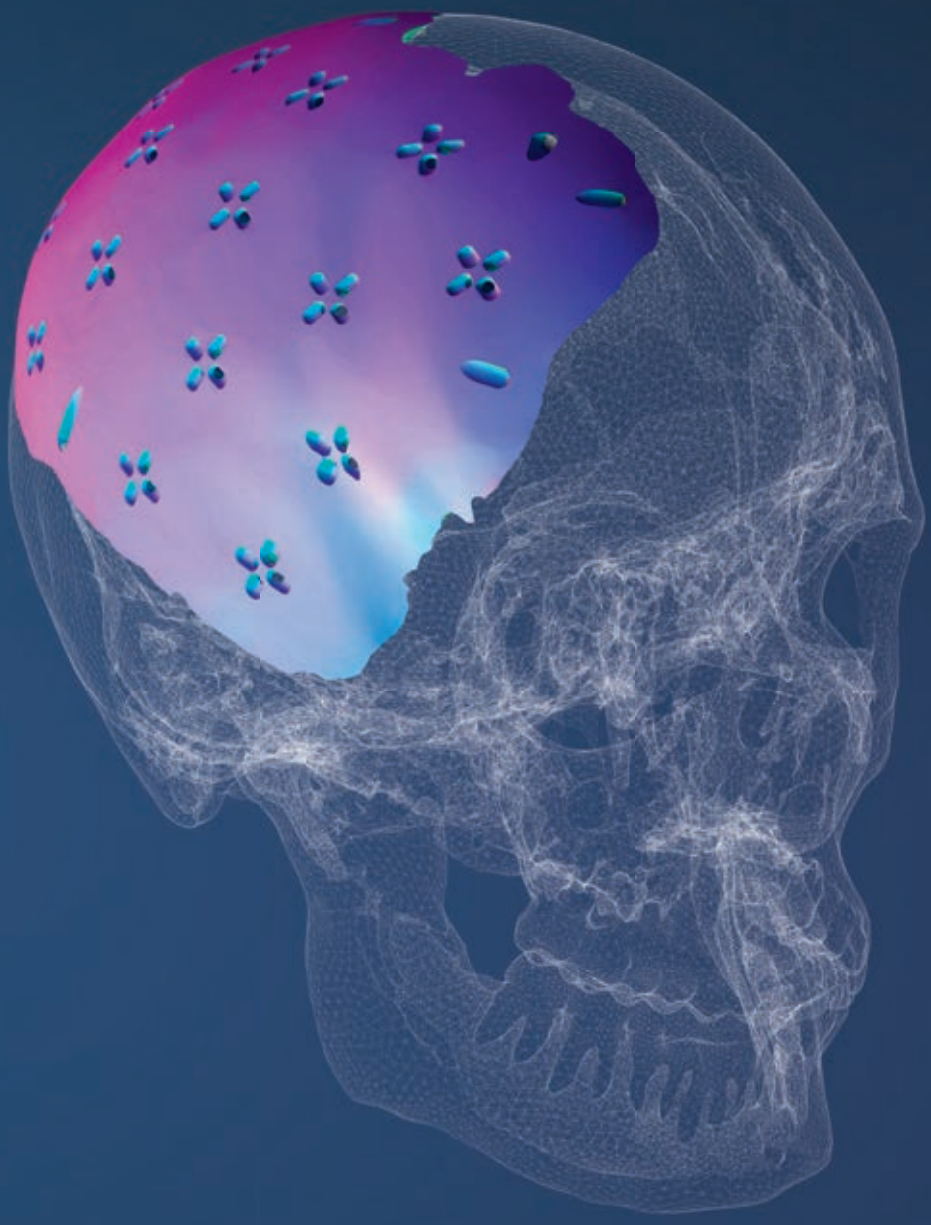
Clinical relevance of current materials for cranial implants

Towards an optimal patient-specific implant material



Sophie E. C. M. van de Vijfeijken

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Financial support for printing and distribution of this thesis was kindly supported by: HenrySchein Dental, KLS Martin, KNMT, Straumann, ExamVision, Xilloc, NVMKA, ACTA

This research in this thesis is supported by the Dutch Technology Foundation STW (Project Nr. 14326; CranioSafe), which is part of the Netherlands Organisation for Scientific Research (NWO), and which is partly funded by the Ministry of Economic Affairs.

Clinical relevance of current materials for cranial implants
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Academic thesis, University of Amsterdam, The Netherlands

ISBN: 978-94-6332-491-5

Cover picture: Niels Klop (design), Ruud Schreurs (jaws)
Layout: Ferdinand van Nispen tot Pannerden, Citroenvlinder DTP&Vormgeving, *my*-thesis.nl
Printing: GVO drukkers & vormgevers, Ede

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Clinical relevance of current materials for cranial implants

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ACADEMISCH PROEFSCHRIFT
ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op woensdag 8 mei 2019 te 13.00 uur

door
Sophie Elisabeth Catharina Maria van de Vijfeijken
geboren te Nijmegen

PROMOTIECOMMISSIE

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Voor mijn lieve ouders

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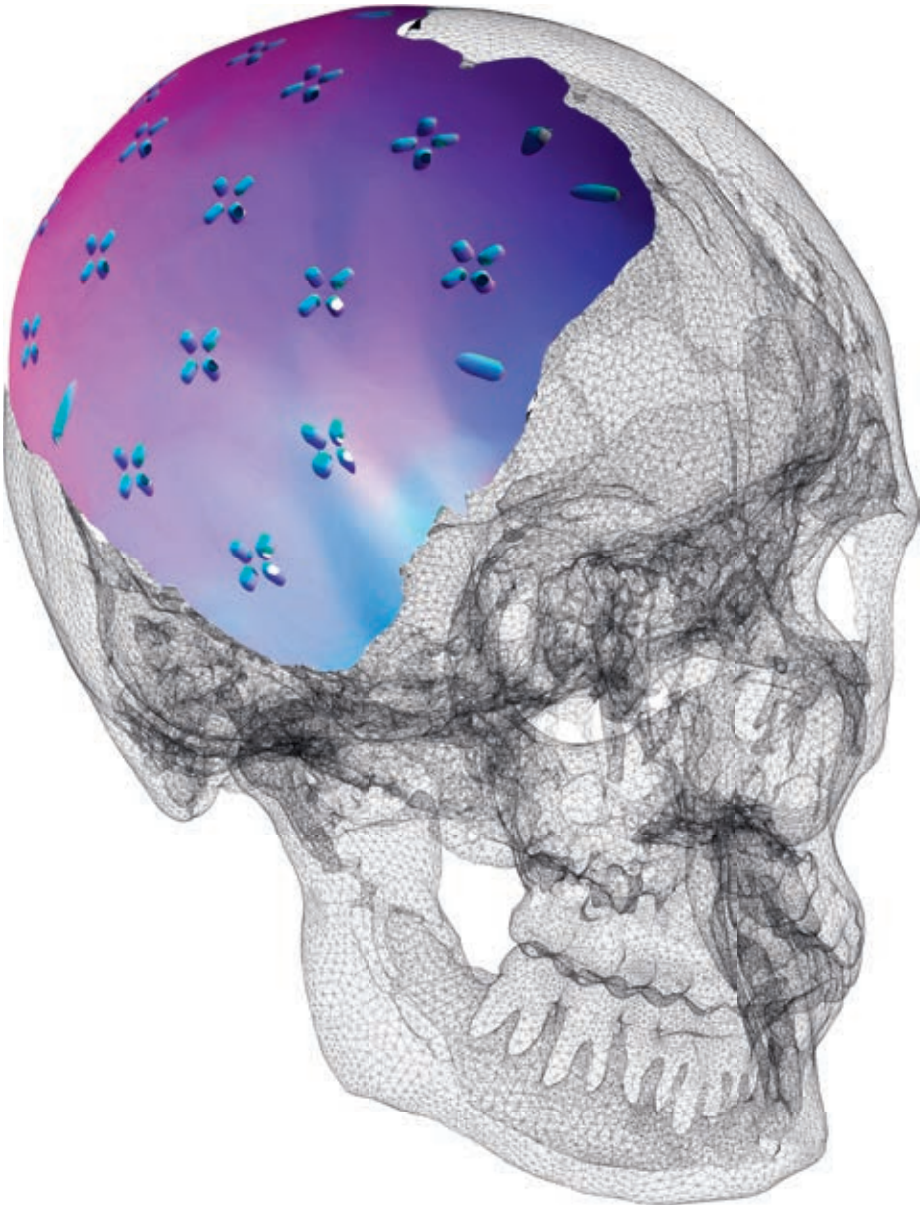
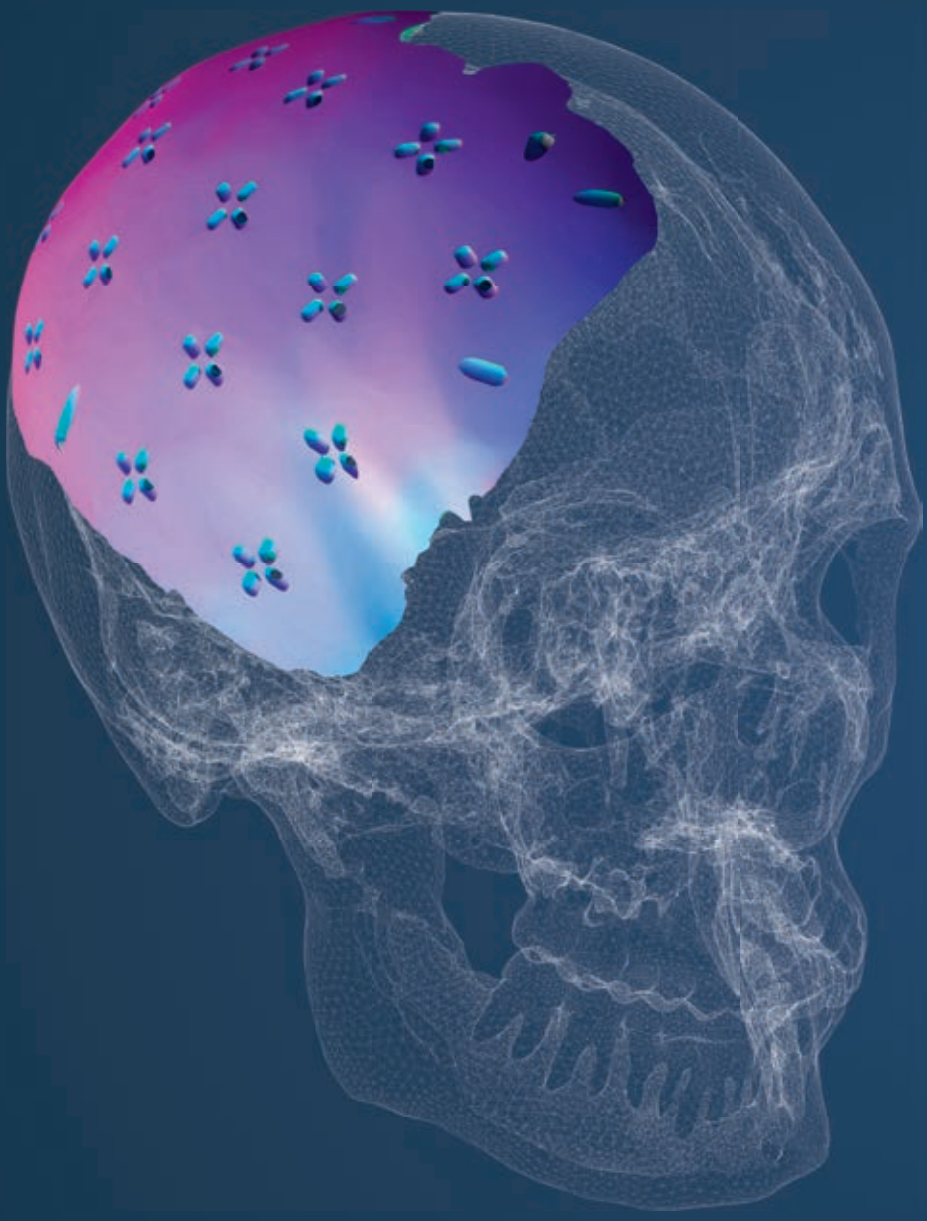


PART

Introduction



CHAPTER 1

General introduction and outline of this thesis

GENERAL INTRODUCTION

The skull consists of the neurocranium and viscerocranium, it protects the brain, the source of cognition, logical thinking, imagination, creativity, emotion and memory. Protection of the brain by the skull is essential to the living human.

Decompressive craniectomy and cranioplasty

Decompressive craniotomy or craniectomy is a life-saving neurosurgical procedure in which part of the cranium is removed to reduce raised intracranial pressure (Figure 1A + 1B). This may result from, for example, cerebral edema or hemorrhage due to traumatic brain injury, cerebral infarction, subarachnoid hemorrhage, hemorrhagic strokes, neoplasms, or intracranial infections[1–5].

Figure 1: A) Intact cranium B) Cranium after decompressive craniectomy C) Cranium with a cranioplasty *in situ*

During a decompressive craniot**o**my the removed part of the skull is replaced back into the cranium during the same surgical procedure as the removal of the autologous bone[6]. In some circumstances, this is not possible because of edema of the brain or persistently increased intra-cranial pressure. In such cases the removed part of the skull may be preserved and stored in a bone bank at temperatures as low as -84 °C[7,8] or stored in a surgically created abdominal subcutaneous pocket in the patient[8–11]. The autologous bone can be re-inserted when the patient has recuperated from the acute phase of illness and is neurologically stable[5]. This procedure has the definition decompressive crani**e**ctomy.

The reconstruction of calvarial defects is called a cranioplasty. In some cases the autologous bone may not be available because of multiple fractures, infection, resorption, depletion, or even discontinuation of an institutional bone bank due to increasing storage costs and (inter)national regulations[12,13]. Therefore, artificial, alloplastic materials, for example titanium, poly (methyl methacrylate) (PMMA), hydroxyapatite (HA), and poly(ether ether ketone) (PEEK) are alternative materials to cover the remaining cranial defects[13,14] (Figure 1C). The aim of the cranioplasty is to protect the brain, achieve a good cosmetic outcome, decrease neurologic problems and increase social performance[12].

It has been estimated that cranioplasties are performed at a rate of 25 patients per 1 million people. This – relatively- straightforward procedure remains challenging for surgeons because of the anatomy, aesthetics and functional contouring of the skull. A large number of short- and long-term complications after cranioplasties have been reported, including infection, hematoma and resorption. These complications results in medical, social and economic disadvantages and illustrate that there is no ideal reconstruction method or reconstruction material yet for cranioplasty.

The ideal material for cranioplasties should have specific requirements: good biocompatibility, easy to use, a satisfactory esthetic outcome, inexpensive, mechanical properties similar to human bone, ability to be sterilized, a low-infection rate, and the capacity to integrate with the surrounding bone.

History

Decompressive craniectomy and cranioplasty date back to the year 7000 BC and are among the oldest neurosurgical procedures in history, with a long-term evolution and a wide variety of materials[15]. Cranioplasties have been discovered in many ancient civilizations including the Incas, the Britons, the Asians, the North Africans and the Polynesians[15–17]. Around 2000 BC, a Peruvian skull was found with a hemi-craniectomy on the left frontal side of the cranium with a cranioplasty of a 1 mm thick gold plate *in situ*. At that time shells, gourds, and silver were also used for cranial reconstructions. The choice of material for cranial reconstructions likely depended on the social rank of the Peruvian citizen[15].

In 1505, the surgeon Ibrahim bin Abdullah was the first surgeon who wrote about the repair of cranial defects using goat and canine derivatives in his book 'Wonders of Surgeons' (*Alâim-I Cerrâhin*). This was followed by Fallopius (1523-1562) and Petronius (1565), who both used golden plates for the reconstruction of cranial defects[18]. In 1668, Job Janszoon van Meekeren, a surgeon from Amsterdam, The Netherlands, was the first who described a successful cranial reconstruction in a Russian nobleman who sustained a sword injury to his head. The cranial reconstruction was performed with the skull of a dead dog. The recovery went perfect, but the nobleman was excommunicated from the Russian church, because of religious reasons it could not accept animal bone in a human skull[15,18]. After this surgical intervention monkey, goose, rabbit, calf, and eagle bones were transplanted into the human skull, mostly after perforation and boiling the allograft in water[16,17]. The use of ox horns, buffalo horns, and ivory also gave satisfactory results. However, better results were observed in autologous bone grafts[16]. (Figure 2)

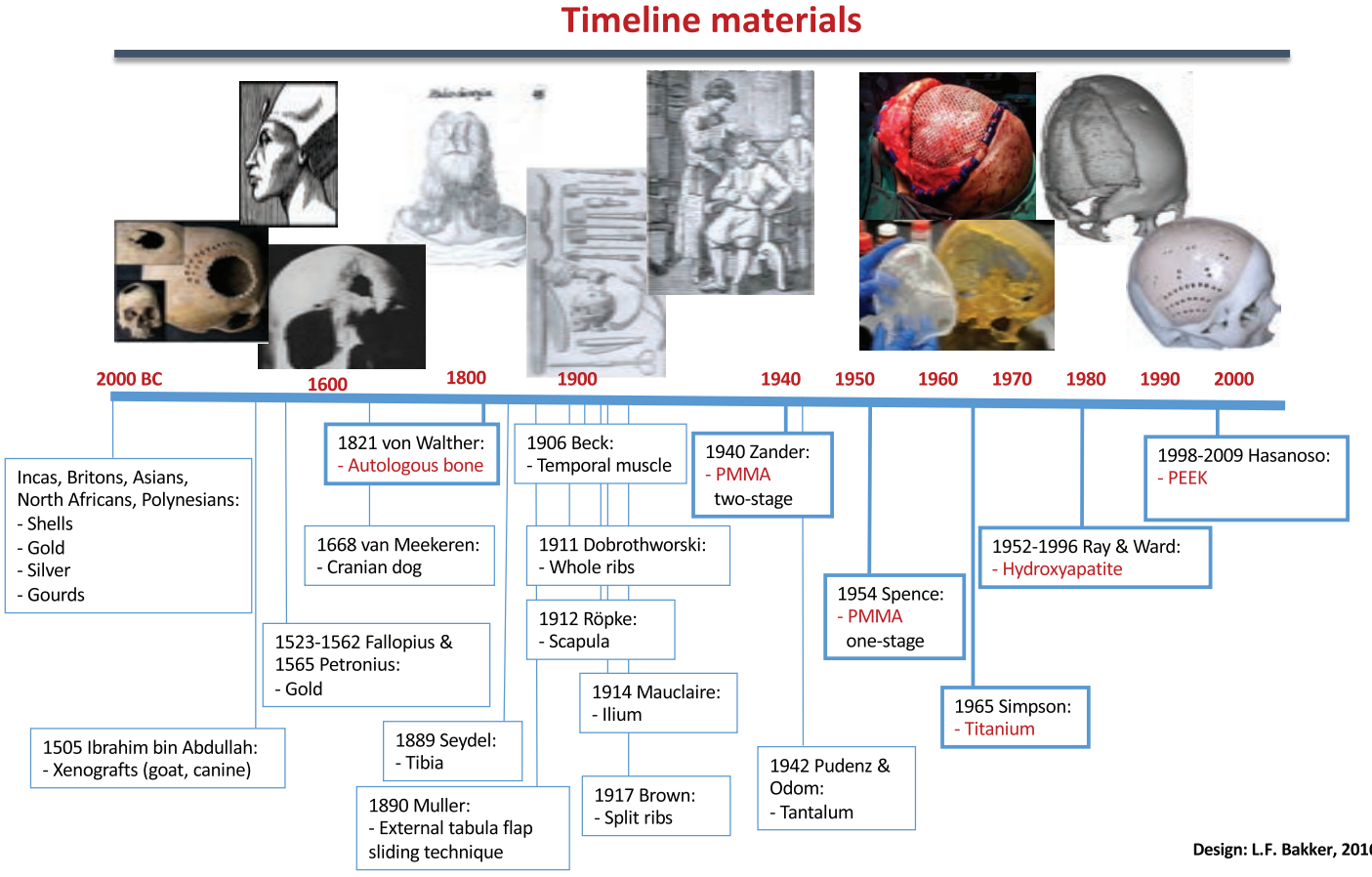


Figure 2: Overview of used materials for cranioplasties[15,16,17,18,21,22,23,24,25,30,35]

Materials used for cranioplasties

Autologous bone

Von Walther performed the first human cranioplasty with autologous bone in 1821. Many other surgeons followed him: Ollier(1859), who believed that the periosteum was the most important tissue for bone regeneration. William MacEwen (1878) successfully inserted fractured calvarial bone and reinserted bone after trepanation. Seydel (1889) used tibial autografts for cranial repair, Muller (1890) developed the "sliding flaps" technique of the external tabula, and Beck (1906) introduced temporal muscle and fascia for the reconstruction of cranial defects. Dobrothworski (1911) used whole ribs, Röpke (1912) scapula, Mauclaire (1914) ilium, and split ribs were described by Brown (1917), all for the repair of cranial defects[17,18].

Nowadays autologous bone is still used for cranioplasties. Autologous bone does not suffer from immune rejection, and bony ingrowth and revascularization have been observed[14,19]. However, it is associated with a high risk of complications.

The most frequently mentioned complications for autologous bone flaps are infection and resorption. Infection ranges from 0% - 30%[14] and is mostly caused by *Staphylococci*, especially *S. Aureus*[20]. Resorption occurs in 0%-50%[19]. Up till today the etiology of resorption is not fully understood. We do know that there is an imbalance between osteoblasts and osteoclasts, because of which parts of the autologous bone will disappear (Figure 3). These complications lead to high re-operation and removal rates of cranioplasties[20].

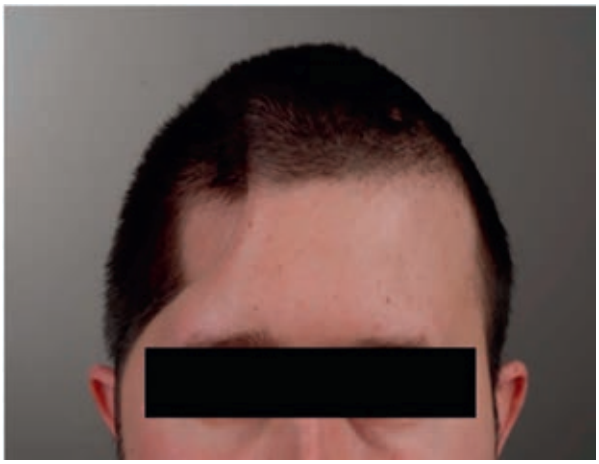


Figure 3: A patient who underwent a cranioplasty of autologous bone; after 18 months resorption was observed.

Metals

For many years, metals have been used for cranioplasties. Booth and Gersten used aluminum and gold in 1890, Geib introduced vitallium in 1941, and tantalum was used by Pudenz and Odom (1942). In 1944, Boldrey discovered stainless steel mesh for cranial reconstructions followed by Scott, Wycic and Murtagh, who introduced a cranioplasty of stainless steel (1956). Thereafter, Simpson introduced titanium cranioplasties in 1965. Many other metals – or combinations – have been used, but most of them are replaced by stronger or better variants.[18] Nowadays, pure metal cranioplasties are obsolete, except for titanium, mostly used as a mesh[21]. Titanium mesh is light-weighted, rigid, has a biological inertness, and resists infection. One of the main disadvantages of titanium is the cause of imaging artifacts and scattering, and it easily conducts heat and cold, which can be a clinical issue[18,21]. The rate of clinical (unwanted) exposure of the titanium mesh after reconstruction has been reported up to 42.2%[21].

Poly (methyl methacrylate) (PMMA)

The German chemist Dr. Otto Rohm patented Plexiglas in 1933, which became very popular. It was used in submarine periscopes and airplane canopies during war. Acrylic was primarily a substance used by dentists[17]. The company Kulser (1936) introduced PMMA by mixing PMMA particles with a liquid monomer and benzoyl peroxide. After the dough stage, it was heated to 100°C and hardened in a stone mold[22–24]. This discovery led to the use of PMMA for the reconstruction of cranial defects in monkeys (1939). Zander was the first surgeon who inserted a two-stage methyl methacrylate cranioplasty into a patient in 1940. Followed by Spence (1954), who developed a one stage method for PMMA-reconstructions. Thereafter, during World War II, when the demand for cranioplasties was high, cranioplasties based on PMMA were frequently used.[25]

PMMA is still one of the most frequently used alloplastic materials for cranioplasties[18]. It is inexpensive, easy to use, and radiolucent. PMMA does not interact with the surrounding tissue, during the hardening process PMMA induces an exothermic reaction, consequently heating the adjacent tissues, is associated with an high infection rate, and controversies exist in literature about its toxicity[14,18,26]. In the last years, a transformation of PMMA cranioplasties is observed. With the use of the CT-scan of the cranial defect of the patient, a mold of the cranial defect can be printed with additional manufacturing. During the cranioplasty procedure, the PMMA particles and liquid are mixed and placed into the mold. After a while, when the cranioplasty has cooled down, it is taken out of the mold. Adjustments can be made and is subsequently used for cranial reconstruction. This is an indirect method for additive manufacturing. Recent technology enables direct printing of an implant with higher accuracy; this is called a Patient Specific Implant (PSI).[27]

Hydroxyapatite

Hydroxyapatite is a substance made out of two different calcium phosphates, mixed with water. It has a hexagonal structure and is similar to human bone in composition and morphology[28,29]. In 1952, Ray and Ward used synthetic hydroxyapatite crystals for the reconstruction of hips and legs of monkeys, dogs and cats[30]. They discovered that the crystals used were transformed into new bone. Hence, they concluded that hydroxyapatite has the property to function as a matrix for bone generation[30].

Hydroxyapatite was further developed by the American Dental Association in 1986 and became available for cranial reconstructions in 1996[31,32]. It has a good osteoconductivity, biocompatibility and it is easy to use[14,16,32]. Hydroxyapatite allows the expansion of the growing skull and results in incorporation into the surrounding bone[16]. The process of the conversion of hydroxyapatite into bone takes time, which means that the material is brittle and may not sufficiently protect the brain[16,17,33].

Poly (ether ether ketone) (PEEK)

PEEK is an organic thermoplastic polymer. It was introduced in the automotive and electrical industries before it was used for medical applications. In the nineties, PEEK became popular in orthopedics, trauma and spinal surgical interventions[25,34]. In 2009 Hasanoso published one of the first cases using PEEK for cranioplasties[35]. With the use of the patients CT-scan, the unaffected side can be mirrored and a symmetrical and aesthetically satisfying PSI patient-specific implant is manufactured using a milling technique[36] (Figure 4). Nowadays, PEEK is an important polymer for medical devices, which is used in different fields of surgery. It has a high mechanical strength and biocompatibility, and does not deform below a temperature of at least 400°C[34]. It has no cytotoxic activity, it does not induce adverse reactions to human tissues[37], and PEEK causes no artifacts in post-operative imaging. PEEK can be manufactured preoperatively as a PSI with satisfactory cosmetic outcomes and reduced operation time[36]. PEEK does not have a bioactive potential[38]. Unfortunately, PEEK is expensive[39], and controversy exists in literature about its effectiveness in covering larger defects as cranioplasty[34,38].

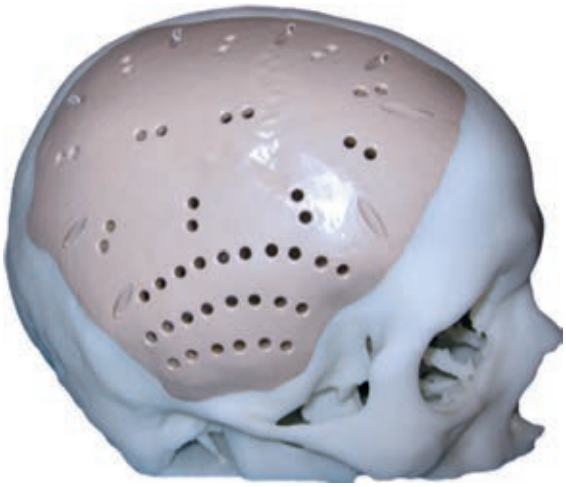


Figure 4: Patient Specific Implant of PEEK
Courtesy of Xilloc Medical, The Netherlands

AIMS AND OUTLINE OF THIS THESIS

This thesis is subdivided into four main parts, covering several aspects of the current materials for cranioplasties and the development and techniques of future methods and materials for cranioplasties: current evidence, current challenges, towards a new approach and toward the ideal material. This is followed by a general discussion of the contents of this thesis and future perspectives in this field.

Part II: Current evidence

The management of decompressive craniectomy and cranioplasty varies greatly between countries, hospitals and neurosurgeons. Regulations, e.g. national guidelines for bone banks and the recent European MDR (medical devices regulations) and costs with or without reimbursements from the government have a tremendous influence on the possibilities and choices for various techniques and materials. Many different materials have been developed and are being used in daily practice. In **Chapter 2** all available evidence is summarized in patients who underwent cranioplasty using either autologous bone or alloplastic materials.

The principal outline of this thesis is to investigate and understand the clinical issues of different materials used for cranioplasties. If the individual factors can be identified that influence the clinical problems related to the current materials used for cranioplasties, more advanced materials may even be developed to reduce intra-operative and clinical complications.

Part III: Current challenges

The reasons for failure of existing materials for cranioplasty is important for the development of new materials. If the shortcomings are known, they may be camouflaged or even avoided. In part III of this thesis, different materials used for cranioplasties in clinical settings are explicated, in order to assess the advantages and disadvantages of the various materials.

After a decompressive craniectomy, a cranioplasty is mandatory to protect the brain and restore cranial esthetics. Autologous bone may be used for cranial reconstructions. However, reimplantation of preserved autologous bone is known to have a substantial risk of infection and bone flap resorption, not seldom resulting in loss of the autologous bone flap. In order to identify and quantify the risks of failure of autologous bone flaps, a two-center retrospective study is performed **(Chapter 3).**

Patient-specific allogenic reconstruction is a typical example of advances in the medical technology. It demonstrates improvement of patient-relevant outcomes. With these technologies, it is possible to study and evaluate the corresponding clinical findings. In **Chapter 4**, a PMMA (CMW-3) cranioplasty is described, which had been inserted in a patients' cranium 15 years ago, but had to be removed because of neurological complaints, most likely due to fracture of the implant. This case is evaluated by means of gel permeation chromatography (GPC), a micro-CT, finite element analysis (FEA) and flexural strength measurements.

The high infection and resorption rates have led to a search for superior synthetic materials for cranioplasties. In **Chapter 5**, a two-center retrospective study is described, including 38 patients who underwent 40 patient-specific cranioplasties of PEEK to detect possible complications and results.

Part IV: Towards a new approach

To improve the precise outlining of the cranioplasty and the aesthetic outcomes and to shorten operation time, different and relatively new intra-operative techniques may be used.

In **Chapter 6,** three cases are presented who underwent a cranioplasty of PEEK. The resection was guided with resection and control templates. Outcomes were compared with the original patient-specific planning and with 3D comparisons for form.

Squamous cell carcinoma with bony invasion into the scalp is a rarely described phenomenon in the literature. The optimal treatment strategy is still under debate. In **Chapter 7** we present a patient with this anomaly. A novel comprehensive, one-stage surgical treatment is demonstrated and discussed.

Part V: Towards the ideal material

The properties of current materials for cranioplasties are important to understand and to progress to development of new materials. Part V of this thesis comprises two *in vitro* studies: Do different PMMA-based materials include different amounts of residual monomers? does sterilization has an effect on the mechanical properties of PMMA-based materials?

Various areas in healthcare use PMMA: orthopedics, dentists, maxillofacial surgery and neurosurgery. PMMA is cost efficient, radiolucent, light and easy to use. PMMA is formed through the polymerization of liquid methyl methacrylate (MMA) using PMMA powder as a filler to minimize shrinkage. Unreacted MMA (residual monomers) remains in the final product. However, the precise concentrations are still unknown for all PMMA-based materials. In **Chapter 8**, the amount of released, non-polymerized, monomers (residual monomers) is analyzed in four different PMMA-based materials with different compositions and fabrication methods (Vertex Self-Curing, Palacos R + G, DePuy CMW-3, and NextDent C&B MFH).

To reduce surgical time during polymerization the medical device may be manufactured before surgery with use of 3D imaging and additive manufacturing techniques. However, the created cranial implant still needs to be sterilized. This presents a challenge to assure optimal material behavior. Hence, in **Chapter 9**, four different sterilization methods (ethylene oxide, hydrogen peroxide plasma gas, autoclavation, and gamma-irradiation) are used for the sterilization of three different types of PMMA-based materials (Vertex Self-Curing, Palacos R + G and NextDent C&B MFH). To study the mechanical properties, the flexural strength, flexural modulus and impact strength were measured.

Part V General discussion

The overall findings of this thesis are presented in **Chapter 10**, in which the main results are summarized and discussed, followed by a description of the future perspectives.

Summaries of this thesis are presented in **Chapter 11** in English and Dutch, respectively.

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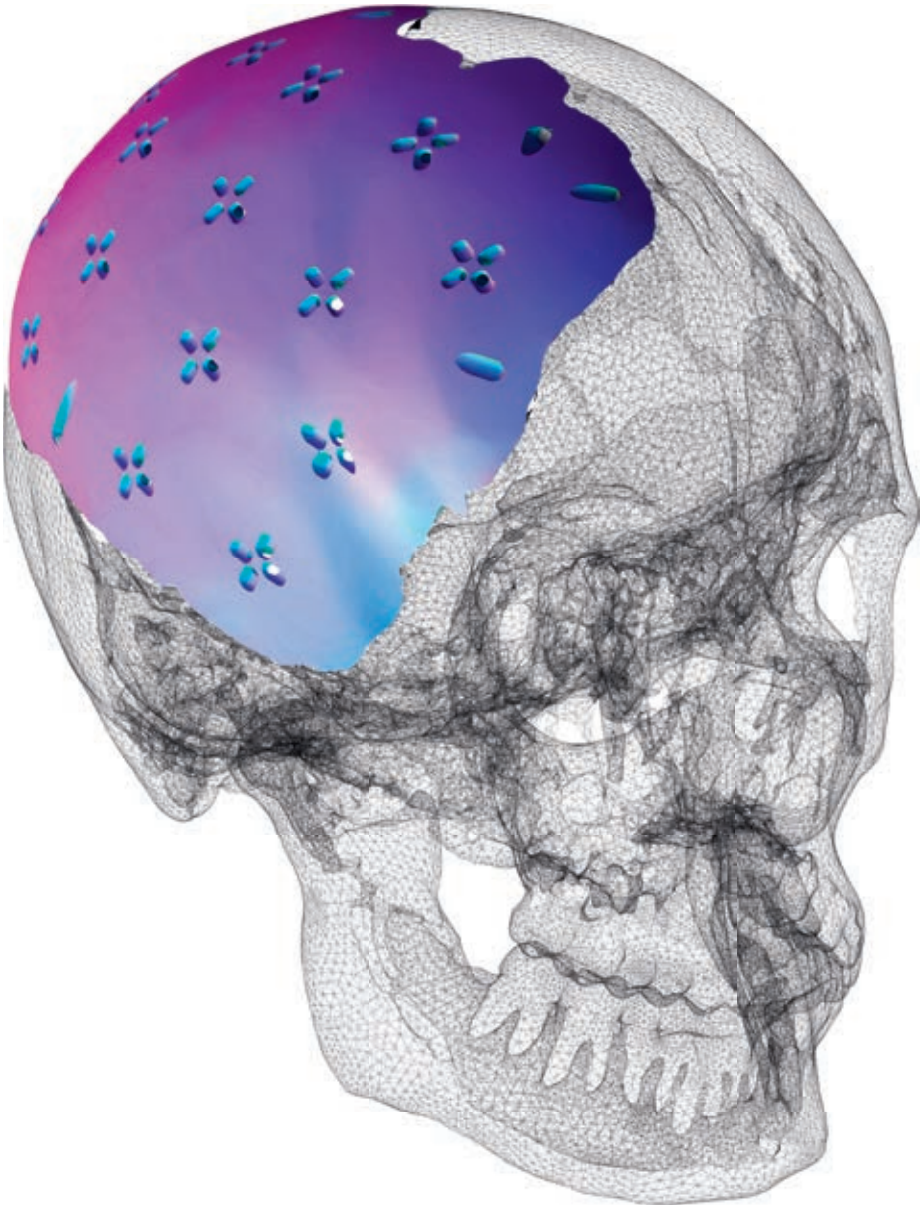
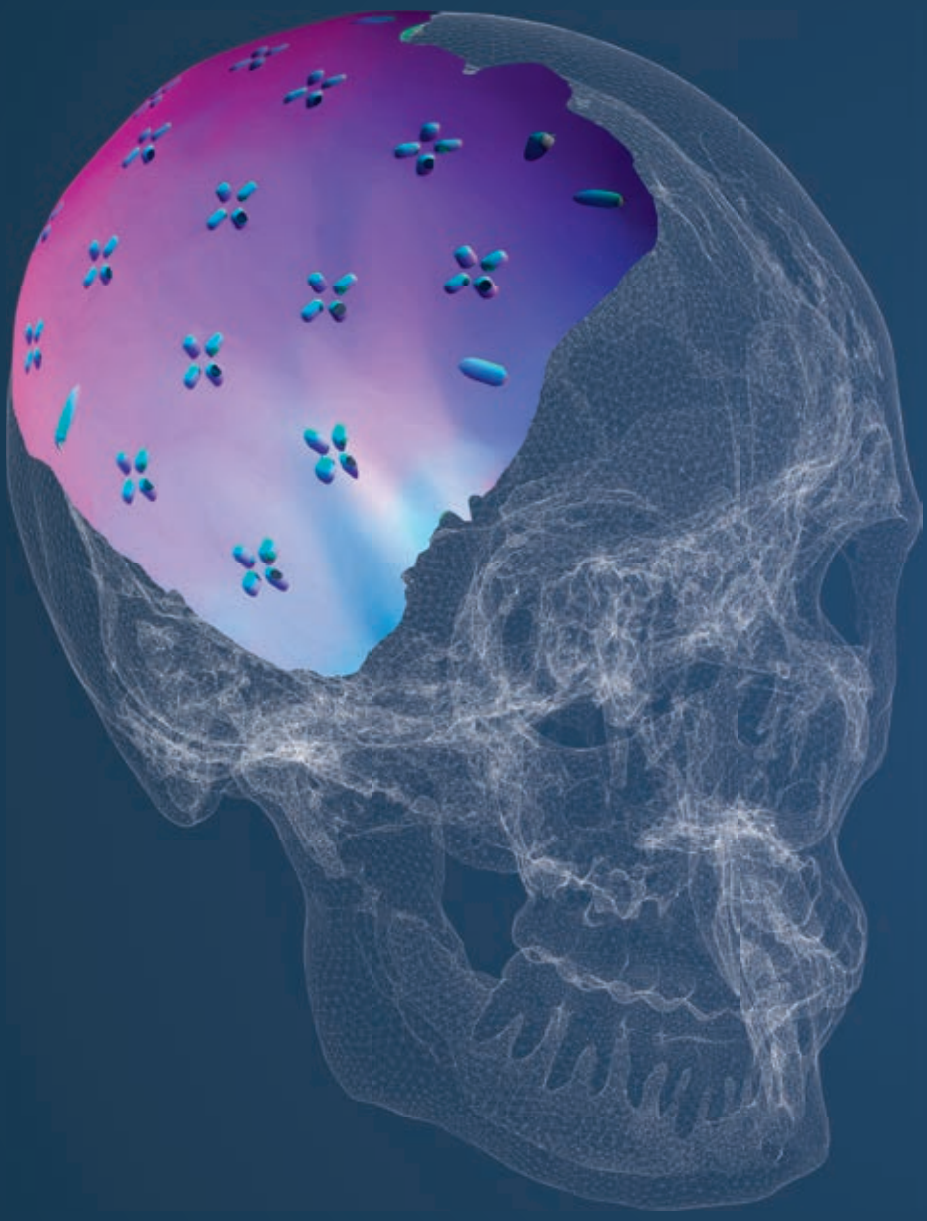


PART II

Current Evidence



CHAPTER 2

A systematic review of the safety of autograft and allograft materials for cranioplasties

S.E.C.M. van de Vijfeijken, T.J.A.G. Münker, R. Spijker, L.H.E. Karssemakers, W.P. Vandertop, A.G. Becking, D.T. Ubbink; on behalf of the CranioSafe Group

This chapter is based on the publication: Autologous bone is inferior to alloplastic cranioplasties Safety of autograft and allograft materials for cranioplasties, a systematic review

Published: World Neurosurgery, 2018

ABSTRACT

Background: Currently, various materials are routinely used for cranioplasty after decompressive craniectomy, each with their own features, potential benefits, and harms.

Objectives: To systematically review available literature about safety (infection, resorption, and removal) of different materials used for cranioplasty for any indication.

Methods: A comprehensive search in MEDLINE, EMBASE, and the Cochrane library was performed for relevant studies published up to January 2017. Study quality was assessed according to the Cochrane Collaboration risk of bias assessment tool, and a set of 27 predetermined parameters was extracted by 2 investigators independently for further analysis.

Results: The search yielded 2 randomized, 14 prospective, and 212 retrospective studies, totaling 10,346 cranioplasties in which 1952 (18.9%) complications were reported in patients between 0 and 90 years old. Overall, study quality was low and heterogeneity was large. Graft infections and resorption were most prevalent: overall infection rate was 5.6%. Autologous cranioplasties showed an infection rate of 6.9% versus 5.0% in combined alloplastic materials, including poly(methyl methacrylate) with 7.8%. Resorption occurred almost exclusively in autologous cranioplasties (11.3%). The greatest removal rate was reported for autologous cranioplasties (overall: 10.4%), which was significantly greater than that of combined alloplastic materials (overall: 5.1%; risk difference = 0.052 [95% confidence interval: 0.039-0.066]; NNT = 19 [95% confidence interval: 15-25]).

Conclusion: Available evidence on the safety of cranioplasty materials is limited due to a large diversity in study conduct, patients included, and outcomes reported. Autografts appear to carry a greater failure risk than allografts. Future publications concerning cranioplasties will benefit by a standardized reporting of surgical procedures, outcomes, and graft materials used.

INTRODUCTION

In patients who underwent a decompressive craniectomy, a cranioplasty is commonly required to protect the brain, restore aesthetics, relieve neurological symptoms, as well as for psychosocial reasons[1]. The number of cranioplasties performed has increased over the last years, reaching 20-25 per million inhabitants per year in 2010 (in Europe, Middle East and Africa)[2].

Autologous bone is widely used for cranioplasty, relatively inexpensive, easy to obtain, exhibits good fit and contour, presents no risk of disease transmission and is viable[3]. Bone resorption and infection are the most frequently reported complications, with a large range in degree, timing and occurrence[4-6].

In the past, some cranioplasties were manufactured by molding autologous bone grafts in alginate or plaster. Poly (methyl methacrylate) (PMMA) was cast into the mold and polymerized to avoid the exothermic reaction occurring adjacent to the brain during hardening[7,8]. Currently, PMMA is also used in a customized 3-dimentional (3D) mold to achieve better cosmetic results[9]. Autologous bone may not be available because of fracture, infection, resorption, depletion, or even discontinuation of an institutional bone-bank due to increasing storage costs and (inter)national regulations. In these cases alloplastic materials may be used, e.g. titanium, PMMA, hydroxyapatite (HA), and poly(ether ether ketone) (PEEK)[2,10-12].

Computer-aided design and computer-aided manufacturing (CAD/CAM) and other 3D virtual planning technologies have been applied to overcome the shortcomings of intraoperative molding and allow for the creation of patient-specific implants (PSI). A PSI aims for a perfect fit as the design is based on the patient's computed tomography (CT) or cone-beam CT data. More sophisticated materials enable manufacturing by 3D printing and rapid prototyping techniques, allowing for more complex shapes when personalized and unique shapes are required[13,14]. Consensus on the preferred method or material is lacking. The ideal material is similar to cortical bone, biocompatible, radiolucent, nontoxic, has a low complication rate, is easy to use in the operation room, can be used to create an optimal PSI, brings excellent cosmetic results, and is low in cost[10].

Many studies have been published regarding the possible benefits and potential risks or risk factors of complications after cranioplasty. However, no all-encompassing review has been published to this date. This comprehensive review summarizes all available evidence in patients who underwent cranioplasty using either autologous bone or alloplastic materials regarding their safety, to aid evidence-based decision-making.

MATERIAL AND METHODS

Search strategy

This systematic review was conducted using the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines, methodological standards outlined in the Cochrane Handbook for Systematic Reviewers and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria **(**Figure 1**)**[15,16]. A systematic search of the literature was conducted in MEDLINE, EMBASE and the Cochrane library from their inception until January 26, 2017. Search terms included MeSH-terms in PubMed and EMtree, as well as free text terms. For the Cochrane library free text terms were used. The full search strategies for each database are shown in Supplementary Table 1.

Selection process

Two reviewers (S.V. and T.M.) independently screened all potentially relevant titles and abstracts for eligibility. If necessary, the full text article was checked for the eligibility criteria. Articles were included if they met the following criteria: 1) clinical patient study; 2) a cranioplasty was performed or; 3) a craniectomy in combination with cranioplasty or; 4) a craniotomy with alloplastic material for any patient and any indication and; 5) were written in, or translated to, a Western European language.

Studies were excluded if: 1) the surgical intervention was a craniotomy with simultaneous replacement of the autologous bone graft; 2) non-clinical articles (technical notes, animal studies, laboratory studies, letters, systematic reviews); 3) 6 or more materials were used; or 4) primary outcomes were not reported per material. Disagreements were resolved by consensus or discussed with a third reviewer (D.U.). After the first selection the full text of the articles was obtained for further review.

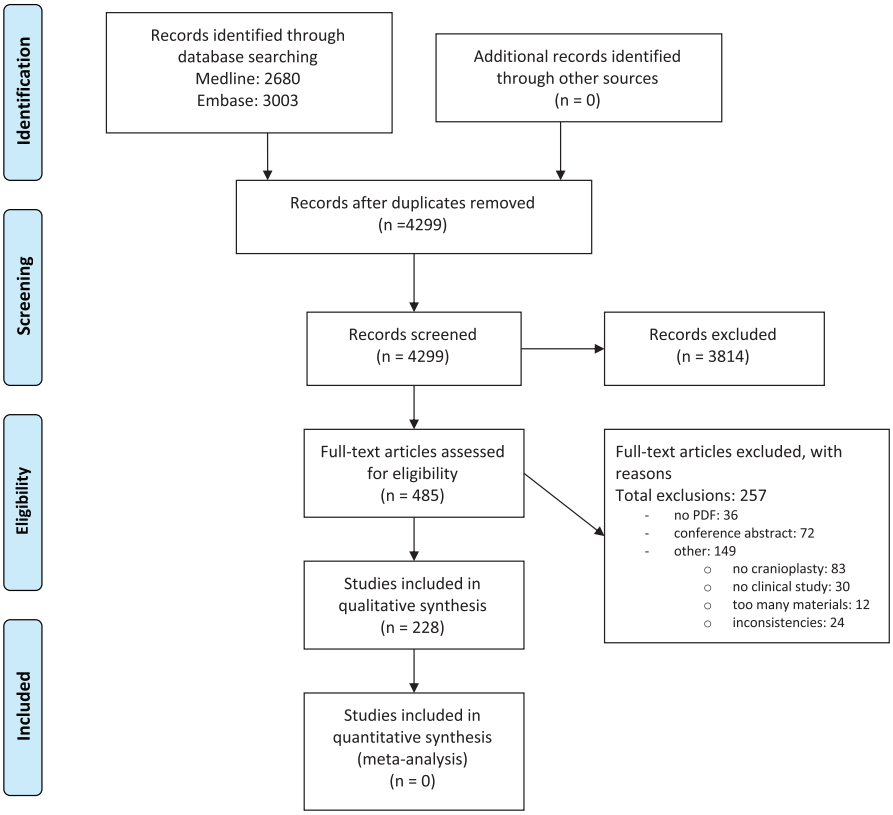


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart illustrating the details of the search and selection procedure.

Quality assessment

Methodological quality of the included papers was assessed by a validity questionnaire on the individual studies using the Cochrane Collaboration tool for assessing risk of bias[17].

Data extraction

The primary safety outcomes are defined as 'infection', 'resorption' and 'removal' rates.

From the selected articles the following parameters were extracted, if reported, on a pre-defined data extraction form: 1) study design; 2) number of patients; 3) number of cranioplasties; 4) cranioplasty material used; 5) sex; 6) age; 7) comorbidities; 8) smoking; 9) indication for cranioplasties; 10) previous cranioplasties; 11) location of the surgical intervention; 12) size of the defect in cm^2; 13) use of antibiotics; 14) use of a drain; 15) involvement of the frontal sinus; 16) operation duration; 17) time interval between decompressive craniectomy and cranioplasty; 18) use of a mold, 3D printing or computer-aided design and computer-aided manufacturing; 19) all reported complications; 20) complication policy; 21) time interval between occurrence of complications and cranioplasty; 22) bacterial strain as cultured from the site of infection; 23) quality of life (QoL) measures; 24) esthetic outcome; 25) neurological functioning; 26) follow-up duration; 27) drop-outs. All data were extracted and verified by two authors (S.V. and T.M.) independently. Timing was recalculated to months according to the Gregorian calendar[18].

Data analysis

Descriptive analysis of the included studies, outcome analysis, assessment of heterogeneity, and any subgroup analysis were performed using IBM SPSS v.24 (IBM Corp., Armonk, New York, USA).

If clinical heterogeneity was limited, a meta-analysis would be performed. Subgroup analysis was planned for each of the cranioplasty materials, and autologous versus alloplastic materials, regarding the primary outcomes. Differences in dichotomous outcomes are described as risk ratios (RRs), risk differences (RDs) and numbers needed to treat (NNTs), each with their 95% confidence intervals (95%CIs). Differences in continuous outcomes are reported as mean differences and their 95% CIs or medians with their interquartile ranges (IQRs). If the included studies are clinically heterogeneous, a range is provided of the outcomes for each of the cranioplasty materials.

RESULTS

Characteristics of included studies

The literature search yielded a total of 5683 eligible papers, of which 228 were eventually included in this systematic review (Supplementary Table 2).

Of the 228 included studies, 212 (93.0%) had a retrospective design. Two hundred one were case series, 20 case reports, 5 cohort studies, and 2 randomized clinical trials. Studies were published between 1952 and January 2017 and were conducted on 6 continents, whereas most of them (216; 94.7%) originated from North America, Europe, or Asia.

Many studies were flawed in their reporting of outcomes; even basic information, such as patient age, sex, or indication for cranioplasty, was not reported in all cases. Only 4.8% of the studies reported on smoking behavior of their patients, whereas 82.5% of studies described the patient's sex (Table 1).

Included studies were quite heterogeneous due to a large variability in surgical procedure, outcome definitions, and patient details. Therefore, no meta-analysis could be performed.

Study sizes ranged from 1 to 672[19] cranioplasties, totaling 10,346 cranioplasties. In 193 studies a single material was used for cranioplasty, whereas in 35 two or more materials were used (Table 2). Autologous bone was the most frequently used material for cranioplasty (n=3335 cranioplasties), whereas PEEK was infrequently used (n=250 cranioplasties). In 112 (60.2%) studies the mean follow-up was longer than 1 year. Complications of cranioplasties were reported in 220 studies. Overall, reported complications ranged from wrinkle formation[20] and vomiting[21] to death[22], without a clear threshold as to the definition of a complication.

Neurological function assessment after cranioplasty was reported in 44 studies, of which 22 used a numerical scale. The Glasgow Outcome Scale (GOS) was reported in 9[8,12,23-29], The Glasgow Coma Scale (GCS) in 17 occurrences[23-27,30-41], and 1 study used the House-Brackmann scale[42].

Table 1: Demographics of the included cranioplasties (n= 10,346)

Parameters	Mentioned in study (%)	Total (%)	Range
Gender (male)	188 (82.5)	4191 / 7749 (54.1)	
Age (years)	200 (87.7)		0-90
Comorbidities	32 (14.0)	1844	
Diabetes Mellitus		51 (2.8)	
Cardiovascular disease		78 (4.2)	
Obesity		7 (0.4)	
Preoperative radiotherapy		116 (6.3)	
Others		133 (7.2)	
Smoking	11 (4.8)	122 (10.8)	
Initial diagnosis	209 (91.7)	8148	
Trauma		3352 (41.1)	
Cerebrovascular		2100 (25.8)	
Infection		222 (2.7)	
Tumor		1365 (16.8)	
Revision reasons		31 (0.4)	
After autologous bone		266 (3.3)	
Epilepsy		5 (0.1)	
Congenital deformation		261 (3.2)	
Others		546 (6.7)	
Site	98 (43.0)	3032	
Unilateral		2720 (89.7)	
Bilateral		101 (3.3)	
Bifrontal		211 (7.0)	
Location	116 (50.9)	4102	
Frontal		627 (15.3)	
Frontotemporo-parietal		535 (13.0)	
Temporo-parietal		79 (1.9)	
Parieto-occipital		12 (0.3)	
Fronto-temporal		538 (13.1)	
Temporal		427 (10.4)	
Fronto-parietal		70 (1.7)	
Fronto-temporo-parieto-occipital		1 (0.0)	
Parietal		265 (6.5)	
Parieto-occipital		11 (0.3)	
Occipital		65 (1.6)	
Parieto-temporal		1 (0.0)	
Other		1471 (35.9)	
Size of defect (cm^2)	100 (48.2)		1.5 – 517.43
Follow-up (months)	185 (81.1)		0 - 803
Dropouts	218 (95.6)	247	

Of 228 included articles, 118 (51.8%) reported on esthetic outcome after cranioplasty. Eighteen were assessed using a grading system, of which 10 used a custom-made questionnaire including a grading system[43-52], 3 studies used the Visual Analog Cosmesis Scale[53-55], 2 the cranial index of symmetry[26,27], and 2 the Odom criteria[56,57]. Rotaru et al. used a 3D-reconstructed CT examination to determine esthetic outcome[20]. In 70 (30.7%) studies an esthetic outcome was mentioned but was subjective as no further measure of evaluation was reported. Thirty-five articles reported esthetic outcome as defined by the patient, 5 as reported by relatives, whereas 14 were assessed by the clinician, and 14 were based on the CT results, of which only 3 were objectively graded. Twelve of these reported on the esthetic outcome as judged by both the patient and the clinician.

Five (2.2%) articles reported QoL after cranioplasty[12,46,52,55,58]. Manrique et al. and Lindner et al. used the specific University of Washington Quality of Life scale and the generic short-form-36 scale, respectively[12,58].

Characteristics of included patients

Indications for a cranioplasty were listed in 209 studies, consisting mostly of trauma (n=3352), cerebrovascular (n=2100), tumor (n=1365), or infection (n=222) (Table 1). Two thousand seven hundred twenty patients underwent unilateral, 101 patients bilateral, and 211 patients bifrontal cranioplasties. The affected cranial bone was mentioned in 116 studies (50.9%). The surface area of the defect was mentioned in 110 studies with a mean of 82.6 cm^2 and ranging between 1.5 cm^2 and 517.4 cm^2. Based on available data from 184 studies comprising 6917 patients, 4191 (60.6%) of them were male. In 200 (87.7%) studies the age was reported and ranged from 0 to 90 years, the mean age was 36.0 years old. Comorbidities were reported in 32 (14.0%) studies. Ten studies mentioned smoking habits.

Surgical characteristics

In 94 studies, the time interval between decompressive craniectomy and cranioplasty was reported, ranging from 0 until 336 months, with a mean of 11.4 months. The use of antibiotics was described in 75 studies, of which some used a combination of antibiotics before, during, and/or after surgery. Seventy studies reported the use of a drain. In 26 papers involvement of the frontal sinus was described. Operation time, as reported in 44 studies, varied between 30 minutes and 544 minutes, with a mean of 146.0 minutes (Table 2).

Table 2: Surgery-specific characteristics of the included cranioplasties (n= 10,346)

Parameters	Mentioned in study (%)	Total (%)	Range
CP material		10346	
Autologous bone	65 (28.5)	3335 (32.2)	
PMMA	60 (26.3)	1644 (15.9)	
Titanium	52 (22.8)	1829 (17.7)	
PEEK	20 (8.8)	250 (2.4)	
Hydroxyapatite	23 (10.1)	905 (8.7)	
Others	58 (25.4)	2383 (23.0)	
Antibiotic	75 (32.9)	3593	
Preoperative	27 (11.8)	1663 (46.3)	
Peri-operative	42 (18.4)	2362 (65.7)	
Post-operative	50 (21.9)	1737 (48.3)	
Drain	70 (30.7)	2303 / 3207 (71.8)	
Involvement of frontal sinus	26 (11.4)	198 / 882 (22.4)	
Operation time (min)	44 (19.3)		30 - 809
Timing CP after DC (months)	94 (41.2)		0 - 336
Manufacturing method	187 (82.0)	7800	
Molding	20 (8.8)	560 (7.2)	
No molding	113 (49.6)	5856 (75.1)	
3D printing	6 (2.6)	125 (1.6)	
3D molding	20 (8.8)	454 (5.8)	
CAD/CAM	24 (10.5)	452 (5.8)	
Punch	4 (1.8)	353 (4.5)	

CP: cranioplasty
PEEK: poly(ether ether ketone)
PMMA: poly(methyl methacrylate)
DC: decompressive craniectomy
CAD/CAM: computer assisted design / computer assisted manufacturing

Methodological quality

Overall, the included studies were of low quality. Risk of selection bias appeared to be high in 97 (42.5%) of the non-randomized studies (n=226), mainly due to not reporting the selection criteria of the included patients (Table 3). In the 2 randomized control trials, patients were blinded for the material used and the studies were imperfect regarding blinding of the care provider and outcome assessor. Furthermore, the groups were relatively small due to the assumed large variability in infection rates per material, resulting in a skewed power.

Table 3: Methodological quality of 226 included observational studies

Quality Question	Yes (N)	%
Clear definition of study population?	226	100
Exclusion of selection bias?	130	57.5
Clear definition of results?	26	11.5
Clear method to determine results?	13	5.8
Outcome determined blind from the intervention?	0	0
Affects this the evaluation of the outcome?	226	100
Follow-up long enough?	79	35.0
Selective lost to follow up excluded?	197	87.2
Are confounders described?	10	4.4
Are the results corrected for confounders? (multi-variate analysis)	10	4.4

Primary outcome measures

None of the outcome measures could be pooled due to clinical heterogeneity, rendering meta-analysis impossible. The overall reported infection rate was 5.6% across all cranioplasty materials used. Autologous cranioplasties showed an infection rate of 6.9%, significantly greater than the combined alloplastic materials (overall: 5.0%; RD = 0.019 [95% CI 0.009-0.030]; NNT = 53 [95% CI 34-116]; RR = 0.73 [95% CI 0.62-0.86]). The lowest infection rate was observed in HA (overall: 3.3%; range: 0-58.8%). The highest infection rate was reported for PMMA (overall: 7.8%; range: 0-50%). Of the 104 studies reporting at least one infection of the cranioplasty (total infected cranioplasties n = 550), 27 included bacteriologic culturing. *Staphylococci* were the most detected infecting agent, causing infection in 90.7% of infected cranioplasties reporting bacterial culture. Specifically, 71.1% tested positive for *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (28.9%) and methicillin-sensitive *S. aureus* (4.1%), 4.1% for *Propionibacterium acnes*, 2.1% for *S. epidermidis*, and 24.7% tested positive for a different bacterial strain. Of these, 16 infected cranioplasties reported multiple strains of bacteria.

Resorption rates were reported in 117 studies. Resorption occurred mostly in autologous grafts, where it was reported in 42 studies and ranged from 0 to 100% with an overall resorption rate of 11.3%.

Cranioplasty removal rate was stated in 194 studies. The lowest graft removal rate was reported for HA (overall: 2.5%). The greatest removal rate was reported for autologous cranioplasties (overall: 10.4%). This was significantly greater than that of the combined alloplastic materials (overall: 5.1%; RD = 0.052 [95% CI 0.039-0.066]; NNT = 19 (95% CI 15-25); RR = 0.50 [95% CI 0.42-0.58]). Overall, removal was required in 6.6% of the cranioplasties in all studies reporting removals.

Other complications

Complications after cranioplasty were reported in 220 studies, with a total complication rate of 18.9%. Hematoma (1.9%), cerebrospinal fluid leak (1.4%), and wound dehiscence (1.1%) occurred most frequently after infection (5.6%) and bone resorption (5.2%) (Table 4).

Autologous bone showed the highest complication rate at 35.7%. HA showed the lowest complication rate at 10.5%. The greatest complication rate was reported by Lee et al.,[59] with 135%, as there were multiple complications (total n = 19) per patient after 14 cranioplasties, although it was unclear how these complications were distributed amongst the patients. The lowest complication rate was reported by Liu et al.,[60]who stated that all 598 patients did not show any complications following 611 cranioplasties. Timing of complications after cranioplasty was reported in 72 studies, ranging from immediately[61] to 9 years[62] after decompressive craniectomy.

Treatment policy after complications

Of the 220 studies reporting complications, 122 mentioned a treatment plan. Removal of the cranioplasty was reported in 6.6% of cases, followed by 2.2% surgeries, and 1.6% cases of expectative policy. Other policies, including antibiotic treatment and wound debridement, were performed in 0.5% of cases (Table 4).

Table 4: Other reported complications and policies after cranioplasty (n= 10,346)

	Total n (%)	PEEK n (%)	PMMA n (%)	Titanium n (%)	Autologous n (%)	HA n (%)	Other n (%)	Unknown n (%)
Complications								
Hematoma	196 (1.9)	9 (4.0)	31 (2.1)	50 (2.8)	58 (2.3)	14 (1.7)	8 (0.3)	26 (2.2)
Seroma	69 (0.7)	1 (0.7)	8 (0.5)	27 (1.5)	9 (0.4)	5 (0.6)	5 (0.2)	14 (1.2)
Infection	550 (5.6)	14 (5.9)	122 (7.8)	93 (5.4)	210 (6.9)	29 (3.3)	82 (3.5)	-
Second trauma	9 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	8 (0.9)	0 (0)	0 (0)
Wound problems	111 (1.1)	3 (1.3)	8 (0.5)	23 (1.3)	27 (1.1)	8 (0.9)	42 (1.8)	0 (0)
Exposure	58 (0.6)	2 (0.6)	11 (0.7)	27 (1.5)	4 (0.2)	13 (1.5)	0 (0)	1 (0.1)
Migration implant	18 (0.2)	0 (0)	7 (0.5)	1 (0.1)	7 (0.3)	0 (0)	1 (0.0)	2 (0.2)
Bone resorption	226 (5.2)	0 (0)	1 (0.2)	0 (0)	222 (11.3)	1 (0.4)	2 (0.2)	-
CSF leak	143 (1.4)	3 (1.3)	10 (0.7)	14 (0.8)	68 (2.7)	1 (0.1)	22 (1.0)	25 (2.2)
Epilepsy	14 (0.1)	1 (0.4)	0 (0)	0 (0)	13 (0.5)	0 (0)	0 (0)	0 (0)
Seizures	74 (0.7)	6 (2.6)	11 (0.7)	24 (1.4)	28 (1.1)	0 (0)	0 (0)	5 (0.4)
Death	44 (0.4)	0 (0)	4 (0.3)	1 (0.1)	35 (1.4)	0 (0)	1 (0.0)	3 (0.3)
Other	440 (4.3)	10 (4.4)	41 (2.8)	123 (7.0)	200 (7.8)	9 (1.1)	49 (2.1)	8 (0.7)
Total	1952 (18.9)	49 (21.3)	255 (16.8)	383 (22.0)	881 (35.7)	88 (10.5)	212 (9.2)	84
Policies								
Expectant	168 (4.8)	11 (4.8)	17 (1.1)	44 (2.5)	72 (2.8)	18 (2.1)	5 (0.2)	1 (0.1)
Surgery	232 (2.2)	11 (4.8)	43 (2.9)	35 (2.0)	117 (4.6)	3 (0.4)	17 (0.7)	6 (0.5)
Antibiotics	30 (0.3)	1 (0,4)	5 (0.3)	10 (0.6)	6 (0.2)	3 (0.4)	3 (0.1)	2 (0.2)
Removal	565 (6.6)	18 (7.4)	104 (7.9)	100 (6.7)	250 (10.4)	21 (2.5)	72 (3.2)	-
Wound debridement	17 (0.2)	0 (0)	4 (0.1)	2 (0.1)	0 (0)	10 (1.2)	1 (0)	0 (0)
Other	5 (0.0)	0 (0)	3 (0.2)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)

PEEK: poly(ether ether ketone)
PMMA: poly(methyl methacrylate)
HA: hydroxyapatite

Neurological function

The GCS and GOS scores varied from 5 to 15 and 1 to 5 respectively. Twenty-two of 44 studies reported the neurological outcome in a subjective manner. Both numerical and subjective studies showed high heterogeneity ranging from 'Nine of 12 (75%) patients with neurological disability showed some improvement in neurological status'[63] to the GOS 'improved significantly after the cranioplasty'[8].

Costs

Twenty-one studies reported costs, ranging from implant cost to total medical expenses. PMMA implants were less expensive than PEEK and titanium implants. The least-expensive PMMA implant was 35 GBP[64], the most expensive PMMA implant was 1300 USD after 3D printing[65]. The costs of PEEK ranged from 5000 USD[66] to 20,522 USD[67]. Titanium cranioplasties cost between 2000 GBP[64] and 5050 EUR[55]. Total surgery costs for PSIs of PEEK and titanium were reported to be 15,532 EUR (of which 10,000 EUR for the implant), compared with 10,849 EUR for autologous replacement[68]. Gilardino et al.[69] reported a total cost of 28,560 USD for treatment with PEEK, whereas autologous treatment costs were 25,797 USD.

Esthetic outcome

Most patients were satisfied or highly satisfied with the eventual esthetic outcome. All of the studies reporting both patient and clinician satisfaction showed they were in agreement.

Quality of Life

Five studies reporting the QoL showed an improvement after cranioplasty. Manrique et al.[58] reported that 3 of 4 patients had returned to a similar state as before the skull defect, whereas 1 patient reported dissatisfaction with his appearance and had an overall fair QoL as measured with the Head and Neck Outcome Questionnaire from the University of Washington. Lindner et al.[12] used the short-form-36 questionnaire to evaluate the subjective QoL and stated patients treated with a titanium or HA cranioplasty were "more satisfied at the end of the study than at the beginning". Moser et al.[52] described that 82.4% of the patients had an improved QoL postoperatively, based on 10 easy-to-understand questions in the German language. Cabraja et al.[55] showed all patients had a "considerable improvement in their QoL following calvarial reconstruction" and would "undergo cranioplasty again". Also Kamyszek et al.[46] noted a "clear positive trend" in QoL and 85% of patients "would undergo the procedure again".

DISCUSSION

This systematic review shows that cranioplasties are associated with a high complication rate, particularly when using autologous bone, mainly because of the high infection and resorption rates and subsequent graft removal.

Resorption occurred most frequently in autologous bone, which is inherent to the tissue and may compromise the structural integrity. Resorption in allografts is limited to the interface between implant and surrounding bone and may therefore be less likely to occur. Other complication rates in autologous bone cranioplasties are more similar to, for example, HA, which is the main mineral constituent of bone. PEEK is custom made preoperatively, requires less surgical time, and has no burrs that require removal.

To date, 228 studies on the safety of cranioplasties are available, published during a 65-year span. However, a large variety exists in reported primary and secondary outcomes, and their definitions, as well as the protocols applied for cranioplasties, which makes meta-analysis futile. Meta-analyses in some reviews were conducted with heterogeneous studies[70], whereas other reviews largely focused on a subjective analysis of the most commonly used materials[10]. Corliss et al.[4] included 48 studies (n=5346 patients) and related the way of storage (abdominal pocket or cryopreservation) of autologous bone flaps for cranioplasties to survival rates. They found a total infection rate of 7.32% (n=2937) in the cryopreservation group versus 7.08% (n=527) in the abdominal pocket group. Resorption rate in 19 studies was 9.66% (n=1826) in the cryopreservation group and 7.69% (n=341) in the abdominal pocket group. Malcolm et al.[5] reported similar infection rates, but the materials used for cranioplasty were not reported. Punchak et al.[71] found an infection rate of 6% in a meta-analysis of 15 studies applying 183 PEEK cranioplasties. These reviews had a limited scope, disregarding putative confounders such as patient population, comorbidities, defect location and size, time between decompressive craniectomy and cranioplasty, material, antibiotics usage, frontal sinus involvement, or drain placement.

Beside the clinical results evaluated in this review, physical properties of the various materials may also influence procedure safety. A better understanding of these properties is vital in the development of future materials for cranioplasty. Of the products commonly used, titanium has a good biocompatibility, shows resistance to infection, and appears to be mechanically stable[11,72]. However, titanium is expensive. Furthermore, it is radiopaque and easily conducts heat and cold[10]. PMMA is widely used for cranioplasty, relatively inexpensive, light in weight, easy to use, and radiolucent. Nonetheless, PMMA is associated with disadvantages, such as a greater infection rate, and it does not facilitate bone ingrowth and revascularization[10]. In addition, the residual monomer is considered to be toxic[73-76]. In this systematic review, an overall infection rate of 7.8% was noted. PMMA is mostly formed intraoperative, without polishing. Bacterial adhesion and biofilm deposition is stimulated by irregularities, which could contribute to an increased infection rate[77]. HA is an established material for cranioplasty. It is biocompatible and similar to the mineral structures of human bone. This allows the implant to be broken down over time and replaced by newly formed bone. However, before remodeling has taken place the HA is brittle and vulnerable to fracture. It therefore seems most suitable for small defects[78]. PEEK is a relatively new material for cranioplasties. It has high structural stability and can be sterilized using various methods without deformation. However, PEEK has some disadvantages: the material itself is costly and it has no bioactive potential[71,79].

Combining multiple existing materials allowed for the development of new cranioplasty products, for example, a titanium mesh used in combination with different types of bone cement[10]. In addition to commonly used materials, other new materials for cranioplasty are being developed, such as bioactive fiber-reinforced composite implant, hard tissue replacement polymer and carbon fiber reinforced polymer[80-82]. Most of these materials, however, have merely been evaluated in preliminary studies with small patient groups.

Resorption rates up to 50%[83] have been observed for autologous cranial reconstructions, and there is evidence suggesting that younger patients may have significantly greater resorption rates. Greater metabolic activity in younger patients could lead to quicker resorption, but the exact mechanism responsible for this complication is unclear[84]. This phenomenon suggests that young patients may be better served by an immediate alloplastic reconstruction.

Study limitations

Virtually all currently available evidence on the safety of cranioplasty materials is retrospective, limiting the amount of relevant data available for review.

Reliability of the reported infection rates in the included studies was questionable, because a significant number of studies synonymized infection and removal of the cranioplasty after infection or did not specify their definition of infection. Malcolm et al.[5] already noted this wide range of definitions for infection. This was also true for the definition of resorption. Neurologic functioning and aesthetic outcome were often reported subjectively and were sometimes included as a complication.

HA likely was used in smaller and safer located defects resulting in skewed conclusions. It may also be prevalent in pediatric situations, to accommodate a growing skull; naturally, these patients have a greater capacity for recovery than elderly patients. This review did not correct for these parameters, and future studies should aim to verify these results.

In some studies, the amount of cranioplasties, whether it was unilateral or not, and the affected cranial bone was not reported. In these cases, we assumed the number of patients was equal to the amount of cranioplasties.

A number of the non-primary outcome complications could not be attributed to a material as only studies that did not report the primary outcomes per material were excluded.

CONCLUSION

Implications for practice

This systematic review of a substantial body of evidence offers insufficiently strong evidence to conduct a meta-analysis or support the use of any material over another for cranioplasty. However, available evidence does show a significantly lower removal rate for alloplastic materials for cranioplasty than for autologous bone. Hence, autologous bone is dissuaded for cranioplasty after decompressive craniectomy.

Implications for research

Based on this review, well-conducted prospective studies are warranted to generate convincing evidence on which allograft material is preferable for cranioplasty. Uniform reporting guidelines, including likely confounders, will help improve the quality of the conduct and reporting of studies in this realm and allow proper comparison between studies. This may lead to standardization of surgical protocols and development of better materials for cranioplasty and ultimately an evidence-based choice of allografts for patients who require cranioplasty. These guidelines should, at a minimum, provide clear definitions of infection and resorption, the two most reported complications in cranioplasties.

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Supplemental Digital Content

S.1: Search terms

Embase Classic+Embase <1947 to 2017 January 25>

#	Searches	Results
1	exp craniotomy/	26776
2	exp decompressive craniectomy/ or exp craniectomy/	7145
3	((skull or cranial) adj3 (defect* or reconstruction*)).ti,ab,kw.	4785
4	cranioplast*.ti,ab,kw.	2410
5	craniectom*.ti,ab,kw.	4793
6	exp biomaterial/	53815
7	exp polymer/	622561
8	exp polymer/	622561
9	exp titanium/	41166
10	exp "poly(methyl methacrylate)"/	15197
11	exp prosthesis/	209622
12	exp implant/	621105
13	exp bone graft/	33875
14	exp bone transplantation/	49754
15	exp allograft/ or exp "prostheses and orthoses"/	385145
16	alloplastic.ti,ab,kw.	3093
17	poly-ether-ether ketone.ti,ab,kw.	314
18	polyether ether ketone.ti,ab,kw.	157
19	polyetheretherketone.ti,ab,kw,rn.	1054
20	exp polyetheretherketone/	1004
21	peek.ti,ab,kw,rn.	1722
22	titanium.ti,ab,kw,rn.	53017
23	Poly methyl methacrylate.ti,ab,kw,rn.	13284
24	PMMA.ti,ab,kw,rn.	8604
25	thermoplastic.ti,ab,kw.	2806
26	(implant or implants).ti,ab,kw.	164900
27	Hydroxylapatite.ti,ab,kw,rn.	3485
28	hydroxyapatite.ti,ab,kw,rn.	30890
29	biomaterial*.ti,ab,kw.	30709
30	prothesis.ti,ab,kw.	1676
31	((autolo* or autog*) adj3 bone).ti,ab,kw.	18398
32	(bone adj2 graft*).ti,ab,kw.	30895
33	((autog* or autol*) adj2 implant*).ti,ab,kw.	2578
34	bone flap.ti,ab,kw.	1414
35	((three dimension or 3 dimension or 3D) adj3 print*).ti,ab,kw.	2552
36	(ae or co or si or to).fs.	3152291
37	exp postoperative complication/	599934
38	exp infection/	3341915
39	(safe or safety or side-effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.	1804566
40	infecti*.ti,ab,kw.	1742165
41	complication*.ti,ab,kw.	1121251
42	risk.ti,ab,kw.	2272184
43	1 or 2 or 3 or 4 or 5	38982
44	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	1545313
45	36 or 37 or 38 or 39 or 40 or 41 or 42	9099835
46	43 and 44 and 45	3003

S.2: Included studies in this systematic review[1-228]

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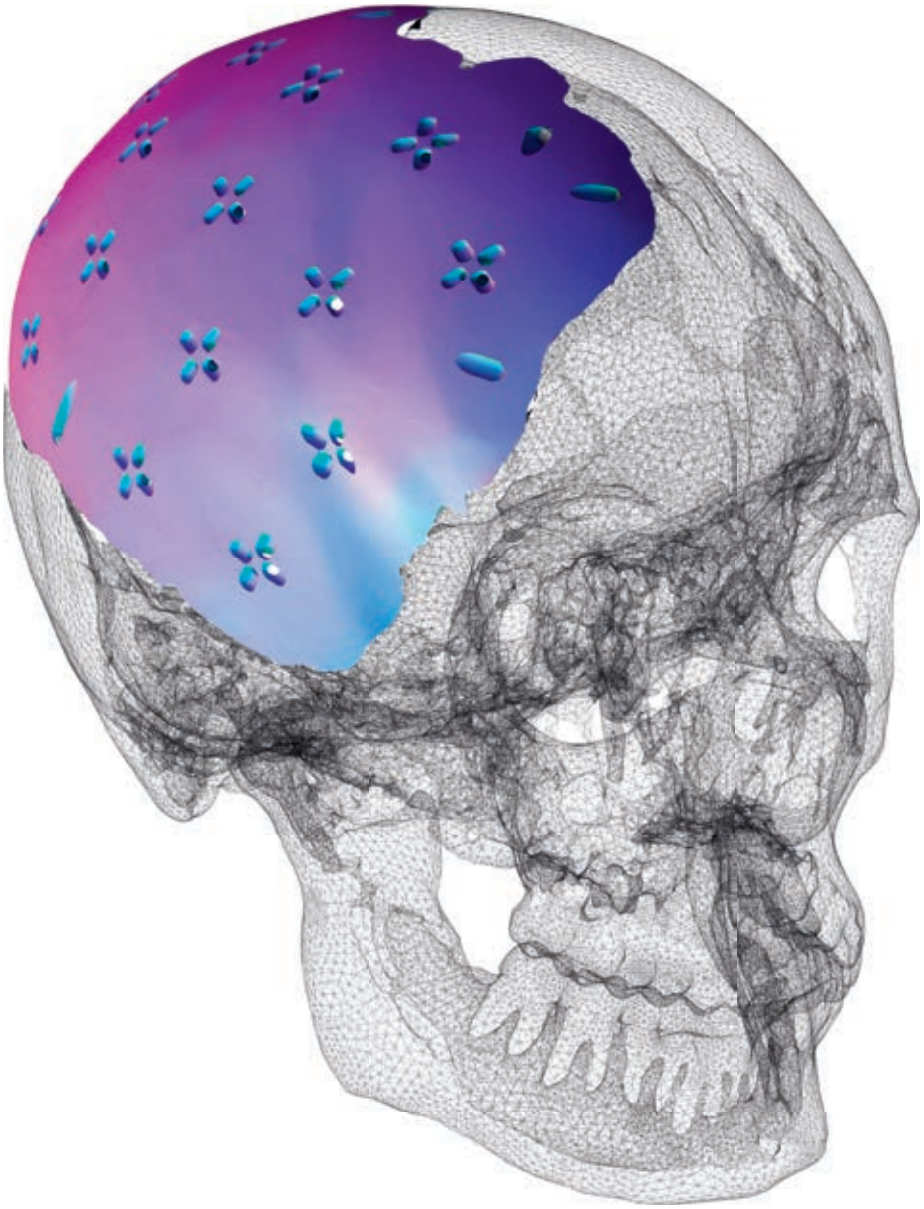
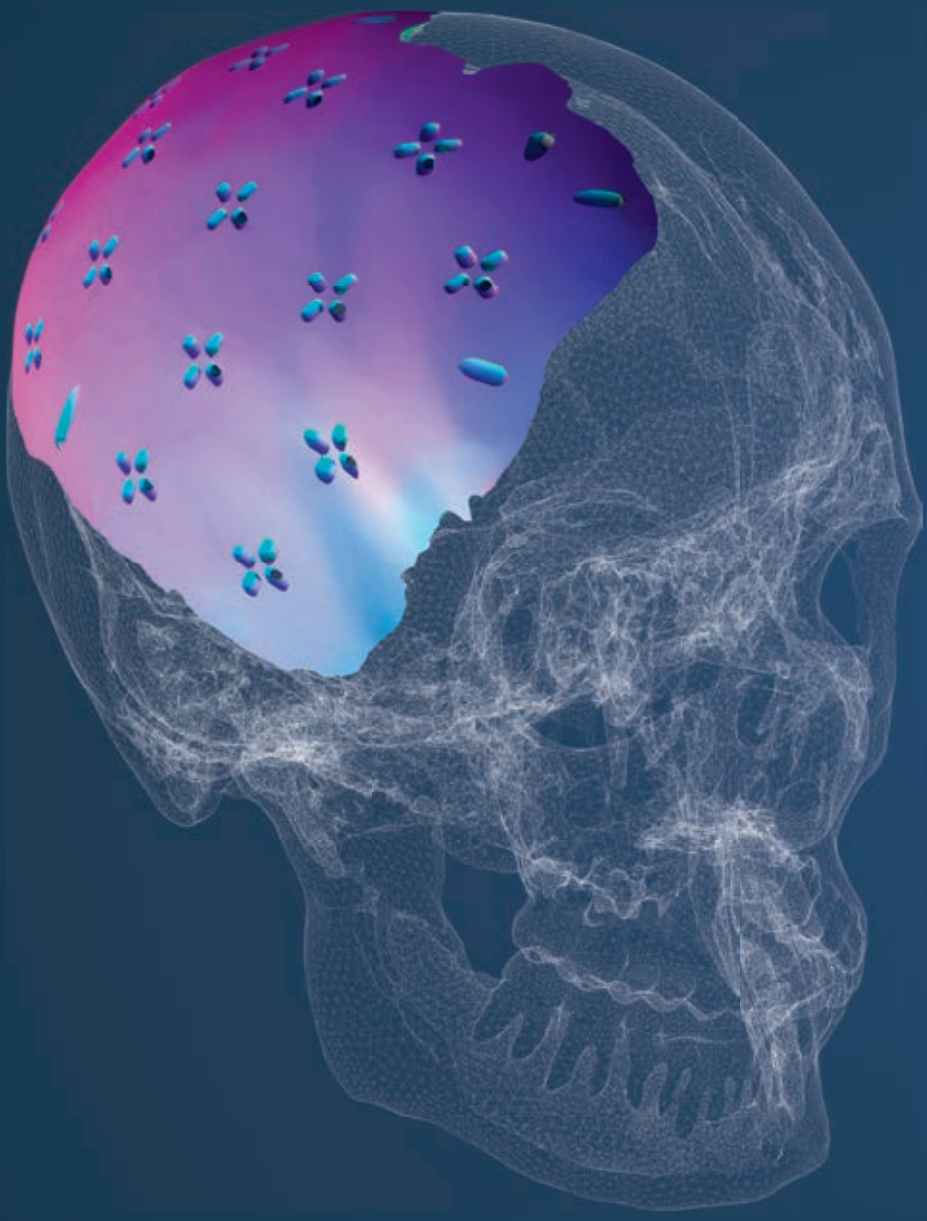


PART III

Current Challenges



CHAPTER 3

Factors predicting the failure of autologous cranial reconstructions

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This chapter is based on the publication:
Factors related to failure of autologous cranial reconstructions after decompressive craniectomy

Published: Journal of Cranio-Maxillo-Facial Surgery, 2019

ABSTRACT

Background: Cranioplasty is customary after decompressive craniectomy. Many different materials have been developed and used for this procedure. The ideal material does not yet exist, while complication rates in cranioplasties remain high. This study aimed to determine factors related to autologous bone flap failure.

Methods: In this two-center retrospective cohort study, 254 patients underwent autologous bone cranioplasty after initial decompressive craniectomy between 2004 and 2014. Medical records were reviewed regarding patient characteristics and factors potentially related to bone flap failure. Data were analyzed using univariable and multivariable regression analysis.

Results: Independent factors related to overall bone flap failure were: duration of hospitalization after decompressive craniectomy [OR: 1.012 (95%CI: 1.003–1.022); p=0.012], time interval between decompressive craniectomy and cranioplasty [OR: 1.018 (95%CI: 1.004–1.032); p=0.013], follow-up duration [OR: 1.034 (95%CI: 1.020–1.047); p<0.001]. In patients with bone flap infection, neoplasm as initial diagnosis occurred significantly more often (29.2% vs. 7.8%; RD 6.5-42.5%) and duration of hospitalization after decompressive craniectomy tended to be longer (means 54 vs. 28 days, MD 26.2 days, 95%CI -8.6 to 60.9 days). Patients with bone flap resorption were significantly younger (35 vs. 43 years, MD 7.7 years, 95%CI 0.8-14.6 years) and their cranial defect size tended to be wider than in patients without bone flap resorption (mean circumference 39 vs. 37 cm; MD 2.4cm, 95% CI -0.43 to 5.2cm) and follow-up duration was significantly longer (44 vs. 14 months, MD 29 months, 95%CI 17-42 months).

Conclusion: A neoplasm as initial diagnosis, longer hospitalization after decompressive craniectomy, larger time interval between decompressive craniectomy and cranioplasty and longer follow-up duration are associated with a higher risk of failure of autologous bone flaps for cranioplasty. Patients with these risk factors may be better served with an early recovery program after decompressive surgery or an alloplastic material for cranioplasty.

INTRODUCTION

Decompressive craniectomy is a lifesaving neurosurgical procedure, in which a part of the skull is removed to reduce raised intracranial pressure, resulting from cerebral edema or hemorrhage due to traumatic brain injury, cerebral infarction, subarachnoid hemorrhage, hemorrhagic strokes, neoplasm, or intracranial infections.[1–4] Following decompressive craniectomy, reconstruction of the cranial defect is mandatory in order to protect the brain, enhance social acceptance, and restore cranial esthetics. Moreover, it may reduce neurologic symptoms, including the syndrome of the trephined and sinking skin flap syndrome. [2,4–12]

Autologous bone can be used for cranial reconstructions as it is biocompatible, inexpensive, does not trigger immuno-rejection[11], and can be effective as a substrate for bony ingrowth and revascularization[13–15]. In delayed cranial reconstructions, the autologous bone flap is usually stored in a bone bank and re-inserted when the patient is neurologically stable. Storage techniques may significantly alter bone viability; storage temperatures between 8 ºC and -84 ºC have been reported.[6,11,15–20] There is no consensus on the optimal time interval between decompressive craniectomy and cranioplasty; different wide-ranging thresholds have been used in the literature[9,21–26].

Reimplantation of preserved autologous bone has a high risk of infection (0%-26%) [2,11,18,19,27–30] and bone flap resorption (1%-50%),[4,6,12,13,16,22,27,30] often resulting in loss of the autologous bone flap.[31]

The aim of this study was to determine independent predictive factors for the failure of autologous bone flaps used for cranioplasty in patients who had undergone decompressive craniectomy.

MATERIALS AND METHODS

Study design and patient population

In this retrospective case series, 276 consecutive patients were included after a decompressive craniectomy and cranioplasty with autologous bone in separate procedures, performed between January 2004 and December 2014 in two centers [Academic Medical Center (Amsterdam) (n=183) and Elisabeth-Tweesteden Hospital (Tilburg) (n=93)] in the Netherlands. Both centers used identical protocols and procedures that did not change during the study period. Twenty-two patients were excluded because of bilateral defects to conserve homogeneity of the patient group in this study (N=10), or due to lack of follow-up, transfer to a different hospital, which may or may not have been in the Netherlands (N=7), missing data (N=4) and one non-disease related death 21 days after cranioplasty. Thus, a total of 254 consecutive patients were analyzed in this study.

Ethical consideration

This observational study was conducted using the STrengthening the Reporting of OBservational studies in Epidemiology guidelines (STROBE guideline) [32,33]. The study protocol was approved by the medical ethics review board of the AMC (protocol nr. W18_030 # 18.046).

Surgical procedure

After decompressive craniectomy, the removed autologous bone flap was rinsed with 0.9% NaCl, dried with sterile gauze, packed into three sterile transplantation bags, and stored in the local bone bank at -80°C. Cranioplasty was performed as soon as the patient was medically and neurologically stable, and the wound had fully healed and was free of clinical signs of infection. Thirty minutes before incision, prophylactic antibiotics of a first-generation sodium cephalosporin (Kefzol®, Eurocept) were administered. If possible, the scar of the decompressive craniectomy was reopened and the edges of the cranial defect were made visible and accessible. The autologous bone flap was, if necessary, remodeled by minor adjustments and fixed to the skull, with either sutures or plates and screws. If the temporal muscle was dissected, it was suspended to the inserted autologous bone flap with sutures. A subgaleal drain was inserted for some patients, at the surgeon's discretion. The skin was closed in two layers and a bandage was applied. All patients underwent standard postoperative care: patients received standard paracetamol post-operative and, if necessary, stronger analgesics were administered. Antibiotics were prescribed postoperatively at the discretion of the surgeon. All patients were seen at least once after the cranioplasty.

Data collection

Clinical data were collected by reviewing the medical records of each patient by two independent researchers (C.G. and S.V.). Extracted parameters were: location of hospital, gender, age at the time of cranioplasty, co-morbidities (diabetes mellitus, cardiovascular disease, or both), smoking habits, initial indication for decompressive craniectomy (cerebrovascular, trauma, neoplasm, infection), time interval between decompressive craniectomy and cranioplasty, length of cranioplasty procedure (scored from scalp incision to closure), duration of hospitalization after decompressive craniectomy and cranioplasty, failure of cranioplasty, in which year the decompressive craniectomy and cranioplasty were performed, and follow-up duration (calculated from the moment of replacement of the autologous bone flap until the last patient contact before December 2014). The neurologic status before and after cranioplasty was not specifically recorded in this study, as it was deemed to have no substantial effect on the outcome of the cranioplasty.

Recorded reasons for autologous bone flap failure included: 1) infection (defined as a clinical infection that required surgical removal), 2) resorption (defined as symptomatic or radiographic resorption where the remaining autologous bone did not protect the brain anymore or the cosmetic outcome was not acceptable), 3) subcutaneous fluid collections, and 4) hemorrhage. A procedure was classified as successful if the autologous bone flap was inserted successfully and no postoperative removal of the autologous bone flap was performed by the end of the study period, or as unsuccessful, in case of the removal of the autologous bone flap.

Defect size measuring

The CT-scans after decompressive craniectomy were retrieved and reviewed. Post-operative 3D virtual models of the CT- scans were rendered in an in-house developed software tool. This tool was developed with C++ in Microsoft Visual Studio 2015 (Microsoft Corporation, Redmond, WA, USA). After reconstructing the 3D-models, landmarks were manually placed on the border of the defect to measure the circumference of the defect (Figure 1).

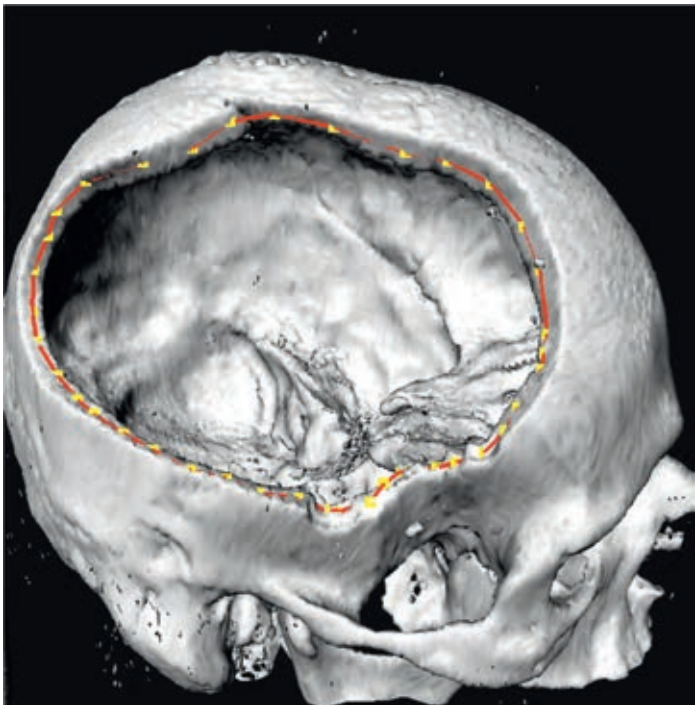

Figure 1: Example of cranial defect circumference measurement; in this case 42.6 cm.

Statistical analysis

Multivariate stepwise binary logistical regression analyses were used to identify independent predictive factors for failure of autologous bone flaps. Possible predictive factors were derived from the literature. Non-significant factors were manually and sequentially removed until only significant parameters remained. Odds ratios (OR) and their 95% confidence intervals (95% CI) were determined for significant predictive parameters. Univariable analyses were conducted to detect any differences in patients with and without infection or resorption of the bone flap. Differences in continuous variables were expressed as mean differences (MD) with their 95% CIs, differences in dichotomous variables were presented as risk differences (RD) with their 95%Cis. A Number Needed to Treat (NNT) or Number Needed to Harm (NNH) was calculated is case of a significant RD. Statistical analysis was performed with IBM SPSS Statistics 24.0 (Armonk, NY, USA).

RESULTS

Patient characteristics

This study included 254 patients (165 from the Amsterdam University Medical Centers, 89 from the Elisabeth-Tweesteden Hospital) who underwent a decompressive craniectomy and cranioplasty with autologous bone in the period 2004-2014. The median age of the patients was 45 years (IQR: 30–53 years), and 51% were males (n=130). Initial indications for decompressive craniectomy were cerebrovascular (n=125), traumatic brain injury (n=93), neoplasm (n=25), or infection (n=11). Of the included patients 12.2% had a smoking habit at the moment of the cranioplasty, 37.7% did not, 3.1% had quit smoking and in 46.9% smoking habits could not be retrieved. Median follow-up duration was 175 days (IQR: 55.50–706.3 days) after cranioplasty (Table 1).

Surgery-specific characteristics

In 236 of the 254 included patients (92.9%) a post-craniectomy CT-scan was performed. Median defect circumference was 38.5cm (IQR 33.4-41.5cm), ranging from 13.5 to 49.7cm. Median time interval between decompressive craniectomy and cranioplasty was 133 days (IQR: 83.0–199.5 days) (Table 1).

Failure of autologous bone flaps

Of the 254 included patients, the autologous bone flap had to be removed in 52 (20.5%) cases (Table 1). Causes of removal were: infection in 24 (46.2%) cases; resorption in 23 (46.2%); subcutaneous fluid collections in 3 (5.8%); and hemorrhage in two (3.8%) cases. This outcome was not influenced by the year in which the surgical interventions were conducted. Characteristics of patients who suffered flap failure due to infection or resorption are shown in Table 1.

Table 1: Summary of patient characteristics

	N (%)	Failure N* (%)	Success N (%)	Resorption N (%)	Infection N (%)
Number of patients	254 (100)	52 (20.5)	202 (79.5)	23 (44.2)	24 (46.2)
Gender					
Male	130 (51.2)	31 (23.8)	99 (76.2)	15 (65.22)	12 (50.0)
Age [years; median (IQR)]	45.0 (30.0-53.0)	42.5 (29.0-54.0)	45.0 (32.0-53.0)	29.0 (20.0-54.0)	46.0 (32.5-61.25)
Comorbidities					
Cardiovascular disease	37 (14.6)	9 (24.3)	28 (75.7)	3 (13.0)	6 (25.0)
Diabetes	17 (6.7)	3 (17.6)	14 (82.4)	1 (4.3)	1 (4.2)
Cardiovascular disease and diabetes	5 (2.0)	1 (20.0)	4 (80.0)	1 (4.3)	0 (0.0)
No relevant comorbidity	195 (76.8)	39 (20)	156 (80)	18 (78.3)	17 (70.8)
Initial diagnosis					
Cerebrovascular	125 (49.2)	26 (20.8)	99 (79.2)	13 (56.5)	12 (50.0)
Trauma	93 (36.6)	16 (17.2)	77 (82.8)	8 (34.8)	5 (20.8)
Tumor	25 (9.8)	9 (36.0)	16 (64.0)	1 (4.3)	7 (29.2)
Infection	11 (4.3)	1 (9.1)	10 (90.9)	1 (4.3)	0 (0.0)
Defect circumference [cm; median (IQR)]	38.5 (33.3-41.6)	38.5 (29.2-42.8)	38.4 (34.3-41.3)	397.28 (34.8-44.5)	32.4 (24.6-42.1)
Time interval between decompressive craniectomy and cranioplasty [days; median (IQR)]	133 (83.0-199.5)	158.5 (90.8-223.5)	125.5 (82.8-191.25)	171 (116.0-224.0)	145.5 (83.3-221.8)
Length of cranioplasty [minutes; median (IQR)]	110 (79.0-140.0)	114 (83.3-142.5)	108.5 (77.25-140.0)	126.0 (104.0-143.0)	83.5 (55.5-131.3)
Hospitalization [days; median (IQR)]					
After decompressive craniectomy	21 (11.8-38.0)	21.5 (11.0-46.8)	21.0 (12.0-36.25)	22.0 (14.0-38.0)	20.5 (7.75-64.8)
After cranioplasty	3.0 (2.0-7.0)	3.0 (2.0-19.8)	3.0 (2.0-5.75)	3.0 (2.0-11.0)	4.0 (2.0-21.3)
Time to cranioplasty failure [days; median (IQR)]	112.0 (18.0-553.0)	112.0 (24.3-579.3)	not applicable	618.0 (259.0-884.0)	51.5 (24.25-133.0)
Follow-up [days; median (IQR)]	175.5 (55.0-706.3)	713.5 (328.8-1567.3)	97.0 (52.0-406.8)	1229.0 (705.0-1952.0)	424.5 (260.0-1154.3)

*Reasons for failure were resorption, infection, subcutaneous fluid collections and hemorrhage

Overall complication rate

Possible predictive parameters included in the regression model were: gender, age at the time of cranioplasty, co-morbidities (diabetes mellitus, cardiovascular disease, or both), initial indication for decompressive craniectomy (cerebrovascular, trauma, neoplasm, infection), time interval between decompressive craniectomy and cranioplasty, length of cranioplasty procedure (scored from scalp incision to closure), duration of hospitalization after decompressive craniectomy and cranioplasty, failure of cranioplasty, the year of the decompressive craniectomy and cranioplasty, and follow-up duration (calculated from the moment of replacement of the autologous bone flap until the last patient contact before December 2014). Significant independent predictive parameters were: duration of hospitalization after decompressive craniectomy [OR: 1.012 (95%CI: 1.003–1.022); p=0.012] (this OR means that each additional day of hospitalization leads to 1.2% more risk of flap failure); time interval between decompressive craniectomy and cranioplasty [OR: 1.018 (95%CI: 1.004–1.032); p=0.013] (each additional week between decompressive craniectomy and cranioplasty leads to 1.8% higher risk of flap failure); and follow-up duration [OR: 1.034 (95%CI: 1.020–1.047); p<0.001] (i.e., each additional month of follow-up leads to 3.4% higher risk of failure of the bone flap).

Infection

A neoplasm as initial diagnosis occurred more frequently in patients with infection (29.2% vs. 7.8%; RD 21.3%; 95%CI 8.4-38.3%; NNH 5; 95%CI 3-12). The duration of hospitalization after decompressive craniectomy tended to be longer in those with an infected bone flap (means 54 vs. 28 days, MD 26.2 days, 95%CI -8.6 to 60.9 days).

Resorption

Younger patients had a significantly higher risk of bone flap resorption (35 years in the resorption group vs. 43 years in those without resorption; MD 7.7 years, 95%CI 0.8-14.6 years) as well as those with a longer follow-up duration (44 vs. 14 months, MD 29 months, 95%CI 17-42 months). A larger cranial defect size tended to have some influence (mean circumference 39 vs. 37cm; MD 2.4cm, 95% CI -0.43 to 5.2cm).

DISCUSSION

This study shows that cranioplasties with an autologous bone flap fail frequently. One in every five autologous bone flaps eventually had to be removed because of infection, bone flap resorption, subcutaneous fluid collections, or hematoma. Several factors were found to be related to bone flap failure.

Complication rates in cranial reconstructions are high, often resulting in removal of the reconstruction[2,4,6,11–13,16,18,19,22,27–31]. Current literature reports a median removal rate of 10.4% (ranging from 0-50%) for autologous bone flaps and for combined alloplastic cranioplasties 5.1%[31].

Age

Age has been postulated as an influencing factor for the emergence of infections after cranioplasty with autologous bone. Higher metabolic activity in young patients could lead to quicker resorption, but the exact mechanism responsible for this is unclear.[12,13,30,34,35] Resorption rates of 1%-50%[4,6,12,13,16,22,27,30,36] have been observed for autologous bone flaps, while younger patients may have even higher resorption rates[12,22,26,30,36,37]. The present study confirmed this association.

Indication for decompressive craniectomy

In this study, an association was found between a neoplasm as the initial diagnosis for decompressive craniectomy and higher infection rates. This patient population did not receive standard radiotherapy as a possible explanation for this association. The current literature also does not offer an explanation, but the slow onset of this disorder likely has a negative impact on recovery, as these patients generally have a suboptimal health condition.

Defect size

Larger craniectomies are considered an essential means of decompression as a life-saving intervention. However, a larger size of the defect tended to foster bone flap resorption. This possible correlation is supported by previous studies, showing that cranial defects above 75cm^2 were associated with a resorption rate above 60%.[13] Fan et al.[37] reported a significant correlation between bone resorption and cranial defects larger than 100 cm^2. On the other hand, Schoekler and Trummer reported a slightly higher resorption rate in patients with cranial defects over 120 cm^2, but did not find a significant correlation[16]. Similarly, Dünisch et al. did not show a significant association between complications and the size of the defect[22]. Bone graft incorporation depends on the amount of vascularization and resumption of osteogenesis in terms of the formation of bone bridges between the outline of the cranial defect and the reimplanted autologous bone flap.[38] With a larger defect size more revascularization and bone formation needs to occur, which may imply that resorption in larger defects is more likely.

Duration of hospitalization after decompressive craniectomy

In the present study, an association was found between the duration of hospitalization after decompressive craniectomy and the overall complication rate, as well as the infection rate. This may be caused by the overall condition of the patient, comorbidities, newly developed diseases, neurological and surgical outcomes, complications, and rehabilitation period after decompressive craniectomy[1]. To better understand the predictive factors that influence complication rates after cranioplasty, and thereby the length of hospital stay, the surgical outcomes after decompressive craniectomy need to be quantified. Early recovery programs after surgery are known to shorten the length of stay[39], and may also be applicable in acute situations like cranial decompression surgery to reduce the risk of eventual flap failure.

Time interval between decompressive craniectomy and cranioplasty

The time interval between decompressive craniectomy and cranioplasty is often considered as a potential risk factor for complications like flap failure,[8,21] which was confirmed in this study. On the other hand, several studies did not find such an association[6,22,26]. As a consequence, no consensus on the optimal time interval between decompressive craniectomy and cranioplasty exists. Many studies distinguish an 'early' and 'late' group, with varying thresholds; 2 weeks, 2 months, 3 months, and even 6 months have been reported.[16,21,26,28,29,36,40,41] It has been recommended that the cranioplasty be performed at a later stage to avoid operating in a possibly contaminated wound[4]. In contrast, recent findings suggest the cranioplasty may be better performed at an earlier stage to reduce the burden on the patient. Moreover, it may prevent the syndrome of the trephined, and lead to better neurological improvement.[4,21,42]

Schuss et al. showed a significantly lower resorption rate when the autologous bone was reinserted within two months after decompressive craniectomy. Bone flap resorption was observed after about three months after cranioplasty[36]. Brommeland et al. showed a significantly higher resorption rate in delayed cranioplasties[30]. This phenomenon may suggest that if cranioplasty is considered at a later stage in patients who are neurologically unstable, an alloplastic reconstruction may be preferred. Schoekler and Trummer reported a mean interval of 419 days before resorption was observed. However, the timing between decompressive craniectomy and cranioplasty did not significantly influence bone resorption. Still, they recommended the use of an alloplastic cranioplasty when the cranioplasty was planned within two months after the decompressive craniectomy[16].

A possible reason why resorption is dependent on the time interval between decompressive craniectomy and cranioplasty is the cell viability in the bone graft. The literature reports that autologous bone stored in bone banks at -80°C contains viable cells. It is likely that these cells respond differently to cold storage. If osteocytes in some patients are more vulnerable, this may lead to worse outcomes due to increased resorption.[43] On the other hand, bone flaps kept frozen for 19 months have been shown to maintain the capacity for revascularization[38].

Follow-up duration

A substantial proportion of the autologous bone flaps fail in time. Hence, patients with a long-life expectancy may be better served with an alloplastic cranioplasty. In the long run, when resorption of an autologous bone flap occurs, the protection of the brain is diminished, fracture is more likely, and esthetics will be compromised due to atmospheric air pressure. It may therefore be advisable to develop a protocol to extend the follow-up period. This may result in a more timely intervention when there are clinical signs for failure of the bone flap, which may reduce definitive bone flap failures in time.

Limitations of this study

The retrospective nature of this study implies a risk of reporting bias, as it was limited to the available information documented in patient charts, including whether or not antibiotics were given. This led to patient exclusions because of unknown follow-up data, which is likely to occur if the follow-up period was uneventful and patients would have no need to visit their surgeon. Thus, the present findings about failure rates might be slightly exaggerated. In addition, the association between bone flap failure and various parameters was statistically significant but with a limited clinical relevance due to the relatively small number of patients available. The impact of these parameters on clinical practice deserves further investigation.

Second, in this study resorption and infection were defined clinically in case of flap removal, although this was not verified microbiologically. However, we think this would not have influenced the results of this study substantially.

Third, the circumference rather than the surface area of the defect was used for the measurements. Because the skull has convex and concave areas, the measurement of the surface area of the defect is complicated. However, the measured circumference is likely to give a reliable indication of the defect in the cranium of the patient.

Fourth, this study only included autologous bone that was stored in the freezer at -80°C. However, other options for bone storage are mentioned in the literature. Corliss showed no significant differences between cryopreservation and storage in an abdominal pocket for resorption (9.7 vs 7.7), infection (7.3 vs 7.1) or reoperations (15.9 vs 7.6)[44]. Another study showed a resorption rate of 20% after bone flap sterilization and storage in a refrigerator at 8°C[6]. Nowadays, numerous alloplastic materials have been developed for cranioplasties, each with their own benefits and potential harms. The most frequently reported materials are poly(methyl methacrylate) (PMMA), poly (ether ether ketone) (PEEK), titanium, hydroxyapatite. However, there is still no consensus on the optimal material for cranial reconstruction[31].

CONCLUSION

The risk of autologous bone flap failure in patients who underwent decompressive craniectomy is considerable, especially in those operated for a neoplasm. Patients with a longer hospitalization time after decompressive craniectomy may benefit from an early recovery program after surgery to eventually reduce failure of the cranioplasty, or by the use of an alloplastic material for cranial reconstruction. This also holds for patients with a large cranial defect and those with a longer life expectancy. There is still no consensus about the time interval between decompressive craniectomy and cranioplasty. A randomized trial could help make an evidence-based decision when to proceed with the cranioplasty. Finally a standard follow-up protocol may improve early detection and reduce the risk of failure of an autologous bone flap.

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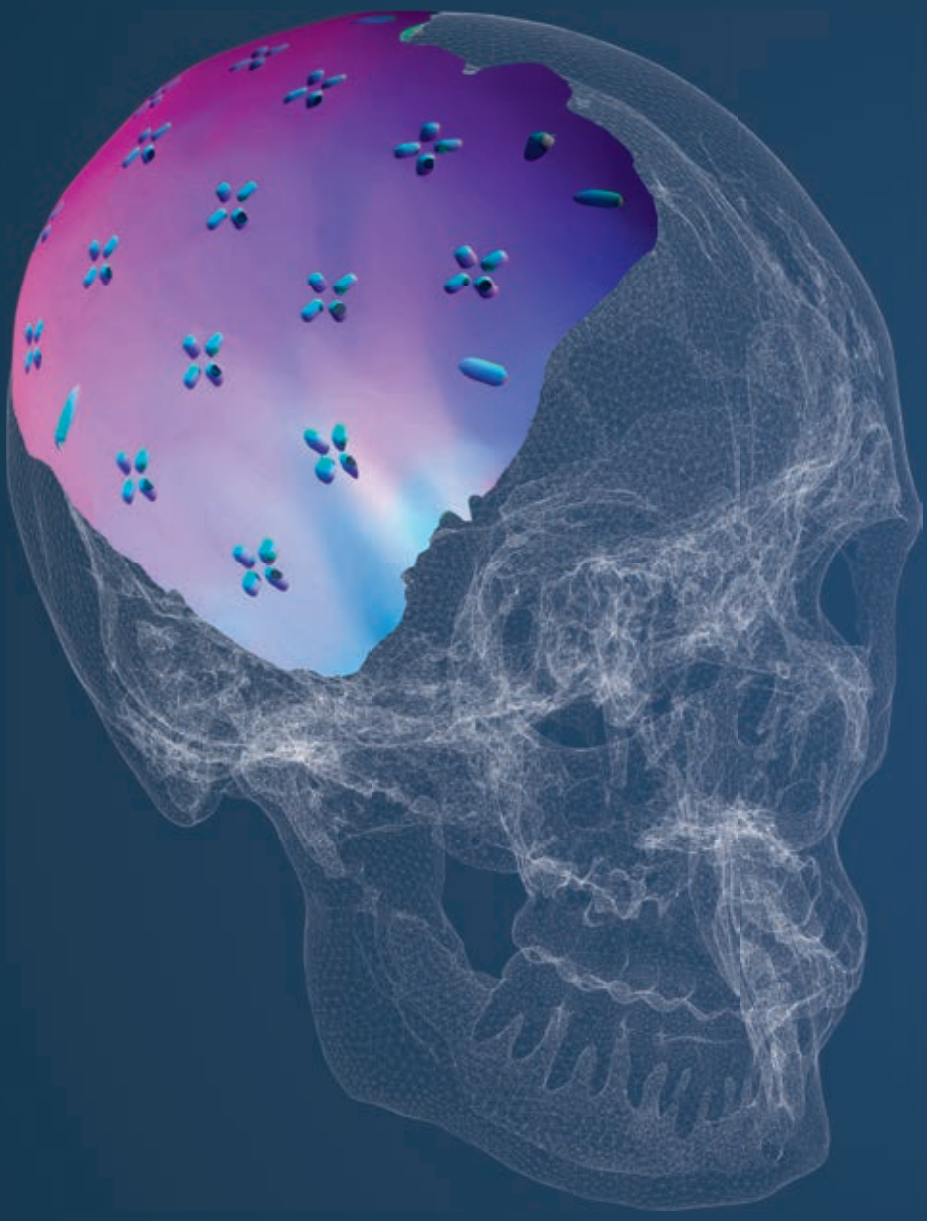

CHAPTER 4

The properties of an *in vivo* fractured PMMA cranioplasty after 15 years

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This chapter is based on the publication:
Properties of an In Vivo fractured Poly(Methyl Methacrylate) cranioplasty after 15 years

Published: World Neurosurgery, 2018

ABSTRACT

Background: In 2001, a 27-year-old man was diagnosed with a meningioma with skull bone involvement. A craniectomy was performed and a CMW-3 poly(methyl methacrylate) cranioplasty was manually manufactured to reconstruct the remaining cranial defect. In 2016, he complained about progressive neurologic impairment. A CT-scan revealed that the cranioplasty had fractured into four dislocated pieces. Removal was indicated and during the same operation a poly(ether ether ketone) patient-specific implant was inserted.

Materials and Methods: The fractured cranioplasty was compared to freshly prepared CMW-3 specimens to determine whether the material properties had changed during 15 years *in vivo*. Gel permeation chromatography, micro-computed tomography, and flexural strength tests were performed. The fracture itself was analyzed using finite element analysis.

Results: The polydispersity index and molecular weight were not significantly different for the fractured cranioplasty and CMW-3. The fractured cranioplasty contained a total porosity of 10.7%, CMW-3 cured at atmospheric pressure 4.1%, and 0.06% when it is cured at 2.2 bar. The flexural strength of the CMW-3 cured at 2.2 bar was significantly higher than both the fractured cranioplasty and CMW-3 cured at atmospheric pressure. Finite element analysis showed stress of 12.2 MPa under a load of 100 N on a weak spot.

Conclusion: This *ex vivo* study shows that CMW-3 after 15 years *in vivo* was not influenced in molecular weight or flexural strength. However, the design of the implant and the handling of the poly(methyl methacrylate) seem important factors to improve mechanical properties of cranial reconstructions.

INTRODUCTION

After decompressive craniectomy a cranioplasty is recommended to protect the brain, improve esthetics, and increase psychosocial well-being.[1–5] Most documented materials for cranioplasty are autologous bone, titanium, poly(methyl methacrylate) (PMMA), hydroxyapatite (HA), and poly(ether ether ketone) (PEEK), each with their own benefits. However, there is still no consensus on the optimal material for cranial reconstructions.[6,7]

One of the most frequently used alloplastic materials is PMMA, which was developed in 1901 by Dr. Otto Röhm and was adopted early in aeronautical engineering[8]. After several years PMMA was introduced in the clinic and was gradually applied for dental applications, hip- and knee arthroplasties, and cranial reconstructions[8–12].

Especially in cranial reconstruction, material handling has undergone a transformation in the last decade. Traditionally, PMMA powder and MMA liquid are hand-mixed and cured directly in the cranial defect[9,12]. An important disadvantage of this procedure is the high temperatures reached during curing, which could inadvertently be transferred to the bone, dura, and brain. Nowadays, a 3-dimensional (3D) mold of the cranial defect can be manufactured to produce patient-specific implants (PSIs). Subsequently, PMMA is pressed into a mold and cured. After cooling down, minor adjustments can be made to the implant after which it is placed into the cranial defect[13–16]. There is extensive literature available on the behavior of PMMA; however, controversy exists especially toward toxicity[17]. An important remaining question is whether the material behavior of PMMA changes over time in nonload-bearing locations in the human body, such as the calvarium.

Advances in medical technology, such as patient-specific allogenic reconstruction, have led to an improvement of patient outcomes[18]. Therefore, it is important to understand *in vivo* material behavior over time. It is also important to understand why implants fail, so the design and material may be further improved on.

In this study a 15-year-old *ex vivo* cranioplasty was retrieved. The chemical, structural, and mechanical properties of this fractured cranioplasty were evaluated to investigate changes of these properties in the human cranium and to find the origin of the failure.

MATERIALS AND METHODS

Case

In 2001, a 27-year-old man, with diabetes mellitus type II, visited the department of neurosurgery with complaints of sensory disturbances in the right side of his body, character changes, diminished vision, and dysphasia. Magnetic resonance imaging was performed and the patient was provisionally diagnosed with a bilateral parieto-occipital meningioma with reactive changes of the cranial bone (Figure 1). A total resection was indicated, and a direct reconstruction of the cranial defect planned.

A bi-coronal incision was performed, a skin flap detached, and involved bone surgically visualized and removed. The resulting defect had a circumference of 400mm. After tumor resection and closure of the dura, a PMMA cranioplasty was prepared according to the manufacturer's instructions using CMW-3 (DePuy International Ltd., Leeds, United Kingdom). The malleable PMMA was put into the defect for the correct size and molding, after the dura was protected with damp gauzes. After hardening small adjustments were made with a burr to create a perfect fit. After this, the cranioplasty was fixed with sutures. After closure of the skull defect a subcutaneous wound drain was placed. The total operation time was approximately 14 hours with 4.5 L blood loss. The pathologic diagnosis was as expected: meningotheliomatous (syncytial) meningioma (World Health Organization grade I) with ingrowth into the cranial bone.

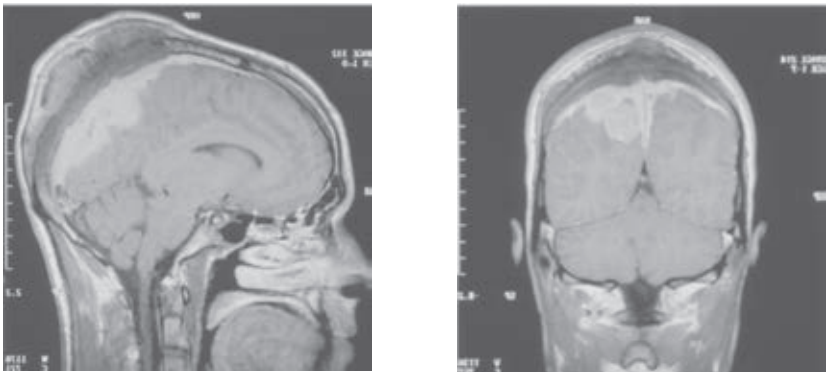

Figure 1: Preoperative sagittal (left) and coronal (right) T1-weighted MR-image after intravenous gadolinium.

In the years following the initial cranioplasty the patient had multiple epileptic seizures; with the use of lamotrigine these did not recur. The patient lived by himself, was eventually permitted to drive a car, and did not have any complaints. In 2016, 15 years after the initial cranioplasty, he complained about progressive headaches, memory impairment, poor vision, inability to operate motor vehicles, and unstable gait. The patient could not recall any trauma involving the cranioplasty. On physical examination, the cranioplasty was palpable and seemed loose. A computed tomography scan with 3D reconstruction revealed that the cranioplasty had fractured into four pieces, which were dislocated **(**Figure 2A).

Removal of the fractured PMMA cranioplasty was indicated, and during the same operation a PEEK PSI was inserted **(**Figure 2B and 2C). The shards of the fractured implant were sealed in separate plastic bags, and stored at 4 °C in the dark. The PSI operation was complicated by a postoperative epidural hematoma which was surgically evacuated. After two months the patient visited the outpatient clinic and reported an improvement of his symptoms.

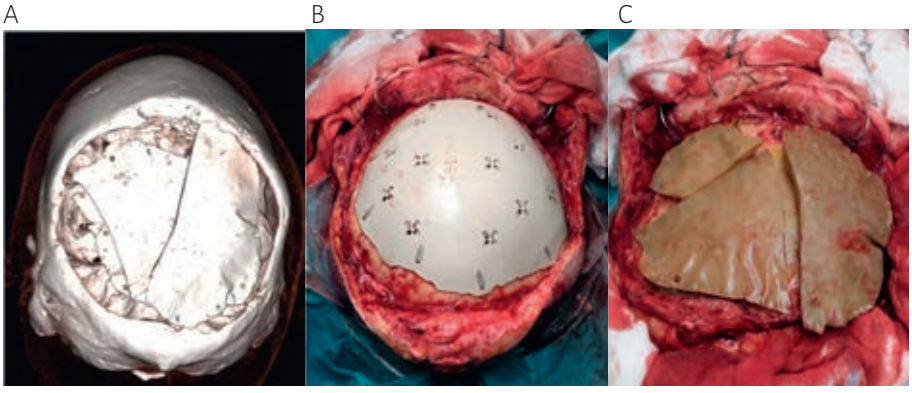

Figure 2: A) 3D reconstruction (left) of the fractured cranioplasty and the remaining dislocated shards. B) PEEK cranioplasty *in situ*. C) Fractured CMW-3 cranioplasty *in situ*.

Three analytical techniques, gel permeation chromatography (GPC), micro-computed tomography (μCT) and flexural strength, were used to determine whether the chemical, structural, and mechanical properties of CMW-3 had changed during 15 years *in vivo*. With the use of finite element analysis (FEA), the mechanical behavior of the fractured implant was analyzed to better understand the underlying reasons for failure.

Specimen preparation

The fractured cranioplasty was compared to fresh specimens of CMW-3 (PMMA). Following the manufacturer's instructions, the PMMA particles (40.0 g) were mixed with MMA liquid (17.9 g) in a vacuum holder. The malleable CMW-3 was put into a nylon 3D printed cranial mold. One specimen was cured for 30 minutes at atmospheric pressure, another was cured for 30 minutes at a pressure of 2.2 bar.

Gel permeation chromatography

The average molecular weights and their distributions were assessed by gel permeation chromatography. Four small samples were collected from the edge of the fractured implant. To compare, 2 fresh samples of CMW-3 were retrieved. In total 6 samples were analyzed using GPC to determine the relative molecular weights. The samples of the fractured implant were washed with demi-water to remove as many blood stains as possible, and all samples were measured in duplo.

Suspensions were formed by mixing each sample in tetrahydrofuran (THF) while stirring and heating, resulting in sample concentrations of around 2 mg/mL. These suspensions were filtered to remove the present non-soluble salts and additives, and injected into the GPC column (300 x 7.5 mm, 3 µm particles, Mixed-C and Mixed-D columns connected in series (Polymer Labs, currently Agilent Technologies, Santa Clara, California, USA)). The mobile phase consisted of tetrahydrofuran at 1 mL/min and 40 °C. Ultraviolet/visible photodiode array (UV/Vis-PDA) and refractive index (RI) detectors were used to analyze the samples and were compared to polystyrene standards.

Porosity and density

The porosity was determined by measuring the density and using 3D µCT. The density of the specimens was measured using a Mettler Toledo AT261 (Greifensee, Switzerland) analytical balance. Micro-CT data were acquired using a SKYSCAN 1272 (Bruker, Kontich, Belgium) with the following settings: voltage = 100 kV, current = 100 µA, exposure time = 31.2 s, pixel size = 6.7 µm, and 1200 projection angles. The porosity was determined with CTAn software (v1.7.17; Bruker, Kontich, Belgium).

Flexural strength

The fractured implant and the CMW-3 specimens were sawed with a 0.3-mm-wide diamond saw (Ukam Industrial, Valencia, CA, USA) into x-10-x 13-mm rectangular specimens (10 (n=10 per group) and wet grinded with standard metallographic grinding paper (P500, P1000, and P1200). The specimens from the fractured cranioplasty were harvested from the center of the implant. Before testing the specimens were immersed in a water bath at 37.0 ± 1.0 °C for 50 ± 2 h. The flexural strength was determined at 37.0 ± 2.0 °C, using a three-point-bending test with a crosshead speed of 1.0 mm/min and a distance between the supports of 10.0 mm. Each specimen was tested until fracture. The ultimate flexural strength (σ) was calculated using the following equation:

$$\sigma = \frac{3\,F\,l}{2\,bh^2}$$

where F is the maximum load exerted [in newtons], l is the distance between the supports [in millimeters], b is the width and h is the height of the specimen [in millimeters].

Finite element analysis

The fractured cranioplasty (Figure 3) was visually inspected and a simplified 3D model was created to predict the stresses in the expected point of failure (Figure 4). More precisely, this point showed typical characteristics of an initial point of fracture, the so-called mirror-hackle zone [19,20], a groove originating near the edge of the implant, and an exposed pore located at the thinnest portion of this groove. Finite Element modeling was carried out using FEMAP software (FEMAP 11.1.0, Siemens PLM Software, Plano, Texas, USA); the analyses were performed with Nastran software (NX Nastran; Siemens PLM Software, Plano, Texas, USA).

The implant and surrounding bone were modeled into a sphere-like shape with an outside diameter of 140 mm. The thickness of the implant model was chosen as 4.5 mm, the average thickness of the fractured implant. The dimensions of the groove and exposed pore in the broken implant were measured using digital dial calipers (Mitutoyo, Kawasaki, Japan). The models were composed of 17,345 parabolic tetrahedron solid elements. The implant was fixed to the patients' cranial bone during surgery and held into place by surrounding tissues; therefore the interface between the implant and the surrounding bone was designed as fixed, allowing no movement in any direction. Material characteristics of the models were: PMMA: Young's modulus = 2158 MPa (experimental result of the fractured cranioplasty), Poisson ratio = 0.38; bone: Young's modulus = 15 GPa, Poisson ratio = 0.3. Two analyses were performed using different loads at the outside of the implant and perpendicular to the surface. One with a load of 100 N on the central node and one with a load of 100 N on the node opposite to the weak spot. The material properties used in the models are shown in Table 1.

Table 1: The maximum tensile stress (σ), in MPa, and the Young's modulus (E), in GPa, of the materials used in the models.

Material	σ	E
Bone	-	10
Implant	70	2.2

The maximum tensile stress (solid maximum principle stress) and the displacements in the implant and surrounding bone layer were calculated. In post-processing, the contour option 'average elemental', without use of the 'corner data', was used to visualize the results.

The amount of absorbed energy in the implant under load was calculated as follows:

$$E = \frac{1}{2} F\, tf$$

Where *E* is the absorbed energy [in joules], *F* is the applied load [in newtons], and *tf* is the displacement in the direction of the applied load [meters].

The absorbed energy upon hitting a flat surface was calculated using the following:

$$E = \frac{1}{2} m v^2$$

Where E is the absorbed energy [in joules], m is the mass [in kilograms], which was assumed to be 2.25 kg, half of the mass of the patient's head (4.5 kg [21]) as it is supported at one side, and v is the speed [in meters per second]. Using these equations, the corresponding speed was calculated at which an impact with a flat and hard surface would cause the maximum tensile stress required for fracture.

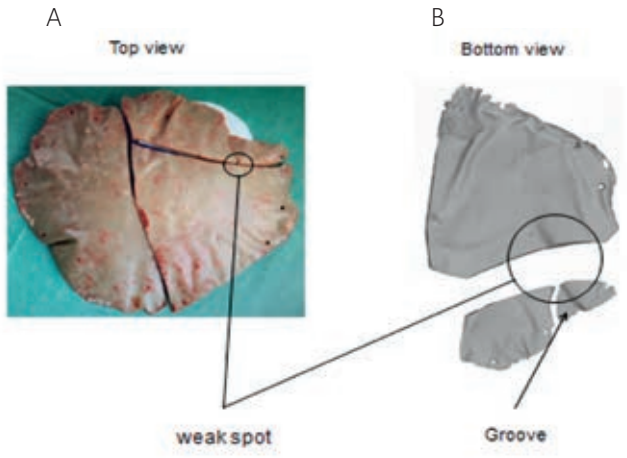

Figure 3: A)The fractured PMMA cranioplasty and B) 3D models created from the computed tomography data from the shards surrounding the suspected point of failure.

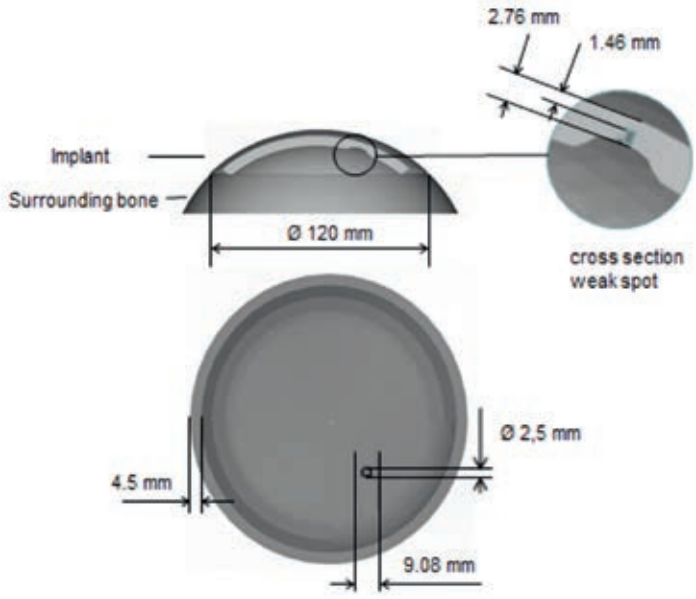

Figure 4: Simplified model of the cranioplasty before fracture.

Statistical analysis

The flexural strength data were statistically analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test ($\alpha = 0.05$) in SPSS version 24.0 (IBM, Armonk, NY, USA). Student's t-test was used to analyze the GPC data.

RESULTS

In this *ex vivo* study a CMW-3 PMMA fractured cranioplasty, which was part of the patient's cranium for 15 years, was compared to fresh specimens of CMW-3 cured at 2.2 bar and at atmospheric pressure. To determine whether the chemical, structural, and mechanical properties of CMW-3 change over time GPC, µCT, and flexural strength tests were performed. The fracture itself was analyzed using FEA.

Gel permeation chromatography

All samples were analyzed using RI detection since PMMA does not contain chromophores; the UV/Vis-PDA detector therefore, did not produce useful data (Figure 5). The number average molecular weight (M_n), weight average molecular weight (M_w), Z average molecular weight (M_z), and polydispersity index (PDI) are comparable for each group respectively (Table 2).The PDI was not significantly different for the fractured implant and CMW-3 ($p = 0.94$). No significant difference in M_n ($p = 0.76$), M_w ($p = 0.70$), or M_z ($p = 0.78$) was detected between the implanted material and CMW-3.

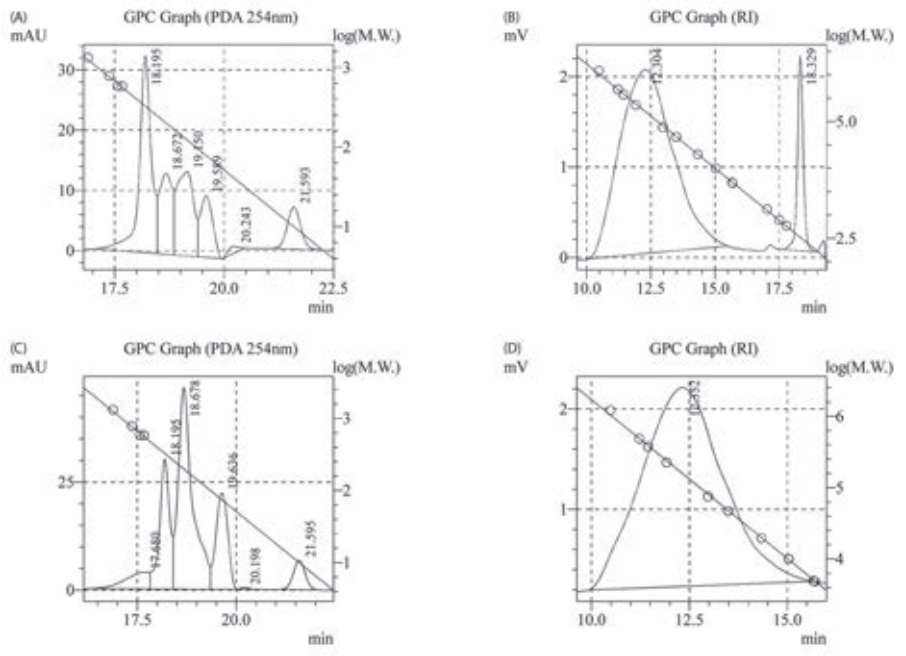

Figure 5: A and B) Representative gel permeation chromatography curves of the fractured PMMA cranioplasty, C and D) CMW-3. A and C depict the results from the ultraviolet/visible photodiode array detector at 254 nm, B and D depict the results from the refractive index detector.

Table 2: Representative gel permeation chromatography results of the implant and reference samples, M_n, M_w, and M_z data, in g/mol, are relative to polystyrene standards.

Material	Sample #	M_n	M_w	M_z	PDI
Implant	1	90,138	238,850	488,988	2.65
	2	96,789	245,156	504,793	2.53
	3	87,441	218,874	404,050	2.50
	4	87,706	241,354	487,383	2.75
CMW-3	1	88,232	234,735	471,701	2.66
	2	95,322	245,214	491,876	2.57

Porosity

The density of the fractured cranioplasty was 1.147 g/cm^3, while the densities of CMW-3 were 1.156 (cured at atmospheric pressure) and 1.246 g/cm^3 (cured at 2.2 bar). This results in a macroscopic porosity of 7.9% for the fractured cranioplasty and 7.3% for CMW-3 cured at atmospheric pressure. The µCT of the fractured cranioplasty showed a total porosity of 10.7%. The specimen of the CMW-3 cured at atmospheric pressure had a porosity of 4.1% and the specimen of CMW-3 cured at 2.2 bar had a porosity of 0.06%. (Figure 6)

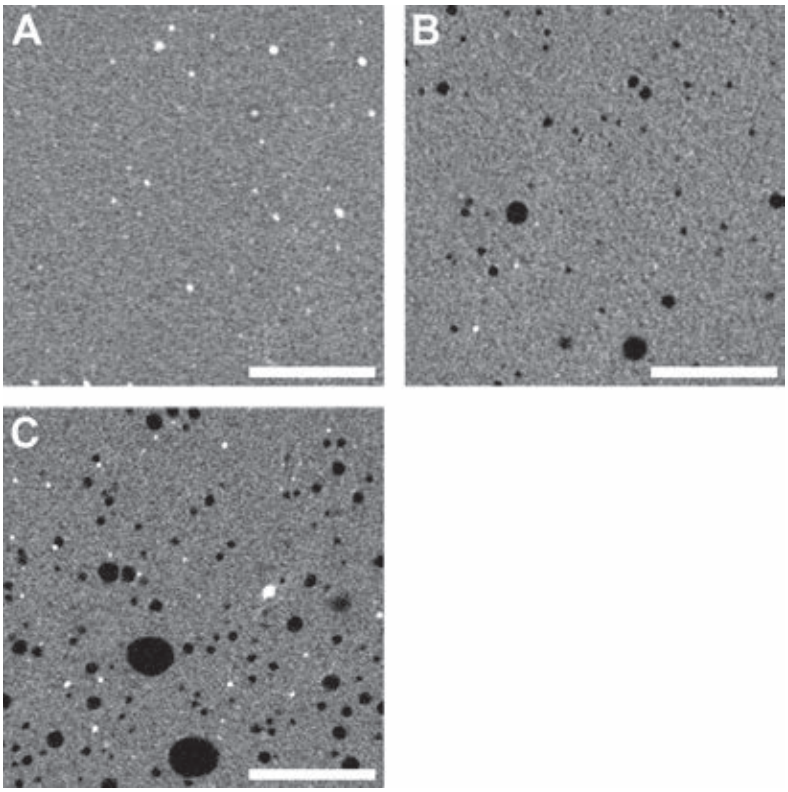

Figure 6: A)Representative micro-computed tomography slices of CMW-3 cured at 2.2 bar B), CMW-3 cured at atmospheric pressure, and C) the fractured cranioplasty. Pores are visualized in black and filler particles in white. Scale bar: 2 mm

Flexural strength

The results of the mechanical tests and statistical analysis are summarized in Table 3. The flexural strength of the fractured cranioplasty and CMW-3 cured at atmospheric pressure was not significantly different, however, the flexural strength of CMW-3 cured at 2.2 bar was significantly higher than both of the aforementioned groups.

Table 3: Flexural strength (σ), in MPa, of the fractured implant and control specimens.

Material	Pressure	σ
Fractured Implant	Atmospheric	61.4 (17.4)[a]
CMW-3	Atmospheric	72.1 (9.1)[a]
CMW-3	2.2 bar	92.5 (4.0)[b]

Values given as mean and standard deviation (SD). Identical letters indicate no significant difference between the groups. n=10 per group.

Finite Element Analysis

The maximum tensile stresses in the models under a load of 100 N in respectively the center and the weak spot in addition to the resulting translations are shown in Table 3 and Figure 7. The stress under the load of 100 N on the weak spot was 12.2 MPa. Since the material displays linear elastic behavior, a load of 503 N is needed to fracture the implant. This load corresponds with hitting a flat and hard surface at a speed of 0.42 m/s which results in a similar fracture stress.

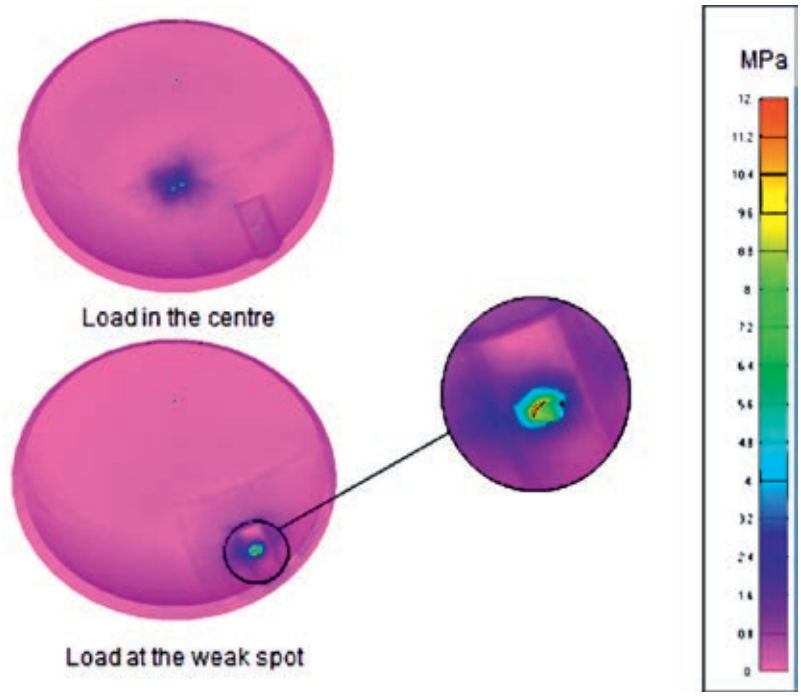

Figure 7: Tensile stresses, in MPa, resulting from a load of 100 N perpendicular to the top surface of the implant model. The implant model is depicted from a bottom view.

Table 4: Maximum tensile stress (σ_{max}), in MPa, and the total translation (l), in mm, resulting from a load of 100 N perpendicular to the top surface of the implant model at the specified location.

Location	σ_{max}	l
Center	3.8	0.091
Weak spot	12.2	0.159

DISCUSSION

This *ex vivo* study reports the material properties of a fractured PMMA cranioplasty made of CMW-3, after being part of the human cranium for 15 years, and fresh specimens of CMW-3. The following trends were observed: (I) the chemical and mechanical properties of CMW-3 did not significantly change during the 15 years *in vivo* (II) failure of the cranioplasty can be attributed to the heterogeneity in thickness and porosity (III) improvements in the mechanical properties of PMMA cranioplasties can be achieved by ensuring a consistent thickness of the cranioplasty, and by curing the implant under increased pressure.

Failed cranioplasties are generally not subjected to further investigations beyond basic microbiological evaluation in cases of infection. In our study, a single failed PMMA cranioplasty was analyzed and compared to fresh specimens of CMW-3. It is crucial to determine how the human body influences material properties of such implants over time, to ensure optimal clinical outcomes and possibly prevent further operations for the patient.

PMMA-based polymers have been used for many years in medical devices with their specific formulations and applications. It is used intra-operatively for fixation of artificial joints to bone, for dentures, and for cranial reconstructions[8–12]. The information on chemical and mechanical behavior of PMMA following long-term implantation in the cranium is scant. In the literature,1 patient was victim in a bicycle accident after cranioplasty which resulted in a fractured PMMA cranioplasty[22]. Marchac et al. included 32 patients who underwent a cranioplasty with PMMA, one cranioplasty was removed because of fracture due to trauma[23]. In another study a patient underwent a computer-based titanium mesh cranioplasty which fractured spontaneously. The authors hypothesized that the fracture of the implant occurred because of continuous pressure on the implant during the night, when the patient slept on the affected side[24]. Fracture is more frequently described in cranioplasties manufactured from hydroxyapatite[25,26]. Staffa et al.[25] reported 25 patients who all underwent a cranioplasty of hydroxyapatite, of which one cranioplasty fractured due to trauma. Stefini et al.[26] included 1549 patients with an hydroxyapatite cranioplasty, four were reported as fractured. The low incidence rate of fracture of cranioplasties could be due to underreporting of this complication in the literature. It is also possible that patients have no complaints and therefore do not notice the fracture.

The effects on molecular weight and mechanical properties for PMMA bone cements used for fixation of artificial joints is reported on in the literature. Hughes et al.[27] reported a 12% drop in molecular weight of Palacos® (Smith & Nephew Inc., London, United Kingdom) used for fixation of the hip following 15 years *in vivo*. The molecular weight of Simplex® (Stryker Howmedica Osteonics, Inc., Mahwah, New Jersey, USA), retrieved from hip fixation, was reduced by 46% after 23 years. After 16 years no significant reduction in molecular weight was found for Simplex® used for knee fixation[27]. CMW1 cement, retrieved from hip fixation, was stable *in vivo* and did not show a reduction in molecular weight, even after more than 20 years. In our study the molecular weight of CMW-3 did not significantly change during 15 years in the human cranium.

By manually manufacturing the cranioplasty during surgery, the local thickness and shape are difficult to control. The fractured PMMA cranioplasty in our study was manually manufactured and had a thickness of less than 3 mm at several locations, and point defects even up to 1.5 mm, carrying an inherent higher risk of fracture. Nowadays, this risk can be mitigated by the use of a 3D-printed nylon mold. After the mold is manufactured, it can be sterilized and used for reconstruction. During surgery PMMA can be cured following manufacturer's instructions and put into the mold when it is moldable. Because of the mold, the PMMA can be evenly distributed with a consistent thickness, which results in fewer weak points in the implant and should therefore make it more resistant to fracture. By using a mold the high temperatures reached during polymerization do not need to be suppressed to prevent damage of the underlying tissues, leading to a final implant with a higher degree of polymerization.[13–16] Preoperative, *ex vivo* manufacturing of a PMMA cranioplasty would allow for an even better control of the environmental conditions, especially increased pressure, during polymerization, which leads to a reduced PDI and improved mechanical and biocompatibility properties.

Macroporosity can occur when PMMA is prepared by hand due to air getting entrapped in the material. Using a vacuum system leads to a lower macro-porosity in PMMA. Similar trends are observed when reducing the speed of mixing and decreasing the amount of strokes. However, when PMMA is mixed under vacuum conditions the micro-porosity is increased as the boiling point of the liquid MMA component is lowered.[12] Our study shows reduced porosity in the CMW-3 cured at atmospheric pressure with the use of a 3D printed mold compared to the fractured implant and a further reduction in micro-porosity when cured at 2.2 bar. As reported in the literature, the flexural strength in our study is influenced by the porosity.[28] With increased porosity, the flexural strength is reduced. The location and distribution of the pores is important, as pores near the midline will experience lower stresses.

To understand why this PMMA cranioplasty fractured, FEA was performed. The FEA confirmed that the stresses increased from the center to the point defect under a load of 100 N. The load of fracture of 503 N will most probably not be reached in daily life as patients are assumed to be more vigilant and careful. However, hitting the head on a hard surface at a speed of 0.42 m/s might easily occur. The patient might not even remember such a minor incident, as the patient in this case could also not recall a trauma involving the cranioplasty. The FEA model is a simplified model, modelled only with the defect at the suspected weak spot and without underlying tissues. Only the bone surrounding the implant is included. The stresses and consequently the displacements are very concentrated and of such a low level away from the weak spot that detailing of the environment is not of significant influence (Figure 7). The pressure in the head in a normal healthy human ranges from 70 mm to 180 mm water column[29]. This pressure results into a upward load distributed over the entire implant, lowering the stresses but is hardly of influence on a concentrated load of 503 N.

These combined findings suggest that fracture of a PMMA cranioplasty is more likely to occur when features such as a reduced thickness, high porosity, and pores located near the surface are situated closely together, and an impact occurs at that specific location.

Limitations of this study

This study included only one PMMA cranioplasty for analysis. To have more reliable conclusions, a larger number of fractured PMMA cranioplasties should ideally have been included. In this study tissue formation, behavior, and changes in time have not been taken into consideration. These properties may be important and may influence failure rates in clinical circumstances, as such they should be investigated in future studies.

CONCLUSION

This ex vivo study shows that a CMW-3 cranioplasty after 15 years in vivo had not resulted in a change in molecular weight or flexural strength. However, the design and the manufacturing of the PMMA cranioplasty seem to be important factors for possible improvements in cranioplasties. By curing PMMA under increased pressure, the porosity is reduced As a result the flexural strength is increased.

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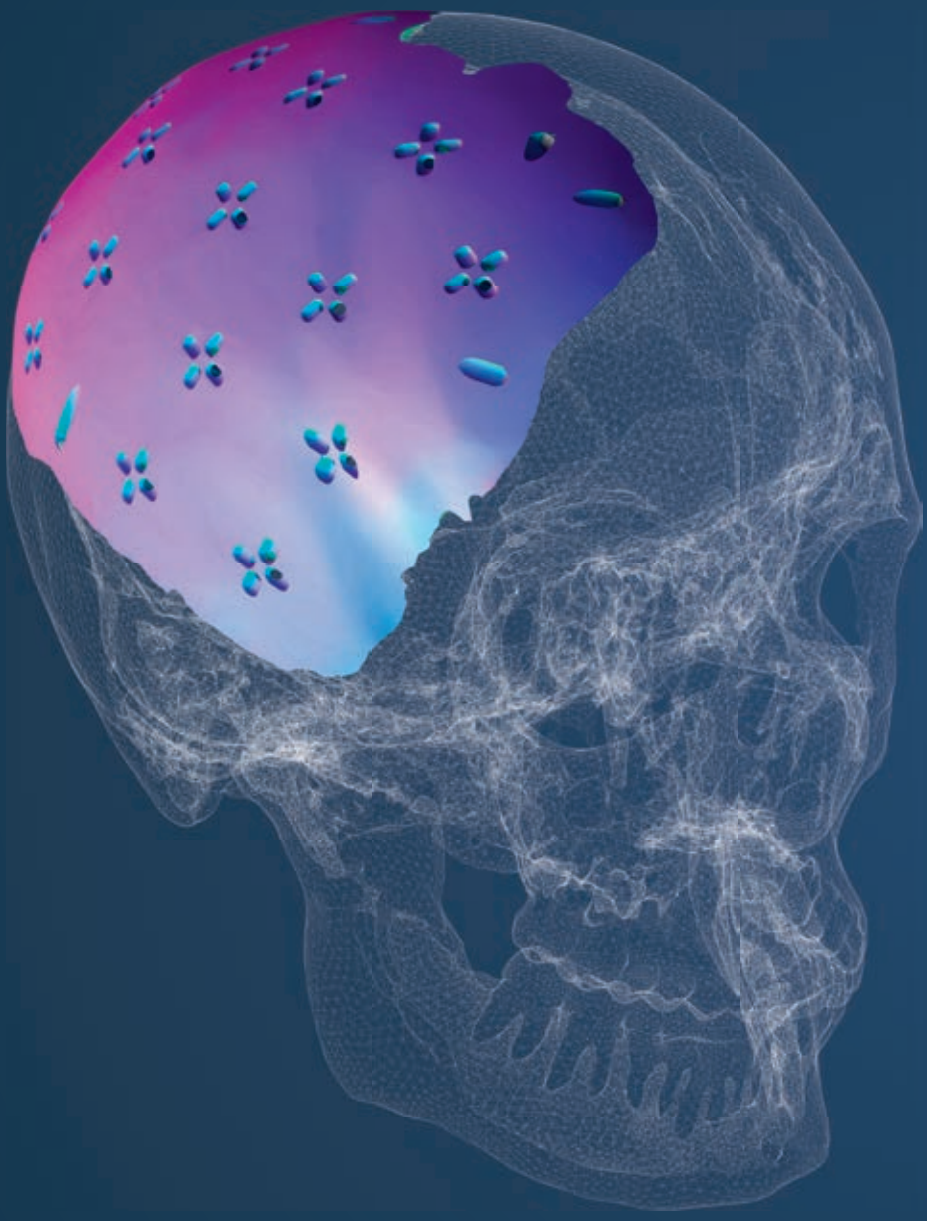

CHAPTER 5

Outcome in patient-specific PEEK cranioplasty:

A two-center cohort study of 40 implants

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This chapter is based on the publication:
Outcome in patient-specific PEEK cranioplasty: A two-center cohort study of 40 implants

Published: Journal of Cranio-Maxillo-Facial Surgery, 2016

ABSTRACT

Objective: The best material choice for cranioplasty following craniectomy remains a subject to discussion. Complication rates after cranioplasty tend to be high. Computer-assisted 3-dimensional modeling of poly(ether ether ketone) (PEEK) was recently introduced for cranial reconstruction. The aim of this study was to evaluate patient- and surgery-related characteristics and risk factors that predispose patients to cranioplasty complications.

Material and methods: This retrospective study included a total of 40 cranial PEEK implants in 38 patients, performed at two reference centers in the Netherlands from 2011 to 2014. Complications were registered and patient- and surgery-related data were carefully analysed.

Results: The overall complication rate of PEEK cranioplasty was 28%. Complications included infection (13 %), postoperative hematoma (10 %), cerebrospinal fluid leak (2.5 %) and wound-related problems (2.5 %). All postoperative infections required removal of the implant. Nonetheless removed implants could be successfully re-used after re-sterilization.

Conclusion: Although overall complication rates after PEEK cranioplasty remain high, outcomes are satisfactory, as our results compare favorably to recent literature reports on cranial vault reconstruction.

INTRODUCTION

Cranioplasty aims to repair a defect in the cranium and is one of the oldest neurosurgical procedures. Archeological evidence dates back to 3000 BC and suggests that the Incas performed skull reconstruction using gold plates[1]. In the 16th century Fallopius also recommended repair with gold plates[2] and one century later, in 1668, the Dutch surgeon van Meekeren reported on the repair of a cranial defect in a Russian soldier with bone derived from a dog skull[2].

Cranioplasty provides protection to the underlying brain and is performed for both functional and esthetic reasons. It aspires neurologic recovery, as described with reconstruction for the sinking scalp flap or syndrome of the trephined[3-8]. Disadvantages to delayed cranioplasty involve a temporarily unprotected brain as well as an aesthetic deformity[9]. Timing seems to be important in the neurological outcome of patients but also in avoiding complications[10]. Cranioplasty is most commonly performed after previous craniectomy for traumatic brain injury, stroke, after intracranial tumor surgery and intracranial infections[11-21].

Material choice for cranioplasty is still controversial, which brings complexity to this seemingly straightforward procedure[10,22-24]. Harvest sites for autologous bone grafts include iliac crest, rib, sternum, scapula and the skull[25]. At present, autologous bone flap replacement using the previously removed bone flap is the most common practice. Autologous bone does not exert immune rejection and is effective as a substrate for bone ingrowth and revascularization. Besides this autologous bone reconstruction has relatively low costs[26]. However, there is a risk of infection, resorption and in this case its strength gradually reduces. This has led to a search for synthetic materials[8,10,24,27-29]. At present, there are primarily 3 classes of allografts: metal, ceramic and polymer[30]. Titanium is the only metal still in use. It is a biocompatible material with a low infection rate [31]. Nonetheless titanium has certain disadvantages: the material is expensive and leads to artifacts on imaging[27,32]. Furthermore, it is a very strong material that shows no deflection in cases of traumatic stress and consequently it has no protective energy-absorbing properties[31]. Hydroxyapatite is a ceramic, which is known to be a good scaffolding material for bony ingrowth[30]. Unfortunately, it is rather limited for use in larger defects because of its brittleness and low tensile strength[33,34]. Poly(methyl methacrylate) (PMMA), a polymer, has been widely used because of its low cost, radiolucency and lack of thermoconduction. Nonetheless it is associated with complications such as infection, fragmentation and a lack of incorporation[27,35].

Computer-assisted design (CAD) and computer-assisted manufacturing (CAM) has been used to make titanium, hydroxyapatite and PMMA implants. Prefabrication of a patient-specific implant (PSI) reduces operation time and produces superb cosmetic results[30]. Recently, computer-assisted 3-dimensional modeling of poly (ether ether ketone) (PEEK), another polymer, has been successfully introduced for cranial reconstruction[36,37]. It is a strong and highly thermoplastic material. It resembles titanium in its perfect intraoperative fitting and its resistance to aggressive sterilization procedures (heat and ionizing radiation). On the contrary, the elasticity and energy-absorbing properties of PEEK match closer to bone than the mechanical properties of titanium. And unlike titanium, it is a radiolucent and a non-magnetic material, facilitating postoperative imaging[25,31,37-39]. PEEK has a few disadvantages: it has no bioactive potential and the costs related to the manufacturing of a PSI are high[39].

The aim of this study is to evaluate patient- and surgery-related characteristics and risk factors that predispose patients to an increased risk of complications after PEEK cranioplasty.

MATERIAL AND METHODS

Study design and patient population

This retrospective study included 38 consecutive patients who underwent 40 PEEK cranioplasties from 2011 to 2014 in the Academic Medical Center Amsterdam (24 cranioplasties) and the St. Elisabeth Hospital Tilburg (16 cranioplasties). Both centers used identical protocols and procedures for skull reconstruction by means of PSI. The current series included all patients who underwent PEEK cranioplasty. No patients were excluded. The study protocol was approved by the local medical-ethical review board (local protocol no. L87.2015; METC no. Nw 2015-38).

Data collection

Data collection included the following patient parameters: gender, age at time of PEEK cranioplasty, medical comorbidities (diabetes, cardiovascular disease, obesity (body mass index > 30), preoperative radiotherapy, smoking, indication for craniectomy (trauma, stroke, tumor, infection) and side of surgery (unilateral, bilateral, frontal). Surgical reports were carefully analysed with regard to the timing of cranioplasty. A difference was made between immediate and delayed cranioplasty. Cranioplasty was defined as 'immediate' when there was no interval between craniectomy or removal of previous cranioplasty with autologous bone or PMMA. Delayed PEEK cranioplasty was performed after after an interval of wound healing, leaving the brain temporarily unprotected. The time between previous surgery (craniectomy or cranioplasty) and PEEK cranioplasty was listed, as well as the number of surgeries prior to PEEK cranioplasty and the complication-rate after previous cranioplasty using autologous bone or PMMA. Other surgery-related data that were collected included preoperative shaving of the surgery site, incorporation of the previous scar into the skin incision or use of additional incisions, suspension of the temporal muscle, intraoperative placement of a subgaleal drain and operation time and the size of the defect. Defect size was measured with the use of 3D software (Maxilim software (Medicim NV, Mechelen, Belgium) and Autodesk 3ds Max 2012 (Autodesk Inc. USA)), which takes into account the curvature of the skull (Figure 1).

The main outcome parameters were defined as the presence of any complication after PEEK cranioplasty (infection, hematoma, cerebrospinal fluid (CSF) leak, wound-related problems) and the need for any medical (use of antibiotics) or surgical intervention (drainage of a hematoma, surgical repair of a CSF leak, use of a reconstructive skin flap, removal of the implant) after cranioplasty.

Follow-up reports of the neurological status of patients were studied. Patients who had a normal neurological status before and after PEEK cranioplasty were excluded. Patients or their relatives were contacted by phone to obtain a subjective evaluation of the evolution of the neurological status after PEEK cranioplasty. A simple rating scale was scored as follows: 1: significant neurological deterioration; 2: moderate deterioration; 3: no change; 4: moderate improvement; 5: significant improvement.

Preoperative planning

Computed tomography (CT) scans of the cranium were acquired using a high-resolution protocol as required for preoperative 3D planning and design of the PEEK implant (Xilloc Medical BV, Maastricht, the Netherlands, 29 cranioplasties; DePuy Synthes, Zuchwil, Switzerland, 7 cranioplasties; 3di GmbH, Jena, Germany, 4 cranioplasties).

Surgical procedure

Prophylactic antibiotics (intravenous Cefazolin 2000 mg) were administered 30 minutes before incision. A skin flap was raised and if present, an autologous bone flap or PMMA PSI was removed. After dural exposure the bony edges of the skull defect were exposed to fit the PEEK PSI (Figure 1). Pre-formed holes in the PSI were used for dural tack-up sutures. In recent PEEK cranioplasties, the need for additional miniplate fixation could be eliminated with the tangential InterFix technology (Xilloc), in which case the screws were tangentially directed into the bone edges. If indicated, the temporal muscle was suspended to the PSI through the pre-formed holes. In selected cases a subgaleal drain was placed. There was no consensus about the placement of a drain, so the decision was left to the preference of the surgeon and the present conditions. The skin was closed in two layers and a circumferential pressure bandage was applied. All patients underwent standard postoperative care.

Statistical analysis

Categorical data are presented as absolute values and percentages, continuous, normally distributed data as means and standard deviations (SD), while time intervals are presented as medians and interquartile ranges (IQR). Potential risk factors associated with complications after the use of PSI were extracted with Chi-square tests. A p-value ≤ 0.05 was considered statistically significant. Data analysis was performed using SPSS 23.0.

Figure 1. Clinical illustration
Left panel: Preoperative (*top*), early (*middle*) and late (*bottom*) post-operative photographs
Middle panel: 3D CT reconstruction of cranium and defect illustrating planning of PEEK reconstruction (blue).
Right panel: Intra-operative photographs showing right (*top*) and left (*middle*) PEEK cranioplasty nicely adapting to the contours of the defect; intra-operative photograph after closure (*bottom*).

RESULTS

Patient characteristics

Table 1 lists a detailed summary of patient and surgery-specific factors. In total 40 PEEK cranioplasties were performed in 38 patients. Two patients had bilateral cranial defects. The median follow-up period was 19.1 months (IQR 12.5-30.6). The average age at PEEK cranioplasty was 43.2 ± 18.1 years (range 8-84) with a male predominance (61% male). Fifteen patients (39%) had one or more associated comorbidities: cardiovascular disease in 10 (26%), obesity in 7 (18%) and diabetes in 2 (5%) patients. No patient had received radiotherapy. Ten patients (26%) were smokers at the time of cranioplasty. Indications for the primary craniectomy were stroke (39%), trauma (34%), tumor resection (21%) and infection (5%). Craniectomy resulted in unilateral convexity defects in 32 patients (84%), bilateral convexity defects in 2 patients (5%, Figure 1) and frontal defects in 4 patients (11%). Frontal sinus involvement was present in 1 patient.

Time to cranioplasty

Figure 2 gives a schematic overview of the management until final PEEK cranioplasty.

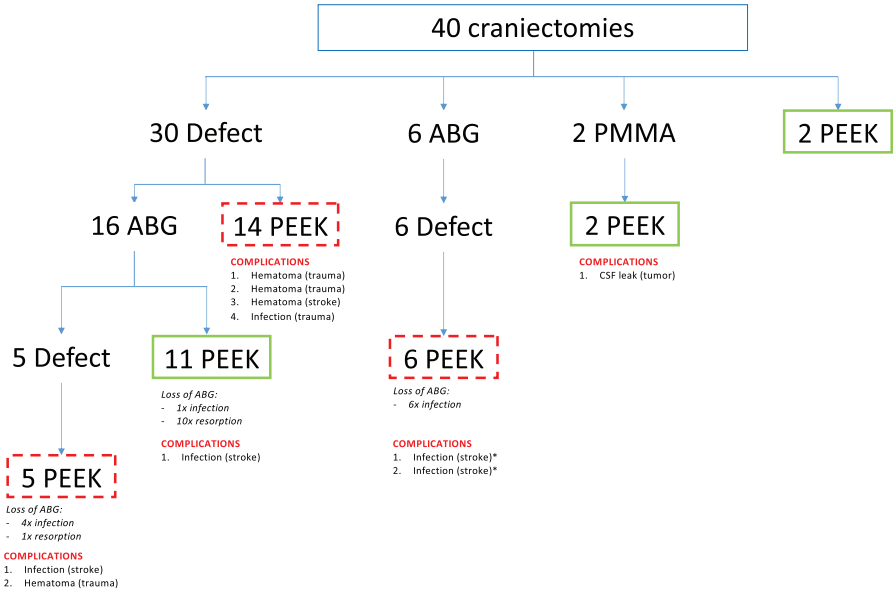
Twenty-two (55%) out of 40 autologous bone grafts were replaced, 6 of them at the time of craniectomy and 16 of them in a delayed fashion after preservation at -80°. These bone grafts failed due to infection (*n* = 11) or resorption (*n* = 11). Ten of the 11 infected bone grafts were treated with debridement and delayed cranioplasty. Ten out of 11 bone graft failures due to resorption were treated with immediate cranioplasty.

Eighteen (45%) of the 40 autologous bone grafts could not be replaced due to damage caused by trauma (*n* = 11), the presence of intra-osseous tumor tissue (*n* = 4), brain swelling or hemorrhage (*n* = 3). In two of these 18 cases, PMMA was used for reconstruction of the defect at the time of craniectomy. These implants failed due to a subcutaneous CSF collection. Two PSIs were placed at the time of craniectomy with removal of an intra-osseous tumor (meningioma) and 14 PEEK cranioplasties occurred in a delayed fashion.

The median interval between previous surgery and PEEK cranioplasty was 4.7 months (IQR 0-7.7). The mean number of surgeries prior to PEEK was 1.9 ± 1.1 (median 2.0, range 0-4). In 25 cases (63%) the implant sites were considered complex because more than one surgery was performed prior to PEEK cranioplasty.

Surgery-specific characteristics

The average cranial defect measured 106.3 ± 46.1 cm^2 (range 11-181). The largest craniectomy defects were found in stroke patients and after severe brain trauma. The operative field was shaved in 63% of surgeries. The previous scar was fully reused in 88%. An additional incision was made in 13% with a new incision in 8% and a partial reuse of the scar in 5%. In 50% of cases the temporal muscle was suspended to the PSI. A subgaleal drain was placed in 55% of the surgical procedures. The mean operation time was 126 ± 60.4 minutes (median 111, range 40-337).



ABG = autologous bone graft *: Final loss of PEEK cranioplasty

Figure 2. Schematic overview regarding cranioplasty timing
The complications after PEEK cranioplasty are given with the initial indication of craniectomy between brackets.
Solid border: immediate PEEK cranioplasty; 2 complications were seen in 15 cranioplasties.
Dashed border: delayed cranioplasty; 9 complications were seen in 25 cranioplasties.

Overall complications

Twenty-nine PEEK implants (73%) were without any complication. 11 complications were seen in 11 patients. Complications (28%) consisted of infection (n = 5), hematoma (n = 4), CSF leak (n = 1) and wound-related problems (n = 1). Ten cranioplasties (25%) required additional surgery. Three (epidural) hematomas were surgically evacuated, one CSF leak needed surgical repair and one patient had a skin flap necrosis, which was reconstructed with a latissimus dorsi flap. Five PEEK implants (12.5%) were removed due to infection. In three of these patients the same PSI was re-used after sterilization after 1.8, 3.8 and 8.0 months, without further complications. Two patients refused re-operation and consequently a permanent loss of PEEK cranioplasty was seen in 5%. There was no mortality observed within six months after PEEK cranioplasty. The overall infection rate after cranioplasty was 13%. *Staphylococcus aureus* was the predominant pathogenic microorganism in four of these five cases. One patient with a postoperative (subgaleal) hematoma received conservative treatment, without the need for additional surgical intervention. Postoperative subcutaneous seroma formation was observed in four cases and resolved spontaneously in all. The median time between PEEK cranioplasty and the presentation of complications was 35 days (n = 11, IQR 4.5-90.5).

Complication predicting factors

The number of complications associated with the patient- and surgery-specific factors is listed in Table 1. Statistical analysis of the different risk factors did not show a significant increase in complication rates.

There was no significant difference in mean age between patients who developed a complication (50 ± 18 years) and those who did not (40 ± 18 years). The presence of comorbidity did not seem to be related to a higher complications rate, except for patients with vascular comorbidity. They were more likely to get any complication than patients without vascular disease (40% vs. 25%). This was also found for smoking behavior (40% vs. 25%). Concerning the original indication for craniectomy, tumor patients were less likely to develop complications (13% vs. 33%) and stroke patients were more likely to get complications (40% vs. 22%). Although cranioplasty timing did not show statistical significance, we observed 9 of 11 complications (82%) in the delayed cranioplasty group. After previous cranioplasty with autologous bone, and even in those cases where autologous bone was lost due to infection, no association with higher complication rates was found. One case of skin flap necrosis was observed in a patient where additional incisions were made. When comparing PEEK PSI's with InterFix technology and other PSIs we did not find a significant difference in the complication rate (28% vs. 27%).

Neurological status assessment

Neurological status assessment is summarized in Figure 3. One patient was lost to follow-up (N/A). Eighteen patients had a normal neurological status before and after cranioplasty. Ten patients (53%) with neurological impairment showed no change in neurological status after PEEK cranioplasty. Eight patients (42%) showed a moderate improvement and one patient (5%) showed a significant improvement of the neurological status following PEEK cranioplasty. There were no patients showing neurological deterioration after PEEK reconstruction.

Table 1: Detailed summary of included patient and surgery-specific factors

	N (%)	Mean (± SD)	N of complications (%)
Patient characteristics	38 patients		
Gender			
Male	23 (61)		7 (30)
Female	15 (40)		4 (27)
Age (years)		43.2 ± 18.1	
Comorbidities			
Diabetes	2 (5)		0 (0)
Cardiovascular disease	10 (26)		4 (40)
Obesity	7 (18)		0 (0)
Preoperative radiotherapy	0 (0)		0 (0)
Smoking	10 (26)		4 (40)
Initial diagnosis			
Trauma	13 (34)		4 (31)
Stroke	15 (39)		6 (40)
Infection	2 (5)		0 (0)
Tumor	8 (21)		1 (13)
Defect site			
Unilateral convexity	32 (84)		9 (28)
Bilateral convexity	2 (5)		1 (50)
Frontal	4 (11)		1 (25)
Time to PEEK cranioplasty	40 implants		
Timing of cranioplasty			
Immediate cranioplasty	15 (38)		2 (13)
Delayed cranioplasty	25 (63)		9 (36)
Previous cranioplasty			
With autologous bone graft	22 (55)		5 (23)
Without autologous bone graft	18 (45)		6 (33)
Number of previous surgeries		1.9 ± 1.1	
Surgery-specific characteristics	40 implants		
Defect size (cm^2)		106.3 ± 46.1	
Shaving	25 (63)		5 (20)
Additional incision	5 (13)		2 (40)
Suspension of temporal muscle	20 (50)		6 (30)
Drain	22 (55)		8 (36)
Operation time (min)		126.0 ± 60.4	

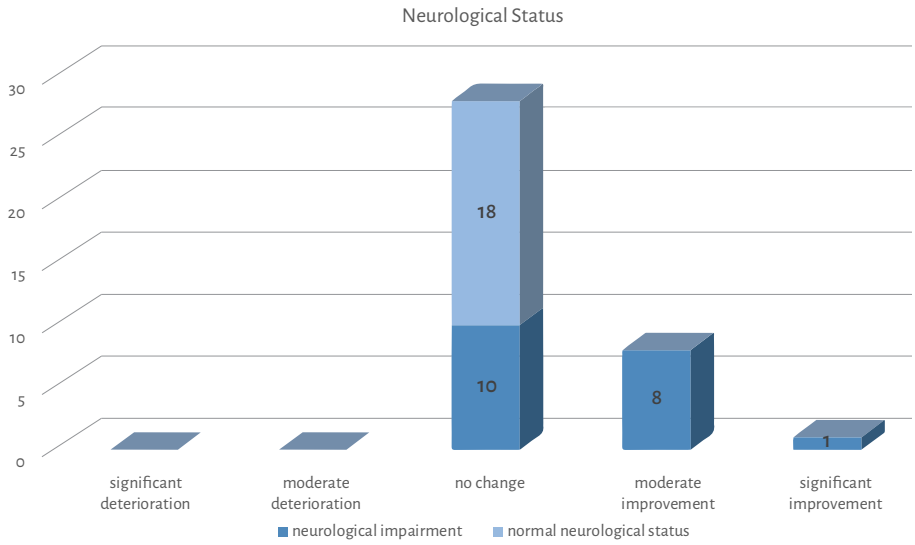


Figure 3. Neurological status assessment

DISCUSSION

Although the surgical technique of cranioplasty has been established a long time ago, complication rates are still relatively high and the best method to reconstruct large skull defects remains a matter of debate. This study describes our experience with PEEK cranioplasties.

In line with findings from previous large studies, we found that PEEK cranioplasty is associated with a significant risk of post-operative complications[22,27,45,49]. Literature to date mainly focuses on failure rates and re-operation rates are rarely reported.

Large studies on autologous cranial grafts report failure rates up to 40% due to resorption or infection (defined as an infection requiring removal of the bone graft) [27,40-43]. Resorption did not occur with PEEK cranioplasty. The infection rate in our series (defined as the invasion and multiplication of micro-organisms that are not normally present within the body) was 13%, which is comparable to the reported infection rates after autologous and allograft cranioplasties[10,22,27]. In line with the literature, *S. aureus* appeared to be the most common pathogenic microorganism[44-46]. Although infection rates in this study were comparable to infection rates after autologous cranioplasties, PEEK has the important advantage of the possibility to be repeatedly sterilized with no significant changes in its mechanical behavior[37]. Therefore most of the implants could be replaced after a period of time and final loss was only recorded in two patients who refused re-operation (5%).

Patient characteristics

A non-significant, but positive relation between age, vascular comorbidities, smoking behavior and complications was found in our study. A relationship with other medical comorbidities was not found. The association between age and complication rates is well known[47,48]. Conflicting results on associations with medical comorbidities have been reported in the literature[27,40,48].

With regard to the initial indication for craniectomy, stroke patients were more likely to get complications after PEEK cranioplasty; this is consistent with literature findings and most likely reflects age in combination with (vascular) comorbidities[47,48]. Remarkably, cranioplasty in tumor patients was associated with a trend towards a lower infection rate, which contrasts to the literature reporting higher complication rates in tumor patients due to perioperative corticosteroid treatment, nutritional problems and chemo- and/or radiotherapy[22,47]. Tumor patients in our series however had a meningioma and did not receive chemotherapy nor radiotherapy.

Time to cranioplasty

Timing of cranioplasty is a controversial issue. The main argument for early cranioplasty is to avoid the syndrome of the sinking scalp flap. Furthermore, early cranioplasty is often advised because of easier tissue dissection and the possibility of early active rehabilitation, but can be contraindicated in contaminated wounds[10,47,49]. Likewise we performed a delayed cranioplasty when the autologous bone graft was lost due to infection and immediate cranioplasty when the autologous bone graft was lost due to resorption. Recent literature reports however did not show a difference in complication rates between early and late cranioplasties[10,50]. In our series, delayed cranioplasty tends to predispose to an increased risk of complications in comparison to immediate cranioplasty. One explanation could point towards the more arduous tissue dissection due to the formation of adhesions between the dura and subcutaneous tissues. Current literature also reports higher complication rates in patients who have had two or more previous surgeries[40,45], a finding we could not confirm in this study.

Surgery-specific characteristics

No association was found between the complication rate and defect size, shaving of the operation site and suspension of the temporal muscle. Due to an extensive vascularization, scalp wounds usually heal well and are not very susceptible to necrosis. We recorded one case of skin flap necrosis as a result of multiple previous surgeries with additional incisions compromising blood supply. In contrast with the literature[27,40,50], an increased operation time was not associated with an increased complication rate. We could not relate the placement of a drain to the formation of a postoperative hematoma on the one hand, nor to the development of a postoperative infection on the other hand[22,47]. Moreover the indication for drain placement can be biased towards more complex cases.

Neurological status assessment

Although the rating scale used for neurological assessment after PEEK cranioplasty was a simple ordinal scale based on subjective judgment, our results suggest a (moderate) improvement of the neurological status in several cases. An unprotected brain has to function under the atmospheric pressure which can result in a local vascular dysfunction, also known as the syndrome of the sinking scalp flap or syndrome of the trephined [3,5,6]. A cranioplasty can thereby improve cerebral blood flow, resulting in an improvement of the neurological status and recovery[5,6]. Consequently, cranioplasty may not only be useful for cerebral protection and aesthetic improvement, but the current data also suggest that cranioplasty can result in neurological improvement.

Limitations

The small sample size leads to an inherent low statistical power and therefore no firm conclusions can be drawn. No direct comparison with different cranioplasty techniques was made. The present study also poses certain limitations due to its retrospective nature; complications were necessarily obtained from file studies. Prospective trials are needed to further elucidate the relationship between specific risk factors and the outcome after PEEK cranioplasty.

CONCLUSION

Cranioplasty carries a significant risk of postoperative complications, not infrequently requiring reoperation. PEEK cranioplasty showed comparable complication rates to the literature reporting on cranioplasties using autologous bone grafts or allografts. Outcomes after cranial vault reconstruction using PEEK implants however compared favorably because of the advantage of re-sterilization and possibility of reuse.

Acknowledgement

The authors thank L. Dubois, MD, DDS, PhD, oral and maxillofacial surgeon, for participating in the surgical management of some of the included patients.

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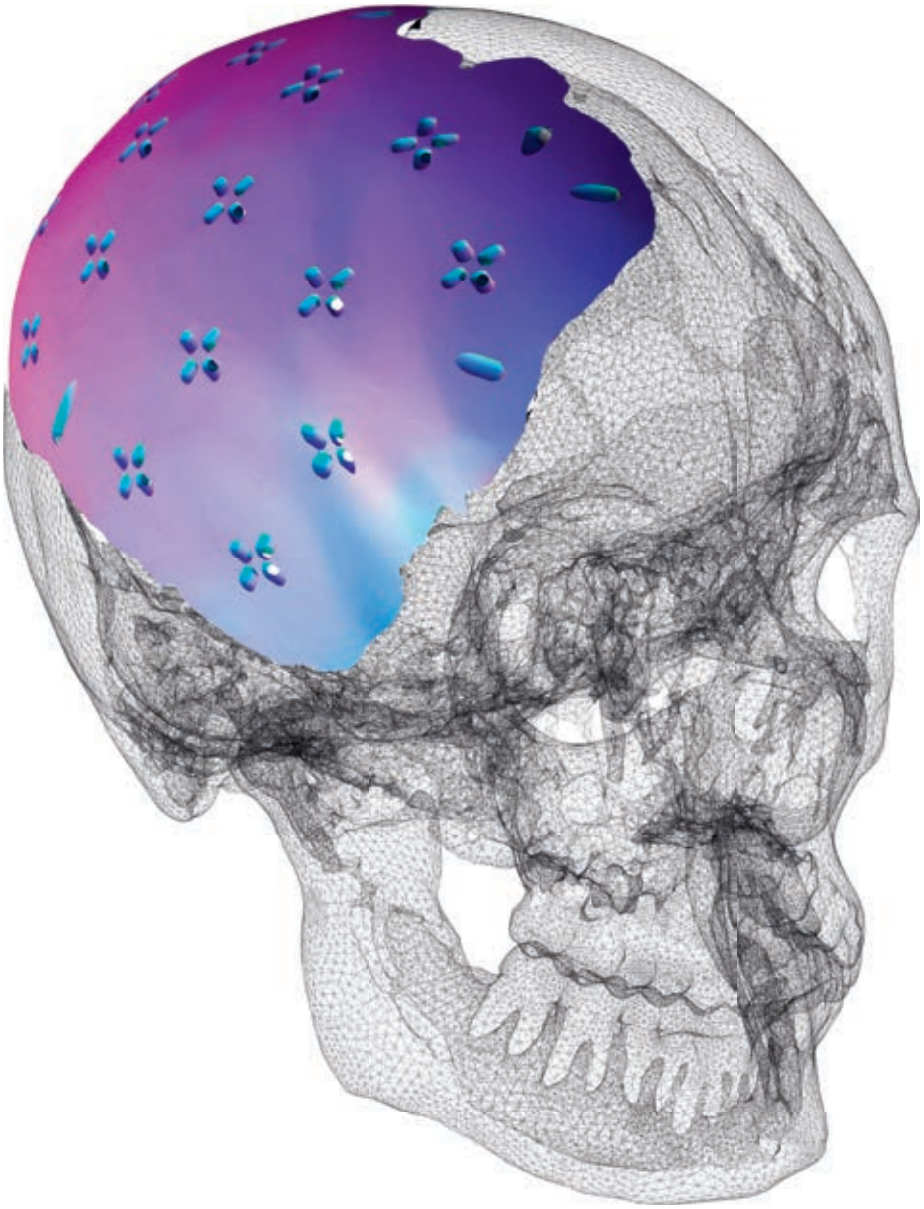
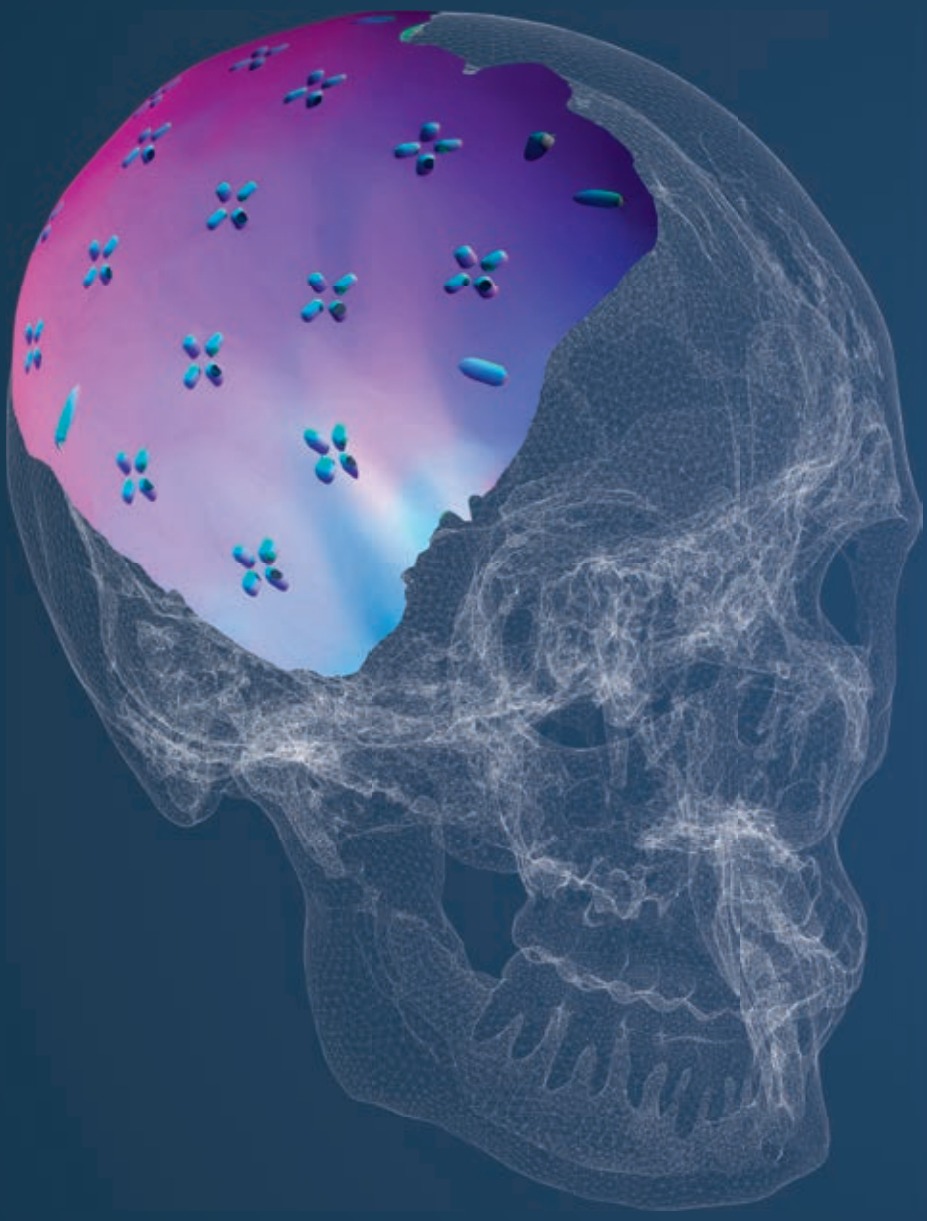


PART IV

Towards a new approach



CHAPTER 6

The use of cranial resection templates with 3D virtual planning and PEEK patient-specific implants

S.E.C.M. van de Vijfeijken, R. Schreurs, L. Dubois, A.G. Becking; on behalf of the CranioSafe Group

This chapter is based on the publication: The use of cranial resection templates with 3D virtual planning and PEEK patient-specific implants: A 3 year follow-up.

Published: Journal of Cranio-Maxillo-Facial Surgery, 2018

ABSTRACT

Purpose: The aim of this study was to evaluate the accuracy of resection templates in cranioplasties to facilitate a one-stage resection and cranial reconstruction.

Patients and methods: In three cases, cranial resections were combined with direct reconstructions using the principles of computer-assisted design, manufacturing and surgery. The precision of the resection template was evaluated through a distance map between the planned and final result.

Results: The mean absolute difference between the planned and actual reconstructed contour was less than 1.0 mm. After 3 years, no clinical signs of infection or rejection of the implants were present. The computed tomography scans showed no irregularities, and the aesthetical results remained satisfactory.

Conclusion: One-stage resection and cranial reconstruction using a resection template, control template and a prefabricated patient-specific implant of poly(ether-ether-ketone) (PEEK) proves to be a viable and safe method.

INTRODUCTION

The skull is a complex part of the skeleton, with convex and concave areas. It protects the brain from external impact and can be seen as the base for the facial skeleton. During decompressive craniectomy, a part of the cranial vault is removed for surgical access to reduce intracranial pressure caused by trauma, tumor, haemorrhage and empyema[1].

The removed part of the cranial vault can be re-inserted immediately after decompressive craniectomy. In some cases this is not possible because of swelling or increased intra-cranial pressure. In this situation the cranial reconstruction will be performed at a later stage, when the patient is neurologically stable[2]. Resorption and infection are frequently seen in cranial reconstruction, which makes removal of the affected cranial vault necessary[3]. The remaining defect may cause both functional and aesthetic problems, making reconstruction necessary. Ideally, the appropriate cranial reconstruction does not affect the patient's anatomy, thus ensuring optimal fit and contouring.

The design of a patient-specific implant (PSI) can be based on the patient's Computed Tomography (CT) data, using computer-aided design, manufacturing and surgery (CAD/CAM-CAS). Small inaccuracies in the design can lead to an impaired intra-operative fit. CAS aims to predict and mitigate intraoperative obstacles, ensuring an optimal fit of the PSI. If removal of the autologous bone is required, the original outline of the cranial defect may be difficult to predict. An example is the presence of persistent bony bridges in case of partial resorption of the autologous bone flap (Figure 1A). A resection template may be used to create a predetermined outline (Figure 1B and 1C).

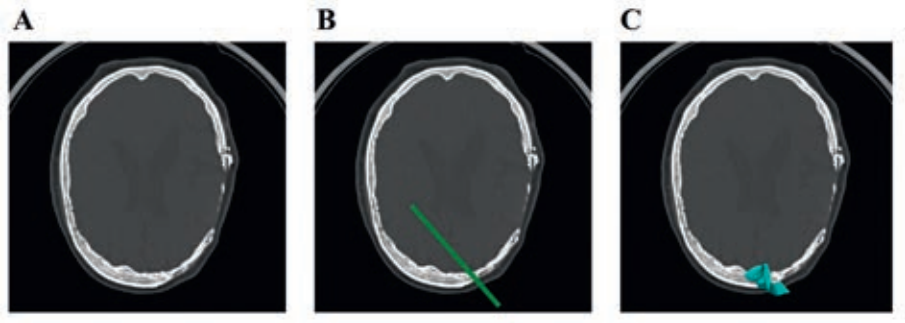


Figure 1: CT axial slice with A) resorption of autologous bone B) resection outline C) planned resection template.

In a non-acute setting, as in tumor removal, a combined craniectomy and cranioplasty can be preoperatively planned with the use of CAD/CAM-CAS. In preoperative virtual planning, a resection template may be designed to enable a one-stage surgical procedure for resection and reconstruction with a PSI. This prevents a lidless period (in which the patient needs to wear a helmet), avoids the need for a second surgical procedure and may lower complication rates and costs. In this study, the accuracy of resection templates for cranioplasty is critically evaluated with the aim in developing a reliable fail-safe and time-sparing cranial reconstruction using CAD/CAM-CAS technology.

Material and Methods

Three consecutive patients underwent cranial resections and reconstructions with the use of resection templates, control templates and a pre-fabricated PSI of poly(ether ether ketone) (PEEK).

Patient one: This 60-year old female, underwent a right temporal decompressive craniectomy because of acute subdural hemorrhage after trauma. She used acenocoumarol for atrial fibrillation and has hypertension in her medical history. After 4 months, the patient was neurologically stable and underwent a cranial reconstruction with autologous bone which, was stored in a bone bank at -80°C. Twenty-two months after reinsertion of the autologous bone the patient complained about headache and vertigo. A CT-scan was performed and resorption of the autologous bone was observed (Figure 2A). Removal of the autologous bone was planned in the same procedure as the insertion of the PSI with the use of resection templates (Figure 2B, 2C). After the reconstruction, a post-operative CT-scan was acquired to verify the position of the implant (Figure 2D). A distance map was generated between the planned position of the PSI and the achieved location post-operatively for quantification of the result (Figure 2E).

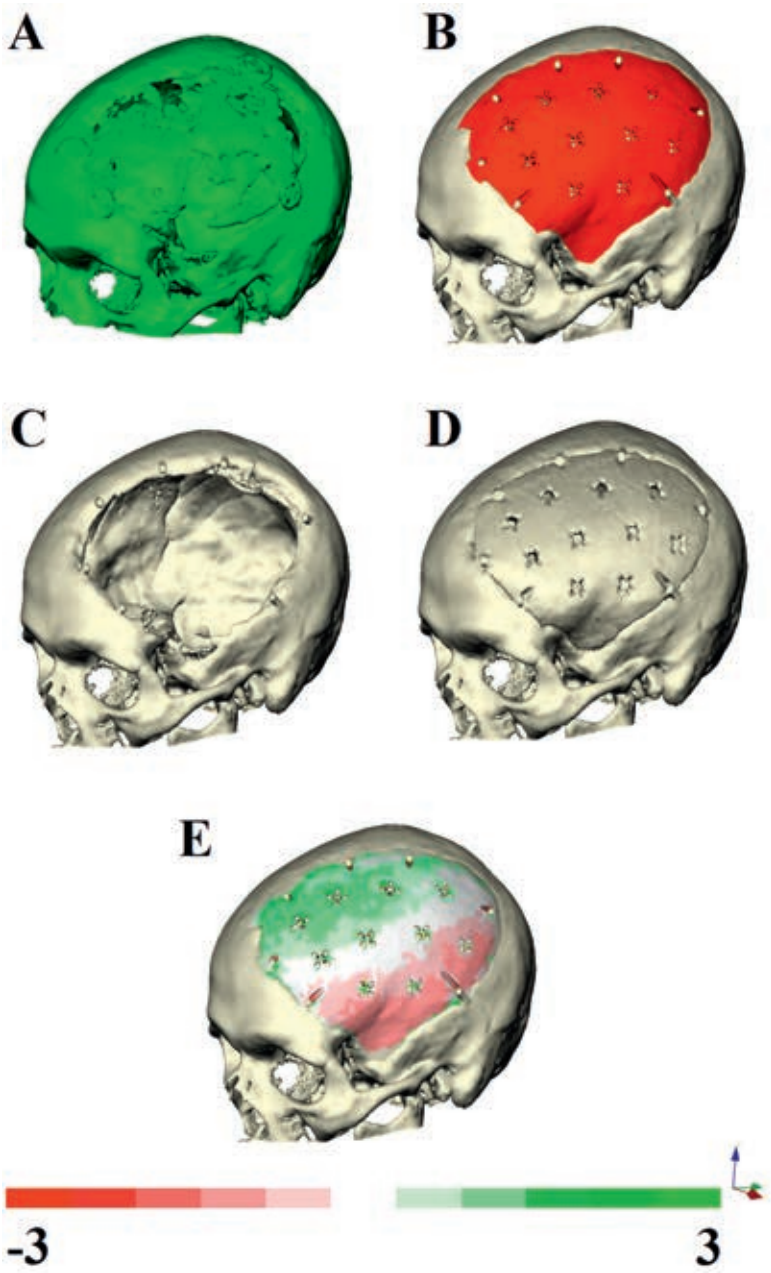


Figure 2: A) Resorption of autologous bone / bony bridges B) Preoperative planned patient specific implant of poly (ether ether ketone) (PEEK) C) Post-operative resection D) Post-operative inserted PSI E) Distance map between the planned contour of the patient specific implant and the achieved contour postoperatively. Green indicates a positive displacement; red indicates a negative displacement.

Patient two: This 45-year old male underwent a craniotomy because of a left frontal ossifying meningioma. He had obstructive sleep apnea in his medical history. After six weeks, the autologous bone was removed due to infection and an antibiotic treatment was started. Sixteen months later, when the patient was medically and neurologically stable, the cranial reconstruction was planned. Since bone resorption was observed on the CT-scan a resection template was used to create a clear outline of the defect (Figure 3). The PSI of PEEK was inserted immediately without intra-operative adjustments to the PSI.

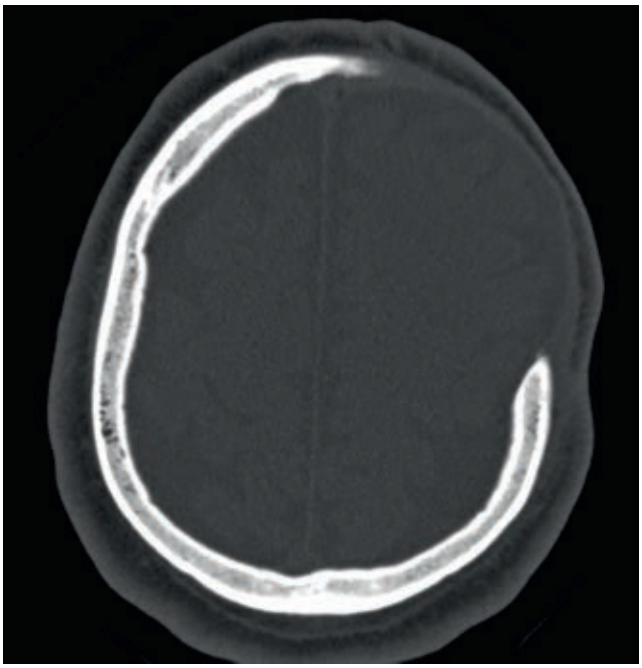


Figure 3: Axial slice of the CT-scan of the skull contour without patient specific implant

RESULTS

Patient three: This 40-year old female, without co-morbidities, was diagnosed with a left frontal ossifying meningioma and was scheduled for one-stage resection and reconstruction with a PEEK PSI. The actual procedure is described in detail on the next page:

Representative case of one-stage resection and reconstruction

Preoperative planning

A CT-scan (Philips Brilliance 64, 120 kV, 285 mAs, 25x15 cm FOV, 512x512 matrix size, 1.0 mm slice thickness, 0.5 mm slice increment, kernel D (hard-tissue)) of the cranium was acquired for preoperative planning (Figure 4). A volumetric segmentation of the meningioma was defined and the resection of the meningioma was planned with a 2.0 cm margin. To create a symmetrical and aesthetically satisfying PSI, mirroring was applied to overlay the unaffected, contralateral half of the cranium on the affected side. The resection template was designed based on the planned resection and existing patient's anatomy. A second template with a shape identical to the PSI (control template) was designed to fine-tune the resection and verify that the PSI would fit in one try (Figure 4).

After agreement on the design of the PSI, it was fabricated in poly(ether ether ketone) (PEEK) using a milling technique (Xilloc Medical BV, Geleen, the Netherlands). The resection template and fitting template were 3D printed in nylon using selective laser sintering.

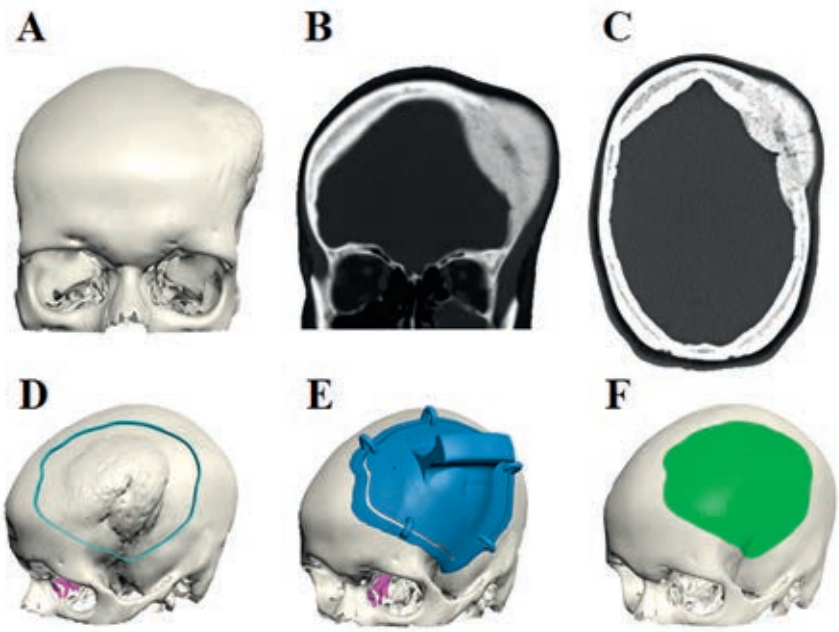


Figure 4: A) 3D rendering of CT data, B) CT coronal coupe, C) CT axial slice. Preoperative planned, D) resection outline of the meningioma, E) nylon resection template, F) patient specific implant designed by using a mirroring technique

Surgical procedure

Intraoperatively, the meningioma was surgically exposed and the temporal muscle was partially detached from the orbit and pterion (Figure 5A). The resection template was temporarily fixed with ten 10 mm screws. The resection of the meningioma was performed with a piezo-surgical instrument (Figure 5B). The resected meningioma and pathologically involved dura mater were consequently removed (Figure 5C). A subgaleal flap was transferred and sutured to close the dural defect. The control template was used to resect excess bony ledges that would hamper a good fit. Tangential burr holes were created following the InterFix® guide and the PSI was fixed to the surrounding bone (Figure 5D). The temporal muscle and fascia were partially sutured to the PSI with Xsuture® (Figure 5E). Total operating time was 430 minutes. No intra-operative complications occurred. After three years, no clinical signs of infection, haemorrhage, or other complications relating to the implant were observed. The aesthetic result remained satisfactory as subjectively judged by patient and clinician. The post-operative CT-scan showed no irregularities.

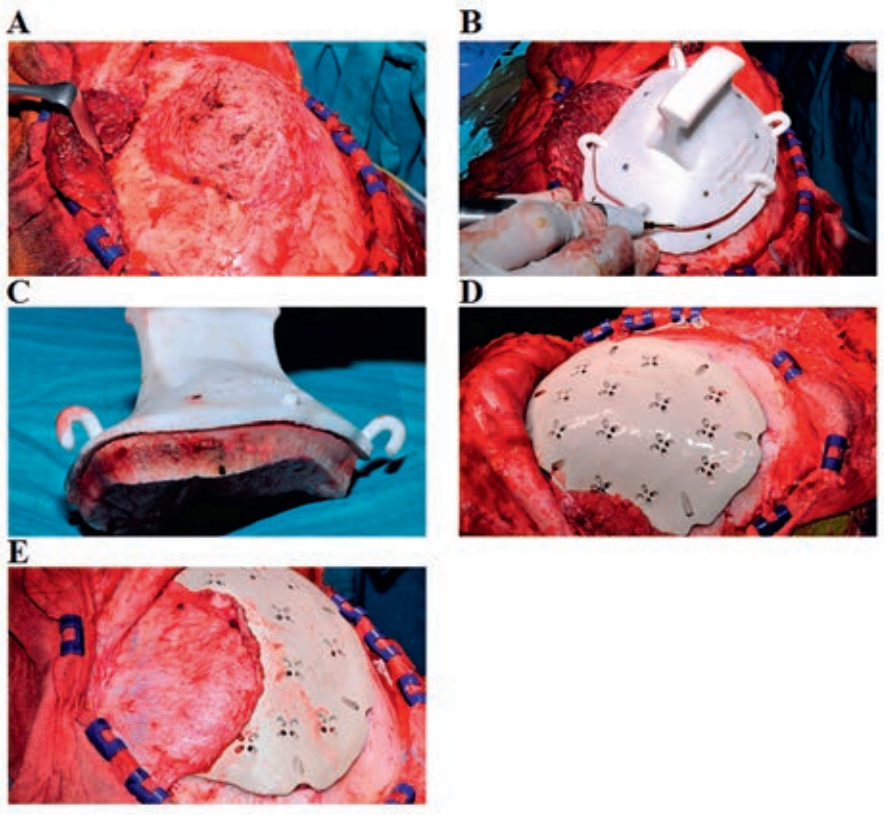


Figure 5: Intra-operative photographs of A) exposed meningioma, B) fixed nylon resection template, C) total resection of the meningioma, D) fixed PEEK patient specific implant, E) suspension of temporal muscle.

DISCUSSION

This study reports the use and accuracy of resection templates and control template in cranial reconstructions. Cranioplasty with autologous bone has a relatively high complication rate. Resorption and infection are the most mentioned complications in literature, that lead to removal of the cranioplasty[1,3,4]. One-stage reconstruction can reduce postoperative complications, due to an accurate fit of the PSI, avoidance of a second procedure, and a reduction in overall operating time.

A representative case of a total resection of an ossifying meningioma and reconstruction with a PEEK PSI in a one-stage surgical procedure using a resection template is described in detail. This technique has been developed to reduce the burden on the patient. Since only one surgical procedure is required, hospitalisation time is reduced and no helmet needs to be worn during revalidation. During surgery, this technique prevents extensive intra-operative positioning, achieves an accurate PSI fit (absolute mean difference <1.0mm), and seems to reduce operation time. In this case, after three years, no complications were observed and the aesthetic result was satisfactory.

The procedure is relatively new, although similar techniques are described in literature[5–8]. In this study, the resection outline of the meningioma was virtually preplanned according to the CT-scan. Other studies describe intermediary steps. For example, the craniectomy of the affected bone is pre-planned on a plaster head phantom based on a CT-scan. This allows the surgeon to draw the outline of the desired resection on the phantom[5]. Other surgeons perform the craniectomy on the gypsum phantom, acquire a CT-scan of the phantom with the defect, and a silicon mold is created based on this CT-scan[6].

The use of the indirect molding technique is well described in the literature. With the use of a CT-scan and mirroring technique a mold of different materials can be created[6,7]. Different techniques to fabricate the final PSI are mentioned. Poly (methyl methacrylate)(PMMA) can be mixed by hand intra-operatively and casted into the mold. Post-processing of the implant on the operating room is required because the burrs will prevent a good fit. Due to limitations in the operating room, post-processing is performed with a surgical knife[7]. The preoperative manufacturing of PSI of PMMA is also described[8]. This reduces the aforementioned limitation, yet still often is fabricated by an indirect molding technique[9].

The cranioplasty in this study is made of PEEK, a relatively new material used for this purpose. PEEK shows good chemical resistance because of its resonance-stabilized and aromatic structure[10], has long term stability in wet environments, and can resist temperatures up to 260°C[11,12]. PEEK can be sterilizedin an autoclave or with gamma-sterilization without significant changes to the material properties; it can be repeatedly sterilized[13,14]. It is radiolucent without artefacts on (postoperative) imaging[15]. The mechanical properties of PEEK are comparable to cortical bone; biocompatibility is good without release of ions or constituents. These properties make PEEK a suitable material for medical implants[15,16]. PEEK is a versatile material, suitable for CAD-CAM technology using a direct production method: no mold or intra-operative production procedures are necessary[17].

PEEK is not bioactive, so a PEEK surface will not integrate with the surrounding tissues as bone. PEEK cranioplasty is recommended to be used with fixation material, e.g. osteosynthesis[15,16]. The risk of infection is one of the main disadvantages and the most important complication reported in literature[18]. Higher costs are an important issue too. A PEEK PSI, including a resection template and a control template, adds up to approximately 7500 EUR including work-up in the Netherlands. However, the preoperative planning time is approximately 1 hour. With only one procedure is needed, total cost and surgical time are likely lower compared to a two-staged surgical procedure. Raw PEEK is a relatively expensive material which has to be milled; in this process, a great portion of the material becomes unusable[19].

Other designs for resection templates in cranial defects have been recently described. In the design of Carolus et al., only the outline of the resection is established in the template[20]. In our study the resection template forces the surgeon to follow the resection outline through the use of an inner and outer piece of the template. The inner part of the resection template ensures that the meningioma can removed in one piece (figure 4C). The design of the resection template is important to make the surgical intervention easier and reduce operation time.

A one-stage approach, with the use of saw templates, is used in other surgical, for instance in secondary orbitozygomatic complex reconstruction after trauma[21,22,23,24,25]. Fixation of the resection template is planned on the existing screw hole positions to ensure accurate resection and enable subsequent reconstruction. The saw template technique is also used to combine resection and reconstruction in head and neck oncologic resection with bony mandibular reconstruction with vascularized fibula grafts [24,5]. Three surgical guides can be designed for different intra-operative steps in this comprehensive procedure: a resection template for the resection of the mandibular tumor, a resection template for the execution of the fibular osteotomy, and a reconstruction template for the final reconstruction[22].

Evaluation of the accuracy of templates is describes in several studies[21,25,26]. Weijs et al. calculated the difference in angulation of the screws and actual resection plane compared to the planned resection in oromandibular reconstructions[25]. Mascha et al. evaluated the accuracy of oromandibular reconstructions by measuring distances between corresponding landmarks on the mandibular rami on the pre- and postoperative CT-scans[26]. Here, the accuracy was calculated with the use of a continuous distance map of the PSI compared with its planned location.

Conclusion

One-stage craniectomy and reconstruction using a prefabricated resection template, control template, and PEEK PSI seems to be a viable and safe technique. Resection templates enable the use of a PSI for secondary cranial reconstruction in a one-stage surgical procedure. It can reduce operation time and number of surgical procedures, and may reduce cost. A major advantage for the patient is absence of a lidless and risky period, with an immediate aesthetically satisfying result.

Acknowledgment

Special thanks goes to R.D. Vreeken, 3D specialist in oral and maxillofacial surgery, and Dr. A.R. Wittkampf, oral and maxillofacial surgeon, for sharing their experience in this field.

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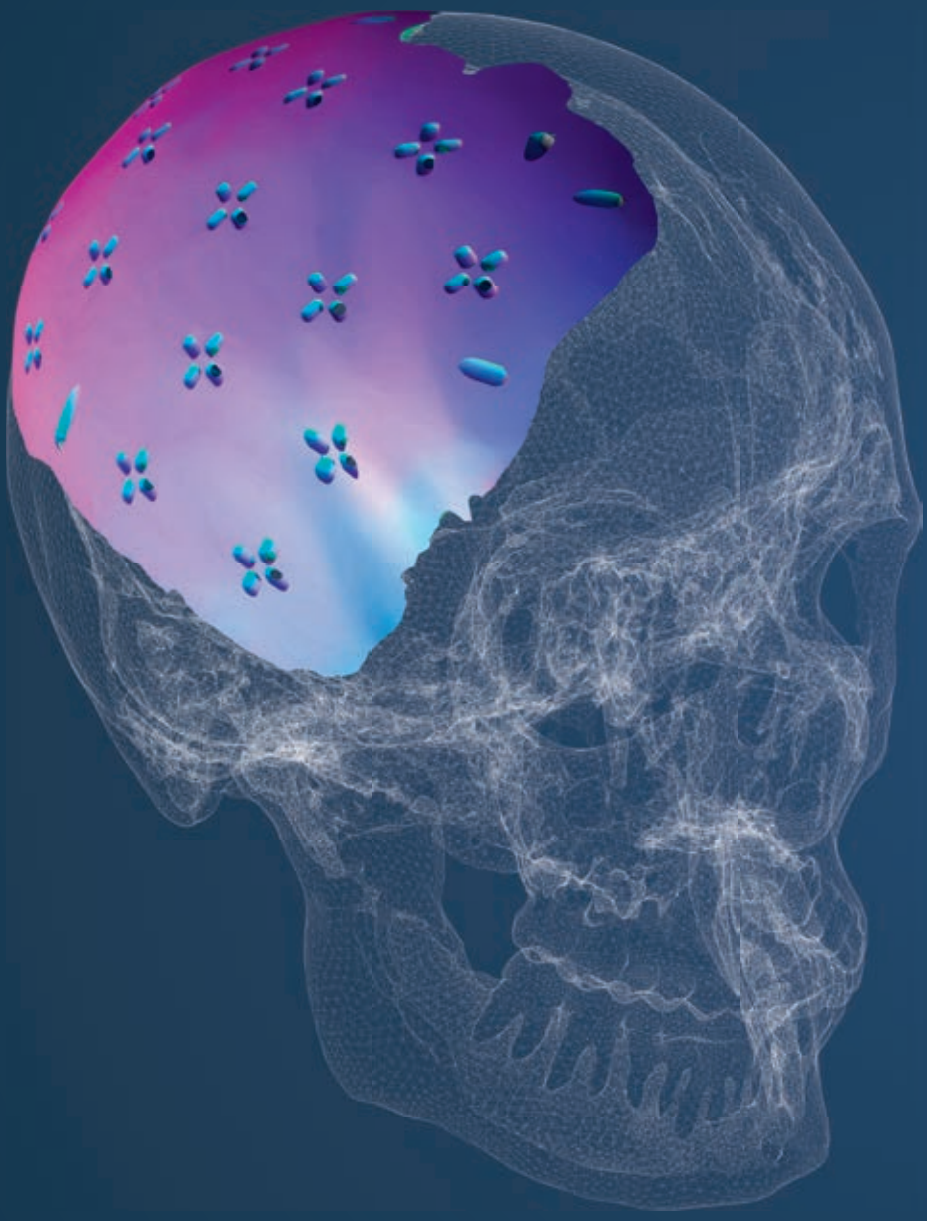

CHAPTER 7

Is 3D virtual planning in cranial reconstruction for advanced cutaneous squamous cell carcinoma of the skull an option?

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This chapter is based on the publication: Is 3D virtual planning in cranial reconstruction for advanced cutaneous squamous cell carcinoma of the skull an option?

Submitted

ABSTRACT

Background: Cutaneous squamous cell carcinoma is a common type of malignant skin disorder. An uncommon feature is local bony invasion, as can rarely be seen in lesions on the scalp. The optimal treatment strategy in these rare cases is still under debate.

Objective: The aim of this case report is to present a one stage 3D planned surgical resection and reconstruction of a cutaneous squamous cell carcinoma with bony invasion into the scalp and to discuss the alternative options and potential pitfalls.

Materials and Methods: A patient diagnosed with rT4N0M0 cutaneous squamous cell carcinoma of the scalp underwent a cranial resection and reconstruction in one stage. With the use of Computer-Assisted-Design and Computer-Assisted-Manufacturing a Patient Specific Implant (PSI) of Poly (Ether Ether Ketone) was manufactured. After the PSI was inserted, it was covered with a latissimus dorsi muscle and a split-thickness skin graft.

Results: Intra-operatively the resection template generated an accurate resection and accurate and fast placement of the PSI. The reconstruction had a clinical satisfactory esthetic result, but was hampered by the development of a small wound dehiscence was observed over the postoperative course.

Conclusion: 3D planned resection and reconstruction for composite defects of the skull after resection of a cutaneous squamous cell carcinoma of the scalp with bony invasion may lead to an accurate and predictable resection and accurate and fast placement of the PSI. However, patient specific characteristics should be considered to assess potential risks and benefits before opting for this one- stage treatment strategy.

INTRODUCTION

Actinic keratosis is a high prevalence premalignant skin disorder. Commonly, the affected area shows multiple undefined erythematous scaling papules or plaques of 1-3 mm. Due to the variable and nonspecific c linical presentation, diagnosis and treatment are frequently delayed. Untreated actinic keratosis may develop into malignant cutaneous squamous cell carcinoma (cSCC). [1]

CSCC is a common type of skin cancer with a high prevalence, especially in elderly and in immunosuppressed patients[2–4]. CSCC presents mostly on sun exposed surfaces of the skin such as the underarm, face and scalp. The preferred location is the external ear and lower lip[3,5]. CSCC initially starts with an asymptomatic painless, rough patch of the skin which may progress into an ulcerated tumor with radial spread at diagnosis[6,7].

For cSCC in general, but also for lesions located on the scalp, local bony invasion remains an uncommon feature. When the cranium is affected, there is no consensus about the optimal treatment strategy (radiotherapy vs surgery)[8]. In case of surgery, reconstruction of these composite defects by cranioplasty in addition to soft tissue reconstruction may be recommended because of better protection of the brain, increase of psychosocial aspects and improvement of esthetic outcome[9–13]. Time interval between diagnosis and surgery in case of craniectomy for cSCC, allows for preoperative digital surgical planning. This gives the surgeon the opportunity for 3D planned cranial resection and symmetric reconstruction of the cranial vault in one stage. Besides the most important advantage of saving the patient additional surgical procedures, it may also help to achieve more accurate and predictable resection margins.

The aim of this case presentation is to demonstrate a one stage 3D planned surgical resection and reconstruction of a recurrent cutaneous squamous cell carcinoma of the scalp with bone invasion, followed by discussion of alternative options and potential pitfalls.

MATERIAL AND METHOD

Case

An 82-year-old Caucasian fair skinned male visited the department of Head and Neck Surgery and Oncology with complaints of an itchy and tender red, scaling and non-healing skin of the scalp since four months.

The patient had undergone multiple surgical procedures for a cutaneous squamous cell carcinoma of the scalp, after which he underwent external beam radiation therapy (20 x 3 Gy) two years prior to presentation because of a recurrent lesion. Furthermore, the medical history of the patient included hypertension and Waldenstrom macroglobulinaemia.

At physical examination a crusted and ulcerated lesion with a diameter of approximately 7 cm was observed. Centrally of the ulceration the tabula externa was visible. (Figure 1) The principal clinical diagnosis was osteoradionecrosis of the skull, however biopsy demonstrated a recurrent cSCC.

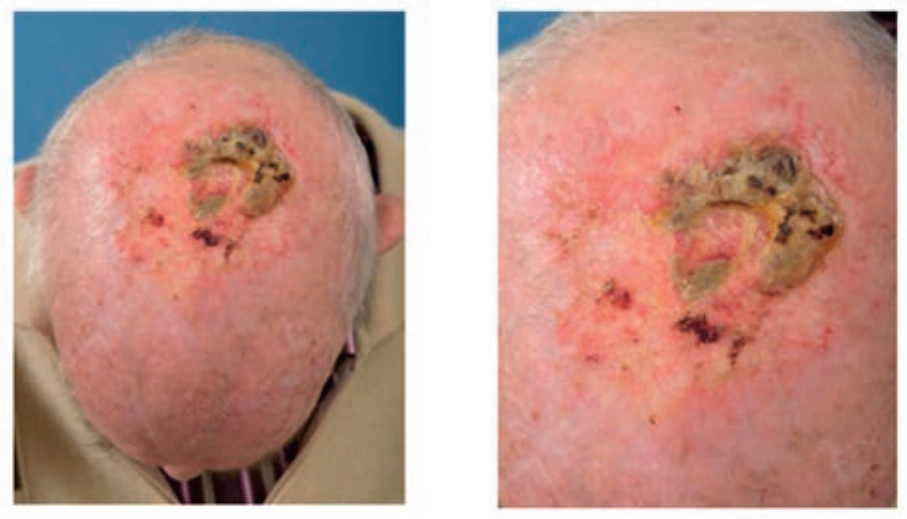

Figure 1: Clinical presentation of the ulcerated and crusted lesion on the scalp with a diameter of 7 cm and centrally exposure of the underlying cranial bone.

Standard work-up included a CT-scan and MRI, demonstrating an osteolytic defect of the tabula externa and interna suspected of bony invasion without dural involvement (Figure 2). Regional and distant metastasis were excluded by an ultrasound of the regional lymph nodes and FDG-PET/CT. Extension of the radial spread was evaluated by dermatoscopia combined with mapping by multiple histological tissue sampling. The tumor was staged as a rT4aN0M0 cSCC according to the AJCC Cancer Staging Manual, 8th edition [14].

A total resection was indicated with direct reconstruction of the cranial defect. The reconstruction was planned with a cranioplasty of poly(ether ether ketone)(PEEK) covered by a free latissimus dorsi muscle-only flap (LD) and a split skin graft of the anterolateral thigh to cover the muscle.

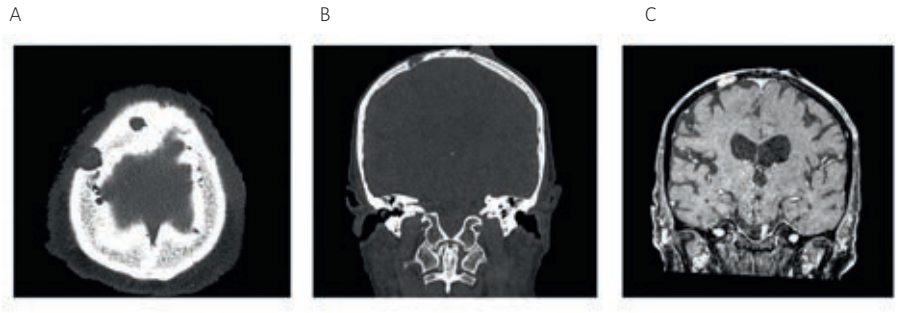

Figure 2: A) Axial and B) coronal slides of the computer tomography demonstrating bone invasion. C) MRI images excluded dural involvement.

Preoperative planning

For the preoperative planning a CT -scan of the neurocranium (Siemens SOMATOM Definition AS+, 120 kV, 179 mAs, 512x512 matrix size, 0.6 mm slice thickness, kernel D (hard-tissue)) was performed. On the CT-scan segmentation of the tumor, including a bony margin of 1 cm around the osteolytic defect, was performed (Figure 3A). Using MedX (Illinois, USA) software, a resection template and cranioplasty were designed (Figure 3B&3D). For final intra-operative adjustments and to ensure a good fit of the cranioplasty, a control template was also constructed (Figure 3C).

In the design, navigation landmarks for positioning of the resection template were incorporated. The resection template and control template were 3D printed in nylon using selective laser sintering. The cranioplasty was milled of PEEK (Xilloc Medical BV, Geleen, the Netherlands).

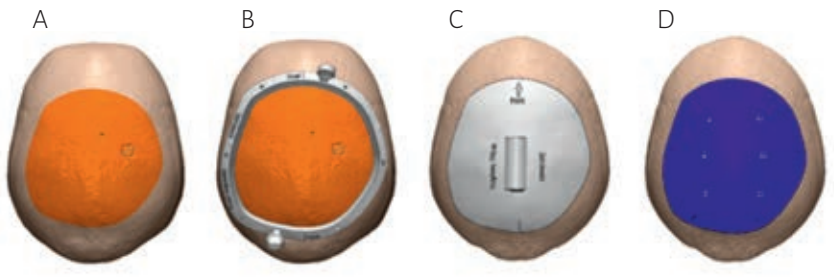

Figure 3: The 3D virtual planned resection and reconstruction with a PEEK cranioplasty. A) Segmentation of the tumor. B) Design of the resection template. C) Design of the control template. D) Design of the cranioplasty.

Surgical procedure

Preoperatively 2 gram cefalozin was administered intravenously and continued during the surgical procedure 1 gram every 4 hours. The patient was placed in right lateral position with the head fixated with the Mayfield clamp. Navigation (Brainlab, Munich, Germany) for the perfect position of the resection template was calibrated and installed. After this, a sterile operation field was created according to normal procedures.

Phase I – Tumor resection

The soft tissue outline of the cSCC including at least 1 cm free margin was marked and the skin incision was performed. After the skin incision, a careful subperiosteal dissection was performed to allow proper positioning of the resection template (Figure 4A). Periosteal attachment around the region of bony invasion was maintained.

The resection template positioning was controlled with the use of navigation and fixed with 4 screws of 6 mm into the skull. Four burr holes, two frontal and two parietal, were prepared and the craniectomy was performed guided by the resection template. (Figure 4B&4C) With the use of the control template adjustments were made to allow a proper fit of the Patient Specific Implant (PSI) of PEEK in a later stage of the surgical procedure.

Phase II – Dissection of temporal artery and vein simultaneous with harvesting of the latissimus dorsi flap

After tumor resection, dissection of a free LD flap with the thoracodorsal artery as vascular pedicle was performed. Simultaneously, the superficial temporal artery and external jugular vein were dissected and prepared as recipient vessels for arterial and venous anastomosis of the vascular pedicle after free tissue transfer.

Phase III - Reconstruction of the skull

Before definite placement of the PSI, six absorbable dural suspension sutures were placed to fix the dura to the PSI. Thereafter, the PSI could be positioned and fixed to the skull with osteosynthesis material (KLS Martin Group, Tuttlingen, Germany) and 10 screws of 5 mm (Figure 4D).

After fixation of the PSI, the free LD flap could be detached from its vascular pedicle and transferred to the skull. It was ensured that the PSI was completely covered by the LD flap. A vest-over-pants inset [15] was used to prevent bone exposure at the flap-scalp junction and increase the distance between the implant and wound edges (Figure 4E). The vascular pedicle was anastomosed to the recipient vessels and perfusion of the flap was controlled with a doppler ultrasonography.

Coverage of the LD flap was performed with a split-thickness skin graft from the anterolateral thigh, which was meshed (1:1.5) (Figure 4F). A local wound dressing was applied.

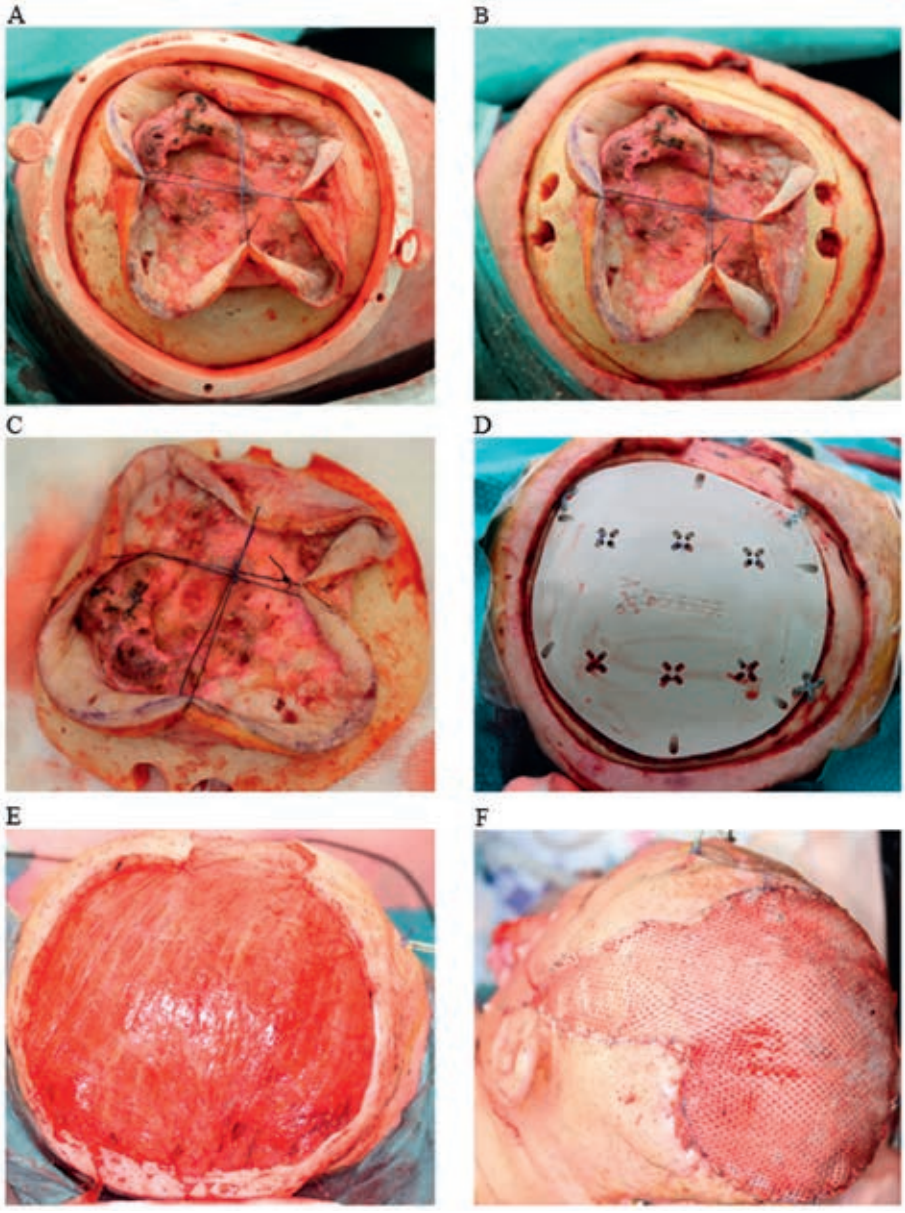

Figure 4: A) The navigation guided positioning of the resection template. B & C) The craniectomy performed guided by the resection template with two burrholes anterior and posterior. D) Definite placement of the patient specific implant. E) Vest-over-pants inset of the free latissimus dorsi muscle-only flap covering the implant and implant-bone interface. F) Coverage of the latissimus dorsi muscle with a meshed split-thickness skin graft of the anterolateral thigh to allow for epithelization.

Post-operative course and histology

After two days the head bandage was removed. The LD flap remained vital. There were no neurological complications in the direct postoperative course.

On the 14th postoperative day the patient collapsed and sustained direct head trauma without loss of consciousness. Neurological examination was unremarkable. A hematoma between the implant and the LD flap occurred. No surgical intervention was initiated and the hematoma resolved partially. Unfortunately a wound dehiscence of 1 x 2 cm was observed on the most distal aspect of the muscle flap where the hematoma sustained. This area was debrided and wound dressing was applied. After 21 days of hospitalization the patient went home in good condition (Figure 5A&5B). A small area of dehiscence over the implant persisted, which has remained stable during the complete first year of follow-up (Figure 5C).

The pathologic examination showed a squamous cell carcinoma of the skull with underlying bone destruction and surrounded by actinic keratosis. There were no signs of perineural spread of lymphovascular invasion. Surgical margins were free of tumor.

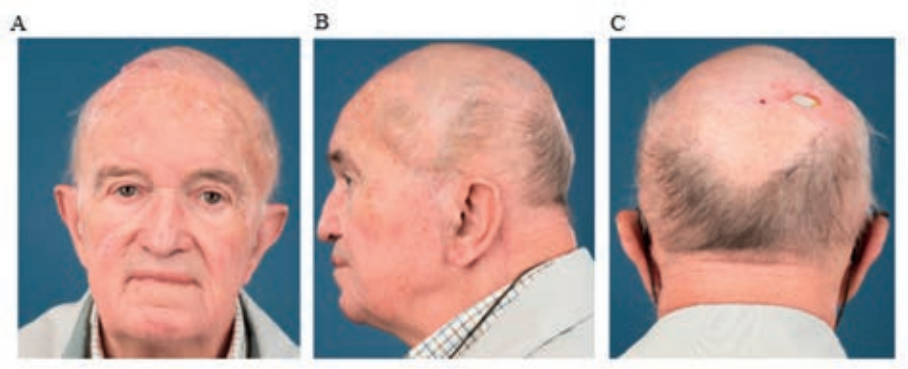

Figure 5: A&B) Postoperative situation 4 months after surgery with a symmetric reconstruction of the cranial vault, which will improve as further atrophy of the muscle continues . C) Unfortunately, there is a stable dehiscence over the implant, showing on the right posterolateral side of the skull. It might be safer to perform the surgery in two phases, in order to prevent this complication.

DISCUSSION

In this case report the feasibility of a one stage virtual planned surgical removal and reconstruction of a recurrent and previously irradiated cutaneous squamous cell carcinoma with invasion into the underlying skull is presented. Also, the potential complications that may occur and management are discussed.

Cutaneous squamous cell carcinoma (cSCC) of the scalp is not uncommon. Predisposing factors include chronic actinic damage, prior treatment with ionizing radiation, immunosuppression, chronic scarring, and certain genodermatosis[16]. They represent approximately 2% of all skin cancers, with a male predominance presumably due to androgenic alopecia[7,16–18]. In contrast, advanced cSCC of the scalp with invasion of the underlying skull has a rare occurrence and clinical decision making is severely hampered by the lack of experience reported in literature.

Non-melanoma skin cancer of the scalp is most commonly staged according to the TNM (tumor, node, metastases) staging system [14]. Staging is an important tool in prognostic stratification. The majority of cSCC is detected at an early stage and classified as low risk. Their prognosis is good with a low incidence (< 5%) of metastases[19,20]. Successful treatment is usually achieved with soft tissue excision and scalp reconstruction using primary closure, local flaps or skin grafting. A small subset of lesions has more unfavorable characteristics, in which the incidence of nodal metastasis is significantly increased (16-47%) and prognosis is worse[20–27]. Although the exact value of negative prognostic factors is still debated, most authors agree that size of the lesion (>2 cm), depth of invasion (>4 mm), incomplete excision, recurrent setting, differentiation grade (poorly differentiated), presence of perineural or lymphovascular invasion and certain locations (lip, external ear, temple, forehead, anterior scalp) harbor an increased risk for nodal metastasis and/or local recurrence[21–24]. Patients factors (immunosuppression), particularly in the setting of an organ transplantation, may also play a pivotal role in recurrent disease[21,23,24]. It is of utmost importance to identify these patients with high risk cSCC to dictate appropriate work up and management strategy.

Based on best level of evidence, various national and international multidisciplinary guidelines provide treatment recommendations to aid clinicians to obtain best possible loco-regional control in case of high risk lesions[25–29]. Although first line treatment is complete surgical excision with histopathological control of excision margins, the optimal surgical margins are unknown. For high risk tumors, a margin of at least 6 mm is considered necessary, although experts may consider an extended margin of 10 mm to be safer[25–29]. If a R0 resection is not feasible, the patient refuses surgery or in the adjuvant setting, radiotherapy can be considered[25–27,29]. Data on elective lymph node dissection or sentinel lymph node biopsy are not conclusive[21,25–27,29]. Therefore, strict lymph node examination during follow-up is recommended until more clinical data become available.

When compared with cSCC in general, scalp lesions may have some complicating characteristics unique to this anatomic site. First, the presence of hair follicles at this location are known to potentially delay accurate diagnosis. Secondly, the microscopic extent of the tumor can be difficult to delineate and exceed clinical apparent margins, as the subgaleal plane offers little resistance to tumor and facilitates radial spread[6,16]. Also, extensive actinic damage with field cancerization and multiple foci of invasive growth, could impede defining clinical margins. Thirdly, accurate diagnosis of minimal invasion into the cranium may be difficult. This accurate diagnosis is of importance, because bone involvement requires resection of the affected bone. In these cases, the surgeon should consider a CT scan or obtain bone chips for microscopic examination, as pitting of bone has not always proven to be reliable[16]. And fourthly, when bone resection is needed, many open questions remain with respect to the optimal reconstructive approach regarding the need for cranioplasty and ideal soft tissue coverage.

Different critical decisions have to be made when addressing composite scalp and calvarial defects after tumor removal of the skull. Various techniques and timing are described in literature for both soft tissue coverage and hard tissue reconstruction. Concerning soft tissue coverage, irradiated wound beds or need of adjuvant radiotherapy, sizeable defects and prior surgeries make microvascular free tissue transfer frequently unavoidable in their management. Various free flaps have been described to reconstruct scalp defects. These include the LD[30–32] and the anterolateral thigh flap (ALT)[33,34], which have been accepted as the workhorse flaps for reconstruction of large scalp defects. Alternatives include radial free forearm flap (RFFF)[32], rectus abdominis flap[32,35,36] and others[32,37,38]. Certain authors consider the LD flap the first choice because of its large surface, predictable blood supply, ease of harvesting, excellent vascularity and long vascular pedicle[15,39,40]. Others, consider the ALT flap the preferable choice, because of its minimal donor site morbidity, lengthy and sizeable pedicle and possibility to harvest in supine position[41–43]. It is well known that immobilized denervated muscles are vulnerable to atrophy[44]. The ALT might be associated less with atrophy related complications compared to LD flaps, although there is lack of evidence to support one superior flap choice over the other[43].

Some authors have managed composite defects in the same manner as scalp only defects to successfully avoid potential complications and morbidity, with application of a soft tissue flap alone[8,45]. Although they heal satisfactory and demonstrate no major recipient site complications in the postoperative course, the limitations of this strategy are an abnormal cranial contour and absence of protection of cranial contents that is conferred by cranioplasty. These patients have to adhere to the standard precautions of patients who do not have solid protection of their intracranial contents.

Consequently, most authors advise a form of cranioplasty alongside microvascular soft tissue coverage. Biocompatible autologous bone, which has long time been considered the golden standard in neurosurgical and craniofacial literature[12,34,46–50], has a high complication rate including infection (0-26%) and resorption (1-50%) with a high removal rate[51]. Especially, in case of tumor invasion into the skull, the use of autologous bone is limited by donor sites and finite number and size. Alloplastic materials may overcome these shortcomings and offer a solution for optimal protection of the brain and satisfactory aesthetic outcome. Different materials are developed for cranioplasty, each with their own advantages. The ideal material is biocompatible, radiolucent, resistant to ionizing radiation and heat, MRI compatible, easy to use, and allows a low cost preoperative design and manufacturing to achieve an aesthetic satisfying result[51]. Unfortunately, this material does not exist yet. Titanium, poly(methyl methacrylate) (PMMA), poly(ether ether ketone) (PEEK) and hydroxyapatite are the most mentioned materials. Titanium is radiopaque and appears to conduct heat and cold which makes a full cranioplasty of titanium not a good option for cranioplasty[47]. It is well known that a titanium mesh may cause artefacts on a CT or MRI, which could impede follow-up of cranioplasty patients after oncological resection[52]. Also, when inserted directly on the dura it may cause scalp thinning and penetrate the overlying tissue[53]. PMMA is a radiolucent, relatively cheap and easy to use material. However, this material is manufactured using liquid MMA in combination with PMMA particles. Different studies describe the potentially toxic and adverse effects of MMA[54]. Hydroxyapatite is similar to the mineral phase of human bone and can stimulate bone formation. However, the material itself is very brittle until replaced by bone, the exact time interval is unknown and depends on patient specific factors[47]. The question also remains if hydroxyapatite has any bone formation capability when used in prior irradiated tissues. PEEK is a more modern plastic, resistant to high temperatures, has a good biocompatibility and mechanical characteristics comparable to cortical bone. However, the material itself is expensive and without bioactivity[55]. The reported overall complication rates for simultaneous cranioplasty and microvascular free tissue transfer are high (21.0%-57.9%)[40,41,43]. The main shortcoming and serious complication of using alloplastic materials are the potential for infection and exposure, which might require removal of the cranioplasty.

Reported infection and exposure rates reported range from 0% by Lipa et al., up to 14,6% by Chao et al., 25% by Sosin et al., and 38% by Afifi et al.[15,40,41,43]. Among these studies cranioplasty materials differed. If risk factors, such as radiotherapy or infection are present, some authors advise against the use a one stage free flap reconstruction with alloplastic material because of potentially higher recipient site complications[41]. Chao et al., did not find preoperative or post-operative radiation to be associated with development of recipient site complications. However, in patients with a history of infected cranial bone or alloplastic cranioplasty, they did recommend a staged approach with direct free tissue transfer alone and subsequent delayed calvarial reconstruction. The average interval between soft tissue and bone reconstruction was 6.0 ± 1.8 months. Atrophy of the LD flap did not limit the ability to perform a delayed cranioplasty, and no difficulty was experienced in flap elevation from the underlying dura[40].

Nowadays, with the use of CAD-CAM techniques, preoperatively the resection outline can be marked keeping a safe margin to the tumor and a resection template can be manufactured. During the operation the resection template can be positioned and fixed accurately to the skull guided by navigation. This helps the surgeon to follow the planned resection outline and results in a highly accurate and predictable resection of the tumor which may potentially minimize future recurrences. The PEEK cranioplasty implant can be designed accordingly to the shape of the predicted defect and allow a perfect fit[56]. Because of the non-bioactive nature of PEEK it will not securely adhere to the surrounding bone. To improve the stability of the cranial implant a good edge contact is necessary. A sawing edge of 45 degrees during the craniectomy would allow the eventual implant (also with a 45 degrees edge) to be supported across the entire bone-implant contact surface. Such design features could easily be incorporated in the preoperative design phase.

In the described case, there were multiple factors making this a high risk cSCC, including recurrent setting and size of the lesion. Local wound problems and pain had severe impact on the quality of life of the patient. Accommodated by shared surgical decision-making and not as much the inherent value of human life, a decision to intervene was made through a close dialogue of this frail and elderly patient, family and health care providers[57]. Non-operative alternatives were unattractive regarding the exposed bone with tumor invasion and history of prior radiotherapy. A one stage surgical treatment was decided upon with the aim to eradicate the tumor and affected tissues, to achieve stable tissue coverage of the defect and enable the patient to return to prior activities with protection of the intracranial content with a cranioplasty. The CAD-CAM produced resection templates allowed for an accurate resection with tumor free margins as planned and proper fit of the alloplastic cranioplasty. Unfortunately, this digital workflow did not prevent the occurrence of wound dehiscence and implant exposure, which is most feared in this type of surgery. However, it did lead to predictable margins, a more rapid and easy surgical procedure and accurate fast placement of the cranioplasty. Potentially, a delayed cranioplasty, would have prevented wound dehiscence problems, as described by Chao et al.[40].

CONCLUSION:

Composite defects of the scalp and cranium resulting from invasive squamous cell carcinoma are known to be a reconstructive challenge and associated with a high rate of complications and morbidity. This first report of a one stage 3D virtual resection and reconstruction, demonstrates the advantages of an accurate and predictable resection and accurate fast placement of the designed cranioplasty. Unfortunately, this did not overcome the complication of wound dehiscence and implant exposure. The possible benefits and risks should always be assessed in relation to the patient's diagnosis, co-morbidity and life-expectancy. For high risk cases and unfavorable local conditions such as previous infections, radiotherapy or exophytic tumors, a multiple staged approach seems to remain the most predictable treatment strategy.

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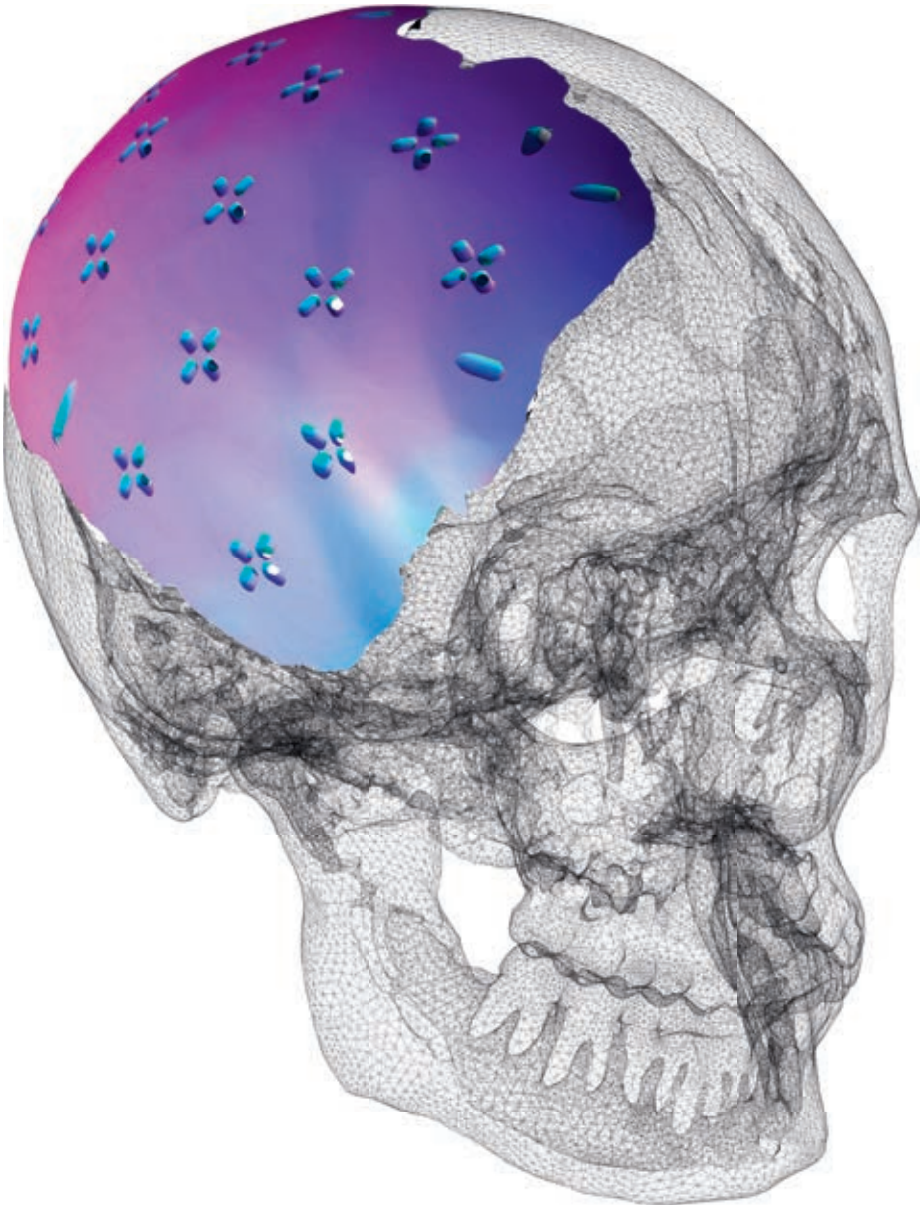
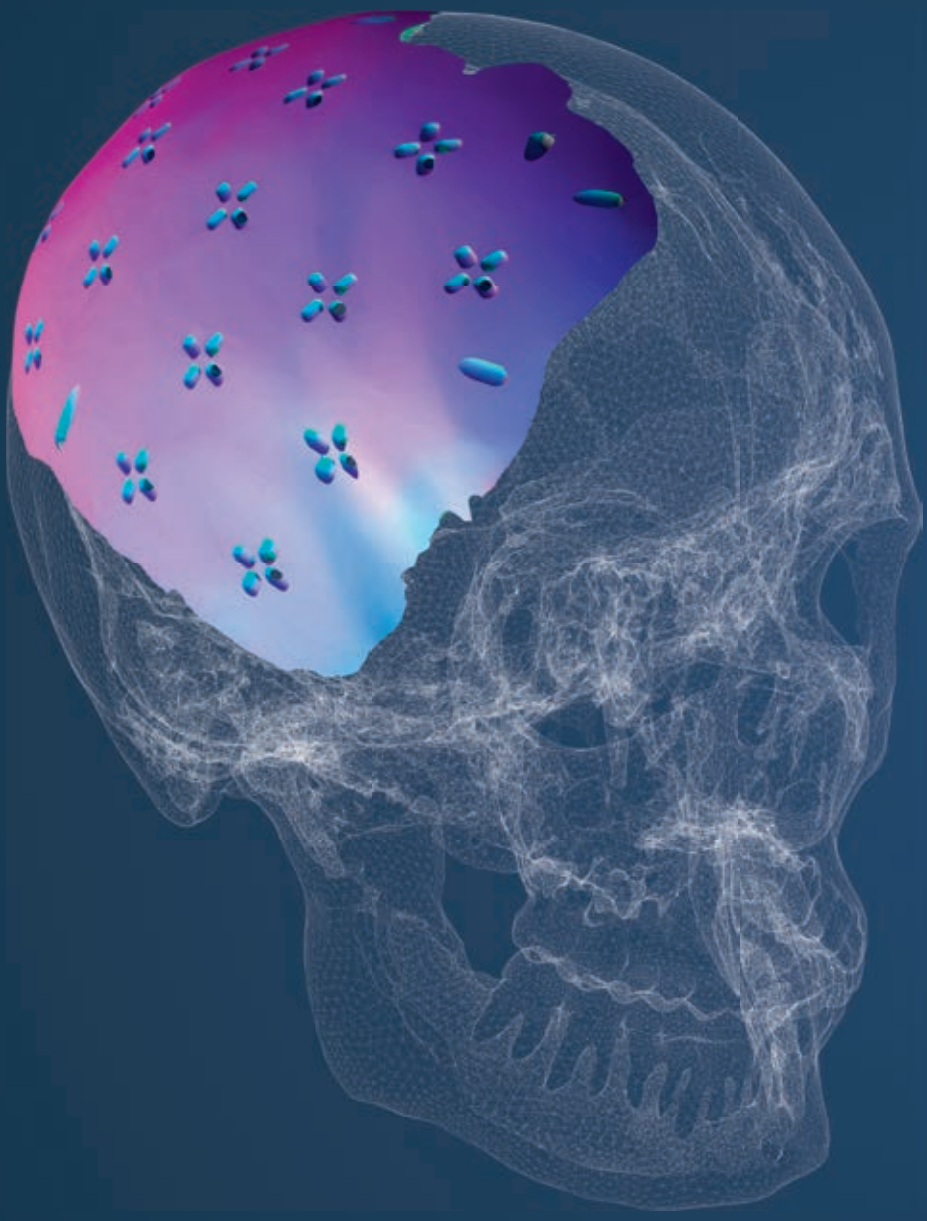


PART V

Towards the ideal material



CHAPTER 8

Leachables from patient-specific implants produced by 3D printing compared to conventional PMMA-based alternatives

S.E.C.M. van de Vijfeijken, T.J.A.G. Münker, C.J. Kleverlaan,
A.G. Becking; on behalf of the CranioSafe Group

This chapter is based on the publication: Leachables from patient-specific implants produced by 3D printing compared to conventional PMMA-based alternatives

Submitted

ABSTRACT

Background Poly(methyl methacrylate) (PMMA) has been widely used in healthcare for dental prostheses, fixation of hip implants, and skull reconstructions. PMMA is formed through the polymerization of liquid methyl methacrylate (MMA) and PMMA powder. Unreacted MMA (residual monomers) remain in the final product, however, the precise concentrations are not known for all PMMA-based materials.

Objectives The aim of this study is to investigate whether different compositions and fabrication methods of PMMA-based materials differently release residual monomers.

Material and Methods Four representative PMMA-based materials (Vertex Self-Curing, Palacos R+G, NextDent C&B MFH, and DePuy CMW-3) with different compositions were examined by reversed-phase high-performance liquid chromatography (HPLC). The released residual monomer concentration was measured in water at 37.0 ± 1.0 °C and at time points between one hour and 14 days.

Results The different PMMA-based materials demonstrate concentrations of released residual monomers between 22.8 and 78.8 µg/g after 14 days. NextDent C&B MFH, a poly(dimethacrylate), released a significantly lower residual monomer concentration (22.8 µg/g) after 14 days compared to the other materials.

Conclusion Different compositions of PMMA-based materials show different release patterns and quantities of residual monomers. The novel polymer, NextDent C&B MFH, released the lowest amount of residual monomers.

INTRODUCTION

Poly(methyl methacrylate) (PMMA) has been widely used in different fields of healthcare, as a bone cement in orthopedics, as dentures or orthodontic applications in dentistry, and in craniofacial reconstructions in maxillofacial surgery and neurosurgery [1–4]. PMMA is formed through the polymerization of methyl methacrylate (MMA) using PMMA powder as a filler to minimize shrinkage. The conversion is not complete and some unpolymerized MMA, so-called 'residual monomers', remains in the final PMMA product[5]. MMA is known to cause various skin irritations and has toxic effects on neuronal cells and the respiratory system[1]. However, there is inadequate indication for alleged carcinogenicity according to the International Agency for Research of Cancer of MMA in humans[1,6].

The amount of residual monomers typically varies between 2% and 6%[7] and may depend on: the initial polymer to monomer ratio[8], the method of polymerization[8–10], the processing method[11], and the use of a water-bath after preparation[12]. Auto-, heat-, and photopolymerization are well-known techniques for the preparation of PMMA. Curing under pressure decreases porosity and increases the degree of conversion, reducing the amount of residual monomers[13]. Additionally, due to the increased temperature and chain mobility, the degree of conversion may further increase, resulting in an even lower amount of residual monomers. If a water bath is used during the polymerization the amount of residual monomers decreases[10]. Furthermore, the amount of residual monomers decreased post-polymerization following 10 minutes incubation in a water bath at 37.0 ± 1.0 °C [14]. Residual monomers influence the material properties of PMMA, i.e. water resorption, biocompatibility, hardness and dimensional stability[5].

The aim of this study is to evaluate the release of residual monomers from PMMA-based materials in water at 37.0 ± 1.0 °C using different compositions and fabrication methods of PMMA.

MATERIALS AND METHODS

This study examines whether different compositions and fabrication methods of PMMA-based materials release different amounts of residual monomers.

Specimen preparation

Four representative materials - Vertex Self-Curing (Vertex-Dental, The Netherlands), Palacos R+G (Heraeus, Germany), NextDent C&B MFH (NextDent, The Netherlands), and DePuy CMW-3 (DePuy International Ltd., United Kingdom) - were used (Table 1). A mold of a half cylinder 40 mm (height) by 28 mm (outer radius) with 6.0 mm thickness was designed using Netfabb software (Autodesk Inc., CA, USA) and 3D printed out of a poly-(dimethacrylate) on a Rapidshape D30 printer (Rapidshape, Heimsheim, Germany). Vertex Self-Curing, Palacos R+G, and DePuy CMW-3 were hand mixed following the manufacturer's instructions and were used to fill the 3D printed mold.

Table 1: Specifications of the PMMA-based materials used in this study.

Material / *Application*	Ingredients powder	Ingredients liquid
Vertex Self-Curing[a] *Denture*	Poly(methyl methacrylate), benzoyl peroxide, various pigments	Methyl methacrylate, N,N-dimethyl-p-toluidine, ethylene glycol dimethacrylate
Palacos R+G[b] *Bone cement*	Gentamicin, poly(methylacrylate, methyl methacrylate), zirconium dioxide, benzoyl peroxide, colorant E141	Methyl methacrylate, N,N-dimethyl-p-toluidine, hydroquinone, colorant E141
NextDent C&B MFH[c] *Personalized medical device*	-	Methacrylate oligomer, methacrylate monomer, inorganic filler, phosphine oxides
DePuy CMW-3[d] *Bone cement*	Gentamicin sulphate, poly(methyl methacrylate), benzoyl peroxide, barium sulphate	Methyl methacrylate, N,N-dimethyl-p-toluidine, hydroquinone

[a] Vertex-Dental, Soesterberg, The Netherlands [b] Heraeus, Hanau, Germany [c] NextDent, Soesterberg, The Netherlands
[d] DePuy International Ltd., United Kingdom

The inverted design of the mold was used for the 3D printed cylinders of NextDent C&B MFH. After printing, the cylinders were immersed in ethanol twice (respectively three and two minutes) under ultrasonic vibrations. The cylinders were dried for 10 minutes prior to a post-curing period of 30 minutes in a ultra violet lightbox (NextDent LC3D-PrintBox, Soesterberg, The Netherlands). Three cylinders of each material were prepared, sharp edges were wet grinded with standard metallographic grinding paper (P500, P1000, and P1200).

All specimens were stored under standard laboratory climate conditions (22.0 ± 1.0 °C and 50 ± 10% humidity) in a dark environment for 20 ± 4 hours.

Twelve bottles with 200 mL of distilled water were prepared and stored in a stove with a continuous temperature of 37.0 ± 1.0 °C. The bottles were sealed airtight. When the temperature of the distilled water reached 37.0 ± 1.0 °C, the half cylinders were inserted into the bottles. Immediately after the cylinders were added (t=0), the first measurement was conducted by taking a 0.5 gram sample of the distilled water from each of the twelve bottles. Subsequent samples were taken after 1, 2, 4, 8, 12, 24, 48 and 72 hours, 7 and 14 days. During this time, no water was added to the bottles. All the samples were stored at 7.0 ± 1.0 °C in a dark environment until further analysis.

High-performance liquid chromatography (HPLC)

All samples were analyzed using a reversed-phase high-performance liquid chromatography (HPLC) system (Shimadzu LC-20AT) with Diode Array (DA) detectors and a 'Zorbax Eclipse Plus C18 Analytical Column'. MMA stock solutions (0.41, 1.03, 2.06, 4.13 and 8.25 µg/mL) in acetonitrile were measured on the HPLC to create a calibration curve relating the area under the curve [mV*s], at the peak locations, and the concentration [µg/mL].

Liquid Chromatography/Mass Spectrometry (LCMS)

LC/MS analyses of the different peaks in the HPLC samples were performed using a 'Waters XSelect HSS' HPLC with a 'C18 2.1x50 mm, 3.5 µm' column (Waters Chromatography B.V., The Netherlands) with a formic acid/acetonitrile/Milli-Q running solution interfaced to a 'Bruker Amazon 230 SL' MS (Iontrap and Dionex Ultimate 3000 (HPLC)) using positive electrospray ionization. Spectra were scanned over a mass range of *m/z* 70-550, taking an average of 10 spectra and using an ion spray voltage of 4.5 kV, a source temperature of 325 °C, and a nebulizer gas flow rate of 50 L/min.

Statistical Analysis

Pseudo first order kinetics curves were fitted to the data in GraphPad Prism 5 (GraphPad Software, CA, USA) to investigate the influence of different compositions and fabrication methods on the amount of released residual monomers (α=0.05) using:

$$M(t) = M_0 * (1 - e^{-k*t})$$

where M in the quantity of released monomer [µg/g] at time t [h], M_0 is the quantity of released monomer at t = 0 [µg/g], and k is a constant [-].

RESULTS

In this *in vitro* study, different fabrication methods and compositions of PMMA-based materials were compared to determine if they release different amounts of residual monomers over time and if the release patterns of these residual monomers are different.

High-performance liquid chromatography (HPLC)

The results of the leachable residual monomers are summarized in Table 2 and fits of pseudo first order kinetics curves for the leaching process are graphically depicted in Figure 1. Corresponding non-linear regression variables are presented in Table 3.

NextDent C&B MFH does not appear to release monomers past the first time point (1 hour), whereas Vertex Self-Curing, Palacos R+G, and DePuy CMW-3 do release monomers over a longer period. NextDent C&B MFH released more residual monomers in the first hour compared to the other materials, indicating that all monomers in this material that can leach out do so in the first hour, whereas this takes more time for the other materials. This is confirmed in the pseudo first order kinetics model where NextDent C&B MFH has a doubling time of 0.59 hours, however the release profile does not follow a pseudo first order kinetics profile (R^2 = 0.13). After 48 hours all materials surpassed the cumulative release of NextDent C&B MFH. The doubling time of Vertex Self-Curing and DePuy CMW-3 are similar at around 8 hours, Palacos R+G is higher at approximately 13 hours, however this is not a significant difference.

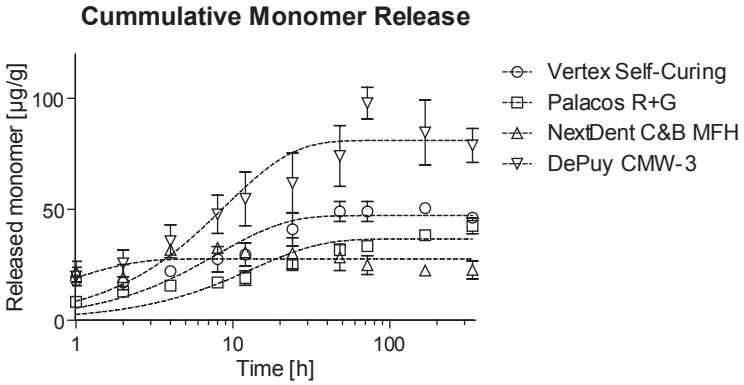


Figure 1: Cumulative residual monomer release during 2 weeks incubation in water at 37 °C with fitted pseudo first order kinetics curves.

Liquid Chromatography/Mass Spectrometry (LC/MS)

Multiple peaks are visible in the HPLC spectrum of NextDent C&B MFH. LC/MS was performed to determine the substances present in these peaks and whether these are in fact related molecules with a common precursor. This leads to an increased concentration of released monomers (this was assumed in Table 2 & 3 and Figure 1). If this is not the case the concentration of released monomers is actually lower, but multiple different molecules are released. The MS spectra prove that these multiple peaks are indeed containing multiple related derivatives of the monomers in NextDent C&B MFH. No traces of other chemicals such as the initiator system, catalyst, or colorants were detected in the MS detector, indicating these substances were not present at concentrations above the detection limit.

Table 2: Cumulative residual monomer release in µg/g MMA per PMMA during 2 weeks incubation in water at 37 °C.

Time (hours)	1	2	4	8	12	24	48	72	168	336
Vertex Self-Curing	18.02 (1.85)	17.04 (1.66)	22.14 (0.98)	27.51 (5.78)	29.62 (5.20)	41.04 (7.53)	46.47 (6.22)	49.05 (4.49)	50.59 (1.96)	46.26 (2.23)
Palacos R+G	8.31 (0.83)	12.93 (1.37)	15.68 (1.74)	17.07 (1.06)	19.07 (3.31)	24.87 (0.30)	31.61 (0.79)†	33.41 (0.95)†	38.33 (2.26)	42.54 (3.49)
NextDent C&B MFH	21.94 (4.57)†	19.49 (5.63)†	31.77 (0.23)†	32.68 (0.47)	30.68 (0.20)†	30.23 (7.02)	28.40 (5.90)	24.89 (4.26)	22.47 (1.32)†	22.75 (4.05)
DePuy CMW-3	19.73 (4.10)	25.63 (5.98)	35.67 (7.41)	47.74 (8.58)	54.76 (12.12)	61.81 (13.49)	74.05 (13.67)	97.81 (7.14)	84.70 (14.63)	78.83 (7.67)

Values given as mean and standard deviation (SD); n=3
†: n= 2

Table 3: Pseudo first order ($Y = Y_o * (1-\exp(-k*X))$) release profiles of Vertex Self-Curing, Palacos R+G, and NextDent C&B MFH. X = time in hours; Y = quantity MMA per PMMA in µg/g; k = constant; τ = half-life in hours; T_d = doubling time in hours

Material	Y_o	k	τ	T_d	R^2
Vertex Self-Curing	46.6 (42.8-50.3)	0.13 (0.09-0.17)	7.75 (5.90-11.3)	5.37 (4.09-7.81)	0.75
Palacos R+G	36.7 (33.0-40.2)	0.07 (0.05-0.10)	13.4 (10.0-20.0)	9.28 (6.98-13.84)	0.79
NextDent C&B MFH	27.7 (25.2-30.1)	1.17 (0.34-1.99)	0.86 (0.50-2.91)	0.59 (0.50-2.91)	0.13
DePuy CMW-3	81.0 (73.8-88.2)	0.11 (0.07-0.15)	8.89 (6.65-13.4)	6.16 (4.61-9.29)	0.78

DISCUSSION

This *in vitro* study reports the leaching behavior of four representative PMMA-based materials which are used for medical devices. The following trends were observed: (I) the amount of leached monomers significantly differs for different PMMA-based materials (II) release patterns of residual monomers significantly differ for different PMMA-based materials (III) the novel PMMA-based material NextDent C&B MFH demonstrates a significantly lower total cumulative concentration of leached residual monomers but a higher initial release.

Kühn reports that Palacos R+G released approximately 185 µg MMA per g PMMA over a two week span into 5 mL water using specimens with a volume of 0.45 cm^3 and area of 4.5 cm^2. The accumulated release of MMA from 8 different PMMA-based materials ranged approximately between 185 and 470 µg/g. Palacos R contained approximately 4% residual monomers immediately following curing, this dropped to roughly 1.5% after 1 day.[7] In this study, the specimens (volume: 18.85 cm^3, area: 72.5 cm^2) were placed in water after 20 ± 4 hours. The thickness of the specimens was 6 mm, since this is comparable with the human skull[15,16]. The specimen thickness has been shown to have a significant influence on the content of residual monomers[11]. It is unknown whether this has an effect on the leaching behavior of MMA. Literature reports a significant increase in leaching when a sample was put in a larger volume of extraction solution[17]. This, in addition to the difference in volume to surface ratio, may explain the lower values reported here in comparison to literature [7]. These effects should increase the values found in our study compared to the study by Kühn[7], as their extraction volume and specimen thickness were significantly lower. However, their reported values are significantly higher than ours, probably due to the previously mentioned effects. The actual monomer exposure for the patient in a clinical setting, where upon cooling down the medical device is immediately placed into the patient, is thus likely higher than the reported values in this study and may be more in line with the values reported by Kühn[7].

Differences in the composition of PMMA-based materials result in different quantities and release patterns of residual monomers present within the polymerized material. These differences may originate from subtle differences in the concentration and type of activator, catalyst, or filler particles which may have an impact on the degree of conversion and consequently the amount of residual monomers. Palacos R+G likely contains less activator than DePuy CMW-3[7] which should result in a final PMMA product with longer polymer chains and more crosslinks, and thus a higher molecular weight. Due to this structure it should be more difficult for residual monomers in Palacos R+G to release into water, resulting in a slower release pattern and a lower cumulative concentration of leached monomers. Different crosslinking agents may influence the hydrophobicity of the final product. This may enable, or hinder, leaching of residual monomers into surrounding water-based fluids.

Adverse reactions to PMMA bone cements are reported. Cardiovascular dysfunction, fat-embolic events, and hypotension are described in patients who underwent a PMMA cemented knee or hip implant in orthopedics[1,18]. Dentistry patients with dentures based on PMMA can experience a burning sensation, redness, swelling, and pain at the palate, tongue, and oral mucosa[2]. Symptoms of neurological dysfunction are described after PMMA craniofacial reconstruction[19,20]. During preparation of PMMA, respiratory problems such as irritation of the airways and shortness of breath are reported in literature[21,22]. Residual monomers may leach into water, saliva, or other bodily fluids and can be toxic to the human body[7,8,12]. PMMA-based materials used for dental applications release MMA into saliva for up to one week after insertion, with a three times higher concentration near the surface of the implant[23]. The release of MMA into protein-rich solutions (native saliva) was significantly lower than the release into protein-free solutions (protein-free saliva or water)[24]. This likely reduces potentially toxic effects of leached MMA in physiological situations. Plasma concentrations of MMA during arthroplasty peaked shortly after cement implantation (30 seconds[25] to 2 minutes[26]), and were cleared quickly, more than half of the MMA was cleared during the transpulmonary passage[26].

Immersion of polymerized PMMA-based materials in a 60 °C water bath for 30 minutes during a post-polymerization heat treatment increased the degree of conversion. However, this post-treatment did not markedly affect the slight *in vitro* cytotoxicity observed in L-929 fibroblasts[27]. Endothelial cells lost their normal phenotype and adherence to one-another and to the substratum, they rounded up, and detached from the surface upon contact with MMA[22]. Cytotoxicity was also observed in human oral fibroblasts[8]. Other studies showed that 0.1-1.0 µg/mL of MMA activated tissue factor and consequently the coagulation of human blood[22]. Polymerized PMMA-based materials which were put into contact with platelet-rich plasma induced activation of platelets. This may contribute to the occurrence of deep venous thrombosis following arthroplasty, but may also release growth factors stimulating bone formation[28].

PMMA-based materials with different compositions are currently used for similar surgical interventions. In medicine, an optimal implantation material is mandatory with respect to safety, ease-of-use, and the eventual aesthetic outcome. As reported in this study, these materials showed significantly different quantities of leached residual monomers in water over a two week period. The composition of PMMA influences the mechanical properties[7,29,30] and may potentially influence cellular interactions and adverse events. Combined, this suggests that the composition of PMMA-based materials has a significant influence on the success rate. Medical professionals and the manufacturer should strive for optimal compositions for specific applications.

If possible, preoperative manufacturing of medical devices may allow for better control on the final chemical, mechanical, and biological properties. This also allows for a post-polymerization treatment by immersion in water for longer than 24 hours to decrease the release of residual monomers. Preoperatively manufacturing of the medical device reduces duration of surgery, exposure of medical professionals to MMA vapor, and burden on the surgeon.

CONCLUSION

Different compositions of PMMA-based materials showed different release patterns and quantities of residual monomers. The novel polymer, NextDent C&B MFH, released the lowest amount of monomers. It is therefore advisable to develop specific compositions of PMMA-based materials for different applications in the medical field. Especially for neurosurgical applications an optimized material may prove to be advantageous due to the proximity to the cerebral meninges and the brain.

Acknowledgements

We especially thank Brian Jacobs for sharing his expertise in this field.

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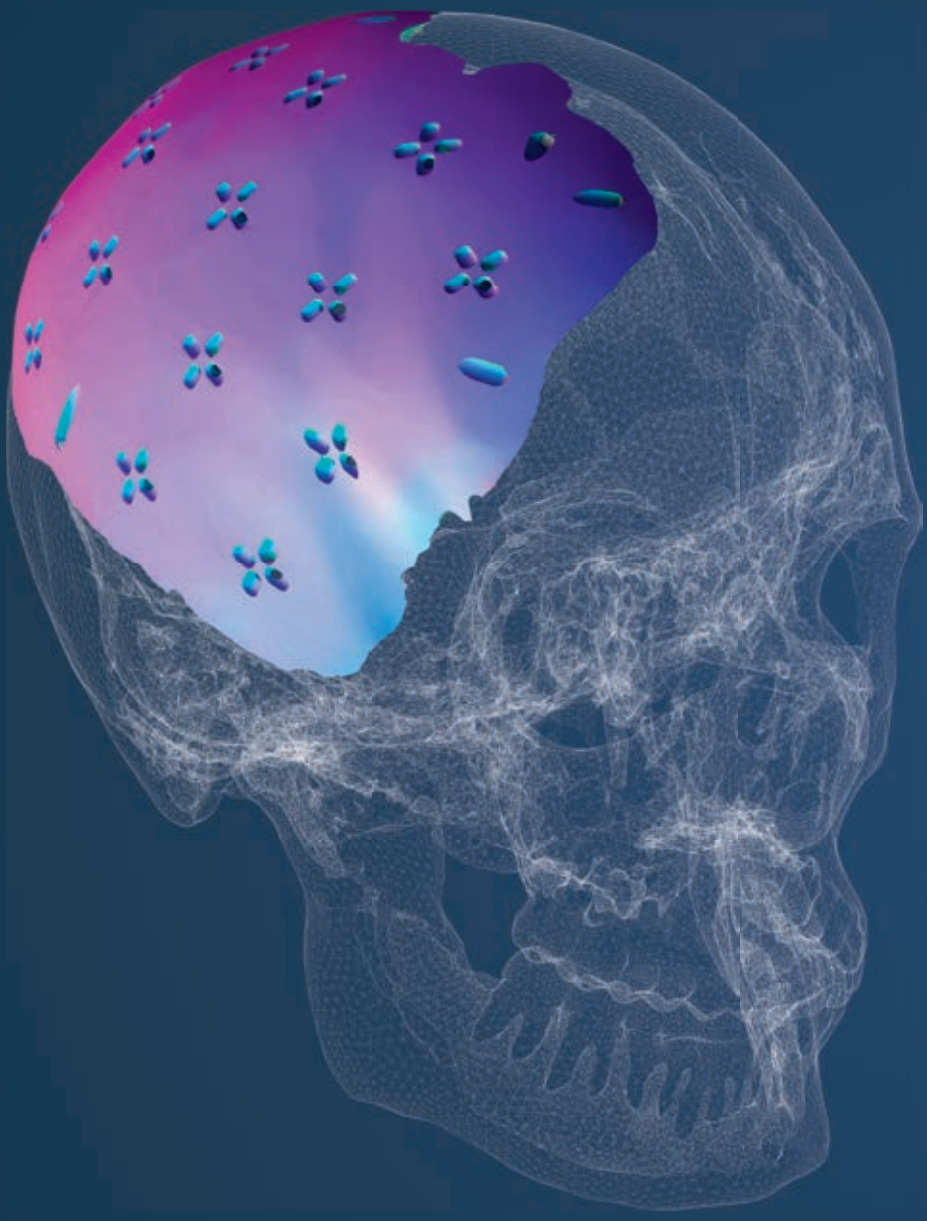

CHAPTER 9

Effects of sterilization on the mechanical properties of poly(methyl methacrylate)-based personalized medical devices

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This chapter is based on the publication: Effects of sterilization on the mechanical properties of poly(methyl methacrylate)-based personalized medical devices

Published: Journal of the Mechanical Behavior of Biomedical Materials;2018

ABSTRACT

Background: Nowadays, personalized medical devices are frequently used for patients. Due to the manufacturing procedure sterilization is required. How different sterilization methods affect the mechanical behavior of these devices is largely unknown.

Materials and methods: Three poly(methyl methacrylate) (PMMA) based materials (Vertex Self-Curing, Palacos R+G, and NextDent C&B MFH) were sterilized with different sterilization methods: ethylene oxide, hydrogen peroxide gas plasma, autoclavation, and γ-irradiation. Mechanical properties were determined by testing the flexural strength, flexural modulus, fracture toughness, and impact strength.

Results: The flexural strength of all materials was significantly higher after γ-irradiation compared to the control and other sterilization methods, as tested in a wet environment. NextDent C&B MFH showed the highest flexural and impact strength, Palacos R+G showed the highest maximum stress intensity factor and total fracture work.

Conclusion: Autoclave sterilization is not suitable for the sterilization of PMMA-based materials. Ethylene oxide, hydrogen peroxide gas plasma, and γ-irradiation appear to be suitable techniques to sterilize PMMA-based personalized medical devices.

INTRODUCTION

Poly(methyl methacrylate) (PMMA) has been widely used in different fields of healthcare. It is used as bone cement for fixation of knee and hip implants in orthopedics, as the base of dental prosthesis, for cranial reconstruction in neurosurgery, and for many other medical devices.[1] PMMA is light, radiolucent, cost efficient, and easy to use. However, it is associated with complications such as infection[2]. The exothermic polymerization of PMMA can cause burn injuries if applied directly onto tissues and there are indications that residual monomers are toxic to the body[1].

The mechanical properties of personalized medical devices are essential for long-term survival. These properties may be affected by storage time, pre-treatment, sterilization and the location of the inserted medical device in the body. PMMA demonstrates increased flexibility in a liquid environment compared to a dry environment, and storage at 37°C makes PMMA less resistant to fracture than storage at 21°C[3].

The most common sterilization methods for medical applications are ethylene oxide gas (EtO), hydrogen peroxide gas plasma (HPGP), autoclavation, and γ-irradiation[4]. These sterilization methods are important as PMMA-based medical devices are not only prepared by powder and liquid mixing in the operating room, but pre-fabricated 3D-printed methacrylate-based materials and ex vivo polymerization are also used[5-7]. The advantage of 3D-printing is a better control on the shape and material properties of the medical device. Manufacturing the medical device before surgery reduces surgical times and removes limitations to the environmental conditions during polymerization, enabling optimizations that may lead to better clinical outcomes. However, the device then needs to be sterilized, this presents a challenge to retain optimal material behavior.

The sterilization of PMMA powder is usually performed by γ-irradiation, except for Palacos, which is sterilized using EtO[8]. The liquid MMA monomer is sterilized through membrane filtration[8-11]. γ-irradiation of PMMA results in chain scission, detectable through a decrease in molecular weight[9,11-13]. This directly influences mechanical properties such as fracture toughness, fatigue, and flexural strength[9,10,12].

The effect of autoclave, EtO, and hydrogen peroxide (H_2O_2) sterilization, on the chemical structure and surface morphology of PMMA is previously described[4]. However, it is still unknown how these sterilization methods affect mechanical properties of cured PMMA. Therefore, the aim of this study is to investigate the effect of sterilization methods: EtO, HPGP, autoclavation, and γ-irradiation on the mechanical properties of PMMA-based personalized medical devices.

MATERIALS AND METHODS

The effects of sterilization with EtO, HPGP, autoclavation, and γ-irradiation on the mechanical properties of PMMA-based personalized medical devices were investigated (Table 1). Since the mechanical properties of the PMMA-based materials may vary depending on the application, three different types were investigated: Vertex Self-Curing, Palacos R+G and NextDent C&B MFH (Table 2).

For each material the flexural strength, flexural modulus, fracture toughness, and impact strength were determined after sterilization and compared to the unsterilized control. All test methods for determining the mechanical properties were taken from the appropriate standards, e.g. ISO 20795-1:2013 and ISO 179-1:2010[14,15].

Palacos R+G (Heraeus, Hanau, Germany) and Vertex Self-Curing (Vertex-Dental, Soesterberg, The Netherlands) were hand mixed and prepared according to the manufacturer's instructions. These specimens were molded using a stainless-steel mold. Curing of Vertex Self-Curing followed in a water-filled pressure cooker for ten minutes at 55°C and 2.5 bar.

NextDent C&B MFH (NextDent, Soesterberg, The Netherlands) was 3D printed in a horizontal direction with a Rapidshape D30 (Rapidshape, Heimsheim, Germany) based on digital light processing (DLP). These specimens were washed in ethanol twice (three minutes and two minutes, respectively) under ultrasonic vibrations and dried for ten minutes prior to a 30 minutes post-cure in a LC3D-PrintBox (NextDent, Soesterberg, The Netherlands).

All specimens were wet grinded with standard metallographic grinding paper (P500, P1000 and P1200) and visually inspected for a smooth surface without porosities and irregularities. Sterilization was performed seven to ten days post-polymerization and the specimens were stored at least 72 hours under standard laboratory climate conditions (22 ± 1°C and 50 ± 2% humidity).

Flexural strength and flexural modulus

Eighteen series of ten rectangular specimens (64.0 ± 1.0 × 10.0 ± 0.2 × 3.3 ± 0.2 mm), one per material and sterilization method, were produced. The width and height of the specimens were measured by dial caliper before sterilization. After sterilization and prior to testing, the specimens were immersed in a water bath at 37.0 ± 1.0°C for 50 ± 2 h. The flexural strength was tested in a water bath at 37.0 ± 1.0°C, using a three-point-bending test (supporting bars span of 50.0 ± 0.1 mm) in a universal testing machine (Mecmesin Imperial 1000, West Sussex, UK) with a crosshead speed of 5.0 mm/min. Each specimen was tested until fracture or until the maximum curvature was reached. To calculate the ultimate flexural strength, σ and the flexural modulus, E, Equation 1 and 2 were used.

$$\sigma = \frac{3Fl}{2bh^2} \qquad (1)$$

$$E = \frac{F_1 l^3}{4bh^3 d} \qquad (2)$$

where F is the load [N], l is the distance between the supports [mm], b is the width and h is the height of the specimen [mm].

Fracture Toughness

Eighteen series of ten rectangular specimens (39.0 × 8.0 ± 0.2 × 4.0 ± 0.2 mm), one per material and sterilization method, were produced. The specimens were notched on the centerline with a sawing blade to a depth of 3.0 ± 0.2 mm. A pre-crack was made with a sharp blade with a thickness of 0.55 mm to a depth of 100 - 400 µm. An optical microscope was used to check the depth of the pre-crack. The width and height of each specimen was measured with a dial caliper. After sterilization and prior to testing the specimen were immersed in a water bath at 37 ± 1.0°C for 7d ± 2 h, followed by a water bath at 23.0 ± 1.0°C for 60 ± 15 min. The fracture toughness was measured using a three-point bending test (supporting bars span of 32.0 ± 0.1 mm) under dry conditions using the universal testing machine with a crosshead speed of 1.0 mm/min. The specimens were loaded until fracture. The maximum stress intensity factor, K_{max}, in MPa $m^{1/2}$ was calculated with Equation 3.

$$K_{max} = \frac{f P_{max} l_t}{(b_t h_t^{3/2})} \times \sqrt{10^{-3}} \quad (3)$$

where P_{max} is the maximum load exerted on the specimen [N], h_t is the height and b_t is the width of the specimen [mm], l_t is the span [mm] and f is a geometrical function, dependent on x in Equation 4, where a is the crack length consisting of the notch and the pre-crack [mm].

$$f(x) = 3x^{1/2}[1.99 - x(1-x)(2.15 - 3.93x + 2.7x^2)]/[2(1+2x)(1-x)^{\frac{3}{2}}];\ x = \frac{a}{h_t} \quad (4)$$

The total fracture work, W_f, in J/m² was calculated using Equation 5.

$$Wf = \frac{U}{[2b_t(h_t - a)]} \times 1000 \quad (5)$$

where a, h_t and b_t are the same as for Equation 3. U [N mm] is the area under the load/displacement curve that is defined by Equation 6.

$$U = \int P_d \Delta \quad (6)$$

Unnotched Charpy impact strength

Eighteen series of ten rectangular specimens (62.0 ± 1.0 × 6.0 ± 0.2 × 4.0 ± 0.2 mm), one per material and sterilization method, were produced. The specimens were placed in a Karl Frank 53301 testing machine with a supporting bars span of 50.0 mm and a pendulum energy of 0.5 J for Vertex Self-Curing and Palacos R+G, and 1.0 J for NextDent C&B MFH. The Charpy impact strength, a_{cU}, was calculated in kJ/m² with Equation 7.

$$a_{cU} = \frac{E_c}{hb} \times 10^3 \quad (7)$$

where E_c is the corrected energy absorbed by breaking the test specimens [J], h is the height and b is the width of the specimen [mm].

Data were statistically analyzed using one-way analysis of variance (ANOVA) followed by Tuckey's *post hoc* test ($\alpha = 0.05$) in SPSS version 24.0 (IBM, Armonk, NY, USA).

RESULTS

The results of the mechanical tests and the statistical analysis are summarized in Table 3 and representative curves for the flexural strength and toughness are graphically depicted in Figure 1. The autoclave-sterilized specimens were excluded from the results and the statistical analysis due to deformation or exfoliation during the sterilization process.

Table 1: Specifications of the sterilization methods (autoclavation, ethylene oxide (EtO), hydrogen peroxide gas plasma (HPGP) and γ-irradiation).

Sterilization Technique	Specifications	ISO norm
Autoclavation	121 °C for 16 min or 134 °C for 3.5 min	17665:2006
EtO	-	11135:2014
HPGP	Sterrad	11737:2006
γ-irradiation	26.4 – 29.4 kGy from Cobalt-60	11137-1:2015

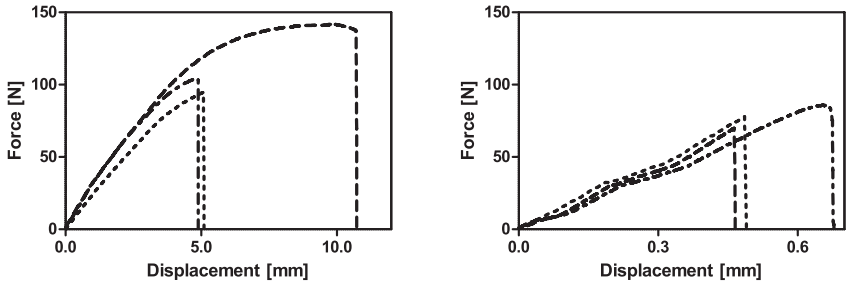

Figure 1: Force displacement graphs of representative flexural strength (left) and toughness (right) tested specimens of Vertex Self-Curing (dot), Palacos R+G (dot-dash) and NextDent C&B MFH (dash).

Flexural strength and flexural modulus

NextDent C&B MFH had a significantly higher flexural strength (σ) for each sterilization method compared to the other materials. Vertex Self-Curing had a significantly higher flexural strength for γ-irradiation and HPGP compared to Palacos R+G. The flexural strength of γ-irradiated specimens was significantly higher than the otherwise sterilized and control specimens for all materials.

NextDent C&B MFH had a significantly higher flexural modulus (E) than Vertex Self-Curing for control specimens. For HPGP sterilized specimens, NextDent C&B MFH showed a significantly higher flexural modulus compared to Vertex Self-Curing and Palacos R+G. EtO sterilized Palacos R+G showed a significantly higher flexural modulus than Vertex Self-Curing. For Vertex Self-Curing and Palacos R+G none of the sterilization methods showed a significant difference compared to the control specimens. However, NextDent C&B MFH showed a significantly reduction after EtO sterilization, and a significant increase upon HPGP sterilization.

Table 2: Specifications of the PMMA-based materials used in this study.

Material / *Application*	Ingredients powder	Ingredients liquid	Batch number	Expiration date
Vertex Self-Curing[a] *Denture*	Poly(methyl methacrylate), benzoyl peroxide, various pigments	Methyl methacrylate, N,N-Dimethyl-p-toluidine, ethylene glycol, dimethacrylate	XN423P02 (shade 5) XN341L29	04-2022 03-2022
Palacos R+G[b] *Bone cement*	Gentamicin, poly(methylacrylate, methyl methacrylate), zirconium dioxide, benzoyl peroxide, colorant E141	Methyl methacrylate, N,N-dimethyl-p-toluidine, hydroquinone, colorant E141	-	-
NextDent C&B MFH[c] *Personalized medical device*	-	Methacrylate oligomer, methacrylate monomer, inorganic filler, phosphine oxides	XN305N01 (shade N3)	-

[a] Vertex-Dental, Soesterberg, The Netherlands [b] Heraeus, Hanau, Germany [c] NextDent, Soesterberg, The Netherlands

Fracture Toughness

Palacos R+G showed a significantly higher maximum stress intensity factor (K_{max}) compared to the other materials. For the HPGP sterilization specimens, it was significantly higher than NextDent C&B MFH. Following EtO sterilization, Vertex Self-Curing and Palacos R+G showed a significantly higher maximum stress intensity factor than NextDent C&B MFH. Upon HPGP sterilization NextDent C&B MFH showed a significant increase. Other sterilization methods had no significant effect on the maximum stress intensity factor of the materials.

Palacos R+G had a significantly higher total fracture work (W_f) compared to the other materials for each sterilization method. The sterilization methods had no significant influence on the total fracture work of the materials.

Impact strength

NextDent C&B MFH showed a significantly higher Charpy impact strength (a_{cU}) after γ-irradiation and HPGP sterilization compared to the other materials. NextDent C&B MFH also had a significantly higher Charpy impact strength compared to Palacos R+G for the control. There was no significant difference found in the Charpy impact strength between the sterilization methods for Vertex Self-Curing and Palacos R+G. For NextDent C&B MFH there was a significant increase of the Charpy impact strength after γ-irradiation.

Table 3: Flexural strength (σ) in MPa, flexural modulus (E) in MPa, maximum stress intensity factor (K_{max}) in MPa $m^{1/2}$, total fracture work (W_f) in J/m² and Charpy impact strength (a_{cU}) in kJ/m² of the different materials after sterilization with ethylene oxide (EtO), hydrogen peroxide gas plasma (HPGP) and γ-irradiation.

		Control	EtO	HPGP	γ-irradiation
σ	Vertex Self-Curing	66.8 (4.3) ^{A,a}	66.4 (2.7) ^{A,a}	68.3 (3.3) ^{B,a}	80.0 (3.4) ^{B,b}
	Palacos R+G	61.6 (2.8) ^{A,a}	63.8 (1.8) ^{A,a}	60.2 (2.5) ^{A,a}	70.6 (3.2) ^{A,b}
	NextDent C&B MFH	91.8 (6.3) ^{B,a}	89.2 (3.5) ^{B,a} †	94.0 (3.4) ^{C,a} †	109.3 (2.6) ^{C,b}
E	Vertex Self-Curing	2166 (160) ^{A,a}	2165 (68) ^{A,a}	2212 (104) ^{A,a}	2265 (87) ^{A,a}
	Palacos R+G	2256 (85) ^{AB,a}	2307 (76) ^{B,a}	2226 (90) ^{A,a}	2244 (49) ^{A,a}
	NextDent C&B MFH	2374 (118) ^{B,b}	2221 (78) ^{AB,a}	2521 (96) ^{B,c}	2238 (55) ^{A,ab}
K_{max}	Vertex Self-Curing	1.70 (0.34) ^{A,a}	1.87 (0.35) ^{B,a}	1.98 (0.21) ^{AB,a}	1.83 (0.21) ^{A,a}
	Palacos R+G	2.18 (0.31) ^{B,a}	2.40 (0.20) ^{C,a}	2.24 (0.35) ^{B,a}	2.31 (0.22) ^{B,a}
	NextDent C&B MFH	1.42 (0.09) ^{A,a}	1.63 (0.12) ^{A,ab}	1.80 (0.14) ^{A,b}	1.77 (0.20) ^{A,ab}
W_f	Vertex Self-Curing	476.7 (163.2) ^{A,a}	562.9 (193.2) ^{A,a}	579.9 (93.2) ^{A,a}	494.5 (97.6) ^{A,a}
	Palacos R+G	940.0 (151.3) ^{B,a}	981.1 (123.7) ^{B,a}	948.6 (135.7) ^{B,a}	832.0 (74.8) ^{B,a}
	NextDent C&B MFH	331.4 (34.1) ^{A,a}	421.8 (51.0) ^{A,a}	443.5 (77.5) ^{A,a}	405.3 (66.4) ^{A,a}
a_{cU}	Vertex Self-Curing	7.6 (1.8) ^{AB,a}	7.8 (2.5) ^{A,a}	7.3 (1.1) ^{A,a}	6.5 (2.5) ^{A,a}
	Palacos R+G	4.7 (1.0) ^{A,a}	4.5 (1.4) ^{A,a}	4.5 (0.9) ^{A,a}	4.0 (1.1) ^{A,a}
	NextDent C&B MFH	10.5 (4.0) ^{B,ab} ‡	7.3 (1.9) ^{A,a}	11.1 (2.3) ^{B,bc} ʠ	14.2 (3.8) ^{B,c}

Values given as mean and standard deviation (SD). Identical letters indicate no significant difference between the groups. Capital letters indicate differences between the materials (split by sterilization method), the lowercase letters indicate differences between the sterilization methods (split by material).

†: n<10 because maximum strength could not be calculated, since some specimens did not fail during testing.

‡: Test was repeated because of an inordinate high standard deviation, both tests are combined in this result.

ʠ: n=9 because one specimen was broken during the sterilization process.

DISCUSSION

PMMA-based polymers have been used for many years in medical devices with their specific formulations and applications. No reports on a systematic investigation of the mechanical properties using the same ISO standards are available (bone cement (ISO 5833) or dental (ISO 20795-1:2013 and ISO 179-1:2010)), making comparison between the reported values difficult. Literature reports the flexural strength (56.3 MPa), flexural modulus (2213 MPa), the toughness (2.03 MPa $m^{1/2}$), and total fracture work (897 J m^{-2}) of Palacos R+G[16,17]. The impact strength reported for Palacos R without gentamicin was 4.1 kJ m^{-2} [18]. For Vertex Self-Curing the flexural strength (79.6 MPa) and flexural modulus (2.38 GPa) are reported[19]. Currently, there is no data available on the mechanical properties of NextDent C&B MFH. These values reported in literature are in line with the findings presented in this study.

From the measured mechanical properties of the different materials the following trends were observed (I) an increase in flexural strength (σ) resulted in decreased toughness (K_{max} and W_f), (II) an increase in flexural strength (σ) resulted in increased impact strength (A_{cU}) and (III) an increase in toughness (K_{max} and W_f) resulted in decreased impact strength (A_{cU}). The latter is contradicting with finding of Lewis and Mladsi [18], where a positive correlation was found between the toughness (K_{max}) and impact strength (A_{cU}). The toughness and impact strength are two independent properties, which are related to the ductile or brittle nature of the material[20]. Brittle polymers fail through nucleation of voids and initiation and propagation of brittle cracks resulting in catastrophic failure. The polymers have yield strengths higher than their ultimate or breaking strengths, and thus a low crack initiation *and* low crack propagation energy in impact[20]. Ductile polymers fail by crazing or matrix shear yielding. Both mechanisms lead to high crack initiation energy, but to a low propagation energy at impact. As a result one can expect a high unnotched impact strength, but a low notched impact strength[20].

In this study Palacos R+G and Vertex Self-Curing have a comparable flexural strength and flexural modules, however, Vertex Self-Curing is more brittle compared to Palacos R+G (Figure 1). According to Perkins and Lewis et al., one should expect that the unnotched impact strength of Palacos R+G exceeds the impact strength of Vertex Self-Curing[10,20]. However, the experiments showed a decrease of impact strength, suggesting that Palacos R+G fails at impact by a brittle polymer mechanism, e.g. voids in the material. This seems plausible because Palacos R+G has macroscopically visible voids in the material and contains 10% zirconium dioxide[21] as filler for radio opacity, which are most probably not chemically incorporated in the matrix and can act as a void.

Beside the composition of the material, the effect of the sterilization procedure was investigated. In general, autoclave sterilization is one of the most common sterilization methods[4]. In this study it caused specimens to deform or exfoliate due to the high temperatures and pressurized steam, which exceed the glass transition temperature (T_g) of Palacos R (100°C)[21]. A material that deforms or exfoliates during sterilization is not desirable for medical devices, therefore autoclave sterilization was excluded from further analysis. HPGP and EtO did not tend to significantly change material properties. In contrast, the flexural strength of all three materials increased significantly following γ-irradiation. Literature reports a decrease in molecular weight of PMMA upon γ-irradiation due to chain scission, this directly relates to worsening of the mechanical properties[9-12]. γ-irradiation increases the amount of scission, it follows therefore that it may also increase side-group scission. An increase in flexural strength originating from additional crosslinking thus seems unlikely, instead it could originate from a change in wettability of the material. These materials show a significant reduction in flexural strength when immersed in water. A reduction in hydrophilic side-groups due to γ-irradiation induced side-group scission may thus effectively increase the flexural strength compared to the control when both are incubated in water following sterilization, even though the molecular weight is lower.

Most related research regarding bone cements is performed in the field of orthopedics, which use the ISO 5833 norm to determine mechanical properties. Since Vertex Self-Curing and NextDent C&B MFH are mostly used as dental acrylics, which have different demands compared to bone cement applications, ISO 20795-1:2013 and 179-1:2010 norms were applied in this study. ISO 5833 would allow better comparison to the available literature, however, the bone cements are tested in dry conditions after 24 hr. This results in over estimation of the mechanical properties[22]. The current ISO 5833 standard does do not mimic the conditions or environment in which the material is used clinically and should be revised and preferably harmonized with more realistic dental ISO standards, which use 37°C in water (2 – 7 days).

When comparing the above mentioned materials, NextDent C&B MFH performs better than the other materials on flexural strength and modulus, as well as impact strength. However it also has significantly lower toughness and shows a more brittle behavior, especially compared to Palacos R+G which appears more ductile. This is in line with literature, as an increase in crosslink density lowers the fracture toughness and limits the total crack-tip strain[20]. NextDent C&B MFH is a poly(dimethacrylate) and therefore has significantly more crosslinks than the other two materials. Due to crosslinking in the materials tested, thermoset polymers with similar chemical compositions may show similar trends to the results presented in this study, although this requires further investigation.

There is no influence of EtO on the molecular weight of PMMA reported in literature, suggesting that EtO does not influence the mechanical properties of PMMA. The results reported in this study show no significant difference between unsterilized and EtO sterilized specimens. However, EtO is a toxic gas and requires a long period - up to fifty days - of degassing[9, 12, 23].

This study did not take into consideration the effect of sterilization on biocompatibility of the materials and leaching of potential harmful substances, i.e. unreacted monomer and activator. It should be noted that the powder and liquid components of PMMA used in the operating room are sterilized before use, γ-irradiation is often used to sterilize the powder component[8]. These properties are crucial for clinical use and should be investigated in future studies.

CONCLUSION

This study provides an overview of the influences of different sterilization methods on the mechanical properties of PMMA-based personalized medical devices. Autoclave sterilization is not suitable for the sterilization of PMMA-based materials. EtO, HPGP, and γ-irradiation appear to be suitable techniques to sterilize PMMA-based personalized medical devices. γ-irradiation could even increase the effective flexural strength in a wet environment.

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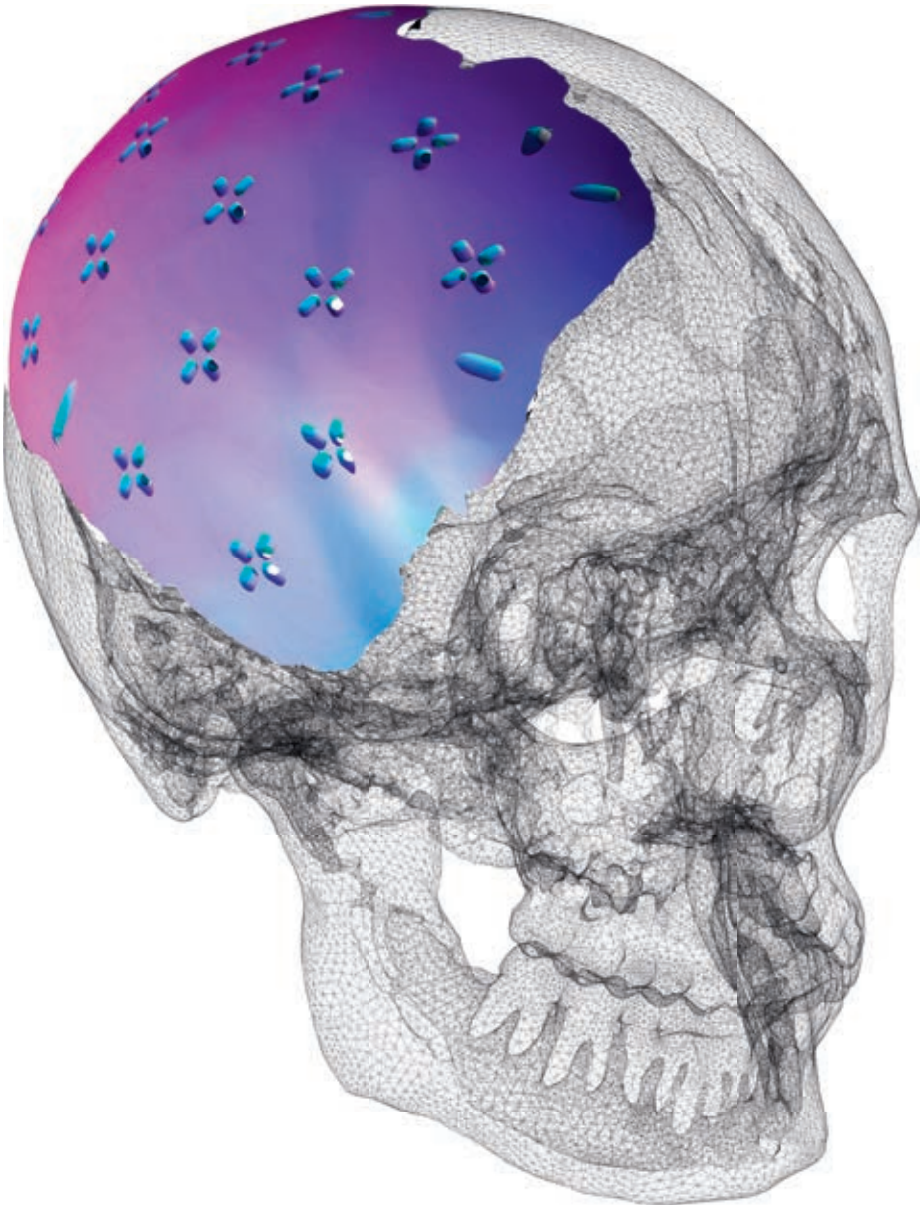
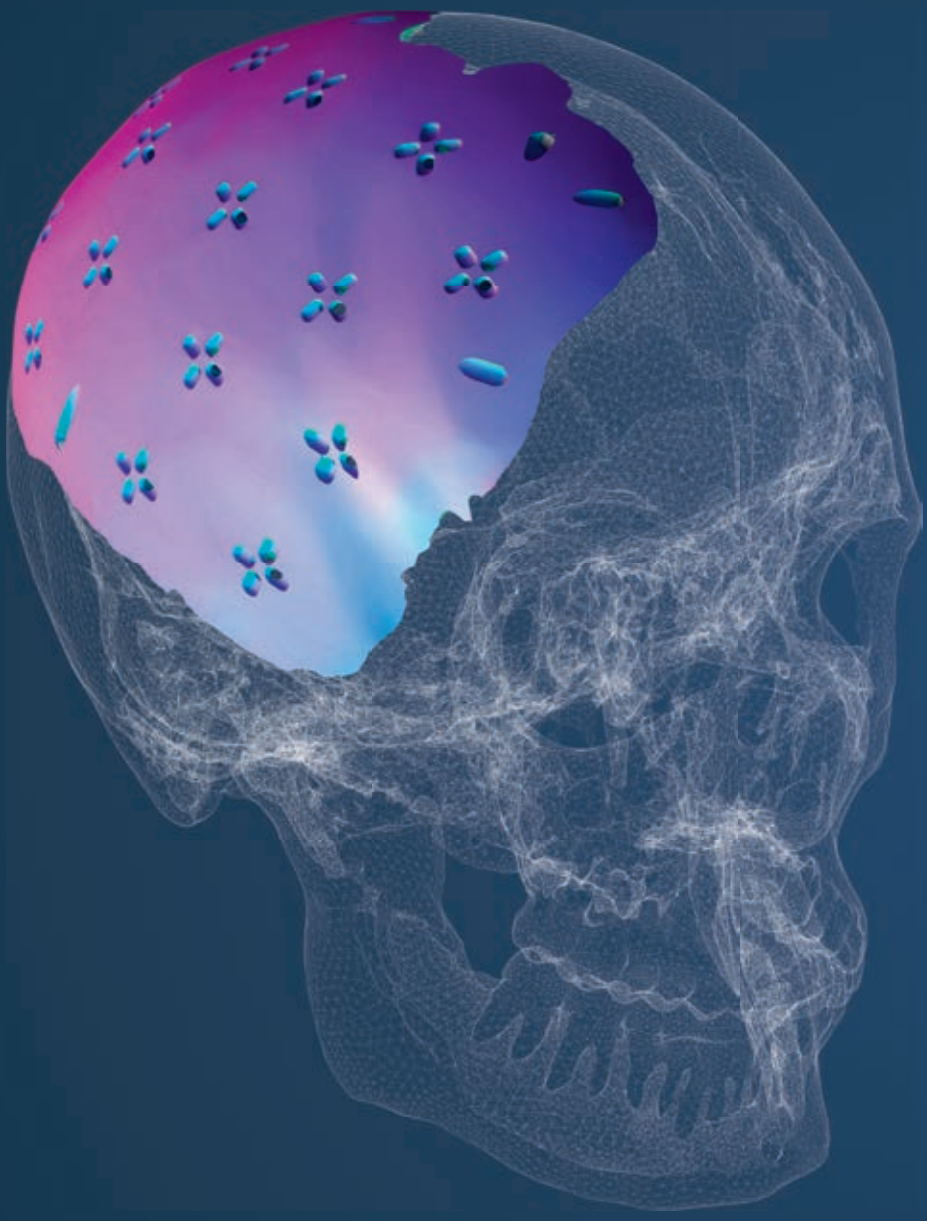


PART VI

General discussion



CHAPTER 10

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The objective of this thesis was to identify and to fill gaps in the current understanding of techniques and materials for cranioplasties by analyzing the available evidence and systematically collecting and evaluating data. We made a step forward towards the prerequisites and development of a new material for cranioplasties. Despite the new findings in this thesis, our research has not yet standardized the management of cranioplasties. Literature research was often restricted by studies with small patient samples, the inability to carry out a study that would offer convincing evidence, and the limited amount of currently available evidence regarding cranioplasties. This hinders clinical practice, but also complicates the design and execution of methodologically sound studies on cranioplasties. In this chapter, we reflect on our research findings and offer some possibilities for future developments, in which several challenges must be overcome.

Lack of definitions, protocols and guidelines

One of the main findings in this thesis is that there is no standard treatment and no standardized or generally accepted protocol for decompressive craniectomy nor cranioplasty.

The available literature shows that the definition of complications, including infection and resorption, diverges widely[1,2]. Multiple factors need to be considered according to the nature of the cranial defect and the medical prognosis; systemic and local factors; size and form of the defect; goals of the reconstruction (protection and/or cosmesis), the choice of material and the manufacturing process.

One of the materials mostly used for cranioplasties is autologous bone. Autologous bone is associated with high resorption rates[3]. A commonly described definition for resorption discerns two types of resorption: thinning of the bone mass on imaging or by palpation (type I), and complete lysis of the inner and outer tabulae with loss of cerebral protection, requiring revision (type II)[2,4]. Most patients do not undergo a standardized follow-up CT-scan, unless the patient experiences symptoms, as pain, discomfort or cosmetic impairment. The lack of a standardized follow-up protocol including a CT-scan leads to underreporting of resorption rates. The resorption process differs among patients: some patients will not notice any resorption of the autologous bone at all and if a patient is asymptomatic, the need for a routine post-operative CT-scan in the follow-up is debatable.

On the other hand, a CT follow-up protocol for autologous bone might be considered for the follow-up of the bone integrity and surveillance of early signs of resorption and loss of the protective function of the reconstruction. If resorption is detected the patient may be encouraged to wear protection or an alloplastic cranioplasty might be considered.

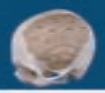
Materials for cranioplasties

A wide range of materials for cranioplasty with different advantages and disadvantages exists[3] (Table 1). No gold standard is available for the reconstruction material. The optimal reconstruction material may vary, depending on the patient characteristics and various clinical settings.

With the current evidence, autologous bone for cranial reconstructions may be abolished for various reasons, but mainly because of its high resorption rate[3]. In **chapter 3** we found a resorption rate of 9.1%. This number is based on the cranioplasties that were removed due to complaints of resorption (e.g. pain, cosmesis or a palpable defect). A prerequisite for autologous bone preservation is an adequate and regulated bone bank. The increased demands for quality control and the novel regulations for bone banks in hospitals hamper the application of autologous bone for cranial reconstructions in many institutes and countries. The increased expertise and evolution of 3D virtual planning software and additive manufacturing (CAD/CAM) techniques allows the surgeon to choose for alloplastic cranial implants as a good alternative. This is especially the case in economically developed countries. On the other hand, hospitals need the equipment and expertise in terms of 3D planning software, 3D printers or CAD/CAM machines. Apart from these factors, the surgical team needs experience with the implantation of alloplastic materials and enough financial resources should be available to design and manufacture an alloplastic cranioplasty. In countries where a virtual planned and printed cranioplasty is not an option, autologous bone may be the best option for reconstruction, at least in order to protect the brain initially. For this purpose the autologous bone should be stored in a freezer or in an abdominal pocket.

Most frequently used alloplastic materials for cranioplasties are PMMA, titanium, hydroxyapatite and PEEK. Each material has its own specific characteristics (Table 1).

Table 1. Characteristics of materials used for cranioplasties

	Autologous Bone 	PMMA 	Titanium 	Hydroxyapatite 	PEEK 
Aesthetics	✗	○	✓	○	✓
Biocompatibility	✓	✓	✓	✓	✓
Costs	✓	✓	✗	✓	✗
Exothermic reaction	✓	✗	✓	✓	✓
Intra-operative adjustments	✓	✓	✗	✓	✓
Regenerates into bone	✗	✗	✗	✓	✗
Resterilization	✗	✗	✗	✗	✓
Safe for the surgeon	✓	○	✓	✓	✓
Thermal conduction	✓	✓	✗	✓	✓
Thermal stability	✗	✗	✗	✗	✓
Toxicity	✓	○	✓	✓	✓
Possible to manufacture 3D PSI	✗	○	✓	✗	✓

✓ Successful results provided in earlier studies
✗ Negative results provided in earlier studies
○ No consensus in literature, further research is required

The various materials differ substantially as to their suitability. Many different types of PMMA or PMMA-based materials are available in the medical field. PMMA is a reconstructive polymer, which is formed through the polymerization of PMMA particles with a liquid MMA. This conversion is never complete and residual monomers will remain in the implant. These residual monomers may cause toxic reactions[5] and it is not possible to 3D print PMMA yet. PMMA does not have the properties for bony ingrowth, and therefore no commensurately growth with the cranium will follow. PMMA is relatively cheap, easy to use and radiolucent.

Not all hospitals have the opportunity to use computer software for designing and manufacturing a cranioplasty. But some surgeons do use molds for example of nylon, plaster, or silicon -(virtually designed or not) to improve the esthetic outcome of PMMA cranioplasties[6]. In those cases there are a number of options to mechanically improve the cranioplasty. As shown in **chapter 4** the manufacturing of PMMA cranioplasties under pressure ensures reduced porosity in the material. The results of chapter 4 lead to the advice to manufacture all PMMA cranioplasties preoperatively, in a safe environment under pressure of at least 2.2 bar to increase the mechanical properties. There are more benefits to manufacturing the cranioplasty preoperatively. One important advantage is that the cranial implant can be virtually designed using 3D planning software. Based on such a 3D planning, the implant can be manufactured using computer-aided manufacturing techniques. Another benefit could be that the polishing of the cranioplasty after manufacturing can be applied, resulting in a reduced biofilm and less bacterial adhesion[7]. This may result in less re-operations due to a decreased number of infected cranioplasties. In our opinion, preoperative planning and manufacturing of the cranial implant leads to a more predictable surgical intervention and may result in a better fitting implants[6].

PEEK is used for Patient-Specific Implants (PSI) in adults. With the use of the patient's CT-scan and dedicated software it is possible to design a cranioplasty with an accuracy of at least 1 mm[6]. In **chapter 5** no significant prediction factor was found for the failure of PEEK cranioplasties in 40 cranioplasties. PEEK is a relatively new material used in cranial reconstructions and at the moment it is mainly used for secondary reconstructions[8]. This may be the main reason why it shows a relatively high general complication rate, in particular infections[3,8]. If PEEK could be used for the initial reconstruction the infection rate may be less because the overall health condition of the patient is better.

Using preoperatively planned and designed cranial implants, the operation time will be shortened because it is then possible to design and manufacture the cranioplasty before the operation. PEEK has a high biocompatibility, high chemical resistance and a low toxicity[9]. PEEK does not have osseointegration abilities[9] and thus no commensurately grow with the cranium will occur, so it seems that PEEK is not a preferable material in pediatric patients.

Titanium is also a material used for cranioplasties. It has a low infection rate, high biocompatibility and has biological inertness. On the other hand, it is radiopaque and conducts cold and heat. The costs of a titanium implant are relatively high[10]. Current literature recommends ***titanium*** cranioplasties for the pediatric population [11–13]. However, this material still seems to be suboptimal. Until the age of 20 years, the cranium grows physiologically[14]. Before the age of 20 years a titanium cranioplasty is therefore not the optimal solution since it will not grow commensurately with the cranium. This may result in higher complication and reoperation rates and may require a new cranioplasty at a later age. This is also the case for PMMA and PEEK implants, and therefore these are not recommended for the reconstruction of cranial defects in growing children. Similarly, autologous bone appears to be suboptimal for cranial reconstruction in children due to the higher resorption and infection rates that were found in earlier studies in this population[3,15]. ***Hydroxyapatite*** is reported to be a better option for the pediatric population, because of its ability to regenerate bone[11]. Studies have proven that hydroxyapatite will convert into bone. An important disadvantage of hydroxyapatite is that it will remain brittle for a prolonged period of time (probably several months till years). This implies that the patient may not be sufficiently protected and needs to wear a helmet for a longer period of time[16].

Optimization of the cranioplasty procedure

Another challenge is to optimize surgical treatment of the reconstruction after a decompressive craniectomy. Different tools for further optimization were described in **chapter 6**. A 3D virtually designed template and mold can be used to generate a pre-planned outline of the defect and create an exact fit of the concomitantly manufactured cranioplasty[6]. The surgeon follows the outline of the template to create the defect as planned. This may also be feasible in acute situations, as confection templates and implants can be used in for example primary trauma and in vascular emergencies.

Choosing an optimal treatment strategy for reconstruction of a skull defect after ablative tumor surgery presents another interesting dilemma for additional research. In these less acute situations, there is more time to plan preoperatively. Various techniques and timing of surgery have been described in literature for both soft tissue management and bony reconstruction. There is no standard treatment strategy for clinical decision-making in these low-volume high-complex cases. Patient and tumor treatment factors, such as (neo)adjuvant radiotherapy, prior treatments, medical history and comorbidity in frequently old and frail patients, may further hamper decision-making in reconstructing cranial defects. This is why an innovative technique was used in **chapter 7** by applying a virtual pre-surgical 3D planning with the use of a patient-specific cranioplasty of PEEK. This technique aims for optimized control of the resection margin and less intra-operative dilemma's. Wound dehiscence is still a feared complication in these cases. Since bone invasion is unpredictable and varying, an individual approach for calvarian reconstruction in every oncological case will be necessary. Adequate clinical reporting of larger case-series may produce guidelines for this patient group in the near future. Meanwhile, the different clinical, surgical and patient-specific aspects should be taken into account.

Towards a new material

Based on the current knowledge, an ideal material for cranioplasties should:

- be sterile and have anti-bacterial properties
- have osteo-inductive and/or osteo-conductive properties
- exert similar protective characteristics as human bone
- demonstrate no toxicity
- be easy to polish
- be easy to use intraoperatively
- have stable and consistent mechanical properties
- be easy for computer assisted additive manufacturing
- have low costs

In **Chapter 8** different PMMA materials were investigated. This chapter showed that each of these materials, have their own release pattern of residual monomers. C&B MFH, a PMMA-based material designed for 3D printing, proved to have the lowest amount of residual monomers in total. The most residual monomers were released in the first hour for all materials investigated. If this material would be used for cranioplasties in the future, it is recommended to leave the cranioplasty in water at 37°C for at least 60 minutes to enable the residual monomers to leach out the material to reduce toxicity.

Another important characteristic is the ability to sterilize an implant. All cranioplasties should be sterile before they can be implanted in the patient. **Chapter 9** investigated the effect of different sterilization protocols on different types of PMMA or PMMA-based materials. The sterilization method could significantly influence the material properties of cranial implants. We showed that ethylene oxide gas (EtO), hydrogen peroxide gas plasma (HPGP) and γ-irradiation are suitable techniques for the sterilization of PMMA without impact on the material properties. The use of γ-irradiation promotes the effective flexural strength and it seems that the material becomes stronger in a wet environment. Before a new material is used for creating a cranial implant it is important to also investigate the effect of the sterilization process on the mechanical properties of the material. Biological responses of the sterilization process are important, as the material surface may change due to the sterilization itself, with a possible different impact on the human tissue.

FUTURE PERSPECTIVES

Based on recently published literature it is plausible that the need for cranioplasties will increase in the future[17]. Cranioplasties are necessary until bone-induction and/or bone-conducting methods are available. But as long as those medical devices are not developed for this purpose the patient still depends on a cranioplasty to ensure protection of the brain and to improve quality of life. As described in this thesis there is still a need for the development a new material for cranioplasty which includes the properties as mentioned above. Hence, we propose some studies that would contribute to a convincing, evidence-based answer on the question which material will be preferred for a cranioplasty.

A ***randomized clinical trial*** (RCT) should be conducted to gain further insight into the specific characteristics and biological behavior of different materials (titanium, PMMA, hydroxyapatite and PEEK) used in adult patients requiring a cranioplasty. Before commencing such an RCT, a ***Delphi Study*** is advocated to reach consensus on common procedures for cranioplasty. Important parameters to take into account in this study are:

- material used for cranioplasties
- use of antibiotics
- use of surgical drains
- post-operative wound care
- time interval between the decompressive craniectomy and cranioplasty with a alloplastic material.

The primary outcome measure of this future **RCT** needs to be subsequent implant loss, since this is particularly relevant for the patients involved. Additionally, morbidity, number of reconstructive surgeries or the need for permanent protection are important secondary outcome parameters.

Our systematic review described in **chapter 2**[3] showed that the usability of the material as perceived by the surgeons was not taken into account. Details about wound care were also lacking. These two aspects should be included in future research. In this RCT study the surgeon who performs the cranioplasty procedure should assess the usability of the material during surgery, the need for additional intra-operative adjustments and surgery time required to install implant. In general, the time of surgery corresponds with increasing infection rates. Wound care after cranioplasties has never properly been defined or studied in the literature. Variation in the wound care protocol may also affect infection rates. The design of the scalp incision is believed to influence complication rates and should therefore be recorded in the RCT study. The initial incision should be performed over unaffected bone, outside the area of reconstruction, to permit ideal soft tissue coverage and facilitate uneventful wound healing. On the other hand, incision and closure lines over an implant may lead to increased infection rates, especially in case of wound dehiscence.

Whilst patient recruitment in a RCT will take a substantial amount of time, the development of new materials for cranioplasties should not be discontinued in the meantime. Each PMMA subtype has a specific release pattern of residual monomers. To investigate what the effect of residual monomers is on human cells, particularly on cells of the dura and the effect on the surrounding bone, an ***in vitro*** study seems indicated. To optimize anti-bacterial properties and reduce infection rates of the cranioplasty, some innovations may be considered:

1) an anti-bacterial substance could be added to the cranioplasty material that elutes from the material cranioplasty;
2) little holes or corridors may be added in the cranioplasty material that are filled with anti-bacterial substance, which is slowly released from the material during the crucial period of healing time;
3) an anti-bacterial foam or spray that could be applied over the cranioplasty or parts of the cranioplasty to prevent the forming of biofilm and bacterial adhesion.

THE NEXT STEP

The development of a new material for cranioplasty should tackle the current disadvantages.

Recent developments in ***Bioprinting*** may be provide a solution for the development of materials used for cranioplasties. The past decade 3D bioprinting has increased in popularity, as well as the applicability in clinical practice. A lot of research has been performed in this field over the past decade. 3D bioprinting is the utilization of 3D printing and 3D printing–like techniques to combine cells, growth factors, and biomaterials to fabricate biomedical parts that maximally imitate natural tissue characteristics. 3D bioprinting utilizes the layer-by-layer method to deposit materials known as bio-inks, extrusion-based bioprinting, laser-assisted bioprinting and even 4D bioprinting, to create tissue-like structures that are later used in medical and tissue engineering fields[18,19]. Wang et al. and Gao et al. both describe the first steps towards bone bioprinting. Wang et al. introduced the use of hierarchical porous and recombinant human bone morphogenetic protein-2(rhBMP-2)-loaded calcium phosphate nanoparticle/poly(L-lactic acid) (PLLA) nanocomposite scaffolds. The well-designed 3D printed scaffolds exhibited hierarchical porous structure and tunable osteoconductivity and osteoinductivity[20]. Gao et al. used acrylated peptides and PEG hydrogel with human mesenchymal stem cells for the formation of robust bone combined with cartilage[21].

If bioprinting could be used for the reconstruction of cranial defects, the patient's own cells (e.g. stem cells) would ideally be used for the regrowth of a cranioplasty to replace the removed part of the skull. The anatomy of the human skull is complex because of its vascularity and multiple layers of bone. Apart from the complex anatomy the defects tend to be relatively large. Bioprinting a cranial reconstruction will therefore be challenging. To prevent bone resorption, a supplement developed from growth factors could be necessary to prevent the increased activity of osteoclasts.

Nowadays, bioprinting is relatively expensive, but it is expected that these costs will decrease in time. In the future this may become an affordable and stable solution for patient in the need for cranioplasty.

A FUTURE CRANIOPLASY PATIENT CASE

In the future the planning phase and manufacturing of cranioplasties should be easier, faster and cheaper. This may be realized in the near future by the introduction of several innovative changes in the workflow from craniectomy to cranioplasty and beyond. This is exemplified in the following scenario:

Case: A patient gets involved in a car accident. During the ride in the ambulance to the hospital, the neurological situation deteriorates.

Phase I: If the ambulance were to have the mobile equipment to perform a 3D scan of the head, an intracranial hemorrhage can be diagnosed. On arrival at the hospital, the intracranial pressure is measured to determine whether a decompressive craniectomy is indicated. A decompressive craniectomy with the optimal circumference is performed to either remove the hemorrhage or to lower the elevated pressure.

Phase II: After decompressive craniectomy, a patient-specific early recovery program starts [22]. This program ensures an optimal condition of the patient and an early recovery. This can be realized by means of an adjusted diet, optimum pain control, motivation to quit smoking and drink alcohol and a good sleeping rhythm to improve the patient's condition, with or without a (virtual) physical therapist. This program helps to reduce hospital stay, reduce postoperative complications, avoid stress and reduce insulin resistance[23]. In the end this program reduces costs because of the limitation of the parameters described above.

Phase III: When the patient is neurologically stable and fit for surgery, the process of a new cranioplasty is started. First, a conversation with the patient and/or his family is needed to know the patient's preferences concerning the choice of the material to be inserted. This helps in the decision for a material that best fits the patient, both literally and figuratively speaking[24]. Patients should be aware of the advantages and disadvantages of the available options for reconstruction to facilitate a shared decision-making process. In the future artificial intelligence could probably be used to support the decision-making process[25].

Phase IV: All patients and surgeons will prefer a cranioplasty that has the highest accuracy, reliability and least complications. For this purpose a 3D scan (e.g. a CT scan or a MRI scan) of the cranial defect should be loaded in a dedicated computer program to design the optimal cranioplasty with a perfect fit and perfect aesthetics. Ideally, such a program should be able to virtually create the optimal cranial implant without human input. This might be possible with the use of novel algorithms using statistical shape models[26]. Databases containing 3D data of a large number of healthy controls forms the bases for such a shape model. The available 3D data of the patient to be treated can be automatically analyzed using the developed statistical model. The statistical model will provide the optimal implant to cover the defect and create the 3D design of the implant automatically. After the implant has been created automatically in the computer program the design and fit in the skull defect can be demonstrated to the patient. Finally, a soft tissue simulation should be created by the computer program to illustrate to the patient how the esthetical outcome will be after surgery.

Phase V: Immediately after the design of the cranioplasty has been completed stem cells of the patient will be used for the production of the cranioplasty. This is combined with the artificial / newly developed extracellular matrix or mineral components of bone in a specially developed bioprinter and results in a cranioplasty made out of the patient's own material.

Phase VI: During the re-opening of the cranial defect, the cranioplasty that has been manufactured using bioprinting can be inserted in the defect. The fixation of the cranioplasty to the skull will be without fixation of screws, but with the use of osteogenesis the cranioplasty will fixed soon to the surrounding bone.

Conclusion

This thesis has answered some important research questions and brought new insights on materials currently used for cranioplasties. Further standardization of definitions, diagnostic criteria, complications, standardized treatment protocols, and outcome measurements are still needed to ensure an evidence-based choice for materials in cranioplasties. Technological innovations and the development of new materials will be an important factor in improving the treatment of cranial reconstructions. The ultimate goal is to find an ideal and safe cranioplasty material for both patients and healthcare workers, with a low infection rate and long-term protection of the brain, preferably with limited costs.

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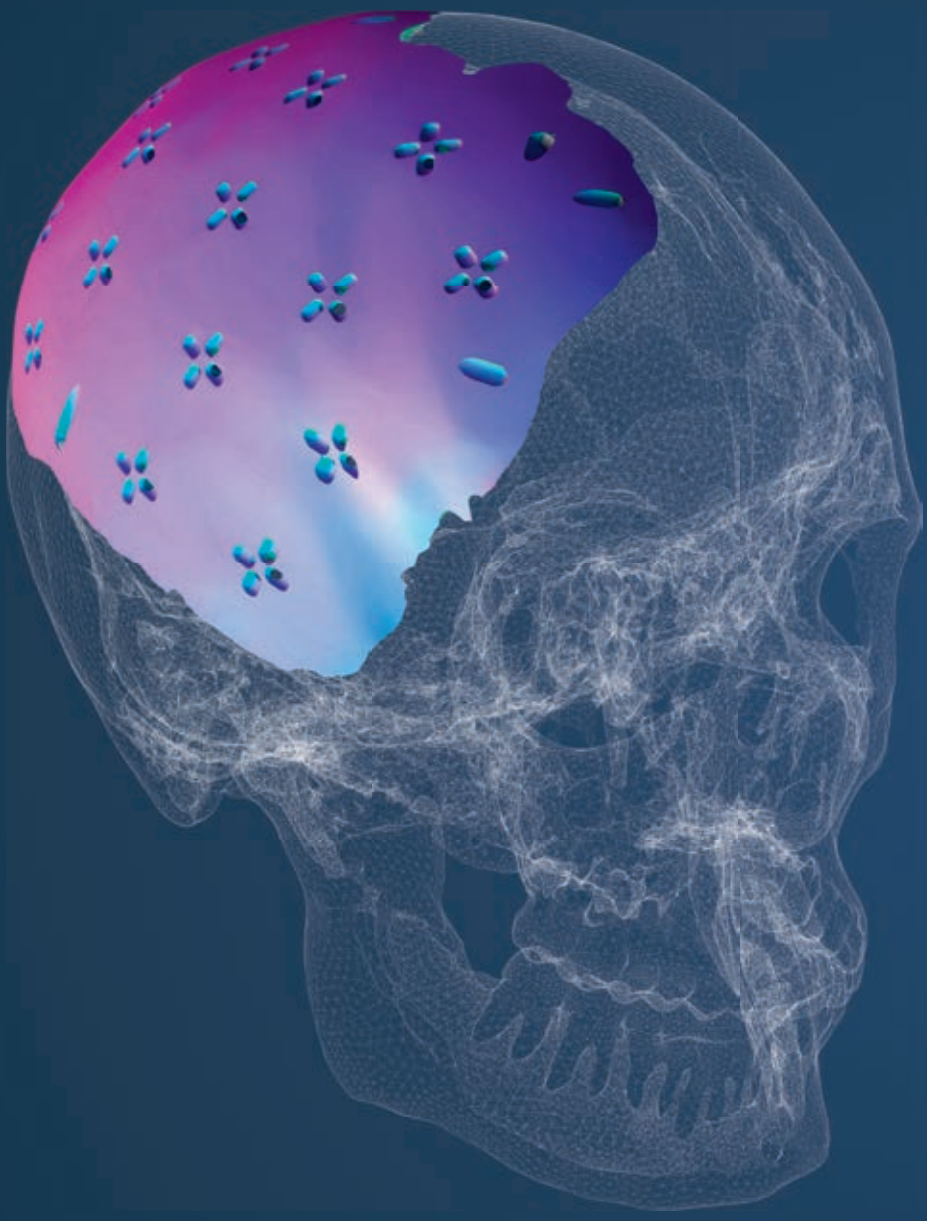


CHAPTER 11

Summary & Nederlandse samenvatting

SUMMARY

Part I: Introduction

The brain is one of the most important organs of the human body. It ensures that human beings can perform conscious actions and movements, and to have thoughts and emotions. The skull (i.e. the neurocranium) protects the brain from external impact, atmospheric pressure and harbor sensory organs.

In **Chapter 1** the consequences of skull pathology are outlined. Due to a trauma, cerebrovascular event, infection or neoplasm, intracranial pressure may increase, which leads to a life-threatening condition. To reduce the intracranial pressure, a decompressive craniectomy can be performed, in which part of the skull is removed. Typically, the removed skull bone flap is reinserted during the same surgical procedure as an immediate autologous reconstruction. In exceptional cases, for example if the brain is too swollen, blood coagulation is disturbed, or the patient is neurologically unstable, the neurosurgeon may decide not to reinsert the autologous bone flap. In these cases, the removed bone is stored in a freezer with an average temperature of -80 °C, or in an abdominal pocket of the patient. If the patient is neurologically stable and his general condition is satisfactory, the autologous bone is reinserted in a second surgical intervention. This reconstruction is also known as a cranioplasty. In some cases it is not possible to replace the autologous bone, for example if it has been lost due to fragmentation, if there is an infection, or if there is no bone bank available for cryopreservation. In these cases the use of an alloplastic material is an alternative solution. Many different materials have been developed and are used daily for cranioplasty. The materials principally mentioned in literature are autologous bone, titanium, poly(methyl metacrylate) (PMMA), hydroxyapatite and poly (ether ether ketone).

The principal outline of this thesis was to investigate and understand the clinical issues of different materials used for cranioplasty. If we can grasp the clinical problems related to the current materials used for cranioplasties, an even more advanced material might be developed to reduce intra-operative and clinical complications.

Part II: Current evidence

Chapter 2 provides a systematic review of the literature addressing post-operative complications after cranioplasty. All patients in the 228 included studies underwent decompression craniectomy and received an autologous or alloplastic cranioplasty in a later stage. All reported complications were extracted and analyzed. Interpreting the results of this meta-analysis was difficult due to low methodological quality of the included studies and heterogeneity of the outcome measures, in terms of a large variation in surgical procedures, patient characteristics, and outcome definitions. For this reason no 'superior' material for cranioplasties could be identified. Infection and resorption were the most frequently reported complications. Autologous cranioplasties were found to have an infection rate of 6.9%, versus 5.0% in alloplastic cranioplasties. Resorption was reported only after autologous cranioplasties (11.3%). Consequently, autologous cranioplasties had to be removed more frequently than alloplastic cranioplasties (10.4% versus 5.1%). It was concluded that the use of autologous cranioplasties should not be encouraged in any circumstance.

Part III: Current challenges

For the development of a new material for cranioplasty, it is important to understand the reasons for failure of the existing materials for cranioplasties. Thus, the advantages and disadvantages of the various materials need to be weighed.

In order to identify the risks of failure of autologous bone flaps, a two-center retrospective study was performed **(chapter 3).** The included patients (n=254) underwent unilateral decompressive craniectomy. The autologous bone was reinserted in a subsequent surgical procedure. In 52 (20.5%) patients the autologous bone failed; in 24 (9.4%) due to infection and in 23 (9.1%) due to resorption. The associated factors for removal of the autologous bone were 1) the hospitalization time after decompressive craniectomy, the time between decompressive craniectomy and cranioplasty, and the follow-up duration after the cranioplasty. Removal of the cranioplasty due to an infection was associated with having a neoplasm as reason for decompression (29.2% versus 7.8%) and a longer hospital stay after decompressive craniectomy (54 days versus 28 days). Cranioplasty removal because of bone resorption was associated with a younger age (35 years versus 43 years), a larger circumference of the cranial defect (39 cm versus 37 cm) and a longer follow-up after the cranioplasty.

In **chapter 4**, a PMMA (CMW-3®) cranioplasty is described, which had been inserted in the human cranium for 15 years and had to be removed due to neurological complaints, which were most likely caused by fracture of the implant. To get more insight in material behaviors over a long period of time in the human body a gel permeation chromatography (GPC) and a micro-CT were performed and the flexural strength was measured. The fracture itself was analyzed with the use of finite element analysis (FEA). This showed that the design of the implant and the manufacture method of PMMA are important factors concerning the mechanical properties of a PMMA cranioplasty.

In **Chapter 5**, a two-center retrospective study is described, including 38 patients who underwent 40 patient-specific cranioplasties of PEEK. Patient and surgical characteristics, as well as associated factors for developing complications after a PEEK cranioplasty were studied. A total of 11 (27.5%) complications were observed, requiring the removal of 10 (15%) cranioplasties. Of these, 5 (12.5%) had an infection, 3 (7.5%) a hematoma, 1 (2.5%) a cerebrospinal fluid leakage and 1 (2.5%) persistent wound dehiscence. Of the 5 cranioplasties with an infection, 3 cranioplasties were again sterilized and reinserted with 100% success. No significant predictive factors were found for the failure of patient-specific cranioplasties of PEEK.

Part IV: Towards a new approach

In some patients, it is desirable to know the precise outline of the resection prior to the (decompressive) craniectomy. Therefore, resection molds and control templates may be used to improve accuracy and reduce operation time.

In **chapter 6,** three cases are described using a resection template and a control template for the direct insertion of a PEEK cranioplasty. The precision of the resection template was evaluated by a so-called distance map, showing that the planned cranioplasty deviated less than 1.0 mm from the actually inserted cranioplasty. After a three year follow-up there were no infections, no removed cranioplasties, no irregularities on the post-operative CT-scan, and the aesthetic outcome was satisfactory.

Chapter 7 presents a patient with a squamous cell carcinoma with bony invasion into the scalp, a rarely described phenomenon in the literature. The craniectomy was performed using a resection template and a control mold. For the reconstruction, a cranioplasty of PEEK was inserted, including a latissimus dorsi flap with a split-thickness skin graft. Clinically and aesthetically, the reconstruction was satisfactory. However, the reconstruction was complicated by a wound dehiscence, which was stable after one year

Part V: Towards the ideal material

For the development of new materials for cranioplasty, the material properties are crucial. These must be stable, safe and strong. In chapters 8 and 9, *in vitro* studies were performed with different types of PMMA.

In **chapter 8**, the amount of released, non-polymerized, monomers (residual monomers) was analyzed in four different PMMA-based materials with different compositions and fabrication methods (Vertex Self-Curing, Palacos R+G, DePuy CMW-3 and NextDent C&B MFH). The specimens were inserted in bottles filled with distilled water at 37.0° C. After several time intervals – ranging between 1 hour and 14 days - a sample was taken from the water. With the aid of high-pressure liquid chromatography (HPLC), the percentage of released residual monomers was determined. Different patterns of released residual monomers were found. NextDent C&B MFH showed the lowest percentage of released residual monomers (23.9 µg/g). After the first hour, this material showed the highest amount of released residual monomers. However, after one hour no more release of residual monomers was detected from this material. Hence, this composite of PMMA could be a good option for a new material for cranioplasties.

In **chapter 9**, three different types of PMMA-based materials (Vertex Self-Curing, Palacos R+G and NextDent C&B MFH) were sterilized with four different methods (ethylene oxide, hydrogen peroxide plasma gas, autoclavation, and gamma-irradiation).

Flexural strength, flexural modulus and impact strength were measured. The flexural strength of all materials studied was significantly increased by gamma-irradiation as compared to the non-sterilized specimens. NextDent C&B MFH had the highest flexural and impact strength. Palacos R + G demonstrated the highest maximum stress intensity and total fracture work. It was concluded that autoclave sterilization should not be used because of the deformation of the material due to the high temperature and pressurized steam. Ethylene oxide, hydrogen peroxide plasma gas and gamma-irradiation, are preferable methods for sterilization of PMMA-based medical implants.

Part V: General discussion

This thesis ends with **chapter 10,** in which the research findings are discussed and future perspectives on these topics are delineated. The need for clear definitions, protocols and guidelines is argued, current used different materials are criticized and characteristics of the ideal material for cranioplasties is highlighted. Possible technological innovations are presented. In the future perspectives a proposal for a Delphi Study, RCT and new *in vitro* study is described. Followed by possibilities of bioprinting for cranioplasties. A case in which manufacturing the cranioplasty of the future is presented at the end of the future perspectives.

This chapter ends with the conclusion of this thesis: an ideal and safe cranioplasty material needs to be developed for the long-term protection of the brain.

NEDERLANDSE SAMENVATTING

Deel I: Introductie

Het brein is een van de belangrijkste organen van het menselijk lichaam. Het stuurt het lichaam aan om bewuste handelingen uit te voeren, bewegingen te kunnen maken, gedachten en emoties te hebben en deze te tonen of juist verborgen te houden. Het is belangrijk dit aansturende gedeelte van de mens te beschermen tegen impact van buitenaf. De schedel is een belangrijke fysieke barrière met als doel bescherming van het brein en de toevoerende en afvoerende systemen. In **hoofdstuk 1** worden de gevolgen van schedelverwondingen beschreven.

Door een trauma, een cerebrovasculair accident, een infectie of een neoplasma (al dan niet kwaadaardig) kan de intracraniële druk in het cranium verhoogd worden. Een decompressieve craniëctomie is een –meestal levensreddende– chirurgische interventie waarbij een gedeelte van de schedel wordt verwijderd om de intracraniële druk te laten dalen. In de meeste gevallen wordt het uitgenomen schedeldak in dezelfde chirurgische interventie nog teruggeplaatst. In uitzonderlijke gevallen is het brein te gezwollen, is de bloeding niet te stelpen of is de patiënt neurologisch zo slecht dat de uitgenomen botlap niet terug kan worden geplaatst. In deze gevallen kan de uitgenomen botlap bewaard worden in de vriezer (cryopreservatie) met een temperatuur van ongeveer -80°C of bewaard worden onder de huid van de buik van de patiënt. Als de patiënt neurologisch stabiel is en zijn algemene conditie het toelaat, kan ervoor worden gekozen om de autologe botlap weer terug te plaatsen in de schedel van de patiënt. Deze reconstructie wordt ook wel een cranioplastiek genoemd. In bepaalde gevallen is het niet mogelijk om de autologe botlap terug te plaatsen, bijvoorbeeld als het gefragmenteerd is, er sprake is van infectie of de wet- en regelgeving het bewaren van de autologe botlappen in de botbank niet toelaat. In deze gevallen kan ervoor gekozen worden om een cranioplastiek van een alloplastisch materiaal te vervaardigen. Over de jaren zijn er veel verschillende materialen ontwikkeld voor cranioplastieken. De meest genoemde zijn: autoloog bot, titanium, poly (methyl metacrylate) (PMMA), hydroxyapatiet en poly (ether ether ketone) (PEEK). **Hoofdstuk 1** geeft een overzicht van de gebruikte materialen voor cranioplastieken door de jaren heen.

Het doel van dit proefschrift is om een inventarisatie te maken van de klinische complicaties die optreden bij verschillende materialen die gebruikt worden voor cranioplastieken. Op basis van deze bevindingen kan er wellicht een (nieuw) materiaal geselecteerd of ontwikkeld worden om daarmee de kans op intra-operatieve en klinische complicaties te verkleinen en de algehele resultaten voor de patiënt te verbeteren.

Deel II: Huidige bewijs

Hoofdstuk 2 geeft een overzicht van alle complicaties die na een cranioplastiek kunnen optreden. Alle patiënten van de geïncludeerde studies (n=228) ondergingen een decompressieve craniëctomie en kregen in een later stadium een cranioplastiek (autoloog of alloplastisch materiaal). Alle complicaties werden genoteerd en geanalyseerd. Het interpreteren van de gevonden resultaten werd bemoeilijkt door lage methodologische kwaliteit van de artikelen en de heterogeniteit van de uitkomstmaten, zoals grote variatie in chirurgische procedures, patiëntkenmerken en uitkomstdefinities. Om deze reden kon er geen superieur materiaal voor cranioplastieken geïdentificeerd worden. Infectie en resorptie waren de meest voorkomende complicaties. Autologe cranioplastieken hadden een infectierisico van 6.9%, alloplastische cranioplastieken 5.0%. Resorptie werd alleen waargenomen na cranioplastieken met een autoloog implantaat (11.3%). Bovengenoemde complicaties zorgden ervoor dat autologe cranioplastieken vaker verwijderd moesten worden in vergelijking met alloplastische cranioplastieken (10.4% versus 5.1%). Hieruit volgt dat het gebruik van autologe cranioplastieken niet kan worden aanbevolen.

Deel III: Huidige uitdagingen

Om een nieuw materiaal voor cranioplastieken te kunnen ontwikkelen is het belangrijk om te weten waardoor eerdere cranioplastieken gefaald zijn, zodat er hier in de toekomst bij het creëren van een nieuw materiaal op geanticipeerd kan worden.

Om te inventariseren wat de risico's zijn op het falen van autologe botlappen, werd een retrospectieve studie uitgevoerd in twee centra **(hoofdstuk 3)**. De geïncludeerde patiënten (n=254) ondergingen een unilaterale decompressieve craniëctomie en in een tweede chirurgische interventie werd de autologe botlap teruggeplaatst. Bij 52 (20.5%) patiënten werd de autologe botlap verwijderd, bij 24 (9.4%) vanwege infectie en bij 23 (9.1%) vanwege resorptie. Mogelijke risicofactoren die geleid hebben tot verwijdering van de autologe botlap waren de opnameduur in het ziekenhuis na de decompressieve craniëctomie, de tijd tussen de decompressieve craniëctomie en het terugplaatsen van de autologe botlap en de follow-up duur na het terugplaatsen van de autologe botlap. Patiënten bij wie de autologe botlap moest worden verwijderd vanwege infectie hadden vaker een neoplasma (29.2% versus 7.8%) en deze patiënten zijn na de craniëctomie langer in het ziekenhuis opgenomen geweest (54 dagen versus 28 dagen). Verwijdering van de autologe botlap vanwege resorptie bleek geassocieerd met een jongere leeftijd (35 jaar versus 43 jaar), een grotere omtrek van het craniaal defect (39 cm versus 37cm) en een langere follow-up na de cranioplastiek (44 maanden versus 14 maanden).

In **hoofdstuk 4** is een PMMA (CMW-3®) cranioplastiek geëvalueerd die na 15 jaar in de schedel alsnog verwijderd moest worden vanwege neurologische klachten. Deze zijn naar alle waarschijnlijkheid ontstaan vanwege een breuk in het implantaat. Er werd een gel-permeatie chromatografie (GPC) uitgevoerd, een micro-CT werd vervaardigd en de buigsterkte werd gemeten. De fractuur zelf werd geanalyseerd door middel van een eindige element analyse. Hieruit bleek dat zowel het ontwerp van het implantaat als de productie van de PMMA cranioplastiek belangrijke factoren zijn betreffende de mechanische eigenschappen.

In **hoofdstuk 5** werden 38 patiënten geïncludeerd die in totaal 40 patiënt-specifieke cranioplastieken ondergingen van poly (ether ether ketone) (PEEK) in twee verschillende centra. De patiënt- en chirurgische karakteristieken, alsmede de risicofactoren voor het ontwikkelen van complicaties na een PEEK cranioplastiek werden in kaart gebracht. In totaal werden 11 (27.5%) complicaties genoteerd waarvan 10 (25%) cranioplastieken werden verwijderd. Vijf (12,5%) patiënten hadden een infectie, 3 (7.5%) een hematoom, 1 (2,5%) een liquorlekkage en 1 (2,5%) patiënt had een wondprobleem. Van de 5 cranioplastieken met een infectie zijn er 3 cranioplastieken opnieuw gesteriliseerd en teruggeplaatst met 100% succes. Er werden geen significante predictiefactoren gevonden voor het falen van PEEK patiënt-specifieke cranioplastieken.

Deel IV: Richting nieuwe benaderingen

In sommige casus is het wenselijk om de precieze planning van de resectie voorafgaand aan de (decompressieve) craniëctomie te weten en deze tijdens de operatie toe te passen. Resectiemallen kunnen hiervoor gebruikt worden.

In **hoofdstuk 6** werden drie casus beschreven waarin gebruik werd gemaakt van een resectiemal en een controlemal, beiden pre-operatief gepland en vervaardigd, zodat de decompressie craniectomie en het plaatsen van een cranioplastiek van PEEK in een chirurgische interventie kon plaats vinden. De precisie van de resectiemal werd geëvalueerd door een afstandsmap waar bij de geplande cranioplastiek minder dan 1.0 mm afweek van de daadwerkelijk geïmplanteerde cranioplastiek. Na 3 jaar zijn er geen infecties opgetreden, geen cranioplastieken verwijderd, de CT-scan liet geen oneffenheden zien en de esthetische uitkomst was fraai.

Hoofdstuk 7 beschrijft een patiënt met een plaveiselcelcarcinoom met doorgroei in de schedel, hetgeen in de literatuur weinig beschreven wordt. De craniëctomie is vervaardigd met behulp van een resectiemal en een controlemal. Voor de reconstructie is er gekozen is voor een cranioplastiek van PEEK inclusief latissimus dorsi flap met een huidtransplantaat. De craniale reconstructie werd gecompliceerd door een wonddehiscentie die tot een jaar na de operatie stabiel bleef, verdere follow-up is geïndiceerd.

Deel V: Richting een nieuw materiaal

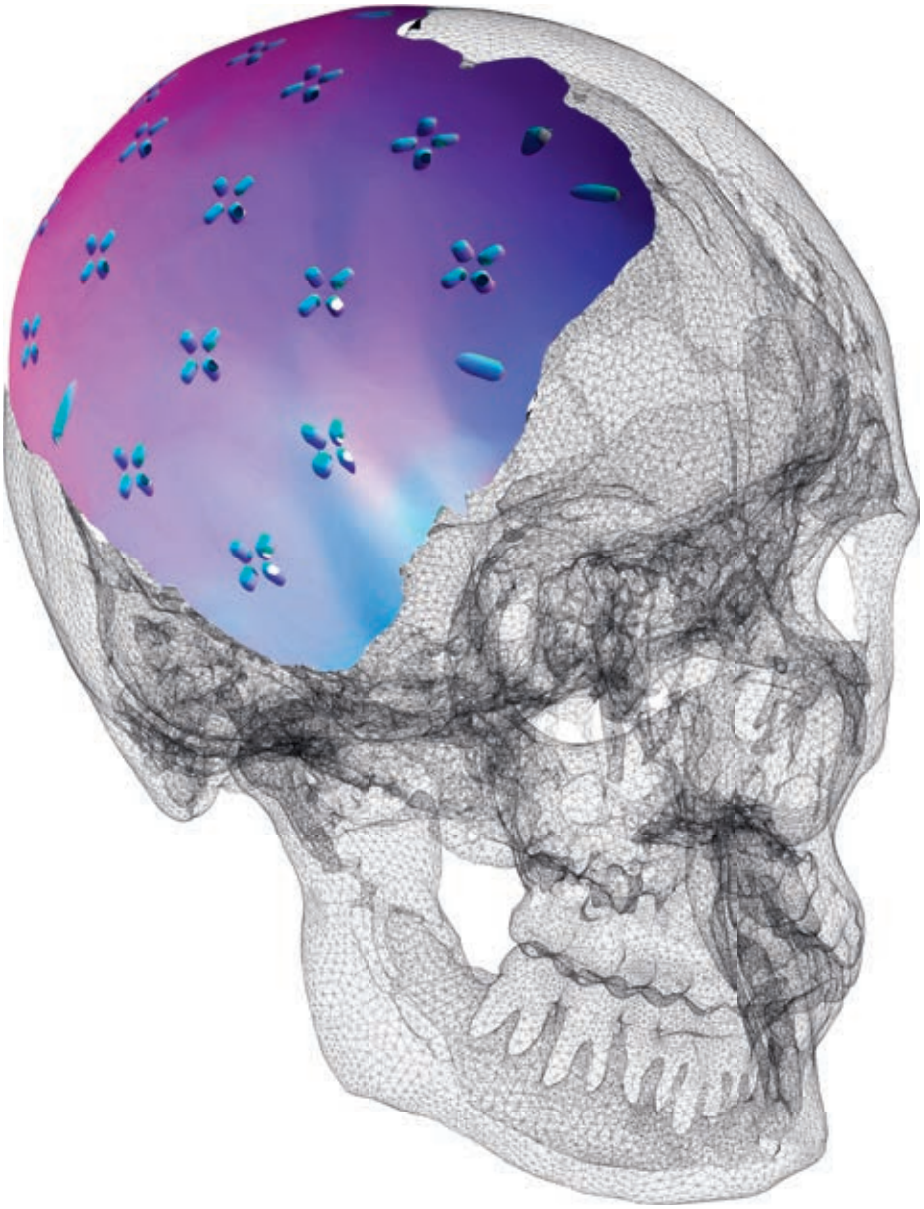
Voor het ontwikkelen van nieuwe materialen voor cranioplastieken zijn de materiaaleigenschappen belangrijk. Stabiliteit, veiligheid en sterkte zijn de minimale vereisten.

In **hoofdstuk 8** werd de hoeveelheid 'lekkende'niet-gepolymeriseerde monomeren (restmonomeren) geanalyseerd in vier verschillende soorten PMMA-achtige materialen (Vertex Self-Curing, Palacos R+G, DePuy CMW-3 en NextDent C&B MFH). De specimens werden vervaardigd middels verschillende samenstellingen en fabricatiemethoden. De specimens werden toegevoegd aan flessen gevuld met 37°C gedestilleerd water. Na verschillende tijdsintervallen - tussen 1 uur en 14 dagen - werd een monster genomen van het water en met behulp van hoge druk vloeistofchromatografie (HPLC) werd het percentage residuale monomeren bepaald. Verschillende patronen van 'lekkende' restmonomeren werden gemeten, waarbij na 14 dagen sommige PMMA-achtige materialen nog niet 'uitgelekt waren'. NextDent C&B MFH had het laagste percentage lekkende restmonomeren (23.9µg/g). In het eerste uur liet dit materiaal de meeste lekkage van restmonomeren zien, maar na een uur 'lekte' er bijna geen monomeren meer uit het materiaal. Hieruit kunnen we concluderen dat specifieke samenstellingen van PMMA-achtige materialen ontwikkeld zouden moeten worden voor verschillende toepassingen in de medische wereld, specifiek als het gaat om neurochirurgische toepassingen waarbij het MMA zich in de nabijheid van de meningen bevindt.

In **hoofdstuk 9** werden drie verschillende soorten PMMA-achtige materialen (Vertex Self-Curing, Palacos R+G en NextDent C&B MFH) op vier verschillende manieren gesteriliseerd (ethyleenoxide, waterstofperoxide plasma gas, autoclaaf en gamma-irradiatie) om vervolgens de buigsterkte, buigingsmodulus en slagsterkte te meten. De buigsterkte van alle materialen nam significant toe door gamma-irradiatie in vergelijking met de niet-gesteriliseerde specimens. NextDent C&B MFH had de hoogste buigsterkte en slagsterkte. Palacos R+G had de hoogste maximale stressintensiteit evenals de totale breek arbeid. Concluderend kan sterilisatie middels een autoclaaf niet gebruikt worden voor het steriliseren van PMMA-achtige materialen voor medische implantaten, deze zullen door de hoogte van de temperatuur en de stoom onder druk vervormen. Ethyleenoxide, waterstofperoxide plasma gas en gamma-irradiatie daarentegen kunnen wel hiervoor gebruikt worden.

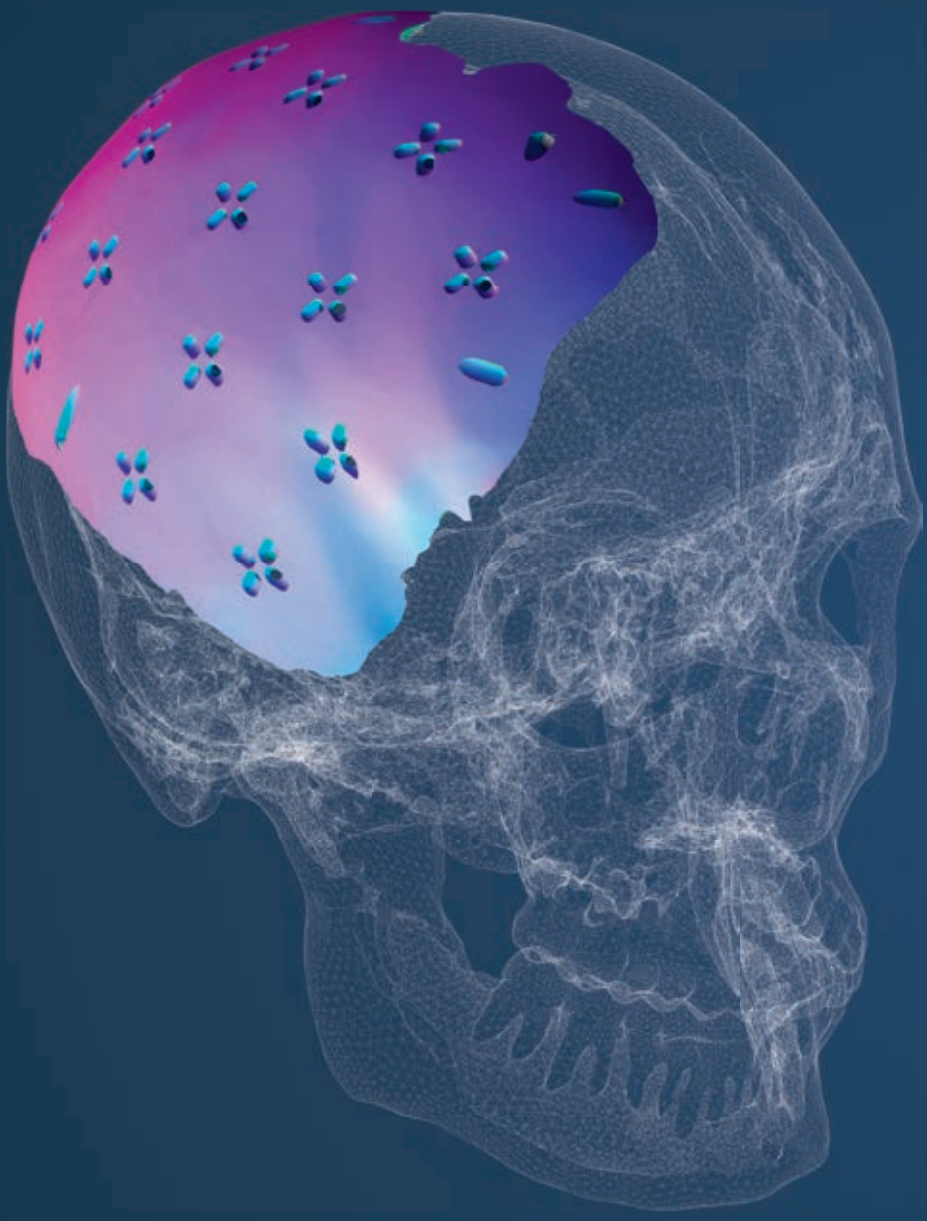
Deel VI: Algemene discussie

Dit proefschrift wordt afgesloten met **hoofdstuk 10** waarin de onderzoeksresultaten worden bediscussieerd en vooruitzichten op deze onderwerpen worden besproken. De noodzaak van duidelijke definities, protocollen en richtlijnen is vastgelegd, de huidige materialen die gebruikt worden voor cranioplastieken wordt bekritiseerd evenals de kenmerken van het ideale materiaal voor cranioplastieken. Mogelijke technologische innovaties worden gepresenteerd. Er wordt een voorstel gedaan voor een Delphi-studie, RCT en nieuwe *in vitro* studies zijn beschreven. Dit wordt gevolgd door mogelijkheden van bioprinting voor cranioplasties. Een casus betreffende het vervaardigen van cranioplastieken in de toekomst wordt gepresenteerd



PART VII

Appendices



List of publications

List of publications

Peer reviewed full-text publications

In this thesis

S.E.C.M. van de Vijfeijken, T.J.A.G. Münker, R. Spijker, L.H.E. Karssemakers, W.P. Vandertop, A.G. Becking, D.T. Ubbink, on behalf of the CranioSafe Group. Autologous bone is inferior to alloplastic cranioplasties: Safety of autograft and allograft materials for cranioplasties, a systematic review. *World Neurosurgery, 2018 September; 117:443-452.e8*.

S.E.C.M. van de Vijfeijken, C. Groot, D.T. Ubbink, W.P. Vandertop, P.R.A.M. Depauw, E. Nout, A.G. Becking, on behalf of the CranioSafe Group. Factors related to failure of autologous cranial reconstructions after decompressive craniectomy. *Journal of Cranio-Maxillo-Facial Surgery, 2018 September; on line available*

S.E.C.M. van de Vijfeijken, T.J.A.G. Münker, N. de Jager, W.P. Vandertop, A.G. Becking, C.J. Kleverlaan, on behalf of the CranioSafe Group. The properties of an *in vivo* fractured PMMA cranioplasty after 15 years. *World Neurosurgery, 2019 March;123:e60-e68*

S.E.C.M. van de Vijfeijken, J. Jonkergouw, E. Nout, T. Theys, E. van de Casteele, H. Folkersma, P.R.A.M. Depauw, A.G. Becking. Outcome in patient-specific PEEK cranioplasty: A two-center cohort study of 40 implants. *Journal of Cranio-Maxillo-Facial Surgery, 2016 September;44(9):1266-1271*.

S.E.C.M. van de Vijfeijken, R. Schreurs, L. Dubois, A.G. Becking, on behalf of the CranioSafe Group. The use of cranial resection templates with 3D virtual planning and PEEK patient-specific implants: A 3 year follow-up. *Journal of Cranio-Maxillo-Facial Surgery, July;1010-5182(18)30191-4*.

T.J.A.G. Münker, **S.E.C.M. van de Vijfeijken**, C.S. Mulder, V. Vespasiano, A.G. Becking, C.J. Kleverlaan, on behalf of the CranioSafe Group. Effects of sterilization on the mechanical properties of poly(methyl methacrylate)-based personalized medical devices. *Journal of the Mechanical Behavior of Biomedical Materials, 2018 May;81:168-172*.

Submitted for publication

S.E.C.M. van de Vijfeijken, K.M. Slot, S.D. Strackee, A.G. Becking, J. de Lange, L. Smeele, W.H. Schreuder; on behalf of the CranioSafe Group. Is 3D virtual planning in cranial reconstruction for advanced cutaneous squamous cell carcinoma of the skull an option?

S.E.C.M. van de Vijfeijken, T.J.A.G. Münker, C.J. Kleverlaan, A.G. Becking; on behalf of the CranioSafe Group. Leachables from patient-specific implants produced by 3D printing compared to conventional PMMA-based alternatives

Other

C.R.A. Verlinden , **S.E.C.M. van de Vijfeijken**, D.B. Tuinzing, A.G. Becking, G.R. Swennen. Complications of mandibular distraction osteogenesis for acquired deformities: a systematic review of the literature. *International Journal of Oral and Maxillofacial Surgery, 2015 August;44(8):956-64*.

C.R.A. Verlinden, **S.E.C.M. van de Vijfeijken**, D.B. Tuinzing, E.P. Jansma, A.G. Becking, G.R. Swennen.
Complications of mandibular distraction osteogenesis for developmental deformities: a systematic review of the literature. *International Journal of Oral and Maxillofacial Surgery, 2015 January;44(1):44-9*.

C.R.A. Verlinden, **S.E.C.M. van de Vijfeijken**, E.P. Jansma, A.G. Becking, G.R. Swennen. Complications of mandibular distraction osteogenesis for congenital deformities: a systematic review of the literature and proposal of a new classification for complications. *International Journal of Oral and Maxillofacial Surgery*, 2015, January;44(1):37-43.

K.H. Karagozoglu, J. Buter, C.R. Leemans, D.H. Rietveld, **S.E.C.M. van de Vijfeijken**, I. van der Waal. Subset of patients with verrucous carcinoma of the oral cavity who benefit from treatment with methotrexate. *British journal of oral and maxillofacial surgery, 2012 September;50(6):513-8*.

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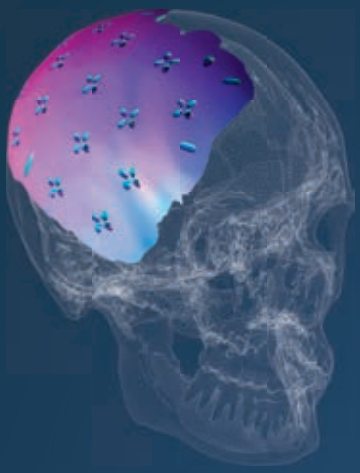

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Chapter 2

Published as:

Autologous bone is inferior to alloplastic cranioplasties ***Safety of autograft and allograft materials for cranioplasties, a systematic review***

Authors:

S.E.C.M. van de Vijfeijken, T.J.A.G. Münker, R. Spijker, L.H.E. Karssemakers, W.P. Vandertop, A.G. Becking, Ubbink; on behalf of the CranioSafe Group

Published in: World Neurosurgery, 2018

Author contributions:

Conceived and designed the study:	SV, TM, AB, DU
Performed the study:	SV, TM, RS
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Critically revised the manuscript:	LK, WV, AB, DU

Funding sources:

Funding provided in part through departmental and institutional sources and by a technology and innovation grant from the Technology Foundation STW (CranioSafe; project number: 14326).

Conflicts of interests:

The authors declare there is no conflict of interest pertaining to the data presented in this article.

Chapter 3

Published as:

Factors related to failure of autologous cranial reconstructions after decompressive craniectomy

Authors:
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Published in: Journal of Cranio-Maxillo-Facial Surgery, 2019

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Funding sources:
Funding provided in part through departmental and institutional sources and by a technology and innovation grant from the Technology Foundation STW (CranioSafe; project number: 14326).

Conflicts of interests:
The authors declare there is no conflict of interest pertaining to the data presented in this article.

Chapter 4

Published as:

Properties of an in vivo fractured Poly(Methyl Methacrylate) cranioplasty after 15 years

Authors:

S.E.C.M. van de Vijfeijken, T.J.A.G. Münker, N. de Jager, W.P. Vandertop, A.G. Becking, C.J. Kleverlaan; on behalf of the CranioSafe Group

Published in: World Neurosurgery, 2019

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Funding sources:

Funding provided in part through departmental and institutional sources and by a technology and innovation grant from the Technology Foundation STW (CranioSafe; project number: 14326).

Conflicts of interests:

The authors declare there is no conflict of interest pertaining to the data presented in this article.

Chapter 5

Published as:

Outcome in patient-specific PEEK cranioplasty: A two-center cohort study of 40 implants

Authors:

S.E.C.M. van de Vijfeijken, J. Jonkergouw, E. Nout, T. Theys, E. van de Casteele, H.Folkersma, P.R.A.M. Depauw, A.G. Becking

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Funding sources:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interests:

The authors declare there is no conflict of interest pertaining to the data presented in this article.

Chapter 6

Published as:

The use of cranial resection templates with 3D virtual planning and PEEK patient-specific implants: *A 3 year follow-up.*

Authors:

S.E.C.M. van de Vijfeijken, R. Schreurs, L. Dubois, A.G. Becking; on behalf of the CranioSafe Group

Published in: Journal of Cranio-Maxillo-Facial Surgery, 2018

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Funding sources:

Funding provided in part through departmental and institutional sources and by a technology and innovation grant from the Technology Foundation STW (CranioSafe; project number: 14326).

Conflicts of interests:

The authors declare there is no conflict of interest pertaining to the data presented in this article.

Chapter 7

Submitted as:

Is 3D virtual planning in cranial reconstruction for advanced cutaneous squamous cell carcinoma of the skull an option?

Authors:

S.E.C.M. van de Vijfeijken, K.M. Slot, S.D. Strackee, A.G. Becking, J. de Lange, L.E. Smeele, W.H. Schreuder; on behalf of the CranioSafe Group

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Funding sources:

Funding provided in part through departmental and institutional sources and by a technology and innovation grant from the Technology Foundation STW (CranioSafe; project number: 14326).

Conflicts of interests:

The authors declare there is no conflict of interest pertaining to the data presented in this article.

Chapter 8

Submitted as:

Leachables from patient-specific implants produced by 3D printing 2 compared to conventional PMMA-based alternatives

Authors:

S.E.C.M. van de Vijfeijken, T.J.A.G. Münker, C.J. Kleverlaan, A.G. Becking; on behalf of the CranioSafe Group

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Funding sources:

Funding provided in part through departmental and institutional sources and by a technology and innovation grant from the Technology Foundation STW (CranioSafe; project number: 14326).

Conflicts of interests:

The authors declare there is no conflict of interest pertaining to the data presented in this article.

Chapter 9

Published as:

Effects of sterilization on the mechanical properties of poly(methyl methacrylate)-based personalized medical devices

Authors:

T.J.A.G. Münker, S.E.C.M. van de Vijfeijken, C.S. Mulder, V. Vespasiano, A.G. Becking, C.J. Kleverlaan; on behalf of the CranioSafe Group

Published in: Journal of the Mechanical Behavior of Biomedical Materials, 2018

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Conceived and designed the study:	TM, SV
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Funding sources:

Funding provided in part through departmental and institutional sources and by a technology and innovation grant from the Technology Foundation STW (CranioSafe; project number: 14326).

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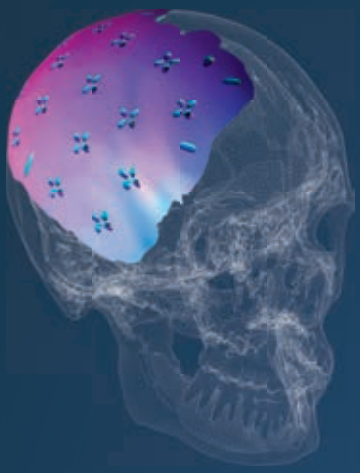


PhD portfolio

PHD PORTFOLIO

Name PhD student:	Sophie E.C.M. van de Vijfeijken
PhD period:	May 2016 – March 2019
PhD Supervisiors:	Prof. dr. A.G. Becking
	Prof. dr. C.J. Kleverlaan

General courses	Year	ECTS
Scientific writing in English – Graduate School- Academic Medical Center	2016	1.5
Oral presentation in English- Academic Medical Center	2017	0.8
Basic course in legislation and organisation for clinical researchers (BROK)- Academic Medical Center	2016	2.0
AMC World of Science- Academic Medical Center	2016	0.7
Clinical Epidemiology: Randomized Clinical Trials- Academic Medical Center	2016	0.6
Clinical Epidemiology: Systematic reviews- Academic Medical Center	2015	0.6

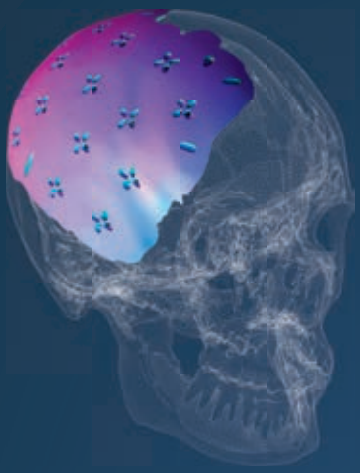
Specific courses	Year	ECTS
Medical Statistics, Wetenschapsbureau Linnaeusinstituut, Spaane Gasthuis, Haarlem, the Netherlands	2015	2.0
Symposium: Medical 3D printing, Academic Medical Center, Amsterdam, the Netherlands	2016	1.0
Introduction to Medical Microbiology, Academic Medical Center Amsterdam, the Netherlands	2016	1.0
Research Integrity, Academic Centre for Dentistry Amsterdam, Amsterdam, the Netherlands	2017	1.0
Evidence Based Surgery, , Amsterdam the Netherlands	2017	2.1
Symposium: Medical 3D printing, Amsterdam, the Netherlands	2016	0,25

(Inter)national conferences	Year	ECTS
23th Congress of the European Association for Cranio Maxillo Facial Surgery - London - UK	2016	0,75
Najaarsvergadering NVMKA 'Innofacion', Utrecht, the Netherlands	2016	0,75
Najaarsvergadering NVMKA, Den Haag, the Netherlands	2017	0,75
24th Congress of the European Association for Cranio Maxillo Facial Surgery - Munich - Germany	2018	0,75

Oral presentations	Year	ECTS
Een twee center cohort studie in 40 patiënt specifieke PEEK cranioplastieken, *Najaarsvergadering NVMKA 'Innofacion', Utrecht, the Netherlands*	2016	0,5
Factors related to failure of autologous cranial reconstructions after decompressive craniectomy, *23th Congress of the European Association for Cranio Maxillo Facial Surgery - London - UK*	2016	0,5

Introduction CranioSafe *CranioSafe meeting, Academic Medical Center, Amsterdam, the Netherlands*	2016	0,5
Autologous bone is inferior to alloplastic cranioplasties; safety of autograft and allograft materials for cranioplasties, a systematic review *CranioSafe meeting, Academic Medical Center, Amsterdam, the Netherlands*	2017	0,5
Cranial defects and reconstructions *Presentation Scientific Afternoon, ACTA, Amsterdam, the Netherlands*	2017	0,5
Start in vitro studies - an Update *CranioSafe meeting, Academic Medical Center, Amsterdam, the Netherlands*	2017	0,5
Technical innovations – an Update *CranioSafe meeting, NextDent Soesterberg, the Netherlands*	2018	0,5
Factors related to failure of autologous cranial reconstructions after decompressive craniectomy, *24th Congress of the European Association for Cranio Maxillo Facial Surgery - Munich - Germany*		
Residual monomers released from PMMA-based patient-specific implants and evaluation of a novel polymer, *24th Congress of the European Association for Cranio Maxillo Facial Surgery - Munich – Germany*	2018	0,5
PhD – An update *CranioSafe meeting, Academic Centre for Dentistry Amsterdam, the Netherlands*	2019	0,5

Supervising, seminars, workshops and symposia	**Year**	**ECTS**
Lieneke Bakker, master thesis, Academic Centre for Dentistry Amsterdam, the Netherlands 'Cranioplasty: polymethyl methacrylate (PMMA) or polyether ether ketone (PEEK) a search for the perfect material *A systematic review of the literature*'	2016	0,5
Valeria Vespasiano and Nina Mulder, bachelor thesis, Academic Centre for Dentistry Amsterdam, the Netherlands '*Mechanical properties of poly-(methyl methacrylate) and poly-(dimethacrylate) after different sterilization methods in relation to cranioplasties*'	2017	0,5
Jantine Yntema, master thesis, Academic Centre for Dentistry Amsterdam, The Netherlands '*Surgical approaches of the lower eyelid in facial trauma: a systematic review of the outcome and complications*' Yearly seminar CranioSafe Guidance and training by the supervisors	2019 2016-2018 2016-2018	0,5 2,0 8,0
Total ECTS		**32,55**



Acknowledgements - Dankwoord

Sticks in a bundle are unbreakable - Kenyan Proverb

Een proefschrift maak je niet alleen, maar met de hulp van vele slimme, leuke, gezellige, intelligente, knappe, eigenwijze, humoristische mensen. Hiermee bedoel ik in de eerste plaats de patiënten, vrijwilligers en hun begeleiders die geheel belangeloos hebben meegewerkt aan dit proefschrift en bovenal mij (in tijden van computers, PubMed en papierwerk) verbonden hielden met de kliniek. Veel dank voor hun/jullie tijd en moeite om meerdere malen naar het AMC te komen. Daarnaast zijn er natuurlijk de mensen die mij geholpen hebben bij het bedenken en uitvoeren van de wetenschappelijke onderzoeken, maar ook de mensen die vertrouwen in mij gehad hebben, tot in de laatste uurtjes door hebben gewerkt en de mensen met wie ik tranen met tuiten gelachen heb.

In elke hoge vreugde mengt zich een gevoel van dankbaarheid – Marie von Ebner-Eschenbach

Prof. dr. A.G. Becking, hooggeleerde promotor, beste Eddy, graag wil ik je bedanken voor het vertrouwen dat je in mij had om het avontuur van 'CranioSafe' aan te gaan. Je liet mij de wereld van evidence zelf ontdekken, mijn eigen onderzoeksideeën nastreven (soms met hier en daar wat bijsturing) en je nam, ondanks je drukke schema, altijd alle tijd (en ik ben niet vaak kort van stof) voor het bespreken van de gang van zaken rondom de lopende onderzoeken. Ik vind het bewonderenswaardig en inspirerend om te zien hoe jij jouw vak uitoefent, dit combineert met wetenschap, hoe jij de juiste mensen bij elkaar weet te vinden voor de perfecte chemie in een team, hoe je mensen weet te enthousiasmeren en je bevlogenheid op zowel klinisch als wetenschappelijk gebied. Tevens wil ik je bedanken dat je mij hebt laten groeien als persoon, voor je adviezen en je rode pen, die dit proefschrift alleen maar beter heeft gemaakt.

Prof. dr. C.J. Kleverlaan, hooggeleerde promotor, beste Cees, met jouw knowledge en praktische kijk op -voor mij zo nu en dan- onbegrijpelijke onderwerpen heb je mij meegenomen in de wereld van materiaalwetenschappen, mij het wiel zelf laten uitvinden (totdat er niks anders op zat mij een eind op weg te helpen) en heb je mij nieuwe inzichten gegeven dat er naast klinisch onderzoek veel meer belangrijk onderzoek nodig is om de kliniek te kunnen verbeteren. Veel dank voor je oplettendheid van alle regels, reglementen en je vertrouwen (al sinds tandheelkunde!) in mij.

Prof. dr. T.J.J. Maal, hooggeleerde co-promotor, beste Thomas, YES gedurende dit proefschrift kreeg jij de titel professor, wat een prestatie! Dankzij jouw rust, analytisch oog, op het juiste moment, de juiste woorden en vragen, zijn er veel studies een stuk beter geworden. Door jouw toegankelijkheid, vriendelijkheid, doe maar normaal dan doe je gek genoeg en werkmentaliteit heb ik de eindsprint van het schrijven van dit proefschrift kunnen inzetten. Heel veel dank voor je kritische feedback, geruststellende woorden 'het is nu écht bijna klaar', het snelle nakijken en de vele telefoontjes (ook op zaterdag en zondag!). Je was onmisbaar.

Prof. dr. D.T. Ubbink, hooggeleerde co-promotor, beste Dirk, opeens was je daar, ook jij kreeg de titel professor tijdens het schrijven van mijn proefschrift, chapeau!! Met jouw helikopterview en inspirerende geest heb jij het vermogen een onderzoek naar een hoger niveau te tillen. Heel wat uren hebben we samen aan de statostiek, statistiek, statystiek gezeten en er was een moment dat ik jouw agenda beter kende dan jijzelf! Altijd was je bereid om nog iets uit te leggen, nog een keer iets na te kijken en ook jouw rode inkt is naar alle waarschijnlijkheid op na dit proefschrift. Veel dank voor je tijd, motivatie en kritische vragen. Dat er in de toekomst nog maar veel latte-frappe-chino's -in combinatie met wetenschap- gedronken mogen worden.

Geachte leden van de leescommissie: Prof. dr. R.R.M. Bos, Prof. dr. A.J. Feilzer, Dr. S. Idema, Prof. dr. P.A.W.H. Kessler, Prof. dr. J. de Lange, Prof. dr. M.A.W. Merkx, Prof. dr. ir. T.H. Smit, veel dank voor uw tijd, het kritisch doornemen van dit proefschrift en uw bereidheid om zitting te nemen in deze promotiecommissie.

Hooggeleerde heer, prof. dr. J. de Lange, Beste Jan, veel dank voor het vertrouwen dat ik bij u de opleiding Mondziekten, Kaak en Aangezichtschirurgie mag volgen. Ik vind het fascinerend om te zien dat u de afdeling in een korte tijd -zowel op wetenschappelijk als op klinisch niveau- heeft laten groeien, dat u open staat voor nieuwe technieken en dat u altijd een luisterend oor biedt (oh ja en een mini-vakantie!). De sfeer is mede dankzij u ontspannen, het vragen om hulp laagdrempelig en geeft u iedereen de ruimte zich te ontwikkelen tot de chirurg die hij of zij wil zijn. Ik kijk uit naar de jaren die voor mij liggen waarin ik hopelijk nog veel van uw kennis en kunde mag leren.

If old answers don't work anymore, start looking for new questions - Prof. dr. Hakman

Alle mensen van de 'CranioSafe Group': Eddy, Erik B., dr. Depauw, Johan, Friso, Cathalijne, Lise, Leander, Bas, Brian, Jerzy, Thomas, Luc, Cees, Dan, Tijmen, Erik N., Connie, dr. van der Pol, Martijn, Prof. dr. Vandertop, mede dankzij jullie heb ik dit proefschrift succesvol kunnen afronden. Dank voor jullie inspiratie, creativiteit, input, kritische vragen, vele ritjes door het hele land voor vergaderingen en vooral voor het delen van jullie brede kennis op verschillende gebieden binnen dit project.

Tijmen, jij werd mijn buddy binnen de 'CranioSafe Groep'. Ik was erg blij dat je instemde om een uitgebreide systematic review te schrijven over cranioplastieken, je gezicht toen ik aan kwam lopen met 4 grote Albert Heijn tassen was verrast (zo zal ik het maar noemen). Tot in de late uurtjes hebben wij samen doorgebikkeld, hebben we ideeën bedacht voor nieuw onderzoek, heel veel koffie gedronken en hebben we gediscussieerd dat het in de toekomst allemaal écht beter zou moeten. Met jouw brede kennis en mijn praktische uitvoering hebben we vele stukken tot een goed eindresultaat kunnen brengen. Je bent super enthousiast over alles wat op je pad komt,en als het iets was wat nog niet eerder gedaan was luidde jouw reactie 'dat móeten we uitzoeken, dat heeft écht nog níemand gedaan'. Met jouw kennis, brains en ideeën ga jij de wetenschap absoluut naar een hoger niveau brengen, daar ben ik van overtuigd!

Luc, veel dank voor je positieve instelling afgelopen 3 jaar. Ik vind jouw vermogen om dingen te combineren wonderbaarlijk (en al helemaal voor een man ;)). Fellowship hoofd-hals oncologie, je eigen promotietraject, CranioSafe, pseudo-co-promotor en daarbij een gezinsleven met drie stoere jongens. Wat was het heerlijk om onderzoeksfrustraties met je te delen, om daarna weer met frisse moed verder te gaan, te brainstormen over onderzoeksopzetten en te genieten van je nuchtere kijk op de perikelen (en niet alleen qua onderzoek maar ook daarom heen) die speelden.

Hooggeleerde heer prof. dr. W.P. Vandertop, dank voor uw tijd en moeite die u gestoken heeft in het lezen, aanpassen en bekritiseren van meerdere studies. Uw kijk op de algemene neurochirurgische patiënt heeft mij veel inzicht gegeven in deze patiëntgroep en ik denk dat wij nog uren kunnen discussiëren over wat deze patiëntengroep nou echt nodig heeft. Hedy, kort maar krachtig! Wat een power, energie, ideeën, creativiteit, spontaniteit, doorzettingsvermogen en ondernemingslust, daar heb ik veel van opgestoken!

Réne, dank voor je meerdere searches, het opzoeken van onvindbare artikelen, cappuccino's en goede adviezen betreffende het schrijven van de systematic review. Joost, veel dank voor het opzoeken, printen en versturen van de vele artikelen die ik heb aangevraagd.

Te gekke elfde en twaalfde afdeling van het ACTA: Jolanda (alias management), Cor, Jan-Harm, Leo, Jacqueline, Arie, Jenneke, Hans, Teun, Ton en roomies: Fereshteh, Dagmar, Yvon, JinFeng, Bia en Cindy, veel dank voor het warme welkom twee jaar geleden. Dank voor de vele koffiebreaks, taart, wijn, snacks, roddels en dank voor het delen van jullie brede kennis en kunde binnen de materiaalkunde en wetenschap. Studenten Lieneke, Valeria en Nina, dank voor jullie inzet, motivatie en hulp tijdens het schrijven van dit proefschift.

The ultimate test of the laughing instinct is that a man should always be ready to laugh at himself—Gamaliel Bradford

Carolyn, wat ben je een heerlijke roomie geweest met het prachtige uitzicht op de elfde. Kaakgewrichtsproblematiek door de vele kauwgom (in alle smaken en kleuren), strak staan van de veel te sterke (maar heerlijke) koffie, de vele whats apps met de nieuwe trends voor jurkjes of schoenen (met in het bijzonder degene met de rode zolen). Ik vind het zo bijzonder om te zien met hoeveel passie en enthousiasme iemand naar een neutrofiel kan kijken, alhoewel ik niet weet of ik het ooit écht zal begrijpen. Met jouw doorzettingsvermogen, kennis, nachtelijke doorwerksessies kom jij er wel.

Education is not the learning of facts, it's rather the training of the mind to think—Albert Einstein

Beste stafleden, Prof. Smeele, Prof. Rozema, Ronald, Judith R, Jacco, Jitske, Leander, JP, Marjolijn en Luc, ten eerste veel dank voor het delen van jullie brede kennis, de motivatie om dit meerdere malen uit te leggen en mij de kneepjes van het vak bij te brengen (er valt nog veel te leren!). Pim, wat ben jij een toegewijde, gedreven dokter, dank voor je kritische feedback, je 24-uurs bereikbaarheid en eerlijkheid tijdens het schrijven van mijn laatste stuk. Stefanie, dank voor je intensieve begeleiding aan het begin van mijn opleiding, je adviezen en hulp.

We're all proud of making little mistakes, it gives us the feeling we don't make any big ones— Andy Rooney

Lieve A(N)IOS, Renée, Maarten, Judith, Willem, Johan, Karel en Jorrit, veel dank voor het delen van jullie kennis, voor de mini-vooropleiding tijdens mijn ANIOS periode, jullie geduld en vertrouwen dat die M3 er echt wel ooit uit zou komen. Dank voor de vele koffietjes, brainstormsessies, maar vooral ook biertjes, mooie verhalen, goeie grappen en gezelligheid. Tom (inmiddels staf), dank voor je tijd en energie die je in mijn ANIOS periode hebt gestoken, aan de haken hebt gestaan en jij mij het gevoel gaf dat ik alles kon vragen en situaties opnieuw kon laten beoordelen. SD, roomie, time flies when you're having fun, dank voor je adviezen, relaxedheid, reflexmomentjes, taart en chocolade op momenten dat het echt noodzakelijk was.

In het bijzonder wil ik bedanken (lieve, slimme, geinige, vol met zelfspot) MC, van zwaan-hangt-aan tijdens mijn semi-arts stage naar collega-vriendin. Ik vind het bijzonder om te zien met hoeveel passie en zéér veel geduld je met je patiënten om gaat en hoeveel je daar voor terug krijgt. Zoveel respect voor jou hoe jij je thuisfront georganiseerd hebt, een super lieve moeder bent, daarbij ook nog een super dokter kan zijn én onvermoeibaar bent. Er zijn een paar dingen die in mijn geheugen gegrift staan: si-a-lo-li-thi-a-sis, die éne sinus frontalis fractuur, iets met teveel, te vroeg pieken en bepaalde liedjes zingen. Ik geniet van onze dagelijkse telefoontjes in de ochtend om de dag voor te bespreken en in de middag om de dag na te bespreken, de vele fotootjes van je twee zonnetjes en ik kijk uit naar de vele etentjes -met wijn- die gegarandeerd zullen volgen.

Te gekke Niels en Ruud, hét 3D team van het AMC!! Ruud, ten eerste veel dank voor het gebruiken van je prachtige boven- en onderkaak voor de kaft van dit proefschrift en wat een radices ;). Wij hebben samen veel pizza's gegeten, ge-researched tot in de late uurtjes, toch nog even de referenties aangepast, veel moreovers/howevers/althoughs weggepoetst en jij hebt met je rode pen meer dan eenmalig verschillende stukken nagelezen en figuren gemaakt. Dank voor je kritische feedback, je doortastendheid, wetenschappelijke inzichten, prachtige muziek, biertjes en goeie grappen.
Nelis, wat heb ik het je lastig gemaakt en wat heb jij dit goed opgepakt!! Veel dank voor de prachtige kaft van dit boek dat jij zonder enige aanwijzing van mij (behoudens, iets met een cranioplastiek lijkt me wel leuk) hebt ontworpen. Dank voor je rustgevende woorden in de laatste fase van het schrijven van dit boekje: ' het komt allemaal wel goed', 'doe rustig aan', 'morgen weer een dag' en 'kom we drinken even een cappuccino'.

Dennis, Esmee, Annemieke, Yvonne R, Yvonne B, Ilse, Rachel, Jasper en Mariëtte, dank voor jullie inzet, hulp en energie, maar ook voor de vele grappen op de werkvloer, creativiteit (Jasper onze uitdagende boldster) en jullie zorgzaamheid (taart, elastiekjes, boterhammen, limonade, water, dextro, vanillevla).
Simone V, Drikje, Willemijn, Antoinette, Guido en Inge, dank voor de eeuwige order reminders, brief controles en rustgevende woorden als er bepaalde formulieren niet of verkeerd waren ingevuld.
Margot, Mandy en Annelies, zonder jullie een héleboel plaque! Dank dat jullie altijd voor ons klaar staan en zo flexibel zijn. Zonder jullie geen pocketsonde die gebruikt wordt waar deze echt voor bedoeld is.
Ingrid, Ingrid, Samira en Erica, dank voor jullie enthousiasme bij ingewikkelde casuïstiek betreffende focus onderzoek, voor jullie flexibiliteit om altijd een patiënt tussendoor te kunnen zien en de vele geleende en nooit teruggeven zakjes met elastiekjes en snoepjes (waar ik wel 6 maanden over gedaan heb om de geheime locatie te kunnen vinden!).

Hooggeleerde heer, prof. dr. M.A.W. Merkx, Beste Thijs, daar sta ik dan, wie had dat ooit gedacht in 2005, toen ik een snuffelstage bij je liep in het Radboud MC. Jij hebt mij –destijds- in korte tijd zo enthousiast gemaakt over Mondziekten, Kaak,- en Aangezichtschirurgie dat ik vanaf toen wist, deze kant wil ik op. Kelly liet mij elementen extraheren, ik heb heftige trauma's gezien (die ik tot op heden kan herinneren) en intensieve OK's meegemaakt.
Kelly, super om te zien dat de wetenschap je een klein beetje bereikt heeft, wie weet volgt er nog een boekje. Heel erg leuk om nog steeds met jou en je gezin contact te hebben!

Charlotte, jij hebt mij een beetje van de wetenschap laten proeven, dat smaakte naar meer, net zoals de sushi en vino.! Veel dank daarvoor. Marinka, dank voor het delen van het kamertje 'zonder deur' en de fles met Legionella ;).

Daarnaast het 3D lab Nijmegen, in het bijzonder Rinaldo Vreeken, dank voor het ontwikkelen voor software om craniale defecten te meten, met mij twee dagen lang de grootte van PEEK cranioplastieken te berekenen (helaas zonder significant resultaat) en jullie kennis binnen de 3D wereld.

Beste Ferdinand, dank voor het design van dit proefschrift, voor je tijd en energie voor de aanpassingen (en dat waren er niet een paar) en voor het prachtige eindresultaat!

Jij bent mijn maatje voor het leven, samen zullen we nog heel wat gaan beleven,
Dansen we rond, drinken we wijn, ook als we stokdoof en gerimpeld zijn - Lief Leven

Lieve Juultje, Majo, May en Lout, al zo lang vriendinnen, zulke verschillende levens en types, maar altijd zijn we er voor elkaar, als we elkaar nodig hebben. We zijn nauw bij elkaars levens betrokken door grote dingen, die we samen van dichtbij hebben meegemaakt. Veel dank voor jullie heerlijke nuchtere en niet nuchtere gesprekken, jullie steun en toeverlaat, voor de grappen die niemand begrijpt (D&P), de vele etentjes en voor alle mooie dingen die we nog samen gaan meemaken! Ik voel mij een rijk mens met jullie om mij heen.

Lieve Flip, Door, Viev, Sop I en Cher, het begon allemaal met de amygdala, sindsdien onafscheidelijk, ondanks coschappen in een ander ziekenhuis! Dank voor de goede adviezen, alle gezellige lunches, koffies, bubbels en etentjes. Dank dat ik bij jullie mezelf kan zijn, dank voor de smerige koffie uit het automaat in het VUmc (5e etage), dank voor de uren gezamenlijk studeren (dat door jullie haalbaar en dragelijk werd), dank voor de ontspannen momenten na die oh zo stressvolle VGT, dank voor jullie lieve woorden als er weer eens een formulier niet goed was, of de back up als ik ergens niet aanwezig was. Dank dat jullie, jullie zijn!

Lieve Frederieke, Robey, Emma v. K., Emma H., Sandra en Bel, dank voor jullie onvoorwaardelijke steun afgelopen periode, jullie interesse en bemoedigende woorden hebben ervoor gezorgd dat dit boekje een feit is geworden. We delen lief en leed, ik kan altijd bij jullie terecht (ook in het midden van de nacht!) en heel veel dank voor alle ontspannende momenten. Lieve Marmot, gedeelde smart is halve smart, you can do it!!

Jij bent anders, niet zoals de mensen om je heen, en gelukkig maar,
je maakt de wereld zoveel mooier, zoals jij is er geen één - Lief Leven

Lieve Ees, als een rots in de branding bij ons in Beverly Bussum, wat heerlijk als jij dinsdag en donderdag bij ons bent en de orde weer op zaken gesteld wordt! Zo heerlijk om te zien hoe dol jij en Fé op elkaar zijn, de konijntjes uitgebreid gevoed worden en de hoeveelheid tekeningen die er gemaakt worden.

Lieve Hans en Martje, je geliefde kan je uitzoeken, je schoonfamilie krijg je erbij, wat dat betreft had ik geen betere liefde kunnen kiezen. Veel dank voor jullie lieve woorden, onuitputtelijke interesse in mijn onderzoek, nalezen van stukken, geruststelling en liefde voor Féline. Ik voel me bijzonder thuis in jullie warme familie.

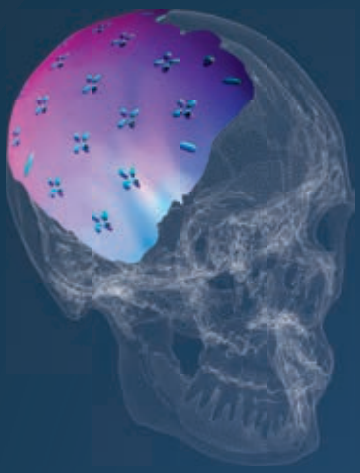
Lieve Fleur, Steven, Lily, Kate en Mick, wat is het toch altijd een heerlijk zooitje ongeregeld bij jullie, maar met een top organisatie en management. Bij jullie staat de deur altijd wagenwijd open, is iedereen welkom, is niks te gek (écht niks) en kan iedereen zichzelf zijn. Lieve Fleuri, ik ben zo blij dat jij vandaag naast mij staat, je bent inmiddels als een zus voor me, met goede raad, schone sokken indien nodig, een luisterend oor en een goed glas wijn op zijn tijd. Ik vind het echt inspirerend, bijzonder en prestigieus hoe jij de organisatie thuis voor elkaar hebt met zo'n top baan, je mag echt super trots op jezelf zijn!! Daarnaast ben je een super lieve moeder, onvermoeibaar, creatief en weet je waar je bij jou aan toe bent, HEERLIJK!

Lieve Broer, twee totaal verschillende personen, maar allebei even gek, altijd in voor een feestje, super trouw en allebei onuitputtelijke energie. Wat ben ik blij dat je vandaag naast mij staat!! Ik ben super trots op jou: je nuchterheid, grappen, doorzettingsvermogen én het vermogen om alles net op het nippertje goed te laten af lopen. Félientje had zich geen betere oom kunnen wensen, als zij je van een afstand ziet aankomen begint zij al te stralen. Je bent de beste!

Lieve papa en mama, wat ben ik trots dat jullie mijn ouders zijn. Al vanaf jongs af aan hebben jullie achter mij gestaan, altijd vertrouwen gehad in mij en zijn jullie altijd betrokken geweest bij de dingen die ik deed. Zonder jullie hulp en steun afgelopen jaren zou ik niet de persoon zijn die ik nu ben, jullie hebben mij altijd gemotiveerd en gesteund mijn droom na te jagen en hebben jullie mij de mogelijkheden kunnen bieden om dit pad te kunnen bewandelen. Jullie liefde voor Féline is onbeschrijfelijk, zo bijzonder om te zien. Ik kan niet wachten op alle mooie momenten die nog komen gaan.

Lieve Féline, lieve kleine Fé'tje, mijn liefste, wat ben ik blij dat jij er bent, mijn liefde voor jou is onvoorwaardelijk. Jouw vrolijke gezichtje maakt mij zo gelukkig (ook om 5.30 in de ochtend), met je lieve lach laat je mij smelten en geef je mij energie om dit boekje af te maken. Als jij 's ochtends ligt te zingen in je bedje en we samen koffie halen om nog even in het grote bed te liggen (en ik me dus weer moet haasten om op tijd te komen) heb ik een heerlijk begin van de dag en kan ik niet wachten totdat we samen 's middags weer naar de vogeltjes kunnen kijken. Ik kijk uit naar alle mooie momenten die wij samen zullen mee gaan maken. Ik weet zeker dat je een fantastische, lieve en zorgzame zus zult zijn voor je kleine zusje.

Aller liefste Jan, mijn steun en toeverlaat, dit zijn écht mijn laatste woorden van dit proefschrift. Je eindeloze geduld met mijn Sophie-minuutjes (80 seconden in 1 minuut), je vermogen om nooit in de stress te schieten en je motiverende woorden om de kansen die op mijn pad komen te grijpen, hebben mij geholpen te kunnen dromen en te kunnen vliegen. Jij jaagt de beren weg, die ik op de weg zie, jij bent mijn rots in de branding en jij geeft mij een extra duwtje in mijn rug als ik niet verder durf. Jij laat mij zijn wie ik ben, alleen maak jij mij nét iets leuker, jij laat mij lachen, en maakt van iedere dag een feestje, jij bent de beste vader die een vrouw voor haar dochter kan wensen, jij bent mijn O_2. Voor altijd de jouwe.



Curriculum Vitae

ABOUT THE AUTHOR

Sophie Elisabeth Catharina Maria was born August 28th 1987 in Nijmegen, the Netherlands, as the daughter from Wim and Marjorie van de Vijfeijken. Together with her brother Joost, she grew up in a warm family.

In 2006, she completed her Athenaeum education at the 'Canisius College' in Nijmegen. During the last year of high school she was intrigued by Oral and Maxillofacial Surgery after a mini-internship at the Radboud University MC, Nijmegen. She started dentistry at the Academic Centre of Dentistry Amsterdam in 2006. She went to Toronto and Moose Factory in Canada for a clinical internship concerning Oral and Maxillofacial Surgery in 2010. During dentistry, she followed a minor in Entrepreneurship at the faculty of Economics and Business at the University of Amsterdam (UvA), which she completed in 2009. After receiving her master's degree in dentistry, she started studying Medicine at the VU University medical centre (VUmc) school of medical sciences in Amsterdam in 2012, where she obtained her master's degree in 2016.

During her studies, she worked as a dentist volunteer in Nepal with the Netherlands Oral Health Society and at the 'Kruispost' in Amsterdam. Sophie then worked as an oral hygienist in the center of Amsterdam, as an assistant at the department of Oral and Maxillofacial surgery at the Kennemer Gasthuis in Haarlem, and as a general dentist at the 'Mondzorgpoli' at the Slotervaart Hospital. Furthermore, she worked in a general dental practice in Maarssen and as a teacher in the department of Oral and Maxillofacial surgery at the VUmc.

In the further context of her extracurricular activities Sophie went in 2009 to Guangzhou as the head of one of the Children's International Summer Villages**.** In 2011 she ran the New York marathon for the foundation Human Right Watch, swam the Amsterdam City Swim in 2012 for the foundation Amyotrophic Lateral Sclerosis and worked two years as a volunteer for the same foundation. During the Olympics in 2012 she worked at the Holland Heineken House in London.

In 2016 she became a member of the 'CranioSafe' research group, which gave her the opportunity to work on research about materials used for cranioplasties after a decompressive craniectomy. This resulted in her PhD research in this field, at the department of Oral and Maxillofacial Surgery at the AMC in Amsterdam under supervision of Prof. dr. A.G. Becking and Prof. dr. C.J. Kleverlaan. In the same year she started first job as an Oral and Maxillofacial surgeon resident at the Academic Medical Center (AMC).

In August 2018 she started her training as an Oral and Maxillofacial surgeon at the Amsterdam University Medical Center (Amsterdam UMC).

Currently, Sophie lives together with her loving partner Jan Brölmann and their daughter, Féline. They are expecting their second daughter.