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# **CBCT IMAGING: REVOLUTIONIZING CLEFT CARE FOR CHILDREN**

**PhD thesis**

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## **List of abbreviations**

ALADA: As Low As Diagnostically Acceptable

ALARA: As Low As Reasonably Achievable

CBCT: Cone-Beam Computed Tomography

CLAP: Cleft lip, alveolus and palate

CLP: Cleft lip and palate

CPGs: Clinical practice guidelines

CT: Computer tomography

DVT: Dental Volumetric Tomography

FS-ICU: Family Satisfaction in the Intensive Care Unit

ICU: Intensive Care Unit

IRF6: Interferon regulatory factor-6

LAC: Linear attenuation coefficient

MR: Magnetic resonance imaging

MTHFR: Enzyme 5,10 Methylene tetrahydrofolate reductase

NAM: Presurgical Nasoalveolar Molding

OHIP-14: Oral Health Impact Profile

OHRQoL: Oral Health-related Quality of Life

PRS: Pierre Robin Sequence

PVRL1: Poliovirus receptor-like-1

SABG: Secondary alveolar bone grafting

SADS: Social Avoidance and Distress Scale

SNP: Single-nucleotide polymorphism

STL: Standard tessellation language

TBX22: T-box transcription factor-22

VPI: Velopharyngeal insufficiency

VPD: Velopharyngeal dysfunction

VPF: Velopharyngeal function

## **1. Introduction**

### **1.1. Cleft lip and palate**

The cleft lip, alveolus, and palate (CLAP) are a birth defect resulting in split(s) in the upper lip, the roof of the mouth (palate), or both. CLP can occur isolated or associated with several inherited genetic conditions or syndromes. The incidence of oral clefts occurs in 1 in 1500 lives, showing one of the most common congenital malformations. In Hungary, the prevalence of CLP is about 2.02%. The origin of CLAP involves a combination of genetic and environmental factors, contributing to its multifactorial etiology. Numerous environmental risk factors can provoke CLP, such as smoking, advanced maternal age, alcohol consumption, folic acid deficiency, some maternal drugs (valproate acid, anticonvulsants, retinoic acid derivatives, thalidomide, and phenytoin) and diabetes mellitus type I (Badovinac et al., 2007, Young et al., 2000).

Numerous genes associated with syndromic CLAP have been identified. Among them, T-box transcription factor-22 (TBX22), poliovirus receptor-like-1 (PVRL1), and interferon regulatory factor-6 (IRF6) play roles in X-linked cleft palate, cleft lip/palate–ectodermal dysplasia syndrome, and Van der Woude and popliteal pterygium syndromes, respectively. Additionally, these genes are implicated in nonsyndromic CLP (Kohli and Kohli, 2012). The enzyme 5,10 Methylene tetrahydrofolate reductase (MTHFR) is crucial for converting 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate within the folate metabolism pathway. The MTHFR C677T single-nucleotide polymorphism (SNP) is susceptible to thermal changes and is recognized as a factor associated with the occurrence of neural tube defects. Additionally, in cases of nonsyndromic cleft lip and palate, mothers carrying the MTHFR C677T genotype have been found to elevate the risk of this condition by 4.6 times. Furthermore, when periconceptional folic acid deficiency is present, the MTHFR thermally labile variant elevates the risk of CLP by 10 times (van Rooij IA et al., 2003).

The presence of genetic syndromes can aggravate not only the incidence of CLP but also the management and treatment of cleft patients. The following syndromes are associated with oral cleft: Stickler (Pierre-Robin sequence), Van der Woude, Goldenhaar, Treacher-Collins, Ectrodactyly-ectodermal dysplasia-clefting, and Velo-cardio-facial (Strong and Buckmiller, 2001). Nearly half of the syndromic patients presented the Pierre Robin Sequence (PRS) or Velo-cardio-facial syndrome. PRS is a developmental

malformation with characteristic features being micrognathia, glossoptosis, and airway obstruction (Gundlach and Maus, 2006). The velo-cardio-facial syndrome is a cardiovascular abnormality with ventricular septal defect and abnormal facies.

## **1.2. The role of velopharyngeal closure**

To understand the cleft pathology, normal palatal development is necessary to be considered. The palate separates the oropharynx and nasopharynx. During embryogenesis, it divides into an anterior bony hard palate and a posterior soft palate that does not contain bone. While the hard palate underlies the bony structure functioning as a structural purpose, the soft palate is included by the muscle fibres and covered with mucus membrane serving a more functional purpose (Weatherley-White et al., 1972). The soft palate participates as an active muscular valve, called the velopharyngeal sphincter. The soft palate includes six pairs of muscles: levator veli palatini, tensor veli palatini, superior constrictor pharyngeus, uvulus, palatopharyngeal, and palatoglossus muscles. The tensor and levator veli palatini muscles are observed to regulate the opening of the eustachian tube and aerate the middle ear preventing recurrent otitis media. The role of the velopharyngeal function is to separate the oral and nasal cavities raising the soft palate up to the posterior pharyngeal wall (Witt and Marsh, 1998). This mechanism aids in proper breathing, swallowing, speech, and blowing. However, the presence of clefts of the soft palate disturbs the movements of the levator muscles leading to velopharyngeal insufficiency. Moreover, insufficient velopharyngeal function can interfere the normal speech development and increase the risk of chronic otitis media and hearing loss.

## **1.3. Classification of the cleft palate**

The cleft can affect not only the soft and hard palate but the alveolus as well. In about 75% of cases, there is also an accompanying alveolar cleft, necessitating subsequent reconstruction of the alveolar bone (Figure 1) (Guo et al., 2011). The compromised development of the maxilla leads to the collapse of alveolar segments and a reduction in maxillary dimensions. The cleft palate can be classified by primary and secondary palates even as complete and incomplete, unilateral and bilateral, and submucous clefts. The primary and secondary palates involve the complete cleft in which no fusion between the

palatal shelves could be observed. Nevertheless, the incomplete cleft is comprised only of the secondary palate, where only an initiate fusion could be detected between the palatal shelves. Further classification of the secondary cleft palate is unilateral and bilateral. The unilateral cleft affects only the side of the midline since only one palatal shelf fuses to the nasal septum. In the case of the bilateral cleft, neither palatal shelves fuse to the nasal septum resulting in defects on both sides of the midline. The submucosal cleft is found under the mucous membrane of the soft palate resulting the insufficient muscular function. It can be difficult to diagnose due to the intact soft palate.



*1. Figure Unilateral Cleft lip, alveolus, and palate (Face Reconstruction Centrum of the Semmelweis University – own image of our cleft team)*

#### **1.4. Treatment options for CLAP patients**

The multidisciplinary management of cleft patients is indispensable for creating a unique and personalized therapy. The coordinated work of several specialists such as the maxillofacial surgeon, ENT specialist and speech therapists, psychiatrists, phoniatics, and orthodontists, is necessary for children with CLAP to receive the appropriate and complex therapy. The surgical interventions practically begin at birth and continue until the end of facial development. For facilitation of the successful treatment, the multidisciplinary team is required to know the economic and social factors that influence the relationship between healthcare providers and patients. In addition, numerous external factors can influence the effectiveness of the treatment like the travel distance, the economic status, or financial circumstances of the of the caregivers, and the extent of parental involvement (Alonso et al., 2020).



Numerous surgical and non-surgical techniques aim to comply with the following major principles:

- Suture placement without tension,
- Repositioning of the soft palate muscles to reconstruct the levator veli palatini,
- Extension and repositioning of the soft palate,
- Reducing exposed bone and areas without mucosal covering in the nose or mouth,
- Sequential closure of both the hard and soft palate in layers (Naidu et al., 2022).

#### **1.4.1. Velopharyngeal Insufficiency**

In cleft care, a frequently encountered clinical concern revolves around the assessment of velopharyngeal insufficiency (VPI), also referred to as velopharyngeal dysfunction (VPD). Ordinarily, the harmonized action of velopharyngeal muscles ensures the proper division between the nasal and oral cavities, a critical function for effective speech and swallowing. However, in cleft patients, this coordination is often compromised due to the congenital anatomical irregularity of the soft palate. Phonation deficiencies commonly associated with VPI encompass hypernasality, nasal turbulence, and diminished vocal intensity (Lewis et al., 1993).

The diagnostic assessment of VPI typically involves a collaborative effort from a multidisciplinary team, comprising speech therapists, radiologists, and surgeons (Glade and Deal, 2016). The evaluation of velopharyngeal function can be conducted through diverse imaging techniques, including flexible nasopharyngoscopy, video fluoroscopy, multiview fluoroscopy, and dynamic magnetic resonance imaging (Witt et al., 1998). As far as our knowledge extends, there is currently no available research on the utilization of dynamic Cone Beam Computed Tomography (CBCT) imaging for diagnosing velopharyngeal insufficiency in individuals with clefts.

The primary cause of velopharyngeal insufficiency (VPI) in cleft palate patients is often attributed to factors such as inadequate length of the palate, insufficient development of the levator veli muscle sling and scarring-induced contraction of the soft palate (velum) (Chen et al., 1994). Additionally, other contributing factors to VPI include conditions like submucosal cleft palate and neurogenic VPI, where inadequate

innervation by cranial nerves affects the velopharyngeal mechanism. In this way, the approach to treating VPI depends on the specific type and underlying cause of the issue. If the problem arises from velopharyngeal mislearning, corrective speech therapy alone is typically sufficient to address the abnormal speech patterns. On the other hand, the treatment of VPI often involves surgical interventions such as tonsillectomy, Furlow Z-plasty, pharyngeal flap, sphincter pharyngoplasty, or posterior pharyngeal wall implant. In certain cases, prosthetic devices may be employed on a temporary or permanent basis as an alternative or adjunctive treatment for velopharyngeal insufficiency (Kummer, 2014).

#### **1.4.2. Closure of alveolar cleft**

Alveolar bone augmentation plays a crucial role in treating patients with orofacial clefts. The timing of this intervention categorizes it into primary, secondary, and tertiary alveolar bone grafting:

- **Primary Alveolar Bone Grafting:** Conducted before the age of 2, after lip repair but before palate repair.
- **Secondary Alveolar Bone Grafting:** Carried out after the age of 2, typically during the mixed dentition phase (6-12 years).
- **Tertiary Alveolar Bone Grafting:** Applied when patients have permanent dentition.

Secondary alveolar bone grafting (SABG), introduced by Boyne and Sands in 1972, has since become the preferred technique for repairing bony cleft defects (Boyne and Sands, 1972). Ideally performed during mixed dentition (6-12 years), this procedure supports adjacent teeth and the erupting canine, positively influencing maxillary growth and development. Numerous studies confirm that secondary alveolar bone grafting does not impede maxillary growth (Chang et al., 2005, Semb, 1988).

Bone grafting can be carried out using two primary approaches: autogenous bone grafts or allogenic bone substitutes. Autogenous bone grafts, harvested from the patient's own iliac crest or rib, have demonstrated favorable success rates, particularly when combined with bone morphogenic proteins. These grafts are effective in supporting tooth placement in the alveolar arch, establishing desirable nasal bone morphology, and

ensuring the stability of orthodontic treatment. Concerns related to harvesting bone from the iliac crest or rib include potential impacts on growth, disturbances in gait, hematoma formation, and morbidity at the donor site. However, many of these complications can be addressed through careful surgical techniques and the use of allograft materials. Allogenic bone substitutes can also be utilized as an alternative to autogenous bone grafts (Wahaj et al., 2016). Advancements in biomaterials, such as collagen membranes, hydroxyapatite crystals, and tricalcium phosphate powder, have expanded the possibilities for repairing alveolar clefts (Kraut, 1987). These biomaterials are increasingly considered for placement in alveolar cleft repair and other dental applications. Nowadays, tissue engineering techniques involving bone marrow stem cells and mesenchymal stem cells extracted and seeded on scaffolds made of materials like polylactic acid, collagen, fibrin, tricalcium phosphate, and calcium carbonate have also gained attention for alveolar cleft grafting and other dental procedures (Fujihara et al., 2005). In terms of radiological evaluation, cone beam CT (CBCT) is a low-dose and efficient approach utilized for evaluation the amount of bone defect on the cleft side prior to surgery. CBCT allows for the measurement of height and faciolingual depth of the bone defect. Furthermore, it can be employed postoperatively to assess the development of bone density, evaluating both the quality and quantity of bone in comparison to the unaffected side. Overall, orthodontic treatment and the utilization of CBCT imaging provide valuable information and aid in the dental preparation and assessment of patients with cleft deformity (Zhou et al., 2015).

### **1.5. Possibilities to improve the care of cleft patients**

There are several possibilities to enhance the quality of care provided to cleft patients. The significance of a multidisciplinary approach in caring for children with clefts cannot be overstated. It is important to establish multidisciplinary teams that include specialists from diverse fields, such as plastic surgeons, oral surgeons, speech therapists, orthodontists, and psychologists, to ensure comprehensive and coordinated care. Moreover, comprehensive education and support to families of cleft patients should be provided, including information on treatment options, post-operative care, and ongoing therapies, showcasing a patient-centered approach and commitment to holistic care. This can empower families to actively engage in the care and decision-making process. The

role of patient outcomes is also necessary since the monitoring and documentation of the surgical outcomes, speech development, functional improvement, and overall satisfaction of cleft patients can offer evidence of the effectiveness of care Nahai et al., 2005).

All professional knowledge and practice could be collected in a common center. Patient-Center Care allows considering the individual needs, preferences, and goals of each cleft patient, involving them and their families in treatment planning and decision-making. The Centers allow support ongoing education and professional development for healthcare providers involved in cleft care to stay updated with the latest advancements, techniques, and evidence-based practices. It is also important to implement regularly monitor and evaluate treatment outcomes, patient satisfaction, and quality of life indicators to identify areas for improvement and ensure continuous enhancement of care.

By exploring these possibilities and implementing relevant strategies, the care provided to cleft patients can be significantly improved, leading to better outcomes and enhanced overall well-being.

### **1.6. Importance of assessing the satisfaction of relatives and patients**

The perioperative phase presents unique challenges due to the anatomical and clinical characteristics of infants with cleft lip and palate. Consequently, monitoring these patients in the intensive care unit (ICU) is a critical aspect of their care. While cleft literature contains numerous studies, research is scarce on the rate of ICU admissions and its underlying causes in the cleft population. Kara et al. showed that the admission rate to the intensive care unit for primary cleft lip and palate (CLP) patients was recorded at 6.2%, with a total of 58 cases (Kara et al., 2021). This comprised an expected rate of 4.8% and an unexpected rate of 1.4%. Notably, there was a statistically significant link between the cleft type and the need for ICU follow-up ( $P < 0.001$ ). Their study highlights the elevated rate of ICU admissions among cleft patients compared to all ICU admissions. Given the unique circumstances of cleft infants, thorough preoperative assessment and the evaluation of postoperative ICU requirements can play a pivotal role in averting postoperative complications.

In recent years, the viewpoints of patients regarding the quality of care and the perspectives of their families have gained growing importance in the field of intensive

care medicine. These factors are now considered as internationally recommended quality measures for evaluating the quality of care in the ICU. This growing emphasis on patient and family experiences during ICU stays has led to a surge in research on family satisfaction (Haave et al., 2021). The Family Satisfaction in the Intensive Care Unit (FS-ICU) questionnaire is a well-established tool for evaluating family satisfaction in the ICU. However, for quality improvement initiatives in ICUs to be effective, it is crucial to rely on easily quantifiable and specific parameters (Schleyer et al., 2013). Typically, these opinions are collected through surveys and personal discussions with family members. The satisfaction of relatives with healthcare services depends on various factors, including the provision of clear information about treatment goals and plans, effective communication, regular updates on the patient's condition, consideration of the financial burden on the family, managing family expectations, providing information about critical illnesses, and adjusting medical interventions in response to changes in the patient's condition (Garg SK, 2022).

Several investigations conducted in different countries underscore the importance of using family satisfaction scores to pinpoint potential areas for enhancing ICU care. These studies consistently highlight that aspects like involving the patient and their family in decision-making, proficient communication, respect, and empathy strongly correlate with overall satisfaction (Schleyer et al., 2013). On the other hand, critics have raised concerns regarding the assessment of patient or family contentment, as these surveys rely on subjective experiences. For instance, patient and family feedback may be considered unreliable due to their lack of formal medical training and the potential influence of factors unrelated to the quality of care. Therefore, when conducting a study on satisfaction and analyzing the data, it is important for the evaluator to exercise caution in interpreting the results and utilizing the data (Garg SK, 2022).

Besides the FS-ICU questionnaire, the Oral Health-related Quality of Life (OHRQoL) questionnaire is also suitable for assessing family satisfaction. Both questionnaires can provide valuable insights into different aspects of patient care and family experiences in a healthcare setting. In the case of individuals with cleft lip and/or palate, it's crucial to determine whether the prescribed treatment sequence positively impacts OHRQoL. Considering the comprehensive impact on an individual's overall well-being, team members should take into consideration a patient's and even their

parents' background, cultural upbringing, past or present experiences with oral health issues and healthcare, current emotional state, treatment expectations, anticipated outcomes, and aspirations for the future when delivering holistic care for CLP. The primary goal of CLP treatment is to enhance the psychological and social well-being of individuals and their parents. It is important to view the patient rather than focusing solely on the affected area. A more profound understanding of the diverse and intricate needs of patients and parents will lead to improved outcomes and more effective teamwork among clinicians.

Sahoo et al revealed that cleft lip and palate conditions have a profound impact on a person's life, affecting functionality and emotions, and posing significant challenges for oral health maintenance. Individuals with clefts experience lower oral health-related quality of life compared to those without clefts across all domains. Interestingly, caregivers perceive their children's oral health-related quality of life more positively than the children themselves, especially in terms of functional well-being, socio-emotional well-being, and overall oral health quality of life. Among different types of CLP, individuals with cleft lips (alveolus) tend to have the highest oral health-related quality of life, while those with clefts on both sides of the mouth have the lowest. However, both patients and their caregivers express the least satisfaction with facial features, nose appearance, and lip appearance (Sahoo et al., 2023).

### **1.7. CBCT is commonly used in CLP patients**

Various visualization methods, video fluoroscopy, flexible nasopharyngoscopy, helical computer tomography (CT), and magnetic resonance imaging (MRI), can be used to assess maxillofacial defects. Each imaging method has its advantages and considerations, and the choice of technique depends on the specific needs and circumstances of the individual patient. When selecting the appropriate imaging method, it is important to consider factors such as the individual patient's needs, the specific goals of the evaluation, potential risks, availability, and the expertise of the medical team (Rudnick and Sie, 2008).

Cone-Beam Computed Tomography (CBCT) has gained popularity in maxillofacial imaging, particularly for assessing head and neck pathologies, including

skeletal, dental, and upper airway deformities. CBCT imaging offers detailed, three-dimensional images of the maxillofacial region. It allows for detailed visualization of skeletal structures, including bones of the face, jaws, and skull. Additionally, it offers precise imaging of dental structures, such as teeth and their roots, allowing for accurate assessment of dental alignment, abnormalities, or pathologies (Khare et al., 2019).

As with any medical imaging technique, consideration should be given to radiation exposure. The potential risks of radiation exposure, especially in young individuals with developing tissues, necessitate careful consideration and optimization of imaging protocols. CBCT imaging generally involves a lower radiation dose compared to conventional CT scans, so it meets strict pediatric radiology guidelines, like the ALARA (As Low As Reasonably Achievable) and ALADA (As Low As Diagnostically Acceptable) guidelines, aimed at minimizing radiation exposure (Oenning et al., 2018).

Presently, more than 220 CBCTs are available in the market, featuring a broad spectrum of hardware and software options that result in varied image quality and effective dose emission (Stratis et al., 2019). However, comparing different CBCT devices or imaging protocols for reducing radiation dose is challenging due to ethical considerations that prohibit multiple scans of a single patient, especially in the pediatric population. This ethical constraint complicates the assessment and optimization of diverse CBCT machines or imaging techniques.

An optimized imaging protocol that balances radiation dose reduction and diagnostic efficacy is recommended for orofacial patients. Nowadays, a new European project from Euratom called 'Dentomaxillofacial Pediatric Imaging: An Investigation Towards Low Dose Radiation-induced Risks Project' (DIMITRA) aims to address the concerns regarding radiation-induced risks in pediatric patients undergoing dental and maxillofacial imaging (Hedesiu et al., 2018).

In pediatric imaging, recommendations often emphasize adjustments in tube voltage (kV), tube current (mA), and voxel size (Pauwels et al., 2015). Most CBCT devices provide the flexibility to modify the aforementioned acquisition parameters. Moreover, the advancements in CBCT technology, such as the utilization of low exposure settings and narrow collimation, have contributed to the reduction of radiation dose (De Mulder et al., 2018). Historically, the Field of View (FOV) has received less attention as a parameter in CBCT optimization. However, adjusting FOV could enable a reduction in

radiation dose without compromising image quality. The ongoing evolution of modern CBCT devices is expected to introduce additional options for individual FOV selection. Consequently, Field of View adjustment could emerge as a crucial element in the optimization strategy, particularly in pediatric cases (Oenning et al., 2018).

### **1.8. Anatomical phantoms for optimizing treatment protocols in CLAP**

Surgical repair of cleft lip and palate requires a detailed understanding of the underlying anatomy, as well as the ability to adapt surgical techniques to each case. Surgeons and medical professionals involved in treating cleft lip and palate typically rely on a combination of medical imaging techniques (such as CT scans and 3D imaging) and computer simulations to plan and guide surgical interventions. These technologies allow for in-depth comprehension of the patient's unique anatomy and aid in the creation of customized treatment strategies. However, anatomical phantoms can also play a key role in general surgical training and education. Moreover, the optimization protocols of imaging techniques require commercial anthropomorphic phantoms in the treatment of dental and maxillofacial defects. While these phantoms can represent human anatomy and emit ionizing radiation similar to a real human, certain factors may affect their applicability and accuracy.

One limitation is the lack of age- and indication-specificity in these phantoms. Human anatomy and tissue characteristics can vary significantly depending on age, pathology, or specific clinical conditions. Using completely normal phantoms may not accurately reflect the specific characteristics of the patient population being imaged, such as pediatric patients with cleft lip and palate or individuals with other craniofacial malformations. This lack of specificity may limit the ability to fully assess the radiation dose and image quality for these specific patient groups (Pauwels et al., 2015).

Additionally, the composition of the phantoms, including human soft tissue, may not accurately replicate the complexities of the human anatomy. Difficulties in regulating the volume of water surrounding the phantoms can lead to unrealistic CBCT images. Moreover, the size of the mandible, skull, and body mass can influence the image quality obtained with these phantoms (Oliviera et al., 2014).

To overcome these limitations, researchers and medical professionals should aim to develop more realistic and patient-specific phantoms that consider the age, indication,



and anatomical variations relevant to the specific imaging task. Oenning et al. created the first age-specific pediatric phantoms, called DIMITRA phantoms, using Mix-D as a soft tissue equivalent material (Oenning et al., 2018). Their validation study has been conducted to assess their suitability for optimization across various CBCT units and protocols (Oenning AC 2020). Despite these advancements, as far as our knowledge extends, there are currently no age-specific pediatric anthropomorphic phantoms specifically designed to simulate individuals with orofacial clefts.

## 2. Objectives

The aim of my dissertation is to highlight the potential of CBCT imaging in enhancing the quality of treatment for children with clefts. It comprehensively examines the major developments achieved in three specific domains within the field of cleft care:

*1. To evaluate the velopharyngeal closure in cleft patients using CBCT*

The presence of clefts of the soft palate can induce velopharyngeal insufficiency resulting in abnormal speech development and possible hearing loss. Nevertheless, it is crucial to utilize suitable imaging techniques for specific treatments. The first aim of the thesis was to present an innovative technological advancement associated with CBCT that can be utilized to evaluate the movements of the soft palate as a promising diagnostic instrument for velopharyngeal insufficiency (VPI).

*2. To assess the 3D visualization, planning, and printing techniques in alveolar cleft repair*

The alveolar cleft closure is the final step of the primary surgical intervention. For its reconstruction, alveolar bone grafting is a crucial component in the comprehensive management of individuals with cleft lip and palate. To determine the required bone amount for alveolar reconstruction, understanding the alveolar cleft's architecture is essential. The second aim of the thesis was to evaluate the results and patients' burdens using a CBCT image technique with a 3D simulation technique integrated with 3D printing to enhance preoperative planning and get more valuable postoperative outcomes.

*3. To Develop CBCT technology with realistic and patient-specific pediatric cleft phantoms*

The final aim of the thesis was to develop CBCT technology to create accurate, patient-specific cleft phantoms. These phantoms served to evaluate image precision and refine CBCT protocols specifically for cleft patients, enhancing diagnostic capabilities and facilitating precise 3D surgical planning.

### **3. Evaluation of the velopharyngeal closure in cleft patients using CBCT**

The previously mentioned three major parts of the thesis are detailed from the methodological, result, and discussion points of view.

#### **3.1. Methods**

To evaluate velopharyngeal closure in cleft patients, we enrolled nine children aged between 6 and 10 years. Ethical approval was obtained from the Semmelweis University Ethical Committee (Approval Nr. 265/2019). The research included nine participants, consisting of:

- three patients with surgically managed unilateral or bilateral cleft lip and palate (UCLP or BCLP) and velopharyngeal insufficiency (VPI),
- three patients with surgically managed unilateral cleft lip and palate or cleft palate (CP) without VPI,
- three non-cleft patients forming the control group.

We used a CBCT device (CineX movie setting, NewTom VGi Evo, QR Verona, Cefla, Imola, Italy) operating at 110 kV tube voltage to acquire images using the dynamic acquisition function. The radiation process, conducted in 0.78-1.5 seconds and utilizing the default 20 frames per millisecond setting, maintained a constant value of 3 mA, an unvarying parameter of the device.

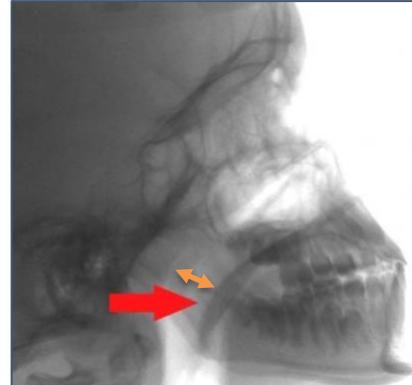
This resulted in a sequence of two-dimensional images that could be converted and played as a video. During the scans, participants were instructed to articulate the word "Coo-coo-reeh-coo," which is commonly used in speech therapy at our cleft center to evaluate velopharyngeal function.

The assessment was conducted by two separate observers, utilizing both 2D images and video. They focused on determining the soft tissue contours of the posterior pharyngeal wall, and the soft palate, and measuring the distance between these structures (Figures 2 and 3). Additionally, fiberscope measurements were carried out on the same set of patients, and these measurements were also assessed by two independent examiners. Subsequently, I conducted a statistical analysis based on the evaluations of the distance measurements. Pearson correlation and Intraclass correlation analyses were

conducted to assess the relationships and agreement, respectively, in the measured parameters.



**2. Figure** Maximum dorso-cranial elevation of soft palate and the sufficient velopharyngeal closure (red arrow). It was made by Krisztián Nagy at the Department of Face Reconstruction Centrum.



**3. Figure** The relaxed position of the soft palate (red arrow) and the distance between soft palate and posterior pharyngeal wall (orange arrow). It was made by Krisztián Nagy at the Department of Face Reconstruction Centrum.

### 3.2. Results

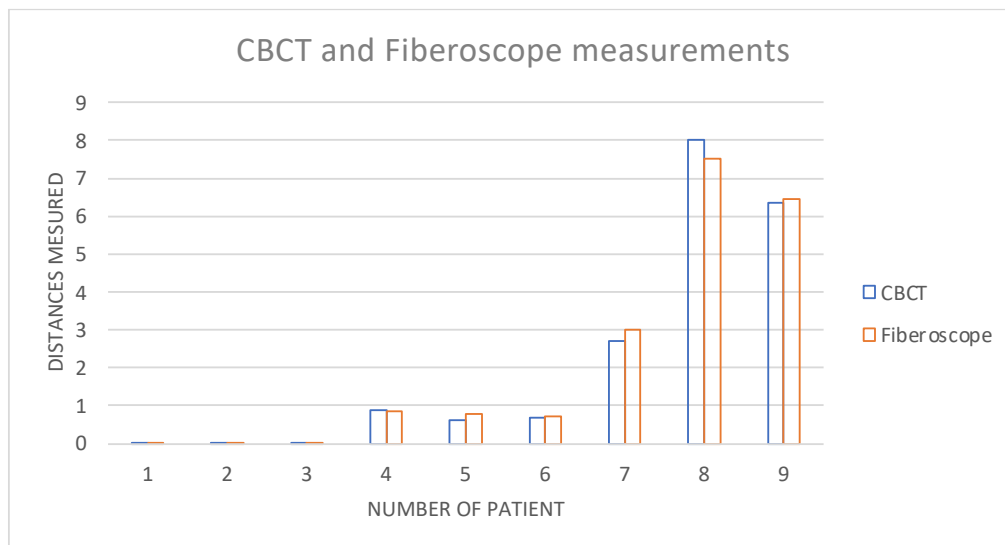
Our findings indicate that the CBCT technique is well-suited for visualizing the structures of the posterior pharyngeal wall and soft palate, as well as accurately determining the distance between them. Based on the literature data and our own prior measurements, fiberoptic examinations have consistently proven to be reliable for isolating the soft palate and posterior larynx wall. Additionally, they have demonstrated effectiveness in examining velopharyngeal function. The data obtained from both CBCT and fiberoptic measurements exhibit a positive correlation, affirming the reliability of the CBCT imaging technique. The Pearson correlation result of 0.99 is shown in Figure 4.

|                 | Observer 1<br>CBCT | Observer 2<br>CBCT | Observer 1<br>FS | Observer 2<br>FS |
|-----------------|--------------------|--------------------|------------------|------------------|
| Observer 1 CBCT | 1                  |                    |                  |                  |
| Observer 2 CBCT | 0,99554095         | 1                  |                  |                  |
| Observer 1 FS   | 0,98997952         | 0,99550094         | 1                |                  |
| Observer 2 FS   | 0,99307567         | 0,99849988         | 0,99333966       | 1                |

**2. Figure** Result of Pearson correlation between CBCT and Fiberscope measurements.

In both CBCT and fiberscope examinations, independent observers were able to discern the soft tissue structure and measure the dorso-caudal position of the soft palate and the ventro-caudal position of the pharyngeal wall (Figure 5).

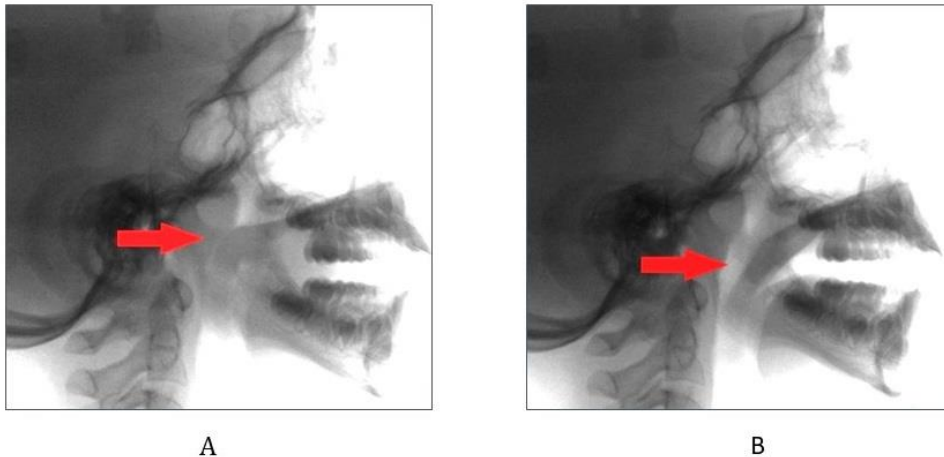
The Intraclass correlation, indicating the agreement between the two methods, was calculated as 0.99, highlighting a high level of concordance.



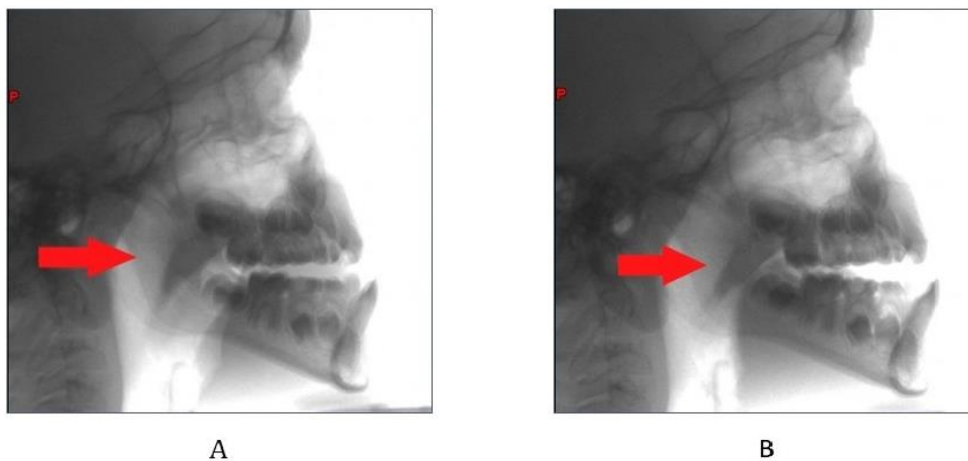
**3. Figure** Measurements of fiberscope and CBCT by two independent observers.

Moreover, CBCT is also effective in visualizing the movement of the soft palate, allowing for the distinction between dorso-cranial elevation of the soft palate and ventro-caudal descent of the posterior pharyngeal wall. In cases of control and unilateral or bilateral cleft lip and palate patients without velopharyngeal insufficiency (VPI), adequate velopharyngeal closure is observed (Figure 6). In contrast, for those with

unilateral or bilateral cleft lip and palate experiencing VPI, velopharyngeal closure is not achieved due to a short soft palate and improper functioning of the levator palati muscle (Figure 7).



**6. Figure** In the case of U/BCLP patients without VPI, the velopharyngeal closure is adequate. Red arrow shows the elevation (A) and descendent (B) of the soft palate. It was made by Krisztián Nagy at the Department of Face Reconstruction Centrum.



**7. Figure** In case of U/BCLP patients with VPI, the velopharyngeal closure is inadequate. Red arrow shows the maximum elevation (A) and descendent (B) of the soft palate. It was made by Krisztián Nagy at the Department of Face Reconstruction Centrum.

### 3.3. Discussion

Various surgical and non-surgical interventions have been introduced for the correction of velopharyngeal insufficiency (VPI). An interdisciplinary team is vital for accurate diagnosis and treatment, where a thorough examination of velopharyngeal function (VPF) plays a critical role in making informed treatment decisions. Multiple diagnostic techniques enable direct observation of velopharyngeal closure or visualization of velopharyngeal muscles.

Flexible nasopharyngoscopy is commonly employed to observe the anatomy and muscular function of the velopharynx during speech. However, its invasive technique is often poorly tolerated by younger patients (Glade and Deal, 2016).

Non-invasive diagnostic tools such as Videofluoroscopy (VFS) and Multiview fluoroscopy are commonly utilized imaging techniques using X-rays for evaluating velopharyngeal function (VPF). They enable the measurement of the structure and movement of the soft palate. However, the process of multiple image acquisitions can be time-consuming and may elevate the radiation dose, which is a concern for young patients with cleft lip and palate (CLP) who are susceptible to the effects of frequent radiographic examinations (Jacobs et al., 2017).

Dynamic magnetic resonance imaging (MRI) is a non-invasive and non-ionizing imaging technology that can address the limitations of other methods. It enables evaluation of velopharyngeal muscle function and morphology, but it may be less reliable in detecting the lateral velopharyngeal wall's motion and closure pattern. However, high costs may hinder its use for diagnosis (Fu et al., 2015).

Traditional helical CT was an initial imaging technology for identifying craniofacial deformities and pathologies, but it has limitations such as high cost, size, and an increased radiation dose. (Perry et al. 2018).

CBCT has become popular in non-invasive diagnostic imaging for dentofacial deformities, including cleft palate patients, owing to its capability to visualize three-dimensional structures (Nakajima et al., 2005). It offers detailed bone imaging with lower radiation exposure and cost, enhancing convenience and comfort for children. CBCT also enables 3D reconstruction of anatomical structures with high spatial resolution, enhancing diagnostic value (Periago et al., 2008).

Our findings demonstrate that the CineX movie setting (NewTom VGi Evo, QR Verona, Cefla, Imola, Italy) can effectively distinguish not only the soft palate and posterior pharyngeal wall but also visualize the soft palate movements and assess velopharyngeal closure. CBCT is a valuable tool for diagnosing velopharyngeal insufficiency and evaluating treatment options, such as autologous fat grafting.

#### **4. Assessment of the 3D visualization, planning, and printing techniques in alveolar cleft repair**

##### **4.1. Methods**

###### **4.1.1. Preoperative assessment of the alveolar defects**

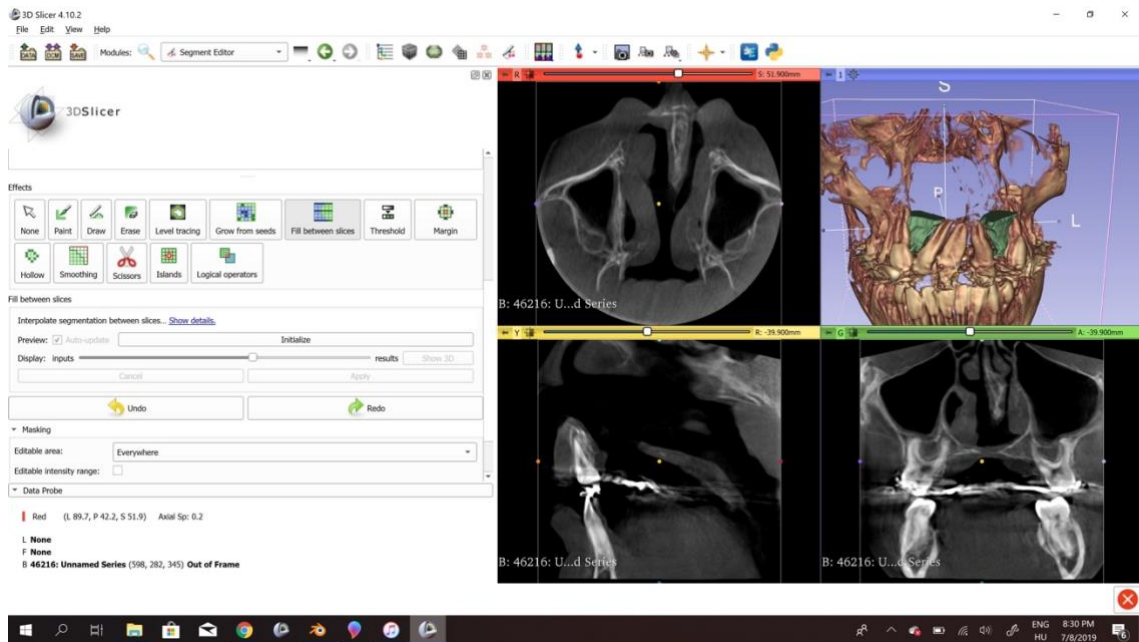
I analyzed data from cleft patients treated for alveolar cleft defects at the Cleft Center of the 1st Pediatric Department, Semmelweis University, Budapest, between September 2017 and September 2020. Each patient received treatment following consistent guidelines from the same surgeon. Preoperative assessment of the alveolar defect included an intraoral examination to confirm the proper transverse alignment between the maxillary segments and the presence of a normal upper arch form.

###### **4.1.2. Using CBCT imaging technique, 3D planning and printing**

Radiologic data from the cleft area were acquired after the decision to proceed with alveolar bone grafting. Our standard protocol included high-resolution CBCT scans of the patient's skull or, at a minimum, the entire maxilla, with the goal of minimizing radiation exposure by avoiding the use of multi-slice CT scans.



With DICOM data obtained from the cleft area, we used specific software, primarily 3D Slicer (www.slicer.org) (Kikinis et al., 2014), to segment the bony defect. This same program enabled us to design the initial shape of the nasoalveolar graft, which could be exported in STL format (Figure 8). Subsequent refinement was carried out using Meshmixer (Autodesk Inc., San Rafael, California, USA). The program completed the final shape and volume of the graft.



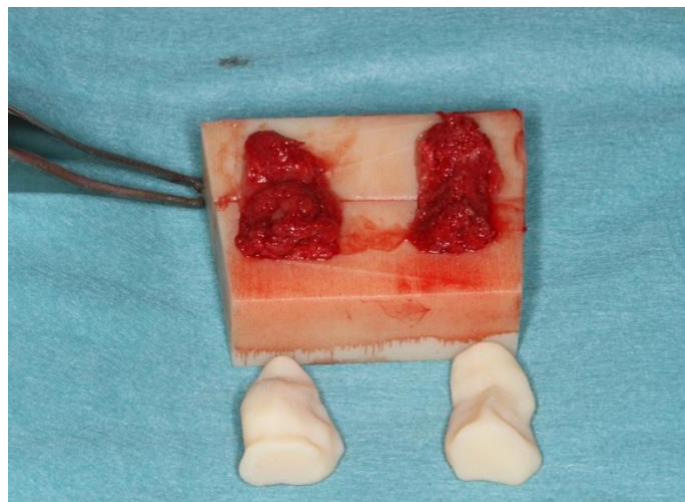
**8. Figure** Planning of the nasoalveolar graft using the Segment Editor module in 3D Slicer. On the right side the MPR and 3D reconstructions of the skull can be seen. 3D models of the grafts are shown in green.

The final step involved creating a mold using CAD software (Fábián et al., 2019), specifically Blender (Blender Foundation, Amsterdam, The Netherlands) (Figure 9).



**9. Figure** Meshmixer program completes the final shape of the graft (A), while CAD program is used to plan the mold of the graft (B).

The designed components, crucial for achieving the desired form of the nasoalveolar graft, were produced through 3D printing using biocompatible materials. We specifically utilized either Med610 resin (Stratasys, Rehovot, Israel) or NextDent Dental SG resin (NextDent B.V., Soesterberg, The Netherlands) to ensure biocompatibility and safety for medical use (Figure 10).



**10. Figure** The ultimate form of the graft precisely matched the initially planned configuration.

In the next step, we harvested autologous cancellous bone from the anterior iliac crest, as established by Boyne and Sands in 1972. This bone was then mixed with Tisseel

fibrin glue (Tisseel 2ml, Baxter, Deerfield, USA), serving to enhance the stability and integrity of the graft material.

After the graft material had properly set and conformed to the desired shape, it was meticulously removed from the mold. This formed graft was subsequently transferred and placed precisely within the cleft site. To encourage hemostasis and support the graft's integration, we inserted a collagen sponge.

#### **4.1.3. Surgical intervention and insertion of the graft**

Simultaneously, another surgical team undertook the vital task of preparing the alveolar cleft site. This involved exposing the cleft by making subperiosteal incisions along the cleft edges, ensuring careful handling of the surrounding tissues. Soft tissue within the bony cleft was meticulously removed, with special attention to preserving the integrity of the bone lamellae.

In cases where a fistula was present, additional steps were taken. The nasal floor mucoperiosteum was carefully mobilized and closed to address the fistula. Once the necessary adjustments had been made, the surgical team proceeded to close both the nasal and palatal layers. Following this, the prepared graft was skillfully inserted into the cleft site. To ensure a tensionless closure, the buccal flaps were approximated. For the final stage of intraoral mucosa closure, fast-resorbing polyglactin sutures were employed, allowing for optimal healing and minimal postoperative discomfort for the patient.

#### **4.1.4. Quality-life questionnaire**

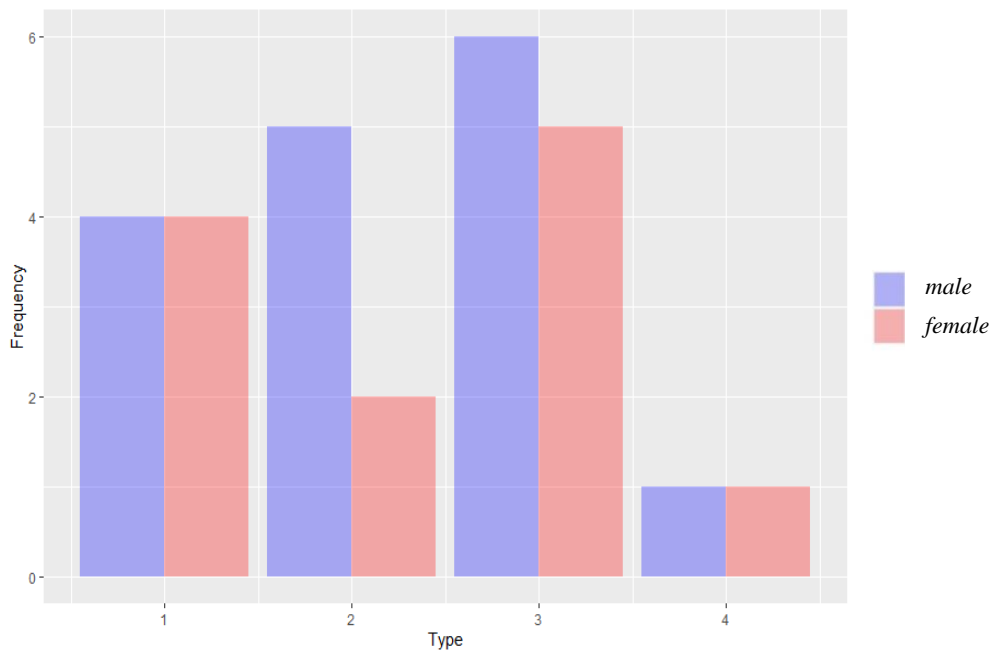
The patient self-perception following surgery was assessed using the quality-of-life questionnaire (OHQoL-U), which comprised 15 questions covering various critical aspects. These aspects included patient-reported outcomes related to wound healing, postoperative swelling, and any instances of bleeding in both the hip and oral regions. The questionnaire also delved into potential changes in weight and alterations in eating habits after the surgical intervention. To understand the postoperative experience more comprehensively, patients were further questioned about the duration of painkiller usage and whether they required additional pain relief beyond the prescribed dosage. The

questionnaire measured patient satisfaction with the surgical outcome as well, capturing valuable insights into the overall experience.

To assess the success of our surgical intervention, I compared the questionnaire data with those from five other articles in the literature. The basis for the comparison rested on the application of the same surgical technique. However, it's worth noting that the referenced articles did not employ computer-assisted surgery planning or 3D printing, unlike our approach. The collected data were analyzed and presented as mean values with standard deviation, consistent with the methodology used in all five articles. Two-way ANOVA supplemented with post hoc Tukey's tests was used to compare the questionnaire results.

## **4.2. Results**

Our results showed that all 28 patients had an average age of  $14.96 \pm 8.82$  years, with a range from 10 to 49 years. Among these patients, 13 were female (46%), and 15 were male (54%). The distribution of alveolar defects, including unilateral cleft lip and palate (UCLP) and bilateral cleft lip and palate with alveolar cleft (BCLP), is illustrated in Figure 11. As indicated by the descriptive statistics, it can be observed that the occurrence of unilateral clefts is comparable between males and females, whereas bilateral clefts are more frequently identified in males. Moreover, both lip and alveolar clefts exhibit an equal distribution across both sexes (Figure 11). However, existing literature suggests a higher prevalence of both unilateral and bilateral clefts in males compared to females, with isolated cleft lip being more common in females (Caroll and Mossey, 2012, Harville et al, 2005). The relatively limited number of cases in this study may contribute to the observed equal distribution of lip and jaw clefts as well as unilateral clefts.



**11. Figure** The gender distribution according to the types of dentofacial deficiency. 1 = unilateral cleft and lip palate (UCLP), 2 = bilateral cleft and lip palate, 3 = cleft and lip palate (CLP), 4 = gnathoschisis. The number of cases is listed on the vertical axis, whereas the type of dentofacial deficiencies is listed on the horizontal axis.

Data analysis revealed that patients required the prescribed antibiotics for an average of approximately 4 days (mean =  $3.77 \pm 1.73$ ). There were no instances of bleeding in the mouth or on the hips, and no major adverse effects leading to permanent issues were reported. Postoperatively, facial swelling lasted for an average of 5 days (mean =  $5 \pm 1.52$ ), while the wound on the hips affected mobility for an average of 8 days (mean =  $7.61 \pm 3.64$ ). Patients noted that the wound in the mouth exhibited more pronounced swelling than the one on the hip, resulting in slower healing and increased pain. Eating difficulties were reported by 19 patients (69%), and 10 patients (38%) experienced weight loss following the surgery (Table 1).

When comparing the questionnaires, our findings revealed that the surgical technique we employed is associated with less pain and a quicker recovery. Patients only require antibiotics for 4 days, which is shorter than the approximately 6 days required for other surgical techniques ( $p = 0.1$ ). Our patients were able to resume their normal physical activities within 8 days, whereas, in the literature, the average time reported was 14 days

( $p = 0.07$ ). In addition, all our patients were satisfied with the surgical intervention, while other reports reported lower satisfaction ( $p = 0.09$ ).

Currently, there is a lack of literature data available to quantify factors such as facial edema, difficulty eating, and weight loss. These outcomes play a significant role in the overall well-being and satisfaction of the patients. It is essential to consider these factors for a more comprehensive understanding of the recovery process and to ensure patient satisfaction.

*1. Table Demographic characteristics of participants*

| Variables                              | Summary of statistic<br>(mean $\pm$ SD) |
|--|---|
| Total participants (n)                 | 28                                      |
| Age (years)                            | 14.96 $\pm$ 8.82                        |
| Gender (n)                             |   |
| Female                                 | 46% (n=13)                              |
| Male                                   | 54% (n=15)                              |
| Type of the dentofacial deficiency (n) |   |
| unilateral cleft lip and palate        | 57% (n=16)                              |
| bilateral cleft lip and palate         | 43% (n=12)                              |
| Need for antibiotics (days)            | 3.77 $\pm$ 1.73                         |
| Swollen face (days)                    | 5 $\pm$ 1.52                            |
| Immobility due to the hip wound (days) | 7.61 $\pm$ 3.64                         |
| Pain was caused by                     |   |
| hip wound                              |   |
| mouth wound                            | 100% (n=28)                             |
| Wound healed more slowly               |   |
| on the hip                             |   |
| in the mouth                           | 100% (n=28)                             |
| Difficulty eating                      | 67% (n=19)                              |

|                                      |             |
|--------------------------------------|-------------|
| Loss of weight following the surgery | 38% (n=10)  |
| Recommendation of surgery            | 100% (n=28) |

### 4.3. Discussion

During the 1950-1960s, primary bone grafting was widely practiced (Eppley et al., 1996, Millard, 1980), but it was later found to have negative effects, such as restricting maxillary growth and causing malocclusion. In the 1970s, to address these issues, secondary bone grafting (SABG) was presented and became the preferred approach for treating nasoalveolar deficiency in cleft lip and palate patients (Boyne and Sands, 1972). SABG aims, during the mixed dentition phase typically between 6 to 12 years of age, to strengthen the maxillary arch and encourage the eruption of permanent teeth within the cleft area (Dempf et al., 2002). By providing increased maxillary stabilization, SABG supports proper tooth eruption (Bajaj et al., 2003), and the success of the alveolar bone grafting relies on the eruption of the canine tooth (Lilja, 2009). This technique offers several advantages, including improved support for proximal teeth, facilitating subsequent orthodontic treatment (Ochs, 1996, Waite and Kersten, 1980), preventing premature loss of teeth near the alveolar cleft, and reducing the risk of oronasal fistulae (Turvey et al. 1984, Boyne and Sands, 1972). However, the presence of permanent canines in the cleft area may interfere with dental development and result in speech abnormalities (Enemark et al., 1985). While concerns had been raised about the potential impact of Secondary Alveolar Bone Grafting (SABG) on antero-posterior and vertical maxillary growth (Uzel et al., 2019; Trotman et al., 1997), recent studies have indicated that it does not have severe negative effects on these aspects (Poleti et al., 2016).

The commonly used autogenous bone graft material for cleft defect is cancellous-marrow iliac bone, known for its successful incorporation and contribution to osteogenesis (ESegna et al., 2020). The mono-block bone graft, initially intended for alar base augmentation according to Horswell and Henderson (2003), was employed by us as a nasoalveolar graft. This choice was made due to its capability to offer suitable support to the nasal base, crucial for the precise restoration of the piriform aperture, while also addressing the alveolar cleft simultaneously. Among different sources of autografts for

alveolar osteoplasty, as suggested by Devlin et al. (2007) and Enemark et al. (2001), we advocate for the use of the iliac crest graft due to its ample volume and safety.

The bony defect's appearance varies in size and shape. In its complete form, it can also deform the piriform aperture, leading to the slumping of the alar base of the nose. The primary objectives of repairing the alveolar cleft deformity include stabilizing the maxillary dental arch, close any persistent oronasal fistulae, improving facial symmetry, supplying bone for tooth eruption, and providing the damaged nasal base (Kalaaji et al., 1999). A novel concept involves using a template to simultaneously complete the piriform aperture and fill the alveolar gap with bone graft. This innovative nasoalveolar graft can offer appropriate nasal base support, elevating the nasal base and precisely completing the piriform aperture.

Utilizing 3D virtual planning offers a unique opportunity to reduce the duration, cost, and morbidity associated with SABG surgery, while simultaneously improving the outcomes of the standard treatment (da Silva et al., 2000). Establishing standardized surgical protocols and defining essential parameters, such as image acquisition and reconstruction, are vital to ensure the effectiveness of preoperative virtual surgical planning (Linderup et al., 2015). CBCT enables the determination and interpretation of 3D anatomical lines and planes as reliable cephalometric landmarks. By integrating CBCT images with 3D planning software, it is possible to establish a reproducible and practical protocol for estimating Secondary Alveolar Bone Grafting (SABG) in patients with cleft lip and palate (CLP) (Spin-Neto et al., 2011). Accurate planning of 3D models and templates requires the identification of appropriate measurement points. Nevertheless, the segmentation protocols may affect the measurements, due to differences in the segmentation process (Fourie et al., 2012).

Using the planning method described above, it becomes possible to accurately measure the exact volume of the defect and design the desired graft shape. To secure the graft, we applied a fibrin sealant. This adhesive mixture comprises fibrinogen and fibronectin, actively promoting graft integration and facilitating the process of wound healing (Engelbrecht et al., 2013, Whitman et al., 1997).

With the assistance of CBCT technology, we obtained a detailed image of the patient's defect, allowing us to create a graft tailored to the specific requirements of the defect. Computer-assisted planning facilitates the shaping and volume control of the graft.



Our developed surgical procedure significantly reduces the time of alveolar reconstruction, employing cancellous grafts tailored to individual needs. However, the time for surgical planning is longer, thus extending the duration of the operation compared to procedures without computer-assisted help.

Various forms are available for reporting treatment outcomes from the patient's perspective. Quality of life questionnaires are recognized as reliable parameters for patient assessment (WHOQOL, 1995). In the field of maxillofacial surgery, the most commonly used questionnaires include the Oral Health Impact Profile (OHIP-14), Social Avoidance and Distress Scale (SADS), and UK Oral Health-related Quality of Life measure (OHQoL-U) (McGrath and Bedi, 2002, Al-Asfour, 2018).

In our study, we utilized a modified OHQoL-U to align with the specific auxiliary surgical technique. The structured questions enabled us to gather information on oral health, the type of maxillofacial defect, gender, pain, and recovery. The survey focused on comparing the healing of hip and mouth wounds.

The advancement of our methodology is substantiated by the results derived from the comparison of questionnaires, indicating that the intervention results in faster recovery and minimal pain. The success and ongoing refinement of the method are underscored by our most recent publication, where we utilized a particulate autogenous tooth graft and a novel split-thickness papilla curtain flap in place of an autologous hip bone.

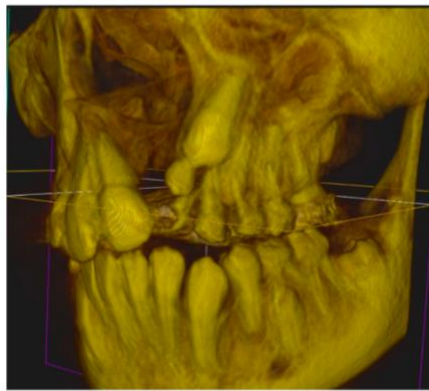
## **5. Creation of realistic and patient-specific pediatric cleft phantoms**

### **5.1. Methods**

#### **5.1.1. Natural skull selection and initial CBCT scanning**

Six pediatric skulls, ranging in age from 5 to 10 years, were obtained with the approval of the Hungarian Natural Museum (SE RKEB number: 265a/2019, Budapest, Hungary). These skulls displayed remarkably well-preserved anatomical structures. It's noteworthy that all the skulls exhibited excellent preservation of both bone and dental tissue, with no indication of large metallic restorations, dental posts, or implants.

The CBCT images of the current patient served as a reference point, facilitating the realistic planning of the cleft. We conducted initial CBCT scans of skull using the NewTom VGi evo system (NewTom, Verona, Italy) with a high-resolution protocol (Figure 12). The scanning parameters included a field of view measuring 12x8 cm and a voxel size of 0.2mm. These scans were saved in the Digital Imaging Communications in Medicine (DICOM) format for subsequent processing. The initial assessment identified the existence of dental germs, absent teeth, and mesiodens. None of the skulls exhibited substantial metal restorations or dental implants that might impact image quality through scattering.

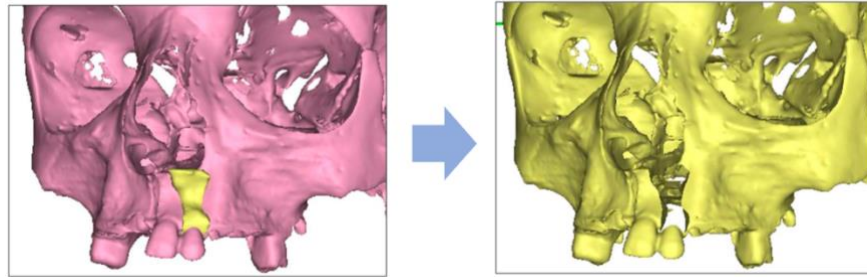


*12. Figure Initial CBCT scan of the skull (FOV: 12x8 cm, voxel size: 0,2 mm, VGI Evo, New Tom, Verona, Italy)*

### **5.1.2. Segmentation, virtual design, and creation of artificial clefts**

The CBCT DICOM files of the skulls were individually imported into Mimics® software (version 21, Materialise, Leuven, Belgium) for further analysis. The initial step involved the segmentation or volumetric reconstruction of the skeletal tissue. This was accomplished by applying predefined threshold values based on image intensity. To optimize visibility and reduce computational demands, a region of interest (ROI) was specifically cropped to encompass the maxillary area. Subsequent fine-tuning of the segmented region was performed using a variety of tools, including region growing, multiple-slice editing, and contour editing functions.

Following the segmentation process, artificial clefts were designed on the left side of the skull, considering the higher frequency of cleft occurrence on this side (Figure 13). Multiple-slice editing techniques were employed to create a virtual cleft defect that closely mirrored the clinical and radiographic images of actual patients with cleft deformities. These references served as a guiding framework for the design process, ensuring a realistic and accurate representation of the cleft defect.



**13. Figure** To create the artificial cleft, Mimics® software was used.

Next, the segmented skull and artificial cleft were saved in standard tessellation language (STL) format and imported into 3matic® software (version 14, Materialise, Leuven, Belgium) for the purpose of designing cutting guides. The aim was to replicate the pyramid-like shape of cleft defects, so two cutting guides, namely frontal and palatal,

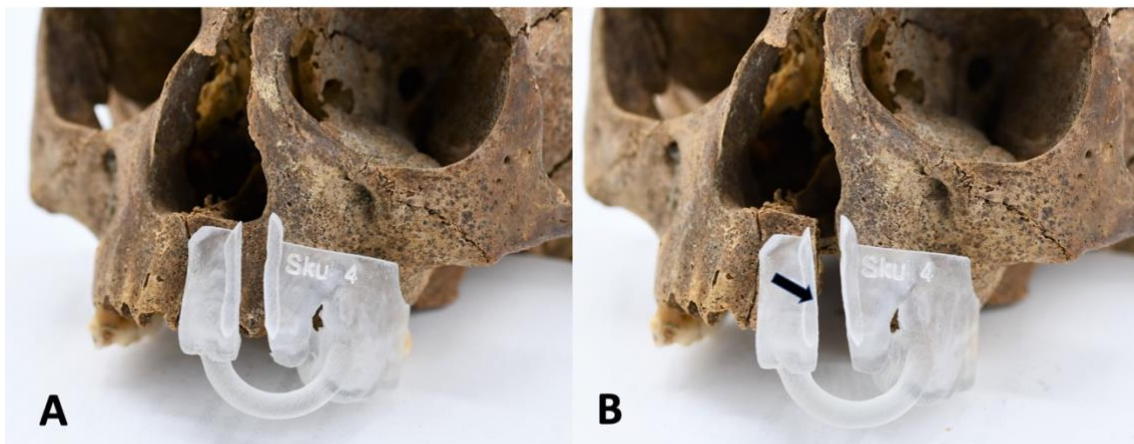


**14. Figure** Using cutting guides for the creation of the artificial skull on the previously segmented skull.

were created. To mark two distinct surfaces on the segmented artificial cleft, namely the frontal and palatal surfaces, the 'mark brush' function was used within the software. Subsequently, separate guides were designed for each of these surfaces.

The 'create a line' function was then employed to establish two cutting angles for each guide. Through a series of operations, including 'extrusion,' 'hollowing,' and 'boolean subtraction/wrap,' a solid base was formed to serve as the foundation for the cutting guides. In the case of the frontal guide, a connecting ring and rim were thoughtfully added to enhance stability during the cleft surgery. Following that we utilized an Objet30 Prime 3D printer (Stratasys, Rehovot, Israel) and employed Med610 resin (Stratasys, Rehovot, Israel) to print the cutting guides (Figure 14).

Finally, the critical surgical phase involved an experienced maxillofacial surgeon who skillfully used piezoelectric and rotating surgical instruments to create artificial clefts on the phantoms. The surgeon followed the contours outlined by the cutting guides with meticulous precision, resulting in accurate and realistic artificial clefts, as depicted in Figure 15.



*15. Figure A: before making the artificial cleft B: the arrow showed the locations of the artificial cleft.*

### **5.1.3. Skull coverage**

A soft tissue equivalent material, known as Mix-D, was prepared and applied to the cleft skulls using the method proposed by Brand et al. (Brand et al., 1989). The original recipe introduced by Jones and Raine (Jones and Raine, 1949) was utilized, which involved the following components: 500 g of Mix-D prepared in fractionated portions, including 304 g of paraffin wax, 152 g of polyethylene, 32 g of magnesium oxide, and 12 g of titanium dioxide. The addition of polyethylene was followed through mixing and melting, with an additional 20 minutes of heating.

To ensure safety during the material's preparation, manipulation, and skull coverage, a fume hood was employed. Before the application of Mix-D, the skulls were carefully covered with crepe tape (a paper with adhesive resin–rubber-based, 24 mm width; 3M, Maplewood, MN) to prevent excessive infiltration into cranial cavities and interdental spaces. Subsequently, the skulls were immersed in the melted Mix-D solution until the superior orbital arch. This immersion process was repeated multiple times until a consistent and uniform layer of Mix-D enveloped the skulls. After 24 hours, the skulls were inverted and secured at the region of the zygomatic arches. Any remaining excess material on dental surfaces or interdental spaces was meticulously removed using heated carving tools.

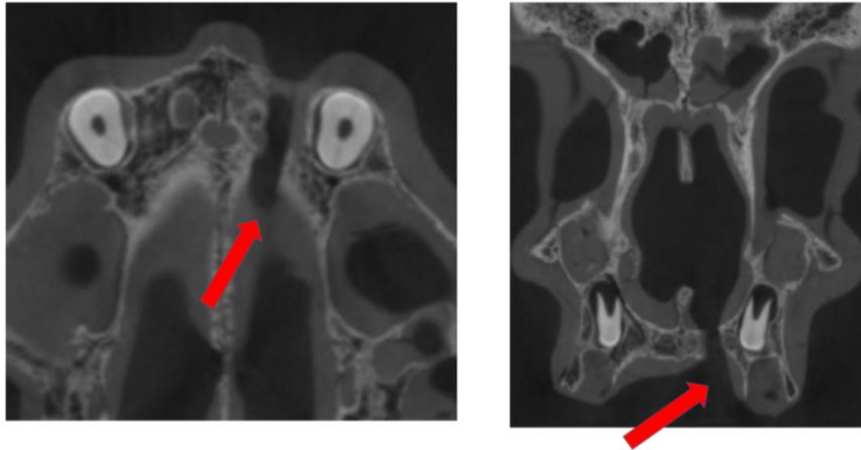
The resulting phantoms, which featured cleft skulls covered in Mix-D, were termed 'Dimicleft pediatric skull phantoms.' The entire collection was collectively named the 'Dimicleft series'.



**16. Figure** *Dimicleft pediatric skull phantom*

#### 5.1.4. CBCT scanning

The radiological quality of the Dimicleft phantoms was rigorously assessed by obtaining CBCT images using the same protocol, mirroring the initial scan conditions. To ensure objectivity and accuracy, two dentomaxillofacial radiologists conducted the evaluation (Figure 17).



**17. Figure** *The final CBCT scan with the same protocol as the initial scan condition.*

The assessment focused on several critical aspects, including the presence of any air bubbles, cracks, or inhomogeneities within the images. Additionally, the radiologists evaluated the alignment of the covering material and the lifelike appearance of the artificial clefts created on the phantoms. This comprehensive evaluation process was essential to validate the accuracy and fidelity of the phantoms in replicating clinical conditions.

Preliminary comparative measurements regarding the usage of different CBCTs have already been conducted on phantom skulls created within the Dimitra project framework (Oenning et al., 2018). The foundation for this comparison stemmed from a comprehensive article that initially compared 3 CBCT devices and 18 protocols (EzEldeen et al., 2017). The Dimitra project subsequently refined and conducted its own examination on phantom skulls. Based on the Dimitra project, we conducted a comparison of 9 protocols using 2 CBCTs on dimicleft phantoms.

## 5.2. Results

Our research demonstrated that all anatomical phantoms were successfully replicated in vivo conditions, providing optimal image quality as confirmed by radiologists. The Mix-D material effectively filled large bone cavities, such as the orbit, maxillary sinus, and nasal cavity, ensuring a seamless connection between soft tissue equivalent and bony structures. This closely resembles a real patient's CBCT scan, where both soft and hard tissues align perfectly without any gaps.

Virtual planning facilitated the precise design of an artificial cleft on the phantom, while 3D printing allowed for the creation of templates ready to be applied at the cleft site. The artificial clefts in the phantoms accurately represented the size, location, and extent of real clefts, providing essential information for surgical planning. Before actual surgeries, the entire virtual planning process, template adaptation, and surgical procedures were successfully tested on a 3D-printed Dimicleft phantom. This test confirmed the accurate fit and stability of the surgical guides and demonstrated the precision of the surgical approach.

The comparison of different CBCT protocols enabled us to determine the minimal exposure dose with optimal image quality. As a result, the ideal combination of image quality and maintaining an optimal radiation dose was achieved through high-resolution imaging with a voxel size of 0.2 mm. By adjusting the Field of View (FOV) size, we were able to enhance image quality without altering the radiation dose, tube voltage, or tube current. The highest image quality was achieved with a 12x8 cm FOV, 0.2 mm voxel size, 3 mA tube current, and 110 kV tube voltage (Figure 18).

| Protocol number                   | Machine   | Protocol name | Voxel (mm) | FOV (cm) | Rotation (°) | Tube voltage (kV) | Tube current (mA) |
|-----------------------------------|-----------|---------------|------------|----------|--------------|-------------------|-------------------|
| 1                                 | Accuitomo | Reference     | 0.125 HiFi | 10x5     | 360          | 90                | 5.0               |
| 2                                 | New Tom   | Standard mode | 0.2        | 5x5      | 360          | 110               | TCM               |
| 3                                 | New Tom   | Eco mode      | 0.2        | 5x5      | 360          | 110               | TCM               |
| 4                                 | New Tom   | Standard mode | 0.2        | 8x5      | 360          | 110               | TCM               |
| 5                                 | New Tom   | Eco mode      | 0.2        | 8x5      | 360          | 110               | TCM               |
| 6                                 | New Tom   | Standard mode | 0.2        | 10x5     | 360          | 110               | TCM               |
| 7                                 | New Tom   | Eco mode      | 0.2        | 10x5     | 360          | 110               | TCM               |
| 8                                 | New Tom   | Regular mode  | 0.2        | 12x8     | 360          | 110               | TCM               |
| 9                                 | New Tom   | Eco mode      | 0.2        | 12x8     | 360          | 110               | TCM               |
| 9 protocols x 6 skulls = 54 scans |           |               |            |          |              |                   |                   |

**18. Figure** High-resolution imaging with a voxel size of 0.2 mm, 12x8 FOV, 3 mA tube current and 110 kV tube voltage.

### 5.3. Discussion

Managing radiation dose for routine maxillofacial CBCT examinations remains a significant concern, especially when dealing with young patients and sensitive surrounding tissues, which can be more vulnerable to cellular damage (Pawels et al., 2015). Therefore, optimizing head and neck imaging for pediatric patients is of utmost importance to minimize potential risks.

An optimized imaging protocol has been suggested for orofacial patients, with a recommended sequence of diagnostic images in accordance with European guidelines, aiming to ensure justification and enhancement of imaging methodologies (De Mulder et al., 2018). By using low exposure settings and narrow collimation, radiation dose reduction and prevention of secondary malignancies have been progressively realized (Gijbels et al., 2004). Although some studies have shown that reducing tube current (mA) can still maintain acceptable image quality, there are limitations to further lowering the exposure level (Periago et al., 2008).

The issue of radiation exposure in pediatric cleft patients has become a significant concern due to the higher risk of cellular damage (Pauwels et al., 2015). Therefore, it is essential to develop specialized phantoms designed for pediatric age groups to assess and optimize CBCT image quality in individuals with cleft conditions, considering various diagnostics and treatment planning protocols. Currently, no age- and indication-specific phantoms exist, making the creation of Dimicleft pediatric skull phantoms a valuable technical report.

Dimicleft phantoms were designed to replicate realistic anatomical conditions with accurate 3D visualization. In contrast to unrealistic commercial phantoms, these skulls are derived from actual pediatric cleft patients, facilitating thorough 2D and 3D image quality assessment as well as optimization strategies. So, the Dimicleft phantoms offer an image quality in CBCT that is clinically equivalent to real patient examinations. Moreover, these phantoms were suitable for determining the optimal radiation dose, leading to a significant reduction in radiation.

Key parameters of the phantoms' soft and hard tissue-mimicking materials include the tissue's linear attenuation coefficient (LAC) for photoelectronic absorption, physical density, and effective atomic numbers (Kikinis et al., 2014). Existing phantoms often lack



the properties of one of these materials, making Dimicleft phantoms a promising alternative, effectively mimicking soft tissue with Mix-D coverage.

However, the drawback of phantom skulls is their inability to account for errors caused by the movement of child patients. Additionally, these skulls are currently designed only for one-sided clefts. Finally, the absence of cervical vertebrae, while enhancing image quality, may introduce distortions in a real-life practice. Our ongoing objective is to compare other CBCT protocols in patients with clefts.

## 6. Conclusion

The holistic management of orofacial clefts in children involves a collaborative team approach, providing personalized care from prenatal stages to completion of necessary treatments, including potential surgery, around age 22. Clinical practice guidelines (CPGs), such as those by Mink van der Molen et al. (2021), aim to enhance the care quality of cleft patients by utilizing robust scientific evidence. These guidelines ([www.agreetrust.org](http://www.agreetrust.org) as of 17 September 2021) are developed in line with established standards and are regularly updated to address knowledge gaps and guide future research for more comprehensive treatment insights (Figure 19). The CPGs encompass 11 major fields of CLP treatment: Genetic testing, Administering food, *Lip and palate surgical repair*, Hearing problems, *Hypernasality*, *Orthodontic treatment*, *Bone grafting procedure*, *Psychosocial Guidance*, Dentistry, Osteotomy versus distraction osteogenesis, and Rhinoplasty.



**19. Figure** Overview of the phases of CPGs development. (Mink van der Molen AB et al., 2021)

CBCT's utility in cleft patient care begins early in life, aiding in diagnosis. Customized palate plates can be created to prevent tongue insertion. Lip repair usually occurs around six months, with palate closure at 18 months. From age two, the focus shifts to speech therapy and dental eruption monitoring, with CBCT used only for dental issues. CBCT is pivotal during mixed and permanent dentition for orthodontics and prosthetic rehabilitation. Alveolus grafting at ages nine to twelve requires 3D CBCT. In

adolescence, CBCT guides orthodontic decisions and surgical planning. After bone growth, it's essential for orthognathic surgery. CBCT also helps assess airway volume, nasal morphology, and septum position.

Hence, for children with cleft conditions, there is a crucial need for a standardized examination protocol since CBCT covers every step of CLP treatment. This protocol should determine the ideal age for the initial CBCT examination and should comprehensively address all stages of treatment while minimizing the number of exposures.

Dinu et al revealed the value of CBCT examinations in children with cleft conditions, the optimal age for the initial CBCT exposure, and the criteria warranting a CBCT examination (Dinu et al., 2022). Their study showed that accurate evaluation and diagnosis of CLP cases undeniably depend on 3D imaging. CBCT scans before age eleven lack reliability in predicting dental issues, jaw relationships, and bone graft needs. Planning for orthognathic surgery and assessing transversal deficiencies can be postponed until after age twenty. Delaying the initial CBCT examination in cleft children until age ten, aligning with alveolar bone grafting procedures, is recommended. Nevertheless, Continual refinement of imaging protocols, coupled with ongoing research and technological progress, can continue to enhance the optimization of radiation doses in CBCT imaging for orofacial condition assessment, as noted by Periago et al (2008).

Our aim was to highlight the technical and conceptual innovations of CBCT that have the potential to significantly improve cleft patient care, especially in the areas of velopharyngeal insufficiency leading to hypernasality, bone grafting procedures with psychosocial guidance, and the development of realistic, patient-specific pediatric cleft phantoms.

### **6.1. The significance of CBCT in the evaluation of the velopharyngeal closure in cleft patients**

The thesis pointed out that CBCT imaging has emerged as a highly valuable and sophisticated diagnostic tool, revolutionizing the way soft palate movements, separable soft tissue structures, and velopharyngeal closure are visualized and assessed. This cutting-edge technology empowers surgeons and speech therapists to comprehensively

evaluate the elevation of the soft palate both before and after surgical interventions, providing critical data for informed decision-making in diagnostics and treatment planning.

The rapid and non-invasive nature of CBCT imaging confers significant advantages, not only in terms of patient comfort but also in expediting the assessment process. By swiftly capturing detailed 3D images, CBCT allows the real-time visualization of soft palate movement that can assist speech therapists in tailoring exercises for improved velopharyngeal closure and speech outcomes.

In conclusion, the integration of CBCT imaging has significantly enhanced the landscape of diagnosing and treating soft palate and velopharyngeal closure issues. Its non-invasive nature, coupled with its capacity for precise visualization, has paved the way for patient-centered care and evidence-based interventions. As this technology continues to evolve, its transformative potential will shape the future of oral and maxillofacial treatments, propelling the field toward improved patient experiences and better treatment outcomes.

## **6.2. The role of CBCT in computer-assisted surgery planning and printing in alveolar cleft repair**

Over the past three years, our dedicated team of researchers and medical professionals has been actively engaged in refining a sophisticated surgical planning and treatment process aimed at addressing alveolar defects in both unilateral and bilateral cleft patients. This cutting-edge approach combines the power of advanced imaging technology, specifically CBCT scans, with state-of-the-art 3D software simulation. By utilizing CBCT scans, we were able to obtain detailed and precise images of the patient's anatomical structures, which allowed us to create patient-specific graft molds using 3D software simulation. This personalized approach has revolutionized the way we approach bone harvesting, enabling us to perform minimally invasive procedures with the utmost precision, ensuring that only an appropriate amount of bone is harvested for each patient's unique needs.

One of the key breakthroughs in our methodology lies in the integration of 3D-manufactured graft molds and fibrin glue during the bone graft insertion process. This

innovative combination facilitated unparalleled accuracy in shaping and controlling the volume of the bone graft, resulting in enhanced outcomes and increased potential for successful graft integration. Our patients' comfort and overall experience were at the forefront of our approach. Patients who underwent this novel procedure appreciated the minimal discomfort and quick recovery, a significant departure from their expectations of a more complex surgery.

While our initial findings are promising, we recognize the importance of continuing our research to determine the long-term efficacy of this method and its impact on the integration of the bone graft. A thorough evaluation of graft success rates, functional outcomes, and the long-term stability of these grafts will contribute significantly to validating the benefits of this cutting-edge approach and its potential to improve the lives of cleft patients.

### **6.3. Innovative use of CBCT: realistic and patient-specific pediatric cleft phantoms.**

To revolutionize the application of CBCT imaging technology in pediatric cleft care, Dimicleft phantoms introduce a pioneering paradigm shift. While various optimization protocols for CBCT have been validated using different anthropomorphic phantoms, a notable gap remains – the absence of dedicated pediatric phantoms that faithfully replicate the diagnostic and treatment challenges encountered in real clinical practice.

The combination of CBCT with Dimicleft phantoms presents an opportunity to reduce radiation exposure without compromising image quality. Moreover, Dimicleft demonstrates a commitment to patient safety and the responsible use of radiological technology.

However, it's essential to acknowledge certain limitations associated with Dimicleft phantoms. One notable limitation is the absence of movement artifacts, which may differ from real patient scenarios where movement can impact image quality. Additionally, Dimicleft phantoms may primarily simulate unilateral cleft conditions, potentially affecting their applicability to bilateral cases. Understanding these aspects is crucial for a comprehensive evaluation and utilization of Dimicleft in the context of pediatric cleft care and radiological research.

In summary, the combination CBCT with Dimicleft phantoms offers multifaceted contributions to pediatric cleft care:

- Research Advancements: Using Dimicleft phantoms with CBCT in radiological research provides deep insights into cleft-related imaging intricacies, forming the principles for evidence-based guidelines and protocols that enhance overall cleft care quality.
- Individualized Treatment: Tailored phantoms facilitate the development of personalized treatment plans for pediatric cleft patients. Simulating specific anatomy and cleft conditions allows surgeons to refine approaches, leading to enhanced surgical outcomes and improved patient experiences.
- Reduced Radiation Exposure: Dimicleft phantoms play a key role in minimizing radiation exposure for pediatric cleft patients through systematic studies and CBCT protocol optimization. This ensures a safer and more responsible use of CBCT technology, particularly crucial for radiation-sensitive young patients.

Continuous Improvement: As Dimicleft phantoms with CBCT become standard in radiological research, ongoing advancements in diagnostic accuracy, treatment planning, and postoperative assessment are developed.

In summary, the introduction and utilization of Dimicleft phantoms represent a significant milestone in the field of pediatric cleft CBCT imaging. Their integration into research initiatives not only streamlines imaging protocols but also enhances the opportunities for individualized, evidence-based care stands as the cornerstone of pediatric cleft management.

## 7. Summary

In conclusion, the thesis provided a comprehensive exploration of multiple facets of cleft lip and palate (CLP) treatment, with a primary focus on harnessing the advantages of CBCT imaging. The research encompassed a wide spectrum of treatment modalities, diagnostic methodologies, and surgical strategies, all centered on leveraging the capabilities of CBCT technology. Within this framework, the thesis yielded three key outcomes:

1. *The significance of CBCT in the evaluation of the velopharyngeal closure in cleft patients*

CBCT imaging serves as a rapid, non-invasive diagnostic tool for visualizing soft palate movements and detecting velopharyngeal closure. It allows pre- and post-operative assessment of soft palate elevation, aiding surgeons and speech therapists in decision-making.

2. *The role of the 3D visualization, planning, and printing techniques in alveolar cleft repair*

We developed a surgical treatment sequence for alveolar defect reconstruction in CLP. CBCT scans guided 3D software-based graft mold preparation for minimally invasive bone harvesting. 3D manufactured graft molds with fibrin glue allowed precise bone graft insertion. Patient follow-up showed less pain and faster recovery.

3. *Novel technical innovation: realistic and patient-specific pediatric cleft phantoms*

Dimicleft phantoms provide a viable alternative for assessing image quality and optimizing CBCT protocols in pediatric cleft patients. They yield clinically equivalent images and can improve radiological guidelines in future cleft-based studies.

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## **9. Bibliography of the candidate's publications**

### **Original publications on the topic of the dissertation:**

Pálvölgyi L, Kesztyűs A, Shujaat S, Jacobs R, Nagy K. Creation of Dimicleft radiological cleft phantom skulls using reversed virtual planning technique. *Dentomaxillofac Radiol.* 2023 Oct;52(7):20230121. doi: 10.1259/dmfr.20230121. Epub 2023 Jun 22. PMID: 37395648; PMCID: PMC10552124.

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