

		Without IDR (n=39) Mean ±SD	Within-subject *p*-value	With IDR (n=18) Mean ±SD	Within-subject *p*-value	Cross-sectional analysis *p*-value	Between-subject *p*-value
Symptom scales[a]							
Pain	T_0	45.2 ±27.0	0.34	35.7 ±28.2	0.08	0.30	0.46
	T_1	37.6 ±31.5		18.1 ±18.7			
Swallowing	T_0	27.1 ±26.7	0.48	19.0 ±23.9	0.17	0.38	0.62
	T_1	33.7 ±32.9		32.7 ±26.2			
Senses problems	T_0	10.1 ±16.5	0.05	15.5 ±31.0	0.44	0.50	0.89
	T_1	22.0 ±25.2		25.6 ±35.8			
Speech problems	T_0	26.8 ±24.4	0.43	15.9 ±21.2	0.60	0.18	0.87
	T_1	20.4 ±21.6		20.4 ±21.6			
Trouble with social eating	T_0	42.9 ±36.7	0.68	25.0 ±28.5	0.45	0.15	0.42
	T_1	38.5 ±31.1		34.0 ±32.7			
Trouble with social	T_0	20.9 ±25.6	0.95	19.0 ±24.9	0.5	0.83	0.59
contact	T_1	21.3 ±23.9		13.3 ±15.3			
Less sexuality	T_0	43.8 ±37.9	0.95	28.8 ±33.4	0.31	0.30	0.61
	T_1	39.5 ±37.9		16.7 ±19.7			
Symptom items[a]							
Teeth	T_0	27.8 ±32.8	0.29	22.2 ±32.8	0.89	0.65	0.45
	T_1	16.7 ±34.3		24.2 ±33.6			
Opening mouth	T_0	41.7 ±34.3	0.23	31.0 ±38.0	0.48	0.37	0.91
	T_1	53.8 ±38.1		41.0 ±33.8			
Dry mouth	T_0	44.0 ±34.3	0.93	40.5 ±26.7	0.67	0.74	0.76
	T_1	44.8 ±33.5		46.2 ±39.8			
Sticky saliva	T_0	43.1 ±38.7	0.95	31.0 ±27.6	0.84	0.31	0.92
	T_1	43.8 ±40.1		33.3 ±33.3			
Coughing	T_0	34.7 ±32.6	0.47	21.4 ±28.1	0.16	0.21	0.62
	T_1	28.1 ±34.0		7.7 ±20.0			
Felt ill	T_0	25.0 ±34.4	0.81	14.3 ±25.2	0.86	0.31	0.96
	T_1	22.9 ±29.9		12.8 ±16.9			
Pain killers (%)	T_0	76.0	**0.04**	42.9	0.12	**0.04**	0.76
	T_1	50.0		15.4			
Nutritional supplements	T_0	45.8	0.14	28.6	0.33	0.29	0.89
(%)	T_1	65.6		46.2			
Feeding tube (%)	T_0	24.0	0.79	21.4	0.38	0.86	0.31
	T_1	28.1		7.7			
Weight loss (%)	T_0	54.2	**0.03**	42.9	**0.01**	0.50	0.67
	T_1	18.8		7.7			
Weight gain (%)	T_0	8.3	0.11	14.3	0.46	0.56	0.56
	T_1	25.0		23.1			

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; FFF, free fibula flap; SD, standard deviation; IDR, implant-based dental rehabilitation. Note: bold printing indicates $P < 0.05$. T_0 was defined as the period from 6 months before FFF reconstruction until the FFF reconstruction. T_1 was defined as the period after completing implant-based dental rehabilitation (i.e. after placement of the dental superstructure). For patients who did not undergo implant-based dental rehabilitation T_1 was defined as the period after FFF reconstruction. [a] High scores reflect more severe symptoms.

The results of the within-subject analysis of the EORTC QLQ-C30 and EORTC QLQ-H&N35 scales are shown in Table 6.2 and 6.3. Patients in the group with IDR showed no

significant differences between T_0 and T_1 for all scales of the EORTC QLQ-C30. In the EORTC QLQ-H&N35, weight loss was significantly less at T_1 compared to T_0 (95% Confidence Interval (CI), 0.06–0.68; *p=0.01*). Patients in the group without IDR had significant better scores at T_1 compared to T_0 for the domains emotional functioning (95% CI, 4.51 – 32.96; *p=0.01*), insomnia (95% CI, -33.3 – -1.53; *p=0.03*), pain killers (95% CI, 0.1 – 0.10; *p=0.04*) and weight loss (95% CI, 0.04 – 0.88; *p*=0.03). The course of these domains (emotional functional, insomnia, pain killers and weight loss) are plotted in Figures 6.2 and 6.3.

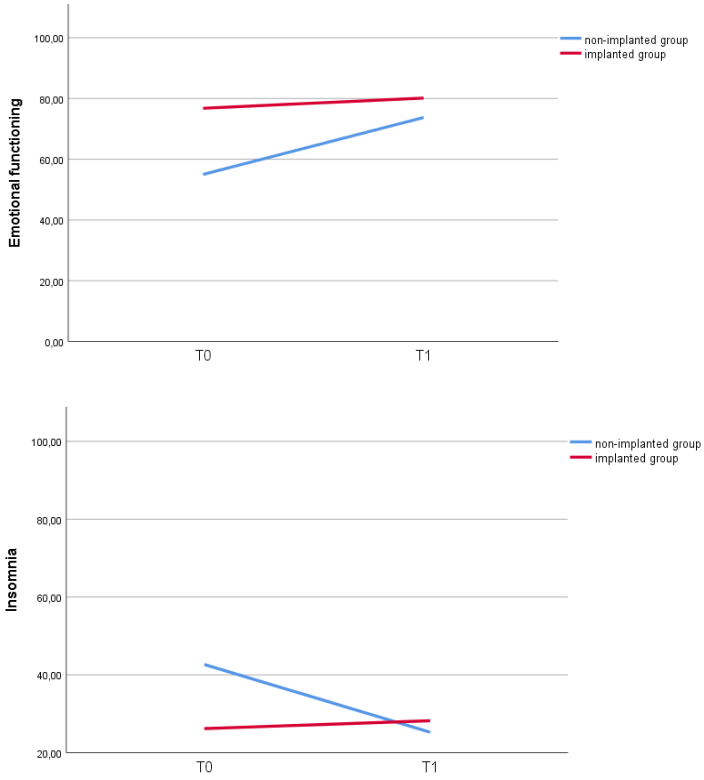

Figure 6.2 Mean EORTC QLQ-C30 and QLQ-H&N35 scores at T_0 and T_1 for scales with statistically significant changes in the within-subject analysis for patients who had undergone implant-based dental rehabilitation after FFF reconstruction and those who did not.
Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; FFF, free fibula flap; Patients who had not undergone implant-based dental rehabilitation (blue lines) showed significant differences between T_0 and T_1 for the domains emotional functioning (P = 0.01) and insomnia (P = 0.03). Patients who had undergone implant-based dental rehabilitation (red lines) showed no significant differences between T_0 and T_1. T_0 was defined as the period from 6 months before FFF reconstruction until the FFF reconstruction. T_1 was defined as the period after completing implant-based dental rehabilitation (i.e. after placement of the dental superstructure). For patients who did not undergo implant-based dental rehabilitation T_1 was defined as the period after FFF reconstruction.

There were no significant differences in the mean changes of all the EORTC QLQ-C30 and EORTC QLQ-H&N35 scores between T_0 and T_1 for patients who had undergone IDR compared to those who did not (Tables 6.2 and 6.3).

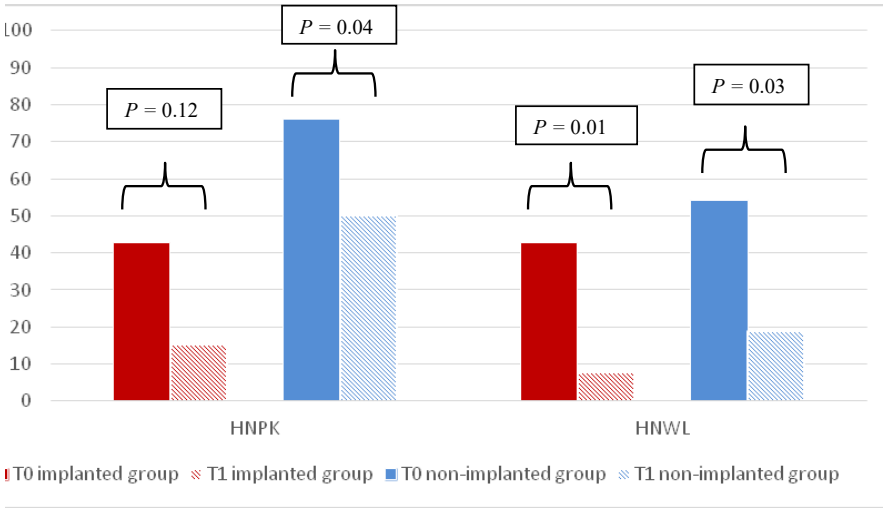

Figure 6.3 EORTC QLQ-H&N35 scales at T_0 and T_1 with statistically significant changes in the within-subject analysis for patients who had undergone implant-based dental rehabilitation after FFF reconstruction and those who did not. Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; FFF, free fibula flap; HNPK, Head and Neck Pain Killers; HNWL, Head and Neck Weight Loss. Patients who had not undergone implant-based dental rehabilitation (blue) showed significant differences between T_0 and T_1 for the domains HNPK (p=0.04) and HNWL (p=0.03). Patients who had undergone implant-based dental rehabilitation (red) showed significant differences between T_0 and T_1 for the domain HNWL (p=0.01). T_0 was defined as the period from 6 months before FFF reconstruction until the FFF reconstruction. T_1 was defined as the period after completing implant-based dental rehabilitation (i.e. after placement of the dental superstructure). For patients who did not undergo implant-based dental rehabilitation T_1 was defined as the period after FFF reconstruction.

Discussion

To date there is limited evidence on patient-reported outcomes of IDR in terms of HRQoL with validated questionnaires.[8] This study evaluated the course of HRQoL in HNC patients who had undergone IDR after maxillofacial reconstruction with an FFF and compared it to those who did not. In our cross-sectional analysis, patients who had undergone IDR seem to have better HRQoL at T_0, compared to those who did not. However, only few domains in the EORTC QLQ-C30 and QLQ-H&N35 showed significance. In a study population of 38 patients who had undergone FFF

reconstruction of which 23 patients received dental implants, similar findings were reported using cross-sectional analysis.[14] The major drawback for this specific analysis is the one-time measurement. Therefore, it is difficult to evaluate the influence of IDR on HRQoL.

Dholam et al. used within-subject analysis to evaluate HRQoL with the EORTC QLQ-C30 and QLQ-H&N35 in 12 patients who had undergone dental implantations after FFF reconstruction.[12] They reported minimal differences in HRQoL after IDR, compared to the situation before FFF reconstruction. The authors explained this finding by the high expectations regarding treatment outcome most patients had, which could not be achieved. We found similar results using within-subject analysis, as only the domain weight loss reached significance after IDR, compared to the situation before FFF reconstruction. With this analysis it is difficult to evaluate the effect of IDR on the HRQoL as there is no control group.

To better answer the question to what extend IDR may have contributed to HRQoL, we compared the differences in the course of HRQoL between patients who commenced IDR and those who did not. Interestingly, HRQoL seems to marginally change in patients who had undergone dental rehabilitation after FFF reconstruction. And, although baseline HRQoL scores may be poorer in patients who do not commence dental implantation after FFF reconstruction, the course of HRQoL seems to be very similar. This finding is reflected in the statistical analysis, as there were no significant differences in HRQoL in patients who commenced IDR, compared to patients who did not. Furthermore, the clinical relevance of these marginally changes in HRQoL scores is debatable.

One prospective clinical trial reported a significant improvement in HRQoL after IDR in patients who had undergone FFF reconstruction.[16] However, it is difficult to translate these findings to oncological patients, because 65% of the patients were reconstructed for benign disease and the majority did not receive radiotherapy. Additionally, all edentulous cases were excluded. In our study population most patients were edentulous and 85% received radiotherapy.

To date, there are no widely accepted instruments to evaluate the effects of oral rehabilitation on HRQoL.[20] And, although the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires are well validated, these questionnaires could lack sensitivity to identify changes in oral HRQoL. For example, both questionnaires do not address problems related chewing/eating solid food, choking/gaging and dentures. Additionally, HNC

patients have endured different life events compared to a healthy individual and may address other significance to oral function.

Although no significance was found, symptom scales directly related to oral function, including swallowing, speech problems and trouble with social eating, seem to increase over time for patients who commenced IDR and those who did not. As emphasised by other authors, these results may not only be caused by functional deficits, but biopsychosocial aspects could have a profound influence on these findings.[21,22] Interestingly, patients seem to report a minimal increase in problems with their teeth after completion of the IDR (T_0, 22.2; T_1,24.2). In contrast, patients who did not commence IDR seem to report a decrease in problems with their teeth (T_0, 27.8; T_1, 16.7). An explanation for this latter finding may be that patients who did not receive dental implants experienced tumour-related problems that impact HRQoL at baseline and improved after oncological therapy.

Patients included in this study had undergone successful ablative surgery and maxillofacial reconstruction with an FFF. The majority of patients were edentulous in the reconstructed jaw, and all patients who started IDR received a technically well-fabricated dental prosthesis. In our institution, these (edentulous) cases are mainly ''bone-driven'' reconstructed; i.e. the lower border border of the usually atrophied mandible is reconstructed aiming at sufficient facial (chin) projection. To give sufficient support to the soft tissues of the cheek and lower lip, we prefer a removable prosthetic construction which can be optimally designed, both functionally and cosmetically. Moreover, a removable prosthesis may give better access for oral cleaning and may benefit the clinical outcome of dental implants.

In our experience there seems to be other contributing factors that determine oral function besides adequate reconstruction of the oral anatomy, including remaining sensory and motoric functions of the (peri-)oral tissues. Interestingly, a recent study found weak correlations between objective tests of masticatory performance, swallowing and patientreported outcomes.[23] Studies are needed on this topic to evaluate the effect of different factors on oral function and HRQoL, such as remaining natural dentition, occluding functional units, defect size and defect location. To optimize remaining oral function a multidisciplinary approach can be helpful with a maxillofacial prosthodontist, speech therapist, plastic surgeon, oral and maxillofacial surgeon and ENT-specialist.[24]

Investigating HRQoL in HNC patients who commence IDR after FFF reconstruction is difficult, as the study design is prone for selection bias. With our concept with delayed

implant placement, only those patients who are motivated and have relatively good prognosis, commence IDR.[10,11] This selection bias is illustrated by the significant difference in edentulism in the reconstructed jaw between patients who received dental implants and those who did not. Although, the effect of remaining occluding teeth has not been investigated in patients reconstructed with an FFF, there is evidence that remaining occluding teeth may have a positive effect on masticatory performance in HNC patients.[25] Additionally, it seems that radiotherapy and ASA class III are represented more in the group without IDR. As demonstrated, both factors have a significant impact on HRQoL.[16,26,27]

We retrospectively analysed HRQoL data, resulting in some heterogeneity in the timepoints of HRQoL collection. Furthermore, the small sample size could have influenced the results of this study and made comparison between and within groups difficult. Future prospective studies should not only focus on more robust data but should also assess HRQoL at predetermined timepoints for patients who undergo dental rehabilitation after FFF reconstruction, particularly, information on HRQoL after finishing the oncologic treatment, compared to HRQoL after completion of IDR.

Although there were differences in HRQoL before oncological therapy between HNC patients who had undergone IDR after maxillofacial FFF reconstruction and those who did not, there seem to be no significant differences in the course of HRQoL between both groups. Prospective studies on HRQoL with validated, specific questionnaires focusing on oral functioning are necessary on this topic to improve and shape treatment strategies for this specific patient group. Patients should be informed to have realistic expectations regarding the outcome of IDR.

References

1. Brown JS, Barry C, Ho M, Shaw R. A new classification for mandibular defects after oncological resection. Lancet Oncol. 2016;17(1):e23-30.
2. Brown JS, Shaw RJ. Reconstruction of the maxilla and midface: introducing a new classification. Lancet Oncol. 2010;11(10):1001-8.
3. Urken ML, Buchbinder D, Weinberg H, Vickery C, Sheiner A, Parker R, et al. Functional evaluation following microvascular oromandibular reconstruction of the oral cancer patient: a comparative study of reconstructed and nonreconstructed patients. Laryngoscope. 1991;101(9):935-50.
4. Urken ML, Roche AM, Kiplagat KJ, Dewey EH, Lazarus C, Likhterov I, et al. Comprehensive approach to functional palatomaxillary reconstruction using regional and free tissue transfer: Report of reconstructive and prosthodontic outcomes of 140 patients. Head Neck. 2018;40(8):1639-66.
5. van Gemert JTM, Abbink JH, van Es RJJ, Rosenberg A, Koole R, Van Cann EM. Early and late complications in the reconstructed mandible with free fibula flaps. J Surg Oncol. 2018;117(4):773-80.
6. Lodders JN, Schulten EA, de Visscher JG, Forouzanfar T, Karagozoglu KH. Complications and Risk after Mandibular Reconstruction with Fibular Free Flaps in Patients with Oral Squamous Cell Carcinoma: A Retrospective Cohort Study. J Reconstr Microsurg. 2016;32(6):455-63.
7. Kumar BP, Venkatesh V, Kumar KA, Yadav BY, Mohan SR. Mandibular Reconstruction: Overview. J Maxillofac Oral Surg. 2016;15(4):425-41.
8. Wijbenga JG, Schepers RH, Werker PM, Witjes MJ, Dijkstra PU. A systematic review of functional outcome and quality of life following reconstruction of maxillofacial defects using vascularized free fibula flaps and dental rehabilitation reveals poor data quality. J Plast Reconstr Aesthet Surg. 2016;69(8):1024-36.
9. Schulten EA, Winters HA, Koch AE. [Reconstruction after surgical treatment of head and neck cancer: surgical and prosthetic possibilities]. Ned Tijdschr Tandheelkd. 2008;115(4):215-23.
10. Smolka K, Kraehenbuehl M, Eggensperger N, Hallermann W, Thoren H, Iizuka T, et al. Fibula free flap reconstruction of the mandible in cancer patients: evaluation of a combined surgical and prosthodontic treatment concept. Oral Oncol. 2008;44(6):571-81.
11. Lodders JN, Leusink FKJ, Ridwan-Pramana A, Winters HAH, Karagozoglu KH, Dekker H, et al. Long-term outcomes of implant-based dental rehabilitation in head and neck cancer patients after reconstruction with the free vascularized fibula flap. J Craniomaxillofac Surg. 2021;49(9):845-54.
12. Dholam KP, Bachher GK, Yadav PS, Quazi GA, Pusalkar HA. Assessment of quality of life after implant-retained prosthetically reconstructed maxillae and mandibles postcancer treatments. Implant Dent. 2011;20(1):85-94.
13. Hundepool AC, Dumans AG, Hofer SO, Fokkens NJ, Rayat SS, van der Meij EH, et al. Rehabilitation after mandibular reconstruction with fibula free-flap: clinical outcome and quality of life assessment. Int J Oral Maxillofac Surg. 2008;37(11):1009-13.
14. Jacobsen HC, Wahnschaff F, Trenkle T, Sieg P, Hakim SG. Oral rehabilitation with dental implants and quality of life following mandibular reconstruction with free fibular flap. Clin Oral Investig. 2016;20(1):187-92.
15. Roumanas ED, Garrett N, Blackwell KE, Freymiller E, Abemayor E, Wong WK, et al. Masticatory and swallowing threshold performances with conventional and implant-supported prostheses after mandibular fibula free-flap reconstruction. J Prosthet Dent. 2006;96(4):289-97.
16. Kumar VV, Jacob PC, Ebenezer S, Kuriakose MA, Kekatpure V, Baliarsing AS, et al. Implant supported dental rehabilitation following segmental mandibular reconstruction- quality of life outcomes of a prospective randomized trial. J Craniomaxillofac Surg. 2016;44(7):800-10.
17. Duman-Lubberding S, van Uden-Kraan CF, Jansen F, Witte BI, Eerenstein SEJ, van Weert S, et al. Durable usage of patient-reported outcome measures in clinical practice to monitor health-related quality of life in head and neck cancer patients. Support Care Cancer. 2017;25(12):3775-83.
18. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

19. Bjordal K, Ahlner-Elmqvist M, Tollesson E, Jensen AB, Razavi D, Maher EJ, et al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. EORTC Quality of Life Study Group. Acta Oncol. 1994;33(8):879-85.
20. So WK, Chan RJ, Chan DN, Hughes BG, Chair SY, Choi KC, et al. Quality-of-life among head and neck cancer survivors at one year after treatment--a systematic review. Eur J Cancer. 2012;48(15):2391-408.
21. Locker D, Clarke M, Payne B. Self-perceived oral health status, psychological well-being, and life satisfaction in an older adult population. J Dent Res. 2000;79(4):970-5.
22. Dornan M, Semple C, Moorhead A. Experiences and perceptions of social eating for patients living with and beyond head and neck cancer: a qualitative study. Support Care Cancer. 2022;30(5):4129-37.
23. Vermaire JA, Raaijmakers CPJ, Verdonck-de Leeuw IM, Jansen F, Leemans CR, Terhaard CHJ, et al. Mastication, swallowing, and salivary flow in patients with head and neck cancer: objective tests versus patient-reported outcomes. Support Care Cancer. 2021;29(12):7793-803.
24. Vosselman N, Alberga J, Witjes MHJ, Raghoebar GM, Reintsema H, Vissink A, et al. Prosthodontic rehabilitation of head and neck cancer patients-Challenges and new developments. Oral Dis. 2021;27(1):64-72.
25. de Groot RJ, Merkx MAW, Hamann MNS, Brand HS, de Haan AFJ, Rosenberg A, et al. Tongue function and its influence on masticatory performance in patients treated for oral cancer: a five-year prospective study. Support Care Cancer. 2020;28(3):1491-501.
26. Korfage A, Schoen PJ, Raghoebar GM, Bouma J, Burlage FR, Roodenburg JL, et al. Five-year follow-up of oral functioning and quality of life in patients with oral cancer with implant-retained mandibular overdentures. Head Neck. 2011;33(6):831-9.
27. Schoen PJ, Raghoebar GM, Bouma J, Reintsema H, Burlage FR, Roodenburg JL, et al. Prosthodontic rehabilitation of oral function in head-neck cancer patients with dental implants placed simultaneously during ablative tumour surgery: an assessment of treatment outcomes and quality of life. Int J Oral Maxillofac Surg. 2008;37(1):8-16.

Chapter 7

General discussion and conclusions

General discussion

Since the early 1990s, microvascular free tissue surgery has become an essential technique in the reconstruction of head and neck cancer patients. However, post-operative complications (POCs) following free flap surgery are unfortunately common in these patients.[1-3] POCs do not only impact a patient's physical and psychological health in the short and long-term, but also consume healthcare and economic resources.[4,5] Although free flap reconstruction in head and neck cancer patients has been highly reliable in terms of flap-related outcomes, there is limited information on other clinical outcomes, including surgical and systemic POCs in homogeneous cohorts. Additionally, there seems to be a paucity in data regarding the effects and complications of implant-based dental rehabilitation in head and neck cancer patients who had undergone maxillofacial reconstruction with a fibula free flap.

The studies described in this thesis aimed to provide more information on the occurrence and prediction of POCs in surgical oral cancer patients undergoing free flap reconstruction. A particular focus was given to the clinical outcomes of patients who were reconstructed with a fibula free flap, including implant-based dental rehabilitation and its effect on quality of life.

In **Chapter 2** a retrospective study is described that investigated the occurrence of POCs in patients who underwent primary free flap reconstructions following ablation of oral cancer. It was found that the incidence of POCs was high (35%), which is consistent with findings from other studies.[3,6-8] However, it is important to note that our study classified all POCs dichotomously, regardless of their severity, and included them in the statistical analyses. As a result, the true impact of POCs on the patient's (long-term) course cannot be fully determined based solely on these numbers. While these findings do raise awareness of the potential for POCs during the postoperative period, further research is needed to fully assess their impact.

There is currently a lack of consistency in scoring and grading POCs in surgical head and neck patients. This can result in subjective evaluations of POCs that vary among surgeons and institutions. POCs related to lower grades, such as wound healing problems, are particularly susceptible to debate. This issue has been addressed by other authors[9] and further evidenced by the varying rates of POCs reported in the literature (ranging from 9% to 64%).[3,7,10-17] Recent publications, including one with robust prospective data focusing on mainly oral tumour sites, have reported similar numbers to those in Chapter 2.[6,8] However, as previously discussed, our study may have underreported the incidence of pulmonary and donor site complications compared to

other studies[6,17], suggesting that the true incidence of our POCs is likely even higher than reported in Chapter 2.

Standardized grading systems, such as the Clavien-Dindo classification, have been proposed to address the issue of inconsistent grading of POCs in head and neck cancer patients.[18] However, the fact that almost exclusively studies with prospective data have used the Clavien-Dindo classification in surgical head and neck cancer patients reflects the difficulty in accurately grading the severity of a complication with retrospective chart reviews.[6,8,19] Furthermore, even in a prospective setting, interpretation of the Clavien-Dindo grading system remains subject to variation.[9] To improve consistency and accuracy in reporting POCs in surgical head and neck cancer patients, future studies should aim to utilize a standardized grading system. Despite its potential downsides, the Clavien-Dindo classification may be a valuable tool in creating a uniform reporting method, facilitating a more precise comparisons of POC rates between studies.

The identification of key predictors for POCs in reconstructed head and neck patients proved to be challenging and may be explained by its multifactorial aetiology.[20] In addition, some variables that were analysed in our study seem to be interdependent, further complicating the matter. In our study, we associated prolonged anaesthesia time with systemic POCs, which is in line with the literature demonstrating that longer operating times independently increase both surgical and systemic POCs.[6,8,14,16,17] While the most obvious explanation for this association is the reflection of the surgical complexity in the operating time, we did not observe an increase in surgical POCs, unlike other studies.[6,8] This suggest that other factors may be involved. One proposed explanation is that the patient's characteristics, such as advanced age, comorbid conditions and poor performance status, might affect their physiological capacity, consequently leading to an inability to fully recover from the stress of undergoing general anaesthesia and surgery, resulting in unfavourable outcomes.[21]

Interestingly, the duration of the operation is somewhat adjustable, underscoring the need to identify methods to shorten operating time. It is thought that surgeons can achieve this by engaging in thorough pre-operative surgical planning and obtaining extensive surgical training. For instance, the use of virtual surgical planning has been found to reduce operating time in osseous reconstructions by over an hour.[22] Other approaches, such as enhancing the efficiency and communication of the entire surgical team, seem to be worthwhile in head and neck free flap surgery.[23] Although minimizing operating time can reduce hospital resources and costs, further research is necessary to determine whether such reductions can improve clinical outcomes.

In this study, peri-operative red cell transfusion was associated with a hospital stay of more than 15 days. Several authors associated blood transfusion with various adverse outcomes, including hospital readmission[24], surgical and medical POCs[8,25], decreased long-term survival[8], extended hospital stay[25] and ICU stay.[26] The exact reason for why blood transfusion leads to adverse outcomes, is not yet fully understood. While some of these outcomes may be related to transfusion reactions, this explanation does not account for all negative outcomes.[27] It's worth nothing that blood transfusion is not merely a cause of POCs. In fact, it can be a lifesaving measure for patients with bleeding complications. In our opinion, red blood cell transfusion could, to some extent, be a surrogate for factors that increase the likelihood of needing a transfusion, such as tumour stage, complexity, length and type of operation. Other authors suggest that red cell transfusion may also reflect a patient's nutritional and general health status.[3] Both hypothesis could contribute to a more prolonged hospital stay.

Currently, there are no established guidelines or specific cut-off points for when to administer blood transfusions to patients undergoing free flap surgery. Some surgeons may choose to administer blood transfusions more liberally in order to optimize flap perfusion and oxygenation, while others may follow a more restrictive approach. Interestingly, studies have shown that there is no significant difference in flap outcomes between the two transfusion protocols in reconstructed head and neck cancer patients.[25,28] However, the occurrence of medical POCs may be affected.[25,28] To prevent adverse outcomes and reduce hospital stays, a restrictive transfusion policy is preferred. If possible, alternatives to blood transfusion such as iron or B12 supplementation should be considered for both pre- and post-operative phases. If blood transfusion is deemed necessary, patients should be closely monitored during the postoperative course. Future studies should focus on prospective data regarding transfusion protocol, clear indications for transfusion and its effect on patients clinical outcomes, including POCs.

One POC that has received insufficient attention in head and neck cancer surgery, is the occurrence of venous thromboembolism (VTE), as its rates have not been thoroughly established in the literature. In **Chapter 3,** it was demonstrated that the incidence of symptomatic VTE was relatively low (0.4%) in surgical oral cancer patients when thromboprophylaxis was used. If the analysis was restricted to patients who had undergone free flap reconstructions, the incidence increased slightly to 0.5%.

A recent review on VTE in oncological head and neck free flap surgery found an overall VTE rate of 1.5%, which is slightly higher than the incidence observed in our study.[29] However, this difference may be explained by the inclusion of two studies in the review

that reported significantly higher incidences of VTE (13 and 26%).[30,31] One study included asymptomatic VTEs, of which the majority were superficial VTEs, thus limiting the clinical relevance of these numbers.[30] In the other study, chemo-thromboprophylaxis was not administered regularly, which could have contributed to a higher VTE incidence.[31]

In our study, 4.2% of patients (7 out of 189) who underwent free flap reconstruction experienced bleeding-related complications, with 43% (3 out of 7) requiring re-operation. While these numbers seem to be non-negligible, it is important to note that this study did not include a control group without chemo-thromboprophylaxis, making it difficult to draw definitive conclusions. However, a recent review of three studies that evaluated the effect of chemo-thromboprophylaxis on bleeding complications in head and neck cancer patients who underwent free flap reconstruction showed that all three studies reported an increased risk for haemorrhage (up to 6-fold), despite differences in pharmacologic agents used.[31,32]

Most studies recommend to consider chemo-thromboprophylaxis for head and neck cancer patients if the benefits outweigh the risk of bleeding complications, and risk stratification should be employed based on the guidelines of the American College of Chest Physicians (ACCP). However the ACCP guidelines do provide specific recommendations for head and neck cancer patients. If these recommendations are followed for plastic and reconstructive surgery, chemo- and mechanic thromboprophylaxis may be indicated in head and neck cancer patients, particularly those receiving free flap reconstruction.[33,34] To give some perspective in these considerations, in a recent survey including 74 head and neck reconstructive surgeons almost all indicated to use chemo-thromboprophylaxis.[35]

In summary, despite several years have passed since the publication of the data in Chapter 3, little progress has been made in terms of available evidence. Only three retrospective studies on VTE have been published since then[32,36], limiting the ability to make evidence-based decisions regarding the use of thromboprophylaxis in reconstructed head and neck cancer patients. Ideally, prospective randomized trials should be conducted to determine whether the benefits of chemo-thromboprophylaxis outweigh the risk of bleeding complications. However, the feasibility of such studies is questionable due to the low incidence of VTE in the head and neck patient population, which would require a large patient cohort.

Reconstruction of segmental mandibular defects after surgical resection of oral cancer is a challenging procedure in head and neck surgery. The use of fibula free flaps has

been associated with an increased risk for POCs[1], including flap failure[37,38], compared to soft tissue free flaps. The study described in **Chapter 4** aimed to investigate POCs in patients who had undergone a segmental mandibulectomy and reconstruction with a fibula free flap for oral cancer. Within the first year of follow-up, 47 patients out of 86 patients (55%) experienced POCs. Similar to the results in Chapter 2, these numbers demonstrate the risk for POCs in this specific patient group, but should be carefully interpreted.

Two recent studies investigating mandibular reconstruction with a fibula free flap have reported comparable results regarding POCs.[39,40] Both studies, found that over 50% of patients experienced one or more complications, which is in accordance with our findings. However, in contrast to our data, both studies included patients with benign disease, such as ameloblastoma, trauma and osteomyelitis. Moreover, one study did not report on systemic complications, and the other study included patients subjective perception of abnormal function as a POC.

Active smoking, mandibular reconstruction in the symphyseal region and TNM staging groups >II were identified as risk factors for surgical complications, while age >60 years and a Charlson Comorbidity Index (CCI) >2 were associated with systemic complications. These findings are consistent with other studies that investigated POCs in head and neck cancer patients undergoing free flap reconstruction. The role of age in increasing the risk for POCs is still debated, as comorbid conditions may also have an impact. In a recent study of 1972 head and neck free flap patients, the authors observed a correlation between age and medical complications, as well as between comorbid conditions and POCs, independent of age.[21] These results suggest that both age and comorbid conditions are independent predictors of POCs. Several studies stress the need for pre-operative screening to optimize comorbid conditions.[6,21] Although there is evidence in other surgical disciplines on the effectiveness of such interventions for decreasing POCs[41], its effect in reconstructive head and neck cancer patients requires validation. Particularly because the timeframe between the first consultation until surgical treatment is relatively short (generally 2-4 weeks) for head and neck patients. Moreover, this timeframe is one of the quality indicators in the Dutch Head and Neck Audit (DHNA) and needs to be as short as possible because treatment delay may have a negative impact on the patient's outcomes.[42]

With exemption of smoking habits, most variables are relatively unchangeable and its clinical value is mostly informative regarding risk stratification and it may be helpful during the informed consent process and for selecting surgical patients. Although there were variations in study populations, a recent meta-analysis found a significant impact

of smoking on surgical complications in head and neck free flap surgery.[43] Remarkably, the meta-analysis did not show an increase in flap failures. While cessation of smoking habits is recommended for various reasons in surgical head and neck cancer patients, the true effect of smoking cessation interventions on the reduction of POCs has not been studied in the reconstructive head and neck population. As most head and neck cancer patients smoke cigarettes, the effect of smoking cessation on POCs could be more profound than anticipated. Especially when considering data from the orthopaedic surgery literature where POCs were reduced by more than 2-fold with a 6-week intervention programme to stop smoking.[44] Therefore, future studies should focus on addressing this knowledge gap in the reconstructive head and neck population.

For different reasons, an uneventful post-operative course is a worthwhile goal to strive for in head and neck cancer patients. However, (radical) opportunities to reduce POCs and its severity have yet to be discovered in the head and neck cancer population. In an attempt to improve patient care, McMahon et al. described an implementation of local institutional, as well as healthcare system quality improvement initiatives.[20] Despite these initiatives that targeted peri-operative care[45], POCs were not reduced over almost a decade. And, although the field of head and neck cancer changed during that period, they concluded that POCs are ''somewhat predictable, prevalent and recalcitrant''. These findings confirm the difficulty in reducing adverse outcomes, and, POCs may be inherent to the head and neck cancer population that undergo free flap reconstruction.

A potential key to improving outcomes in surgical head and neck patients could be preoperative prehabilitation. This approach involves optimizing or improving patients' functional capabilities to better withstand the demands of a surgical procedure. The effects of these programs have been studied in other surgical oncological disciplines with optimistic results[46,47] and it is gaining traction in head and neck cancer surgery.[48] These therapeutic interventions not only target smoking cessation and optimization of comorbid conditions but can also include physical and cognitive exercise and (individualized) nutritional support. As these programs require patient effort and there is a relative short timeframe, their effects on the clinical outcomes, including POCs should be further studied.

Chapter 5 provides a comprehensive evaluation of a combined surgical and prosthodontic concept of dental rehabilitation in head and neck cancer patients following oncological treatment and reconstruction with a fibula free flap. Although it is mentioned that implant-based dental rehabilitation is the ''ultimate goal'' after jaw

reconstruction with a fibula free flap, it was shown that with our concept this is only reserved for a minority of the reconstructed patients. Moreover, although most patients that received a dental superstructure achieved functional rehabilitation, the amount that did not achieve a functional rehabilitation should not be neglected (21%). This suggest that our criteria for commencing dental rehabilitation may be too blunt to identify those patients that can benefit from this additional prosthetic treatment.

All reconstructions and dental implants described in Chapter 5 were placed free-handed without using surgical drilling and cutting guides. However, with the advancements in virtual surgical planning, it is now possible to place dental implants with high accuracy at prosthetically desirable positions in a fibula free flap. This technique can be used in both primary and secondary implant placements[49-51], with primary implant placement having the advantage of reducing rehabilitation time and operative burden for patients.[51-53] By utilizing virtual surgical planning in primary implant placement, the number of dental implants inserted in reconstructed head and neck cancer patients can be increased.[53] Although this technique is not routinely used in the reconstructed oncological population, a recent study reported a 78% completion rate of dental rehabilitations in an oncological cohort.[52] Unfortunately, similar to most other studies on this topic, no information was provided on what happened after completion of the dental rehabilitation, in particular, whether or not patients wore the dental superstructures and functioned satisfactory.[53] Noteworthy, in 22% of the patients dental implants were inserted and not used due to recurrent disease or complications during follow up. An important and unanswered question in primary implant placement, is that it is unclear whether the benefits experienced by patients who complete dental rehabilitation outweigh the ''loss of resources'' and costs of those patients with unused dental implants. Furthermore, the potential negative effects on flap-related outcomes are still not thoroughly studied and need to be further investigated.

In Chapter 5 the reasons for not commencing dental rehabilitation were reviewed. Most of these reasons may not be resolved with primary implant placement aided with virtual surgical planning. Until it is better understood which reconstructed head and neck cancer patients attain proper function and benefit from implant-based dental rehabilitation, it seems that secondary implant placement is still the preferred option for this specific population.

Irradiation of the fibula free flap and smoking have been identified as significant predictors for dental implant failure. Furthermore, and maybe even more important, irradiation of the fibula flap was associated with prosthetic treatment failure. The data

in this study showed a high risk for dental implant failure and necrosis of the fibula free flap for actively smoking patients with irradiated grafts. Therefore, caution should be exercised when considering secondary dental implant placement in actively smoking patients with irradiated fibula-flap reconstructed jaws. Patients should be clearly informed about this increased risk for treatment failure.

To build upon the findings described in Chapter 5 and to gain a better understanding of the impact of implant-based dental rehabilitation, in **Chapter 6** its effect was assessed on the health-related quality of life in head and neck cancer patients who had undergone reconstruction with a fibula free flap. Surprisingly, using the questionnaires EORTC QLQ-C30 and EORTC QLQ-H&N35, the study did not found a clear difference in the course of health-related quality of life following implant-based dental rehabilitation.

It could be argued that the small and heterogeneous study population may have contributed to the lack of significant results. However, upon reviewing the mean changes in health-related quality of life scores in Chapter 6, it appears that most scores only changed marginally, raising questions about their clinical relevance. This is especially true for scores that are directly related to dental rehabilitation, including swallowing, speech, social eating, social contact and teeth.

To date, there is limited literature on the effects of implant-based dental rehabilitation on patient-reported outcome measures (PROMs) in the reconstructed head and neck population.[53,54] Further prospective studies are needed to justify implant-based dental rehabilitation in patients who have undergone reconstruction with a fibula free flap. These studies should not only investigate the impact on health-related quality of life but also the effect on specific functional abilities including speech, chewing and swallowing. In this respect objective measuring instruments may be useful. Additionally, the effect of radiotherapy, lip competence, remaining occlusal functional units, soft tissue defect, type of osseous defect, mouth opening and function of motoric and sensory nerves should be studied on both patient-reported and functional outcomes.

Limitations of the studies in this thesis

The main limitation of the studies presented in this thesis is their retrospective nature. The data were collected by reviewing the medical charts of the patients, which could potentially lead to inaccuracies and incomplete data. For example there is a possibility that some POCs were missed, as seen in the underreported numbers of certain complications, such as respiratory and donor site complications. While attempts were

made to score every POC of any severity in Chapters 2-5, the retrospective nature did not always allow for grading of severity, making it difficult to determine the true impact on a patients postoperative course.

Another limitation is the relative small cohorts described in Chapters 4, 5 and 6, which may have been underpowered to achieve statistical significance and made subgroup analyses difficult to perform. However, a strength of these studies is the comprehensive analysis with long-term follow up in a relative homogeneous cohort of mainly oral cancer patients. Granular data were available from different specialities, allowing for collaboration and the ability to combine datasets for more information on implant-based dental rehabilitation and its effect on health-related quality of life. Additionally, the inclusion of data from the Center for Special Care Dentistry (Stichting Bijzondere Tandheelkunde Amsterdam) allowed for follow-up of patients who received a superstructure on dental implants, a time point where most available studies in the literature stop. Overall, while there are limitations of the studies presented, they provide a true reflection of how patient care is provided and offer valuable insight into the clinical outcomes of oral cancer patients who have undergone free flap reconstruction.

Conclusions

The studies described in this thesis add to our knowledge of the clinical outcomes in oral cancer patients undergoing free flap reconstruction.

Postoperative complications are common in patients who undergo primary free flap reconstructions following ablation of oral cancer. Prolonged anaesthesia time and red cell transfusion were significantly associated with systemic complications and prolonged hospital stay, respectively.

Similarly, it seems that more than half of the oral cancer patients who undergo tumour ablation and simultaneous reconstruction with a fibula free flap experience postoperative complications during the first postoperative year. Active smoking, mandibular reconstruction in the symphyseal region and TNM staging groups >II were identified as predictors for surgical complications, while age >60 years and a Charlson Comorbidity Index >2 were significantly associated with systemic complications.

The occurrence of symptomatic venous thromboembolism was rare in surgical oral cancer patients when thromboprophylaxis was used.

Implant-based dental rehabilitation, if started, can be achieved in the majority of head and neck cancer patients after reconstruction with a fibula free flap. However, no significant differences could be found in the course of health-related quality of life between head and neck cancer patients who had undergone implant-based dental rehabilitation after jaw reconstruction with a fibula free flap and those who did not.

The clinical value of most identified predictors for adverse outcomes are largely informative regarding risk stratification and may be helpful during the informed consent process and for selecting surgical patients.

References

1. Wu CC, Lin PY, Chew KY, Kuo YR. Free tissue transfers in head and neck reconstruction: complications, outcomes and strategies for management of flap failure: analysis of 2019 flaps in single institute. Microsurgery. 2014;34(5):339-44.
2. Hazari A, Walton P. The UK National Flap Registry (UKNFR): A National Database for all pedicled and free flaps in the UK. J Plast Reconstr Aesthet Surg. 2015;68(12):1633-6.
3. Clark JR, McCluskey SA, Hall F, Lipa J, Neligan P, Brown D, et al. Predictors of morbidity following free flap reconstruction for cancer of the head and neck. Head Neck. 2007;29(12):1090-101.
4. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos CL. The economic burden of head and neck cancer: a systematic literature review. Pharmacoeconomics. 2014;32(9):865-82.
5. McMahon J, Handley TPB, Bobinskas A, Elsapagh M, Anwar HS, Ricciardo PV, et al. Postoperative complications after head and neck operations that require free tissue transfer - prevalent, morbid, and costly. Br J Oral Maxillofac Surg. 2017;55(8):809-14.
6. Eskander A, Kang S, Tweel B, Sitapara J, Old M, Ozer E, et al. Predictors of Complications in Patients Receiving Head and Neck Free Flap Reconstructive Procedures. Otolaryngol Head Neck Surg. 2018;158(5):839-47.
7. Borggreven PA, Kuik DJ, Quak JJ, de Bree R, Snow GB, Leemans CR. Comorbid condition as a prognostic factor for complications in major surgery of the oral cavity and oropharynx with microvascular soft tissue reconstruction. Head Neck. 2003;25(10):808-15.
8. Li D, Wang C, Wei W, Li B, Liu H, Cheng A, et al. Postoperative Complications of Free Flap Reconstruction in Moderate-Advanced Head and Neck Squamous Cell Carcinoma: A Prospective Cohort Study Based on Real-World Data. Front Oncol. 2022;12:792462.
9. Monteiro E, Sklar MC, Eskander A, de Almeida JR, Shrime M, Gullane P, et al. Assessment of the Clavien-Dindo classification system for complications in head and neck surgery. Laryngoscope. 2014;124(12):2726-31.
10. Pohlenz P, Klatt J, Schon G, Blessmann M, Li L, Schmelzle R. Microvascular free flaps in head and neck surgery: complications and outcome of 1000 flaps. Int J Oral Maxillofac Surg. 2012;41(6):739-43.
11. Pohlenz P, Blessmann M, Blake F, Li L, Schmelzle R, Heiland M. Outcome and complications of 540 microvascular free flaps: the Hamburg experience. Clin Oral Investig. 2007;11(1):89-92.
12. Haughey BH, Wilson E, Kluwe L, Piccirillo J, Fredrickson J, Sessions D, et al. Free flap reconstruction of the head and neck: analysis of 241 cases. Otolaryngol Head Neck Surg. 2001;125(1):10-7.
13. van Gemert JT, van Es RJ, Rosenberg AJ, van der Bilt A, Koole R, Van Cann EM. Free vascularized flaps for reconstruction of the mandible: complications, success, and dental rehabilitation. J Oral Maxillofac Surg. 2012;70(7):1692-8.
14. Ferrier MB, Spuesens EB, Le Cessie S, Baatenburg de Jong RJ. Comorbidity as a major risk factor for mortality and complications in head and neck surgery. Arch Otolaryngol Head Neck Surg. 2005;131(1):27-32.
15. Farwell DG, Reilly DF, Weymuller EA, Jr., Greenberg DL, Staiger TO, Futran NA. Predictors of perioperative complications in head and neck patients. Arch Otolaryngol Head Neck Surg. 2002;128(5):505-11.
16. Singh B, Cordeiro PG, Santamaria E, Shaha AR, Pfister DG, Shah JP. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg. 1999;103(2):403-11.
17. McMahon JD, MacIver C, Smith M, Stathopoulos P, Wales C, McNulty R, et al. Postoperative complications after major head and neck surgery with free flap repair--prevalence, patterns, and determinants: a prospective cohort study. Br J Oral Maxillofac Surg. 2013;51(8):689-95.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
19. le Nobel GJ, Higgins KM, Enepekides DJ. Predictors of complications of free flap reconstruction in head and neck surgery: Analysis of 304 free flap reconstruction procedures. Laryngoscope. 2012;122(5): 1014-9.

20. McMahon J, Abraham J, McMahon GC, Zubair F. Postoperative complications in patients undergoing major head and neck surgery requiring free tissue transfer - how do we improve? . Front Oral Maxillofac Med 2022 4(12).
21. Sweeny L, Curry JM, Crawley MB, DiLeo M, Bonaventure CA, Luginbuhl AJ, et al. Age and Comorbidities Impact Medical Complications and Mortality Following Free Flap Reconstruction. Laryngoscope. 2022;132(4):772-80.
22. Wang YY, Zhang HQ, Fan S, Zhang DM, Huang ZQ, Chen WL, et al. Mandibular reconstruction with the vascularized fibula flap: comparison of virtual planning surgery and conventional surgery. Int J Oral Maxillofac Surg. 2016;45(11):1400-5.
23. Ibrahim A, Ndeti K, Bur A, Sykes K, Shnayder L, Tsue T, et al. Association of a Lean Surgical Plan of the Day With Reduced Operating Room Time for Head and Neck Free Flap Reconstruction. JAMA Otolaryngol Head Neck Surg. 2019;145(10):926-30.
24. Carniol ET, Marchiano E, Brady JS, Merchant AM, Eloy JA, Baredes S, et al. Head and neck microvascular free flap reconstruction: An analysis of unplanned readmissions. Laryngoscope. 2017;127(2):325-30.
25. Puram SV, Yarlagadda BB, Sethi R, Muralidhar V, Chambers KJ, Emerick KS, et al. Transfusion in head and neck free flap patients: practice patterns and a comparative analysis by flap type. Otolaryngol Head Neck Surg. 2015;152(3):449-57.
26. Denis B, Gourbeix C, Coninckx M, Foy JP, Bertolus C, Constantin JM, et al. Maxillofacial free flap surgery outcomes in critical care: a single-center investigation looking for clues to improvement. Perioper Med (Lond). 2022;11(1):11.
27. Goodnough LT. Risks of blood transfusion. Crit Care Med. 2003;31(12 Suppl):S678-86.
28. Skoog H, Chisolm P, Altonji SJ, Moore L, Carroll WR, Richman J, et al. Moving to a more restrictive transfusion protocol: Outcomes in head and neck free flap surgery. Am J Otolaryngol. 2022;43(1):103268.
29. Cramer JD, Shuman AG, Brenner MJ. Antithrombotic Therapy for Venous Thromboembolism and Prevention of Thrombosis in Otolaryngology-Head and Neck Surgery: State of the Art Review. Otolaryngol Head Neck Surg. 2018;158(4):627-36.
30. Kakei Y, Akashi M, Hasegawa T, Minamikawa T, Usami S, Komori T. Incidence of Venous Thromboembolism After Oral Oncologic Surgery With Simultaneous Reconstruction. J Oral Maxillofac Surg. 2016;74(1):212-7.
31. Clayburgh DR, Stott W, Cordiero T, Park R, Detwiller K, Buniel M, et al. Prospective study of venous thromboembolism in patients with head and neck cancer after surgery. JAMA Otolaryngol Head Neck Surg. 2013;139(11):1143-50.
32. Cevik J, Middleton R, Ramakrishnan A, Cabalag M. Rationalizing post-operative prophylactic anticoagulation in reconstructive head and neck cancer patients: a review. ANZ J Surg. 2021;91(12):2610-6.
33. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-e96S.
34. Stevens SM, Woller SC, Baumann Kreuziger L, Bounameaux H, Doerschug K, Geersing GJ, et al. Executive Summary: Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021;160(6):2247-59.
35. Venkatesh KP, Ambani SW, Arakelians ARL, Johnson JT, Solari MG. Head and Neck Microsurgeon Practice Patterns and Perceptions Regarding Venous Thromboembolism Prophylaxis. J Reconstr Microsurg. 2020;36(8):549-55.
36. Saadoun R, Bengur FB, Moroni EA, Surucu Y, Veit JA, Khan NI, et al. Assessment of BMI and Venous Thromboembolism Rates in Patients on Standard Chemoprophylaxis Regimens After Undergoing Free Tissue Transfer to the Head and Neck. JAMA Otolaryngol Head Neck Surg. 2022;148(11):1051-8.
37. Suh JD, Sercarz JA, Abemayor E, Calcaterra TC, Rawnsley JD, Alam D, et al. Analysis of outcome and complications in 400 cases of microvascular head and neck reconstruction. Arch Otolaryngol Head Neck Surg. 2004;130(8):962-6.
38. O'Brien CJ, Lee KK, Stern HS, Traynor SJ, Bron L, Tew PJ, et al. Evaluation of 250 free-flap reconstructions after resection of tumours of the head and neck. Aust N Z J Surg. 1998;68(10):698-701.

39. van Gemert JTM, Abbink JH, van Es RJJ, Rosenberg A, Koole R, Van Cann EM. Early and late complications in the reconstructed mandible with free fibula flaps. J Surg Oncol. 2018;117(4):773-80.
40. Verhelst PJ, Dons F, Van Bever PJ, Schoenaers J, Nanhekhan L, Politis C. Fibula Free Flap in Head and Neck Reconstruction: Identifying Risk Factors for Flap Failure and Analysis of Postoperative Complications in a Low Volume Setting. Craniomaxillofac Trauma Reconstr. 2019;12(3):183-92.
41. Leeds IL, Canner JK, Gani F, Meyers PM, Haut ER, Efron JE, et al. Increased Healthcare Utilization for Medical Comorbidities Prior to Surgery Improves Postoperative Outcomes. Ann Surg. 2020;271(1): 114-21.
42. Jaarrapportage 2019 Dutch Head and Neck Audit 2019 [Available from: https://dica.nl/jaarrapportage-2019/dhna.
43. Garip M, Van Dessel J, Grosjean L, Politis C, Bila M. The impact of smoking on surgical complications after head and neck reconstructive surgery with a free vascularised tissue flap: a systematic review and meta-analysis. Br J Oral Maxillofac Surg. 2021;59(3):e79-e98.
44. Moller AM, Villebro N, Pedersen T, Tonnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet. 2002;359(9301):114-7.
45. Dort JC, Farwell DG, Findlay M, Huber GF, Kerr P, Shea-Budgell MA, et al. Optimal Perioperative Care in Major Head and Neck Cancer Surgery With Free Flap Reconstruction: A Consensus Review and Recommendations From the Enhanced Recovery After Surgery Society. JAMA Otolaryngol Head Neck Surg. 2017;143(3):292-303.
46. Driessen EJ, Peeters ME, Bongers BC, Maas HA, Bootsma GP, van Meeteren NL, et al. Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: A systematic review. Crit Rev Oncol Hematol. 2017;114:63-76.
47. Bundred JR, Kamarajah SK, Hammond JS, Wilson CH, Prentis J, Pandanaboyana S. Prehabilitation prior to surgery for pancreatic cancer: A systematic review. Pancreatology. 2020;20(6):1243-50.
48. Steegmann J, Bartella AK, Kloss-Brandstatter A, Kamal M, Holzle F, Lethaus B. A randomized clinical trial on the efficacy of a patient-adapted autonomous exercise regime for patients with head and neck cancer. J Craniomaxillofac Surg. 2020;48(3):187-92.
49. van Baar GJC, Lodders JN, Chhangur C, Leeuwrik L, Forouzanfar T, Liberton N, et al. The Amsterdam UMC protocol for computer-assisted mandibular and maxillary reconstruction; A cadaveric study. Oral Oncol. 2022;133:106050.
50. Seikaly H, Idris S, Chuka R, Jeffery C, Dzioba A, Makki F, et al. The Alberta Reconstructive Technique: An Occlusion-Driven and Digitally Based Jaw Reconstruction. Laryngoscope. 2019;129 Suppl 4:S1-S14.
51. Alberga JM, Vosselman N, Korfage A, Delli K, Witjes MJH, Raghoebar GM, et al. What is the optimal timing for implant placement in oral cancer patients? A scoping literature review. Oral Dis. 2021;27(1):94-110.
52. Allen RJ, Jr., Nelson JA, Polanco TO, Shamsunder MG, Ganly I, Boyle J, et al. Short-Term Outcomes following Virtual Surgery-Assisted Immediate Dental Implant Placement in Free Fibula Flaps for Oncologic Mandibular Reconstruction. Plast Reconstr Surg. 2020;146(6):768e-76e.
53. Salinero L, Boczar D, Barrow B, Berman ZP, Diep GK, Trilles J, et al. Patient-centred outcomes and dental implant placement in computer-aided free flap mandibular reconstruction: a systematic review and meta-analysis. Br J Oral Maxillofac Surg. 2022;60(10):1283-91.
54. Wijbenga JG, Schepers RH, Werker PM, Witjes MJ, Dijkstra PU. A systematic review of functional outcome and quality of life following reconstruction of maxillofacial defects using vascularized free fibula flaps and dental rehabilitation reveals poor data quality. J Plast Reconstr Aesthet Surg. 2016;69(8):1024-36.

Chapter 8

Summary

Samenvatting

Summary

Microvascular free tissue transfer have become indispensable in the reconstruction of head and neck cancer patients. Postoperative complications (POCs) are unfortunately common in the reconstructive head and neck population. This thesis aimed to provide more information on the occurrence and prediction of POCs in surgical oral cancer patients undergoing free flap reconstruction. A particular focus was given to the clinical outcomes of patients who were reconstructed with a fibula free flap, including implant-based dental rehabilitation and its effect on quality of life.

In **Chapter 1** a general introduction on this topic with background information is given. In addition, the aim of the studies are outlined.

The study described in **Chapter 2** retrospectively investigated POCs in patients who had undergone primary free flap reconstructions after surgical treatment of oral cancer. POCs were defined as any adverse developments that required intervention, compromised the postoperative course or when readmission to the hospital was required. Surgical complications were defined as adverse events considering the flap, recipient site or donor site. Systemic complications were defined as medical adverse events not considering the flap, recipient site or donor site.

A significant amount of patients developed POCs of any grade of severity. Surgical complications occurred in 32% of the patients and systemic complications occurred in 8% of the patients. Three patients (1.6%) died during hospital admission and 11.1% of the patients returned to the operating room, in most cases for debridement of a total or partial free flap necrosis. Donor site complications were noted in 5.3% of the patients.

Prolonged anaesthesia time and red cell transfusion were associated with systemic complications and prolonged hospital stay, respectively. Although both variables are difficult to modify, these may create awareness during the postoperative course and may be informative in the preoperative phase for patient selection and during the informed consent process.

Chapter 3 gives an estimation of the occurrence of symptomatic venous thromboembolism (VTE) in surgical oral cancer patients. Medical charts were retrospectively reviewed to gather data. In total 233 patients were included who had undergone 244 operations (189 surgical procedures with simultaneous free flap reconstruction).

Despite almost all patients (97%) were classified as having the highest risk for VTE, this study showed that the occurrence of VTE in surgical oral cancer patients seems to be rare, if thromboprophylaxis is used (overall incidence of 0.4 %). Known risk factors, including operating time, type of operation, donor site and level of risk were not associated with VTE.

Four percent of the patients (7/189) who underwent free flap reconstruction had a bleeding-related complication of which 43% (3/7) needed a re-operation. We could not recommend the use of routine thromboprophylaxis as there was no control group without thromboprophylaxis. Therefore, thromboprophylaxis could be advocated in patients with obvious and serious risk factors.

Chapter 4 focused on POCs in patients who had undergone reconstruction of segmental mandibular defects with free fibula flaps after surgical ablation of oral cancer by retrospectively reviewing patient charts. All segmental mandibular defects were free-handedly reconstructed. The same definitions for POCs were used as described in Chapter 2.

During the first year of follow-up, POCs occurred in 47 patients (54.7%). Twenty-eight patients (32.6%) had surgical complications, 10 patients (11.6%) had systemic complications and 9 patients (10.5%) had surgical and systemic complications. Three patients (3.5%) had a total flap failure and six patients (7.0%) a partial flap failure. A quarter of all patients needed a re-operation during the first year after surgery for various reasons. Donor site complications were noted in 3.5% of the patients.

Active smoking, mandibular reconstruction in the symphyseal region, and TNM anatomic stage group >II were associated with surgical complications. Age >60 years and a Charlson Comorbidity Index (CCI) >2 were identified as predictive factors for systemic complications.

With exemption of smoking habits, most variables are relatively unchangeable and its clinical value is mostly informative regarding risk stratification and it may be helpful during the informed consent process and for selecting surgical patients.

In Chapter 5 a retrospective study is described on head and neck cancer patients who had undergone implant-based dental rehabilitation after jaw reconstruction with a fibula free flap. Different dental implant and prothestic-related outcomes were comprehensively evaluated.

In total, 161 dental implants were placed secondarily in 44 fibula free flaps, with a mean follow-up of 4.9 years. The implant survival was significantly different in irradiated fibula free flaps (55%) compared to the implant survival in non-irradiated fibula free flaps (96%). According to the Albrektsson criteria, implant success was 40.4% in irradiated fibula free flaps, and 61.4% in non-irradiated fibula free flaps. The main reason for not achieving success were dental implant failure and non-functional ('sleeper') implants.

Implant-based dental rehabilitation was started 45 times in 42 patients, out of 150 patients who had undergone 161 fibula free flap reconstructions. Three patients underwent a second attempt after the initial fibula graft was lost. The most important reasons for not commencing implant-based dental rehabilitation was residual or recurrent disease. In 37 patients dental rehabilitation was completed of whom 29 eventually functioned satisfactory. Interestingly, despite a technical good prosthesis, four patients were unable to wear the dental prosthesis due to poor oral function and requested removal of the superstructure.

Irradiation of the fibula free flap and cigarette smoking seemed to be significant predictors for dental implant failure and attainment of functional dental rehabilitation. Having both risk factors simultaneously may be associated with an extreme high risk for dental implant failure and necrosis of the fibula free flap. Therefore, the latter patients should be clearly informed about this increased risk for treatment failure.

As a follow-up to the results described in Chapter 5 and to better understand the effect of implant-based dental rehabilitation, **Chapter 6** evaluated the effect of this treatment on the health-related quality of life in head and neck cancer patients who had undergone reconstruction with a fibula free flap. A second aim was to compare the course of the health-related quality of life in patients who had undergone implant-based dental rehabilitation after reconstruction with a fibula free flap (n=19) to those who had not (n=38). Health-related quality of life was evaluated with the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) and the module specifically designed for head and neck cancer patients (EORTC QLQ-H&N 35).

At baseline (before fibula reconstruction), almost all EORTC scores seemed better in patients with implant-based dental rehabilitation compared to patients without implant-based dental rehabilitation. However in the cross-sectional analysis, only emotional functioning, cognitive functioning, diarrhoea, use of painkillers were significantly different. These differences are probably the effect of our selection criteria

for patients who commenced implant-based dental rehabilitation. Health-related quality of life did not seem to substantially change after completing implant-based dental rehabilitation compared to baseline values, as weight loss was the only domain that reached significance in the within-subject analysis.

When the mean changes of all the EORTC QLQ-C30 and EORTC QLQ-H&N35 scores were analysed in both groups, no significant differences could be found in the course of health-related quality of life for those who had undergone implant-based dental rehabilitation compared to those who had not. Although this study has limitations, patients should be preoperatively informed regarding this finding to have realistic expectations regarding the outcomes of this additional treatment.

In **Chapter 7** the results of the studies described in this thesis and their clinical relevance are discussed from a broader perspective and recommendations for future research are presented.

Samenvatting

Vrij gevascularisseerde weefseltransplantaten hebben een prominente plaats verworven in de reconstructie van defecten in het hoofd-halsgebied na oncologische chirurgie. Postoperatieve complicaties (POCs) komen frequent voor na oncologische chirurgie in het hoofd-halsgebied met gelijktijdige reconstructie. Deze thesis had als doel meer informatie te verkrijgen over POCs en het voorspellen hiervan bij patiënten die aansluitend op de chirurgische behandeling van een mondholtetumor zijn gereconstrueerd met vrij gevascularisseerde weefseltransplantaten. Hierbij lag de nadruk op de klinische uitkomsten bij patiënten die zijn gereconstrueerd met een vrij gevascularisseerde fibulalap, inclusief de dentale rehabilitatie met implantaten en het effect hiervan op de kwaliteit van leven.

Hoofdstuk 1 betreft een algemene introductie over genoemd onderwerp met een beschrijving van de context, waarna de doelstellingen van de diverse onderzoeken waarop het proefschrift berust, nader worden uiteengezet.

In het retrospectieve onderzoek, zoals beschreven in **hoofdstuk 2**, wordt de incidentie van POCs gegeven na oncologische resectie van mondholtekanker en gelijktijdige reconstructie met een vrij gevascularisseerd weefseltransplantaat. POCs werden in dit onderzoek gedefinieerd als een ongewenste uitkomst van de behandeling, hetgeen leidde tot een interventie, een gestoord postoperatief beloop of een heropname in het ziekenhuis. Chirurgische complicaties bestonden uit transplantaat-gerelateerde, wondbed-gerelateerde en donorplaats-gerelateerde complicaties. Systemische complicaties bestonden uit medische complicaties die niet onder chirurgische complicaties konden worden geclassificeerd.

Uit dit onderzoek bleek dat een aanzienlijk aantal patiënten een of meer POCs ontwikkelt na oncologische resectie van mondholtekanker en gelijktijdige reconstructie met een vrij gevascularisseerd weefseltransplantaat. In 32% van de patiënten was er sprake van een chirurgische complicatie en in 8% van de patiënten een systemische complicatie. Drie patiënten (1.6%) overleden tijdens de ziekenhuisopname en 11.1% moest tijdens de opname opnieuw geopereerd worden. De belangrijkste reden hiervoor was een necrotectomie van een volledige of gedeeltelijke necrotische vrije lap. Donorplaats-gerelateerde complicaties werden gezien in 5.3% van de patiënten.

De duur van de anesthesie en een bloedtransfusie bleken voorspellers voor het optreden van systemische complicaties respectievelijk de duur van de ziekhuisopname. Ondanks dat deze variabelen lastig te beïnvloeden lijken, kunnen ze wel van waarde

zijn tijdens de monitoring van het postoperatieve beloop. Tevens kunnen deze factoren waardevol zijn in de preoperatieve fase met betrekking tot de patiëntselectie en tijdens de 'informed-consent' procedure.

In **Hoofdstuk 3** is retrospectief gekeken naar de incidentie van symptomatische veneuze trombo-embolieën (VTE) na oncologische resectie van mondholtekanker. In totaal werden 233 patiënten geïncludeerd met 244 chirurgische procedures (189 chirurgische procedures waren gecombineerd met een vrije lap-reconstructie).

Ondanks dat bijna alle patiënten (97%) geclassificeerd konden worden in de hoogste risicocategorie voor VTE, bleek de incidentie toch laag te zijn in deze specifieke patiëntengroep (incidentie 0.4%). Bekende risicofactoren (onder andere operatieduur, type operatie, type vrije lap en het geclassificeerde risico voor VTE) waren in deze studie niet geassocieerd met het ontstaan van VTE.

Vier procent van de patiënten (7/189) die na oncologische chirurgie tevens een reconstructie met een vrije lap ondergingen, hadden een bloeding-gerelateerde complicatie. Van deze patiënten onderging 43% (3/7) een heroperatie. Aan de hand van de bevindingen in dit onderzoek kunnen we het routinematig gebruik van tromboseprofylaxe niet adviseren na oncologische resectie van mondholtekanker. Dit wordt verklaard doordat er geen controlegroep met patiënten was die geen tromboseprofylaxe gebruikten. Daarom lijkt het verstandig tromboseprofylaxe voor te schrijven aan patiënten met duidelijke risicofactoren.

In **Hoofdstuk 4** wordt de incidentie van POCs retrospectief onderzocht na oncologische resectie van mondholtekanker en gelijktijdige reconstructie van segmentale mandibuladefecten met vrij gevasculariseerde fibulatransplantaten. Alle onderkaken werden zonder zaag en/of boormallen gereconstrueerd ('free-handed'). In dit onderzoek werden dezelfde definities voor POCs gebruikt, zoals beschreven in Hoofdstuk 2.

Gedurende het eerste jaar van de follow-up werden bij 47 patiënten (54.7%) één of meer complicaties vastgesteld. In totaal hadden 28 patiënten (32.6%) een chirurgische complicatie, tien patiënten (11.6%) een systemische complicatie en negen patiënten (10.5%) hadden zowel een chirurgische als systemische complicatie. Bij drie patiënten (3.5%) trad een volledige necrose van de fibulalap op en bij zes patiënten (7%) een gedeeltelijke necrose van de fibulalap. Ongeveer een kwart van de patiënten werd om verschillende redenen opnieuw geopereerd binnen een jaar. Donorplaats-gerelateerde complicaties werden gezien bij 3.5% van de patiënten.

Roken, reconstructies in de kinregio en TNM ziektestadium >II waren significant geassocieerd met het optreden van chirurgische complicaties. Leeftijd >60 jaar en Charlson Comorbidity Index (CCI) >2 werden geïdentificeerd als voorspellers van systemische complicaties.

Met uitzondering van roken, lijken de meeste voorspellers voor POCs vooral een statisch gegeven te zijn, hetgeen vooral van waarde kan zijn in het kader van risico-inventarisatie. Tevens kunnen de genoemde variabelen waardevol zijn in de preoperatieve fase tijdens de 'informed-consent' procedure en ten behoeve van de patiëntselectie.

In **hoofdstuk 5** wordt de dentale rehabilitatie met implantaten beschreven bij patiënten met hoofd-halskanker die na de ablatieve chirurgie aansluitend een reconstructie met een vrije fibulalap hebben ondergaan. Verschillende implantaat- en suprastructuur-gerelateerde uitkomsten werden onderzocht.

In totaal werden 161 tandwortelimplantaten secundair geplaatst in 44 fibula-lappen. De implantaatoverleving was significant lager in bestraalde fibula-lappen (55%), vergeleken met onbestraalde fibula-lappen (96%). Volgens de Albrektsson-criteria was het implantaatsucces 40.4% in bestraalde fibula-lappen en 61.4% in de onbestraalde fibula-lappen. De belangrijkste redenen voor deze lage succespercentages waren het falen van de betreffende tandwortelimplantaten of het uiteindelijk niet gebruiken van de geplaatste implantaten ('sleepers').

Van de 150 patiënten (met in totaal 161 fibulareconstructies) werd bij 42 patiënten een implantatiebehandeling uitgevoerd ter voorbereiding op de dentale (prothetische) rehabilitatie. Bij drie patiënten werd een tweede implantatiebehandeling uitgevoerd vanwege het ontstaan van een avasculaire necrose van de fibulalap. De belangrijkste reden voor het niet uitvoeren van een implantatiebehandeling was recidief van de ziekte. Ondanks dat bij de meeste patiënten (n=37) een implantaat-gedragen suprastructuur werd geplaatst, functioneerden deze uiteindelijk bij 29 patiënten gedurende de follow-up. Bij vier patiënten werd op verzoek de suprastructuur verwijderd, ondanks een ogenschijnlijk, technisch goed uitgevoerde implantaat-gedragen gebitsprothese.

Bestraalde fibula-lappen en roken bleken significant te zijn geassocieerd met een verhoogde kans op implantaatfalen en een verlaagde kans op een functionele dentale rehabilitatie. Actief rokende patienten met een bestraalde fibulalap hebben mogelijk

een extreem verhoogde kans op implantaatfalen en necrose van de fibulalap. Dit risico zou vooraf duidelijk met patiënten besproken moeten worden.

Om het effect van de dentale rehabilitatie met implantaten beter te onderzoeken, beschrijft **Hoofdstuk 6** het effect van deze behandeling op de kwaliteit van leven in hoofd-halskankerpatiënten na reconstructie met een vrije fibula lap. Een tweede doel was het vergelijken van de kwaliteit van leven in patiënten met een implantaat-gedragen suprastructuur (n=19) versus patiënten zonder een implantaat-gedragen suprastructuur (n=38). De kwaliteit van leven werd gemeten met behulp van de European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) en de module die speciaal is ontworpen voor patiënten met hoofd-halskanker (EORTC QLQ-H&N 35).

Nagenoeg alle EORTC-scores leken hoger te zijn bij aanvang van de studie (voor de fibulareconstructie) bij patiënten met een implantaat-gedragen suprastructuur, vergeleken met patiënten zonder een implantaat-gedragen suprastructuur. Echter, in de 'cross-sectionele' analyse bleken alleen emotioneel functioneren, cognitief functioneren, diarree en pijnstillergebruik significant te zijn. Deze verschillen zouden verklaard kunnen worden door de gebruikte selectiecriteria voor dentale rehabilitatie met implantaten. Bij patiënten met een implantaat-gedragen suprastructuur leek de kwaliteit van leven niet substantieel te veranderen na plaatsing van de suprastructuur ten opzichte van de uitgangssituatie (voor de fibulareconstructie). Gewichtsverlies was het enige EORTC-domein dat significant verbeterde.

Wanneer de gemiddelde veranderingen van alle EORTC QLQ-C30 en EORTC QLQ-H&N35 scores werden vergeleken tussen beide groepen, kon er geen significant verschil worden aangetoond met betrekking tot het verloop van kwaliteit van leven. Rekening houdend met de beperkingen van dit onderzoek, zouden patienten vooraf over deze bevindingen geïnformeerd moeten worden ten einde een realistisch verwachtingspatroon te creëren over de uitkomsten van deze prothetische vervolgbehandeling.

In **Hoofdstuk 7** worden in een algemene discussie de belangrijkste resultaten van dit proefschrift en de klinische relevantie ervan besproken. Tevens worden in dit hoofdstuk aanbevelingen gedaan voor toekomstig onderzoek.

Appendix

List of abbreviations

List of abbreviations

ACCP	-	American College of Chest Physicians
AJCC	-	American Joint Committee on Cancer staging grouping
ALTFF	-	anterolateral thigh free flap
ASA	-	American Society of Anaesthesiologists
BMI	-	body mass index
CCI	-	Charlson comorbidity index
CI	-	confidence interval
COPD	-	chronic obstructive pulmonary disease
CVA	-	cerebral vascular accident
DCIAFF	-	deep circumflex iliac artery free flap
DR	-	dental rehabilitation
DVT	-	deep venous thrombosis
FFF	-	fibula free flap
GCS	-	graduated compression stockings
HBO	-	hyperbaric oxygen therapy
HNC	-	head and neck cancer
HONK	-	hyperosmolar non-ketotic state
HRQoL	-	health-related quality of life
HRT	-	hormone replacement therapy
IDR	-	implant-based dental rehabilitation
KMG	-	keratinized mucosal graft
LMM	-	longitudinal linear mixed models
LMWH	-	low molecular weight heparin
OCP	-	oral contraceptives
OD	-	other disease
ORN	-	osteoradionecrosis
OSM	-	osteosynthesis
PE	-	pulmonary embolism
PMF	-	pectoralis major flap
POC	-	postoperative complication
RD	-	local, regional or distant recurrent malignant disease
RFFF	-	radial forearm free flap
RRD	-	residual or recurrent disease
SD	-	standard deviation
SFF	-	scapula free flap
SPD	-	second primary malignant disease
SSC	-	squamous cell carcinoma
STFP	-	soft tissue supported full prosthesis

TIA	-	transient ischemic attack
UD	-	unknown disease
VTE	-	venous thromboembolism

Appendix

Contributing authors and chapter information

Contributing authors

J.N. Lodders JL
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

S. Parmar SP
Department of Oral and Maxillofacial Surgery, University Hospital Birmingham NHS Trust, Queen Elizabeth Hospital, Edgebaston, Birmingham B15 2TH, United Kingdom.

N.L.M. Stienen NS
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands.

T.J. Martin TM
Department of Oral and Maxillofacial Surgery, University Hospital Birmingham NHS Trust, Queen Elizabeth Hospital, Edgebaston, Birmingham B15 2TH, United Kingdom.

K.H. Karagozoglu HK
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

M.W. Heymans MH
Department of Epidemiology and Biostatistics, University of Amsterdam and VU University Amsterdam, Amsterdam, The Netherlands.

B. Nandra BN
Department of Oral and Maxillofacial Surgery, University Hospital Birmingham NHS Trust, Queen Elizabeth Hospital, Edgebaston, Birmingham B15 2TH, United Kingdom.

T. Forouzanfar TF
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

E.A.J.M. Schulten ES
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

J.G.A.M. de Visscher JV
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

F.K.J. Leusink FL
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

A. Ridwan-Pramana AR
Centers for Special Care in Dentistry (Stichting Bijzondere Tandheelkunde), Department of Maxillofacial Prosthodontics, Amsterdam, The Netherlands

H.A.H. Winters HW
Department of Plastic, Reconstructive and Hand Surgery, Amsterdam University Medical Centre, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

H. Dekker HD
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

G.J.C. van Baar GB
Department of Oral and Maxillofacial Surgery/ Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

M.R. Vergeer MV
Department of Radiation Oncology, Amsterdam University Medical Centers, VU University Medical Center, Amsterdam, The Netherlands.

F. Jansen FJ
Department of Otolaryngology-Head and Neck Surgery, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands.

B.I. Lissenberg-Witte BL
Department of Epidemiology and Data Science, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

I.M. Verdonck-de Leeuw IV
Department of Behavioral and Movement Sciences, Section Clinical Psychology, Vrije Universiteit, Amsterdam Public Health, Amsterdam, The Netherlands.
Department of Otolaryngology-Head and Neck Surgery, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands.

Chapter information

Chapter 2.

Incidence and types of complications after ablative oral cancer surgery with primary microvascular free flap reconstruction.

Published in: *Medicina Oral Patología Oral y Cirugia Bucal,* 2015

Authors:
J.N. Lodders
S. Parmar
N.L.M. Stienen
T.J. Martin
K.H. Karagozoglu
M. Heymans
B. Nandra
T. Forouzanfar

Authors' contributions:
Study concepts and design: JL, TF
Data collection: JL, BN, NS
Data analysis: JL, MH
Manuscript preparation: JL, NS
Manuscript review: JL, SP, TM, HK, MH, TF

Funding sources:
None

Conflicts of interest:
None

Chapter 3.

Incidence of symptomatic venous thromboembolism in oncological oral and maxillofacial operations: retrospective analysis.

Published in: *British Journal of Oral Maxillofacial S*urgery, 2015

Authors:
J.N. Lodders
S. Parmar
N.L.M. Stienen
T.J. Martin
K.H. Karagozoglu
M. Heymans
T. Forouzanfar

Authors' contributions:
Study concepts and design: JL, TF
Data collection: JL, NS
Data analysis: JL, MH
Manuscript preparation: JL, NS
Manuscript review: JL, SP, TM, HK, MH, TF

Funding sources:
None

Conflicts of interest:
None

Chapter 4.

Complications and risk after mandibular reconstruction with fibula free flaps in patients with oral squamous cell carcinoma: a retrospective cohort study.

Published in: *Journal of Reconstructive Microsurgery,* 2016

Authors:
J.N. Lodders
E.A.J.M. Schulten
J.G.A.M. de Visscher
T. Forouzanfar
K.H. Karagozoglu

Authors' contributions:
Study concepts and design: JL, ES, JV, TF, HK
Data collection: JL, HK
Data analysis: JL, TF, HK
Manuscript preparation: JL, HK
Manuscript review: JL, ES, JV, HK, TF

Funding sources:
None

Conflicts of interest:
None

Chapter 5.

Long-term outcomes of implant-based dental rehabilitation in head and neck cancer patients after reconstruction with the free vascularized fibula flap.

Published in: *Journal of Cranio-Maxillofacial Surgery,* 2021

Authors:
J.N. Lodders
F.K.J. Leusink
A. Ridwan-Pramana
H.A.H. Winters
K.H. Karagozoglu
H. Dekker
T. Forouzanfar
E.A.J.M. Schulten

Authors' contributions:
Study concepts and design: JL, FL, ES
Data collection: JL, HD
Data analysis: JL, FL, ES
Manuscript preparation: JL, FL, ES
Manuscript review: JL, FL, AR, HW, HK, TF, ES

Funding sources:
None

Conflicts of interest:
None

Chapter 6.

Implant-based dental rehabilitation in head and neck cancer patients after maxillofacial reconstruction with a free vascularized fibula flap: the effect on health-related quality of life

Published in: *Support Care Cancer,* 2022

Authors:
J.N. Lodders
G.J.C. van Baar
M.R. Vergeer
F. Jansen
E.A.J.M. Schulten
B.I. Lissenberg-Witte
I.M. Verdonck-de Leeuw
T. Forouzanfar
F.K.J. Leusink

Authors' contributions:
Study concepts and design: JL, FL
Data collection: JL, GB
Data analysis: JL, GB, BL
Manuscript preparation: JL, GB
Manuscript review: JL, MV, FJ, ES, BL, IV, TF. FL

Funding sources:
None

Conflicts of interest:
None

Appendix

Dankwoord

Dankwoord

Zonder hulp van mijn promotoren, copromotor, medeauteurs, vrienden en familie was dit proefschrift niet geworden zoals het nu is. Hieronder wil ik graag een aantal personen in het bijzonder bedanken.

Prof. dr. T. Forouzanfar, promotor. Beste Tim, bedankt voor de begeleiding van mijn onderzoek en de kansen die je me hebt geboden. Naast het feit dat ik altijd bij je binnen kon lopen voor vragen, had je altijd de juiste woorden om te motiveren. Gelukkig heb ik niet alleen op het gebied van onderzoek van je mogen leren, maar ook van je klinische kennis en vaardigheden.

Prof. dr. E.A.J.M. Schulten, promotor. Beste Bert, bedankt voor de bijdragen aan de manuscripten en de sparsessies. Door jouw vakinhoudelijke en taalkundige kennis is het proefschrift geworden tot wat het nu is. Jouw oog voor detail is uniek. Daarnaast wil ik je bedanken voor de mogelijkheid om de opleiding tot MKA-chirurg te doorlopen. Ik heb met plezier de (poli)klinische kneepjes van het vak geleerd.

dr. F.K.J. Leusink, copromotor. Beste Frank, dank voor je onuitputtelijke enthousiasme voor onderzoek. Je drive heeft mij meermaals geholpen de juiste energie te vinden voor het afronden van dit proefschrift. De vele brainstorms die vaak tot laat duurde, en vaak zeer vruchtbaar waren, zullen me bij blijven.

De leescommissie, **prof. dr. J.G.A.M de Visscher, prof. dr. L.E. Smeele, prof. dr. C.R. Leemans, dr. E.M. van Cann, prof. dr. M.J.H.Witjes** en **prof. dr. J.C. Jansen,** bedankt voor jullie tijd en de beoordeling en het proefschrift. Tevens wil ik diegene bedanken die hebben plaatsgenomen in de oppositie tijdens de verdediging van dit proefschrift.

Mijn paranimfen, Christopher Tan en Guus van Baar. **Chris,** onze carrière heeft veel ''first-timers'' met voornamelijk hoogtepunten. Samen kiezen trekken in een huisartsenpraktijk tot samen zelfstandig orthognatische chirurgie uitvoeren. Zoals je zelf altijd zegt, ''we weten wat we aan elkaar hebben''. Helaas ook een klein dieptepuntje: onze eerste ''bad-split'' welke voornamelijk jij hebt opgelost. Chris je bent een top collega, maar bovenal een topvriend. Veel succes in het NWZ! **Guus**, dank voor je geduld en je onmisbare input in het onderzoek. De avonturen door de gangen van de het VUmc en ACTA, Rome, Barca, enz. zijn onvergetelijk. Net zoals de KIO's waar we op dag 2 steevast ''wat'' later aankwamen. Zonder jou was het inderdaad 90 : 10 geweest, dank daarvoor. Veel succes met de laatste fase van je opleiding en uiteraard met het verdere vervolg.

drs. K.H. Karagozoglu, beste **Hakki**, ik heb je feedback op mijn manuscripten altijd als waardevolle bijdrage gezien. De uren in de operatiekamer hebben mij een beeld gegeven van de complexe oncologische behandelingen en hebben mijn ambitie aangewakkerd om een fellowship hoofd- hals oncologie te volgen. Tot volgend jaar!

Dear consultants of the department Oral and Maxillofacial Surgery Queen Elisabeth Hospital, Dear mr. **S. Parmar**, dear Sat, Dear mr**. T.J. Martin**, dear Tim, dear **Mr Praveen,** dear Prav, thank you for the opportunity to work with you and your team. It has been a while, but it was a great pleasure doing research in Birmingham and to see such passionate and skilled surgeons. I look forward meeting you again!

prof. dr. J.G.A.M. de Visscher, Beste **Jan**, graag wil ik je ook apart nog bedanken. Het enthousiasme waarmee je werkt, zowel klinisch als wetenschappelijk, is zeer aanstekelijk. De lessen die je me hebt meegegeven zal ik niet snel vergeten.

AIOS MKA-chirurgie, beste **Peter, Elisabeth, Arjan, Chris, Kitty, Guus, Floris, Stan, Robin, Pamela, Jesper, Karel, Jorrit, Thijs** en **Rebecca,** dank voor het aanhoren van mijn eindeloze geklaag en uiteraard ook dank voor het warme bad waarin ik belandde bij de start van mijn opleiding MKA-chirurgie. Door jullie heb ik me altijd zeer welkom gevoeld en ging ik met veel plezier naar mijn werk. Maar misschien wel het belangrijkste, dank voor de avondjes (en wintersporten) met veel gelach (en bier)!

Uiteraard mijn maatjes van tandheelkunde. Als Rotterdams ‘’jongetje’’ studeren in Amsterdam, gelukkig had ik jullie! De onvergetelijke tijden op de Poeldijkstraat tot in de late uurtjes met wat Kumala! **Tim, Duy, Jeffrey, Mark, Han, Kim en Martin** we zijn wat ouder, maar het vervolg op de Poeldijkstraat gaat er zeker komen.

Mijn geneeskunde maatjes, **Anna, Niels** en **Ruben,** het waren mooie tijden en lange dagen als coassistent. Het ritueel om de elk coschap af te sluiten met bier mis ik misschien wel het meeste, de dag daarna overigens niet. Het ga jullie goed! Ik ga ervanuit dat we elkaar tegenkomen op de operatiekamers.

De drie musketiers, **Kevin** en **Jerry**, samen met jullie ben ik opgegroeid in Hoogvliet. Van mijn vrienden ken ik jullie het langst. Toen ik nog dik was, (en jij ook Kevin), hebben we straten en met name de visvijvers van Hoogvliet onveilig gemaakt. Ik heb geweldige herinneringen aan die tijd. Ik kijk uit naar herbeleving van de onvergetelijke avonden stappen, gamen, voetballen, filosoferen enz. Ik wens jullie ontzettend veel geluk in de toekomst!

Mijn schoonfamilie, **Elly, Jan** en **Paul**, dank voor jullie empathie, jullie hulp en steun. Ik prijs me gelukkig met jullie in de familie.

Mijn ouders, **Joop** en **Wilma**, door jullie vertrouwen, liefde en steun ben ik geworden tot wie ik nu ben. Bij jullie kon ik altijd terecht, ongeacht de situatie. Ondanks de gezondheidsuitdagingen die jullie hebben doorstaan, doen jullie er alles aan om er het beste van te maken. Pap, Mam, ik had me geen betere ouders kunnen wensen en ik voel me bevoorrecht en trots om zulke geweldige ouders te hebben.

Mijn zus, **Claudia** en haar partner, **Remko**, we hebben samen veel meegemaakt, van verdriet tot geluk. Ondanks dat we onze eigen wegen bewandelen, merk ik dat onze band niet verwatert. Als ik jullie hulp nodig heb, kan ik altijd bij jullie terecht. Jullie staan altijd voor mij en mijn gezin klaar, waarvoor dank.

Als laatste, lieve, allerliefste **Niki**, ik kan een uitgebreid verhaal schrijven over onze 12 jaar samen, maar dat ga ik niet doen, zoals je me kent. Ik wil je bedanken voor je onvoorwaardelijke liefde, de ruimte die je me hebt gegeven de afgelopen jaren, je steun en ga zo maar door. Zoals we wel eens zeggen, heb je nog wat tegoed van me. Als ik terugdenk aan onze studietijd is er een hoop veranderd. We hebben een fijn gezin met twee gezonde en prachtige kinderen, Pipp en June. Ik ben ervan overtuigd dat we nog vele mooie jaren van geluk voor ons hebben. Maak je geen zorgen, we zullen zeker trouwen. **Pipp** en **June**, mijn geweldige dochters, jullie groeien veel te snel op. Bijna elke dag maken jullie me blij met knuffels en kusjes. Ik ben trots op jullie; met al jullie vrolijkheid en liefde zijn jullie het mooiste in mijn leven."

Appendix

Curriculum vitae

Curriculum vitae

Joni Lodders was born on June 12, 1989, in Rotterdam, the Netherlands. After graduating from the Einstein Lyceum in Hoogvliet, he started his dentistry study in 2007 at the Academic Centre for Dentistry Amsterdam (ACTA). Graduating cum laude from ACTA in 2013, he went on to pursue his medical study at VU University Amsterdam, where he graduated cum laude in 2017. During his medical study, he began his PhD research project on free flap reconstruction and implant-based dental rehabilitation in oral cancer patients. In 2019, he commenced his training in Oral and Maxillofacial Surgery at the Amsterdam University Medical Center, successfully completing it in 2023. Currently, he is undertaking a fellowship in Head and Neck Surgery at the Netherlands Cancer Institute (Antoni van Leeuwenhoek).

Appendix

List of publications

List of publications

In this thesis

Lodders JN, Parmar S, Stienen NLM, Martin TJ, Karagozoglu KH, Heymans M, Baljeet Nandra, Forouzanfar T. Incidence and types of complications after ablative oral cancer surgery with primary microvascular free flap reconstruction. *Medicina Oral Patología Oral y Cirugia Bucal 2015;*20(6):744-750.

Lodders JN, Parmar S, Stienen NLM, Martin TJ, Karagozoglu KH, Heymans M, Forouzanfar T. Incidence of symptomatic venous thromboembolism in oncological oral and maxillofacial operations: retrospective analysis. *British Journal of Oral and Maxillofacial Surgery 2015;53*(3):244-250.

Lodders JN, Schulten EAJM, Visscher JGAM de, Forouzanfar T, Karagozoglu KH. Complications and Risk after Mandibular Reconstruction with Fibular Free Flaps in Patients with Oral Squamous Cell Carcinoma: A Retrospective Cohort Study. *Journal of Reconstructive Microsurgery 2016;32*(06):455-463.

Lodders JN, Leusink FKJ, Ridwan Pramana A, Winters HAH, Karagozoglu KH, Dekker H, Forouzanfar T, Schulten EAJM. Long-term outcomes of implant-based dental rehabilitation in head and neck cancer patients after reconstruction with the free vascularized fibula flap. *Journal of Cranio-Maxillofacial Surgery 2021;49(9):845-854.*

Lodders JN, Baar GJC van, Schulten EAJM, Forouzanfar T, Vergeer M, Jansen F, Verdonck-de-Leeuw IM, Leusink FKJ. Quality of Life in head and neck cancer patients who had undergone implant-based dental rehabilitation after maxillofacial reconstruction with the free vascularized fibula flap. *Support Care Cancer 2022;30(6):5411-5420.*

Other

Lodders JN, Schulten EAJM, Visscher JGAM de, Forouzanfar T, Karagozoglu KH. Reply to Letter to the Editor: Morbidity of the Free Fibula Flap Reconstruction in Head and Neck Malignancies. *Journal of Reconstructive Microsurgery 2017;33(5):379-380.*

Baar GJC van, Leeuwerik L, Lodders JN, Liberton NPTJ, Karagozoglu KH, Forouzanfar T, Leusink FKJ. A Novel Treatment Concept for Advanced Stage Mandibular Osteoradionecrosis Combining Isodose Curve Visualization and Nerve Preservation: A Prospective Pilot Study. *Frontiers in Oncology 2021; 11:630123.*

Baar GJC van, Lodders JN, Chhangur C, Leeuwrik L, Forouzanfar T, Liberton NPTJ, Berkhout ER, Winters HAH, Leusink FKJ. The Amsterdam UMC protocol for computer-assisted mandibular and maxillary reconstruction; a cadaveric study. *Oral Oncol 2022;*133:106050.

Baar GJC van, Lodders JN, Visscher JGAM. Een radiolucente afwijking distaal van de derde ondermolaar. *Ned Tijdschr Tandheelkd 2022;*129(10):391-393.

Lodders JN, Baar GJC van, Visscher JGAM. Een dubbelzijdige witte afwijking van het wangslijmvlies. *Ned Tijdschr Tandheelkd 2022*;129(7-8):338-339.