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LONG-TERM FOLLOW-UP AND COMPUTER-ASSISTED SURGERY IN ORAL AND MAXILLOFACIAL RECONSTRUCTION

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PREFACE

This doctoral thesis consists of five research articles and one review, proceeded by a scientific introduction and concluded by a general discussion, clinical relevance and future recommendations. The research articles follow the standard scientific IMRAD structure (Introduction, Methods, Results and Discussion), and were based on the following peer-reviewed publications:

Article 1

Ma, H., Van Dessel, J., Shujaat, S., Bila, M., Gu, Y., Sun, Y., Politis, C. and Jacobs, R., 2021. Long-term functional outcomes of vascularized fibular and iliac flap for mandibular reconstruction: A systematic review and meta-analysis. *Journal of Plastic, Reconstructive & Aesthetic Surgery*, *74*(2), pp.247-258.

Article 2

Ma, H., Shujaat, S., Bila, M., Nanhekhan, L., Vranckx, J., Politis, C. and Jacobs, R., 2020. Survival analysis of segmental mandibulectomy with immediate vascularized fibula flap reconstruction in stage IV oral squamous cell carcinoma patients. *Journal of Stomatology, Oral and Maxillofacial Surgery*, 123(1):44-50.

Article 3

Ma, H., Van Dessel, J., Shujaat, S., Bila, M., Sun, Y., Politis, C. and Jacobs, R., 2022. Long-term survival of implant-based oral rehabilitation following maxillofacial reconstruction with vascularized bone flap. *International Journal of Implant Dentistry*, *8*(1), pp.1-11.

Article 4

Ma, H., Shujaat, S., Bila, M., Sun, Y., Vranckx, J., Politis, C. and Jacobs, R., 2021. Computer-assisted versus traditional freehand technique for mandibular reconstruction with free vascularized fibular flap: A matched-pair study. *Journal of Plastic, Reconstructive & Aesthetic Surgery*, *74*(11), pp.3031-3039.

Article 5

Ma, H., Shujaat, S., Van Dessel, J., Sun, Y., Bila, M., Vranckx, J., Politis, C. and Jacobs, R., 2021. Adherence to Computer-Assisted Surgical Planning in 136 Maxillofacial Reconstructions. *Frontiers in Oncology*, *11*.

Article 6

Ma, H., Van Dessel, J., Bila, M., Sun, Y., Politis, C. and Jacobs, R., 2021. Application of Three-Dimensional Printed Customized Surgical Plates for Mandibular Reconstruction: Report of Consecutive Cases and Long-Term Postoperative Evaluation. *Journal of Craniofacial Surgery*, 32(7), pp.e663-e667.

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Table of Contents

List of Abbreviations

3D	Three-Dimensional
ASA	American Society Of Anaesthesiologists
CAS	Computer-Assisted Surgery
CBCT	Cone-Beam Computed Tomography
CI	Confidence Intervals
CT	Computed Tomography
CTA	Ct Angiography
DCIA	Deep Circumflex Iliac Artery Flap
HR	Hazard Ratio
MINORS	Methodological Index For Non-Randomized Studies
MOOSE	Meta-Analysis Of Observational Studies In Epidemiology
OCC	Oral Cavity Cancer
OMF	Oral And Maxillofacial
OSCC	Oral Squamous Cell Carcinoma
PEG	Percutaneous Endoscopic Gastrostomy
PRISMA	Preferred Reporting Of Systematic Reviews And Meta-Analyses
PSPP	Patient-Specific 3D-Printed Plates
QOL	Quality Of Life
STL	Standard Tessellation Language
STROBE	Strengthening The Reporting Of Observational Studies In Epidemiology
TTI	Time To Therapy Initiation
VBF	Vascularized Bone Flaps
VFF	Vascularized Fibula Flap
VIF	Vascularized Iliac Flap
VSP	Virtual Surgical Plans

Chapter 1: General introduction, Aims & Hypotheses

1.1 Introduction

The oral and maxillofacial regions, including the oral cavity, jaws, face, skull, head and neck as well as associated structures, are important functional areas of the body.[1] Oral functions, such as mastication, speech, and swallowing, are very important for oral health. Furthermore, saliva influences important aspects of life such as the ingestion and lubrication of food, while the tongue plays a role in holding food clusters in the mouth and transporting them to the pharynx. The base of the tongue produces swallowing pressure in the pharynx.[2] The loss of hard and soft tissue in the oral and maxillofacial region may severely impact the patients' quality of life.[3] What is worse is that facial tissue loss or asymmetry by disease or surgery may seriously affect the patient's mood and even lead to psychological disorders.[4]

With the advancement of modern surgical techniques and concepts, patients with oral and maxillofacial defects caused by maxillofacial diseases can be treated with effective reconstructive surgeries. Moreover, with advancing digital technologies, efficient and accurate computer-assisted oro-maxillofacial surgery has become the mainstream protocol for daily practice.[5]

1.2 Historical background of oral and maxillofacial reconstructive surgery

The resection of lesioned bone due to oral tumor osteomyelitis, and facial trauma will lead to the maxillofacial defect which is always a challenge to the clinicians and surgeons before the 20th century.[6] As mastication, speech and swallowing may be impaired due to the lack of functional dentition. Until the 1900s when Carrel, the first Nobel Prize winner surgeon, repaired and reconstructed defects in the oral area with small intestine tissue grafts.[7,8] However, reconstruction of the hard tissues of the oral cavity was not achieved until 1946 by Dr. Ivy using autologous rib bone.[9] Two decades later, Dr. Taylor used vascularized osteomyocutaneous flaps to repair both hard and soft tissue defects in the maxillofacial region, ensuring adequate blood supply and bone volume, thus achieving a high rate of surgical success and postoperative flap viability.[10] This technique has been overwhelmingly applied since the 1980s.[11] Since then, there are several donor sites for flap transfer to repair the oral and maxillofacial hard and soft tissue defect, such as the forearm flap, small bowed flap, vastus lateralis flap, lateral branchial flap, antebrachial flap, anterolateral thigh flap, and so on.[12,13] Among all of them, vascularized fibula flap, deep circumflex iliac artery flap and scapular flap are the most popular flaps for jaw reconstruction by oral and maxillofacial surgeons.[14-16] According to the characteristics of donor site flaps, there are advantages and disadvantages to different types of flaps. For instance, the sufficient length of fibular bone flap provides the long bony elements of the mandible combined with soft tissue defect.[17] Non-vascular bone grafts are usually a subset of autografts where the graft is completely dependent on the recipient's vasculature and are indicated for defect sizes less than 6 cm. Five centimeters is the maximum defect size that can be reconstructed with NVBG. Beyond 5 cm, the graft needs to provide its blood supply in the form of a vascularized graft, since NVBG is completely dependent on the blood vessels at the recipient site. While, Vascularized free muscle flaps are indicated for complex reconstruction caused by treatment of osteomyelitis or head and neck tumor, such as the defects requiring filling of dead space, coverage of exposed vital structures, or exposed orthopedic and functional reconstruction of muscle loss or absence in congenital conditions.[18] In addition, due to its specific form and cortical structure, this graft type is well suited to replace the condyle.[19] However, the limited bone height makes it difficult for second-stage oral rehabilitation by dental implants.[20] The vascular supply of the peroneal flap is based on the peroneal artery (FA), which arises from the tibiofibular trunk (TTF) after the branching of the posterior tibial artery (PTA). It arises from the tibiofibular trunk (TTF) after branching from the posterior tibial artery (PTA). The tibial trunk continues as the popliteal artery (PA) after branching from the anterior tibial artery (ATA). Preoperative imaging of the vascular status of the lower extremities is mandatory to diagnose any anatomical variants.[21] There is low-quality evidence from one meta-analysis, which suggested that conventional preoperative angiography is necessary for all patients undergoing free fibular flap harvesting. Physical examination alone is not sufficient to detect vascular malformations that may lead to limb compromise or failure to successfully harvest the free fibula.[22] Therefore, the CTA is always required before a fibular bone graft in clinical practice. By contrast, the Iliac is superior than VFF with enough bone height for postoperative dental implant placement.[23] Possible complications of DCIA include injury to the lateral femoral nerve resulting in temporary loss of knee extension, asymmetry and herniation by the removal of both cortical bones.[24] Considering these limitation, some surgeons have contributed to modify the flap for reconstruction. To enhance the bone height, Horiuchi et al, introduced the double barrel for fibular graft. The harvested fibula was cut into several parts, folded into two parallel lengths, and secured along the lower edge of the mandible and the alveolar ridge in order to provide over 4 cm of alveolar height without compromising bone viability.[25] Combined flaps are advocated when the complex defect is caused by extensive composite resection due to T3 or T4 head and neck cancer. From follow-up of patients after an anterolateral thigh free flap combined with a vascularized fibroperiosteal flap, reconstruction of extensive composite defects in the oro-mandibular region seems to be a good treatment option both aesthetically and functionally.[26]

1.3 Historical background of computer-assisted surgery

With advances in computer science and materials science, in 2009 Dr. David and other researchers firstly introduce computer-assisted surgery (CAS) in oral and maxillofacial reconstruction. It refers to a process that includes virtual surgical planning, computer-aided design and modeling/rapid prototyping or computer-aided manufacturing (CAD/CAM) and can also be related to intraoperative navigation and includes virtual surgical planning, computer-aided design and modeling/rapid prototyping, or computer-aided manufacturing (CAD/CAM), which can also be associated with intraoperative navigation.[27] More precise and portable procedures can be performed. This has reduced the time spent in surgery, making it more predictable and reducing the training cycle for young surgeons.

The routine workflow of CAS starts with the acquirement of radiographs from CT, CBCT, or MRI.[28] Then the medical engineer or radiologist will import the saved DICOM data to specialized image processing software, such as Materialise Mimics, which is used to create 3D surface models from 2D image data stacks. These 3D models can then be used in a variety of engineering applications. [29] By pre-processing the raw data, engineers can separate the soft and hard tissues of the region employing threshold segmentation to get the virtual anatomical structure required by the physician.[30] Based on the virtual 3D human structures, the medical engineer can simulate the oral cancer resection and vascularized bone flap preparation and fabrication.[31] After the simulation of the virtual surgery, the medical engineer will design the surgical templates which is a guide designed to direct implant placement, head and neck tumor resection, osteotomy, and graft bone repositioning. Preoperative plans can be transferred to the intraoperative surgical site, and surgical precision, safety and reliability can be improved attributed to the surgical templates.[32] After the printing of 3D models including the skull, bone segments, cutting guides, fabrication gates, the clinicians will pre-bent the reconstructive plates based on the printed models. During the surgery, the surgeon resects the mandible or maxilla according to the cutting guides and then prepares the vascularized bone flap with the help of guided cutting templates. Finally, the grafted bone will be placed to the pre-planned suitable location by the fabrication guide and fixed by the pre-bent reconstructive plates. From a match-pair study, the ischemia time, hospitalization days, ICU days, intraoperative bleeding volume and operation time were decreased in the CAS group compared with the Non-CAS group.[33] Ischemia time, as an indicator influencing the implication of flap survival and outcomes, was significantly decreased which is the main advantage of CAS in vascularized bone graft surgery.[34] However, the drawbacks of CAS can also not be neglected. Firstly, the cost of materials and labor force is much higher than traditional protocol. Then the gap between the virtual surgical design and planned surgery, mechanical errors, human errors, complex or complicated defect conditions and patient condition alteration may lead to non-adherence of CAS.[35] Additionally, the in-house workflow also requires high resolution CT images (at least 1.00 mm per slice) and high-precision 3D printed machine, which is hard for all small or medium-sized regional hospitals around the world.[36]

Additionally, virtual surgical planning with CAD/CAM combined with surgical navigation has become the mainstream method for complex oral and maxillofacial reconstruction. Surgical navigation has been gradually applied in multiply medical areas.[37] The are some indications for navigated surgery: 1) Small jaw bones segments with many bone joints and weak points or regions.2) The surgical region is rich in facial nerves (which affect the motivation of facial muscles) and blood vessels (ischemic necrosis). 3) The maxillofacial region highly susceptible to be in trauma during the surgery.4) Aesthetic associated surgical region.[38]

The application of surgical navigation can minimize the risk and improve the accuracy of surgery.[39] It has many advantages over traditional surgical methods. Firstly, it is superior to two-dimensional image patterns and completely realizes three-dimensional images, which provides much more information to the surgeons. Secondly, in complex anatomical areas of maxillofacial surgery, traditional surgery relies mainly on the surgeon's experience. While assisted by this technology, unskilled surgeons can overcome the narrowed learning curve[40]. In particular, the development of image-guided technology, which allows the surgeon to follow the preoperative design plan in real-time during the surgical operation, has greatly reduced potential accidents during the operation.[41] Third, the use of surgical navigation technology allows for real-time tracking during surgery, which increases surgical accuracy, shortens operation time, and improves surgical efficiency.[42] Therefore, the technology has been applied in various fields, such as temporomandibular joint ankyloses, facial fractures, dental implant placement, foreign body removal, and head and neck tumor surgery.[43-45]

1.4 Oral rehabilitation after jaw reconstruction

The phrase "oral rehabilitation" is used to include several levels of oral treatment. Typically, dentists consider oral rehabilitation to mean the restoration of all teeth in a particular oral cavity. However, when only defective teeth are restored in any oral cavity, this can also be defined as oral rehabilitation.[46] After jaw reconstruction, the patients still face the problem of decreased quality of life because of a non-functional jaw without teeth. In addition, oral rehabilitation after jaw reconstruction is much more complicated. In this thesis, oral rehabilitation means dental implants based or removable prosthodontics dentures.

Prosthetic rehabilitation in patients undergoing reconstructive surgery by bone flaps is challenging for dentists due to the limitation of open mouth, the soft tissue barrier, the cortical bone properties, the limited bone volume, the reconstructive plates intervention.[47] Therefore, the functional rehabilitation of patients with fixed prostheses is not easy to realize. However, some researcher has introduced the concept that combined virtual planning of maxillofacial reconstruction, and virtual dental implant surgery simultaneously. By selecting the ideal position of the prosthesis, the accurate dental rehabilitation can be improved. Reconstruction of the virtual plan with a bone flap, along with dental implants and CAD/CAM plates, allows for early and functional dental rehabilitation. The integrated surgical plan shall involve the virtual plan, and the possible favorable implant position should match the position of the fabricated bone segments.[48]

There are several risk factors, which may lead to a low survival rate of dental implants after jaw reconstruction. The oral hygiene, systemic disease, smoking habit, the adjuvant therapy. Among all of them, radiotherapy is considered the most influential factor. There is reporting that the survival rate of dental implants in irradiated flaps is much lower. Fenlon et al. reported that immediate implant placement and implantation in the irradiated flap area were significantly associated with implant failure.[49] The time is another key factor, which is the key for well oral rehabilitation. Some researchers prefer to perform the dental implant placement simultaneously in the oral and maxillofacial reconstruction. However, considering the recurrence of oral tumor, the complications of the surgery the intervention by the inserted screws, reconstructive plates, and flap survival. More researchers advocated the second stage surgery when six to twelve months after the reconstruction. One may speculate that immediate implant placement and/or radiotherapy involving the area of the flap in which the implant was placed may impair graft viability and lead to implant failure, which needs to be investigated in future studies. khadembaschi et al. reported the negative impact of smoking on overall survival after implantation of composite free flaps reconstructed from benign and malignant lesions in the head and neck.[50] This has been confirmed by various studies due to the higher risk of postoperative infection, marginal bone loss, and implant failure in smokers. Previous evidence suggests that only a few studies have evaluated the relationship between oral hygiene and implant survival after jaw reconstruction. The lower survival rate in patients with poor oral hygiene may be due to plaque build-up that may induce an inflammatory response leading to secondary implant failure due to peri-implantitis.[51,52]

The higher survival rate of implants in native bone compared to grafted bone is consistent with the findings of Ch'Ng et al. and Jacobsen et al. who also reported a higher failure rate of implants placed on bone flaps compared to the native jaw bone.[53,54] The most likely cause could be the effects of radiotherapy, poor oral hygiene, and/or smoking. Previous studies have also observed the detrimental effects of radiotherapy on reconstructed bone and native bone sites, which leads to higher implant failure and an increased risk of patients suffering post-implant surgical complications.[55] To achieve a high implant survival rate after reconstructive surgery, it is crucial to develop a patient-specific treatment plan that takes into account the impact of the above-mentioned risk factors at the individual and cumulative level. For the other patients who are not suitable for dental implants surgery, removable prosthodontics are selected for functional oral rehabilitation. If oral rehabilitation is not able to be established when the flap is lost or occlusal function cannot be established due to the absence of the necessary occlusal muscles and temporomandibular joints, nasal feeding will be inserted to provide necessary nutrition for the patients.

1.5 Fixation materials and methods in oral and maxillofacial reconstruction

To maintain a solid arch of facial contour, oral and maxillofacial defects secondary to oral tumor resection, jaw osteonecrosis, trauma and congenital jaw abnormalities need to be repaired by vascularized bone grafts and fixed by reconstructive plates. And craniomaxillofacial continuity can be restored successfully and effectively.[15,56-58] Such reconstructions and contour corrections can also be achieved with a virtual surgical plan (VSP) in combination with 3D printed surgical models and/or pre-bent titanium plates.[59,60]

The reconstructive titanium plates appear to be ideal materials for fixing bone segments considering the well tolerance with living tissues in vivo and vitro studies.[61,62] Oral and maxillofacial reconstruction with titanium plates alone, or by grafted bone combining the pre-bent titanium reconstructive plates or mini-titanium plates, can provide enough mechanical strength and stabilize the craniomaxillofacial segments. However, there are also disadvantages of reconstructive plates for fixation. In cases, the tumor invading the outer cortex, or when serial excisions with the facial skin are required, it is impossible to pre-bend the reconstructed plate as planned. Perioperative problems include increased costs, surgical complexity, difficulty in using large screws in thin cortex, interference with vascular stalks, and metal fatigue when bending the plate in the sagittal plane. Worse yet, late complications include stress shielding of the grafted bone, palpable hardware, obstruction of the intraosseous implants, which influence subsequent oral rehabilitation.[63,64] With the advantage of easier placement compared with reconstructive plates, lower contour and malleability, the titanium mini-plates promise precise contouring. However, there is no evidence that increased rigidity offered by reconstruction plates influences the rate of plate exposure, surgical infection and bone or plate removal comparing the mini-plates.[65]

Yet and optimally, to achieve patient-specific reconstructive plates with proper screw angulation and implant positions readily in place was advocated recently. The utilization of PSPP and surgical templates have already been applied for various oral and maxillofacial surgery procedures with positive feedback, such as orthognathic surgery, trauma surgery, distraction osteogenesis, cranioplasty, tumor resection surgery.[66-70] While it may provide the surgeon with better accuracy, save time and help to reduce surgical complications, one should bear in mind that it may cost more money and need more effort preoperatively.[71]

During the past decade, there has been an increasing interest in personalized treatment. A virtual surgical plan combined with 3D printing technology has played a significant role in oral and maxillofacial reconstruction. Based on the accumulated advantages of the virtual surgical plan and surgical model and comparison with traditional oral and maxillofacial reconstruction, the CAD/CAM technology applied in surgery was appreciated and recommended by surgeons. From literature reviews, less operation time, better aesthetic results, and decreased incidence rate of complications were frequently reported.[72] However, there were also negative points, such as extra cost of the objects, prolonged surgical preparation period, rejection of implanted material, and undesirable match between the bone and implanted titanium plates.[73] With the advent concept of Precision Medicine in various clinical disciplines, future researchers and surgeons may no longer satisfy with preoperative pre-bent titanium plates and 3D models. Patient-specific, printed titanium implants will gradually become mainstream.[74]

It is easy to find the benefits of patient-specific surgery. By selecting the plate features according to the different patients' conditions, surgeons and medical engineers can customize and provide a patient-specific solution precisely.[75,76] Compared with pre-bent plates, patient-specific plates are 3D-milled based on the anatomy structure, eliminating the time for adaptation. Moreover, the induced stress, which is generated in the surgeries by pre-bent plates, will disappear during the customized surgery. Moreover, the accuracy of PSPP is high saving donor site bone and morbidity, meanwhile reducing unexpected events and complications. However, manufacturing time and material costs are relatively high comparing traditional surgery by or not by pre-bent palates. Additionally, the application universality is limited as the weakness of mechanical strength in patient-specific plates compared to conventional reconstructive palates. Experienced engineers and close collaboration are required.

The application of personalized titanium plates and short-term follow-up outcomes have already been reported in other studies.[77] The biocompatibility was optimal according to the relatively small size of the patient-specific plates, which may reduce contact surface with both hard and soft tissue. Small volume personalized titanium plates may also reduce the artifacts in the postoperative radiological examinations and make it convenient for the second stage of dental implant surgery. Furthermore, the universality of customized plates will lead to a comprehensive application without special morphology limitations. Overall, surgical planning right from the start makes future oral rehabilitation easier and more effective.

1.6 Aims and Hypotheses

The overall aim of this Ph.D. project is to assess the impact of presurgical planning and oral rehabilitation on the clinical outcome (tumor recurrence, pronunciation, physical activity, facial appearance, pain, xerostomia, mental disorder) and the long-term oral function after reconstructive surgery and oral rehabilitation. All the clinical parameters were collected and extracted from patients' clinical follow-up history, auxiliary examination records (pathology and radiology) and surgical history. The main aims are as follows:

1) The long-term outcomes of patients after maxillofacial reconstruction.
2) The pitfalls and pearls of CAS versus traditional freehand procedures.

3) The CAS compliance for initially planned maxillofacial reconstruction and to identify potential influential factors that might affect its adherence to the initially planned CAS.

Hypotheses are:

1). Computer-assisted surgical planning might improve the clinical outcome (operation time, ischemia time, hospitalization days, ICU days and intraoperative bleeding volume).

2). Maxillofacial reconstructive surgical procedures offer optimal compliance to the initially planned CAS. These investigations involve the following topics:

Chapter 2: Long-term functional outcomes of vascularized fibular and iliac flap for mandibular reconstruction: A systematic review and meta-analysis.

Chapter 3: Survival analysis of segmental mandibulectomy with immediate vascularized fibula flap reconstruction in stage IV oral squamous cell carcinoma patients.

Chapter 4: Survival analysis and prognostic factors of dental implants in patients after oral and maxillofacial reconstruction by vascularized flaps.

Chapter 5: Computer-assisted versus traditional mandibular reconstruction by a free vascularized fibular flap: A matched-pair study.

Chapter 6: Adherence of CAS in maxillofacial reconstruction

Chapter 7: Long-term outcomes of three-dimensional printed customized surgical plates for mandibular reconstruction

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Chapter 2: Long-term functional outcomes of vascularized fibular and iliac flap for mandibular reconstruction: A systematic review and meta-analysis

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Abstract

Introduction

To date, there is a lack of evidence related to the long-term evaluation of recipient-site functional outcomes following mandibular reconstruction with vascularized bone grafts. Therefore, the aim of this systematic review and meta-analysis was to evaluate the long-term recipient-site functional outcomes in oral oncology patients requiring mandibular reconstruction with either vascularized fibular flap (VFF) or vascularized iliac flap (VIF).

Methods

An extensive electronic search was conducted in PubMed, Web of Science, Cochrane, and Embase databases for identifying articles published until April 2020. All papers were dual screened for eligibility in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses and Meta-analysis of Observational Studies in Epidemiology guidelines. The risk of bias was assessed using the MINORS tool. A meta-analysis of functional outcome parameters was performed to estimate single incidence rates.

Results

A total of 257 patients with an average follow-up period of over 12 months were included in this meta-analysis, where 174 patients underwent VFF reconstruction and 83 patients involved reconstruction with VIF. The functional outcomes in patients reconstructed with VIF showed improved scoring for mastication, deglutition, diet and speech. Speech showed highest score amongst all functional parameters, whereas, mastication was the most poorly recovered parameter in relation to reconstruction with both flaps. No significant difference in functional outcomes was observed between both flaps.

Conclusion

Current evidence seems to indicate that VIF offers improved long-term recipient-site functional outcomes. Yet, considering a high level of data heterogeneity in published studies, future long-term standardized comparative studies should be conducted.

Introduction

The mandible is an integral part of a human face in terms of both aesthetics and functionality. An intact mandible covers various functions, such as deglutition, speech, mastication, and airway support. Generally, ablative surgery for the treatment of oral and maxillofacial tumors requires mandibular resection which produces significant cosmetic and functional impairment, thereby, leading to poor health-related quality of life (HRQOL).[1] The post-resective mandibular reconstruction not only improves functional and cosmetic outcomes but also provides ample bone for the placement of osseointegrated dental implants which is essential for total oral rehabilitation. [2, 3]

For the past two decades, an improvement in microsurgical techniques and technological advancements have led to constant replacement of non-vascularized grafts (NVG) with free vascularized bone flaps (VBF) for reconstructing critical size mandibular bone defects with soft tissue coverage. The VBF offers a higher success rate of bone union, at the same instance, the cosmetic and functional score is superior compared to that of NVG. [4] For mandibular reconstruction, the most common potential VBF donor sites include scapula, fibula, iliac crest, and radial forearm.[5] The fibular and iliac crest VBFs are more widely accepted as a standard of reconstructing mandibular defects. However, each VBF has certain advantages and limitations with the success rate dependent on the defect site, defect size, donor site morbidity, flap survival, quality of life, and long-term aesthetic and functional outcomes.

Most of the previous studies have focused on the success and survival rate of iliac and fibular VBFs, whereas, long-term evaluation of functional outcomes at the recipient-site which can majorly affect quality of life so far received little attention.[6-10]Additionally, favorable short-term functional outcomes related to oral rehabilitation,[11,12] dental implant stability,[13-15] speech intelligibility,[16, 17] and mastication recovery following fibular and iliac VBF have been reported extensively.[18] Nevertheless, long-term evaluation of functional outcomes at the recipient-site which can majorly affect the quality of life has received little attention.

Therefore, the following systematic review and meta-analysis was conducted to evaluate the long-term recipient-site functional outcomes in oral oncology patients requiring mandibular reconstruction with either vascularized fibular flap (VFF) or vascularized iliac flap (VIF).

Materials and methods

Protocol and registration

This systematic review and meta-analysis was conducted following a predefined protocol registered in PROSPERO (CRD42019123857). The Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed. [19, 20]

PICO question

The review was designed based on the following PICO criteria (population, intervention, comparison, outcome): (P) patients with a mandibular defect following tumour resection, (I) vascularized fibula flap (VFF), (C) vascularized iliac flap (VIF), (O) assessment of postoperative recipient-site functional outcomes at a mean follow-up period of 1 year or more.

Search strategy

We searched PubMed, Web of Science, Cochrane, and Embase for studies published till April 2020. The search strategy combined database thesaurus terms (MeSH and EMTREE) and free terms in abstract and title (Table 1). All references were managed and duplicates were removed in EndNote basic (Web-based program, Clarivate Analytic).

Table 1 Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Study design	All studies reporting on mandibular reconstruction in oral oncological patients with vascularized bone graft	Case reports, case series with <10 patients, opinion articles, review articles, animal, cadaver, in vitro or in vivo studies
Participants	Oncological patients with vascularized bone graft reconstruction (fibular flap and/or iliac flap)	Congenital, traumatic, and children's mandibular defect cases
Follow-up period	$\geq$ 1 year	Less than 1 year
Outcome measures	Functional outcomes (mastication, diet, deglutination, and speech)	Nonfunctional outcomes
Publication year and language	Starting from the year 1955	Before the year 1955, Non-English language publications

Selection of studies

After filtrating databases, excluding duplicates and non-full text articles, two reviewers examined full-text articles and collected data in duplicate following the inclusion and exclusion criteria (Table 2). Literature reviewers, systematic reviews, case reports were not included in this selection but were surveyed as potential sources to find relevant missing articles in the search. The process of study selection was done in two phases, first screening titles, and abstracts, and then reading the full-text of articles meeting the inclusion criteria. At the end of the second phase, the two reviewers (HM and YG) provided a final judgment independently (include, exclude, or uncertain). In cases of disagreement, a third author (JVD) took a final decision for the inclusion after discussion with the first two reviewers in a joint meeting.

Data extraction and study characteristics

Two authors (HM and JVD) independently extracted data from the selected articles. The data were double-checked in a joint session with a third author (YG). The following parameters were extracted from each included study: name of the first author, year of publication, study design, number of participants, gender distribution, mean age, age range, mean follow-up time, follow-up time range, questionnaire type, defect classification, immediate postoperative and long-term flap survival rate. Additional parameters included deglutition, diet, mastication, speech, aesthetics, post-operative complications, oral rehabilitation, and chemo-radiotherapy. In the case of combined or missing parameters, the corresponding authors of the publication were contacted by email to request for the raw data.

Risk of bias assessment

The methodological index for non-randomized studies (MINORS) was utilized for the assessment of the quality of the included studies.[21] Out of the 13 included articles, two studies were categorized as comparative and 11 as non-comparative. A global ideal score of 16 was applied to non-comparative studies and 24 for comparative studies. Risk of bias assessment was scored as not reported (score 0), reported but inadequate (score 1), and reported and adequate (score 2). Discrepancies were resolved by consensus.

Table 2 Summary of study characteristics in the VFF group.

Author, Year	Study design	Participants (N=)	Gender	Mean age (range, years)	Mean follow-up time (range, months)	Questionnaire type	Complications (N, Type)	Adjuvant therapy (N, Type)	Oral rehabilitation (%)	Defect classification	Type of defect
Zhang et al., 2013	RS	31	18 m,13f	58(31-75)	44(24-72)	MOS SF-36/UW-QOL	11 had complications	19 RT or CHT	NR	NR	NR
Zavalishina et al., 2014	RS	11	4 m,7f	56(21-75)	12(NR)	UW-QOL/ Non-validated questionnaire.	3 leg pain,1 skin graft fail, difficulty bearing weight, 1 voice, 1 acute neurologic deficit, 1 wound dehiscence, 1 infected plate, and 1 mobility decrease	5 RT	NR	Urken	All PD
Yang et al., 2014	RS	34	25 m,9f	53(28-65)	27(12-48)	UW-QOL/OHIP-14	3 complicated wound healing, 4 ankle instability	20 RT or CHT	NR	NR	NR
Rogers et al., 2003	RS	15	9 m,6f	55(NR)	28(3-62)	AOFAS Ankle Score/UW-QOL/Hospital Anxiety and Depression Scale	2 flap loss, 6 infections, 5 SSG loss, 1 tendon exposure, 1 transient neurapraxia, others: 6	12 RT	NR	NR	NR
Raoul et al., 2009	RS	24	16 m,8f	46(19-72)	76(NR)	Non-validated questionnaire	NR	4 RT, 2 CHT	71%	Jewer	2 HD, 22 PD
Katsuragi et al., 2011	RS	12	6 m,6f	58(14-80)	16(12-33)	Non-validated questionnaire/Hirose's scoring system	2 salivary fistula, 1 abscess, and 1 partial necrosis of the skin flap	2 RT	51%	Jewer	All PD
Jarefors et al., 2017	RS	17	13 m,4f	67(43-79)	54(14-102)	UW-QOL/PSS (Head and Neck Performance Status Scale)	6 fistula, 4 flap rejection, and 3 suture dehiscence	9 RT, 1 CHT	NR	NR	All PD
Iizuka et al., 2004	RS	28	19 m,9f	58(NR)	45(>24)	Non-validated questionnaire	20 had complications	19RT	36%	NR	All PD
Politi et al., 2012	PS	11	NR	NR	NR	Non-validated questionnaire /UW-QOL/Ankle-Hind foot Scoring System	2 clawing of the great toe, 1 flap failure	NR	91%	NR	Only PD and HD included
Ooi et al., 2014	RS	30	14 m,16f	27(12-59)	59(NR)	Non-validated questionnaire	1 flap infection, 3 wound infection, and 1 haematoma	NR	60%	Jewer	Only PD

*RT: Radiotherapy, CHT: Chemotherapy, RS: Retrospective study, PS; prospective study, NR; Not reported, PD; Partial defect, and HD, Hemimandibular defect.

Statistical analysis

The binomial proportion confidence intervals (95% CI) and weights related to the recipient-site functional outcomes for VFF and VIF were computed separately utilizing Metaprop implemented in Stata v.14 (Stata Corp, College Station, TX, USA).[22] The functional outcomes in individual studies were scored as binary parameters: positive (good, very good or excellent) and negative (normal, bad, worse). The outcome rates were calculated by combining their proportions and estimation of single incidence rates was performed. Forest plots were constructed for the graphic representation of combined estimations. The I^2 statistics was used to quantify the heterogeneity and was classified as either low (25%), moderate (50%), or high (75%). [23, 24] Chi-squared and Fisher–Irwin tests were applied to identify whether the various combined outcome had statistical significance by utilizing SPSS 25(IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).[25]

Table 3 Summary of study characteristics in the VIF group.

Author, Year	Study design	Participants (*N*)	Gender	Mean age (range, years)	Mean follow-up time (range, months)	Questionnaire type	Complications (*N*, Type)	Adjuvant therapy (*N*, Type)	Oral rehabilitation (%)	Defect classification	Type of defect(*N*)
Shen et al., 2012	RS	13	5 m,8f	31(13-60)	18(12-22)	Non-validated questionnaire	NR	3 RT	100%	Jewer	HD: 3 PD:11
Jewer et al., 1989	RS	60	37 m,23f	NR(19-85)	>12(2-60)	Non-validated questionnaire	25 had complications	47 RT	33%	Jewer	HD: 13, PD: 47
Puxeddu et al., 2004	RS	12	11 m,1f	63(57-77)	21(6-64)	Functional Assessment Cancer Therapy General Scale questionnaires (FACT-G)/Performance Status Scale (PSS)	1 flap lost, 2 dehiscence, 4 wound healing	5 RT, 4 CHT, 1 RT+CHT	NR	Jewer	All PD
Rogers et al., 2003	RS	14	9 m,5f	61(NR)	39(6-100)	AOFAS/UW-QOL/HAD Anxiety and Depression Scores	1 flap loss, 2 infection, 1 transient neurapraxia, other problems 5	13 RT	NR	NR	NR
Politi et al., 2012	RS	13	NR	NR	NR	Non-validated questionnaire /UW-QOL/Ankle-Hind foot Scoring System	1 transient femoral palsy, 1 clawing of the great toe	NR	100%	NR	Only PD and HD included

*RT: Radiotherapy, CHT: Chemotherapy, RS: Retrospective study, PS: prospective study, NR: Not reported, PD: Partial defect, and HD: Hemimandibular defect.

Results

Study selection

A total of 1167 records were screened by title and abstract. The full-text was read from 389 articles. Only thirteen articles were considered eligible based on the inclusion criteria. The details of the study selection process are shown in Fig. 1. From the thirteen included studies, one was a non-randomized prospective study,[26] while the other papers were retrospective case series with more than 10 patients.[27-38] Eight articles[27, 29-33, 37, 38] reported on VFF reconstruction, three articles[34-36] included VIF and two articles[26, 28] compared both flaps. From the thirteen selected articles, twelve were included in the quantitative synthesis.

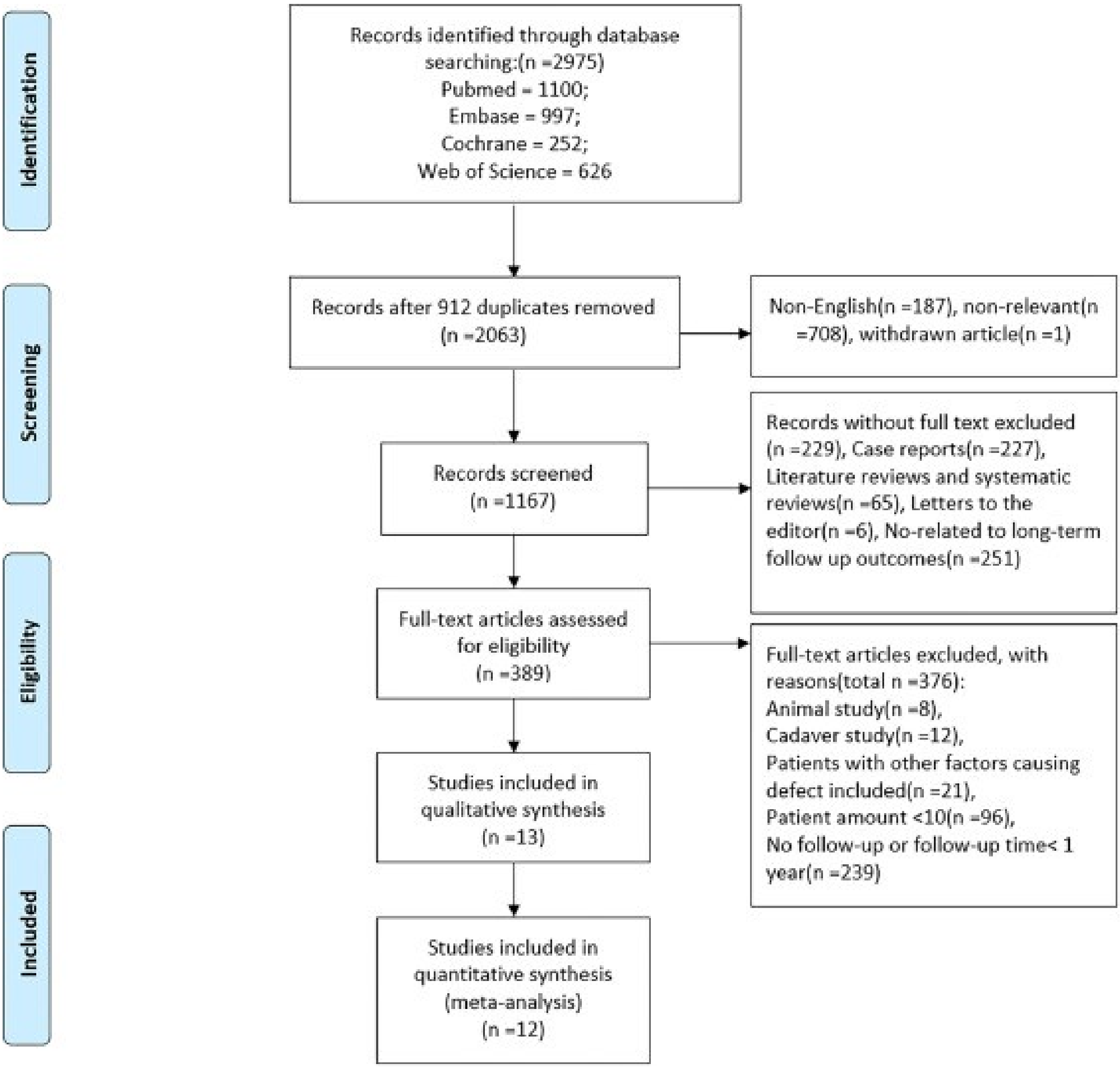

Figure 1. PRISMA flowchart.

Participants characteristics

Eight articles[27, 29-33, 37, 38] reported on reconstruction only with VFF, three articles[34-36] only with VIF and two articles[26, 28] reported comparisons between both flaps. Table 3 and Table 4 illustrate the participants characteristics. A total of 325 patients (194 male, 131 female, age range: 12-85 years)were included with a follow-up of 12 to 76 months, where, 213 patients (124 male, 78 female, age range: 12-80 years) underwent VFF reconstruction and 112 patients (62 male, 39 female, age range:13-85 years) involved reconstruction with VIF. The meta-analysis included 174 patients who underwent VIF reconstruction and 83 with VIF. The University of Washington Quality of Life (UW-QOL) was the most commonly utilized patient-reported validated questionnaire for evaluating the long-term functional outcomes in 6 out of 13 articles. The non-validated questionnaires were applied in 8 studies. [26, 27, 30-34, 39]

Surgical characteristics

The Jewer's method was the most commonly utilized classification method for classifying the mandibular defects.[27, 31, 32, 34-36] The type of mandibular defect was reported and classified in seven out of ten studies for VFF, whereas four out of five VIF studies reported the defect type. All patients in both groups underwent reconstruction of partial/ hemi-mandibular defect, and no studies involved complete mandibular reconstruction. Table 5 describes the number of mandibular defects based on their location (anterior, posterior, combination). All articles reported a flap survival rate after the mean follow-up endpoint. The pre- and/or post-operative radiotherapy was reported in eight VFF studies and four VIF studies. Five studies in the VFF group and three in the VIF group reported that more than half of the patients either received pre- or post-operative radiotherapy (Table 3-4).

Functional outcomes

Figure 2 and Figure 3 shows forest plots illustrating functional parameters scoring in both VFF and VIF groups. Additionally a summary of qualitative positive and negative functional outcomes associated with each VBF has been provided (Table 6). Five studies reported on deglutition in the VFF group and two studies in the VIF group. Both the VFF and VIF group showed improved deglutition at a long-term follow-up. Apart from one study in the VFF group, all other studies observed an improved deglutition in more than 60% of the patients. The meta-analysis showed improved deglutition scoring in the VIF group (0.92, CI: 0.78-0.1.00) than the VFF group (0.70, CI: 0.53-0.85). Nevertheless, no significant difference in improvement was observed.

Five articles reported on mastication in the VFF group and two in the VIF group, where more than 60% of patients showed improved mastication in two VFF studies and one VIF study. The overall masticatory outcome showed a higher score for the VIF group (0.62, CI: 0.42-0.80), whereas, a lower scoring was observed for patients reconstructed with VFF (0.38, CI: 0.03-0.84). No significant difference in mastication scoring was observed.

Nine articles reported on speech in the VFF group and four in the VIF group. All the studies in both groups reported over 60% cases with an improved speech performance, with three VFF studies showing good speech intelligibility in 100% cases.[27, 31, 32] However, the meta-analysis showed better speech in patients with VIF flap (0.93, CI: 0.79-1.00) than VFF (0.89, CI: 0.75-0.99) with no significant difference.

Five articles reported on the diet in the VFF group and four articles in the VIF group. Two studies in both groups reported improved diet scoring in more than 60% of the patients. Most of the patients showed a positive diet recovery in both groups, except for one study where less than half of the patients were able to eat a normal/regular diet. [37] The VIF group showed an improved diet (0.72, CI: 0.23-0.1.00) compared to VFF (0.57, CI: 0.46-0.68) with no significant difference.

Overall, the meta-analysis showed improved functional outcomes in patients reconstructed with VIF. However, no significant difference was observed between the functional parameters of both flaps. At the same instance, a high level of data heterogeneity (>50%) was observed for all parameters, except diet in the VFF group (0%) (Figure 2-3).

Facial aesthetics and quality of life

Eight articles reported aesthetics in VFF and three in the VIF group. Out of these studies, five VFF and two VIF studies showed improved long-term aesthetics in more than 60% of the patients (Table 6). The meta-analysis showed improved facial aesthetics in patients reconstructed with VIF (0.73, CI: 0.34-0.99) rather than VFF (0.70, CI: 0.53-0.85), however, no significant difference was observed. Furthermore, the quality of life was only evaluated in two VFF and one VIF study. [30, 33, 35] All studies showed improved or good QOL without any complaint related to general health. In ten studies, the overall VFF survival rate was 90.8% and 95.2% for the VIF. There was no statistical significance in flap survival rates between both flaps.

Table 4 The number of mandibular defects based on their location.

Flap type	VFF				VIF		
Author, Year	Anterior	Posterior	Combination	Author, Year	Anterior	Posterior	Combination
Zhang et al., 2013	NR	NR	NR	Shen et al., 2012	0	8	6
Zavalishina et al., 2014	0	3	6	Jewer et al., 1989	3	12	45
Yang et al., 2014	11	8	15	Puxeddu et al., 2004	0	8	4
Rogers et al., 2003	NR	NR	NR	Rogers et al., 2003	NR	NR	NR
Raoul et al., 2009	0	15	9	Politi et al., 2012	NR	NR	NR
Katsuragi et al., 2011	2	4	5	Total (*n*)	3	28	55
Jarefors et al., 2017	NR	NR	NR	Percentage (%)	3	33	64
Iizuka et al., 2004	0	12	16				
Politi et al., 2012	NR	NR	NR				
Ooi et al., 2014	1	19	10				
Total (*n*)	14	61	61				
Percentage (%)	10	45	45				

NR: Not reported.

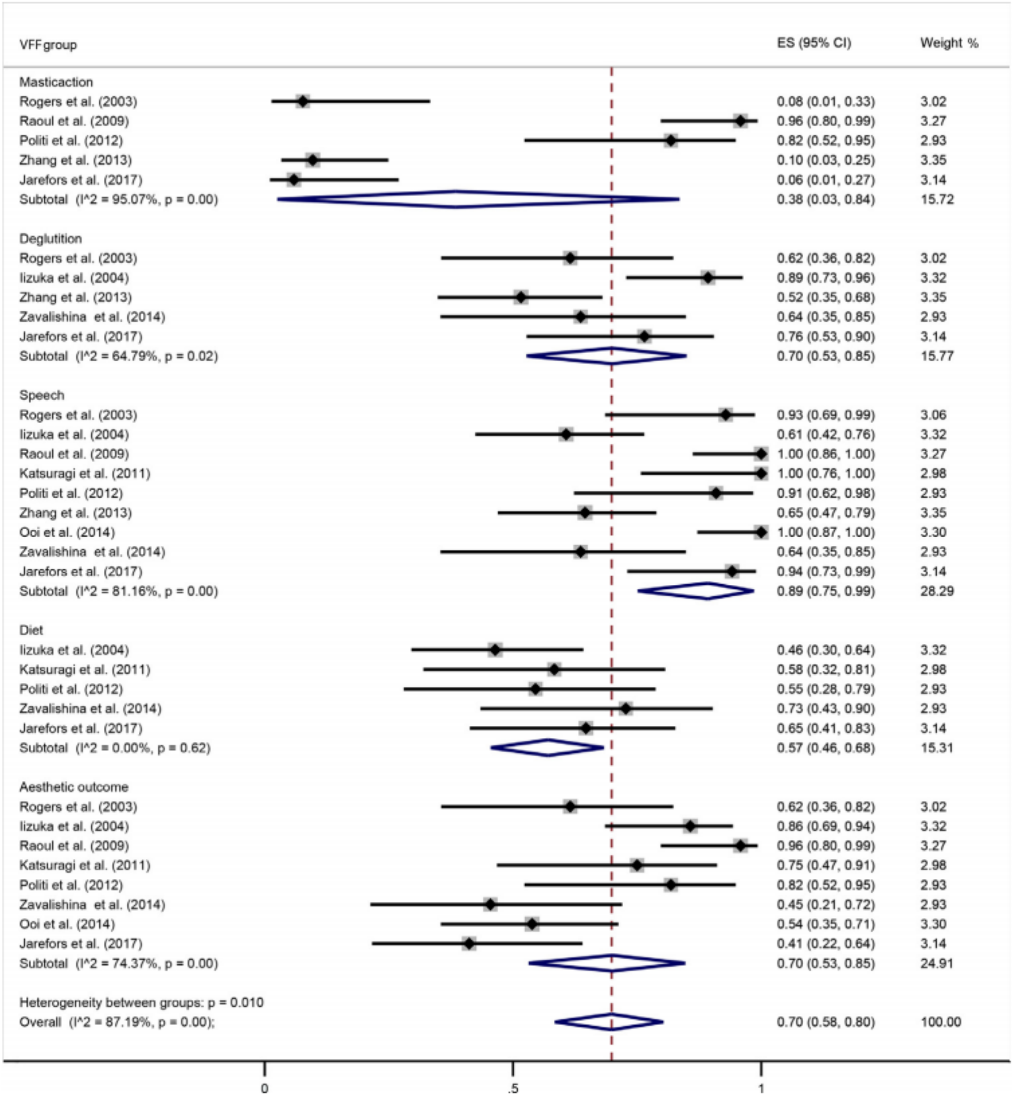

Figure 2 Forest plot illustrating functional parameters scoring in the vascularized fibular flap (VFF) group.

Risk of bias within studies

The MINORS scores applied to the studies showed a median score of 11/63% (CI: 95%) (Table. 7). In relation the non-comparative studies, we may speculate the following:1) All of the articles clearly stated the aim; 2) All of the articles had consecutively recruited patients; 3) Most of the studies prospectively collected data; 4) All studies endpoints were appropriate to the aim of the study; 5) No studies showed an unbiased assessment of the study endpoint; 6) All studies follow-up period was appropriate to the aim of its study; 7) Majority of the studies had more than 5% loss to follow-up; 8) None of the studies prospectively calculated the sample size. For the two comparative studies,[26, 28] the control group was not adequate because there was a historical comparison in these studies, with some confounding factors that could lead to interpretation bias. In the same instance, both comparative studies failed to provide an adequate statistical analysis.

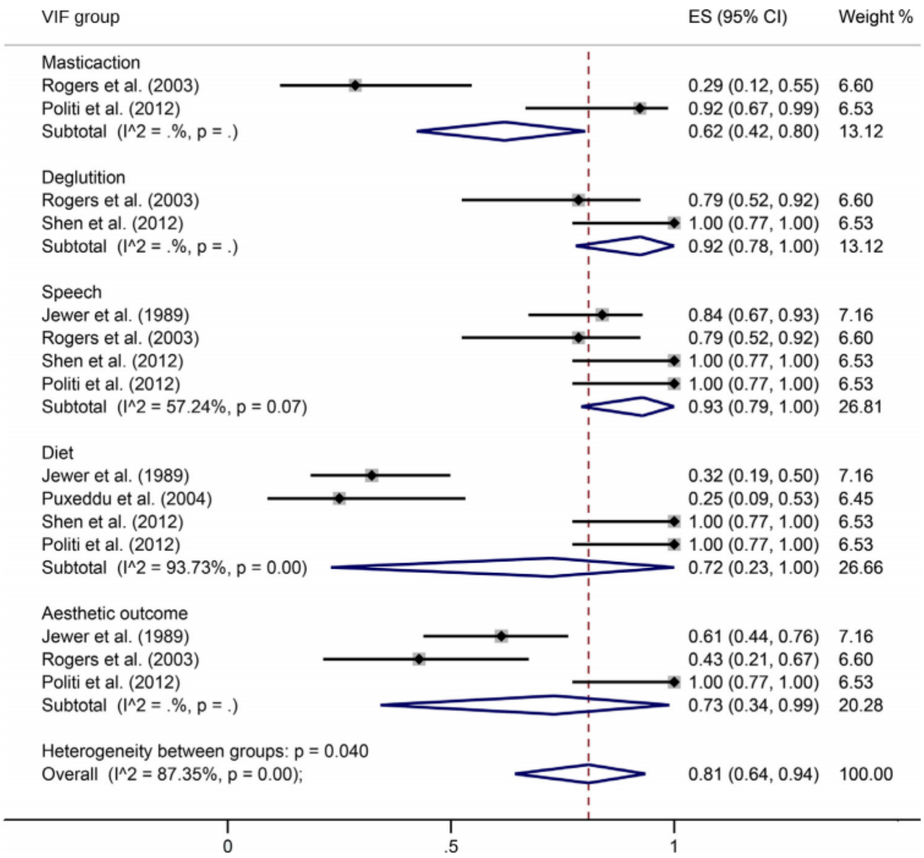

Figure 3 Forest plot illustrating functional parameters scoring in the vascularized iliac flap (VIF) group.

Discussion

The VFF and VIF have been known to be the optimal donor sites for mandibular reconstruction.[40-42] However, the long-term evaluation of functional outcomes related to both sites in critical sized mandibular defects has not been thoroughly reported. The VFF is considered to be a gold standard for mandibular reconstruction. [43]However, its long-term functional outcomes compared to that of VIF at the recipient-site requires more attention. Therefore, the following review was conducted to report on which flap offered the most optimal recipient-site functional results following mandibular reconstruction at a minimal follow-up of one year.

The results of the following study showed acceptable functional outcomes for all parameters. Both VFF and VIF did not show any significant difference in relation to the flap survival rate, functional outcomes and aesthetics, which was in accordance with previous studies. More than 50% of the mandibular defects in both VIF and VFF groups crossed the midline, where an improved scoring was observed in favor of VIF. Additionally VIF offered more favorable functional outcomes, regardless of the defect location. The bone height achieved with VFF is often insufficient and its dense cortical nature is not ideal for osseointegration of dental implants,[44] thereby influencing the postoperative oral rehabilitation which in turn could lead to compromised masticatory performance.[45] In contrast, the VIF flap provides sufficient bone dimensions with an optimal cortical and cancellous component for implant placement in patients with a mandibular defect of up to 10 cm in size.[46] Additionally, the studies included in the review showed that mastication was the most poorly recovered parameter in relation to reconstruction with both flaps, which could also be owed to the pre/post-operative delivery of radiotherapy. As radiotherapy exceeding 50 Gy significantly increases the risk of peri-implantitis and osteoradionecrosis, thereby, implant surgery was not carried out in such patients and traditional removable prosthesis led to minimal improvement in mastication irrespective of the graft type.[47, 48] The diet of patients is directly linked with masticatory performance as the type of food choice relies on the masticatory forces, thereby patients with VIF had improved diet score compared to VFF.

The deglutition was also better in the VIF group, perhaps owing to the fact that more patients receiving VFF suffered from a larger mandibular defect requiring reconstruction. Additionally, surgical reconstruction when combined with radiotherapy has been known to adversely affect deglutition and could be considered as a delineating factor.[49] The deglutition mechanism was also negatively affected in both groups when a scar tissue was present. [50]The VIF provided improved outcomes as all cases in this review were partial mandibulectomies, nevertheless, in total/subtotal mandibulectomies VFF is still considered as the graft of choice based on its greater length. However, no evidence was found assessing the long-term functional outcomes of vascularized bone grafts in total/subtotal mandibulectomy cases.

The main strength of this study was the long-term evaluation of the recipient-site functional parameters following reconstruction with vascularized fibular or iliac bone grafts which has received little attention in previous studies. In the same instance, our review was accompanied with certain limitations. Firstly, the variation in the follow-up period and utilization of non-validated questionnaires resulted in heterogeneity and skewness of the reported data. Secondly, inadequate sample size and loss of patients at follow-up in a few studies led to a lack of adequate power. Thirdly, most of the studies failed to provide the association between radiotherapy and functional outcomes. Finally, some studies failed to report on the type of mandibular defect and the segments of grafted bone flaps which led to reporting bias. However, based on studies that provided information related to the defect, VIF offered better functional outcomes than VFF. Further studies should be carried out utilizing standardized and validated questionnaires to optimize patient-related and surgery-related factors such as, age, follow-up protocol, tumor classification, resection site and flap design which might influence the final outcome.

Conclusion

Although the decision related to the graft selection bases on patient-related and surgeon related factors, defect classification and donor-site morbidity. Nevertheless, current evidence seems to indicate that VIF offers improved long-term recipient-site functional outcomes. Yet, considering a high level of data heterogeneity in published studies, future long-term standardized comparative studies should be conducted to evaluate which vascular flap offers the most optimal recipient-site functional outcomes.

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Table 5 Risk of bias assessment.

MINORS-tool	VFF group								VIF group			Both groups	
Study	Zhang 2013	Zavalishina 2014	Yang 2014	Raoul 2009	Katsuragi 2011	Jarefors 2017	Iizuka 2004	Ooi 2014	Puxeddu 2004	Shen 2012	Jewer 1989	Rogers 2003	Politi 2012
A clearly stated aim	+	+	+	+	+	+	+	+	+	+	+	+	+
Inclusion of consecutive patients	+	+	+	+	+	+	+	+	+	+	+	+	+
Prospective collection of data	+	x	+	x	+	+	+	+	+	x	x	+	+
Endpoints appropriate to the aim of the study	+	+	+	+	+	+	+	+	+	+	+	+	+
Unbiased assessment of the study endpoint	x	-	x	x	x	x	x	x	x	x	x	x	x
Follow-up period appropriate to the aim of the study	+	+	+	+	+	+	+	+	+	+	+	+	+
Loss to follow up less than 5%	-	-	+	x	x	+	-	-	-	x	-	-	x
Prospective calculation of the study size	x	x	x	x	x	x	x	x	x	x	x	x	x
An adequate control group	/	/	/	/	/	/	/	/	/	/	/	x	x
Contemporary groups	/	/	/	/	/	/	/	/	/	/	/	-	-
Baseline equivalence of groups	/	/	/	/	/	/	/	/	/	/	/	-	-
Adequate statistical analyses	/	/	/	/	/	/	/	/	/	/	/	+	-

VFF: Vascularized fibula flap, VIF: Vascularized iliac flap; Red color indicates not reported, yellow reported but inadequate or green reported and adequate.

Chapter 3: Survival analysis of segmental mandibulectomy with immediate vascularized fibula flap reconstruction in stage IV oral squamous cell carcinoma patients

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Abstract:

Purpose: This study aims to assess the survival rate of oral squamous cell carcinoma (OSCC) patients following immediate mandibular reconstruction with vascularized fibula flap (VFF) and to identify risk factors influencing the overall survival rate and postoperative outcomes.

Patients and Methods: Patients suitable for the inclusion criterion diagnosed and treated between January 1996 till June 2019 for OSCC were retrospectively reviewed (n = 74). Potential risk factors and postoperative outcomes were recorded and analyzed.

Results: The overall cumulative survival rate of patients was 0.52 at the end of 5th year. Overall, advanced pN stage ($p = 0.0422$), poor tumor differentiation ($p < 0.0001$), positive/close surgical margins ($p = 0.0209$), vascular invasion ($p = 0.0395$), perineural invasion ($p = 0.0022$) and tumor recurrence ($p = 0.0232$) were significantly related to a decreased cumulative survival. Tumor recurrence was significantly correlated with involvement of positive/close surgical margins, moderate ($p = 0.0488$), poor-differentiated tumors ($p = 0.202$) , extracapsular spread ($p = 0.0465$), absence of the computer-assisted surgery ($p = 0.0014$) and early complications ($p = 0.0224$). Pain was significantly associated with the positive extracapsular spread ($p = 0.0353$) and early complications ($p = 0.0127$).

Conclusion: The five-year survival rate of advanced OSCC patients after segmental mandibulectomy with fibula free-flap reconstruction was 52.4%. Clinical/pathological risk factors such as the pN stage, tumor differentiation, surgical margins, vascular invasion, perineural invasion, tumor recurrence significantly influenced the overall cumulative survival rate.

Introduction

Oral cavity cancer (OCC) is one of the most common subtypes of head and neck cancer accounts for around 25% of all head and neck malignancies. Amongst OCC, oral squamous cell carcinoma (OSCC) is the most prevalent malignant oral tumor worldwide, comprising nearly 90% of all oral tumors.[1] The management of OSCC frequently involves tumor ablation with mandibulectomy when the tumor approaches the alveolar ridge. Tumor resection is performed to ensure a 5mm free margin and this can require marginal or segmental mandibulectomy, depending on the size and location of the tumor.[2, 3] A marginal resection is carried out when the periosteal or cortical bone invasion is observed without the involvement of the mandibular marrow and when sufficient bone height exists, whereas, segmental mandibulectomy is feasible when tumor erodes into the marrow.[4] Generally, the segmental resected defect is reconstructed with either reconstruction plates combing a soft-tissue-only flap or vascularized osseous flaps. In some complex cases, two-flap reconstructions have also been recommended for repairing bone and soft tissue defects.[5] Thus, such complex surgical management most often require meticulous pre, peri and postoperative assessment as well as microsurgical techniques.[6]

With advancements in microvascular free tissue transfer, reconstruction of segmental mandibular defects with osteocutaneous free-flap has become a standard of treatment following ablation of OSCC which offers an improved functional and aesthetic outcome.[7] The segmental bony mandibular defect is most optimally reconstructed primarily with a vascularized fibula flap (VFF) compared to other osseous flaps.[8] Despite the advancement in diagnostic and treatment protocols and improved patient's quality of life (QOL), no marked progress has been observed related to the 5-year survival rate and it remains unchanged. The global estimated 5-year survival rate of OSCC patients is 50-60%.[9, 10] The survival rate and risk factors influencing the postoperative outcomes in OSCC patients with mandibular free-flap reconstruction have been well documented.[11] Nevertheless, only a few studies are available focusing on a specific subset of OSCC and primary reconstruction with VFF. Therefore, the following study was conducted to assess the survival rate of advanced OSCC patients following immediate mandibular reconstruction with VFF and to identify the risk factors influencing the overall survival and postoperative outcomes.

Patients and methods

Patients

This study was approved by the local ethical committee of the University Hospitals of Leuven, Leuven, Belgium (reference number: S63615) and complied with the guidelines of the Declaration of Helsinki. The files of patients diagnosed and treated between January 1996 to June 2019 for OSCC were retrospectively reviewed. The patients who underwent primary ablative tumor resection with segmental mandibulectomy and immediate VFF reconstruction were retrieved from the database. The inclusion criteria involved patients diagnosed clinically and radiologically (CT/MRI) with stage IV OSCC and a follow-up period of one year. The exclusion criteria included non-neoplastic diseases, presurgical distant metastasis, two-staged reconstruction, pre-operative radiotherapy/chemotherapy, and no previous treatment. The tumor was staged according to the American Joint Committee on Cancer (AJCC, 8th edition, 2018) staging system.

The surgical procedure involved tumor resection with a safety margin (5mm for soft tissue, 1cm for hard tissue) and neck dissection. The maxillofacial and microsurgical team, thereafter immediate reconstruction was performed, simultaneously performed the tumor resection with segmental mandibulectomy and VFF harvesting. Post-surgical radiotherapy was administered by the linear accelerator in daily fractions of 2 to 2.2 Gy five times a week for 6 weeks (60-66 Gy). Concurrent chemotherapy consisted of Cisplatin for 6-7weeks (40 mg/m^2 IV weekly). Enteral feeding was provided with percutaneous endoscopic gastrostomy (PEG) or nasogastric tube.

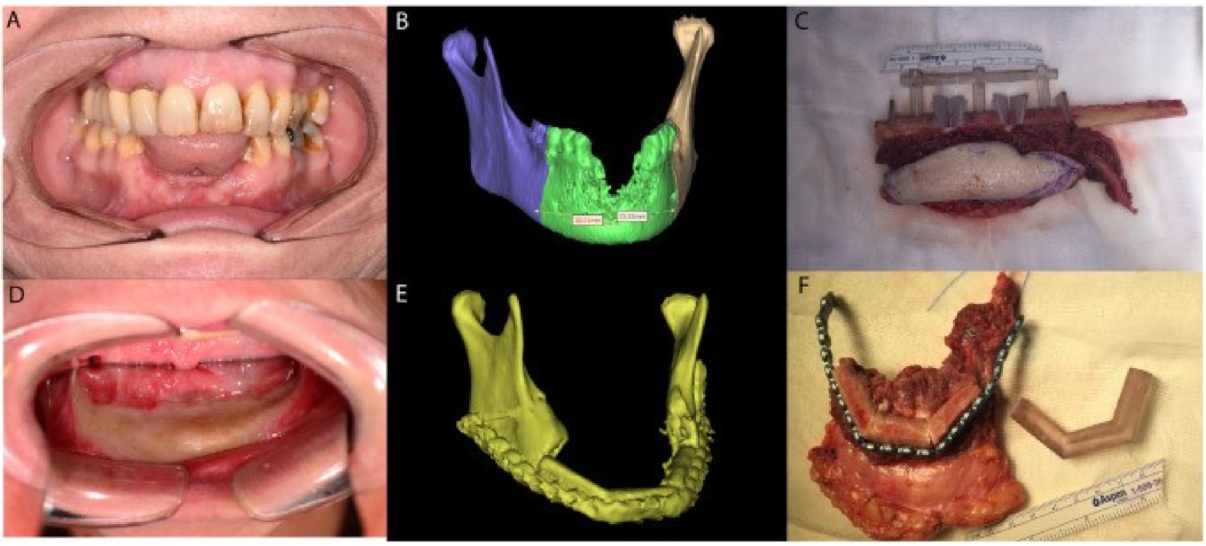

Figure 1. SCC of the mandible in a 70-year-old female. (A) SCC at mandibular symphysis; (B) 3D reconstruction images of preoperative pathological mandible with virtual surgical plan; (C) Fibular flap preparation by patient-specific fibular cutting guide; (D) Intra-oral photo in one year after surgery; (E) 3D reconstruction images of postoperative reconstructive mandible by a vascularized fibular flap; (F) Fibular harvesting by pre-bent titanium plates.

Table 1. Characteristics of the patients, OSCC and therapy

Patients' characteristics	Parameters		Number	Percentage %
	Gender	Male	55	74
		Female	19	26
	Age	≥60	44	59
		<60	30	41
	Tumor site	Tongue	9	12
		Mouth floor	21	28
		Lip	6	8
		Buccal	10	14
		Retromolar	8	11
		Gingiva	20	27
	Tobacco≥10 pack-years	Presence	48	65
		Absence	26	35
	Alcohol≥ 1 drink per day	Presence	41	55
	Systemic disease	Presence	24	32
		Absence	50	68
Tumor characteristics	Tumor site	Tongue	9	12

		Mouth floor	21	28
		Lip	6	8
		Buccal	10	14
		Retromolar	8	11
		Gingiva	20	27
	Pathologic N stage	0	30	41
		1	15	20
		2	27	36
		3	2	3
	Surgical margin	Negative	57	77
		Positive/Close	17	23
	Tumor differentiation	Well	24	32
		Moderate	41	55
		Poor	9	12
	Vascular invasion	Presence	19	26
		Absence	55	74
	Perineural invasion	Presence	16	22
		Absence	58	78
	Extracapsular spread	Positive	15	20
		Negative	59	80
Therapeutic parameters	Adjuvant therapy	S+RT	40	54
		S+RT+CT	26	35
		Surgery only	8	11
	Segments	1	21	28
		2	32	43
		3	21	28
	CAS + cutting guides	Adopted	29	39
		Not adopted	45	61
	Early complications	Presence	33	45
		Absence	41	55
	Defect size	Large	47	64
		Small	27	36

S: Surgery, RT: Radiotherapy, CT: Chemotherapy, CAS: Computer-assisted surgery

Table 2
Overall survival with comparison in classifications.

Variables	Classification	One year	95% CI	Two year	95% CI	Five year	95% CI	Comparison	P-value	P-value*
Overall survial		0.811	0.726–0.905	0.728	0.632–0.837	0.524	0.417–0.659		NA	
Stage pN	0	0.867	0.753–0.997	0.831	0.705–0.978	0.613	0.446–0.844	0–1	0.5228	0.0422
	1	0.8	0.621–1	0.667	0.466–0.953	0.444	0.248–0.797	0–2	0.1984	
	2	0.741	0.593–0.926	0.63	0.471–0.841	0.441	0.288–0.676	0–3	0.9824	
	3	1	1–1	1	1–1	1	1–1	1–2	0.9956	
								1–3	0.9771	
								2–3	0.9762	
Tumor differentiation	Well	0.958	0.882–1	0.917	0.813–1	0.753	0.583–0.972	Well-Moderate	0.0012	<0.0001
	Moderate	0.805	0.692–0.936	0.705	0.578–0.86	0.493	0.358–0.68	Well-Poor	0.0001	
	Poor	0.444	0.214–0.923	0.333	0.132–0.84	0.111	0.018–0.705	Moderate-Poor	0.0744	
Surgical margin	Negative	0.86	0.774–0.955	0.787	0.687–0.902	0.616	0.495–0.767	Negative-Positive	NA	0.0209
	Positive/Close	0.647	0.455–0.919	0.529	0.338–0.829	0.235	0.1–0.554			
Vascular invasion	Absence	0.873	0.789–0.965	0.797	0.697–0.912	0.539	0.414–0.701	Absence-Presence	NA	0.0395
	Presence	0.632	0.448–0.89	0.526	0.344–0.806	0.468	0.288–0.76			
Perineural invasion	Absence	0.879	0.799–0.967	0.792	0.694–0.904	0.612	0.494–0.759	Absence-Presence	NA	0.0022
	Presence	0.562	0.365–0.867	0.492	0.297–0.816	0.188	0.06–0.588			
Recurrence	Absence	0.809	0.703–0.929	0.765	0.652–0.897	0.628	0.496–0.796	Absence-Presence	NA	0.0232
	Presence	0.815	0.681–0.975	0.667	0.511–0.87	0.367	0.222–0.604			

NA: Not applicable.
* P-value for the Cox regression model.

The overall cumulative survival was recorded at first, second, and fifth-year time-point. Clinical examination was performed once every six weeks in the first half-year, every two months until the end of the 1st year, every three months in the 2nd year, thereafter every 6 months. The early complications were recorded within one month following surgery and postoperative outcomes were recorded at one year after completion of adjuvant treatment. The potential risk factors included age, gender, tumor site, defect size, pathological stage N, fibular segments, early complications, tumor recurrence, tobacco consumption, alcohol intake, mental health, systemic disease, surgical margin, adjuvant therapy, vascular invasion, perineural invasion, application of computer-assisted surgery (CAS), mandibular segments and defect size based on James' classification (Small defect size was defined as a type of "Class I" or "Class II", large defect size was defined as "Class III", or "Class IV" according to Brown classification).[12] The postoperative outcomes were recorded and scored as binary data following the completion of adjuvant therapy, which included malnutrition, unintelligible pronunciation, recipient site physical activity, facial appearance, pain, xerostomia, and mental health. All possible predictive factors (age, gender, tumor site, defect size, pathological stage N, fibular segments, early complications, tumor recurrence, tobacco consumption, alcohol intake, mental health, systemic disease, surgical margin, adjuvant therapy, vascular invasion, perineural invasion, applicaton of CAS and cutting guides, mandibular segments and defect size) were collected. A representative case illustration is shown in Figure 1.

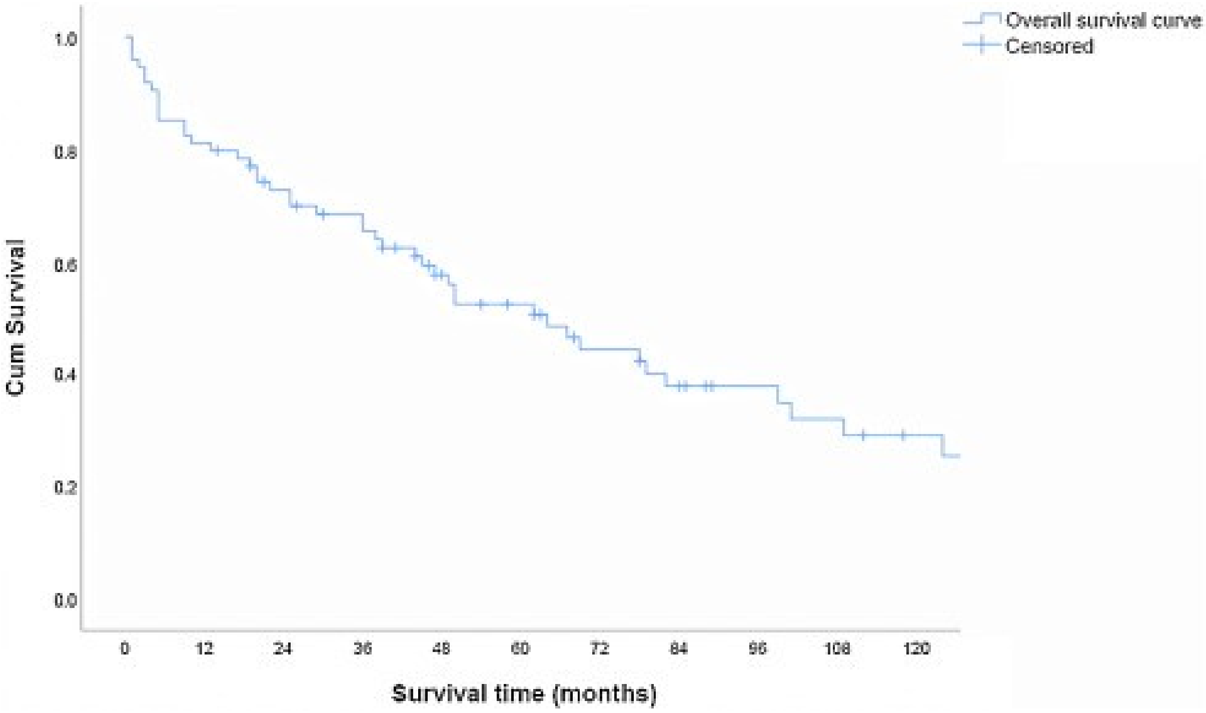

Figure 2. Overall cumulative Kaplan-Meier survival curve.

Statistical analysis

Data analysis was performed with S-Plus 8.0 for Linux (Tibco, Palo Alto, CA, USA). For the survival, Kaplan-Meier curves were calculated. The differences between risk factor variable groups were assessed using Cox's proportional hazards model for variables consisting of two groups and using survival regression with dummy variables for more than two groups. The different groups were compared with each other using the coefficients and their variance-covariance matrix. The relation between the risk factor variables and binary outcomes was assessed by a generalized linear model for binary data using a logit link. The differences between the group of the risk factor variable were calculated using the coefficients of the generalized linear model and their variance-covariance matrix. P-values of all the differences were corrected for simultaneous hypothesis testing according to Tukey.

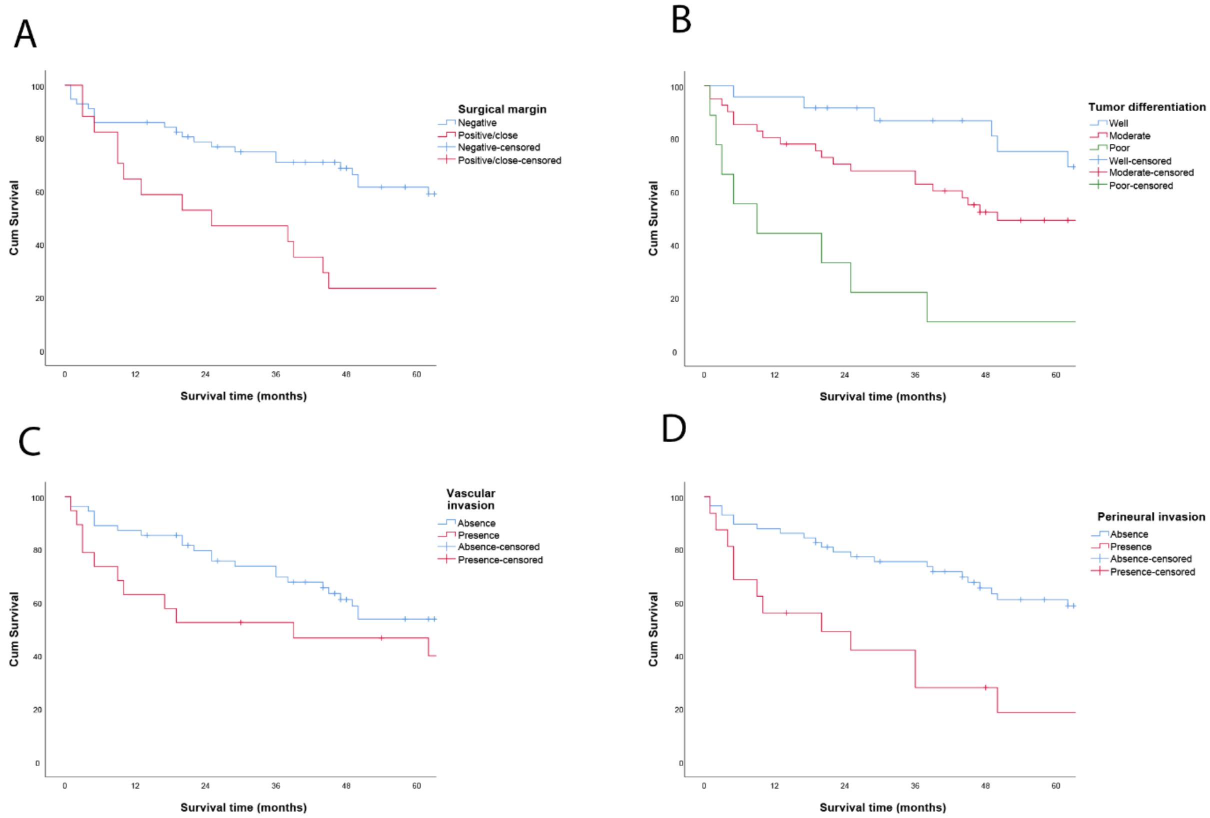

Figure 3. Kaplan-Meier survival curves of the cumulative survival rate by risk factors: In accordance with surgical margin (A); In accordance with tumor differentiation (B); In accordance with vascular invasion (C); In accordance with perineural invasion (D).

Results

Patients characteristics

The database had a record of 516 patients with OSCC. Based on inclusion and exclusion criteria, 74 patients (55 males, 19 females; mean age: 62±10; age range: 25-84 years) could be included in this study. The mean follow-up period was 56 months (median 46, range 1-230 months). For eleven patients, the follow-up was less than one year postoperatively. Supplemental Table 1 presents the patient, tumor, and therapeutic characteristics. Early complications occurred in 45% of the patients, involving total flap failure (8%), wound dehiscence (14%), infection (9%), hematoma (4%), venous thrombosis (4%), and partial flap necrosis (5%). 36 (48%) patients died from OSCC within five years.

Table 3
Postoperative outcomes.

Parameters	Event	Numbers	Percentage %
Successful surgery	Presence	68	92
	Absence	6	8
Tumor recurrence	Presence	27	36
	Absence	47	64
Malnutrition	Presence	16	22
	Absence	58	78
Unintelligible pronunciation	Presence	11	15
	Absence	63	85
Physical activity restriction	Presence	12	16
	Absence	62	84
Unacceptable facial appearance	Presence	5	7
	Absence	69	93
Pain	Presence	15	20
	Absence	59	80
Xerostomia	Presence	11	15
	Absence	63	85
Mental disorder	Presence	8	11
	Absence	66	89

The overall cumulative survival rate at a 95% confidence interval (CI) was 0.81 (CI: 0.72-0.91) at 1st year, 0.73 (CI: 0.63-0.84) at 2nd year and 0.52 (CI: 0.12-0.66) at 5th year (Figure 2). Supplemental Table 2 illustrates the cumulative survival in relation to each risk factor at 1, 2 and 5 year time-points. Overall, advanced pN stage ($p = 0.0422$), poor tumor differentiation ($p < 0.0001$), positive/close surgical margins ($p = 0.0209$), vascular invasion ($p = 0.0395$), perineural invasion ($p = 0.0022$) and tumor recurrence ($p = 0.0232$) were significantly related to a decreased cumulative survival. Figure 3 illustrates the cumulative survival rate in accordance with risk factors.

Postoperative outcomes and tumor recurrence

Supplemental Table 3 illustrates the percentage of patients with favorable/unfavorable postoperative outcomes after adjuvant therapy within one year after surgery. The surgery with free-flap reconstruction was successful in 92% of the patients. It was unsuccessful in 8% of the patients due to patient death (4%) and total flap necrosis (4%). 27 (36%) patients were diagnosed with tumor recurrence, which included regional tumor recurrence (n=10), distant metastasis (n=4), and local recurrence (n=13) during the follow-up period. Supplemental Table 4 describes the correlation and odds ratio between all the risk factors and postoperative outcomes. The surgery success was siginificantly influenced by the extracapsular spread (OR = 10.4, 95% CI = 1.6-67.4, p=0.02). Tumor recurrence was significantly correlated with the involvement of positive/close surgical margins, moderate (OR = 5.5, 95% CI = 1-29.8, p = 0.0488) and poor-differentiated tumors (OR = 14, 95% CI = 1.4-138.8, p=0.202) , positive extracapsular spread (OR = 0.3, 95% CI = 0.1-1, p = 0.0465), CAS (OR=9.9, 95% CI = 2.5-39.1, p = 0.0014) and early complications (OR = 0.3, 95% CI = 0.1-0.8, p = 0.0224). Pain was significantly associated with the positive extracapsular spread (OR = 0.3, 95% CI = 0.1-0.9, p = 0.0353) and early complications (OR = 0.2, 95% CI = 0.1-0.7, p = 0.0127). The presence of systemic diseases significantly influenced the status of mental disorder in patients (OR = 0.2, 95% CI = 0.0-0.9, p = 0.0352). No other significant findings were observed when comparing the risk factors to the outcomes.

Table 4
Odds ratio and statistical significance analysis of risk factors comparison.

Outcomes	Risk factors	Comparison	Odds ratio	95% CI	P-value
Successful surgery	Extracapsular spread	Absence-Presence	10.4	1.6–67.4	0.02
Recurrence	Surgical margin	Negative-Positive/Close	0.1	0–0.5	0.003
Recurrence	Tumor differentiation	Moderate-Well	5.5	1–29.8	0.0488
Recurrence	Tumor differentiation	Poor-Well	14	1.4–138.8	0.0202
Recurrence	Extracapsular spread	Absence-Presence	0.3	0.1–1	0.0465
Recurrence	S+RT+CT	Absence-Presence	0.2	0.1–0.5	0.0025
Recurrence	CAS	Absence-Presence	9.9	2.5–39.1	0.0014
Recurrence	Early complications	Absence-Presence	0.3	0.1–0.8	0.0224
Pain	Extracapsular spread	Absence-Presence	0.3	0.1–0.9	0.0353
Pain	Early complications	Absence-Presence	0.2	0.1–0.7	0.0127
Mental disorders	Systemic disease	Absence-Presence	0.2	0–0.9	0.0352

S: Surgery, RT: Radiotherapy, CT: Chemotherapy, CAS: Computer-assisted surgery.

Discussion

The overall prognosis of OSCC has been comprehensively reported in various studies, however, the prognosis of advanced OSCC patients treated with primary surgery and immediate mandibular reconstruction was rarely reported. In this study, we calculated the cumulative survival rate of OSCC patients with advanced OSCC. Furthermore, we analyzed the effect of risk factors on survival as well as on postoperative outcomes.

Our findings showed an excellent success rate of surgery (92%) with a 52% cumulative overall survival rate of patients at the end of the 5th-year follow-up. The 5-year survival rate was lower when compared to a study by Camuzard et al., which could have been attributed to the difference in tumor characteristics of the studied sample. The positive surgical margins were related to the T-stage of the tumor, N-stage, histopathological features including tumor thickness and the pattern of invasion. As our group of patients involved a higher number of patients with pathological N1-N3 stage and the surgical margin was recorded according to the histological specimen where 17 (23%) were positive/close in our result consistent with similar reports.[13] Furthermore, a positive or close surgical margin always increases the risk of tumor recurrence as an incomplete surgical resection leads to residual tumor tissue which might cause local tumor recurrence and even tumor metastasis.[14] Similarly, inconsistency in survival rate was observed with Sproll et al. which reported on the overall prognosis, unlike this study which focussed on a specific group of patients with strict inclusion criteria. In the same instance, other studies were consistent with our findings concerning the flap survival rate.[15]

The cumulative risk-specific survival curve confirmed patients with pN-stage 0, well tumor differentiation, negative surgical margin, without perineural and vascular invasion showed a significantly high overall survival rate. These findings were consistent with other studies.[16, 17] The factors such as tumor site, age, gender, systemic disease, CAS, and defect size failed to show any significant influence on the survival rate, which was also in accordance with the other studies. Patients with tumor recurrence always received second surgery and extra adjuvant therapy which might have influenced the survival rate. The higher recurrence rate in our study could be related to the extracapsular spread which indicates a higher grade of tumor malignancy or a rapidly progressed tumor, thereby, increasing the degree of recurrence. Therefore, these risk factors should be avoided based on the condition of the patient and making a patient-specific treatment plan.[18] Similarly, our findings were comparable with some studies which showed no association between surgical success and other risk factors such as age, gender, systemic disease, tumor site, tumor classification, and smoking status.

In our study, early complications such as compromised arteriovenous anastomosis, fistula, and wound dehiscence required instant re-exploration to prevent flap necrosis.[19] These added surgical interventions have been known to influence the prolongation of hospitalization and ICU days, increased morbidity and mortality, overall cost, and negative postoperative outcomes.[20] Based on the correlation between risk factors and postoperative outcomes, patients suffering from early complications reported more pain. Although surgical excision of the tumor initially relieves the tumor-related pain, early complications such as infection, hematoma, and nerve compression might have attributed to pain in these patients.[21] Additionally, a positive or close surgical margin leads to a higher tumor recurrence rate from our results. Virtual surgical planning combined with surgical guided templates offers an improved cutting accuracy with three-dimensional visualization of the tumor compared to freehand tumor resection and lack of accuracy of the resection guides might lead to positive resection margins. These may indirectly explain the patients treated with CAS had a lower recurrence rate in our research outcomes.[22-24] The association between systemic disease and mental health is rarely reported, however, we found a significant relationship amongst them. This could have resulted from the tumor treatment or long-term medication adherence for curing the systemic disease as tailored rehabilitation programs on psychological health were utilized for managing patients with mental disorders (anxiety, delirium, and emotion dysregulation).[25]

There were certain limitations associated with the study. Firstly, based on the long period of the evaluation from 1996 to 2019, a historical bias might have been associated with treatment and chemo-radiotherapy strategies. Also, the retrospective and single-center nature of the study might have further acted as a potential source of bias. Moreover, developed surgical concepts, materials, the number of reconstructive surgeons at a tertiary center, and supporting facilities could not be ignored during the long-term follow-up period.[26] Finally, the study involved only traditional clinical-pathological factors without assessing the risk of virological, genomic, and proteomic biomarkers.[27-29]

Conclusion

Based on the 5-year survival rate, segmental mandibulectomy with fibula free-flap reconstruction in advanced OSCC patients offered a success rate of 52.4%. The clinical/pathological risk factors such as the pN stage, tumor differentiation, surgical margins, vascular invasion, perineural invasion, and tumor recurrence significantly influenced the overall cumulative survival rate. Additionally, computer-assisted surgery showed the possibility of decreasing the tumor recurrence rate. Adequate identification of risk factors and their influence on postoperative outcomes at the diagnostic stage may allow tailoring of three-dimensionally oriented patient-specific treatment plans for increasing the survival rate in OSCC patients.

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Chapter 4: Long-term survival of implant-based oral rehabilitation following maxillofacial reconstruction with vascularized bone flap

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Abstract

Aim

The aim of the study was to assess the 5-year cumulative survival rate of implant-based dental rehabilitation following maxillofacial reconstruction with a vascularized bone flap and to investigate the potential risk factors which might influence the survival rate.

Materials and methods

A retrospective cohort study was designed. Inclusion criteria involved 18 years old or above patients with the availability of clinical and radiological data and a minimum follow-up 1 year following implant placement. The cumulative survival rate was analyzed by Kaplan-Meier curves and the influential risk factors were assessed using univariate log-rank tests and multivariable cox regression analysis.

Results

151 implants were assessed in 40 patients with a mean age of 56.43 ± 15.28 years at the time of implantation. The mean number of implants placed per patient was 3.8 ± 1.3 with a follow-up period of 50.0 ± 32.0 months. The cumulative survival at 1-, 2- and 5-years was 96%, 87%, and 81%. Patients with systemic diseases (HR = 3.75, 95% CI: 1.65 – 8.52; $p = 0.002$), irradiated flap (HR = 2.27, 95% CI: 1.00 – 5.17; $p < 0.05$) and poor oral hygiene (HR = 11.67; 95% CI: 4.56 – 29.88; $p < 0.0001$) were at a significantly higher risk of implant failure.

Conclusion

The cumulative implant survival rate was highest at 1st year followed by 2nd and 5th year, indicating that the risk of implant failure increased over time. Risk indicators that seem to be detrimental to long-term survival include poor oral hygiene, irradiated flap and systemic diseases.

Introduction

The reconstruction of oral and maxillofacial (OMF) defects secondary to tumor, osteonecrosis, trauma, and congenital disease represent a daunting task in head and neck surgery and require a multidisciplinary treatment approach. To this end, vascularized bone flaps serve as the gold standard for OMF reconstruction, which commonly includes, vascularized fibula flap (VFF), deep circumflex iliac artery flap (DCIA), and vascularized osteomyocutaneous scapular flap (VOSF).[1-3] These flaps benefit from an adequate blood supply, sufficient bone mass and satisfactory flap survival rate.[4]

One of the most fundamental parts of the care pathway following maxillofacial reconstruction with a free vascularized bone flap involves oral and maxillofacial rehabilitation for the restoration of facial aesthetics, masticatory function, speech, and improvement of the patient's quality of life.[4-6] The patients undergoing bone flap reconstruction for extensive soft and/or hard tissue loss suffer from insufficient oral vestibular space, stability, and retention capacity, which is a prerequisite for the tissue prosthesis.[7-9] Thereby, dental implant-based rehabilitation acts as the most viable treatment option in such cases.

Previously, several studies have investigated the survival rate of dental implants following vascularized bone flap reconstruction.[3] However, only a few studies exist assessing the cumulative survival rate of implants at a long-term follow-up period of 5 years or more. It is also essential to assess the survival rate based on the functionally loaded implants, for determining whether the patients benefit from implant therapy. At present, differences in survival rate exist amongst various studies due to the heterogeneity related to the recruitment of patients with a mixture of non-functional (non-restorable or freestanding implants) and functional implants which could impact the overall cumulative survival rate, where patients with functional implants might be associated with a higher risk of implant failure. Hence, requiring further studies to improve the level of evidence at a long-term level.

Furthermore, the association between implant failure and potential risk factors has not been thoroughly investigated. For instance, an increased risk of implant failure has been documented in patients receiving radiotherapy at a dose of 65 Gy and more.[10] Although, implant placement after radiotherapy has been suggested to be a relatively safe procedure concerning the long-term impact on peri-implant bone resorption.[11] The impact of radiotherapy on implant survival is seldom reported in relation to its placement in the irradiated bone flap compared to the native bone, thereby, leading to an inadequate representation of the survival rate.[12] Other factors, such as systemic conditions and smoking have also been linked with an increased risk of implant failure, however, lack of evidence exists related to their role on the long-term cumulative survival rate.[13] At the same instance, it is not clear whether the presence of multiple risk factors in a patient could lead to a higher implant failure. Hence, it is important to assess the impact of these risk factors both at an individual and cumulative level.

The primary aim of the study was to determine the 5-year cumulative survival rate of implant-based dental rehabilitation following maxillofacial reconstruction with a vascularized bone flap. The secondary aim focused towards identifying potential risk factors, which might contribute towards implant failure.

Materials and Methods

Patients

A retrospective cohort study was designed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[14] The study was approved by the Medical Ethics Committee of the University Hospitals Leuven, Leuven, Belgium (S-63615) and registered at ClinicalTrials.gov (NCT04884126). The sample consisted of patients who underwent OMF reconstruction at the Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, from December 2004 till January 2020. Inclusion criteria involved 18 years old or above patients with the availability of clinical and radiological data (cone-beam computed tomography (CBCT) or multi-slice CT) and a minimum follow-up 1 year following implant placement. Patients with severe systemic diseases (American Society of Anesthesiologists [ASA] physical status scores of III or more) were excluded.[15]

Reconstructive surgery protocol

Considering the inclusion of 16-years of patients' records, there were some time-dependent shifts related to the digitalization of the surgical planning protocol. Patients operated before January 2014 were treated with traditional freehand reconstructive surgery and following that time-point onwards computer-assisted surgery (CAS) was performed with either digitalized or non-digitized dental implant surgery. Preoperative CT (slice thickness < 1 mm; Siemens SOMATOM Definition Edge) and CT angiography were acquired for all the patients. As per CAS protocol, the CT images were imported into a three-dimensional (3D) surgical planning software (ProPlan, Version 2.0/3.0 Materialise, Leuven, Belgium) for the generation of maxillofacial models and performing virtual surgery with osteotomy planes. Thereafter, patient-specific surgical guides were designed in a 3D designing software (3-Matic, Version 9.0-13.0, Materialise, Leuven, Belgium). The cutting guides were exported in Standard Tessellation Language (STL) format and printed using a 3D printer (Connex 350, Stratasys, Eden Prairie, MN, USA). Furthermore, the shape, length, number, and size of titanium plates and screws were comprehensively planned according to the planned dental implant position. The reconstructed segmented was either fixated using titanium miniplates and screw system (2 mm non-locking or 2.3 mm locking, KLS Martin Group, Tuttlingen, Germany) or pre-bent reconstructive plates, manually bent on the 3D printed reconstructed model A fixation tray was used for the guided placement of the reconstructive plates. The screw holes were drilled and osteotomy lines were marked onto the surgical guide. The bone flap was detached from the donor site and modelled according to the templates as planned. Small bony fragments were fixed using screws and plates. Finally, microanastomosis and suturing were performed to close the wound at the recipient site. In patients requiring radiotherapy, it was delivered by a linear accelerator in daily fractions of 2–2.2 Gy five times a week for 6 weeks (60−66 Gy).

Dental implant placement and prosthetic installation

Prior to implant surgery, all patients were referred to an oral hygienist for achieving an optimal level of oral health. Dental implants were either inserted immediately at the time of surgical reconstruction (Stage I) or delayed placement at ≥6 months after grafting (Stage II), depending on the general condition of the patient and administration of adjuvant therapy. The majority of patients who underwent Stage II surgery included the ones who received radiotherapy. The implants were placed in grafted and/or native bone where applicable for ensuring a functional jaw and were inserted at a minimum torque of 35 Ncm using hand ratchet and/or low-speed handpiece. All surgical procedures were performed in compliance with the Brånemark protocol and delayed loading was applied.[16] Before the delivery of the final prosthesis, either a temporary removeable prosthesis or gastrostogavage tube was inserted during the healing phase for the administration of necessary nutrition.

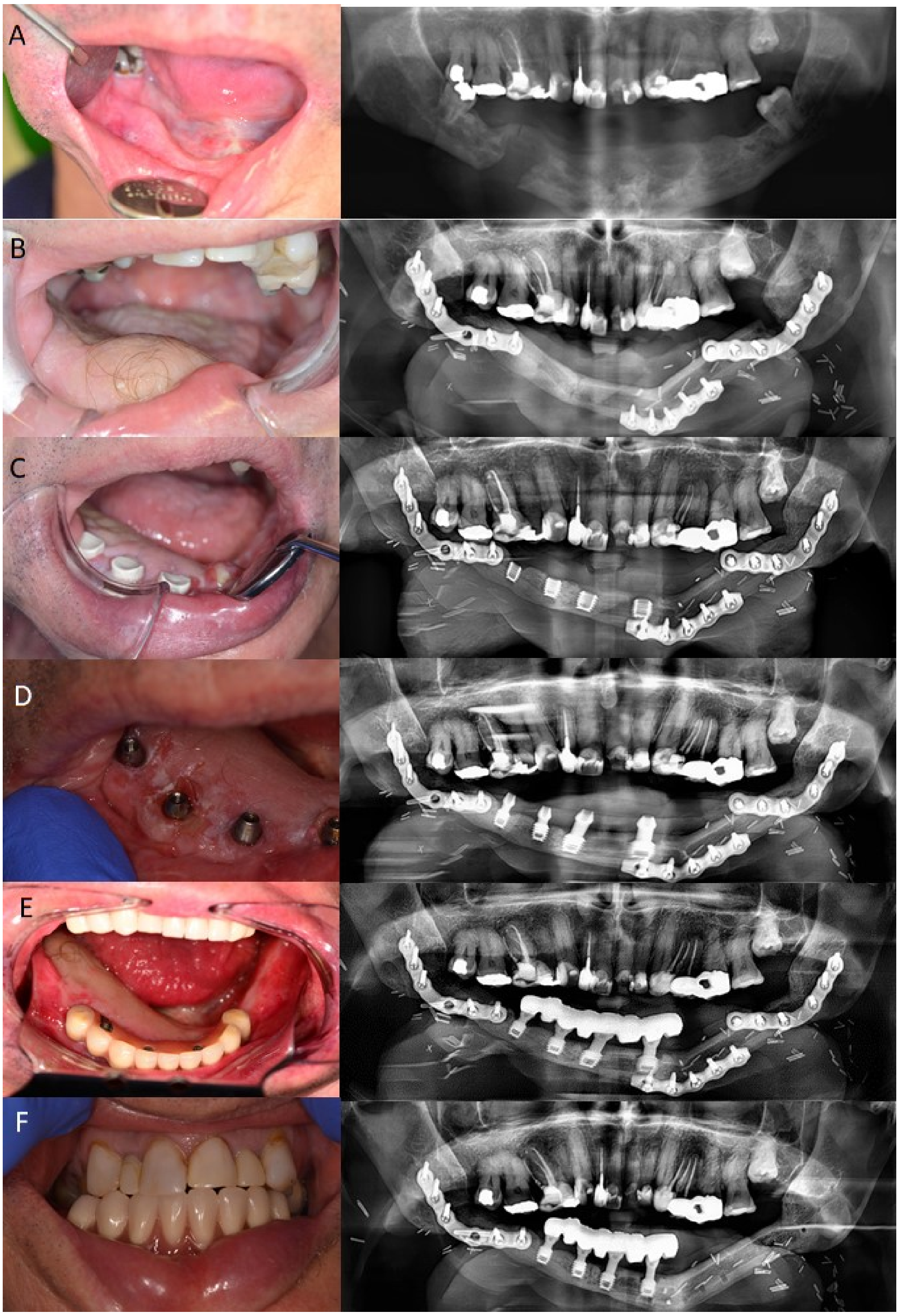

Figure 1. Clinical photos and panoramic radiographs of a sixty-year-old male patient diagnosed with mandibular osteoradionecrosis with mandibular reconstruction. (A) Intraoral photo and panoramic radiography before reconstructive surgery; (B) Intraoral photo and panoramic radiography after mandible reconstruction; (C) Intraoral photo and panoramic radiography after dental implant placement; (D) The stability of inserted implants were well after six months and implant abutments were installed; (E) Fitting restorations are stable in situ after superstructure and dentures instalment; (F) A stable occlusal relationship was confirmed after five years follow-up.

Postoperative follow-up

Clinical examination was performed once every six weeks during the first half-year, every two months until the end of the 1st year and every three months in the 2nd year. Afterward, the timeframe between the examinations was extended up to 6 months. The overall cumulative survival of dental implants was recorded at the follow-up period of 5 years.

The implants were categorized as “success” or “failure” clinically and radiologically according to the ICOI PISA health scale, where the failure was represented by any of the following: pain on function, mobility, more than 50% radiographic bone loss along the implant length and uncontrolled exudate. Non-restorable (sleepers), exfoliated or surgically removed implants were also categorized as a failure.

Implant survival was defined as “the implant remaining in situ at follow-up examination” with either satisfactory or compromised status. Satisfactory survival indicated less than ideal conditions, however clinical management was not required. It was represented by absence of pain on function, no mobility, no exudate history and 2 to 4 mm of radiographic bone loss. On the contrary, compromised survival referred to implants requiring clinical management to avoid implant failure and involved, no mobility, absence or presence of sensitivity on function and exudate, radiographic bone loss of >4 mm (less than one-half length of the implant body) and probing depth of >7 mm.[17] Figure 1 illustrates an example of a case with clinical and radiographic follow-up after reconstructive and dental implant surgery.

Study variables

The recorded parameters included age, gender, smoking, primary etiology (malignant tumor, benign tumor or cyst, osteoradionecrosis, trauma), defect size, flap-type (fibula, iliac, scapula), flap complications, radiotherapy, implant insertion site (mandible, maxilla/ bone flap, native bone), implant insertion stage (stage I, stage II), implant length (≤8 mm, >8mm), poor oral hygiene (characterized by distinct bleeding gums, dry mouth, bad breath, gum disease, tooth decay, and erosion) and presence of systemic disease. The defect size was classified based on Brown’s classification, where, a small-sized defect was defined as “Class I” or “Class II”, and large defects included “Class III”, or “Class IV”.[18, 19]

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY: IBM Corp, USA) and STATA 14.0 (STATA Corp., College, TX, USA). A time-point of five years following implant placement was selected as the censored time for cumulative survival analysis. The Kaplan-Meier curves were used to estimate the implant survival rate and the potential risk factors were compared through log-rank tests. The risk factors with a significant p-value of <0.1 based on the univariate log-rank tests were entered into a multivariable cox regression analysis for controlling the confounding factors and satisfying the assumptions of a proportional hazard model. Hazard Ratio (HR) and 2-sided 95% confidence intervals (CI) for each factor were calculated. A p-value of <0.05 was considered significant.

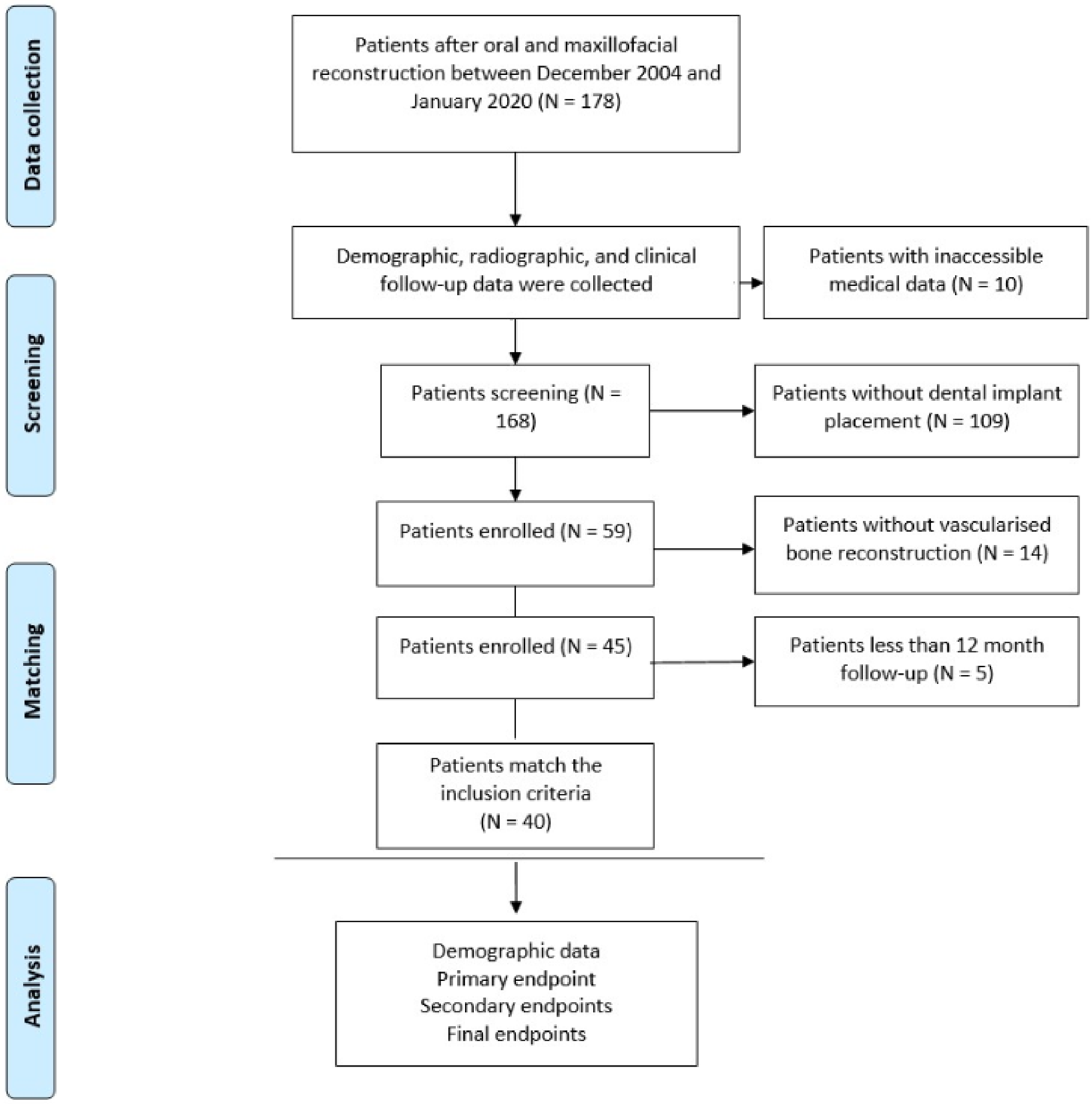

Figure 2. Flowchart of the included patients.

Results

Patient characteristics

Of the data collected from 178 consecutive patients, 138 were excluded based on the following reasons; lack of patient data (n = 10), no insertion of dental implant (n = 109), patients without vascularized bone flap (n = 14), and a follow-up period of less than 12 months following implant placement (n=5) (Figure 2). The final sample consisted of 40 patients (male: 26, female: 14) with a mean age of 56.43 ± 15.28 years at the time of implantation. The majority of patients were male (65%) and active smokers (65%). Twenty-two patients were diagnosed with a malignant tumor, 5 with benign tumor or jaw cyst, 9 with osteoradionecrosis, and 4 with oral and maxillofacial trauma. Mandibular reconstruction was performed in 35 patients and 5 patients underwent maxillary reconstruction. A vascularized fibular bone flap was used in 31 patients followed by 9 vascularized iliac or scapular flaps (Table 1).

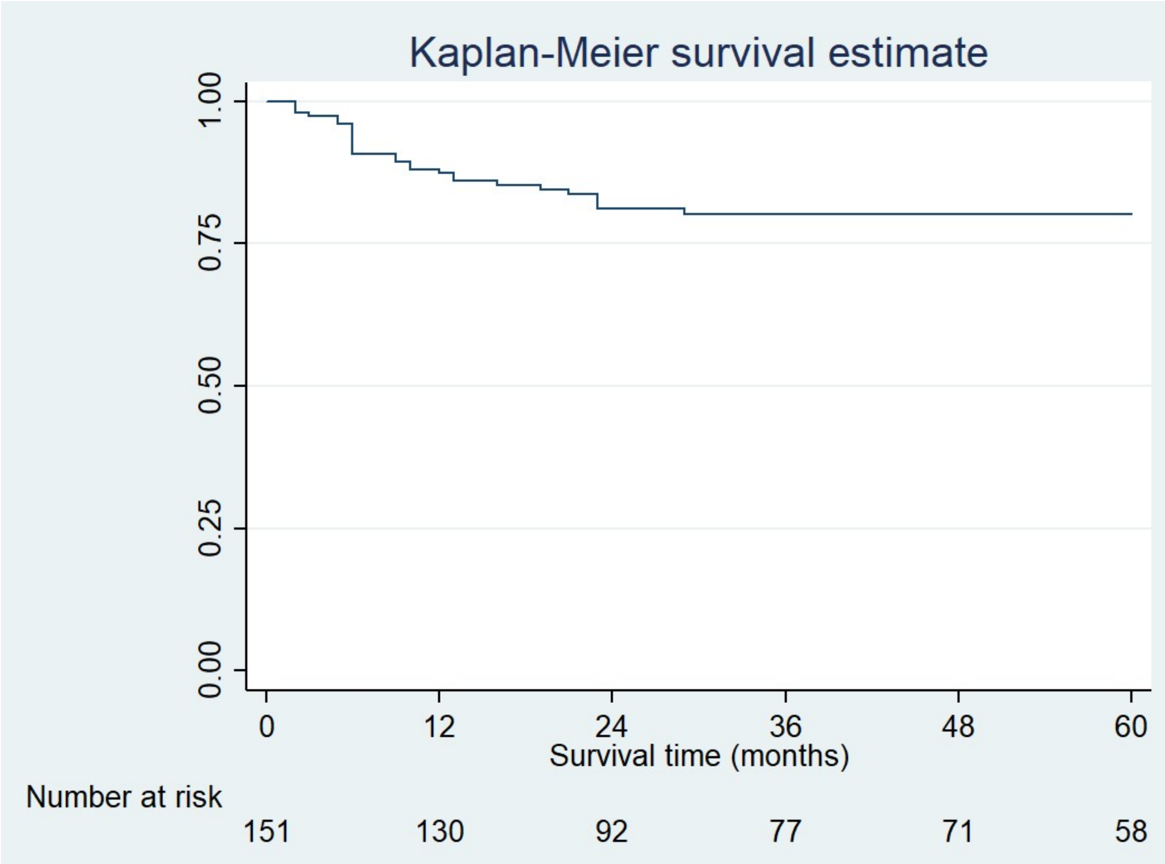

Figure 3. Kaplan-Meier curves of the 5-year cumulative implant survival rate

A total of 151 implants were inserted in 40 patients (vascularized bone flap= 133, native bone= 18). Supplementary Table 1 provide the list of implant brands and models. The mean number of implants per patient was 3.8 ± 1.3 (range: 1-9) with a follow-up period of 50.0 ± 32.0 months. In 15 patients, implants were placed at the region of the irradiated bone flap. In 10 patients (20%) implants were inserted at stage I, while the remaining 30 underwent stage II implantation.

In total, 30 complications occurred (28 implants failed in 15 patients). Table 2 provides a list of complications associated with implant failure, where the main reason was lack of osseointegration (implant failure, n= 17) followed by peri-implantitis (implant failure, n= 5).

Survival analysis

Implant survival at 1-, 2- and 5-years was 96%; 87%, and 81%, respectively (Fig.3), and the median follow-up duration was 50 months. Table 3 describes the overall implant survival rate based on the univariate analysis of the predefined patient characteristics. The following risk factors observed a statistically significant association ($p < 0.1$ in log-rank test) with implant survival: smoking (p=0.004), oral hygiene (p=<0.001), systemic disease (p=0.052), implant insertion stage (p=0.0019), irradiated flap (p=0.001) and flap complications (p=0.057). Figure 4 illustrates the Kaplan-Meier curves of the 5-year cumulative survival rate related to the aforementioned risk factors. Patients with a history of smoking, poor oral hygiene, systemic disease, stage I implant insertion, implant placement in the irradiated flap and flap complications were at a higher risk of implant failure. When entering the risk factors with $p<0.1$ into a Cox regression model, the multivariable analyses showed that the implant survival was significantly lower in patients with systemic diseases (HR = 3.75, 95% CI: 1.65 –

8.52; p = 0.002), irradiated flap (HR = 2.27, 95% CI: 1.00 – 5.17; $p < 0.05$) and poor oral hygiene (HR = 11.67; 95% CI: 4.56 – 29.88; $p < 0.0001$). These factors with significant association were also assessed for implant failure rate at an individual and multifactorial level to observe whether accumulated risk factors induced a higher risk of implant failure compared to individual ones. A combination of systemic disease, poor oral hygiene and irradiated flap showed the highest implant failure rate, followed by a combination of systemic disease and poor oral hygiene (Table 4).

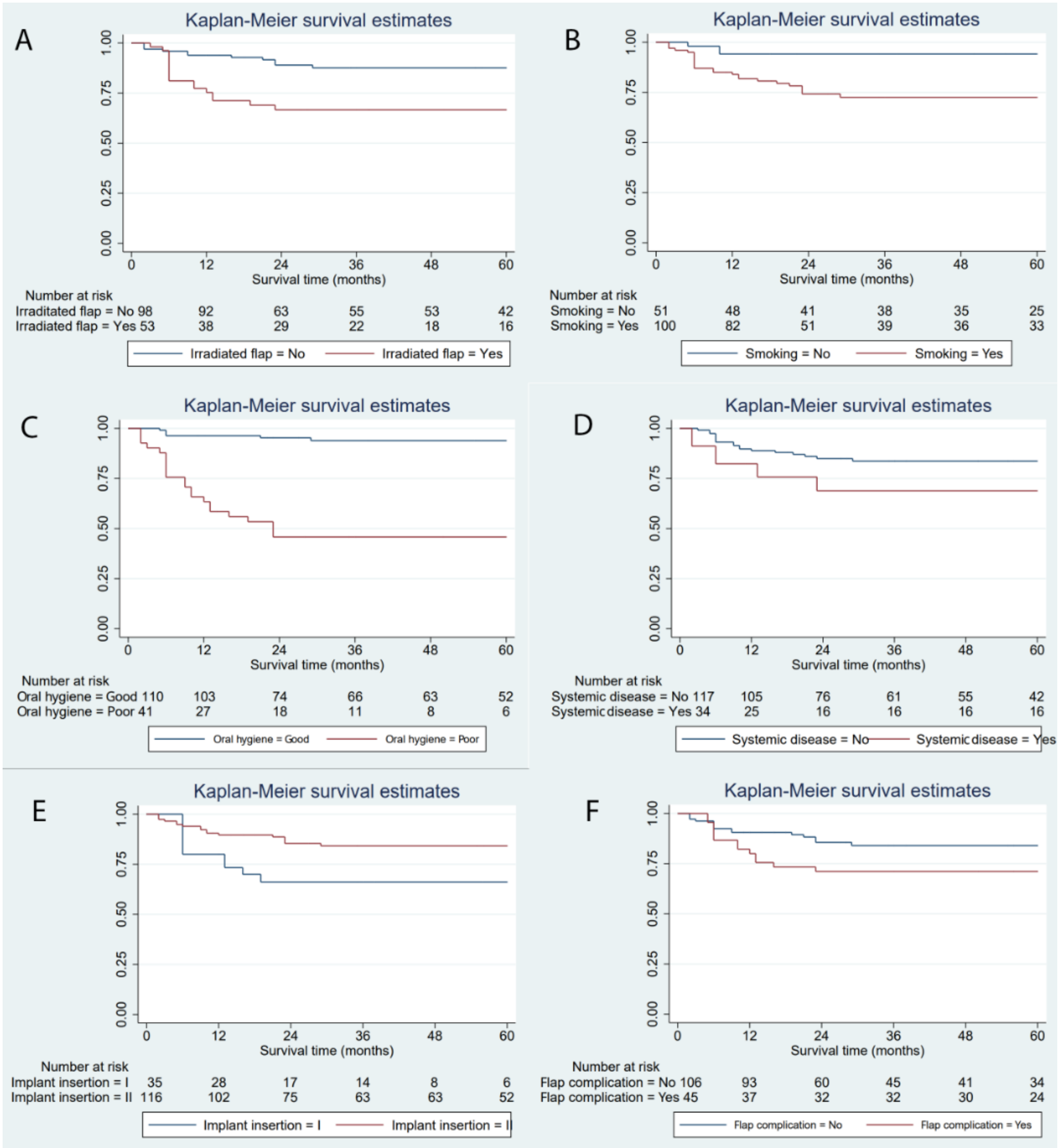

Figure 4. Kaplan-Meier curves of the 5-year cumulative survival rate in relation to the significant risk factors based on univariate log-rank tests. (A) Irradiated flap; (B) Smoking; (C) Poor oral hygiene; (D) Systemic diseases; (E) Implant insertion stage; (E) Flap complications.

Discussion

In this long-term retrospective cohort study, the 5-year cumulative implant survival rate was analyzed following OMF reconstructive surgery with a vascularized bone flap. The potential impact of risk factors on the survival rate was also assessed, which has not been comprehensively reported in the previous studies. The 5-year cumulative survival reported in this study was 81% which was in accordance with a recent systematic review, where the authors found a survival rate of 83.4% following meta-analysis of the pooled data. [12] Additionally, comparable findings were observed with Pellegrino et al. and Alberga et al. who reported a survival rate of 86.5% and 86.4%, respectively.[20, 21] As for the 1-year survival rate, slight inconsistencies were observed. In contrast to the 1-year cumulative survival rate of 96% observed in our study, Goker et al. (85.6%) and Nguyen et al. (87.2%) found a lower survival rate, whereas Pellegrino et al. reported a higher rate (97.2%).[20, 22, 23] These variable findings could be attributed to the different patient characteristics of the studied sample.

Based on the univariate analysis, smoking, implant placement at the region of an irradiated flap, stage I implant insertion, systemic diseases, flap complications and poor oral hygiene showed a lower implant survival rate. Furthermore, the results of multivariable Cox-regression analyses suggested an increased risk of implant failure in patients with irradiated flap, systemic diseases, and poor oral hygiene. No significant association existed between implant survival and gender, etiology, native or grafted bone-implant site, implant length, and flap type.

Fenlon et al. reported that immediate implant insertion (Pearson $\chi 2 = 41.76.18$; $p < 0.001$) and placement in the region of the irradiated flap (Pearson $\chi 2 = 50.18$; $p < 0.001$) were significantly associated with implant failure, which was consistent with the findings of the present study.[24] One could infer that the immediate implant placement and/or radiotherapy involving the flap region where the implant is placed might compromise the vitality of the graft leading to implant failure, which needs to be investigated in future studies. In addition, the importance of flap revascularization cannot be ignored. Generally, revascularization and neovascularization in the recipient bed and surrounding wound edges is sufficient to allow for pedicle division within few weeks following flap transfer.[25] However, the vascular integrity of the recipient bed is compromised in irradiated patients, which could either cause a delayed loss of the flap or negatively affect the dental implant osseointegration and survival rate. This vascular compromise is further increased in smokers, as smoking causes endothelial dysfunction and reduction in alveolar blood supply.[26, 27] Khadembaschi et al. reported a negative impact of smoking on the overall survival following implant placement in composite free flaps for reconstruction of benign and malignant head and neck pathologies.[28] As smokers are at a higher risk of post-operative infection, marginal bone loss and implant failure, which has been confirmed by various studies.[29] Previous evidence suggests only a few studies assessing the association between oral hygiene and dental implant survival rate following jaw reconstruction. The lower survival rate in patients with poor oral hygiene could be attributed to the fact that plaque accumulation might induce an inflammatory reaction leading to secondary implant failure due to peri-implantitis. [30, 31]

Native bone had a higher implant survival rate compared to the grafted bone, which was consistent with Ch'Ng et al. and Jacobsen et al's findings, who also reported a higher implant failure placed in bone flap compared to the native jaw.[32, 33] The most likely reason could be the impact of radiotherapy, poor oral hygiene and/or smoking. However, the limited number of implants placed in the native bone did not allow isolation of specific risk factors, thereby, requiring further studies with a larger sample size to assess the reasons for implant failure. Additionally, the majority of patients in the present study underwent reconstruction with fibular flap, which is mainly composed of dense cortical bone and its thickness has been known to significantly reduce at a long-term follow-up which might also impact the implant survival.[34] Hence, requiring further investigations for assessing survival outcome based on bone thickness, especially if implants are placed immediately at the time of reconstruction.

A relatively lower survival rate of implants was observed in patients with a malignant tumor and osteoradionecrosis, which could have been due to the administration of radiotherapy in a majority of the patients.[35] Previous studies have also observed a detrimental impact of radiotherapy at both reconstructed and native bone sites, which leads to a higher implant failure and patients suffer from an increased risk of post-implant surgery complications.[36] Therefore, the key for having a high implant survival rate following reconstructive surgery is to devise a patient-specific treatment plan considering the influence of the aforementioned risk factors at both individual and accumulative levels. Recent improvements in implant designs, surface modifications and shifts in treatment strategies have improved implant osseointegration and long-term survival rate following surgical reconstruction and radiotherapy. Furthermore, the application of three-dimensional planning and computer-guided implant surgery should also be taken into consideration for increasing the implant survival rate, as it offer several advantages over conventional approaches such as, improved accuracy of dental implant placement, maintenance the periosteal irrigation and possibility of performing a flapless procedure.[37, 38]

The study had certain limitations. Firstly, a historical bias existed due to the inclusion of both freehand and CAS-based techniques with the presence of different adjuvant chemo-radiotherapeutic strategies. Secondly, the assessment of certain individual risk factors and accumulated risk of multiple factors on implant failure rate suffered from a limited sample size with a lack of statistical power, which should be interpreted with caution. Finally, the study involved a consecutive group of patients rather than one specific patient population. Future studies with a larger and standardized sample size are required to reach a definitive conclusion. Despite the limitations, the study provided a comprehensive report of the risk factors associated with implant survival which could allow improving the decision-making process and treatment planning in patients undergoing OMF reconstructive and implant surgery.

Conclusions

The cumulative implant survival rate was highest at 1st year, followed by 2nd and 5th year, indicating that the risk of implant failure increased over time. Risk indicators that seem to be detrimental to long-term survival include poor oral hygiene, irradiated flap and systemic diseases. Prospective studies are warranted to further elucidate the factors contributing towards implant failure, to allow for optimal patient-specific delivery of care while striving for a long-term positive outcome

Table 1. Patient characteristics

Characteristics	Subgroups	NP (N)	NF (N)	NI (N)	NIF (N)
Age (year)	Mean age	56.43 ± 15.28			
	Age range	18 - 85			
Age	≥65	10	6	31	9
	<65	30	9	120	19
Gender	Male	26	7	100	16
	Female	14	8	51	12
Smoker	Yes	26	13	100	25
	No	14	2	51	3
Aetiology	Malignant tumor	22	10	83	17
	Benign tumor or jaw cyst	5	0	16	1
	ORN	9	4	38	9
	Trauma	4	1	14	1
Site	Mandible	35	13	130	26
	Maxilla	5	2	21	2
Flap type	VFF	31	11	131	27
	VIF/ Scapula	9	4	20	1
IF	Yes	15	8	53	17
	No	25	7	98	11
DIIS	I stage	10	5	35	11
	II stage	30	10	116	17
Implant location	Graft bone	32	12	133	26
	Native bone inclued	8	3	18	2
Oral hygiene	Good	27	4	110	6
	Poor	13	11	41	22
Flap complication	Yes	12	6	45	13
	No	28	9	106	15
Implant length	>8 mm	34	11	122	21
	≤8 mm	6	4	29	7
Systemic disease	Yes	9	4	34	18
	No	31	11	117	10

IF: Irradiated flap; ORN: Osteoradionecrosis; VFF: Vascularized fibular flap; VIF: Vascularised iliac flap; VOSF: Vascularized osteomyocutaneous scapular flap; DIIS: Dental implant insertion stage; NP: Numbers of patients who received dental implant(s); FP: Numbers of patients with failed dental implant(s); NI: Numbers of implants; NIF: Numbers of implant failure.

Table 2. Complications associated with implant failure

Reasons	Complications in patients (N)	Dental Implants failure (N)
Fistula	2	5
Exposed/infected bone	1	3
Peri-implantitis	8	5
Osseointegration failure	6	17

Table 3. Implant survival rate based on the univariate log-rank tests

Variables	Classification	Patients (N)	Implants (N)	SR T1 (%)	SD	SR T2 (%)	SD	SR T5 (%)	SD	ST T5 (m)	SD	95% CI		P-value
Age	≥65	10	31	80.6	7.1	69.1	8.7	69.1	8.7	45.3	4.1	37.2	53.4	0.113
	<65	30	120	89.1	2.8	86.5	3.2	83.2	3.6	51.7	1.7	48.3	55.1	
Gender	Male	26	100	89.0	3.1	85.7	3.5	83.3	3.8	51.6	1.9	47.9	55.4	0.233
	Female	14	51	84.3	5.1	82.0	5.5	71.7	7.3	47.0	3.3	40.6	53.4	
Smoking	Yes	26	100	85.0	3.6	74.2	4.6	72.5	4.8	46.8	2.3	42.3	51.3	0.004
	No	14	51	98.0	1.9	94.1	3.3	94.1	3.3	57.0	1.7	53.6	60.3	
Indication	Malignant tumor	22	83	88.0	3.6	81.6	4.3	78.1	4.8	49.2	2.3	44.6	53.8	0.335
	Benign tumor or jaw cyst	5	16	93.8	6.1	93.8	6.1	93.8	6.1	57.3	2.7	52.0	62.5	
	ORN	9	38	76.1	7.0	76.1	7.0	76.1	7.0	48.2	3.5	41.4	55.1	
	Trauma	4	14	91.7	8.0	91.7	8.0	91.7	8.0	56.6	3.3	50.2	63.0	
Site of implants	Mandible	35	130	86.2	3.0	80.0	3.6	78.9	3.7	49.6	1.8	46.0	53.2	0.257
	Maxilla	5	21	95.2	4.6	89.6	7.0	89.6	7.0	55.7	2.9	50.1	61.3	
Flap type	VFF	31	131	86.3	3.0	79.5	3.6	78.5	3.7	49.4	1.8	45.9	53.0	0.133
	VIF/ VOSF	9	20	95.0	4.9	95.0	4.9	95.0	4.9	35.0	1.0	33.1	36.9	
IF	Received	15	53	75.3	5.9	66.7	6.7	66.7	6.7	43.2	3.4	36.6	49.8	0.001
	Not received	25	98	93.9	2.4	89.0	3.3	87.6	3.5	54.3	1.6	51.1	57.5	
DIIS	I stage	10	35	80.0	6.8	66.1	8.5	66.1	8.5	52.5	1.7	49.1	55.8	0.019
	II stage	30	116	90.5	2.7	85.4	3.4	84.2	3.6	43.0	4.2	34.7	51.3	
Oral hygiene	Good	27	110	96.4	1.8	95.3	2.1	93.9	2.4	57.2	1.1	55.0	59.4	0.000
	Poor	13	41	65.9	7.4	45.8	7.8	45.8	7.8	33.1	4.0	25.3	40.8	
Flap complication	Present	12	45	82.2	5.7	71.1	6.8	71.1	6.8	45.6	3.4	38.9	52.2	0.057
	Absent	28	106	90.6	2.8	85.6	3.6	84.0	3.9	52.4	1.8	48.9	56.0	
Implant location	Grafted bone	32	133	87.2	2.9	79.5	3.6	79.5	3.6	49.9	1.8	46.4	53.4	0.382
	Native bone	8	18	94.4	5.4	94.4	5.4	86.6	9.0	54.6	3.6	47.4	61.7	
Systemic disease	Present	8	34	82.4	6.5	68.9	8.2	68.9	8.2	44.5	4.1	36.4	52.6	0.052
	Absent	32	117	89.7	2.8	84.9	3.4	83.7	3.6	52.2	1.7	48.8	55.5	
Implant length	>8 mm	34	122	88.5	2.9	82.7	3.5	81.5	3.7	50.9	1.8	47.4	54.5	0.484
	≤8 mm	6	29	86.2	6.4	75.6	8.0	75.6	8.0	48.3	3.9	40.7	55.9	

SR T1: Survival rate in the first year; SR T2: Survival rate in the second year; SR T5: Survival rate in the fifth year; ST T5: Survival time over the five years; SD: Standardized error; IF: Irradiated flap.

Table 4. Impact of accumulated risk factors on the implant failure rate

Category	Risk factors	Patient in total (N)	Implants (N)	Failure (N)	Failure rate
A	Systemic disease	9	34	10	0.29
B	Oral hygiene	13	41	22	0.54
C	Irradiated flap	15	53	17	0.32
A+B		2	6	5	0.83
B+C		6	21	12	0.57
A+C		2	6	3	0.50
A+B+C		1	2	2	1.00

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Chapter 5: Computer-assisted versus traditional freehand technique for mandibular reconstruction with free vascularized fibular flap: A matched-pair study

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Summary:

Objectives: This study aimed to perform a surgery-related and patient-related outcome analysis of a case-matched series of patients treated with CAS and traditional freehand surgery.

Methods: A total of 153 patients who underwent mandibular reconstruction by VFF were included from Jan 1999 to Dec 2019. The mandibular resection and reconstruction were performed by four experienced oral and maxillofacial surgeons. Reasons for reconstruction were oncologic, osteoradionecrosis, trauma, and osteoporosis. All the patients were followed up postoperatively for at least one year. Eighteen pairs were formed with the matched cohort consisting of a total of 36 patients who underwent primary mandibular reconstruction without additional combined flaps. The surgery-related and patient-related continuous and categorical parameters were assessed in both groups.

Results: The average operation time and bleeding volume in the CAS group were less than the non-CAS group. Additionally, both hospitalization and ICU days were lower in the CAS group without any significant difference. The only significant finding related to surgical parameters was observed for the ischemia time, which was lower in the CAS group.

Conclusions: Computer-assisted surgery indicated improved efficiency considering reduced ischemia time, operation time, and length of hospital stay with lower early complications compared to conventional surgical procedures. It can thus be considered as an optimized alternative to the freehand approach.

Introduction

The restoration of mandibular continuity is crucial both from a cosmetic and functional perspective while maintaining the patient's quality of life.[1] Since the introduction of vascularized fibular flap (VFF) for mandibular reconstruction, it has become a gold standard for the restoration of mandibular defects caused by tumor resection, infection, trauma and congenital anomalies.[2] Amongst the osseous vascularized flaps, VFF remains the most commonly utilized flap for mandibular reconstruction based on its adequate bone and pedicle length, minor donor site morbidity and a high survival rate of both flap and dental implants.[3-5]

The traditional freehand technique for mandibular reconstruction with VFF requires high precision and crafting skills to achieve optimal bony continuity. The graft is secured by either bending plates intra-operatively or by pre-bending the plates on rapid prototype models constructed from the patient's preoperative CT scan. Although for simple defects, the freehand technique might be considered satisfactory. Nevertheless, for complex cases, it can be time-consuming and labor-intensive. Thereby, negatively influencing both functional and aesthetic related outcomes of the patients.[6]

The advent of three-dimensional (3D) computer-assisted surgery (CAS) has provided the reconstructive surgeons with the necessary tools to overcome the challenges of achieving an optimal contour, position and shape of the graft with improved patient-related outcomes following mandibular reconstruction.[7] It allows patient-specific designing and modeling of the cutting guides and pre-bent plates, allowing accurate graft placement to the original shape of the mandible.[8] In comparison to the freehand technique, CAS has become the mainstream choice for mandibular reconstruction with VFF by offering higher accuracy, increased efficiency, improved aesthetic and functional outcomes and reduced operation time.[9] Although several studies had verified the feasibility and morphological accuracy of CAS compared to the freehand technique, nevertheless, there is a gap in the literature related to the comparison of both techniques concerning the surgery- and patient-related parameters. The superiority of CAS for tumor resection and graft harvesting and placement is a well-known fact.[10, 11] However, whether it provides improved outcomes than the traditional approach at follow-up is still questionable. We found no studies comparing the surgery- and patient-related outcomes following mandibular reconstruction with VFF using CAS and traditional surgery. Therefore, this study aimed to perform a surgery-related and patient-related outcome analysis of a case-matched series of patients treated with CAS and traditional freehand surgery. The null hypothesis was that no significant differences in outcomes would be found between CAS and freehand surgery.

Patients and methods

Patients

A single-center retrospective study was conducted following ethical approval from the University Hospitals of Leuven, Leuven, Belgium (Number: S63615) and the study complied with the guidelines of the Declaration of Helsinki. A total of 153 patients who underwent mandibular reconstruction by VFF were included from Jan 1999 to Dec 2019. Mandibular resection and reconstruction were performed by four experienced oral and maxillofacial surgeons and plastic surgeons. Reasons for reconstruction were oncology, osteoradionecrosis, trauma or others. All patients had a segmental bone defect and were indicated for bony reconstruction. The patients were followed up postoperatively for at least one year (every two weeks for three months, then every month until six months and every three months by the end of the 1st year).

Patients were divided into two groups, where group I included patients who underwent mandibular reconstruction utilizing CAS and surgical templates (CAS group), whereas group II involved patients treated with freehand surgery (non-CAS group). Table 1 describes the characteristics of patients in both groups. Later on, both groups' parameters were matched based on the similarities between patient characteristics for performing a matched-pair analysis. In total 18 pairs were formed with the matched cohort consisting of a total of 36 patients who underwent primary mandibular reconstruction without additional combined flaps. Table 2 describes the surgery-related and patient-related continuous and categorical parameters which were assessed in both groups. The continuous parameters included age, American Society of Anaesthesiologists (ASA) score, number of bone segments, operation time, intraoperative blood loss, ischemia time, number of hospitalization and ICU days. The categorical parameters involved, gender, tumor etiology, defect size (classified according to James classification), neck dissection, tracheostomy, complications and post-operative aesthetic functional outcomes.[12] The late complications, aesthetic and functional outcomes were recorded at the follow-up time-point of six months, except recurrence which was recorded until the patients' most recent available evaluation.

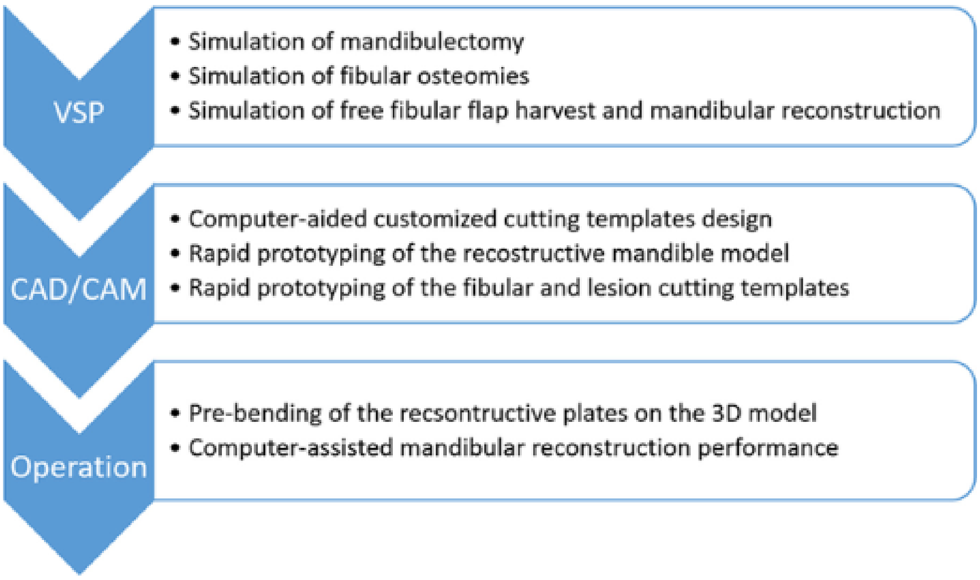

Figure 1 The workflow of the computer-assisted surgery.

Preoperative and intraoperative procedures

Preoperative head and neck computed tomography (CT) and lower extremity CT angiography were acquired for all patients. In the CAS group, CT images (slice thickness<1 mm) were imported into a 3D surgical planning software (Proplan, Version 2.0/3.0 Materialise, Leuven, Belgium). Following discussion with the radiologist, the tumor was delineated and segmented from CT/MRI dataset and a safety margin of 1 cm was planned for the malignant tumors. Virtual surgical planning was performed to determine the mandibular and fibular resection and cut margins with localization of the optimal angles for performing osteotomies. After that, surgical guides were designed utilizing a 3D designing software (3-Matic, Version 9.0-13.0, Materialise, Leuven, Belgium). The generated virtual templates were exported in Standard Tessellation Language (STL) format and printed with a professional 3D printer (Connex 350, Stratasys, Eden Prairie, MN, USA). The reconstructive plates were pre-bent on a 3D printed planned mandibular model. A fixation tray was used for the guided placement of the reconstructive plates. The screw hole locations were drilled and cutting osteotomy lines were marked onto the surgical templates by the surgeons. surgeons (Figure. 1). Intraoperatively, the resection of the lesion was performed utilizing the guided osteotomy templates. Simultaneously, the VFF was harvested and placed onto the defect site according to the virtual surgical plan. In the non-CAS group, all surgeries were performed based on surgeons' experience without applying any pre-bent reconstructive plates and surgical guided templates (Figure. 2).

Table 1 Patient characteristics of the whole cohort (N = 153).

Parameters	Classification	CAS	Percentage (%)	Non-CAS	Percentage (%)	Total	Percentage (%)
Participants	/	52	100.0	101	100.0	153	100.0
Gender	Male	28	53.8	73	72.3	101	66.0
	Female	24	46.2	28	27.7	52	34.0
Age (range)	/	55 (8-81)	/	56 (12-84)	/	56 (8-84)	/
Etiology	Malignant tumor	36	69.2	66	65.3	102	66.7
	Osteonecrosis	13	25.0	26	25.7	39	25.5
	Benign tumor	2	3.8	3	3.0	5	3.3
	Others	1	1.9	6	5.9	7	4.6
Early complications	/	16	30.8	45	44.6	61	39.9
Surgical success	/	49	94.2	90	89.1	139	90.8
Recurrence	/	5	9.6	22	21.8	27	17.6
Average hospitalization days	/	21	/	21	/	21	/
Average ICU days	/	4.5	/	2	/	2.5	/
ASA	1	3	5.8	18	17.8	21	13.7
	2	23	44.2	61	60.4	84	54.9
	3	23	44.2	22	21.8	44	28.8
	4	3	5.8	0	0.0	3	2.0
Defect size	Class I or Class II	20	38.5	38	37.6	58	37.9
	Class III or Class IV	32	61.5	63	62.4	95	62.1
Segments	1	12	23.1	27	26.7	39	25.5
	2	19	36.5	36	35.6	55	35.9
	3 or 3+	21	40.4	38	37.6	59	38.6

ASA: American Society of Anaesthesiologists Classification.

Table 2 Patient characteristics of matched pairs series.

ID	Age	Gender	Etiology	TNM	Follow-up period (month)	Defect type	ASA	Segments	OT (min)	Bleed (ml)	IT (min)	Hospitalization (day)	ICU (day)	Group
1	42	M	Ameloblastoma	/	62	III, IV	2	2	360	180	120	18	5	CAS
2	39	F	Ossified fibroma	/	120	III, IV	2	1	390	250	280	16	1	Non-CAS
3	54	F	ORN	/	74	I, II	2	1	600	300	180	18	8	CAS
4	55	M	ORN	/	123	I, II	1	1	840	500	210	21	3	Non-CAS
5	67	F	ORN	/	30	III, IV	3	3	540	300	180	16	1	CAS
6	74	F	ORN	/	12	III, IV	3	3	600	650	270	5	4	Non-CAS
7	61	F	ORN	/	23	III, IV	3	3	540	300	200	12	0	CAS
8	61	F	ORN	/	25	III, IV	2	3	840	550	300	36	5	Non-CAS
9	23	F	Embryonal rhab-domyosarcoma	pT4N0M0	27	III, IV	2	1	900	300	200	17	11	CAS
10	15	M	Osteosarcoma	pT4N0M0	29	III, IV	1	1	900	400	210	6	1	Non-CAS
11	63	M	ORN	/	63	I, II	3	2	600	500	210	17	5	CAS
12	73	M	ORN	/	40	I, II	3	1	600	500	180	25	15	Non-CAS
13	67	M	SCC	pT4N0M0	17	I, II	2	1	720	300	210	9	2	CAS
14	57	M	SCC	pT4N0M0	19	I, II	2	1	840	300	180	42	21	Non-CAS
15	58	M	SCC	pT1N0M0	38	I, II	3	1	540	500	210	21	4	CAS
16	49	M	SCC	pT1N0M0	14	I, II	3	1	750	500	210	20	2	Non-CAS
17	64	M	SCC	pT4aN2bM0	35	I, II	3	2	660	500	200	37	19	CAS
18	58	M	SCC	pT4aN2bM0	46	I, II	3	2	765	450	180	22	10	Non-CAS
19	66	F	SCC	pT4aN2bM0	64	III, IV	2	3	720	200	180	20	3	CAS
20	75	M	SCC	pT4aN2bM0	15	III, IV	2	2	900	500	200	53	30	Non-CAS
21	59	M	SCC	pT4aN2bM0	44	I, II	4	1	660	500	180	22	4	CAS
22	57	M	SCC	pT4aN2bM0	61	I, II	3	1	705	450	255	57	5	Non-CAS
23	81	F	SCC	pT4N0M0	12	I, II	2	2	600	500	150	22	5	CAS
24	84	M	SCC	pT4N0M0	70	I, II	2	1	660	250	180	33	3	Non-CAS
25	68	F	SCC	pT2N0M0	30	III, IV	3	3	600	500	180	21	5	CAS
26	65	M	SCC	pT4N0M0	88	III, IV	2	3	840	800	240	31	1	Non-CAS
27	51	M	SCC	pT4aN3bM0	49	III, IV	3	2	540	300	200	16	1	CAS
28	51	M	SCC	pT4N0M0	35	III, IV	2	3	780	450	210	22	1	Non-CAS
29	59	M	SCC	pT4N0M0	14	I, II	2	2	660	500	105	23	3	CAS
30	54	M	SCC	pT4N0M0	67	I, II	2	1	600	450	250	16	1	Non-CAS
31	70	F	SCC	pT4aN2b	20	III, IV	2	3	960	300	150	21	2	CAS
32	66	M	SCC	pT4NOM0	45	III, IV	2	3	780	450	210	18	1	Non-CAS
33	58	M	SCC	pT4aN0M0	28	I, II	3	2	600	200	180	28	5	CAS
34	57	M	SCC	pT4apN1M0	14	I, II	2	2	600	500	210	26	6	Non-CAS
35	53	M	SCC	pT4N0M0	21	III, IV	3	3	780	300	150	27	5	CAS
36	66	M	SCC	pT4aN1m0	82	III, IV	2	2	600	400	210	19	1	Non-CAS

ORN: Osteoradionecrosis, TNM: TNM classification, and AJCC 8th Edition.

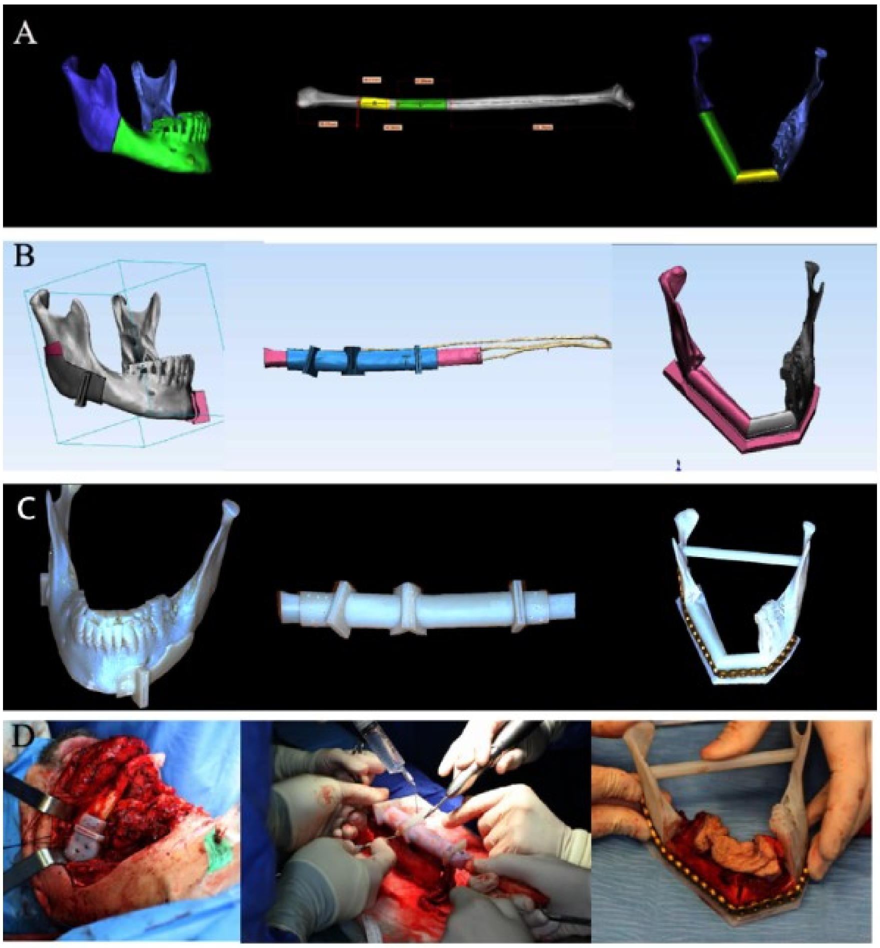

Figure 2 An 80-year-old female oral cancer patient after CAS. Virtual surgical planning (A), computer-assisted surgical templates design (B), preoperational preparation and 3D model printing (C), and computer-assisted surgery performance (D).

Table 3 Continuous data comparison of matched pair series.

Parameters	CAS		Non-CAS		P-value	Unit
	Mean	Median	Mean	Median		
Age	59.1	60	58.7	57.5	0.743	year
ASA	2.61	2	2.2	2	0.79	/
Segments	1.8	1.5	2	2	0.339	/
OT (N,SD)	643±139	600	722±137	757.5	0.064	min
IBL (N,SD)	360±121	300	464±130	450	0.085	ml
IT (N,SD)	177±31	180	221±36	210	<0.001	min
HD (N,SD)	20±6	20.5	26±14	22	0.226	day
ID (N,SD)	4.9±5	4.5	6.2±3	3	0.628	day

SD: Standardized deviation, OT: Operation time, IBL: Intraoperative blood loss, IT: Ischemia time, HD: Hospitalization days, and ID: ICU days.

Measurements and statistics

The matched pairs between CAS and non-CAS were analyzed utilizing a statistical software package (SPSS software, Version 25.0. Armonk, NY: IBM Corp). The mean and median were reported for the continuous parameters. The normally distributed continuous data were compared by students' t-test and the Mann-Whitney test was utilized for the non-parametric data. The categorical data were compared using the chi-square test. A p-value of < 0.05 was considered statistically significant.

Results

The total sample included 101 males (66%) and 52 females (34%) with a mean age of 56.3 years (range: 8-84 years) at the surgery. The patient diagnosis included 102 malignant tumor (67%), 39 osteonecrosis (25%), 5 benign tumor (3%), and 7 mandibular defect cases (5%) secondary to trauma or other reasons (Table. 1). Among the 102 malignant tumor cases, there were 17 patients with positive margins.

Based on the matched pairs, the age deviation was within the range of 10 years. Additionally, the aetiology, defect size, location and number of segments between the two groups were similar. The difference between ASA score between the groups was not more than one ASA grade. The average operation time and bleeding volume in the CAS group were less than the non-CAS group. Additionally, both hospitalization and ICU days were lower in the CAS group without any significant difference. The only significant finding related to surgical parameters was observed for the ischemia time, which was lower in the CAS group (Table. 3, Figure. 3).

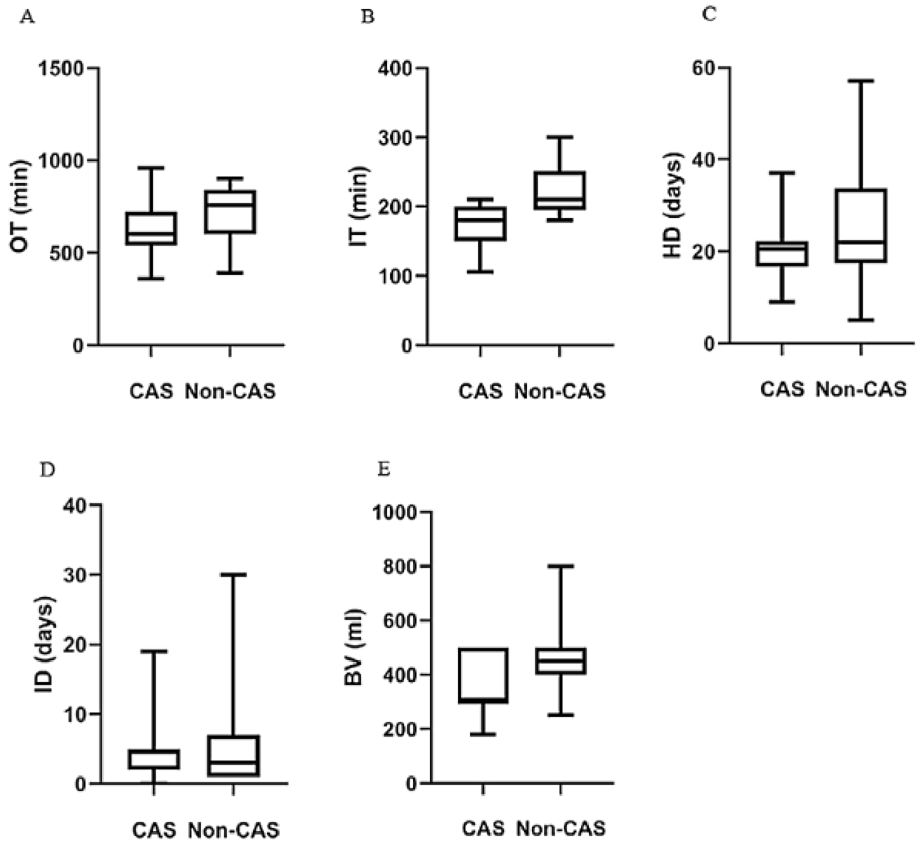

Figure 3 Surgical-related parameter comparisons. Comparison of operation time between the two groups (A), comparison of ischemia time between the two groups (B), comparison of hospitalization days between the two groups (C), comparison of ICU days between the two groups (D), and comparison of intraoperative bleeding volume between the two groups (E).

The intraoperative neck dissection, tracheotomy, defect size, postoperative adjuvant therapy and postoperative functional outcomes showed no significant difference between the two groups. Concerning the early complications, the CAS group showed fewer complications compared to the non-CAS group. Four early complications were in the CAS group (two fistulae, one infection, and one donor site wound dehiscence) and eight early complications in the non-CAS group (four flap loss, two recipient site delayed wound healing, one donor site delayed wound healing and one infection). However, no significant difference was observed between both groups (Table. 4).

Table 4 Categorical data comparison of matched pair series.

Parameters	CAS (N, %)		Non-CAS (N, %)		P-value
Gender (M/F)	10/8	56%/44%	15/3	83%/17%	0.146
Etiology (MT/ON/BT)	13/4/1	72%/22%/6%	13/4/1	72%/22%/6%	1
Neck Dissection	12	67%	12	67%	1
Tracheotomy	15	83%	15	83%	1
Defect size (Class I, II/ Class II, IV)	9/9	50%/50%	9/9	50%/50%	1
S/S+RT/S+RT+CT	4/9/5	22%/50%/28%	3/10/5	22%/50%/28%	0.738
Medical complication	2	11%	9	50%	0.31
Early Complication	4	22%	8	44%	0.157
failure	1	6%	0	0%	0.31
Malnutrition	4	22%	2	11%	0.371
Unintelligible pronunciation	1	6%	2	11%	0.546
Physical activity restriction	3	17%	3	17%	1
Unacceptable facial appearance	1	6%	1	6%	1
Pain	5	28%	3	17%	0.423

MT: Malignant tumor, ON: Osteoradionecrosis, BT: Benign tumor; S: Surgery, RT: Radiotherapy, and CT: Chemotherapy.

Discussion

Computer and template-assisted surgery has played an irreplaceable role in modern surgery during recent years. With the help of preoperative computer-based reconstruction, surgeons can visualize the lesion and its relationship to the surrounding anatomical structures. Thereby, avoiding thermal injury to adjacent structures, increasing reconstructive accuracy and improving postoperative outcomes.[13] However, the evidence is lacking in the comparison of surgery- and patient-related outcomes between freehand traditional surgery and CAS. Most of the reported evidence is related to the virtual surgical plan's postoperative accuracy. Although, an accurate reconstructive surgery can contribute to facial symmetry, however, the prognostic and survival parameters outweigh the aesthetic component significantly.[14] Therefore, in the present study only surgery and patient-related outcomes were investigated to observe whether CAS offered improved outcomes compared to freehand surgery. Unlike previous studies that utilized a control group or designed subgroup analysis based on the number of osteotomies, a matched pair cohort was designed to control the heterogeneity related to aetiology, defect size, reconstructive site, type of flap, age, gender and any other related parameters.[15]

Our findings suggested a reduction in operation time, ischemia time, hospitalization days, ICU days, and bleeding volume following CAS compared to freehand surgery. These findings were in accordance with other studies.[16, 17] As the reconstructive models and surgical templates reduce the surgeons' intra-operative decision making which resulted in the reduction of operation and ischemia time. Although other studies found a reduction in ischemia and bleeding time with CAS, however, inconsistency was observed concerning the significance of the reduction. Our findings were consistent with those of Mitchel et al, which also reported a significant reduction in ischemia time, whereas, no significant reduction in overall operation time was observed in the CAS group. They reported 50 minutes shorter ischemia time in CAD/CAM fibula free flap group ($p = 0.004$) and 23 minutes shorter operation time ($p = 0.21$). Sanjay et al. reported a significant reduction in operation time ($p < 0.0001$) which could be explained based on the difference in the type of surgery and surgical interventions.[11] The ischemia time in both CAS and non-CAS groups was less than the safety limit of 5 hours[20], however, the early complications rate was higher in the non-CAS (44%) than the CAS group

(22%). Although the early complication rate was lower in the CAS group nevertheless no significant difference was observed when compared with the Non-CAS group. These findings were consistent with other studies.[18, 19] For further reducing the complication rate, one solution might be designing tailor-made disease-specific resection osteotomies instead of conventional mandibular straight-line osteotomies which is less invasive and can preserve vital anatomical structures in the mandibular region.[20] Ren et al also reported a reduced reconstruction and operation time duration in the CAS compared to the conventional surgery group. However, they showed less duration in contrast to our findings, which could be attributed to the fact that most of the cases in their study were benign tumors having a smaller extent of resection compared to our group of patients where most patients had a malignant tumor. [21]

The present study suggested a decrease in ICU days in the CAS group based on the matched pair analysis which was consistent with some studies that also found the patients treated utilizing CAD-CAM technology showed a decrease in complication rate and an improved outcome. However, when considering the complete cohort there were some patients with severe complications in the Non-CAS group which could have resulted in an overall bias. Nevertheless, the matching pairs allowed to overcome the reporting bias seen within the whole cohort of patients.

The surgical success rate was nearly equivalent in both groups, as based on evidence no relationship exists between prolonged surgical time and surgical success.[19] Similarly, no significant difference existed between both groups related to postoperative outcomes, which might be due to CAS's inability to avoid tissue injury secondarily to ablative resection and reconstruction.[22] For instance, the physical activity restriction rate and facial aesthetics were equal in both groups. Only pain and nutritional status showed better results in the non-CAS group compared to the CAS group. This variability in both groups could have resulted due to the amount of soft tissue resection mainly the masticatory musculature, bite force and tissue sclerosis which were not evaluated in the study.

With limited surgical experience, junior surgeons also could benefit from CAS. CAS can compensate for their insufficient clinical expertise and help to reduce the learning curve span.[23] Even though overall CAS allowed improved surgery- and patient-related outcomes compared with the freehand approach, cost-effectiveness should be further addressed. Costs for template and pre-bent plates can go over 1000 Euro, whereas, patient-specific titanium plate designs and printing can reach up to 3000 Euro, excluding the labor cost of medical engineers and clinicians.[24]

The present study had certain limitations. Firstly, the retrospective nature of the study did not allow for a standardized evaluation of the postoperative parameters which were recorded subjectively during the clinical examination. Secondly, the difference in surgeons' experience might have led to a selection bias. Thirdly, a relatively small sample size based on the matched pairs could have confounded the results. A larger sample in a matched pair might enable further understanding of how CAS benefits the patients' outcomes and quality of life.

Conclusions

Computer-assisted surgery indicates improved efficiency considering reduced ischemia time, operation time, and length of hospital stay with a decreased number of early complications. It can thus be considered as an optimal alternative to the freehand approach.

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Chapter 6: Adherence to computer-assisted surgical planning in 136 maxillofacial reconstructions

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Abstract:

Objective:

To investigate the adherence to initially planned maxillofacial reconstructions using computer-assisted surgery (CAS) and to identify the influential factors affecting its compliance for maxillofacial reconstruction.

Patients and methods:

A retrospective analysis of 136 computer-assisted maxillofacial reconstructive surgeries was conducted from January 2014 to June 2020. The categorical parameters involved age, gender, disease etiology, disease site, defect size, bone flap segments, and flap type. Apart from descriptive data reporting, categorical data were related by applying the Fisher-exact test, and a p-value below 5% was considered statistically significant ($P < 0.05$).

Results:

The main reasons for partial or non-adherence included unfitness, patient health condition, and other subjective reasons. Out of the total patient population, 118 patients who underwent mandibular reconstruction showed higher CAS compliance (83.9%) compared to the 18 midface reconstruction (72.2%) without any statistically significant difference ($p = 0.361$). Based on the size of the defect, a significantly higher CAS compliance ($p = 0.031$) was observed with a minor defect (80.6%) compared to the large-sized ones (74.1%). The bone flaps with two or more segments were significantly ($p = 0.003$) prone to observe a partial (15.4%) or complete (12.8%) discard of the planned CAS compared to the bone flaps with less than two segments. The malignant tumors showed the lowest CAS compliance when compared to other disorders without any significant difference ($p = 0.1$).

Conclusion:

The maxillofacial reconstructive surgical procedures offered optimal compliance to the initially planned CAS. However, large-sized defects and multiple bone flap segments demonstrated a higher risk of partial or complete abandonment of the CAS.

Introduction

Reconstructive maxillofacial surgery following tumor resection, trauma, osteonecrosis, and other infectious diseases is vital for restoring facial aesthetics, function, oral rehabilitation and improving the patient's quality of life (QOL).[1] Depending on the complexity of the defect, the reconstruction might range from a local flap with secondary bone grafting to microvascular free flap surgery. The maxillofacial region mandates special care from a surgeon as it occupies a central position concerning the aesthetics and functionality, as an inadequate reconstruction might negatively influence the final outcome.[2]

Previously, maxillofacial reconstruction with the traditional freehand technique offered a challenge for optimally repositioning the grafted segments and maintaining facial symmetry. However, with the advent of computer-assisted surgery (CAS) and three-dimensional (3D) printing, the reconstructive surgical accuracy and patient- and surgery-related outcomes have significantly improved.[3, 4] Additionally, CAS has also played a vital role in improving the oral rehabilitation by increasing the predictability of replacing missing teeth with both first- and second-stage dental implant placement in the grafted region.[5] Thereby, making CAS an indispensable tool for reconstructive surgery.

Over the past few years, the significant technological advancements and availability of surgeon-friendly software programs have led to the domination of CAS for maxillofacial reconstruction compared to its conventional counterpart by offering multiple advantages, which commonly include, improved resection accuracy, reduction in the operation, ischemia and hospitalization time, improved functional and aesthetic outcomes and minimization of the intersegmental gap size. [6-8] At the same instance, the disadvantages such as preparation and planning time, and cost aspects cannot be ignored.[9-11] Although, multiple centers now offer in-house CAS services for decreasing the time to therapy initiation (TTI).[12] However, an issue still exists where certain centers with low-volume of reconstruction cases rely on out-of-house services, which might cause a delay in the delivery and treatment time, in turn leading to further growth of the tumor.[13] All these limiting CAS factors should be taken into consideration, as TTI has been known to be an influential factor for pathologic tumor upstaging, where an untimely intervention might lead to further tumor progression and increased mortality.[14, 15]

Various studies have focussed on the accuracy and reproducibility of the CAS for maxillofacial reconstruction. However, a lack of evidence exists pertaining to the CAS compliance during the reconstructive procedures. It is questionable whether a surgeon completely adheres to the planned CAS.[16] Previous studies reporting on the CAS compliance have only briefly reported whether the planning was executed entirely, partially, or abandoned and also failed to assess the factors which might influence its adherence.

Therefore, the present study was conducted to investigate the CAS compliance for initially planned maxillofacial reconstruction and to identify potential influential factors that might affect its adherence to the initially planned CAS.

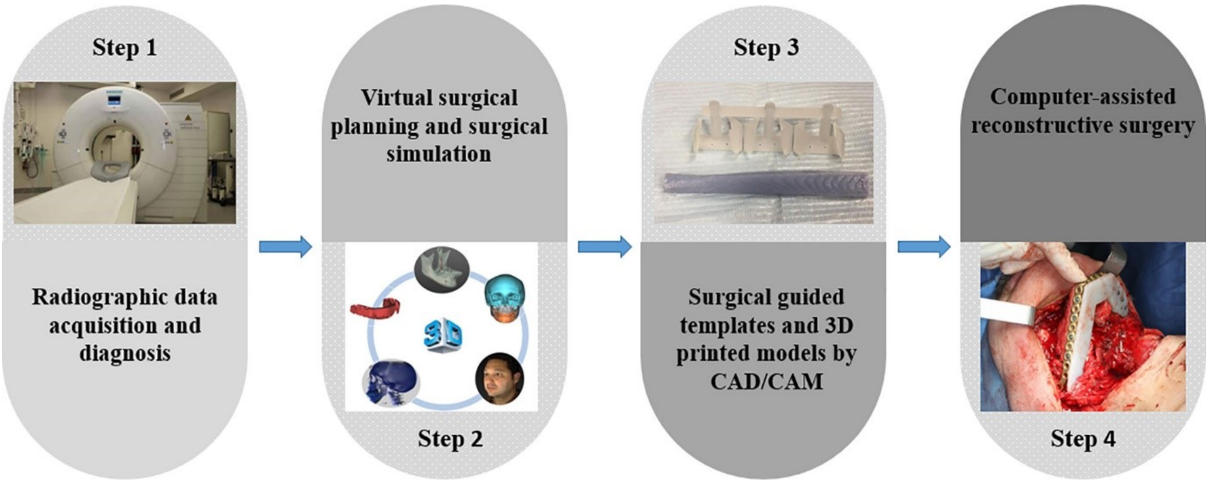

Figure 1. Workflow of Computer-assisted surgery in our single center.

Material and Methods

The Local Ethics Committee approved the study (reference no.: S63615) and was conducted in compliance with the World Medical Association Declaration of Helsinki on medical research (clinicaltrials.gov, NCT04895319). A total of 210 patients who underwent CAS-based maxillofacial reconstruction were screened from January 2014 to June 2020. The inclusion criteria involved patients undergoing maxillofacial reconstruction with CAS, which included virtual surgical planning, CAD-CAM surgical guides/templates, and pre-bent plates on 3D printed models. The workflow in our single-center was illustrated in Figure 1. Reasons for reconstruction were oncologic, osteoradionecrosis, trauma, and osteoporosis. Patients undergoing computer-assisted implant surgery and orthognathic surgery were excluded. All computer-assisted surgeries were planned by an experienced clinical engineer in discussion with the oral and maxillofacial surgical team. The virtual planning was performed to determine the resection, cut margins, and localize the optimal angles for performing osteotomies. After that, surgical cutting guides were designed utilizing a 3D designing software (3-Matic, Version 9.0-13.0, Materialise, Leuven, Belgium). The generated virtual templates and the planned 3D skeletal model were exported in a Standard Tessellation Language (STL) format and printed with a professional 3D printer (Connex 350 3D printer, Stratasys, Eden Prairie, MN, USA). The reconstructive plates were pre-bent on the 3D-printed model. A fixation tray was applied for the guided placement of the reconstructive plates. The screw holes' locations were drilled and marked onto the surgical template by the surgeon (Figure 2).

The patients were divided into three groups depending on the CAS compliance either during the pre-operative or intra-operatively, which included; complete adherence, partial adherence, and no adherence (Figure 3). The recorded categorical parameters involved disease etiology classified by either malignant or non-malignant tumor, disease site (mandible or midface), bone flap segments (< 2 or ≥ 2 segments), and flap type (bone flap or others). (The defects were classified based on Brown classification, where class I, II of mandibular defect and class I, II, V, VI of maxillary and midface defect were defined as a small defect; Class III, IV of the mandibular defect and class III, IV of maxillary and midface defect were defined as a large defect.[17, 18]

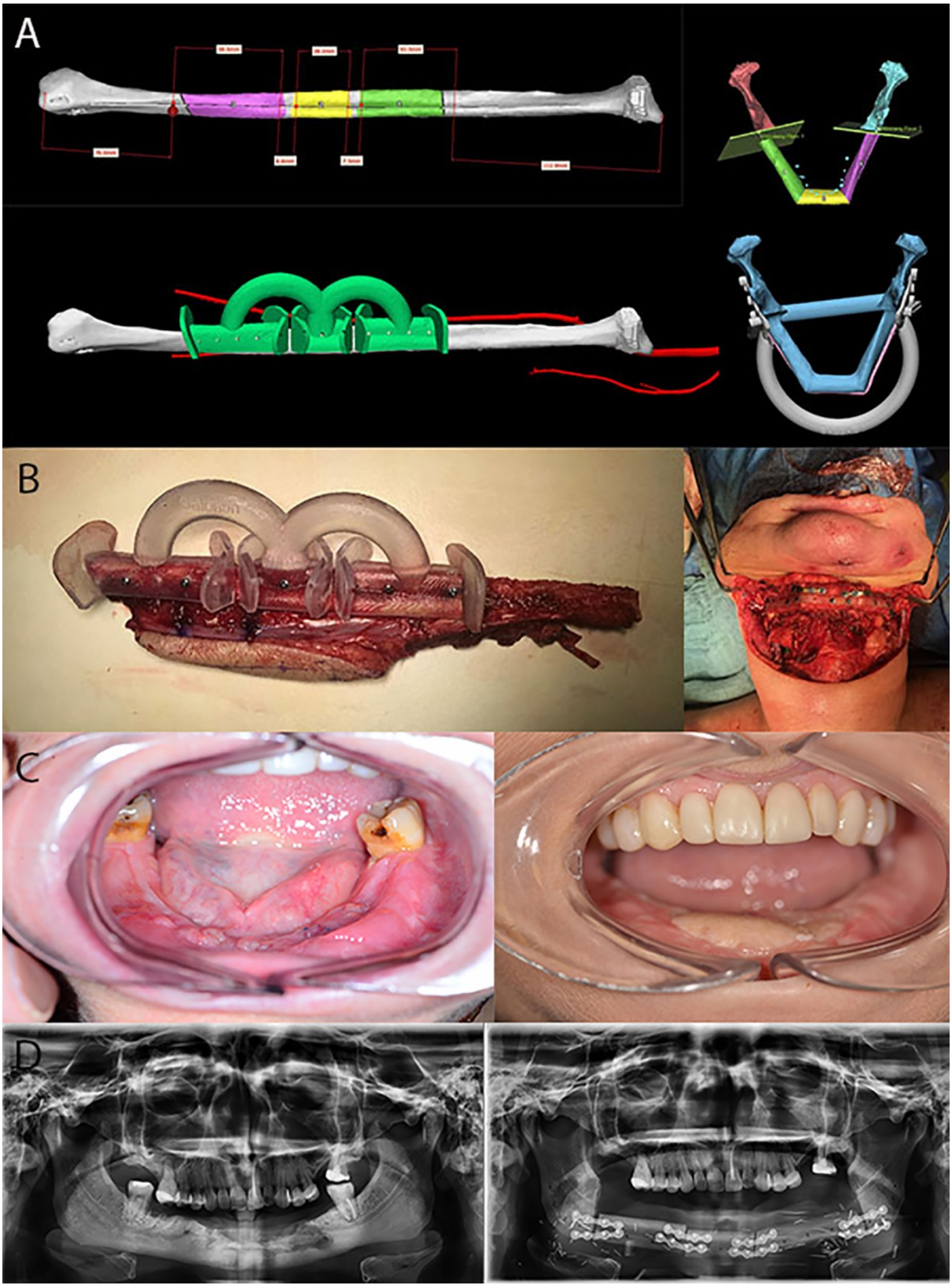

Figure 2. Computer-assisted surgical planning and execution for a squamous cell carcinoma reconstruction. (A) Preoperative virtual analysis and planning. (B) Fibular graft fabrication assisted by guided templates. (C) Preoperative and postoperative intraoral photos of squamous cell carcinoma resection with mandibular reconstruction. (D) Preoperative and postoperative panoramic radiographs.

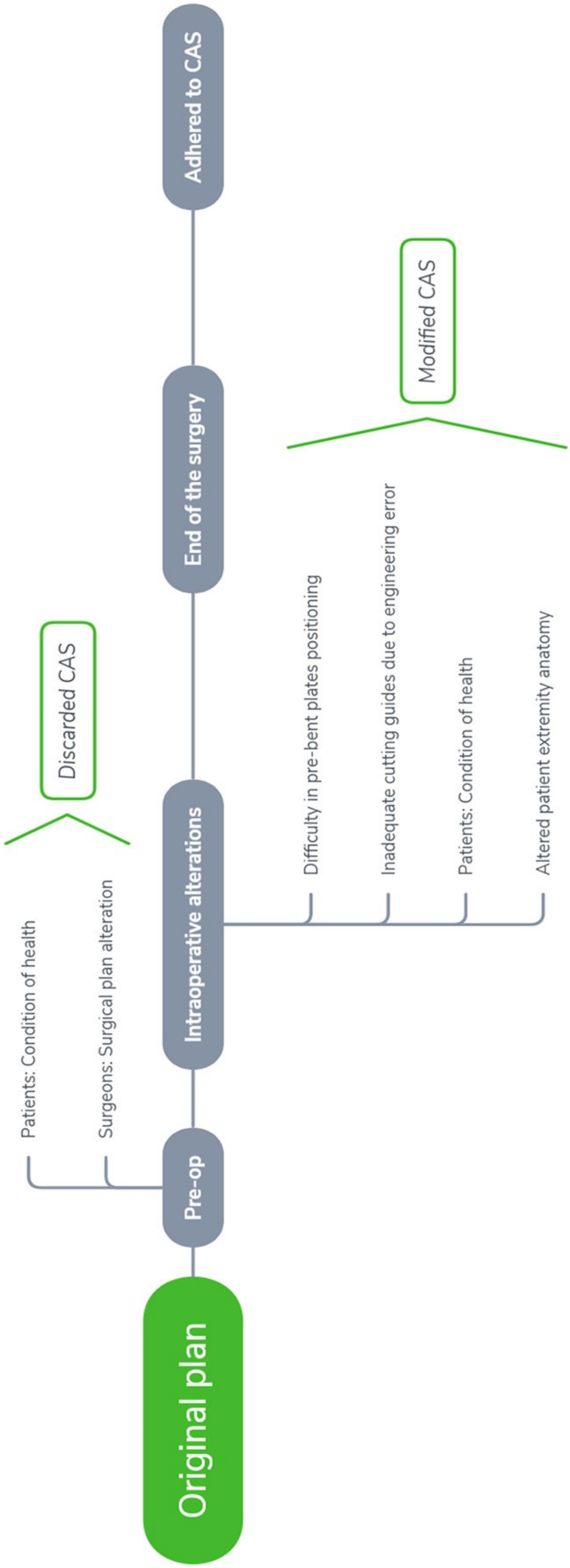

Figure 3. Flowchart of surgical adherence to computer-assisted surgery.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY: IBM Corp, USA). Mean values and standard deviation were recorded for all parameters. The categorical data were compared by applying the Fisher-exact test. A p-value below 5% was considered statistically significant ($p < 0.05$).

Table 1. Patients characteristics.

Parameters	Classification	Numbers (N)	Percentage (%)
Gender (M/F)		78/58	57.4/42.6
Age (mean, SD)		55.8 ± 18	/
Adherence of CAS	Complete	112	82.4
	Partial	14	10.3
	Discarded	10	7.4
Etiology	Malignant tumor	72	52.9
	Benign tumor/cyst of jaw	13	9.6
	Trauma	16	11.8
	ORN	25	18.4
	Others	10	7.4
Disease site	Mandible	118	86.8
	Midface	18	13.2
Defect size	Small	72	52.9
	Large	64	47.1
Bone graft segments	0	20	14.7
	1	38	27.9
	2	39	28.7
	>2	39	28.7
Flap type	Fibula	88	64.7
	Iliac	22	16.2
	Scapula	6	4.4
	Plates or prosthesis only	20	14.7

CAS, Computer-assisted surgery; ORN, Osteoradionecrosis.

Results:

Following inclusion and exclusion criteria, clinical and image data of 136 consecutive patients (58 females, 78 males, mean age: 55.8 ± 18 years) undergoing CAS-based maxillofacial reconstruction were served further analysis. Table 1 describes the patient- and surgery-related characteristics, where the majority of the patients were diagnosed with malignant tumor (n = 72) followed by maxillofacial trauma (n=16), benign tumor or odontogenic keratocyst (n=13), osteoradionecrosis (n=25) and temporomandibular joint ankyloses/ congenital maxillofacial defect (n=10). The main reasons for partial abandonment of the planned CAS included unfitness of the cutting guide (n = 4) and pre-bent plates (n = 2), patients health condition (n=7). Figure 4 illustrates an example of a case showing partial CAS compliance. In contrast, the complete discard of CAS was mainly attributed to subjective reasoning (Table 2).

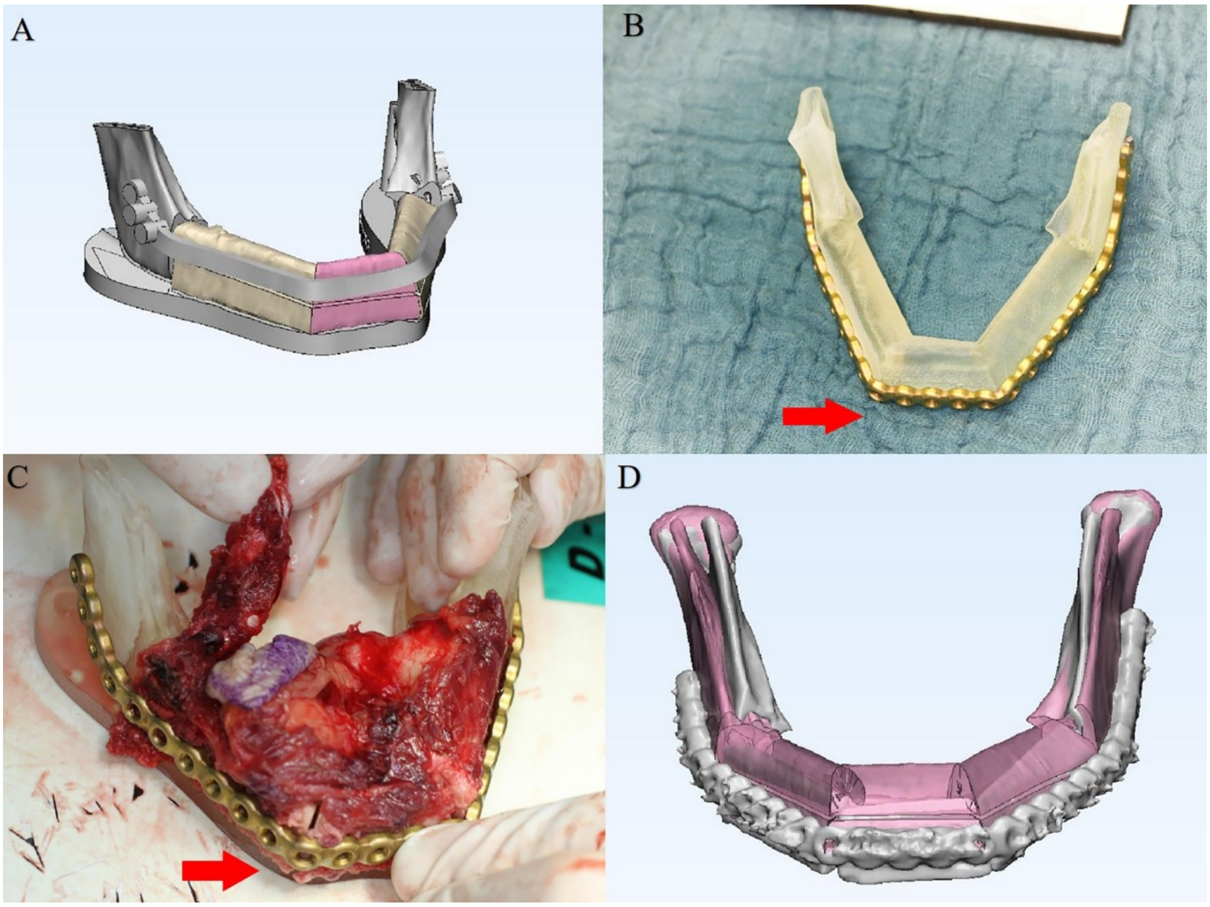

Figure 4. A 56-year-old patient with mandibular squamous cell carcinoma showing partial computer-assisted surgical compliance. (A) Virtual surgical planning for mandibular reconstruction. (B) Plate prebending on the 3D printed model. (C) Intra-operative plate bending modified due to unfitness. (D) Postoperative superimposition verifying the 3-D deviation of the reconstructed region compared with the original virtual surgical plan.

Table 3 describes the factors influencing the compliance to the planned CAS. When evaluating the CAS compliance based on the defect site, patients who underwent mandibular reconstruction showed higher complete adherence (83.9%) compared to the midface reconstruction (72.2%) without any statistically significant difference (p = 0.361). Based on the size of the defect, a significantly higher conformity to the CAS (p = 0.031) was observed for patients with a minor defect (80.6%) compared to the large-sized ones (74.1%). The bone flaps with more than two segments were significantly (p=0.003) prone to observe partial (15.4%) or complete discard of the CAS (12.8%). The malignant tumors showed the lowest conformity to the CAS when compared to other disorders without any significant difference (p=0.1). As for the patients treated with a bone flap, complete adherence was significantly higher (85.3%, p=0.016) when compared with the non-bony flap group (65.0%).

Table 2. Partially executed or discarded plan with reasons.

Influential factors	Reason	Numbers	Outcome
Unfitness	Guided templates	4	Partially executed plan
	Pre-bent plates	2	Partially executed plan
Patients' health conditions	Tumor growth	2	Partially executed plan
	Tumor growth	1	Discarded plan
	Bone displacement	1	Partially executed plan
	Altered extremity	2	Partially executed plan
	Complex maxillary defect	1	Partially executed plan
	Death	1	Discarded plan
Subjective reasons	Surgical protocol changes	2	Partially executed plan
	Treatment plan alteration	3	Discarded plan
	Unaffordable cost	2	Discarded plan
	Patients' non-compliance	3	Discarded plan

Table 3. Influential parameters on the adherence of CAS.

Parameters	Classification	Total (n)	Complete adherence (n)	Percentage	Partial adherence (n)	Percentage	Not adherence (n)	Percentage	P-value
Site	Mandible	118	99	83.9%	11	9.3%	8	6.8%	0.361
	Midface	18	13	72.2%	3	16.7%	2	11.1%	
Defect size	Small	72	58	80.6%	6	8.3%	8	11.1%	0.031
	Large	64	99	74.1%	8	9.3%	2	6.8%	
Segments	<2	58	56	96.6%	2	3.4%	0	0.0%	0.003
	≥2	78	56	71.8%	12	15.4%	10	12.8%	
Aetiology	Malignant tumor	72	55	76.4%	11	15.3%	6	8.3%	0.1
	Non-malignant tumor	64	57	89.1%	3	4.7%	4	6.3%	
Flap type	Bone flap	116	99	85.3%	8	6.9%	9	7.8%	0.016
	Others	20	13	65.0%	6	30.0%	1	5.0%	

Discussion

The present study explored the conformity to CAS-based surgical planning for maxillofacial reconstructive procedures and investigated the influence of the parameters to identify the reasons it was partially executed or wholly discarded.

The present study's findings suggested that the unfitness of the guided templates and patients' health condition were most commonly observed in the partially abandoned CAS, whereas complete CAS discard was based on subjective reasoning. The factors which could have attributed to the reduced CAS compliance might include CT data segmentation accuracy, medical engineer proficiency, or precision of the printed stereolithographic model. Any error occurring due to the aforementioned factors would influence the CAS compliance. Besides, a prolonged waiting time for the surgery or an early CT scan in oncology patients caused the further growth of the malignant tumors, thereby requiring partial or complete discard of the plan. It should be kept that the CAS-based surgical planning and implementation only rely on the hard tissue, without considering the intra-operative influence of the soft tissue. The soft tissue and musculature have been known to forcefully position the bone flap in complex reconstructive procedures, which is not considered at the treatment planning phase and might lead to partial or complete discard of the CAS.[19] Therefore, a surgeon should be aware of the biomechanical deformation of the soft tissue during CAS, and a patient-specific soft tissue predictive model should be generated based on the CT data, and finite element analysis at the planning phase improved planning.

Efanov et al. assessed the adherence to CAS for maxillofacial reconstruction and their findings were consistent with the results of the current study.[20] However, their sample mostly involved orthognathic surgery patients, with only six patients requiring free tissue transfer, unlike our study where orthognathic surgical procedures were excluded to reduce the risk of bias. Hanken et al. reported a relationship between surgical accuracy and the number of bone flap segments for the maxillofacial reconstruction, where higher deviations occurred between virtual and real segment position in patients requiring reconstruction with two or three fibular or iliac crest segments compared to a single segment.[21] The accuracy of CAS decreases with the increased number of segments, which might explain the partial adherence or complete discard. Previous evidence failed to report whether the defect size decreases the CAS compliance. Our findings suggested that a large-sized defect and increased bone segments were more prone to lower CAS compliance, especially in cases involving condylar region or mandibular angle where unfitness of pre-bent plates was mainly observed.

A variety of approaches can establish the improvement in CAS. Effective and constant communication between the surgeon and medical engineer might significantly improve the planned CAS. As the incomplete adherence not only leads to an increased risk of intra-operative complications but is also associated with higher financial costs if the plan is changed at the pre-operative stage.[22] For improving the virtual planning and CAS, it is recommended to utilize a CT image with a slice thickness of less than 1mm and to advocate a professional 3D printing for printing the skull model to improve the contouring of the pre-bent plates.[6] Another option could be the 3D printing of the patient-specific titanium plates which offers improved accuracy compared to the traditional pre-bent plates.[23] Regarding the cutting guides, patient-specific titanium alloy cutting guides could be an alternative to improve fitness. These guides are thinner than the polyamide guides, allowing easier intraoral placement and decrease the amount of periosteal stripping and cutaneous resection.[24]

The study had certain limitations. Firstly, the quantitative accuracy of the CAS was not assessed. Secondly, the retrospective nature of the study could have acted as a medium of bias. Thirdly, sample distribution was heterogeneous, mainly involving reconstruction following resection of the malignant tumors. Future studies should investigate the amount of error induced at each step of the planning to understand better and improve complex reconstructive procedures.

Conclusion

CAS-based maxillofacial reconstructive surgery offered optimal conformity to the initially executed plan. However, large-sized defects and an increased number of bone flap segments led to a higher rate of partial or complete abandonment of CAS. Thereby, a surgeon should be aware of the possibility of non-adherence to the planned CAS for complex reconstructive procedures.

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Chapter 7: Application of 3D printed customized surgical plates for mandibular reconstruction: report of consecutive cases and long-term postoperative evaluation

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Abstract:

This study aims to evaluate the use of customized surgical plates in patients with mandibular defects concerning postoperative aesthetics and functional outcomes during the two-year follow-up. Preoperative virtual surgical plans (VSP) and patient-specific 3D-printed plates (PSPP) were tailored for consecutive patients. Preoperative preparation, surgical produces, postoperative aesthetics, and functional outcomes were described in detail. The average follow-up period was over two years. In the presented clinical cases, aesthetic and functional outcomes were reported to be satisfactory.

Introduction

Segmental mandibular defects secondary to tumors, jaw osteonecrosis, and comminuted mandibular fractures may cause serious mutilation hampering oral function (deglutition, mastication, speech) and impacting quality of life. In some cases, it may also cause certain psychological problems owing to impaired facial appearance.[1] Due to the benefit of vascularized bone grafts or reconstructive plates, mandibular continuity can be restored successfully and effectively.[2-5] Such reconstructions and contour corrections can also be achieved with a virtual surgical plan (VSP) in combination with 3D printed surgical models and/or pre-bent titanium plates.[6, 7]

Mandibular reconstruction with titanium plates alone, or by grafted bone combining the pre-bent titanium reconstructive plates or mini-titanium plates, can provide enough mechanical strength and stabilize the mandibular segments. Yet and optimally, one should try to achieve patient-specific reconstructive plates with proper screw angulation and implant positions readily in place. The utilization of PSPP and surgical templates have already been applied for various oral and maxillofacial surgery procedures with positive feedback, such as orthognathic surgery, trauma surgery, distraction osteogenesis, cranioplasty, tumor resection surgery.[8-12] While it may provide the surgeon with better accuracy, save time and help to reduce complications, one should bear in mind that it may cost more money and need more effort preoperatively.[13]

This study aims to evaluate a series of patients with mandibular reconstruction by 3D printed patient-specific titanium plates concerning postoperative aesthetics and functional outcomes during the two-year follow-up.

Materials and methods

In the oral and maxillofacial department, University Hospital of Leuven, Leuven, Belgium eight consecutive patients with a mandibular defect were recruited to be preoperatively planned by personalized printed plates. This study was approved by the local ethical committee of the University Hospitals of Leuven, Leuven, Belgium (reference number: S63615). Five consecutive patients were performed with PSPP from January 2017 to June 2017, however one patient was lost to follow-up. Finally, four patients were included in this case series (two females, two males, age from 17 to 83 years) and their patient characteristics are noted in Supplemental Table 1. One patient was diagnosed with mandibular fracture secondary to osteoporosis; the other two suffered from oral radionecrosis; the last one was diagnosed with ossifying fibroma. The mandibular defect size was referred to as the Jewer classification.[14] All patients gave their informed consent for treatment with the customized virtual surgical plan.

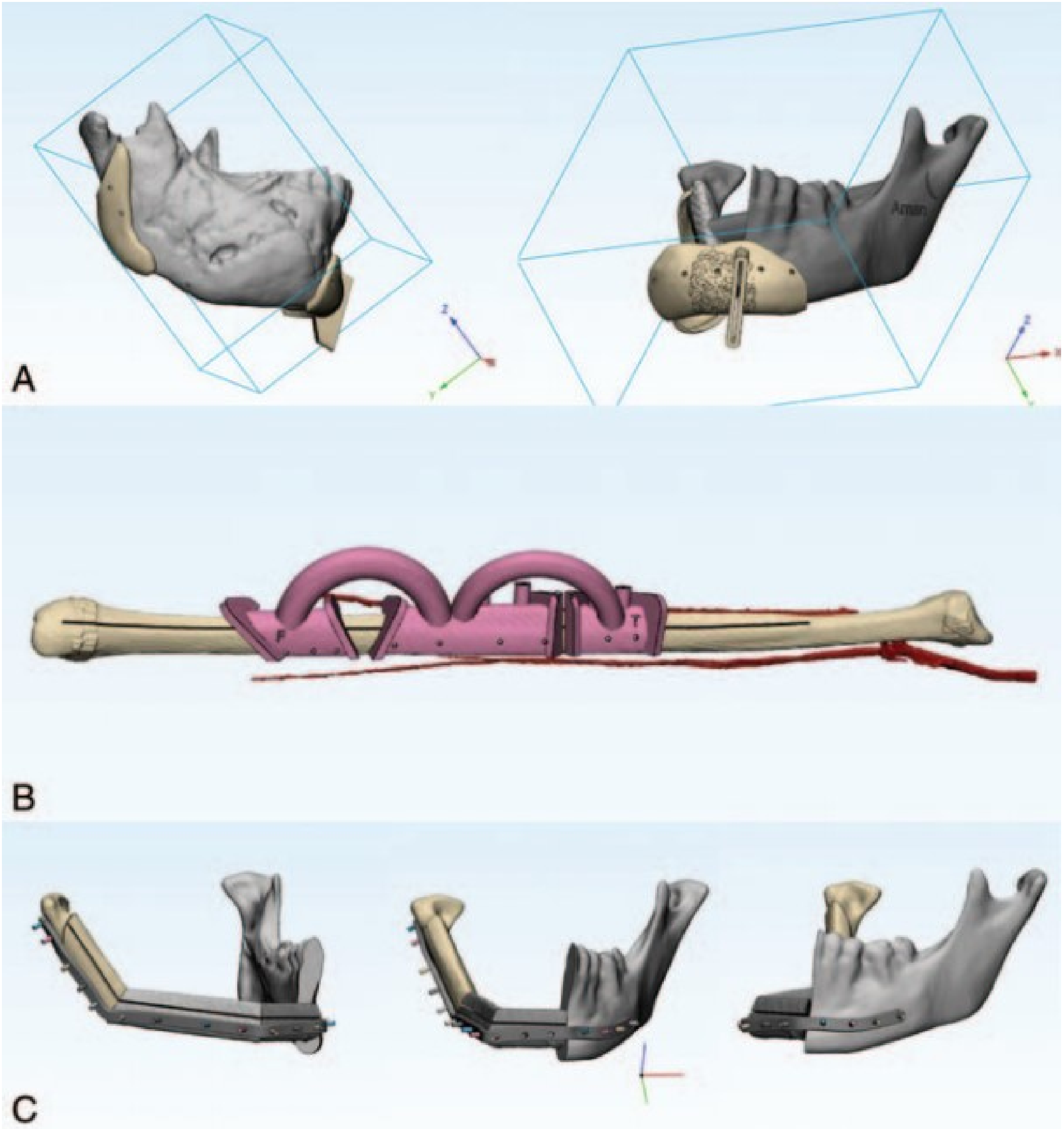

Figure 1. Virtual surgical plan. (A) Tumor cutting guided design. (B) Fibular cutting guided design. (C) Fibular harvesting, and patient-specific 3D-printed plates design. 3D, three-dimensional.

Preoperative planning

For all patients, a multislice CT scan was obtained before surgery. For the patient with vascularized bone graft, both CT scans of the head and neck region and CT angiography (CTA) of the double lower extremity were acquired preoperatively. Images were saved in DICOM format and imported to ProPlan CMF 3.0 (Materialise, Leuven, Belgium). Presurgical resection and reconstruction were carried out, with a virtual surgical plan for the reconstruction of the mandible and fibula. According to defect size, position, and fibula segment lengths, virtual resection, and fibula bone graft were designed (Fig. 1). After three dimensional design, segmental parts were exported to 3-Matic medical 13.0 (Materialise, Leuven, Belgium) to generate guided templates, mandibular model, and customized reconstructive plates (Fig. 2). The physical mandibular model and guided templates were printed by Connex 350 3D printer (Stratasys, Eden Prairie, MN, USA), while PSPP were printed by Concept Laser's M2 cusin machine (KLS Martin Group, Tuttlingen, Germany). For patients without bone graft, the PSPP were built based on the contour of their mandible to repair and strengthen their mandibular continuity by the same skilled medical engineer.

Figure 2. Guided templates, mandibular model, and customized reconstructive plate.

Surgical protocol

All patients underwent general anesthesia with nasal intubation. Visor flap (modification of the mandibulotomy approach without lip split) was applied in all the patients.[15, 16] The mandibles were exposed via a longitudinal incision, attached muscles were bluntly separated to avoid nerve and salivary gland injury in the submandibular region. After the lesioned bone was removed totally, then the customized 3D printed plates (Titanium-printed 2.0 osteosynthesis plate and multiple 2.4 Synthes locking osteosynthesis screws) were placed and fixed in the planned position. For patient three, vascularized fibular bone segments were prepared according to 3D-printed surgical guided templates, and non-vascularised iliac bone was combined with fibula in the buccal side by screws (1.5 Synthes screws) to compensate for the inadequate vertical and horizontal graft bone (Fig. 3).

Postoperative outcomes and follow-up

Postoperative intraoral and extraoral images were taken, while aesthetic and functional outcomes were evaluated during routine consultations at 1 and 2 years follow-up. Complications, oral status, and aesthetic outcomes were self-reported with good, acceptable, or unacceptable. The mean follow-up time was 26.6 months. The postoperative 3D mandible model was created and registered to the preoperative planning in Mimics software (version Medical 21, Materialise, Leuven, Belgium), and then the error analysis was performed.

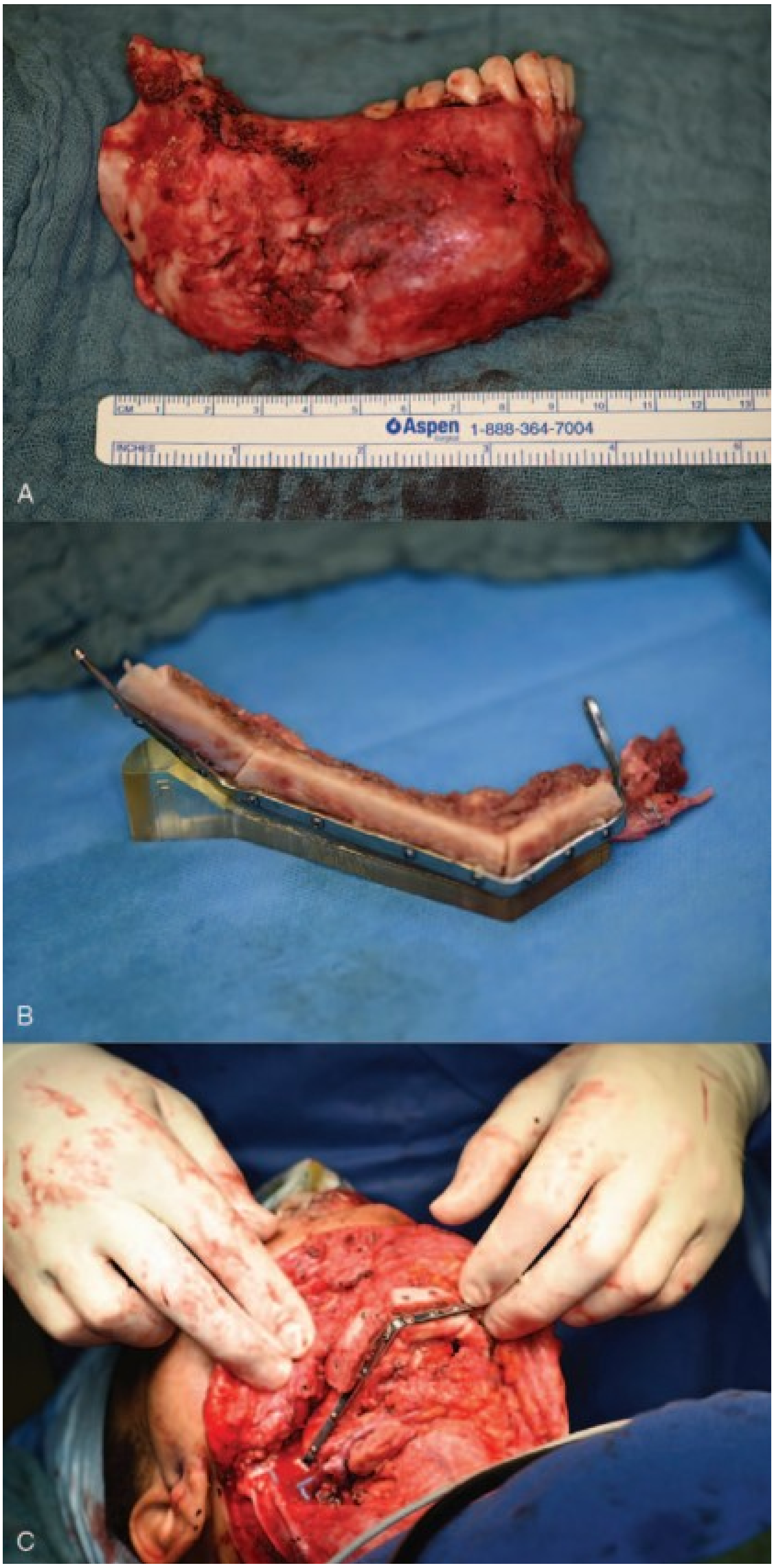

Figure 3. Intraoperative photos. (A) Tumor specimen. (B) Fibular flap preparation. (C) Fibular harvesting.

Figure 4. Extraoral photos. (A) Before surgery. (B) Two years after surgery.

Case presentation

Case 1

Patient one was an 83 years old male who presented with mandibular osteoradionecrosis secondary to chemoradiotherapy of right tonsil squamous cell carcinoma. The patient's intra-oral examination was characterized by right mandibular exposed bone, limited mouth opening and pain. The patient was diagnosed with stage III osteoradionecrosis and a panoramic radiograph showed extensive osteonecrosis at the right mandibular body.[17] During the half-year follow-up postoperative, there was small intraoral dehiscence, no plate exposure and minor swelling without infection extra-orally.

During one year and two years of follow-up, the patients' photos showed excellent facial contour. No bone osteolysis was found around the fixation screws, and no plate position change was spotted. The patient was satisfied with the operative outcomes and no complaints.

Case 2

Patient two was a 70 years old female diagnosed with mandibular fracture secondary to osteoporosis who received an open reduction with internal fixation surgery two months before this surgery. Intra-oral examination showed that the patient was completely edentate but with a prosthesis. Additional panoramic radiographs showed a pronounced atrophic lower jaw with full resorption of the alveolar bone (only four mm thickness).

At a 3-month follow-up, wound healing was uneventful. The patient had a percutaneous endoscopic gastrostomy (PEG) probe and did not need a prosthesis. From the multi-slice CT, osteosynthesis material and bone fragments were in the planned position. At 2 years follow-up, the patient did not report pain or signs of infection, nor mandibular mobility restriction.

Case 3

Patient three was a 17 years old female diagnosed with ossifying fibroma of the mandible. From a speech detection, there was a barrier to normal conversation. The prominent mandibular asymmetry with hard hyperplastic expansion was found from the observation.

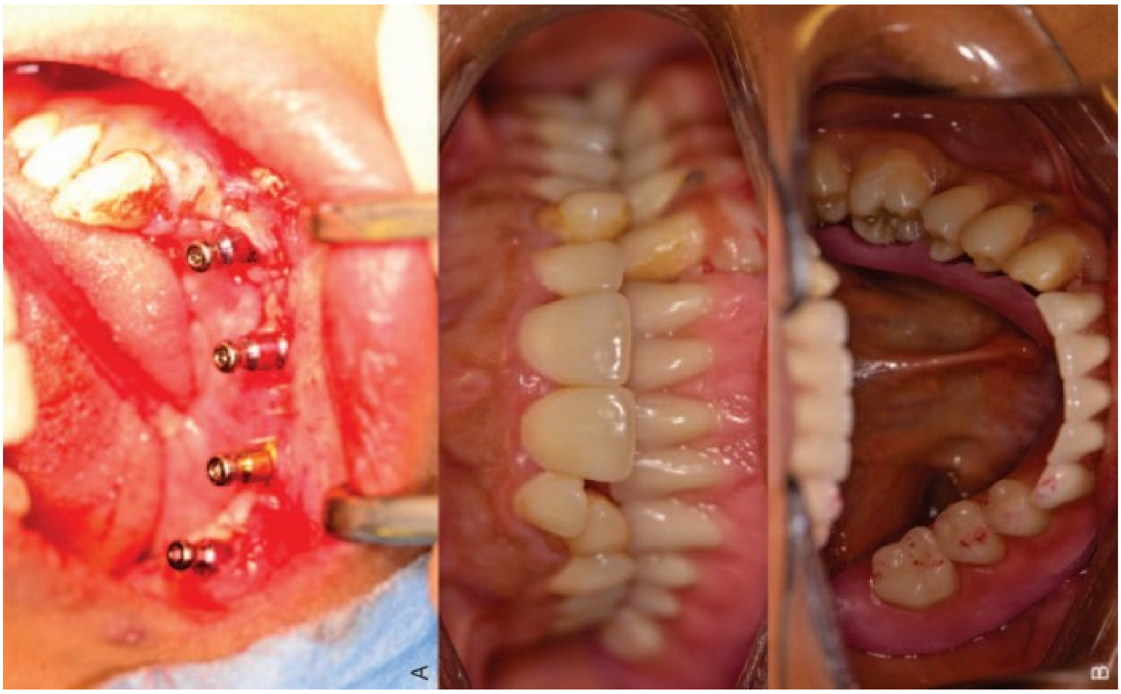

Figure 5.Oral rehabilitation. (A) Dental implant placement. (B) Intraoral photos after oral rehabilitation.

Figure 6. (A) Panoramic radiograph before surgery. (B) Phase II dental implant placement.

Clinically, significant swelling of the right jaw was seen and felt from the anterior to the posterior of the right side. From an intra-oral examination, the occlusal plane is oblique, the gingiva was smooth and white. The maximum mouth opening was 39 mm. Cone-beam computed tomography (CBCT) showed high-density imaging that led to a volumetric increase of the mandibular from teeth 31 to the mandibular notch, including the corruption of the cortical bone, particularly in the vestibular bone region, where an irregular bone tissue was also visible. Multi-slice CT showed expansive, bulky osseous injury, assembling in the right mandible corpus, extending into the ramus with characteristics consistent with fibrosis. And the CTA showed normal anatomy and appropriate patency of the arteries in both lower limbs. The preoperative biopsy indicated ossifying fibroma.

Two months postsurgically, the intra-oral wound healed without infectious stigma. Panoramic radiograph and CT showed a good position of the reconstructive plates. The speech was recovered at one and two years follow up, and the maximum mouth opening had gradually improved to 38mm. By comparison of preoperative and postoperative standardized clinical photos, an aesthetic appearance was well present (Fig. 4). One year after surgery, dental implant surgery (33,42,44,45) was performed to restore the missing teeth with a fixed implant-supported prosthesis. Occlusion was restored and swallowing had returned normal (Fig. 5). The panoramic radiograph showed a symmetric reconstruction of the mandible and stable peri-implant bone (Fig. 6). The two 3D models (preoperative surgical plan and postoperative mandible reconstruction) obtained were first aligned, taking into consideration fixed reference landmarks on the virtual planning and postoperative CT scan to obtain the most accurate 3D overlap. The average mean error obtained after performing an accuracy evaluation of our reconstructions was 1.1 mm (Fig. 7).

Case 4

Case four was a 66-year-old man who was diagnosed with stage III osteoradionecrosis (45-47). Mandibulectomy was performed to remove the sequestrum according to the guided cutting guide and customized titanium plates were applied to reconstruct the mandible defect as planned. From a 30 months follow-up period, there were no complications, while the postoperative and aesthetic outcomes were reported by the patient to be acceptable.

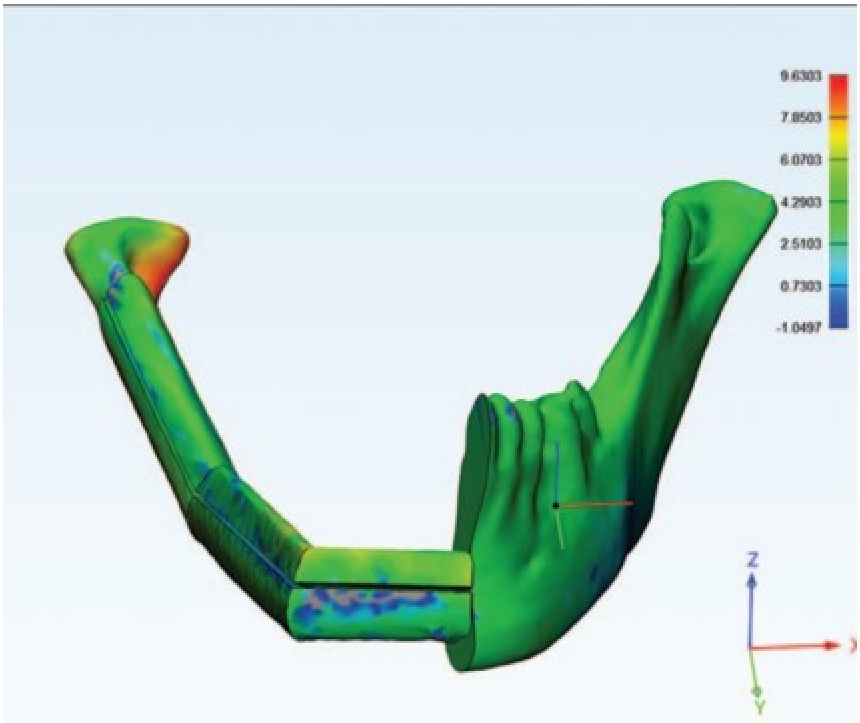

Figure 7. 3D accuracy analysis. 3D, three-dimensional.

Discussion

From this 2-years case series, all patients recovered uneventfully from the mandibular reconstruction with both optimal aesthetic and functional outcomes. All patients did not resisted with the personalized virtual surgical plan and customized prosthetics, no complaints were received during the consultation. The virtual surgical plans combined with PSPP were successfully placed from the postoperative radiographs; well bone healing and symmetric mandibular contour were found.

During the past decade, there has been an increasing interest in personalized treatment. A virtual surgical plan combined with 3D printing technology has played a significant role in oral and maxillofacial reconstruction. Based on the accumulated advantages of the virtual surgical plan and surgical model and comparison with traditional oral and maxillofacial reconstruction, the CAD/CAM technology applied in surgery was appreciated and recommended by surgeons to some extent. From literature reviews, less operation time, better aesthetic results, and decreased incidence rate of complications were frequently reported.[18] However, there were also negative points, such as extra cost of the objects, prolonged surgical preparation period, rejection of implanted material, and undesirable match between the bone and implanted titanium plates.[19] With the advent concept of Precision Medicine in various clinical disciplines, future researchers and surgeons may no longer be satisfied with preoperative pre-bent titanium plates and 3D models. Patient-specific, printed titanium implants will gradually become mainstream.[20]

It is obvious to find the benefits of patient-specific surgery. By selecting the plate features according to the different patients' conditions, surgeons and medical engineers can customize and provide a patient-specific solution precisely.[21, 22] Compared with pre-bent plates, patient-specific plates are 3D-milled based on the anatomy structure, eliminating the time for adaptation. Moreover, the induced stress which is normally generated in the surgeries by pre-bent plates will disappear during the customized surgery. Moreover, the accuracy of PSPP is high saving donor site bone and morbidity, meanwhile reducing unexpected events and complications. However, manufacturing time and material costs are relatively high comparing traditional surgery by or not by pre-bent palates. Additionally, the application universality is limited used as the weakness of mechanical strength in patient-specific plates compared to conventional reconstructive palates. Experience in design by dedicated engineering and close collaboration is required.

The application of personalized titanium plates and short-term follow-up outcomes have already been reported in other studies.[23] Nevertheless, long-term outcomes were more welcomed to evaluate the stability of the innovative surgical procedure. In our single-center, there have been six years since the 3D lab was established and long-term follow-up studies were designed. The first patient-specific mandibular reconstruction surgery was performed three years before in our department, and patients were followed up for over two years. From the recorded medical history and examinations, this new surgical procedure took nearly seven to eight hours less than traditional mandibular reconstruction surgery which would take over no less than ten hours. The biocompatibility was optimal according to the relatively small size of the patient-specific plates which may reduce contact surface with both hard and soft tissue. Small volume personalized titanium plates may also reduce the artifacts in the postoperative radiological examinations and make it convenient for the second stage of dental implant surgery. Furthermore, the universality of customized plates will lead to a comprehensive application without special morphology limitations. Overall surgical planning right from the start makes future oral rehabilitation easier and more effective. This allowed in case 3, to allow for implant placement one year after bone healing, with dental implants perfectly implanted in the planned sites without the need for second stage dental implant surgery.

However, the cost of manufacturing and preparation is a non-negligible factor.[24] Owing to the difference in the health insurance system between countries, patients in some countries or under some circumstances could not afford the cost of the personalized medical service.

Considering the costs and time involved in this VSP strategy, the patient sample remained limited. Future studies should allow for larger patient samples, to allow drawing clinically meaningful and reliable conclusions. Another limitation was the retrospective nature and evaluation mainly determined on the history of the patients' medical files and the patient's subjective reporting on oral function and aesthetic outcomes.

None of the patients in this case-series are concerned with primary oncological resection and reconstruction. As such there was no time-constraint, unlike in primary treatments of oral cancer. VSP strategy is not only time and cost consuming but also induces a significant time delay in treatment since the PSPP needs to be ordered, validated, approved, and delivered which takes at least four weeks in this case series. This disadvantage only will be solved when point-of-care printing of titanium constructs will become mainstream.

Conclusion

In summary, no severe complications occurred during follow-up. All patients recovered with the satisfactory restoration of the symmetric orofacial contour with good oral function. Based on the postoperative radiological examinations, continuity of mandible was established with good bone healing assisting customized reconstructive plates. Studies with a larger sample size are welcomed to allow for thorough cost-benefit analysis and more robust conclusions and recommendations towards the clinical practice.

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Chapter 8: General discussion, conclusions, clinical relevance and future recommendations

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Discussion

Maxillofacial reconstructive surgery after tumor resection, trauma, osteonecrosis and other infectious diseases is essential to restore facial aesthetics, function, oral rehabilitation and improve the patient's quality of life (QOL).[1] In **chapter 1**, we generally introduced the past, present, and future of the oral and maxillofacial reconstruction, and its associated research background. And then, in **chapter 2,** by comparing the functional outcomes of oral tumor patients after mandibular reconstruction in a fibular and iliac flap, we perform a systematic review and meta-analysis.[2] VFF and VIF are considered the best donor sites for mandibular reconstruction.[3-5] Meanwhile, VFF is considered the gold standard for mandibular reconstruction.[6] However, its long-term functional outcomes require more attention compared with recipient-site VIF. Therefore, we performed the following review to report which flap provided the most optimal functional outcome at the recipient site after mandibular reconstruction with a minimum follow-up time of one year.

Furthermore, based on the questions from **chapter 2**, we aim to investigate the concerned parameters and outcomes of patients after oral cancer and patients' oral rehabilitation after jaw reconstruction. After two retrospective studies in **chapter 3**, we verify the vascularized fibular flap is reliable in mandibular reconstruction in advanced OSCC patients, and the outcomes of the patients from long-term follow-up are acceptable.[7] Moreover, oral rehabilitation is crucial for the patients as it is closely related to mastication, speech and facial appearance.[8] To investigate the oral rehabilitation of patients after jaw reconstruction, we also analyze the cumulative survival rate of dental implants and their associated risk factors in patients after jaw reconstruction in **chapter 4**.

Previously, maxillofacial reconstruction with conventional free flap techniques was challenging in terms of optimal placement of the grafted segments and maintaining facial symmetry.[9] However, with the advent of computer-assisted surgery (CAS) and three-dimensional (3D) printing, the reconstructive surgical accuracy and patient- and surgery-related outcomes have significantly improved.[10] In **chapter 5**, we design a match pair study, which is believed as an effective method to delineate the heterogeneity between the control group and the experimental group. From this comparative study, we find that the CAS provides optimal outcomes compared with freehand surgery.[10] However, the pitfalls of CAS cannot be neglected with the extra cost of time and supplies. Moreover, the mechanical and human errors may also lead to an inaccurate CAS with partial or non-compliance surgery.[11] Additionally, the lengthy preoperative preparation and associated costs have become a drawback of the technique and have hindered the development of CAS.[12] Depending on each patient, patient-specific surgical plans, guided cutting templates, and dental implant guidelines must be uniquely designed, which can take anywhere from 3 hours to 10 hours for an experienced medical engineer. There may even be more effort and cost savings regarding the second plan due to changes in tumor growth or anatomical location before surgery.[13]

Previous studies reporting on the CAS compliance have only briefly reported whether the planning was executed entirely, partially, or abandoned and also failed to assess the factors which might influence its adherence. Therefore, we designed the cohort study in **chapter 6** to investigate the adherence of CAS in oral and maxillofacial reconstruction. We primarily verify the reliability of CAS in daily practice, however, there are still some influential factors that should be carefully taken into consideration by the surgeons and medical engineers. In addition, how to reduce the preparation time cost of material and labor force are still unanswered now. Considering these subjective reasons, standardized workflow to guide how to evaluate a CAS while specifying the surgical constraints is welcomed based on the type of surgery.[14] Finally, in **chapter 7** to verify the application of customized 3D printed plates in mandibular reconstruction, we collect consecutive patients' data after personised virtual surgical planning and printed plates. From this case series study, we confirm the reliability and advantages by long-term follow-up.

However, because of the nature of retrospective studies and other confounding factors, there are also some limitations in this thesis. In **chapter 2,** the variation in the follow-up period and utilization of non-validated questionnaires resulted in heterogeneity and skewness of the reported data. Our inclusion criteria were the mean follow-up period above 12 months, however, few cases may be less than 12 months. Although we have contacted the authors and asked for the raw data for meta-analysis. Some researchers were unable to provide complete data. Therefore, our data analysis was based on the overall patients (mean follow-up> 12 months). Secondly, inadequate sample size and loss of patients at follow-up in a few studies led to a lack of adequate power. Thirdly, most of the studies failed to provide the association between radiotherapy and functional outcomes. In **chapter 3,** based on the long period of the evaluation from 1996 to 2019, a historical bias might have been associated with treatment and chemo-radiotherapy strategies. Moreover, developed surgical concepts, materials, the number of reconstructive surgeons at a tertiary center, and supporting facilities could not be ignored during the long-term follow-up period.[15] Finally, the study involved only traditional clinical-pathological factors without assessing the risk of virological, genomic, and proteomic biomarkers.[16-18] Also, in **chapter 4,** owing to the characteristics of the cohort study design, patient-centered outcomes were not allowed As a limitation of the study, we could not record the patient-centered outcomes by T-Scan Novus (an objective assessment tool used to evaluate the occlusion of a patient), Implant Stability Quotient (ISQ, a scale from 1 to 100 and is a measure of the stability of an implant). Similarly, in **chapter 5**, the difference in surgeons' experience might have led to a selection bias. Thirdly, a relatively small sample size based on the matched pairs could have confounded the results. In **chapter 6**, sample distribution was heterogeneous, mainly involving reconstruction following resection of the malignant tumors. In **chapter 7**, eight consecutive patients recruited were planned with personalized printed plates. However, some of their treatment methods changed, which lead to limited sample size.

Conclusions

In **chapter 2**, based on the result of the systematic review and meta-analysis, the decision related to the graft selection bases on patient-related and surgeon-related factors, defect classification and donor-site morbidity. Current evidence seems to indicate that VIF offers improved long-term recipient-site functional outcomes. While in **chapter 3,** in the cohort studies, based on the 5-year survival rate, segmental mandibulectomy with fibula free-flap reconstruction in advanced OSCC patients offered a success rate of 52.4%. The clinical/pathological risk factors such as the pN stage, tumor differentiation, surgical margins, vascular invasion, perineural invasion, and tumor recurrence significantly influenced the overall cumulative survival rate. Moreover, in **chapter 4**, we have investigated the early cumulative implant survival rate in our cohort. Risk indicators that seem to be detrimental to long-term survival include poor oral hygiene, irradiated flap and systemic diseases. Our result is similar to some reports which indicate implantation before radiation therapy and immediately during tumor resection surgery is referred to as the critical implantation period, while implantation after radiation therapy, regardless of the time interval, is referred to as the secondary implantation period with lower dental implant survival rate. In **chapters 5 and 6**, computer-assisted surgery indicates improved efficiency considering reduced ischemia time, operation time, and length of hospital stay with a decreased number of early complications. It can thus be considered as an optimal alternative to the freehand approach. CAS-based maxillofacial reconstructive surgery offered optimal conformity to the initially executed plan. However, large-sized defects and an increased number of bone flap segments led to a higher rate of partial or complete abandonment of CAS. Thereby, a surgeon should be aware of the possibility of non-adherence to the planned CAS for complex reconstructive procedures. Finally, the long-term follow-up of PSPI in patients after mandibular reconstructive, proves that it is an alternative way for oral and maxillofacial reconstruction considering the benefit of the advantages.

Future perspective

From this series of studies in this thesis, all the virtual surgical planning is based on the experience of the medical engineer and surgeons. However, even a skilled medical engineer cannot promise the cutting guide and virtual surgical plan are the best for each case because of the limitation of human error. With the advent of artificial intelligence (AI), this problem may be solved in the future. A subfield of AI is machine learning (ML), which learns inherent statistical patterns in data and ultimately makes predictions about unseen data. Deep learning is an ML technique that uses multiple layers of mathematical operations to learn and infer complex data such as images. AI may relieve burdensome daily tasks, the health of a larger population at a lower cost. It can also facilitate customized, predictive, preventive dental practice. However, due to limited availability, accessibility, structure and comprehensiveness of data, lack of methodological rigor and standards in their development, and practical issues surrounding the value and usefulness of these solutions, also including ethics and liability. There is still a long way from pilot studies to mature applications in daily dental applications.[19] Recently, various artificial intelligence (AI)-based networks have been deployed to overcome errors associated with disease diagnosis, segmentation of models, and simplifying such digital workflows.[20] Most of these AI-based machines- or deep learning networks have been applied for diagnosing the disease or classifying the teeth and skeletal structures and have provided methods to precisely segment even in the presence of artifacts.[21] For instance, Xu et al, have established a method for mandibular 3D segmentation network combining multiple convolutional modules and edge-supervised from CT scans in that has better segmentation performance, effectively improves segmentation accuracy and reduces segmentation deficiencies, which improve the segmentation efficiency of the surgeon. It also has a broad application prospect in future mandibular reconstruction surgery.[22] However, AI-based surgical planning, which is considered a crucial part of disease treatment, is rarely reported. Moreover, there are no randomized controlled trials published to verify the application of artificial intelligence-assisted oral and maxillofacial reconstruction up to date. If the algorism of the AI-driven method can be established successfully, we believe it can also be popularised in other disciplines such as orthopedics and neurosurgery, save an amount of time and effort for the clinicians and reduce patient waiting time for virtual surgical planning.

The application of AI for automated diagnosis and treatment plans has immeasurable potential and value in oral and maxillofacial reconstruction.[23, 24] It is believed that the achievement of AI-based solutions for oral and maxillofacial surgical applications will greatly decrease the errors from human factors and provide a faster and more accurate personalized oro-maxillofacial reconstruction and rehabilitation treatment.

Moreover, since the concept of “precision medicine” which aims to maximize the health care quality by customizing the process to personalized treatment was advocated,[25, 26] researchers found quantitative medical images analysis may improve the diagnostic, prognostic and predictive accuracy. Lambin et al, firstly introduced the term “radiomics” which refers to the extraction and analysis of a large number of advanced quantitative imaging features at high throughput from medical images obtained by CT, PET-CT, or MRI.[27] Since then it has become more and more important in medical imaging studies, especially for cancer research. Not only is the explosion of quantitative data is an ideal environment for a machine learning approach, but also the large-scale standardized data make the validation of the radiomics based decision support systems for precision health care possible.[28] Moreover, with the help of radiomics, radiology can move from a subjective perceptual skill to an objective discipline.[29] However, there are also some intrinsic challenges such as the availability of numerous standardized data, the heterogeneity between different studies (modals) and the hindrance on radiologists' understanding of results from mathematical processes.[30]

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SUMMARY

The jaw bones are an integral part of the human face in terms of both aesthetics and functionality. Jaw bones are essential for vital oral motor functions, such as deglutition, speech, mastication, and airway support. Generally, ablative surgery for the treatment of oral and maxillofacial tumors requires jaw resection which produces significant cosmetic and functional impairment, thereby, leading to poor health-related quality of life (HRQOL). Reconstructive maxillofacial surgery following tumor resection, trauma, osteonecrosis, and other infectious diseases is vital for restoring facial aesthetics, function, oral rehabilitation and improving the patient's quality of life. Depending on the complexity of the defect, the reconstruction might range from a local flap with secondary bone grafting to microvascular free flap surgery. The maxillofacial region mandates special care from a surgeon as it occupies a central position concerning the aesthetics and functionality, as an inadequate reconstruction might negatively influence the outcome.

The thesis started with a general understanding of oral and maxillofacial reconstruction based on one systematic review and meta-analysis in **Chapter 2.** The overall aim of this Ph.D. project is to assess the impact of presurgical planning and oral rehabilitation on the clinical outcome and the long-term oral function after reconstructive surgery and oral rehabilitation. In **Chapter 3,** a cohort study was performed to provide comprehensive clinical evidence of the association between risk factors and cumulative survival rate of OSCC patients. Potential risk factors and postoperative outcomes were recorded and analyzed. The results suggested that the 5-years overall cumulative survival rate of patients was 0.52. Overall, advanced pN stage, poor tumor differentiation, positive/close surgical margins, vascular invasion, perineural invasion and tumor recurrence were significantly related to a decreased cumulative survival. Tumor recurrence was significantly correlated with involvement of positive/close surgical margins, moderate, poor-differentiated tumors, extracapsular spread, computer-assisted surgery and early complications. Pain was significantly associated with the extracapsular spread and early complications.

Similarly, we aimed to investigate the survival rate of placed dental implants in patients after jaw reconstruction in **Chapter 4**. The cumulative implant survival at 1-, 2- and 5-years was 96%, 87%, and 81%, respectively. Based on the multivariable regression analysis, patients with systemic diseases, irradiated flap and poor oral hygiene were at a significantly higher risk of implant failure.

Subsequently, in **Chapter 5** we investigated the application of CAS versus freehand surgery by analyzing the clinical parameters. The surgery-related and patient-related continuous and categorical parameters were assessed in both groups. The average operation time and bleeding volume in the CAS group were less than the non-CAS group. Additionally, both hospitalization and ICU days were lower in the CAS group without any significant difference. The only significant finding related to surgical parameters was observed for the ischemia time, which was lower in the CAS group. Furthermore, with the question that the CAS is 100% reliable in daily practice, a retrospective analysis of 136 computer-assisted maxillofacial reconstructive surgeries was conducted in **Chapter 6**. The main reasons for partial or non-adherence included unfitness, patient health condition, and other subjective reasons. Based on the size of the defect, a significantly higher CAS compliance was observed with a minor

defect compared to the large-sized ones. The bone flaps with two or more segments were significantly prone to observe a partial or complete discard of the planned CAS compared to the bone flaps with less than two segments. The malignant tumors showed the lowest CAS compliance when compared to other disorders without any significant difference.

Finally, to investigate the clinical application of 3D printed customized surgical plates for mandibular reconstruction. In **chapter 7**, a case series study was conducted indicating that no severe complications occurred during follow-up. And all patients recovered with the satisfactory restoration of the symmetric orofacial contour with good oral function. Based on the postoperative radiological examinations, continuity of mandible was established with good bone healing assisting customized reconstructive plates.

The findings of this doctoral thesis showed that CAS is superior to traditional freehand protocols in oral and maxillofacial reconstruction, while the compliance of CAS may be influenced by complicated defect conditions. In addition, the long-term follow-up studies showed that positive surgical margin, vascular or neural invasion and poor tumor differentiation are risk factors affecting survival rate of OSCC after jaw reconstruction, which should be taken into consideration by the clinicians.

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Chapter 2: Hongyang Ma and Jeroen Van Dessel: study design, manuscript preparation, statistical analysis, data analysis, and interpretation. Prof Reinhilde Jacobs and Prof Constantinus Politis: study supervision. Yifei Gu, Jeroen Van Dessel and Yi Sun: data collection. Michel Bila, Jeroen Van Dessel, Sohaib Shujaat, Prof Reinhilde Jacobs and Prof Constantinus Politis: contributed to the manuscript review, critical revision for important intellectual content. All authors contributed to the article and approved the submitted version.

Chapter 3: Hongyang Ma: study design, manuscript preparation, statistical analysis, Wim Coucke: data analysis, and interpretation. Prof Reinhilde Jacobs and Prof Constantinus Politis: study supervision. Michel Bila, Sohaib Shujaat, Prof Lloyd Nanhekhan, Prof Jan Vranckx, Prof Reinhilde Jacobs and Prof Constantinus Politis: contributed to the manuscript review, critical revision for important intellectual content. All authors contributed to the article and approved the submitted version.

Chapter 4: Hongyang Ma and Jeroen Van Dessel: study design, manuscript preparation, statistical analysis, data analysis, and interpretation. Prof Reinhilde Jacobs and Prof Constantinus Politis: study supervision. Jeroen Van Dessel and Yi Sun: data collection. Michel Bila, Jeroen Van Dessel, Sohaib Shujaat, Prof Reinhilde Jacobs and Prof Constantinus Politis: contributed to the manuscript review, critical revision for important intellectual content. All authors contributed to the article and approved the submitted version.

Chapter 5: Hongyang Ma and Sohaib Shujaat: study design, manuscript preparation, statistical analysis, data analysis, and interpretation. Prof Reinhilde Jacobs and Prof Constantinus Politis: study supervision. Hongyang Ma and Yi Sun: data collection. Michel Bila, Sohaib Shujaat, Prof Reinhilde Jacobs and Prof Constantinus Politis: contributed to the manuscript review, critical revision for important intellectual content. All authors contributed to the article and approved the submitted version.

Chapter 6: Hongyang Ma and Sohaib Shujaat: study design, manuscript preparation, statistical analysis, data analysis, and interpretation. Prof Reinhilde Jacobs and Prof Constantinus Politis: study supervision. Jeroen Van Dessel and Yi Sun: data collection. Michel Bila, Jeroen Van Dessel, Sohaib Shujaat, Prof Jan Vranckx, Prof Reinhilde Jacobs and Prof Constantinus Politis: contributed to the manuscript review, critical revision for important intellectual content. All authors contributed to the article and approved the submitted version.

Chapter 7: Hongyang Ma and Yi Sun: study design, manuscript preparation, statistical analysis, data analysis, and interpretation. Prof Reinhilde Jacobs and Prof Constantinus Politis: study supervision. Jeroen Van Dessel and Yi Sun: data collection. Michel Bila, Jeroen Van Dessel, Prof Reinhilde Jacobs and Prof Constantinus Politis: contributed to the manuscript review, critical revision for important intellectual content. All authors contributed to the article and approved the submitted version.

PERSONAL CONTRIBUTION

The author, Hongyang Ma, conceived the projects, collected, and managed the animal and radiological data, analyzed the data and wrote the research publications by scientific support of her promotors. Prof. Reinhilde Jacobs and Prof. Constantinus Politis, and all the co-authors. Accordingly, Hongyang Ma is the first author of all the thesis chapters and corresponding research papers.

CONFLICT OF INTEREST

The authors declare no conflicts of interest with respect to publication of this work.

CURRICULUM VITAE

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Publications

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