Niina Salokorpi

TREATMENT OF CRANIOSYNOSTOSES
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Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 12 of the Department of Paediatrics, on 10 November 2017, at 12 noon

UNIVERSITY OF OULU, OULU 2017
Salokorpi, Niina, Treatment of craniosynostoses.
University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Centre Oulu; Oulu University Hospital
Acta Univ. Oul. D 1428, 2017
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract
This work evaluated the safety and effectiveness of operative techniques used in cranioplasty surgery and outcomes of these surgical methods.

In study I the feasibility of endocranial fixation in frontal remodeling surgery for metopic and coronal synostosis was established. Good to excellent aesthetic results were seen in 96% of cases evaluated by a surgeon at the time of follow-up. Three patients out of 27 had complications requiring revisions. No mortality or permanent morbidity, nor complications related to endocranial placement of the plates were seen. Thus it was verified that placing resorbable material intracranially reduces the aesthetic impact without hindering the final result.

Study II found that posterior cranial vault distraction procedures produced a mean increase of 25% in intracranial volume. This proved to be an effective technique for treating a variety of craniosynostosis with significant shortage of intracranial volume. 3D photogrammetric imaging was found to be a suitable non-ionizing method for evaluation of cranial volume increase following distraction. In study III a new tool was developed and successfully used for the intraoperative guidance of distractor device placement to ensure congruent vectors and thus reduced complications of these surgical procedures.

In study IV long-term functional and aesthetic outcomes of the surgical treatment for sagittal synostoses in patients reaching adulthood was examined. The mean follow-up time was 26.5 years and the patients were 18 to 41 years old at the time of follow-up. The patients treated for sagittal synostosis were equally satisfied with their facial appearance as were their age and gender matched controls. Independent panels found patients’ appearance to be slightly less attractive, but the difference was less than 10 mm on a 100 mm Visual Analogue Scale, representing a low clinical significance. Patients’ socioeconomic situation such as education, housing, employment and marital status equaled controls with similar frequencies of headaches, mental problems or health issues as the controls.

Keywords: 3D photogrammetric imaging, cranioplasty, craniosynostosis, distraction, facial aesthetics, intracranial volume, outcome, resorbable plates
Tässä tutkimuksessa selvitettiin kallon saumojen ennenaikaisen luutumisen (kraniosynostoosi) leikkausmenetelmien tehokkuutta ja turvallisuutta sekä pitkäaikaisia tuloksia.

Leikkausmenetelmä, jossa epämuotoinen kallo uudelleenmuotoilla ja luiset osat kiinnitetään toisiinsa kallon sisäpuolelle asennettavilla ja kudokseen hajoavilla levyillä oli tehokas ja luotettava (N=27). Jälitarkastuksessa tulostot arvioitiin erinomaiseksi tai hyväksi 96 %:lla tapauksista. Leikkaushoitoa vaativia ongelmia tai komplikaatioita esiintyi kolmella, mutta pysyvä haittaa ei jäänyt. Komplikaatiot eivät johtuneet levyn sijainnista kallon sisällä.

Saumojen ennenaikaisesta luutumisesta johtuvaa kallon tilavuuden alentumaa hoidettiin venytys- ja kallovenyttymis-ohjainilla (N=30). Menetelmällä saavutettiin keskimäärin 25 %:n lisääntyminen tilavuudessa, ja se soveltui erityisen hyvin potilaille, joilla tarvitaan suuri tilavuuden lisääntyminen. Leikkaustekniikkaan ei liittynyt sojaa komplikaatioita. Tulosta arvioitiin osalla potilaita kallon tiltamottaisella valokuvauksella, joka perinteisistä seurantamenetelmissä poiketen ei altistu ionisoivalle säteilylle, ja se osoittautui käytökelpoiseksi seurantamenetelmäksi.

Venytyshoitoa varten kallon pintaan kiinnitetätäpidennyslaitteita tulee asettaa yhdensuuntaisesti, ja se on teknisesti haasteellista. Työssä kehitettiin kirurginen instrumentti, jolla venytetut voidaan luottavasti asetella samansuuntaisiksi. Uusi tekniikka ehkäisee mekaanisia ongelmia, joita muuten voisi ilmetä erisuuntaisten venytymien edetessä.

To my family
Acknowledgements

This study was carried out at the departments of paediatric surgery and neurosurgery, University of Oulu.

First of all, my deepest gratitude goes to my supervisor, Professor Willy Serlo, M.D., Ph.D., Head of the Department of Paediatric Surgery, Oulu University Hospital, for this opportunity to work and learn under his guidance. He introduced me to this subject and pediatric neurosurgery in general. His endless enthusiasm to acquire and teach new knowledge never ceased to impress me. Thanks also for introducing me to this study group and to the pediatric neurosurgery community as well as for good companionship on the many trips we made. Without his guidance, fatherly support and help this dissertation would not have been possible. My sincere gratitude also goes to my other supervisor, Professor Pertti Pirttiniemi, D.D.S., Ph.D., for all the time and support you gave me. I am truly indebted to Professor György K. Sándor, D.D.S., M.D., Ph.D. who made enormous work with this study including revising the language of the thesis and original publications, and who has always been kind and supportive to me.

I am grateful to docent Juha-Jaakko Sinikumpu, M.D., Ph.D., for his excellent writing skills and valuable comments during the whole process and to Tuula Savolainen, D.D.S., for her friendship and for her great contribution to collecting the data. I am truly thankful to Kaisu Serlo, for her exceptional helpfulness and empathy in the out-patient clinics and for her great work as a research nurse, who made the long-term follow-up study happen. I also want to thank Tarmo Areda, M.D., Ph.D., Heleia Nestal Zibo, M.D., D.D.S., Tarja Iber, M.D. and Leena Ylikontiola, M.D., D.D.S., PhD for helping me to collect the data and write the articles. I am thankful to Leonid Satanin, M.D., C.Sc., and to Anna-Sofia Silvola, D.D.S., Ph.D., for all their support, advices and valuable comments. I am thankful to Päivi Tapanainen, M.D., for his patience in teaching me the principles of biostatistics.

I am grateful to Katrin Gross-Paju, M.D., Ph.D. and Professor Toomas Asser, M.D., Ph.D., Head of Neurosurgery Department, Tartu University Hospital, as well as to Professor John Koivukangas, M.D., Ph.D., and Sanna Yrjänä, M.Sc., Ph.D., for introducing the research work to me, for inspiring and supporting me.

I am thankful to Päivi Tapanainen, M.D., Ph.D., Head of the Division of Children and Adolescents, for her support and providing facilities in regard to the study. I owe my gratitude for arranging time for me to work on the thesis project to Susanna Yli-Luukko, M.D., Head of Division of Orthopedics and Neurosurgery and especially to docent Timo Kumpulainen, M.D., Ph.D., Head of the Department
of Neurosurgery, also for an opportunity to work and learn neurosurgery and pediatric neurosurgery under his guidance. His unbeaten clinical expertise, operative skills, patience and empathy are exemplary.

I want to express my gratitude to the referees of the thesis Professor Federico DiRocco, M.D., Ph.D., and docent Arto Immonen, M.D., Ph.D., for their thorough review of the manuscript and for their constructive criticism and valuable advice, which substantially improved the quality of this manuscript.

I also want to thank my follow-up group: Professor Kyösti Oikarinen, D.D.S., Ph.D., Professor John Koivukangas, M.D., Ph.D., and docent Timo Kumpulainen M.D., Ph.D., for their time and experience.

The support of my present and past co-workers in the Department of Neurosurgery, Maija Lahtinen, M.D., Sami Tetri, M.D., Ph.D., Anna-Leena Heula, M.D., Juho Tuominen, M.D., Tatu Koskelainen, M.D., Mikko Kauppinnen, M.D., Matti Heiskari, M.D., Ph.D., Hannu Rönty, M.D., Ph.D. and Professor Esa Heikkinen, M.D., Ph.D., as well as Mirva Nätyynki, M.D., Cheng Qian, M.D., Miro Jänkälä, M.D., was invaluable to me during this work. I also express my gratitude to all the paediatric surgeons, paediatric anaesthesiologists and paediatric radiologists with whom I have been involved for their work. I want to express my gratitude to personnel of the paediatric operation department, the paediatric intensive care ward, the paediatric surgery out-patient clinics and the ward who have helped me in multiple ways over the years. Particular thanks go to Kaisa Rahko for her excellent illustrations and for her assistance during the operations.

I want to thank all the patients, lay persons and the dentists who have participated in this study and given their time. It is my hope that this study may help us to understand and help our patients better.

This study has been financially supported by VTR-grant from Oulu University Hospital, The Foundation for Pediatric Research, Finland, Alma and K. A. Snellman Foundation, Oulu, Finland. These grants are gratefully acknowledged.

I am thankful to my parents who not only have loved and encouraged me but also who have taught me to work hard with determination. I want to thank all my friends for being there for me.

This thesis is dedicated to the closest people of my life. I owe my loving thanks to my husband Jyrki, my daughter Emma and my step-daughters Karolina and Kamilla for the love and joy you have given me. Jyrki thanks for your constant love, support and understanding during all these years. I am so privileged to have you in my life.

29th August, 2017

Niina Salokorpi
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>3D</td>
<td>three-dimensional</td>
</tr>
<tr>
<td>CI</td>
<td>cephalic index</td>
</tr>
<tr>
<td>CT</td>
<td>computer tomography</td>
</tr>
<tr>
<td>FGFR</td>
<td>fibroblast growth factor receptors</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>ICV</td>
<td>intracranial volume</td>
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<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>MCID</td>
<td>minimally clinically important difference</td>
</tr>
<tr>
<td>MSX2</td>
<td>homeobox containing gene</td>
</tr>
<tr>
<td>TWIST</td>
<td>a basic helix-loop-helix transcriptor factor</td>
</tr>
<tr>
<td>OHIP</td>
<td>Oral Health Impact Profile</td>
</tr>
<tr>
<td>OHIP-14</td>
<td>14-item Oral Health Impact Profile</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>PCVD</td>
<td>posterior cranial vault distraction</td>
</tr>
<tr>
<td>PGA</td>
<td>Polyglycolic acid</td>
</tr>
<tr>
<td>PLA</td>
<td>poly(lactide/polyactic acid)</td>
</tr>
<tr>
<td>PLLA</td>
<td>poly-L-lactic acid</td>
</tr>
<tr>
<td>PLDA</td>
<td>poly D,L-lactic acid</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>TMC</td>
<td>trimethylene carbonate</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


IV Salokorpi, N., Savolainen, T., Sinikumpu, JJ., Ylikontiola, L., Sándor, G.K., Pirttiniemi, P., Serlo, W. Outcomes of 40 nonsyndromic sagittal craniosynostosis patients as adults: A case-control study with 26.5 years of postoperative follow-up. Manuscript.
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1 Introduction

Craniosynostosis is a congenital anomaly with premature closure of one or more sutures between cranial bones, resulting in abnormal head growth and facial dysmorphism (Flaherty, Singh, & Richtsmeier, 2016). Treatment of craniosynostoses is surgical, with wide variety of techniques used depending on the number and the location of prematurely ossified sutures. Suboptimal treatment may result in cosmetic deformities, psychological, cognitive and developmental sequelae in the later life (Bellew & Chumas, 2015; Blount, Louis, Tubbs, & Grant, 2007; Kapp-Simon et al., 2012; Speltz, Kapp-Simon, Cunningham, Marsh, & Dawson, 2004).

In order to improve the quality and effectiveness of surgical treatment it is important to evaluate the outcomes of surgery, not only from the surgeon’s point of view, or by performing objective cephalometric measurements, but more importantly by developing more patient-centered approaches. The present study was undertaken to evaluate the results of different operative techniques used in craniosynostosis treatment.
2 Review of the literature

2.1 Normal growth of the human skull

The human skull is made up of nine bones forming the neocranium and 14 bones forming facial skeleton. These bones articulate with one another by the means of fibrous joints or sutures and synchondrosis (Beederman, Farina, & Reid, 2014; Rice, 2008). Sutures are made of two osteogenic fronts and a cellular mass of mitotic mesenchymal cells, lying between dura mater and the ectoperiostal layer (Flaherty et al., 2016). Cranial vault bones grow by new bone formation at the sutures and by remodelling of their inner and outer surfaces to accommodate and fit the growing brain (Flaherty et al., 2016; Opperman, 2000; Rice, 2008). Bone growth sites at the sutures of the cranial vault remain dormant until stimulated to make bone by external signals arising from the growing brain. Animal and in vitro experiments show that dura mater participates in signalling and thus in determining fusion or patency of the overlying sutures, especially in newly formed sutures. More fully developed sutures are able to sustain themselves even in absence of dura (Opperman, 2000). Signals from dura mater are mediated by different growth- and transcription factors (transforming growth factor, fibroblast growth factor receptor, TWIST, and MSX2) (Panchal & Uttchin, 2003). As a result of this tightly regulated and balanced process of osteogenesis and bone remodelling, the skull grows intensively to accommodate the growing brain especially during early childhood with the intracranial volume reaching 77% of adult size by two years and with 90% of the volume reached by the age of five years (Sgouros, Goldin, Hockley, Wake, & Natarajan, 1999). While the metopic suture is the first suture to undergo physiological fusion at approximately nine months of age, other sutures do not fully close until adolescence or even later (Beederman et al., 2014; Cohen, 2005).

2.2 Definition and historical aspects of craniosynostoses

Craniosynostosis is a condition that involves premature fusion of one or more cranial vault sutures causing significant alteration in craniofacial morphology and has the potential for negative neurologic and cognitive effects (Flaherty et al., 2016).

One of the first scientific descriptions of craniosynostosis was given by von Sömmering, who published his book “Vom Baue des menschlichen Körpers” in
1801. He described the structure of the sutures and recognized their primary importance in skull growth, stating that premature fusion of a suture would necessarily result in deformity of the head (Laitinen, 1956). Soon, in 1830 another German anatomist Adolph Wilhelm Otto proposed that when the suture becomes ossified, the marginal bony growth is arrested and this is compensated by growth of the skull along another trajectory. Otto was also the first to describe the small size of the head either by primarily defective brain or by premature fusion of the sutures (Laitinen, 1956). Virchow further developed and popularised the ideas proposed by Otto. He published a work where he defined Virchow’s law, stating that in craniosynostoses skull deformities occur as a result of the cessation of growth across a prematurely fused suture causing compensatory growth along patent sutures in a direction parallel to the affected suture (Mehta, Bettegowda, Jallo, & Ahn, 2010).

In 1866 the first clinical case of craniosynostosis was reported by von Graefe (Laitinen, 1956). In the early 1900s French physicians Apert and Crouzon gave their names to the first recognized complex syndromic craniosynostoses with brachycephalic deformity (Mehta et al., 2010).

With a growing understanding of the role of sutures in skull growth and the consequences of their premature ossification, the first steps towards the treatment of craniosynostoses were warranted.

### 2.3 Pathology and genetics of craniosynostoses

Premature osseous obliteration of sutures leads to fusion of two bones across the suture site. This prevents further bone formation at this site and redirects growth to other patent sutures (Opperman, 2000), altering the global shape of the skull in a predictable way (Fig. 1) (Flaherty et al., 2016). The head shape in craniosynostoses depends on which sutures are prematurely fused, as well as the order and timing of their ossification (Cohen, 2005).
Fig. 1. Variation in cranial vault shape depicted by three-dimensional computed tomography reconstructions of the infant skulls with different types of single-suture craniosynostoses.

The fusion of the cranial sutures and maintenance of suture patency are dependent on the interaction of a large number of cytokines, transcription factors (TWIST, MSX2), growth factor receptors (FGFR-1, FGFR-2, FGFR-3), as well as molecules of extracellular matrix. Different types of mutations in genes encoding these factors have been found to be associated with syndromic forms of craniosynostoses (Panchal & Uttchin, 2003).

While approximately 85% of craniosynostoses cases are not syndromic, by August of 2017 the remaining 15% of craniosynostoses cases could be related to over 200 known syndromes which have been found to be associated with craniosynostoses. This number is growing continuously (McKusick, 2017). At least half of the syndromic cases follow a Mendelian pattern of inheritance (Heuze, Holmes, Peter, Richtsmeier, & Jabs, 2014).

Recently numerous rare gene mutations have been identified in some cases of nonsyndromic craniosynostoses. They usually have incomplete penetrance, since
sometimes family members carrying the mutations have been found to be unaffected or to have craniofacial dysmorphism but not craniosynotosis (Heuze et al., 2014).

2.4 Epidemiology and classifications of craniosynostoses

Craniosynostoses affects one in 2000-2500 live births worldwide. This estimate is related to the number of patients that are treated surgically. When considering the possible undiagnosed cases this number could be much higher (Hunter & Rudd, 1976; Lajeunie, Le Merrer, Bonaiti-Pellie, Marchac, & Renier, 1995; Mehta et al., 2010; Singer, Bower, Southall, & Goldblatt, 1999). Thus craniosynostoses are the second most common group of craniofacial anomalies after orofacial clefts (Flaherty et al., 2016).

Craniosynostoses can be classified in many ways. They can be divided in syndromic or non-syndromic, single or multiple suture synostoses, primary (caused by an intrinsic defect in the suture) or secondary synostosis (caused by another medical condition). Both syndromic and non-syndromic craniosynostoses can present with a single suture involvement or with complex premature fusion of multiple sutures.

Single suture involvement is more common, comprising up 85 – 90% of all craniosynostoses. The most commonly affected suture is the sagittal suture, followed by the metopic and coronal sutures (Kolar, 2011; Singer et al., 1999). Isolated premature fusion of the lambdoid suture is very rare (Kolar, 2011; Wilkie, 2000).

Syndromic craniosynostoses comprise approximately 10 – 15% of craniosynostoses (Heuze et al., 2014). They are generalized disorders of mesenchymal development that often harbour other anomalies (dysmorphic features or developmental defects). The occurrence depends on the type of syndrome. For example, Muenke syndrome, the most common form of syndromic craniosynostoses, has an incidence of 1 in 30,000 births, while Apert syndrome has an incidence of 15 in 1,000,000 births (Agochukwu, Solomon, & Muenke, 2012).

Premature fusion of the sagittal suture causes a scaphocephalic head shape due to diminished skull height and width with compensatory anteroposterior growth (Fearon, 2014). It is the most common type of craniosynostoses, accounting for 40 to 60% of all synostoses with a birth prevalence ranging from approximately 1.8 to 2.5 in 10,000 live births (Di Rocco, Arnaud, & Renier, 2009; Kimonis, Gold,
Premature closure of the metopic suture is called trigonocephaly due to lateral growth restriction of the frontal bones and increased posterior width of the skull (van der Meulen, 2012). The incidence of trigonocephaly has been reported to range from 1 in 700 (Alderman et al., 1988) to 1 in 15,000 births (Lajeunie, Le Merrer, Marchac, & Renier, 1998). Recent reports have noted that its incidence has increased up to 28% of all non-syndromic craniosynostoses (Kolar, 2011; van der Meulen et al., 2009).

Plagiocephaly is a term applied to anterior and posterior flattening/bossing of the skull that can be unilateral or bilateral. Anterior or frontal plagiocephaly is usually caused by premature occlusion of the coronal sutures and posterior plagiocephaly is caused by ossification of the lambdoid suture. Asymmetry caused by outer forces with no premature ossified sutures is called positional plagiocephaly (Cohen, 2005). Premature ossification of the coronal sutures is seen in approximately 24% of patients with craniosynostosis (Kolar, 2011).

### 2.5 Diagnostics

In the majority of cases, an anomalous skull (and face) shape awakens the suspicion for craniosynostosis. In many syndromic cases and in some single suture synostoses the presence of some dysmorphic traits and abnormal head shape becomes apparent immediately after birth (Fearon, 2014; Schweitzer et al., 2012). The diagnosis is clinical. However, most authors recommend radiographic imaging for further diagnostics, with 3 dimensional CT imaging being a gold standard for diagnosing craniosynostoses (Fearon, 2014). Due to the potential negative effects of ionizing radiation in children, including possible developmental delay and increased risk of neoplasia in later life, alternative diagnostic protocols have been proposed (Schweitzer et al., 2012). Physical examination is highly accurate in the diagnosis of single suture synostoses patients (Fearon, 2014; Schweitzer et al., 2012). Ultrasound of the sutures can be a useful tool with infants in the hands of experienced radiologists (Regelsberger et al., 2006; Soboleski et al., 1998).

Plain skull X-rays add valuable information on suture condition, typical secondary deformations of the skull and molding of the inner surface of the skull, with a very low radiation dose and no need of sedation (Schweitzer et al., 2015).

For complex and syndromic synostoses three-dimensional skull CT remains necessary for precise diagnosis and preoperative planning (de Jong et al., 2010).
With growing knowledge about possible intracranial pathologies associated with complex synostoses, brain MRI is becoming a part of preoperative screening. It also allows identification of Chiari I malformations if present and whether it needs to be addressed during the surgery (Cinalli et al., 2005). When planning surgery especially involving the posterior cranial vault in syndromic cases, brain MRI and MR-angiography is highly recommended to identify anatomical variations of the venous system (Cinalli et al., 2005; Thompson, Hayward, & Jones, 1995).

Additional functional studies may be warranted in the diagnostic evaluation. They include ICP measurement, polysomnography for cases with complaints suggestive of obstructive sleep apnea, ophthalmological, otolaryngological and audiological evaluations (de Jong et al., 2010).

Genetic testing is a compulsory part of the diagnostic workup in all cases when a syndromic craniosynostosis is suspected (Agochukwu et al., 2012; de Jong et al., 2010).

2.6 ICP measurement in craniosynostoses

Since the growing brain experiences compression when a suture closes prematurely, children with craniosynostoses, especially multi-suture ones, carry a risk for developing elevated intracranial pressure (ICP) (Renier, Sainte-Rose, Marchac, & Hirsch, 1982). Increased ICP is most often found in cases of multi-suture craniosynostoses (Renier et al., 1982). In patients with craniofacial syndromes like Apert, Crouzon, Pfeifer and Saethre-Chotzen, the increase in ICP may be found in 33% to 87.5% of patients according to different studies (Bannink et al., 2008; de Jong et al., 2010; Marucci, Dunaway, Jones, & Hayward, 2008; Tamburrini, Caldarelli, Massimi, Santini, & Di Rocco, 2005). The long-term consequences of constantly elevated intracranial pressure may lead to cognitive impairment, visual impairment, headaches, emesis, irritability, and altered mental status (Blount et al., 2007). However, the normal range of physiological variations in ICP remains unclear. Also reduced intracranial volume by itself has not been found to predict increased ICP (Gault, Renier, Marchac, & Jones, 1992). In addition to the above-mentioned problems, it is also difficult to compare the results of the different studies on ICP, due to a wide variety of the methods used to measure ICP (Tamburrini et al., 2005). Thus the value of ICP recording in craniosynostosis patients remains unclear (Slater et al., 2008).
2.7 Neurodevelopmental aspects

In cases of syndromic craniosynostoses, neurodevelopmental disturbances are common, especially in individuals with Apert and some types of Pfeiffer syndrome (Agochukwu et al., 2012).

In spite of previous assumptions, children with single suture non-syndromic craniosynostoses may also present with mild cognitive, behavioural and speech disturbances, that are found during tasks that are more challenging, particularly in children approaching school age (Becker et al., 2005; Kapp-Simon, Speltz, Cunningham, Patel, & Tomita, 2007). For example, in a Finnish study including 61 children with non-syndromic single suture craniosynostoses or deformational posterior plagiocephaly, one half of the subjects demonstrated slight or severe defects in early language acquisition. The prevalence of severe language defects was three times higher than in the general Finnish population (Korpilahti, Saarinen, & Hukki, 2012). In another study by Starr and associates, three-year old children with single suture craniosynostoses gained lower scores on neurodevelopmental assessments than did a control group of non-synostotic children (Starr et al., 2012).

One explanation for the presence of neurodevelopmental anomalies in non-syndromic craniosynostoses is that there is a primary anomaly of the brain itself, which might be specific for each type of craniosynostoses. Aldridge and associates have shown that the organization of the brain in single suture craniosynostoses is dysmorphic, with cortical and subcortical dysmorphology (Aldridge, Marsh, Govier, & Richtsmeier, 2002). They also demonstrated that in spite of restoration of the shape of the brain as a result of operative treatment, differences in subcortical morphology remained (Aldridge et al., 2002; Aldridge et al., 2005).

Craniosynostoses have a secondary psychosocial effect. Some patients retain dysmorphic facies that might attract unfavourable attention from strangers and peers. Antisocial, withdrawal, or even aggressive behaviour, poor school performance and difficulty in an educational environment could be responses to peer rejection (Becker et al., 2005).

2.8 Treatment of craniosynostoses

Since the first operative technique for treatment of craniosynostoses was described by the French surgeon Lannelongue in 1890 (Bir, Ambekar, Notarianni, & Nanda, 2014), a variety of techniques have been developed.
There is little evidence for optimal treatment of craniosynostoses. The choice of technique depends on the patient age, type of pathology, experience and philosophy of treatment that rules in the particular institution (Szpalski, Weichman, Sagebin, & Warren, 2011).

Surgery for craniosynostoses has two major aims: to provide sufficient intracranial volume for the brain to grow and develop normally and, second, to normalize head shape and facial appearance (Hankinson, Fontana, Anderson, & Feldstein, 2010; Szpalski et al., 2011). Operative techniques and their benefits compared to each other are currently an area of active research.

### 2.8.1 Evolution of surgical methods

In the beginning of the surgical era, Virchow’s work had a great impact on development of craniosynostosis surgery since the first attempts to treat craniosynostoses were based on his theory (Mehta et al., 2010).

The first publication on the technique of craniosynostosis surgery was published in 1890 by the French surgeon Lannelongue who described a releasing technique, with cutting craniectomy lines along the margins of the fused sagittal suture, leaving the suture itself intact (Fig. 2A) (Bir et al., 2014; Clayman, Murad, Steele, Seagle, & Pincus, 2007). Two years later Lane from San Francisco described the first strip craniectomy of the fused suture itself (Fig. 2B) (Clayman et al., 2007).

Success of the first craniectomy procedures was rather questionable due to lack of distinction between microcephaly caused by incapacity of brain to grow and true craniostenosis, as well as due to the timing of the operations in the course of the disease (Mehta et al., 2010). In 1894 Jacobi reviewed a series of 33 children treated with craniectomy and found a high mortality rate (15 children died). After public denouncement of these practices at a meeting of the American Academy of Pediatrics, craniosynostosis surgery was abandoned for nearly 30 years (Mehta et al., 2010).
In 1920th several studies (by Mehner, Faber and Towne) were published, reporting resection of the ossified suture as a causal treatment for craniosynostoses (Faber, 1962; Laitinen, 1956). Since their results were much better, it inspired further work on this field. The next technique was proposed by Ingraham who suggested covering of the craniectomy margins with a plastic film to prevent re-ossification (Ingraham, Alexander, & Matson, 1948; Laitinen, 1956). Fat tissue was used for same purpose (Merikanto, Alhopuro, & Ritsila, 1987).

In 1977 van der Werf published a method of dural split with dural outer layer dissected, turned over the osteotomy edge and sutured over the outer periosteum done in an attempt to prevent recurrence (van der Werf, 1977).

Meanwhile Moss in 1959 proposed that suturectomy alone did not restore normal calvarial development, but that a complex calvarial procedure was necessary to allow proper growth and expansion of the cranium (Pagnoni et al., 2014). This was followed by the pioneering work of French surgeon Paul Tessier, who described methods of facial osteotomy in patients with Crouzon syndrome (Tessier, Guiot, Rougerie, Delbet, & Pastoriza, 1967). Rougerie et al published in 1971 an article about extensive remodelling surgical technique and brought attention to cosmetic aspects (Rougerie, Derome, & Anquez, 1972). That was the beginning of the modern era of the surgical treatment of craniosynostoses.
2.8.2 Operative techniques for sagittal synostosis

The operative correction of sagittal synostosis, the most frequent type of craniosynostoses, is generally performed before the age of six months (Pagnoni et al., 2014). Modern surgical techniques vary from different cranial remodelling techniques, for example, Renier’s “H” technique (Fig. 2C) (Di Rocco, Knoll et al., 2012) or pi-procedure (Greene & Winston, 1988) to endoscopic strip craniectomies with postoperative moulding therapy with helmets (Berry-Candelario, Ridgway, Grondin, Rogers, & Proctor, 2011; Clayman et al., 2007) or spring-assisted correction (M. L. van Veelen & Mathijssen, 2012; Windh, Davis, Sanger, Sahlin, & Lauritzen, 2008).

2.8.3 Operative technique for metopic synostosis

Operative techniques for trigonocephaly developed from the strip craniectomy to “floating forehead technique” with remodelling of the supra-orbital bandeau (D. Marchac, Cophignon, Hirsch, & Renier, 1978). Nowadays there exists a variety of techniques of the frontal bone remodelling with or without releasing of the supraorbital bar (Aryan et al., 2005; Di Rocco, Arnaud et al., 2012). Also spring-assisted surgery (Maltese, Tarnow, & Lauritzen, 2007) and endoscopic-assisted treatment (Hinojosa, 2012) are used.

2.8.4 Operative technique for plagiocephaly

Anterior plagiocephaly and brachycephaly by fusion of one or both coronal sutures can be treated by fronto-orbital remodelling with bilateral or one-sided frontal advancement (Matushita, Alonso, Cardeal, & de Andrade, 2012; Mesa, Fang, Muraszko, & Buchman, 2011). In syndromic cases with severe facial retrusion, the frontal advancement may be followed by a facial advancement (LeFort III). In severe cases, if necessary, a frontofacial monobloc advancement can be performed (A. Marchac & Arnaud, 2012). Posterior plagiocephaly is usually treated with remodelling cranioplasty (Di Rocco, Marchac et al., 2012; A. Marchac, Arnaud, Di Rocco, Michienzi, & Renier, 2011) whereas positional posterior plagiocephaly can be treated with helmets (Lipira et al., 2010).
2.8.5 Fixation materials

The majority of the above mentioned operative techniques require fixation of the reshaped cranial bones. These can be achieved with conventional screws and plates (Goodrich, Sandler, & Tepper, 2012), biodegradable plates (Arnaud & Renier, 2009) or resorbable sutures (van der Meulen, 2012).

Successful bone fixation is fundamental in frontal cranial remodelling surgery. Fixation devices must maintain the new shape of the cranium following surgery until the new construct is ossified. Historically steel wires, metal plates with screws were used for this purpose (Goodrich et al., 2012). Though easy to use, malleable and strong, these materials had several disadvantages. Local skin irritation, infections, interference with modern imaging technologies, necessity of removal in a second operation, or the risk of intracranial pseudo-migration into the growing skull as well as risk of growth restriction if left unremoved, were among the problems caused by these materials (Arnaud & Renier, 2009; Fearon, Munro, & Bruce, 1995; Goodrich et al., 2012; Orringer, 1998). Resorbable sutures are used as additional means to keep the bones fragments in place (Goodrich et al., 2012; Goodrich, Tepper, & Staffenberg, 2012).

The next advance in craniofacial surgery was the introduction of biodegradable materials in the beginning of 1990s in order to avoid problems of rigid alloy fixation (Ahmad, Lyles, Panchal, & Deschamps-Braly, 2008). Postoperative resorption of the devices after ossification of fixated bony fragments minimized all potential future device-related complications (Eppley et al., 2004).

These resorbable fixation devices are different combinations and formulations of polymer macromolecules. Mainly polylactic acid in its L-isomer (PLA or PLLA) and polyglycolic acid (PGA) are used. These are the same materials that are used in resorbable sutures, thus having a long history of safe use (Eppley et al., 2004). PLLA is hydrophobic and thus resistant to degradation. PGA is hydrophilic, thus prone to early loosening of the polymer bonds and weakening of implant (Eppley et al., 2004). Early plates, made of monomers, tended to cause sterile non-inflammatory granulomas mainly during most active phase of degradation (Goodrich et al., 2012). Copolymers tended to resorb more slowly, thus decreasing the risk of granuloma formation. Blending polymers in different proportions also allowed the building of plates with different strength and resorption profiles (Eppley et al., 2004), as well as with desirable malleability.

Traditionally, the plates fixating the reshaped bones were placed on the outer surface of the skull bones during remodeling cranioplasties. In some cases these plates could be palpated through the skin, especially at early postoperative stages,
sometimes even for a long period of time thus compromising aesthetic results (Ashammakhi et al., 2004; Branch et al., 2017; Losken et al., 2001; Wood, Petronio, Graupman, Shell, & Gear, 2012). Ahmad and associates showed in six patients out of 146 that the plates were palpable under the skin several days after the operation, and three of these patients had plates still palpable after six months of follow-up (Ahmad et al., 2008). Freudlsperger at al. noticed that plates became more visible with time and palpable with a maximum at 12 months. While visibility resolved by 21 months after surgery, 20% remained palpable (Freudlsperger et al., 2014). In a study by Woods and associates 31.7% (44 out of 139) of patients had a visible mass at the site of fixation at some point postoperatively, with 3 patients still having a visible mass at the latest follow-up visit at 304, 345 and 351 postoperative days (Wood et al., 2012).

A surgical technique with placement of the resorbable fixation on the inner surface of the skull for better immediate aesthetic result was reported as a pioneering surgical technique in 2003 by the Oulu Craniofacial Centre team. In 2007 first follow-up results in ten patients were published (W. Serlo, Ashammakhi, Lansman, Tormala, & Waris, 2003; W. S. Serlo et al., 2007). This method allowed for fixating the plate on the inner aspect of the frontal skull and in the outer aspect of the less visible temporal bone, providing satisfactory aesthetic results (W. S. Serlo et al., 2007). It was shown previously in animal experiments, that such placement of the plates did not cause any adverse effects (Peltoniemi et al., 1998). Another innovation by the team was reinforcement of the fragile bone fragments with the plates prior to its bending and contouring (W. S. Serlo et al., 2007).

Since then this method has been used in several centres but the reports on the experience of this method, particularity on its aesthetic outcome, are still scarce (Konofaos & Wallace, 2014; Konofaos, Goubran, & Wallace, 2016; Sauerhammer et al., 2014).

### 2.8.6 Distraction cranioplasties

One of the principal aims of surgery for craniosynostoses is to increase the intracranial volume. This intracranial volume increase can be achieved with a traditional cranioplasty procedure or posterior cranial vault distraction (PCVD). However, the expansion achieved by a one-stage, an all-at once procedure is limited by the ability of the skin and other soft tissues to stretch over the enlarged and reshaped skull. An incremental and dynamic expansion overcomes these limitations by progressive expansion during the postoperative period. This allows
time for the soft tissues to adapt. Springs and distractors can be used for these purposes (Derderian & Bartlett, 2012; Lauritzen, Davis, Ivarsson, Sanger, & Hewitt, 2008).

The use of distractors allows a controlled and gradual shifting of the osteotomized bone fragment in the desired direction. This allows the skin and soft tissues to gradually stretch and to adapt (Nowinski et al., 2012). During the primary procedure one to four distraction devices are implanted. After a latency period of several days the devices are activated usually at a rate of 1 mm a day. After the desired distraction distance is achieved the devices are left in place for at least one month to allow sufficient time for ossification to take place and provide stability. One more operation is required to remove the distraction devices following this consolidation period. Thus PCVD requires prolonged treatment time, during which regular wound care and follow-up is required (Thomas et al., 2014; White et al., 2009).

Distraction can be done in frontal (Hirabayashi, Sugawara, Sakurai, Harii, & Park, 1998), lateral (Imai et al., 2002) and posterior directions (White et al., 2009). Also a multidirectional distraction has been used (Sugawara, Uda, Sarukawa, & Sunaga, 2010).

Numerous studies have shown that by posterior calvarial expansion a far greater volumetric increase can be achieved than by frontal advancement. PCVD can provide better cosmetic results especially in cases with occipital flattening (Choi, Flores, & Havlik, 2012; Derderian et al., 2015). One more benefit of PCVD is that in focusing the manipulation to the posterior structures it leaves the anterior fossa surgically untouched. This means that future surgical procedures (such as frontal orbital advancement) will not be impeded or compromised (White et al., 2009). There is also a growing amount of experience with treating syndromic craniosynostoses using PCVD as a primary procedure. Not only could frontal remodelling be postponed but in some cases it may also be avoided (Goldstein et al., 2013). In a pilot study with a small group of patients posterior cranial vault expansion was calculated to result in as much as a 20% increase in intracranial volume (W. S. Serlo et al., 2011).

Though PCVD is gaining its popularity worldwide, studies are scarce regarding the long-term results, complications and burden of care of this technique.
2.8.7 Timing of the surgery

Timing of the surgery depends on the type of pathology, its severity and clinical manifestation. It is also a question of finding a balance between benefits and risks related to the age of the patient at the time of operation. In a child under 6-12 months the calvaria is thin and malleable, ossification is so good that even big bony defects ossify completely and the brain growing capacity is tremendous (Panchal & Uttchin, 2003). However, early surgery increases the risk of recurrence of the condition and the operative risks are higher. Operating in an older child often requires more extensive procedure and more laborious bone reconstructions (Pagnoni et al., 2014) due to further worsening of the deformities of cranial base, facial skeleton and dental malocclusion taking place while the child with unreleased craniosynostosis grows. Benefits of later surgery include thicker bone for more stable fixation, less impaired growth going forward after operation and better tolerance for the perioperative blood loss (Fearon, 2014).

Improvements in paediatric anaesthesia and intensive care together with refinements of surgical techniques and materials mean that one can operate younger patients. For example, centres experienced in endoscopic treatment of craniosynostoses, prefer to operate single suture synostoses as early as three months of age with minimally invasive repair combined with postoperative moulding devices (helmets) (Jimenez, Barone, Cartwright, & Baker, 2002). Also spring assisted surgery is suitable to small infants as well (M. L. van Veelen & Mathijssen, 2012).

Nowadays, in syndromic patients, the calvarial augmentation is usually done before the age of six months aiming to provide sufficient space for the developing brain. The fronto-orbital area is addressed some years later if necessary (Pagnoni et al., 2014).

2.8.8 Secondary surgery

Approximately 5 to 71% of patients require a re-operation after primary craniosynostosis surgery either due to suboptimal aesthetic results (recurred or residual craniofacial deformity) or due to clinically significant recurrence of craniocerebral disproportion (Foster, Frim, & McKinnon, 2008; Wagner, Cohen, Maher, Dauser, & Newman, 1995; Wall et al., 1994). Arnaud and associates estimated that secondary coronal synostoses appeared in 10% of cases following surgery for scaphocephaly, with 1% requiring cranioplasties due to ICP increase (Arnaud, Capon-Degardin, Michienzi, Di Rocco, & Renier, 2009). Williams and
associates re-operated 6.45% of patients with severe sagittal synostoses initially treated by total vault remodeling (Williams JK et al., 1997).

The frequency of reoperations is approximately two to three times higher in syndromic cases (Foster et al., 2008; Wall et al., 1994). In accordance with this, numerous studies have showed that in syndromic craniosynostoses primarily elevated intracranial pressure could persist or relapse with delay after surgery (de Jong et al., 2010; Marucci et al., 2008; Renier, Lajeunie, Arnaud, & Marchac, 2000; Spruijt et al., 2016; Tamburrini et al., 2005).

It is also well known that re-do surgery in craniosynostosis patients carry a much higher risk of complications than primary operations (Czerwinski, Hopper, Gruss, & Fearon, 2010; Esparza et al., 2008; Sloan, Wells, Raffel, & McComb, 1997).

Tahiri and associates recently reported a new and important finding in several cases with fusion of preoperatively patent lambdoid sutures after PCVD procedures, either due to primary condition or as a result of surgery itself (Tahiri, Paliga, Bartlett, & Taylor, 2015). This requires further investigation.

2.9 Outcome of treatment

The primary objective of any health care intervention is to relieve clinical symptoms, prolong survival and enhance quality of life along with well-being. It may include such aspects as life satisfaction, health perceptions and physical, psychological, social and cognitive well-being (Thoma, Cornacchi, Lovrics, Goldsmith, & Evidence-Based Surgery Working Group, 2008).

Historically the success of the craniofacial surgery is evaluated by objective clinical outcome measures such as anatomical measurements, clinical photographs, radiological images, morbidity, mortality and the necessity for re-do surgery (Tapia et al., 2016; Thoma & Ignacy, 2012). But none of these measures reflects the aspects of what patients consider important.

The facial appearance of craniosynostosis patients can differ from what we say to be “normal”, meaning harmonious, symmetrical, and aesthetically pleasing facial features. Patients may have physical, mental or developmental disabilities related to their primary disease (Allam et al., 2011; Kapp-Simon et al., 2007; Tovetjarn et al., 2012). Suboptimal treatment may result in aesthetic deformities, psychological, cognitive and developmental sequelae in later life (Joly et al., 2016).
2.9.1 Safety of cranioplastic surgery

In the study by Sloan and associates 250 patients who underwent craniosynostosis surgery were reviewed. The complications were present in 6.8% and the mortality was low, 0.8% (Sloan et al., 1997). They also found complication rates to be higher (39%) in syndromic cases than in nonsyndromic cases (3.5%) (Sloan et al., 1997). In the study by Shastin and associates 103 patients were followed prospectively and the complication rate was found to be 35.9%, with zero mortality (Shastin et al., 2017). Both these studies have relatively high numbers of complications due to inclusion of minor problems often dismissed by other authors.

The use of biodegradable plates has been found to be safe. Losken and associates reported that complications requiring reoperation occurred in 4.8% of the patients with single suture craniosynostoses that were operated using biodegradable plates (Losken et al., 2001). In a study by Branch and associates unplanned reoperations were required in 5.4% patients, but there was no permanent morbidity or mortality (Branch et al., 2017).

In a study by Woods the overall complication rate was 2%, delayed foreign body reaction was noted in 0.7% of patients, but all resolved spontaneously (Wood, 2012). In the studies where the resorbable plates have been placed endocranially, no plate related complications were reported (Konofaos et al., 2016; Sauerhammer et al., 2014).

PCVD operations are considered safe with low permanent morbidity and mortality rates. However, much higher frequency of minor complications and unforeseen events, including skin problems and mechanical difficulties with the devices, are reported than with other techniques. This ranges from 12.5% to 80% (Goldstein et al., 2013; Steinbacher, Skirpan, Puchala, & Bartlett, 2011; Thomas et al., 2014; White et al., 2009; Wiberg et al., 2012) (Thomas 2014, White, Steinbacher, Goldstein, Wiberg). In a study by Thomas and associates unplanned operations were required in 19.4% of cases (Thomas et al., 2014). The majority of these unforeseen events were minor and did not hamper the distraction process itself.

Since there is no commonly used classification of complications, unforeseen events are still frequently reported in a descriptive manner using authors’ custom definitions (Shastin et al., 2017). Thus the comparison of numbers presented in different publications has its limitations. The first attempt to standardize the classification of the complications in craniosynostosis surgery was done by Shastin and associates (Shastin et al., 2017).
2.9.2 Evaluation of postoperative craniofacial morphology

The evaluation of the outcome of the treatment can also be done objectively, by evaluating craniofacial morphology based on internal and external landmarks. Such cephalometric data has been obtained from direct anthropometric caliper measurements (Farkas, Katic, & Forrest, 2005; Watson, 1971), cephalograms (Kreiborg, Aduss, & Cohen, 1999), conventional photographs (Farkas & Deutsch, 1996; Mazzoleni et al., 2016) or 3D CT scans (Choi et al., 2012; Fischer et al., 2016; Goldstein et al., 2013).

Conventional photography is being used on a routine basis to follow-up changes of the patients appearance during the treatment and follow-up period (Hilling, Mathijssen, & Vaandrager, 2006; Ozlen, 2011). But the evaluation of aesthetic outcome is subjective from 2 dimensional pictures made from limited angles.

There are only a few studies published where results of craniosynostosis operations were assessed from photographs (Bendon, Johnson, Judge, Wall, & Johnson, 2014; Hilling et al., 2006; Mazzoleni et al., 2016; Metzler et al., 2014; Panchal, Marsh, Park, Kaufman, & Pilgram, 1999). Metzler and associates evaluated outcomes after surgery for metopic synostoses patients a few years after the operation using a narrow 3 point scale. They used panels of lay persons, medical students and maxillofacial surgeons evaluating entire facial photographs and photographs of the smaller sections of the face (Metzler et al., 2014). Probably due to the narrowness of the scale used, there was significant difference in panel evaluations only when small section images were used. Bendon and associates used panels of professionals to evaluate specific morphological findings from pre- and postoperative photographs using 100-unit VAS scale. The panels were asked to grade the severity of scaphocephalic shape of skull, frontal bossing, temporal pinching, occipital bulleting and overall head shape (Bendon et al., 2014). This was a much more precise measurement of aesthetic outcome but again it represented only the degree of pathology from the surgeon’s point of view and not the patient’s attractiveness in general.

Lately non-ionising 3D surface imaging techniques have become available. There are different systems used for this purpose, including stereo-photogrammetry and laser scanning (Barbero-Garcia, Lerma, Marques-Mateu, & Miranda, 2017; Weathers et al., 2014; Wong et al., 2008).

Based on structured light techniques, 3D imaging systems project a random light pattern onto the subject and capture the image with multiple precisely...
synchronized digital cameras set at various angles in an optimum configuration. Three dimensional surface geometry and texture are acquired nearly simultaneously and a single 3D image is produced (Kau, Richmond, Incrapera, English, & Xia, 2007). Images captured by this system are highly repeatable, photo-realistic and 3D anthropometric landmark data is highly reliable (Aldridge, Boyadjiev, Capone, DeLeon, & Richtsmeier, 2005).

3D photogrammetric imaging is feasible for the evaluation of variety of craniofacial deformities (Seeberger et al., 2016; M. C. van Veelen et al., 2016; Wong et al., 2008). Accuracy of 3D photography of the infant head is high, and the method is rapid, easy to apply, non-invasive, and reliable (Schaaf et al., 2010).

Citing Lipira and associates “contemporary 3D imaging modalities, in combination with sophisticated shape analysis techniques, are bridging the gap between aesthetics and mathematics” (Lipira et al., 2010). This method has been successfully used to measure changes in cranial shape (Lipira et al., 2010) and intracranial volume in craniosynostosis patients (Seeberger et al., 2016; M. C. van Veelen et al., 2016).

Thus 3D photography presents a valuable method for craniofacial mapping and objectification of perioperative changes during craniosynostosis correction. It facilitates the option of tracing volumetric changes and changes to symmetry mathematically (Hanis et al., 2010; Wilbrand et al., 2012).

Though increasing numbers of publications are available dealing with volumetric results of posterior cranial vault distraction procedures, they are usually based on evaluations done from highly ionising skull 3D CT scans and the cohorts are small (Derderian et al., 2015; Goldstein et al., 2013; Shimizu, Komuro, Shimoji, Miyajima, & Arai, 2016). There are so far no other series besides our team’s earlier publication (W. S. Serlo et al., 2011), where volumetric analysis is derived from plain cephalograms. There is also a lack of sufficient studies dealing with evaluation of PCVD surgery volumetric results by the means of non-ionising 3D photogrammetric imaging.

### 2.9.3 Aesthetic considerations

One of the main goals of craniosynostosis surgery is to normalize patients’ appearance (Farkas & Deutsch, 1996). Dysmorphic, asymmetrical face and head shape can have negative influences on person’s self-esteem, social relationships and behaviour (Joly et al., 2016).
There are numerous studies on outcome of craniosynostoses, where evaluation is based on presence of postoperative complications and the need for reoperations (Breik et al., 2016; Joly et al., 2016; Ozlen, 2011; Seruya et al., 2011). Whitaker in 1987 proposed assessing the results of craniosynostoses treatment according to the need for additional surgery, with category I – no need for refinements, and categories II to IV reflecting the significance of the further operative correction required (Table 1) (Whitaker, Bartlett, Schut, & Bruce, 1987). This classification has been widely used in many published series (Joly et al., 2016; Lloyd et al., 2016; Mesa et al., 2011; Seruya et al., 2011)). Sloan and associates classified the surgical results into seven classes (Sloan et al., 1997) and Aryan and associates proposed in 2005 simplified version of this classification (Table 2) (Aryan et al., 2005). The later has four categories, where only one category infers the need for operative corrections, while the other three categories correspond to less severe degrees of deformity (Table 2). This was also used previously in our team’s publication (W. S. Serlo et al., 2007).

Table 1. Whitaker categorization of surgical results.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>No need for surgical revision</td>
</tr>
<tr>
<td>II</td>
<td>Minor revision needed</td>
</tr>
<tr>
<td>III</td>
<td>Major alternative bone grafting or osteotomies will be needed</td>
</tr>
<tr>
<td>IV</td>
<td>A major craniofacial procedure will be necessary</td>
</tr>
</tbody>
</table>

Table 2. 4-point classification of surgical results for craniosynostosis surgery. For references see text.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Excellent. No visible or palpable irregularity</td>
</tr>
<tr>
<td>2</td>
<td>Good. Palpable or visible irregularity that does not compromise the overall correction. Deformity observed only by examiner</td>
</tr>
<tr>
<td>3</td>
<td>Fair. Compromised correction. Deformity observed by the third persons/parents. Does not require repeat operation</td>
</tr>
<tr>
<td>4</td>
<td>Poor. Recommended repeat operation either for irregularities or compromised correction</td>
</tr>
</tbody>
</table>

While outcome evaluation from a surgeon’s point of view is mainly limited to the decision making of whether the patient needs additional corrective surgery or not, other options for aesthetic evaluation of outcome are needed.

There are numerous studies in orthodontics evaluating patients’ self-satisfaction with pre- and postoperative aesthetics, as well as third persons (panels)
quantitative evaluation of aesthetic outcome (Claudino & Traebert, 2013; Silvola et al., 2014).

One of the first attempts to determine a correlation between appearance and quality of life (QOL), thus evaluating aesthetic results of the surgery from patient’s point of view was published by Lloyd and associates in 2016 (Lloyd et al., 2016). However, the facial aesthetics was evaluated using the above mentioned Whithaker classification, which is surgeon-oriented. Kluba and associates asked parents how satisfied they were with the results of treatment using a 5-point rating scale (Kluba et al., 2016). Joly and associates evaluated the results after suturectomy for metopic and coronal synostoses by asking children and parents if the head shape was normal in their opinion. They also used the Whithacker scale to evaluate the surgeons’ point of view of the result (Joly et al., 2016). The studies by Metzler and Bendon intended to evaluate surgical results from photographs, but instead of evaluating the attractiveness of patients’ faces the grading was directed to deformity and evaluation of necessity for reoperations (Bendon et al., 2014; Metzler et al., 2014). Neither of these studies reflects sufficiently the results of the surgery from the aesthetical, patient oriented point of view. Another problem of all of the above mentioned studies is that different scales and questions are used. Thus comparison between the studies is challenging. The heterogeneity of the deformities, the wide variety of operative techniques and consequently a small number of patients in each series, makes the comparison even more obscure.

There are so far no publications describing the aesthetic results of frontal remodelling operations with endocranial placement of plates. There are no studies reporting the aesthetic outcome of patients treated for sagittal synostoses with follow-up reaching adulthood.

2.9.4 Craniosynostosis patients as adults

During the last years only a few studies were published evaluating the impact of craniosynostoses on health related quality of life (HRQOL) (Bannink, Maliepaard, Raat, Joosten, & Mathijssen, 2010; de Jong, Maliepaard, Bannink, Raat, & Mathijssen, 2012; Lloyd et al., 2016). However, to date there is no condition-specific Health related Quality of life questionnaire for patients with craniosynostoses. Neither is there a validated instrument to measure the impact of craniofacial dysmorphology on a patient’s psychosocial function (Szpalski et al., 2011).
In the previous studies it was found that the overall quality of life is lower than average in patients with syndromic and complex craniosynostoses (Bannink et al., 2010; de Jong et al., 2012).

In a study of 28 adults with Apert syndrome it was found that the patients managed relatively well in terms of education and employment, although the highest level of education was lower than with controls. The social relations (marriage, number of friends) of these patients appeared to require improvement (Tovetjarn et al., 2012). More optimistic results were reported by Allam and associates who followed up eight Apert syndrome patients for over 15 years and assessed their social and educational progress. It was demonstrated that these patients can function quite well in society, can achieve a high level of education, hold full-time employment, and integrate well socially (Allam et al., 2011).
3 Aims of the study

The goal of this study was to evaluate the safety and effectiveness of operative techniques used in cranioplastic surgery and to evaluate outcomes of different operative methods used for treatment of patients with craniosynostoses.

In order to answer these questions the specific research objectives were set as follows:

1. Is it feasible to use endocranial fixation with resorbable material in craniosynostosis surgery? What are the aesthetic results after surgery for metopic and coronal suture craniosynostoses using this method? What are the typical complications and their frequency? (I)

2. What magnitude of increase in the intracranial volume can be achieved by posterior cranial vault distraction using internal distractors? Is 3D photogrammetric imaging an applicable method for evaluation of cranial volume increase compared with estimations from conventional cephalograms? (II)

3. What kind of tool can facilitate congruent positioning of the distraction devices? (III).

4. What are the long-term aesthetic results in patients operated for sagittal suture craniosynostoses? Is there an association between the patient’s self-satisfaction with their facial appearance in relation to aesthetic evaluations by independent panels?
What socioeconomic situation, somatic health, mental health and self-satisfaction with facial appearance do such patients experience compared with controls? (IV)
4 Subjects and methods

4.1 Subjects and controls

The basic patient cohort of this study consisted of 250 consecutive patients with craniosynostoses that were treated at the Oulu University Hospital between 1977 and 2015. The demographic data of the final study population and follow-up times are presented in the Table 3.

Table 3. Demographic characteristics of the study groups.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Study I</th>
<th>Study II</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>27</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>12</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Males</td>
<td>15</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Age at follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.7 y</td>
<td>5.9 y</td>
<td>27.4 y</td>
</tr>
<tr>
<td>Range</td>
<td>9 mo – 18 y</td>
<td>4 mo – 12 y</td>
<td>18 y – 41 y</td>
</tr>
<tr>
<td>Follow-up time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.2 y</td>
<td>2.9 y</td>
<td>26.5 y</td>
</tr>
<tr>
<td>Range</td>
<td>2 mo – 12 y</td>
<td>1 mo – 6 y</td>
<td>17 – 37 y</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Metopic and coronal synostosis</td>
<td>Syndromic and non-syndromic craniostenosis</td>
<td>Sagittal synostosis</td>
</tr>
<tr>
<td>Operative Procedures</td>
<td>Frontal remodeling surgery with endocranial placement of the resorbable plates</td>
<td>Posterior cranial vault distraction</td>
<td>Craniotomia parasagittalis, suturectomy or H-plasty</td>
</tr>
</tbody>
</table>

y = years, mo= months

The study dealing with endocranial resorbable fixation comprised of 27 cases operated between 2009 and 2013 for metopic (n=10) or coronal (n=17) synostoses at the Oulu Craniofacial Centre (I). The mean age of the patients at surgery was 13.4 months (range 7.6 – 55.2 months). Male-female ratio was 1.25. Particularly, there was a dominance of male patients in metopic synostosis group with only one patient being female.

In study II 30 patients were treated with the posterior cranial vault distraction (PCVD) at the Oulu Craniofacial Centre between January 2009 and December 2015. One of the patients with Apert syndrome had been operated twice using
posterior distraction, first at the age of 3 months and then at the age of 2 years. The follow-up time for the first operation in that case was determined to be the time interval between the first and second procedures. Data regarding on both operations is presented, thus the number of operations analyzed was 31. The mean age of patients at the time of distraction surgery was 2.9 years (3 months to 9 years). The male-female ratio was 1.5. All patients with bicoronal craniosynostoses underwent a genetic analysis for Muenke syndrome. There were 14 patients with syndromic craniosynostoses: Muenke syndrome (n=4), Apert syndrome (n=3), Crouzon syndrome (n=3), Saethre-Chotzen syndrome (n=2) and other syndromes (n=2). Restenosis was an indication for a distraction procedure in eight patients who were treated previously for scaphocephaly. Two patients had bicoronal synostoses but testing showed no Muenke syndrome. Two patients had bilambdoid synostoses. One patient had a Mercedes-Benz type synostosis with premature ossification of both lambdoid and sagittal sutures. One more patient had bicoronal synostosis combined with premature ossification of sagittal suture. One patient had craniocerebral disproportion as a complication of overdrainage of ventriculoperitoneal shunt. One patient had a Chiari I malformation.
Fig. 3. Flow chart of the subjects through each stage of study IV.

The long term follow up study (IV) consisted of 40 patients operated for non-syndromic sagittal synostoses between 1977 and 1998. A total of 171 operations for craniosynostoses during this period were identified from the database of the Oulu University Hospital (Fig. 3). Since the aim was to study long-term outcomes in adulthood, only patients over the age of 18 years at the time of the follow-up examination were included. Only isolated disorders were included and patients with any associated disease such as hydrocephalus or other neurological disease were excluded. A total of 115 patients met the inclusion criteria and were contacted by mail or telephone by a study nurse. Of these, 61 patients were reached and agreed to participate in the study. From 61 patients, one appeared to have slight form of Crouzon. Eight had metopic synostoses while one had isolated unilateral synostosis of the lambdoid suture. Six had one-sided and 3 bilateral coronal synostoses. One patient with sagittal synostosis had hydrocephalus and one patient was re-operated due to the prominent frontal area persisting after primary sagittal synostosis operation and a fusion of coronal sutures was found during surgery. The remaining 40 patients had been surgically treated for sagittal synostoses and thus
were included in study IV. The same amount (40) of age and gender matched controls were randomly selected from the Finnish Population Register Centre. For logistical reasons the controls were recruited from the area of Oulu and its surroundings. The patients’ mean age at a time of surgery was 5.7 months (range 9 days to 45 months). The male-female ratio was 1.7 (Table 3).

4.2 Methods

For the study on the endocranial use of biodegradable plates (I) data on preoperative diagnosis, operations, follow-up visits, results of different imaging modalities and postoperative complications were collected from the patients’ medical records. The follow-up schedule included visits at 1-3, 6 and 12 months after surgery. Thereafter, follow-up continued biannually until the patient reached seven years of age. During follow-up visits, the patients underwent clinical evaluation and parents were interviewed. Also plain radiographs of the skull, photographs and occasionally 3D computer tomography were taken.

For the study on distraction procedures (II) data on preoperative diagnosis, operations, hospital stay, distraction details were recorded. After distractor devices were removed follow-up continued with annual visits until the patient reached seven years of age. During follow-up visits, the patients underwent clinical examination, parents were interviewed, plain radiographs of the skull and photographs were taken. 3D computer tomographs were performed if necessary. In the last five patients 3D photogrammetric images were taken before and after the procedure.

For study III a surgical guide device (Fig. 7) to facilitate the implantation of distractor devices in correct position was developed in collaboration with Mectalent Oy (I).

Both patients and controls included in the late follow-up study IV were invited to the out-patient clinic and had completed their questionaries’ prior to the visit. During the follow-up visit a clinical evaluation was done. The examination of the patients included evaluation of facial appearance, skull shape, the scar, and palpation of the head. Standard photographs and 3D photogrammetric images were taken.

Information regarding patients’ preoperative diagnosis and surgeries was extracted from the medical records.
4.3 Operative procedures (I, II, III, IV)

The operative techniques used in this study, are described in historical order.

In the 1970-s craniosynostoses were operated in the Oulu University Hospital using the suture release technique by Lannelongue. For that purpose two parallel strip craniotomies were done on both sides of prematurely ossified suture with bone over the ossified suture preserved intact. In case of sagittal synostoses these craniotomies reached over the unfused coronal and lambdoid sutures. Silicone membranes were placed to cover bone edges at osteotomies in order to prevent re-ossification (Fig. 2). Nine patients from study group IV were operated using this technique. Since the early 1980-s the technique was replaced by strip suturectomy, with removal of the ossified suture. Out of seven patients (study group IV) operated using this surgical technique in four patients the suturectomy was supplemented with dural split to wrap the bony edges. Since 1985 these methods were subsequently replaced by the “H”-technique. In this technique the ossified sagittal suture was removed with additional bone strips removed behind coronal sutures and in front of the lambdoid sutures on both sides with the final osteotomy defect having a shape of the letter “H”. Then a sub-fraction of temporal bone was done to allow further reshaping of the skull. Rather soon the technique was enriched by adding barrel stave osteotomies to the temporal bone. The later 24 cases from study group IV had surgery performed using this technique.

From 40 sagittal synostosis patients in study group IV two patients were re-operated due to residual scaphocephalic head shapes. One of these patients was operated with linear craniotomy by the Lannelongue technique twice. Another one was operated using this technique at the age of nine days, and 10 months later this patient was operated with strip suturectomy technique in another hospital.

Since the 1980-s craniosynostoses with frontal deformities were operated in Oulu University Hospital using frontal remodelling cranioplasties. Resorbable plates came to use in the early 1990-s. In study I two different operative techniques for treatment of such cases were used depending on the diagnosis of the patient. In both techniques after bicoronal skin incision frontal bone from the anterior fontanel down to approximately 1 cm from above the orbital upper rim was removed in one piece.

In patients with coronal synostoses a supraorbital bandeau was removed and thinned. A resorbable plate was then fixed on the inner surface of the bandeau. Frontal bone was cut into suitable fragments and thinned if necessary. The
fragments were fixed to the bandeau-plate construct with the plate placed on the endocranial surface of the bones.

In metopic synostosis patients, a supraorbital bandeau was not removed, but the prominent interorbital ridge was removed and the fused metopic suture was removed down to the nasofrontal suture. The frontal bone was then also cut into fragments and assembled in a manner improving forehead convexity with resorbable plates placed endocranially. Thus the orbits were left untouched but a suturectomy of the fused metopic suture between the orbits was performed.

In both techniques the operation was finalized by fixing the newly formed bone-plate construct to the outer aspect of the temporal bones on both sides. Final stabilization was achieved by placing resorbable plates on the top of the vertex of the skull in a conventional way. All bone dust and bone chips were collected using a suction trap bone collector and used to fill the bony defects. Fibrin glue was spread on top of the bone dust material filling just prior to covering the bony fragments with periosteum. The major part of the osteotomies by the end of the procedure was covered with resorbable plates or filled with the bone dust.

Posterior cranial vault distraction procedures (PCVD) came to use in 2009 (study II). For PCVD after a bicoronal skin incision, a posterior osteotomy was performed. The occipital osteotomy was intended to extend as low posteriorly as feasible, reaching the torcula or extending even lower in 24 out of 31 cases. The osteotomized bone was detached from the dura in all but one case. After checking for haemostasis, the bone was fixed with initial distraction of few millimeters using two to four distraction devices in accordance with preoperative plan. In order to ensure parallelism of distractors, the new distraction vector guides, described in study III, were used in the last 14 cases. The distraction devices (Biomet Microfixation 1.5 mm CMF Quick-Disconnect Distractors, Biomet Microfixation, Jacksonville, Florida, USA or Mectalent Oy, Oulu, Finland) were fixed to the bone with self-drilling titanium screws (Fig. 4). The number of distractor devices used per patient was: four devices in 18 cases, three devices in six cases and two devices in seven cases.
Along with gained experience and evolution of surgical methods the skin incision was gradually changed to be cosmetically more favorable. Initially when the Lannelongue technique was used, a straight midsagittal incision was preferred. Later straight bicoronal incision was used. In the late 1990-s straight incision was replaced by the zig-zag shaped incision.

4.4 Distraction protocol (II)

After a latency period of several days (mean 6 days, range 4 – 9 days), the distractor devices were activated at a rate of 1 – 2 mm once a day. Each time, prior to activation of the devices, the skin around the activation rods was cleaned and lubricated with antibacterial ointment. After the first few days, the activation was usually continued at home by parents. During this distraction period the patients were followed in the outpatient clinics weekly. The plain lateral view cephalograms were taken at weekly follow-up visits to monitor the distraction process and screen for device failures. At these visits the status of the wounds and skin in the area of the distractors was monitored closely.

When the posterior vault was advanced to its planned position, the activation rods were removed under general anaesthesia. The average time from primary surgery to removal of devices was 27.3 days (range 13 – 43 days). The distractors were left under the skin to keep the distracted bone block in achieved position until the ossification of the bony gap was sufficient. Then the devices were removed.
under general anaesthesia usually from a new short incision done just above the body of distractor. Removal of devices was performed at a mean of 5.2 months (range 3 – 9 months) after the primary operation. Thus each patient had approximately three to four lateral cephalograms taken postoperatively, but no CT scans were taken on routine basis.

4.5 Clinical examination (I, II, IV)

The clinical examination by the staff surgeon (study I and II) or by the author (study IV) included evaluation of facial appearance, skull shape, the scar, palpation of the head for irregularities and ossification defects, signs of infection, instability in the operated area and for possible failure of the device. In study group I plate visibility, palpability, and signs of delayed foreign body reaction were assessed.

The subjective evaluation of surgical outcome was done using the previously described 4-point classification scale (Table 2) (Aryan et al., 2005; W. S. Serlo et al., 2007) and the Whitaker classification (Table 1) (Whitaker et al., 1987).

4.6 Evaluation of the volume gain (II)

4.6.1 Using plain cephalograms

The cephalograms were used to calculate the volume gain after the distraction was completed in patients undergoing PCVD (W. S. Serlo et al., 2011).

The upper part of the skull that includes majority of intracranial space was assumed to have a shape of half ellipsoid. Thus volume and volume change after distraction of the half of an ellipsoid was calculated. The length and half the height of the skull were measured on the preoperative radiographs.

The preoperative volume \( V \) of the skull (half-ellipsoid) was then calculated using the formula:

\[
V = \frac{4 \pi abc}{3}
\]

(1)

Half of the length of skull was named as \( a \) and its heights was \( b \). \( C \) was a half of the width of the skull. In the first several cases \( c \) was measured from frontal view of plain x-rays. There was no significant difference between \( b \) and the \( c \). Also calculation of the skull width from the anterior view appeared to be rather unprecise since its results depended on the angle under which the image was taken. For this
reason further calculations were done assuming that the half-height of the skull was equal to its half-width. Thus the final formula for preoperative skull volume calculation was as follows:

\[ V = \frac{4na h^2}{3} \]  

(2)

The amount of distraction (the linear shift of the bone block) \( d \) was calculated from the radiographs taken after the distraction was completed. The measurements were done close to distraction devices in three different points and the mean of these three measurements was used.

The volume gained by distraction \( V_\Delta \) was then calculated using the formula:

\[ V_\Delta = \frac{nb^2 d}{2} \]  

(3)

The increase of the skull volume was calculated then using the formula:

\[ X = V_\Delta \times \frac{100}{V} \% . \]  

(4)

All measurements were performed by the author using commercially available software (NeaView Radiology, Neagen OY, Finland).

### 4.6.2 Using 3D photogrammetric imaging

3D photogrammetric images were taken from five patients before the PCVD operation and several months (mean 4.8 months, range 3 – 7 months) afterwards. The 3D images were taken in the Natural Head Posture using the 3dMD system (3dMD Cranial, Atlanta, GA, USA) by the author.
Fig. 5. Volumetric analysis using 3D imaging. The postoperative image (gray) is overlaid on the preoperative image (pink).

The change in the individual head volume was then calculated for each patient separately using previously described method (Aarnivala et al., 2015). Postoperative images were overlaid on the preoperative images by superimposing the facial areas (Fig. 5). The commercial software Rapidform2006 (INU5 Technology Inc., Seoul, Korea) was used to process and analyse these images.

4.7 Aesthetic evaluation using photographs (IV)

Facial aesthetic appearance was objectively determined by two independent panels and by two experienced craniofacial surgeons. A series of slides with photographs of the patients and their controls were shown in a random order. Neither panels nor craniofacial surgeons were informed regarding whether a slide contained control person or craniosynostosis patient. Each slide included four images in standard projection of every subject including: anterior view with and without smile, lateral and oblique views (Fig. 6). The slide show included all 62 patients with their controls who came for the follow-up visits. This was done in order to make the range of deformities wider. Each slide was shown for a standard ten seconds during the slide show, to obtain the initial immediate evaluator impression.
Fig. 6. An example of the slide with standard position photographs used for the evaluation of aesthetic result of the surgery in study group IV. An image of a healthy person not included in the study is present with his consent.

4.7.1 The panel groups

The first panel consisted of consultants or residents in orthodontics (one male and three females) and one orthognathic surgeon (female). This panel was referred as the “dentists’ panel”. Another panel consisted of three female and one male, all members of the lay public, having no health care education. They were referred to as the “lay panel”. The members of the panels were not involved in the original treatment of the patients.

The aesthetic outcomes were determined using a 100 mm VAS scale with 0 mm as the least attractive and 100 mm being the most attractive. The following instructions were presented to the panelists: “Please place a cross on the continuous line in a place which best depicts your opinion about the attractiveness of the face on the photographs.”
4.7.2 Evaluation by craniofacial surgeons

In addition to the evaluation by panels, the aesthetic results were also evaluated by two experienced male craniofacial surgeons, involved in some original operations. The same slide show and the scales presented in the tables 1 and 2 were used for these purposes.

4.8 Questionnaire (IV)

The self-reported questionnaire used in the long follow-up study part IV included questions regarding education, housing, marital status, employment, general health, presence of headaches, history of mental disturbances and the need for orthodontic treatment. Participants’ relationship status was recorded as either “single” or “in a permanent relationship” which included those who were married or cohabiting. The participants’ education level was classified into three groups: no professional education (e.g. primary school only), secondary professional education and tertiary professional education (including university education).

The questionnaire also included question: “is there something that bothers you about your facial appearance?” Those who responded positively were asked to clarify. The patients were also asked whether their scar was bothersome.

The participants were also asked to determine their subjective satisfaction regarding facial appearance by using a 100 mm VAS. The question was: “How satisfied are you with your current facial appearance?” In the VAS, 0 mm referred to “very unsatisfied” and 100 mm to “very satisfied”.

4.9 Ethical issues

The study was performed in accordance with the declaration of Helsinki on ethical principles for medical research. The study was approved by Ethics Review Committee of the Northern Ostrobothnia Hospital District (No. 86/2013). Patients and controls filled in informed consent for study IV.

4.10 Statistical methods

In study I and II frequencies and other descriptive details were reported with means and deviations, if needed. Spearman rank correlation test was used for calculating correlations between parameters. T-test was used to compare means between the
diagnostic groups (plagiocephaly versus trigonocephaly). Two-tailed p values were presented.

Nominal variables were analyzed with crosstabs and Pearson Chi-square tests, in cases with small group size Fisher test was used. To compare means between two groups the Levene’s test for equality of variances and t-test for equality of means was used.

To compare linear variables between patients and controls in study IV Pared Samples T-test was used. For nominal variables McNemar test in crosstabs was applied.

To evaluate reliability of the panels the inter-observer reliability was analyzed using intraclass correlation coefficient between the panels and inside the panels between the panel members. The reliability for both panels members was moderate with $p = 0.573$ for the dentists panel and $p = 0.555$ for the lay panel. Reliability between the panels was almost perfect $p = 0.840$.

$P$ values $< 0.05$ were considered as significant.

All statistical analysis was performed using commercially available SPSS for Windows 14.0 software.
5 Results

5.1 Surgical duration and intraoperative blood loss (I, II and IV)

When frontal remodeling surgery was performed with endocranial placement of resorbable plates, the mean operative time was 210 minutes (range 95 – 315 minutes, SD 54.3, 95% CI=188.9 – 231.8). The metopic synostosis group required less operative time (average 170 minutes) than operations for the coronal synostosis group (average 234 minutes). The difference in operation time between the two groups was statistically significant ($p = 0.001$). In one patient who was operated due to sagittal synostosis in the 1970-s the data concerning blood loss and surgical duration was missing. The data on operative details is presented in Table 4.

Table 4. Data regarding details of different operative methods.

<table>
<thead>
<tr>
<th>Operative procedure</th>
<th>Old techniques for sagittal craniosynostosis (N15)</th>
<th>H-cranioplasty for sagittal craniosynostosis (N24)</th>
<th>Frontal remodelling for metopic synostosis (N10)</th>
<th>Frontal remodelling for coronal synostosis (N17)</th>
<th>Posterior cranial vault distraction (N31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (min)</td>
<td>Mean 130.2</td>
<td>60.5</td>
<td>169</td>
<td>234</td>
<td>149</td>
</tr>
<tr>
<td>Bleeding (ml)</td>
<td>Mean 196</td>
<td>89</td>
<td>289</td>
<td>449</td>
<td>310</td>
</tr>
<tr>
<td></td>
<td>Range 28 – 380</td>
<td>15 – 260</td>
<td>90 – 600</td>
<td>150 – 1700</td>
<td>70 – 1300</td>
</tr>
<tr>
<td>Age at operation (months)</td>
<td>Mean 9.1</td>
<td>3.4</td>
<td>12.9</td>
<td>20.6</td>
<td>35.8</td>
</tr>
<tr>
<td></td>
<td>Range 0.3 – 45.3</td>
<td>1.3 – 9.9</td>
<td>7.6 – 22.5</td>
<td>8.9 – 55.2</td>
<td>3 – 109.4</td>
</tr>
</tbody>
</table>

5.2 Distraction guides (II, III)

In order to avoid distractor vector incongruities and conflicts when placing distractor devices during the surgery, a new method to ensure that the distractors are implanted in coherent directions was developed. The method was based on the guides that can easily and temporarily be fitted to the distractors during the implantation of the distractor devices. These guides (Fig. 7A) fit over the
distractor’s body. When the guides are attached to the distractors, their relative directions can easily be checked visually by comparing orientation of the guides.

Fig. 7. The distraction guides. A. The guides are attached to two distractors on a dry skull model to check distractor vector parallelism. B. Guide application during the surgery.

After final fixation of the distractors to the cranial bones, the guides are removed (Fig. 7B). The guides were manufactured to specification by Mectalent Oy (Oulu, Finland). It is possible to fix one or two guides to each distractor in either or both the anterior or posterior directions relative to the distractors activation rods. Fixing two guides to the distractors makes longer lines to be compared visually thus increasing the probability that even smaller angulation errors are detected to prevent excessive convergence or divergence of the vectors of distraction.

After introduction of the guides (study III) facilitating placement of distraction devices in a parallel position, they were used in 14 consecutive cases from study group II. None of these patients had problems with incongruence of the devices’ vectors unlike one case from the previous 17 cases.

5.3 Distraction results (II)

In the PCVD study group (II) the patients were followed on a routine basis with mean follow-up time of 35 months. All turribrachycephalic cases achieved the desired improvement in head shape. In cases with increased ICP, resolution of symptoms was achieved in all cases.

The results of the distraction procedures are presented in Table 5. The mean distraction distance was 2.8 cm (95% CI 27 – 30) ranging from 2.1 cm up to 4.3 cm.
Table 5. Cranial volume increase: patients’ age at the time of operation, distraction distance achieved; and relative volume change (%) calculated from cephalograms.

<table>
<thead>
<tr>
<th>Data</th>
<th>Age at operation (months)</th>
<th>Distraction distance (cm)</th>
<th>Volume change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>34.7</td>
<td>2.8</td>
<td>25.7</td>
</tr>
<tr>
<td>Range</td>
<td>3.4 – 109.4</td>
<td>2.1 – 4.3</td>
<td>16.9 – 39.4</td>
</tr>
</tbody>
</table>

5.3.1 Volume gain measured from cephalograms (II)

Results of the cephalometric measurements are presented in Table 5. The mean volume gain by PCVD in this study population was 275.4 cm³ (95% CI 252.5 – 298.3). Thus the mean achieved increase in cranial volume was of 25% (95% CI 23.0 – 27.0; range 16.9 – 39.4%). The calculated volume increase for each centimeter of distraction was therefore 8.8% of the cranial volume (95% CI 8.4 – 9.3). There were no significant differences in volumetric increases attained between genders.

The absolute volume gain did increase with increase in the age of the patient at the time of the operation ($p = 0.002$). However, the age did not correlate with the relative increase in cranial volume ($p = 0.296$) or with the achieved distraction distance ($p = 0.828$).

The extension of the osteotomy line occipitally below the torcula did not increase the gained volume. Achieved volumetric results were not dependent on whether the distraction was a primary operation or a re-do surgery. Neither did these results correlate with patient’s diagnosis when comparing syndromic cases with the non-syndromic cases or doing estimations for each syndrome separately compared to non-syndromic patients.
5.3.2 Volume gain measured from 3D photographs (II)

In five cases the pre- and postoperative 3D photographs were taken and the change of volume was calculated from these images. The volume calculations for these cases were compared with results of volumetric calculations from cephalograms (Fig. 8). The increase in volume calculated from the 3D images was a mean of 17.4% (range 14.5 – 23.2%) whereas the volumes calculated from cephalograms for same patients gave a mean of 20.8% (range 19.3 – 21.9%).

Thus mean volume gain was 8.1% per centimeter of distracted distance when calculated from cephalograms and 6.7% when calculated from 3D photographs. The statistical significance of this difference could not be evaluated due to the small size of this subgroup.
5.4 Aesthetic results

5.4.1 Evaluation by craniofacial surgeons at follow-up visits (I, IV)

All but one patient’s aesthetic outcome after frontal remodeling procedures with endocranial placement of plates (study I) was judged to be good (N=16) or excellent (N=10) at the follow-up visits using 4-point grading (Tables 2 and 6). In the metopic synostosis group, excellent results dominated, in six out of 10 patients. In the coronal synostosis group excellent results were noted in four patients, and 12 patients were rated as having good results (Table 6). The only patient that was judged as having an unsatisfactory aesthetic result after the first surgery belonged to coronal synostosis group and had craniofrontonasal dysplasia. The patient had significant fronto-orbital dysmorphia with major asymmetry of the skull base. At the time of the first surgery only a partial correction was possible. This was also only patient to be classified as category IV by Whitaker classification (Table 3), with the rest of patients falling into the category I.

From the sagittal synostosis group (study IV) four patients were judged as having fair results, and none was judged as poor. Three out of these four patients were male who had very short hair and were becoming bald. Thus unevenness in the shape of the skull was not masked by their hair style.

Table 6. Aesthetic results of surgery by 4-point grading at follow-up visits according to the type of craniosynostosis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Aesthetic results (number of patients)</th>
<th>Mean follow-up time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Excellent</td>
<td>Good</td>
</tr>
<tr>
<td>Metopic synostosis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Coronal synostosis</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Sagittal synostosis</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>26</td>
</tr>
</tbody>
</table>

The majority of the patients in both study groups (93%, 62 out of 67) achieved good or excellent aesthetic outcome, according to the evaluation by the surgeon on the follow-up visit. When applying the Whitaker categorization all but one case was classified as category I.
5.4.2 Evaluation by the craniofacial surgeons from the photographs (IV)

The following results were not included in the original publications.

The majority of the patients, who were operated for single suture sagittal synostoses achieved good or excellent aesthetic outcomes, according to the evaluations done by the senior craniofacial surgeons from the images taken during the visit (93%, N=37). No cases were rated as having poor (grade 4) results. Also, none was rated as having fair results by both surgeons. The majority of patients (22 and 20 patients) were scored as having excellent results, 15 and 19 as good and accordingly only three and one as fair. None of the patients was rated as having bad results. When calculating the mean score from the evaluation by both surgeons using a 4-point scale, four patients had a mean of 2.5, eight had a mean of 2.0 and the rest had 1.5 or 1.0. Table 7 presents the data regarding these four patients who had a mean score of 2.5. Out of these four patients three were scored as fair as well on personal encounter during the follow-up visit. But one was scored as excellent at personal encounter (Table 7, patient 1). When applying the Whitaker categorization all cases were classified as category 1.

Table 7. The data on patients with average score of 2.5 from the 4 point-scale when evaluated by senior craniofacial surgeons from the photographs.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>4-point grade at follow-up visit</th>
<th>Self-evaluation, mm VAS</th>
<th>Lay panel, mm VAS</th>
<th>Dentists panel, mm VAS</th>
<th>Hair</th>
<th>Operative technique used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>male</td>
<td>39.2</td>
<td>1</td>
<td>93</td>
<td>47</td>
<td>50</td>
<td>short</td>
<td>Craniotomia linearis from sagittal incision</td>
</tr>
<tr>
<td>2</td>
<td>male</td>
<td>34.5</td>
<td>3</td>
<td>78</td>
<td>49</td>
<td>52</td>
<td>bald</td>
<td>Craniotomia linearis from sagittal incision</td>
</tr>
<tr>
<td>3</td>
<td>male</td>
<td>27.6</td>
<td>3</td>
<td>89</td>
<td>51</td>
<td>49</td>
<td>bald</td>
<td>H-plasty from coronal incision</td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>26.0</td>
<td>3</td>
<td>51</td>
<td>50</td>
<td>58</td>
<td>bald</td>
<td>H-plasty from coronal incision</td>
</tr>
</tbody>
</table>
5.4.3 Evaluation by panels (IV)

In the long-term follow-up study IV, regarding the results of appearance evaluation by the dentists panel, the cases achieved lower results than the controls (VAS 62 vs. 69, \( p = 0.002 \)). The similar difference in facial appearance was found by the lay panel (VAS 60 vs. 66, \( p = 0.011 \)) (Table 8, Fig. 9). Age did not correlate with the rating of the facial appearance. However, both the lay and dentists panels tended to give higher scorings for female persons. The dentists panel gave a mean score of 68 mm for females and of 64 mm for males (\( p = 0.116 \)) and the lay panels accordingly scored females as 67 mm and males 61 mm (\( p = 0.009 \)). Six patients and one control received a score less than 50 mm by the lay panel. The dentists panel graded seven patients and one control under 50 mm in the VAS scale.

Table 8. Facial aesthetic evaluation on 100 mm VAS, mean and range. Panels ratings and patients self-satisfaction.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Controls</th>
<th>( \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-satisfaction with appearance, mm VAS</td>
<td>75 (29 – 100)</td>
<td>76 (29 – 98)</td>
<td>0.662</td>
</tr>
<tr>
<td>Dentists panel, mm VAS</td>
<td>62 (36 – 79)</td>
<td>69 (50 – 82)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lay panel, mm VAS</td>
<td>60 (43 – 82)</td>
<td>66 (45 – 85)</td>
<td>0.011</td>
</tr>
</tbody>
</table>
Fig. 9. Ratings of facial appearance as evaluated on the 100 mm VAS scale by the panels and self-satisfaction with own facial appearance in study IV.

When comparing the panels evaluation from the photographs with the evaluation by a surgeon at a personal encounter, there was certain congruency in the results; the panels tended to rate those patients with a lower score who had worse aesthetic results also from the surgeons point of view (Table 9). However, since the fair results group included only four patients, statistical analysis was unreliable.

Table 9. Summary of the results according to 4-point evaluation at follow-up visit for patients operated due to sagittal synostosis. There were no cases with the score of 4 (poor).

<table>
<thead>
<tr>
<th>4-point scoring results</th>
<th>1 – excellent</th>
<th>2 – good</th>
<th>3 – fair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>26</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Dentists panel, mean mm VAS</td>
<td>64</td>
<td>63</td>
<td>50</td>
</tr>
<tr>
<td>Lay panel, mean mm VAS</td>
<td>62</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>Self-evaluation, mean mm VAS</td>
<td>76</td>
<td>76</td>
<td>63</td>
</tr>
</tbody>
</table>
5.4.4 *Patients self-satisfaction with facial aesthetics (IV)*

There was no statistically significant difference in subjective evaluation of one’s own facial appearance between the patients and their controls \( (p = 0.662) \) in the long follow-up study (IV). The VAS mean was 75 mm among the patients and 76 mm among the controls, while the higher result referred to a higher rating of self-satisfaction (Table 8, Fig. 9).

The patients’ own, subjective satisfaction with their facial appearance did not correlate with the results by the panels \( (p = 0.775 \) for the dentists panel and \( p = 0.396 \) for the lay panel). The controls satisfaction with their facial appearance also did not correlate with the results by the panels \( (p = 0.239 \) for the dentists panel and \( p = 0.222 \) for the lay panel).

Though both patients and controls were on average satisfied with their appearance to same extent, there were six patients and two controls who rated their self-satisfaction with their facial appearance to be less than 50 mm on the 100 mm VAS scale. There was some tendency to give to these subjects slightly worse scores than for the rest of the groups by the independent panels, though the difference did not attain statistical significance probably due to its small sample size. Lay persons panels points were 57 vs 61 \( (p = 0.385) \) and dentists panels points were 60 vs 63 \( (p = 0.596) \) for patients, and the same numbers for controls were accordingly 57 vs 66 \( (p = 0.119) \) by the lay persons panel and 60 vs 70 by the dentists panel \( (p = 0.101) \). However, on personal encounter on the follow-up visit only one of these six patients was graded as having fair results, with the rest graded as having good or excellent result. Two of these six patients were operated using old methods and four were operated using “H”-cranioplasty. Thus, proportion of the less satisfied patients according to the operative technique was 12.5% (2 out of 16) and 16.7% (4 out of 24), respectively.

There were four patients who were bothered by the scar. All of them had a biconoral direction of the scar. They all also belonged to the abovementioned group of six patients whose satisfaction was below average.

On the other hand from all the patients whose scar was visible even on photos \( (N = 6) \), only one was bothered by the scar. Thus the visibility of the scar seemed not to be the main reason for more critical grading of the patients’ own appearance.

Thirteen patients (32.5%) and 11 controls (27.5%) answered “Yes” to the question: “Is there something that bothers you in your facial appearance (except the scar)?” (McNemar \( p = 0.804 \)). These groups of patients and their controls did not differ from the rest of the study persons neither in self-evaluation nor in the
attractiveness as evaluated by panels (for patients $p = 0.308$, $p = 0.271$ and $p = 0.659$, for controls $p = 0.069$, $p = 0.306$ and $p = 0.194$ accordingly). Factors mentioned to bother study persons in own facial appearance are summarized in Table 10.

Table 10. Factors that were mentioned to bother study persons regarding facial appearance, study IV. Number of subjects presented for each group.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Head and face shape (except nose)</th>
<th>Dental appearance</th>
<th>Nose shape</th>
<th>Skin</th>
<th>Hair</th>
<th>Eyelids</th>
<th>total</th>
<th>Missing answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Controls</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

The postoperative scar

Postoperative scars, either bicoronal or sagittal in direction, were straight in all patients, not with a zig-zag pattern. The scar was visible in one female patient (6.7%) and in five male patients (20%). All patients who considered the postoperative scar as an aesthetic burden ($N = 4$), had been operated with H-cranioplasty via a bicoronal skin incision. One patient, who was re-operated, experienced pain in the area of the scar on palpation.

5.4.5 The effect of operative technique on aesthetic outcomes (IV)

In order to evaluate the influence of operative technique on the results of the surgery in the study on long-term follow-up after cranioplastic surgery for sagittal synostosis (IV), each technique was analyzed separately. Further, old surgical techniques (16 cases) were compared with the modern technique of H-cranioplasty (24 cases). There were significant ($p < 0.001$) differences between the old and new techniques regarding patient age at operation (9.1 vs. 3.4 months) and age at follow-up visit (32.8 vs. 23.9 years). However, no association between different operative techniques and subjective, patient’s own satisfaction with appearance ($p = 0.801$) or panels’ evaluation of aesthetic results ($p = 0.671$ and $p = 0.922$) were found (Table 11). To confirm these findings the analysis was repeated leaving out three patients from the old operation technique group, who were operated at the age of two years or later. This had no effect on the significance of the result.
Table 11. Comparison between the results of the old and new operative techniques.

<table>
<thead>
<tr>
<th>Operative technique</th>
<th>Self-satisfaction, mm VAS</th>
<th>Dentists panel, mm VAS</th>
<th>Lay panel, mm VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old techniques (N16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>75</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Range</td>
<td>29 – 100</td>
<td>36 – 79</td>
<td>43 – 81</td>
</tr>
<tr>
<td>H-cranioplasty (N24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>73</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>Range</td>
<td>30 – 96</td>
<td>40 – 78</td>
<td>43 – 82</td>
</tr>
</tbody>
</table>

5.5 Surgical complications (I, II, IV)

In study I after frontal remodeling with endocranial placement of resorbable plates, three patients (11%) had complications severe enough to require reoperation. One developed minor detachment of the skin with exposure of the plate, and a plate underlying this part of the wound was removed without later problems. A second patient was found to have unsatisfactory position of the frontal bandeau on routine postoperative imaging. Repositioning of the frontal bandeau was performed a few days after the primary operation, during the same hospitalization. Two other patients developed a postoperative pseudomeningocele, one resolved spontaneously but the other required revision six months after the initial cranioplasty.

There were no other significant unforeseen events or ossification problems in this series. Neither there were any complications related to the endocranial placement of the plates.

In the PCVD study (II) unforeseen events requiring minor interventions occurred in 12 cases. They were either due to skin problems in the area of distractor or due to fractures of distraction devices activating arms. There was one case with postoperative CSF leakage that resolved after the placement of a lumbar drain for five days. Unplanned surgery was required in four patients. Re-alignment of one of the distraction devices was performed in one patient due to conflicting vectors. In three cases all devices were removed and replaced with resorbable fixation plates after the planned distraction endpoint was reached. This was done due to skin problems caused by distractors to avoid further exacerbation of the skin condition. One of these three patients developed a sterile fluid collection of the plate site six month later and required minor wound revision due to it. There were no complications which resulted in permanent morbidity in this series. Neither were there problems with resorption or non-ossification of the bone fragments. In spite
of unforeseen events the distraction was successfully performed to planned extend in all cases.

Two patients out of 40 in the sagittal synostosis study (IV) required re-operations due to the residual scaphocephalic shape of the head. One of these patients experienced pain on palpation in the former suturectomy area revealing defect of ossification. The majority of patients (32 out of 35, in five cases the data was missing) had unevenness of the calvarial bone in the former craniectomy area on palpation, but only in one an ossification defect was suspected. Since no radiological studies were made at the follow-up visits these findings were not confirmed radiologically.

5.6 Life situation, somatic and mental health at late follow-up (IV)

The following data was collected from the questionnaires filled by the adult patients who were operated due to sagittal synostosis and their controls (study IV). Thus all information on medical conditions presented was based on the participant’s own reports.

5.6.1 Headaches and migraine

Having migraine was mentioned by nine (22.5%) patients and 15 (37.5%) controls. Migraine was diagnosed by a doctor in four (10.8%) patients and in ten (27%) controls. Other types of occasional headaches were reported by 23 (57.5%) patients and 22 (55%) controls. There was no significant difference between either of these results (McNemar $p > 0.05$).

5.6.2 General somatic health

A total of 32 (82.1%) patients and 28 (71.8%) of controls reported having no medical concerns or taking routine medications (McNemar $p = 0.424$). No epilepsy was reported in either group.

5.6.3 Mental health

Eleven (27.5%) patients mentioned at the time of their follow-up evaluation that they have or have had mental health problems. Their mean age was 26.3 years. There was also a history of mental problems in eight (20%) of the controls and their
mean age was 30 years. This group of patients and controls was as satisfied with
own appearance as those who did not mention having any mental problems.

5.6.4 Family, socioeconomic status and education

There was no statistically significant difference between the patients and controls
in education, housing, marital status or employment.

Half of the patients (N=21) and controls (N=20) were either being married or
cohabiting (Table 12).

The same number of patients and controls had children (McNemar test \( p = 1.00 \))
with average of 1.7 and 2 children per family. Also the same number of patients
and controls were not renting their apartments but lived in privately owned
apartments (Table 12).

The educational level of the participants, who were still studying, was
considered according to their existing degree (Table 13).

Table 12. Socioeconomic status for patients and controls in study IV. Number of
subjects in each group presented, McNemar \( p > 0.05 \) for all variables.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Living with parents</th>
<th>In permanent relation</th>
<th>Having children</th>
<th>Working</th>
<th>Unemployed</th>
<th>Owning real estate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>5</td>
<td>20</td>
<td>12</td>
<td>25</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Controls</td>
<td>2</td>
<td>21</td>
<td>12</td>
<td>29</td>
<td>3</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 13. Education level for patients and controls in study IV. Number of subjects in
each group presented, McNemar \( p > 0.05 \) for all variables.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No professional education</th>
<th>Professional secondary</th>
<th>Professional tertiary</th>
<th>Students</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>9</td>
<td>19</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Controls</td>
<td>11</td>
<td>16</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>
6 Discussion

The present study was conducted on the one hand to analyse the effectiveness and safety of surgical tools used in craniosynostosis surgery and on the other hand to assess the outcome of the surgeries performed using these tools. Among these were resorbable plates and their endocranial use, distractor devices and their application for PCVD and guides facilitating placement of the distraction devices.

The author studied the outcomes of metopic and coronal synostosis surgery, posterior cranial vault distraction surgery and long-term results of sagittal synostosis correction surgery.

Such evaluation tools as four point scoring, Whitaker categorization, aesthetic evaluation from conventional photographs by independent panels using VAS score, patients’ self-satisfaction using VAS score, cephalometric measurements from cephalograms and finally 3D photogrammetric imaging were used and compared.

6.1 Methodological considerations

Outcome studies can be broadly divided into three categories: clinical efficacy outcomes, patient-reported outcomes, and financial outcomes (Luce, 1999).

While study I and II belong to the group of clinical outcome evaluation from the surgeons point of view, study IV aimed to evaluate outcome using tools from all three categories of studies to collect data meaningful for both patients and surgeons.

When performing studies on outcomes of surgical treatment the length of follow-up is crucial. As Goodrich states, a child operated due to craniosynostosis undergoes dramatic growth changes up to teenage years with the last point for relapse at the beginning of the teenage years. Thus studies on follow-up of at least 12 to 15 years are required for adequate evaluation of surgical results (Goodrich, 2017). The strength of the present study was the length of follow-up for the sagittal synostosis group and its patient-oriented design. So far this is the only study with such long follow-up of patients with isolated sagittal synostoses.

Convincing proof of the superiority of one surgical method over the others requires prospective randomized trials with follow-up times reaching at least in to adolescence. The weakness of the study was the small number of patients.

The best study design for testing the reliability of the 3D photogrammetric method as a tool for evaluation of volumetric changes would include 3D skull CT imaging. However, CT is an ionising imaging method, and it is not used routinely
in the follow-up at the Oulu Craniofacial Centre. To use it only for the study purposes was found to be unjustified.

One major weakness in all long-term follow-up studies on craniosynostoses is the lack of knowledge of the natural course of the disorder if no surgery was performed. Thus it is not known what would have been the aesthetic appearance, stigma of the malformation, somatic and mental health as well as general life situation of the persons with craniosynostoses without treatment.

There can be a bias in case selection for the long-term follow-up study IV. Since not all patients agreed to come, it is not known if the patients who agreed to participate represent sufficiently well the whole cohort. However, this is a minor bias that has to be accepted in studies like this. It is possible that both in the case of patients and controls, the persons with higher level of education are prone to accept the invitations to participate due to better understanding the significance of the studies for the scientific research.

Neuropsychological tests are often included in the follow-up evaluation. Based on the previous reports it was assumed that the patients were doing rather well even if having minor defects in their neurocognitive performance. Thus it was found unjustified to perform such tests to adult patients. Especially, when the findings would not influence on the treatment, rehabilitation, education nor career planning. On the contrary, knowledge of abnormal neurocognitive functions can have negative effects on their self-esteem. The results of the follow-up study IV confirmed this assumption. The patients were doing as well as controls in many aspects of their wellbeing.

Limitation of the present study IV was the lack of preoperative images. It was not possible to evaluate how much the deformity was improved as a result of the surgery.

Unlike many centres (Shah et al., 2011; Wilbrand et al., 2012) at the Oulu University Craniofacial Centre no routine measurement of cephalic index (CI) is done in craniosynostosis patients. Both CI and head circumferences are neither reliable nor informative enough in the follow-up of these patients. This was in accordance with a finding by Leikola and associates who found that CI correlated poorly with intracranial volume in non-syndromic scaphocephalic patients (Leikola, Koljonen, Heliovaara, Hukki, & Koivikko, 2014).

Attention should be drawn to the fact that the results of the long follow-up study IV are applicable only to patients with nonsyndromic sagittal synostosis.
6.2 Surgical duration and bleeding (I, II, IV)

Analysis of operative time and blood loss was not a primary aim of the study. They are presented more for descriptive purposes and no significant conclusion should be done from these data. This data was not included in the original publications.

In all cases, except one, the osteotomized bone was detached from the dura when performing PCVD. The perioperative bleeding was equal to those reported in the literature when the bone block was left attached to the dura (Imai et al., 2002; Steinbacher et al., 2011). While there were no major complications with detaching the bone, there seemed to be no benefits from this. In general, leaving the bone attached to dura is considered less invasive. We have adopted the approach and we are in process of collecting results to analyse the influence of this change.

6.3 Surgeons evaluation of postoperative results

In both studies number I and IV, the same simplified 4-point classification (Table 2) was used to evaluate the postoperative aesthetic results from the clinicians’ point of view. According to this classification (Table 6) the results of frontal remodelling (study I) and scaphocephaly surgery (study IV) were either good or excellent in over 90% of patients.

In study group I the only unsatisfactory result was due to the underlying condition (craniofrontonasal dysplasia).

In sagittal synostoses the unsatisfactory outcome was related to failure of the surgery to normalize the skull shape despite the use of the same remodeling surgery in all these cases. Thus outcome was also probably related to the gravity of the underlying pathology and the tendency to develop some degree of re-synostosis after the primary operation. This finding highlights the variability and the unpredictability of the long term results of the surgery for sagittal synostosis in a small (10%) proportion of patients. Unfortunately the study design did not allow reliable estimation of the re-operations rate after primary sagittal synostosis surgery neither was there data available on preoperative severity of the pathology.

In the long follow-up study (study IV) the 4-point classification results were compared with the panels’ evaluation of facial appearance using a VAS scale. There was some congruency of the results. There were four cases from study IV, where the surgeon evaluation during personal encounter showed the adult patients’ appearance to be fair. In these four cases, all panels and patients themselves also evaluated their appearance to be worse when compared with the other cases.
However, the correlation between these two rating systems could not be properly tested due to the small numbers of the group with fair outcome.

When grading the same patients according to the Whitaker classification, all cases in the sagittal synostosis group with very long follow-up times (study IV) and all but one case in the frontal remodelling group with short follow-up times (study I) fell into the same class. This is because in the 4-point classification only one grade corresponds to the necessity of re-do surgery. The Whitaker classification has three out of the four classes dedicated to grade cases that require reoperations. While evaluating the necessity for re-do surgery, which is crucial during the first years of follow-up, the Whitaker classification was not sensitive enough to evaluate the degree of residual dysmorphia later in life.

The 4-point scale is more specific to the questions of aesthetic outcomes. The 4-point scale is easily applicable to the evaluation of outcomes whether on personal encounter, from the photographs or on the basis of the medical records.

6.4 Outcomes of operations with endocranial placement of resorbable plates

Bone fixation is particularly challenging in coronal suture and metopic suture synostosis. In the Oulu Craniofacial Centre these cases are treated by one-stage fronto-orbital remodelling operations which, as mentioned earlier, require fixation of the reshaped cranial bones. The region of operative interest includes the frontal bone and the orbital rim, which comprise the upper part of the face and thus are crucial for facial appearance. This sets a high standard for symmetry and shape. The thin overlying soft tissues and skin in frontal area makes fixation even more demanding since any unevenness of the bone-plate construct can be not only palpable but may even be visible after operation (Freudlsperger et al., 2015; Wood, 2012). When placing the plates on the inner surface of the frontal bone, the aesthetic result is better immediately after surgery. It also allows using plates in very young patients with thin skin. These endocranial plates have been in use since 1998 and the description of the technique was first published in 2003 (W. Serlo et al., 2003). Later the technique has been proven to be safe also by other groups (Konofaos et al., 2016; Sauerhammer et al., 2014).

When placed endocranially the resorbable plates leave no “traces” in the form of impressions or unevenness of the bone after the plate is resorbed which is a usual finding in cases of superficial plate location. This phenomena of “traces” was noticed earlier and named “bone memory” by Goodrich (Goodrich et al., 2012).
This can possibly be explained by a fact that osteoclastic activity dominates endocranially and osteoblasts are more active at the outer surface of calvarial bone where new bone formation is taking place. Thus the foreign material placed on the outer surface interacts with new bone formation. This process explains intracranial pseudo-migration of metal fixation material. The resorbable plates slow down or prevent the new bone formation at their location until they are resorbed (Goodrich et al., 2012; Sauerhammer et al., 2014).

Insufficient stabilization and difficulties while handling resorbable plates have been reported earlier (Landes & Kriener, 2003). Choosing plates consisting of three different polymers helps to avoid these inconveniences. During the operation the plates made from several polymers were flexible enough to tolerate bending to certain extent at room temperature. After warming in hot water the plates were easily mouldable and rapidly solidifying when cooling, also sustaining repeated warmings, if required. This property can be used when operating on children with very thin and fragile bone. The bone was first reinforced with the plate fixed to its inner surface and a newly created bone-plate construct was heated and moulded to desired extent. This way breaking of the bone was less probable and had no negative influence on the final result.

The plates cannot be placed endocranially in all parts of the skull. This method has been applied mainly to the frontal area, where extracranial plates would cause the most visible harm.

6.5 Outcomes of posterior cranial vault distraction operations

In study II the extent of the distraction was achieved as planned in all cases. In one case completion of distraction required re-operation to resolve conflicts of the device vectors. After the invention and application of the distractor guides (study III) there were no such vector conflicts any longer.

PCVD allowed the attainment of a sufficient increase in intracranial volume and in all patients the preoperative symptoms of raised ICP resolved after operation. From an aesthetic point of view the results were acceptable also in cases with an already scaphocephalic shape of the head. PCVD has less adverse effect from the aesthetic point of view, which is important especially in patients whose shape of the head was normal before operation (W. S. Serlo et al., 2011). In previous studies (Goldstein et al., 2013; White et al., 2009) it was noted that PCVD has a positive influence on frontal cranial morphology. There is a relief in frontal bossing subsequent to posterior distraction in study group II. So far only three out of 14
syndromic cases from this series had to undergo fronto-orbital remodeling surgery later in life. None of two patients with non-syndromic bilateral coronal synostosis required additional cranioplastic surgery (by now 2.5 and 5.5 years of follow-up). But since the protocol of the current study does not include routine CT scans, and since 3D photogrammetry has been used only during the last year of the study period, there is not enough data to objectively prove positive changes in the frontal morphology. Thus there is only subjective data available to support this. The analysis of remodeling of the frontal cranium after PCVD would be an interesting topic for future studies.

The strength of the present study was that this technique was applied to patients with variety of indications. While PCVD is an established method for patients with syndromic craniosynostoses, it has been used also for shunt induced craniocerebral disproportion and for other indications. The present study included eight patients who had been operated earlier due to scaphocephaly and later presented with symptoms craniocerebral disproportion confirmed by ICP measurement and thus requiring re-operation. When performing PCVD in patients with recurrent scaphocephaly the head shape became more scaphocephalic. In all these cases one stage cranial vault remodeling, though being a better choice from aesthetic point of view, was considered to provide insufficient increase in intracranial volume. Thus a decision was made in favor of PCVD. The patients got relief of their symptoms and the aesthetic outcome did not bother neither the patients nor their families.

One interesting indication for PCVD might be cranial expansion in treating a primary Chiari type I malformation. It has been shown by Leikola and associates that cranial expansion procedures reduce the extent of tonsil herniation in patients with craniosynostoses (Leikola, Hukki, Karppinen, Valanne, & Koljonen, 2012). In the present series one patient was diagnosed with Chiari I malformation. This patient remained symptomatic after foramen magnum decompression and duraplasty and the degree of tonsil herniation increased after this procedure. A decision to perform PCVD was done. After the surgery the tonsils elevated 5 mm, and the patient got relief of her symptoms. Although this indication for PCVD is discussed by paediatric neurosurgeons, there is so far no published evidence proving the feasibility of PCVD as a treatment option for primary Chiari type I.

6.5.1 Volume gain measurements and outcomes (II)

Volumetric changes were analyzed on the basis of plain cephalograms. This is a mathematical approximation and not an exact volumetric calculation based on 3D
data. In spite of this the results correlate well with results of the studies performed using 3D CT scans. The present study showed that an average increase in cranial volume was 25% after PCVD. This is in line with previous studies reporting a 21-29% volume gains with this surgical technique when calculated from 3D CT scans (Goldstein et al., 2013; Nowinski et al., 2011).

Also these findings seemed to be in accordance with the first results of 3D photogrammetric analysis. Five patients were imaged with this method both before and after PCVD surgery. For these patients the average increase in ICV was 17.4% as estimated from 3D photographs compared to 20.8% as calculated from cephalograms.

Although, 3D CT is a gold standard when evaluating results of cranioplastic surgery (Fearon, 2014), in the Oulu Craniofacial Centre 3D CT scans are not done on routine basis but are reserved for cases with strict indications thus avoiding ionizing studies whenever possible. Plain cephalograms expose patients to less ionization and sedation is not required while taking these images. In the future 3D photography will be applied more frequently in this field, thus further decreasing need for ionizing studies. This method has already been applied to follow-up outcomes in patients with sagittal synostosis and positional plagiocephaly (Aarnivala et al., 2015; Le et al., 2014).

6.6 Complications and unforeseen events

Neither study I nor II revealed any complications causing permanent morbidity or mortality. This is a very positive finding, because in general, surgery for craniosynostosis is considered to be high risk procedure.

One of the usual intraoperative risks of any craniosynostosis surgery is a dural tear during osteotomy phase. Even if all dural tears are detected and sutured properly, later there can be CSF leakage from the wound or CSF collection under the skin. Sometimes CSF leaks after operation can appear even without intraoperative damage to the dura but as a result of screws “scratching” the dura during distraction process (Goldstein et al., 2013). Two patients in the frontal remodelling group (study I), and one patient in distraction group (study II) had such CSF leak related complications. One patient had a dural tear detected and sutured during PCVD surgery, but postoperatively the patient had CSF leak from the wound and required lumbar drainage for several days. In the other two patients who had frontal remodelling surgery there was no information on intraoperative dural tears. One of the patients had a postoperative pseudomeningocele persisting for several
months after the primary surgery and required minor revision. Another patient was diagnosed with a pseudomeningocele several months after surgery, but this resolved spontaneously. None of these three patients developed meningitis, nor had any other signs of infection. There was no compromise in ossification. Avoiding and managing dural tears during surgery for craniosynostosis remains challenging.

6.6.1 Complications of operations with resorbable fixation (I)

Complications requiring re-operations were observed in three (11%) patients. This was in accordance with previous publications where the same method was used (Konofaos et al., 2016; Sauerhammer et al., 2014). None of these complications was related to the resorbable fixation material itself.

It is reported that resorbable plates can cause sterile inflammatory reactions in some patients (Wood, 2012). No cases with such reactions were observed in this series, which was in accordance with findings in the studies by Konofaus and Sauerhammer (Konofaos et al., 2016; Sauerhammer et al., 2014). One of the patients diagnosed with a small spontaneously resolved pseudomeningocele several months following surgery, possibly had a fluid collection caused by plate resorption rather than CSF collection. But the finding was minor, with no skin changes nor any signs of infection or other complaints. It is possible that sterile inflammation could take place intracranially without any external signs. In the above mentioned studies there was not a single case with intracranial inflammation among the patients who had the postoperative CT scans done. One possible reason for decrease in such inflammatory reactions may be explained by the currently used plate materials. In the Oulu Craniofacial Centre the plates made from three different polymers, poly-L-lactide (LPLA), polyglycolide (PGA) and trimethylene carbonate (TMC), are used. There were no complications related to the plates themselves independent of plate location. Therefore, resorbable plates made from copolymers may be recommended.

6.6.2 Complications of distraction operations (II)

The detailed data on complications of distractions in study group II was not included in the original publications. There were unforeseen events in more than half of the cases in this study group. They mainly consisted of minor skin and mechanical problems of the distractor devices during the immediate postoperative and distraction periods. There were no cases of permanent morbidity or bone flap
resorption. Although distraction was performed to the planned extent in all cases, according to our experience informed commitment of the parents is important when planning a distraction procedure.

The number of distractors to use is a topic of debate. Some authors intend to place just one to two devices in order to avoid mechanical complications related to the devices (Goldstein et al., 2013; Thomas et al., 2014; White et al., 2009; Wiberg et al., 2012). In the Oulu Craniofacial Centre it is preferred to use four distractors whenever feasible, as it not only allows better stability but also deals with the possibility of distractor failure allowing the distraction to continue to completion with the remaining two or three devices. This occurred in two out of 31 cases in study group II.

In spite of the fear of infections due to external rods and thus open skin wounds that could serve as a portal of entry for infections, there was not a single case of systemic infection requiring antibiotics in this study population.

Routine preoperative CT or MR angiograms were not performed to evaluate the vasculature of the region of surgical interest at the time when this series of cases was operated. Since then the authors have become aware of potential abnormal cerebral venous drainage through the planned bone flap and have added MR angiogram when necessary in the preoperative evaluation protocol.

The subject of complications and unforeseen events related to distraction operations will be further analyzed in the next publication.

6.7 Outcome of surgically treated patients with sagittal synostosis as adults (IV)

The aim of study IV was to fill the gap in knowledge on outcomes from patients’ and third persons’ point of view, to find out how the patients are really managing in adulthood when compared to co-eves or controls.

6.7.1 Results of different operative methods (IV)

In the present study there was no difference in outcomes regarding different operative techniques for sagittal synostosis. However, the aim of this study was not to compare different surgical techniques, and it would even be impossible in such retrospective series.
6.7.2 Aesthetic evaluation by participants and panels (IV)

To the author’s knowledge, study IV was the first study where adult craniosynostosis patients were asked to evaluate their own satisfaction with a 100 mm VAS scale with a lay panel evaluating postoperative aesthetic outcome with the same scale.

One very important finding of the present study was that adults who were treated for sagittal craniosynostosis were equally satisfied with their appearance compared to controls independently of age or gender.

Both panels of independent evaluators did rate patients’ appearance to be slightly less attractive when compared to controls. The difference was statistically significant. However, it was less than 10% out of 100 mm VAS scale (7 mm in case of the dentists panel and 6 mm in case of the lay panel’s evaluation). This was in accordance with a previous study by Panchal et al., where assessment of the head shape from photographs was performed by panels of lay and professional observers in the children operated due to sagittal synostosis in the early infancy. In this study controls also tended to receive slightly higher rankings, but the difference was not significant (Panchal et al., 1999).

The difference between controls and patients group in panel evaluation was less than 10 mm. The small difference between the groups raised the question of clinical significance of that difference. Responsiveness of the magnitude of change of any outcome measurement instruments is to be clinically correlated and is open to interpretability (Rhee & McMullin, 2008). In 100-point scales like HRQOL scales a 10-point gain is used as an Minimum Clinically Important Difference (MCID) (Thoma & Ignacy, 2012). In Medline no standard method was found for measuring MCID in VAS scales used for evaluation of aesthetic results of surgery neither earlier (Beaton, Boers, & Wells, 2002) nor currently when the search was performed by the author.

It was previously found that when assessing certain traits in facial shape from photographs by panel evaluators, the reliability was likely to be improved by additional training and further exposure of panel members to the spectrum of possible deformities (Asher-McDade, Roberts, Shaw, & Gallager, 1991; Bendon et al., 2014). This can explain why in the studies evaluating results of orthodontic treatment by panels of lay persons and dentists, the panels of dentists have been stricter in their evaluations (Kokich, Kokich, & Kiyak, 2006). Since in this study facial attractiveness was evaluated in general, not specifically seeking for certain traits neither comparing pre- and postoperative images, it was found unnecessary
to educate the panels. Thus panels were shown in advance before the slide show only one slide of a healthy person not included into the study group itself (Fig. 6).

Asher-McDade and associates have shown that with increasing the number of panelists from three to six the reliability was increased from 0.82 to 0.90, thus allowing a decreased influence of variation between individual evaluators that is to be expected when the facial appearance is scored (Asher-McDade et al., 1991). In this study interobserver reliability was for individual members of panels moderate with $p = 0.573$ for the dentists panel and $p = 0.555$ for the lay panel. When increasing the number of observers in the dentists panel from four to five, the reliability increased up to $p = 0.840$.

When a person is asked to judge “attractiveness” of someone’s face these judgements appear to reflect sexual attractiveness. According to Rhodes, contrary to the popular assumption that beauty is in the eye of the beholder, there appears to be an agreement between men and woman independently of cultural background in the question about what traits make the face attractive. These biologically based preferences are averageness, symmetry and sexual dimorphism (Rhodes, 2006). Thus surgery should aim at restoring facial symmetry and make the shape of the face and head as close to average as possible.

There was no correlation between third persons evaluation of facial appearance and satisfaction with own facial appearance neither in patients, nor in the control group. In contrast with these findings, in cases of patients seeking treatment for malocclusion or aesthetic reasons there was usually some correlation found (Badran, 2010; Silvola et al., 2014).

A lack of such correlation in the present study was probably due to its design. The patients were invited to participate in the study, and they were not seeking treatment.

This finding was also in accordance with the studies on body image. Research done on a number of conditions (e.g. craniofacial anomalies, amputations or burns) found that objective severity of a disfigurement does not predict extent of distress or negative body image (Tiggemann, 2015). This probably explains why visibility of the scar seemed to have no influence on satisfaction with own appearance in the study IV patients.

Though there was no statistical difference between patients and controls in the matter of self-satisfaction with facial appearance, there were slightly more patients than controls among those who graded their satisfaction below general. However, none of these patients during the interview appeared to be significantly dissatisfied with their appearance. For example, none of them showed any interest in further
correction of facial shape or the scar. Though all four of the patients who admitted that the scar bothered them belonged to this group of less satisfied patients, the scar did not seem to be the only or main reason for such dissatisfaction. Also one interesting finding was that none of the patients with parasagittal direction of the wound complained about the scar. Because of the small size of these subgroups only limited conclusions can be drawn.

**6.7.3 General life situation and health issues in patients treated for sagittal synostoses (IV)**

It is essential to assess the impact of the disease and its treatment process on the adult patients when compared with co-eves. It is also essential to assess the degree of psychosocial impact of the disease and its treatment process on patients and their families.

One positive finding was that being operated on sagittal synostosis did not influence patients’ somatic health, education level, employment status or finding a partner. There was no significant difference between the patients and controls in any of these aspects.

According to the Eurostat regional book 2016, 4% of young people aged 25 – 34 live with their parents in Finland (Kotzeva, Brandmüller, & Önnerfors, 2016). That was the case in the control group where two persons were living with parents. In the patient group 5 (12.5%) lived with their parents. This difference was not significant, and can be explained by small study sample. Also this study included younger persons than the above mentioned Eurostat data.

According to the same Eurostat year book, in general in Finland 42.7% of persons aged 30 – 34 years have tertiary education (Kotzeva et al., 2016). Among patients 30% and controls 32.5% had tertiary education. This was less than the average in the population, but the study IV participants were younger and approximately 23% were still studying in order to get higher education. For the analysis students’ education was graded according to their highest accomplished education level. Thus for comparison, in the case of medical students for example, even if they were in their last year of studies, their education level was still classified as primary, not as professional tertiary education.

The general unemployment level in Northern Finland in 2015 was 10 – 15% among persons aged 15 – 74. It was much higher (over 20%) in the age group between 15 – 24 years (Kotzeva et al., 2016). In this study population, only five patients (12.5%) and three controls (7.5%) were unemployed and not studying.
According to the present study IV, regarding patients with isolated sagittal synostosis, there was no difference in somatic health compared to controls. Also no correlation between treated sagittal synostosis and prevalence of headaches or migraine was found. Both, patients and controls, had same frequency of mental problems. A history of mental problems surprisingly did not influence the study persons satisfaction with their own appearance.

6.8 Clinical implications and future perspectives

The study has shown that it is possible to use nonionizing 3D photogrammetric imaging to evaluate volume gain after cranioplastic surgery. Further studies will focus on validating the method comparing to cephalograms and CT scan methods. While, the 3D-camera is expensive, once the investment is made, the use of the camera requires no additional expenses, it is neither time consuming nor technically demanding. Application of this method for follow-up of results of other treatment modalities should be studied, including frontal remodeling, sagittal synostosis surgery and conservative treatment of positional plagiocephaly. This method could also be included in the diagnostic and treatment protocols of the patients with craniosynostoses once validated. It provides an easy and precise method of routine clinical documentation of the changes in patients’ appearance during the treatment and follow-up.

Another application of 3D photogrammetric imaging will be to study the effect on the frontal cranial shape and volume after PCVD.

A standardization of methods for the evaluation of the aesthetic outcomes will facilitate the evaluation of the results between various surgical methods. However, this will remain very challenging. As stated by Goodrich (Goodrich, 2017) an estimation of the aesthetic results with a follow-up of less than 12 to 15 years is of minor value.

Application of PCVD as a treatment modality when dealing with primary Chiari type I malformations might be revolutionary. However, future prospective and randomized studies will show the suitability of this method.

Regarding the skull growth after PCVD the concern arose about timing of device removal after the surgery. Maintaining metal constructs fixed to a rapidly growing young child’s skull can at certain time periods after surgery, when the brain had already occupied the space “won” by the surgery, may start restricting further skull growth (Di Rocco, personal communication, December 2016). Also the
resorbable plates positioned over the patent sutures can have the same growth restricting influence. This topic should be addressed by future research.
7 Conclusions

Generally patients treated for craniosynostoses managed in life as well as controls with equally good aesthetic outcomes. The operative techniques including resorbable plates or distractors were found to be effective.

In answer to the specific questions the following may be concluded:

1. The feasibility of endocranial fixation in craniosynostosis surgery was established. Good or excellent aesthetic results were seen in 96% of cases as evaluated by a surgeon at follow-up. Only three patients out of 27 had complications that required revisions. No mortality or permanent morbidity, nor complications related to endocranial placement of the plates were seen. (I)

2. Posterior cranial vault distraction allowed a mean increase of 25% in intracranial volume. It proved to be an effective technique for treatment of a variety of craniosynostotic conditions with significant shortage of intracranial volume. 3D photogrammetric imaging is a suitable non-ionizing method for evaluation of cranial volume increase following distraction. (II)

3. A new tool was developed and successfully used for the intraoperative guidance of distractor device placement with congruent vectors (III, II).

4. Patients treated for sagittal synostosis were equally satisfied with their facial appearance as their age and gender matched controls. Independent panels found patients appearance to be slightly less attractive, but the difference was only 6-7 mm on a 100 mm Visual Analogue Scale, representing a low clinical significance. Patients’ socioeconomic situation such as education, housing, employment and marital status equaled controls. They had similar frequencies of headaches, mental problems or health issues as the controls. (IV)
List of references


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Original publications


IV  Salokorpi, N., Savolainen, T., Sinikumpu, JJ., Ylikontiola, L., Sándor, G.K., Pirttiniemi, P., Serlo, W. Outcomes of 40 nonsyndromic sagittal craniosynostosis patients as adults: A case-control study with 26.5 years of postoperative follow-up. Manuscript.

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Original publications are not included in the electronic version of the dissertation.
1412. Tauriainen, Tuomas (2017) Complications associated with preoperative anemia, perioperative bleeding and blood transfusions after isolated coronary artery bypass grafting


1414. Pasanen, Ilkka (2017) Stromal cells of mesenchymal origin in breast cancer

1415. Kunnari, Marika (2017) Aikuisväestön hyvinvointiin liittyvät huolet ja hyvinvoinnin heikentäjät


1418. Ouira, Petteri (2017) Search for lifetime determinants of midlife vertebral size : emphasis on lifetime physical activity and early-life physical growth

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