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Evaluation of Virtual Surgical Planning Accuracy and Development of a Statistical Model for Soft Tissue Prediction in Orthognathic Surgery

PhD Program in Bioengineering and Medical-Surgical Sciences

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ABSTRACT

Background

Orthognathic surgery represents the elective method for treating dentoskeletal malocclusions, with the goal of achieving a stable and correct dental occlusion and harmonious facial aesthetics. The development of virtual surgical planning, supported by increasingly precise software, and the in-hospital production of customized devices have enabled better quality post-operative outcomes,, but discrepancies remain between preoperative predictions and postoperative results, especially in the vertical and anteroposterior directions. Furthermore, predicting soft tissue behaviour remains a critical aspect for the aesthetic evaluation of surgical outcomes.

Objectives

This study has main goals. To describe the surgical planning process carried out within the hospital structure. To quantitatively analyze the discrepancies between planned and actual postoperative skeletal movements, assessing the accuracy and clinical significance of the planning; And to study soft tissue displacement following hard tissue displacement, developing and validating a geometric-statistical model based on Partial Least Squares (PLS) regression for the three-dimensional prediction of soft tissue displacement.

Materials and Methods

The study includes 20 patients who underwent combined orthognathic surgery between October 2023 and July 2024, with a minimum follow-up period of 6 months. The morpho- functional outcome was assessed using the FACE-Q|Aesthetics© scale, a modified version of the Katsuragy scale, GAIS, and the Visual Analog Scale (VAS) for pain and aesthetics.

The clinical-surgical outcome was evaluated through comparative analysis of pre- and post- operative 3D models. Discrepancies between planning and actual results were calculated for each landmark in the three spatial directions (left-right, front-posterior, up-down) and statistically analyzed using the t-test/Wilcoxon test, Bland-Altman analysis, and Cohen's effect size. The results indicate high planning accuracy

in the latero- lateral and antero-posterior directions, with more significant errors in the vertical components, which are clinically relevant in specific anatomical areas.

Results

According to virtual planning and follow-up criteria, 13 patients were included in the study—10 females and 3 males. Patients were classified according to the type of dentoskeletal malocclusion. Twelve patients underwent bimaxillary surgery, and one underwent only a Le Fort I osteotomy. Genioplasty was performed in nearly half of the cases. Intermediate and final splints were produced and used in most procedures. No patient reported pain on palpation of the temporomandibular joints or temporal muscles; 2 reported pain in the masseter, and 9 in the pterygoid region. No severe sensory deficits were detected, although 53.9% reported paresthesia. From an aesthetic standpoint, the average satisfaction score increased from 3.8 to 8.4 (VAS), with a marked improvement in facial symmetry. The 3D data showed strong correspondence between the virtual planning and post-operative results for maxillary and mandibular advancements, with minimal bony discrepancies within clinically accepted limits.

Conclusions

For the first time, a fully digital in-hospital virtual planning protocol for orthognathic surgery has been introduced in the Maxillofacial Surgery Department of Hospital – Molinette in Turin. The establishment of the "3D Lab" facilitated effective collaboration between surgeons and engineers. This standardized workflow enables precise transfer of the virtual surgical plan and necessary tools directly to the operating room. Clinical and radiological results confirm the protocol's accuracy, reliability, and temporal stability, as well as the high aesthetic satisfaction of patients. Virtual surgical planning helps bridge the experience gap between senior and junior surgeons, standardizing clinical outcomes and providing valuable training support. Regarding the prediction of the soft tissue the results obtained in this study demonstrated the possibility of modeling soft tissue response through a statistical approach based on Partial Least Squares (PLS), applied to the residuals between geometric prediction and actual post-operative configuration. Even though it is based on a limited number of cases, the model showed consistent

behavior without overfitting, confirming the validity of the method and the robustness of the implemented alignment, normalization, and validation procedures. From a clinical perspective, the developed model represents an autonomous predictive system, capable of estimating soft tissue response based solely on preoperative bone information and planning parameters. From a clinical perspective, the developed model represents an autonomous predictive system, capable of estimating soft tissue response based solely on preoperative bone information and planning parameters.

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1. Introduction

This first chapter aims to briefly present the general principles on which orthognathic surgery is based and to analyse dentoskeletal malocclusions at a clinical, functional and aesthetic level, exposing the pathological problems that derive from them and the specific corrective treatment applied.

1.1 Principles of Orthognathic Surgery

Orthognathic surgery is a maxillofacial surgical method that deals with the treatment of dento-skeletal deformities in which orthodontic therapy alone is not sufficient to resolve the pathological picture. Specifically, the treatment involves osteotomy of the maxillary and/or mandibular bone to modify its positions in the three planes of space, thus giving the patient a stable and functional clinical result over time.

1.2 Classification of Dentoskeletal Malocclusion

Dentoskeletal malformations are alterations in which the dental elements and the bones that support them (maxillary bone and mandibular bone) do not relate to each other in the correct position during bite closure, thus causing functional and aesthetic problems with serious clinical-pathological consequences.

This is a complex pathology that requires the integration of the orthodontic discipline and maxillofacial orthognathic surgery in order to carry out an adequate and specific diagnostic-therapeutic path for each patient.

If left untreated, malocclusions lead to the development of serious joint and functional problems, compromising normal chewing, swallowing, breathing and systemic activities.

Incorrect dental alignment makes chewing difficult with digestive repercussions, while open

bite favors the onset of atypical swallowing characterized by the presence of the tongue in an altered position during the act itself.[1]

The ATM, in addition to undergoing ankylosis with a significant reduction in the oral opening caused by premature joint wear, can develop tension and joint pain manifested by headaches and neck pain.[2] Finally, always at a locoregional level, malocclusion favors snoring and nocturnal oral breathing with the mouth open.

The systemic repercussions concern sleep-related problems such as snoring and sleep apnea (OSA), as well as difficulties in ensuring correct oral hygiene with the development of gingivitis and periodontitis. [3]

Therefore, the treatment of malocclusions is essential to prevent and/or treat chewing function and oral hygiene, as well as breathing, good sleep and facial aesthetics.

The diagnosis of dentoskeletal malocclusions requires a careful clinical examination where the face, dental arches, dental occlusion and oral functions such as chewing, swallowing and phonation are evaluated in order. This is followed by radiographic analyses such as panoramic and cephalometric radiographs as well as the acquisition of volumetric craniofacial CT scans and oral scans. Thanks to these examinations it is possible to obtain a complete virtual visualization of the dental arches and the facial skeletal profile to quantify whether the anomalies are of a dental, skeletal or both nature.

Finally, it is important to integrate the evaluation of the temporomandibular joint and the masticatory muscles to study the presence/absence of functional defects that generate pain and tension.

An analysis of the parameters used to classify malocclusions follows.

Molar ratio

E. Angle defining the “classification of dentoskeletal malocclusions”, still in use, through the study of the occlusal relationship between the upper first molar and the lower first molar:

1. Class I molar relationship: the mesiovestibular cusp of the upper first molar occludes in the central sulcus of the lower first molar. This is the correct dental occlusion relationship.
2. Class II molar relationship: the mesiovestibular cusp of the upper first molar occludes anteriorly to the lower first molar. The causes of this condition can be (1) over-developed maxilla, (2) under-developed mandible or (3) a combination of both.
3. Class III molar relationship: the mesiovestibular cusp of the upper first molar occludes posteriorly to the lower first molar. The causes of this condition may be (1) underdeveloped jaw, (2) overdeveloped jaw, or (3) a combination of both.

Overbite and overjet

The overjet is the distance between the two incisor edges, upper and lower, on the sagittal plane. The normal value is about 1,5-2mm. The overbite is the overlapping of the incised edges, upper and lower, on the vertical plane. The normal value is about 1,5-2mm (Figure 1).

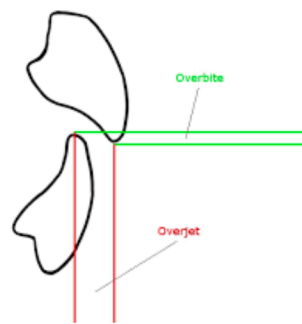


Figure 1. Overbite and overjet

Deep bite

Deep bite is a type of malocclusion in which the upper incisors overlap (“cover”) the lower incisors excessively. Specifically, the overbite is significantly greater than its normal value, reaching 3-4 mm (Figure 2).

Open bite

It represents a type of malocclusion in which there is an absence of coverage and contact between the incisors of the upper and lower jaw when the mouth is closed. At the same time, the molars, or in general the posterior teeth of the dental arch, touch each other. In particular, the overbite has a value lower than 1,5 mm up to being negative (lower than 0 mm) in the most serious conditions (Figure 2).

Cross bite

Pathological condition in which the upper teeth do not properly overlap the lower teeth during mouth closure. Cross bite can be unilateral or bilateral and two types are described:

1. Anterior cross bite, in which the lower front teeth protrude forward compared to the upper front teeth.
2. Lateral cross bite, in which the upper back teeth (premolars and molars) are located inside the corresponding lower teeth (Figure 2).



Figure 2. Deep bite, Open bite and Crossbite

Classification of dentoskeletal malocclusion

Thanks to the study of the molar relationship, the “classification of dentoskeletal malformations” by E. H. Angle is obtained, proposed for the first time in 1899 and still used in the orthosurgical field (Figure 3):

1. First class (class I): the relationship between molars is correct but it is possible to

have dental overcrowding, open bite or deep bite

2. Second class (class II): the first upper molar is anterior to the first lower molar. It includes in turn:

a. 1st Division with increased overjet (over 5mm). Characteristic is the “horizontization” of the upper incisors with respect to the lower ones (dystocclusion) in association with a mandibular retrogenia.

b. 2nd Division with deep bite. Typically manifests with a retroclination of the upper central incisors and is associated with the “short face syndrome”

3. Third class (class III): the first upper molar is posterior to the first lower molar [4]

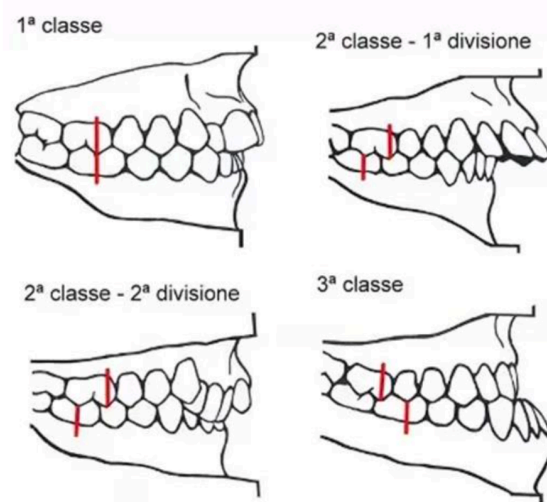


Figure 3. Classification of dentoskeletal malocclusion

1.3 Correction of dentoskeletal defects

Surgical treatment involves the single or combined execution of the techniques described below in order to obtain an optimal result. The type of malocclusion the patient is affected by, the morphological characteristics of the bone, any associated co-pathologies and finally the possible co-interventions on the temporomandibular joint are necessary elements to decide the surgical technique (Le Fort I and/or BSSO and/or Genioplasty) and the approach used (Maxilla-first or Mandible-first).

1.3.1 Le Fort I

Le Fort I osteotomy is a surgery technique used by maxillofacial surgeons to correct malocclusion and maxillomandibular deformities. Maxillary repositioning is guaranteed by the fact that this operation allows movement on all three planes of space. Before performing the osteotomy it is necessary proper orthodontic preparation should be completed so that a correct occlusion can be established.

This surgical procedure takes its name from the horizontal fracture pattern described by Rene LeFort in 1901: the fracture line passes through the lower part of the nasal septum, along the pyriform aperture and continues onto the anterior wall of the maxilla, the pterygomaxillary suture and the pterygoid processes (Figure 4).

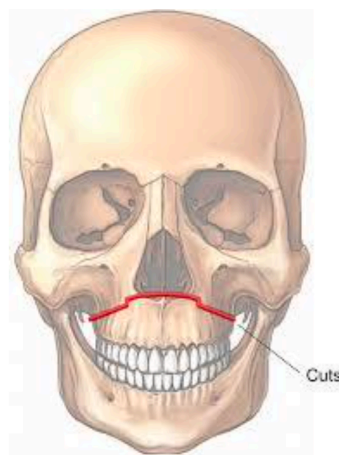


Figure 4. Le FORT I Osteotomy

The first LeFort I osteotomy performed for the correction of dentofacial deformities was described in 1921 by Wassmund and, over time, the technique has continued to evolve confirming its reliability, predictability and safety [5-6]. These principles are further supported by today's virtual surgical planning. [7]

The aim of the method is therefore to realign the jaw with the facial midline, to correct the inclination and to allow bone advancement. Applying the concepts to clinical practice, in class III malocclusions, where maxillary hypoplasia is frequently associated, performing a LeFort I osteotomy with maxillary advancement represents

the standard therapy. While in class II malocclusions, in which mandibular retrognathism is pathognomonic, LeFort I osteotomy, with maxillary repositioning, and mandibular advancement surgery together with genioplasty will constitute the standard treatment in order to obtain a stable aesthetic appearance.

LeFort I osteotomy can be used in combination with Bilateral Sagittal Split Osteotomy (BSSO) to correct secondary maxillary defects observed in asymmetric mandibular deformities.

According to Swennen's treatise, today it is possible to perform the minimally invasive LeFort I osteotomy in 10 precise steps [8].

The procedure is performed under general anesthesia and to control the occlusion more safely, nasotracheal intubation is necessary. It begins by retracting the upper lip thanks to a double soft tissue hook that is applied at the level of the mucosal midline of the lip itself.

The mucosa of the upper lip is first incised from the left upper lateral incisor to the right one, then the deep layers of the soft tissues down to the bone.

The incision of the deep layer is performed from left to right approximately at the level of the nasal base. This is followed by a subperiosteal dissection of the medial pillar of the right maxilla and detachment of the nasal mucosa in the inner part of the right lateral nasal wall.

The procedure is performed again on the contralateral portion of the maxilla.

The nasal mucosa of the nasal floor is removed and a thin U-shaped osteotome is inserted at the level of the septum, just above the anterior nasal spine: tapping the instrument completely releases the septum, which is separated from the nasal floor and the maxilla [8].

The osteotomy is then performed: the cut extends from the lateral maxillary pillar to the medial maxillary pillar, along the piriform border, at the level of the left hemimaxilla. The osteotomy is then performed again mirror-image on the contralateral side.

Once the bilateral osteotomies are completed, the lateral maxillary pillar can be "cut back" in a medio-lateral direction. The lateral nasal osteotomies are completed with a small chisel.

The pterygomaxillary junction is then separated using a large curved osteotome and, placing a finger intraorally, gentle digital pressure is applied, completing the maxillary fracture.

Excessive force is not required at this stage if all osteotomies have been completed correctly. At this point it is possible to mobilize the osteotomized jaw. [9]

1.3.2 Bilateral Sagittal Split Osteotomy

Bilateral sagittal osteotomy (BSSO) is an orthognathic surgical procedure performed to either advance or retract the mandible as needed. It was first described by Schuchardt where three osteotomies were used with the goal of weakening the bone for controlled splitting in the sagittal plane guided by a chisel [10].

In 1957 Trauner and Obwegeser improved the previous surgical technique calling this new variant “vertical splitting of the ascending ramus” [11].

The main advantage was the facilitation of bone healing (Figure 5).

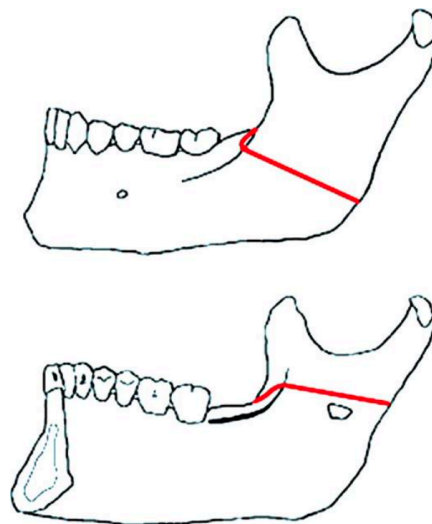


Figure 5. BSSO Osteotomy

This technique involves an incision of the mucosa and periosteum through the mouth followed by an initial horizontal cut on the lateral surface of the mandibular bone.

Subsequently, a second cut is made on the medial surface of the ramus, immediately below the mandibular notch. Both notches are connected by a third and final incision that is almost vertical and parallel to the mandibular ramus. At this point, the two segments can be divided using an osteotome [12].

Depending on the defect to be treated, in case of correction of mandibular prognathism, the distal segment is moved back, while in case of correction of mandibular retrognathia, the distal segment is moved forward.

The procedure ends with a bone suture to maintain the correction. It is important to ensure complete mobilization of the proximal fragment to guarantee better control of the fragments at the time of fixation and to reduce the risk of injury to the inferior alveolar neurovascular bundle.

Obwegeser then revolutionized oral and maxillofacial surgery by introducing BSSO as a standardized and safe procedure, which is performed worldwide to this day in the manner originally described.[13]

In 1958 the Italian surgeon Dal Pont made a further evolutionary change by advancing the horizontal incision from the lateral face of the mandibular ramus to the lateral face of the body of the mandible (Figure 6): in this way a vertical cut is made between the first and second molar [14] .

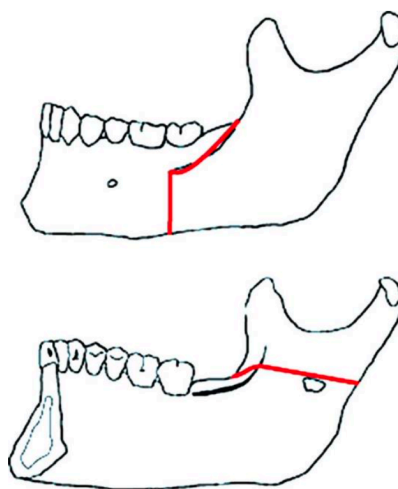


Figure 6. BSSO Osteotomy Modified by Dal Pont

The modification described by Hunsuck in 1967 illustrates a horizontal lingual osteotomy through the cortical bone above the lingula "at the confluence of the temporal crest and the crest of the mandibular neck" ending "above the mandibular foramen". [15]

A final refinement was made by Epker in 1977 (Figure 7, 8): he emphasized the requirement for a complete osteotomy of the lower mandibular cortex with the vertical cut to reduce the risk of unwanted fracture patterns during division [16].

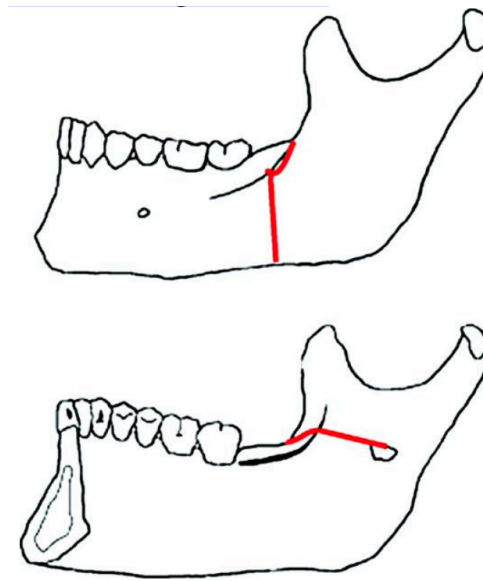
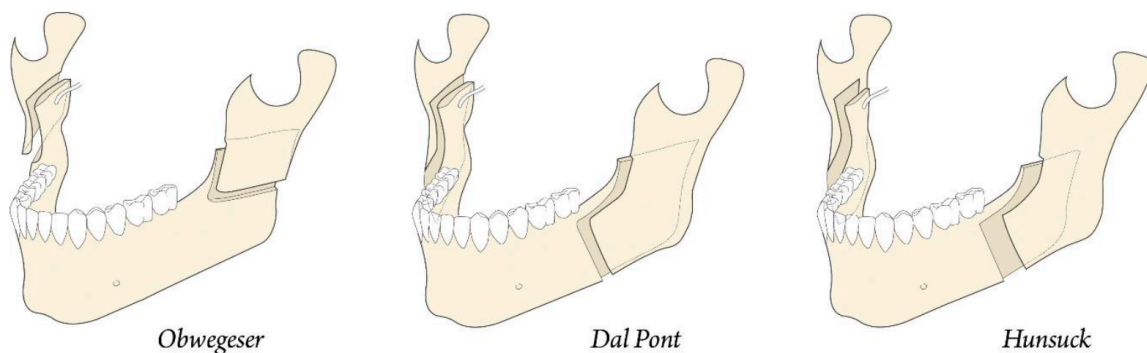


Figure 7-8. BSSO Osteotomy Modified by Epker

Modifications to the methodology made over time have been introduced with the aim of improving surgical convenience, minimizing morbidity and maximizing stability.



1.3.3 Bimaxillary surgery: maxilla-first and mandible-first approach

Bimaxillary orthognathic surgery is widely used to correct dentoskeletal deformities. Since dentoskeletal anomalies frequently involve alterations in both maxillae, it is preferable to perform Le Fort I osteotomy in combination with Bilateral Sagittal Split Osteotomy.

Starting in the mid-1970s, maxillofacial surgeons began to study the differences in surgical sequences to try to establish which was the best approach for the operation (maxilla-first or mandible-first). The surgical sequence is still a matter of debate today, which is why universally accepted guidelines and consensus are still lacking. Specifically, the introduction of rigid internal fixation (RIF) has raised numerous questions about which was the most appropriate osteotomic sequence.[17]

What is beyond doubt is that the decision as to which maxilla to operate first must be made at the time of surgical planning.[18]

According to the maxilla-first approach, after performing the Le Fort I osteotomy, the maxillary bone is figuratively joined to the mandibular bone thanks to the intermediate occlusal splint and the rigid intermaxillary block (BRI). Thanks to this step, the maxilla is relocated to the correct position foreseen by the VSP and fixed with the custom made plates and the fixing screws.

At this point the BRI is removed and the BSSO is performed: the mobile distal segment of the mandible is also repositioned using both the final occlusal splint and the rigid intermaxillary block. The mandible is then osteosynthesized with plates and screws.

The second approach is the mandible-first. In this case, the BSSO is performed first using the rigid internal fixation (RIF); the intermediate occlusal splint allows the repositioning of the mandibular bone using the maxilla as a reference guide. This is followed by the repositioning of the maxillary bone by performing the Le Fort I osteotomy and using the final occlusal splint.

The traditionally used sequence is maxilla-first and its main indications are:

1. Clockwise rotation of the maxilla;

2. The monoblock Le Fort I osteotomy;
3. RIF non feasible;
4. Small maxillo-mandibular advancements.[18]

However, the mandible-first approach is preferable in three specific conditions:

1. Downgrafting of the posterior maxilla, in which it is planned to reposition the posterior maxilla inferiorly;
2. Fragility of the upper jaw bone;
3. Concomitant surgery on the temporomandibular joint (ATM). [19]

It is assumed that the size of the defect to be treated (small/large sagittal movements), the direction of rotation of the maxillomandibular complex (clockwise or counterclockwise) and the need for maxillary segmentations are important deciding factors in the choice of the surgical sequence.

There is therefore no significant difference in surgical accuracy between the two approaches.

Therefore, the choice of the sequence should be based on patient-specific factors rather than on a presumed advantage of one method over the other. [20]

Within the thesis work, the bimaxillary surgical interventions to which the patients were subjected were therefore divided according to the approach used: maxilla-first or mandible- first.

1.3.4 Genioplasty

Genioplasty is a surgical procedure performed to correct chin abnormalities: it involves performing an osteotomy in the chin region of the mandibular bone that alters its three- dimensional position, restoring the general balance of the face. The isolated bone fragment can be translated and rotated in space, in order to place it in the desired position.

The chin region has an important significance in facial aesthetics, in fact its morphological characteristics contribute to the perceived “human character”: a retruded chin is more typically associated with feminine aesthetic traits, while a

prominent chin is properly related to masculine traits. It is understandable how the chin plays a fundamental role in defining the facial characteristics associated with gender. [21]

The first genioplasty was performed in 1942 by Hofer using an extraoral submental approach: the horizontal incision was made just posterior to the submental fold so as to avoid the presence of any visible scar after the operation. [22]

About fifteen years later, in 1957, Trauner and Obwegesser made some changes: the surgical approach became intraoral.[22]

The incision was made at the level of the anterior labial sulcus (Figure 9a) and, through mucoperiosteal dissection along the midline of the mandibular bone, the mental nerve was first identified and then the bone itself was reached (Figure 9b).

It is essential not to cut the mental nerve in order not to lose sensitivity at the level of the chin, lower lip and anterior gingiva.

At this point, the surgeon marks the midline directly on the bone, creates small holes along the planned osteotomy line and performs the incision with the cutting instrument starting from the central point and proceeding laterally. [23]



Figure 9.ab

Depending on the movement that you want to impose on the chin, you need to plan the angle of the osteotomy correctly as it affects the repositioning of the segment (Figure 10).

The mental fragment is then fixed to the mandible using standard miniplates as a means of synthesis, modeled directly in the operating room following the patient's anatomy and combined with screws (Figure 11).

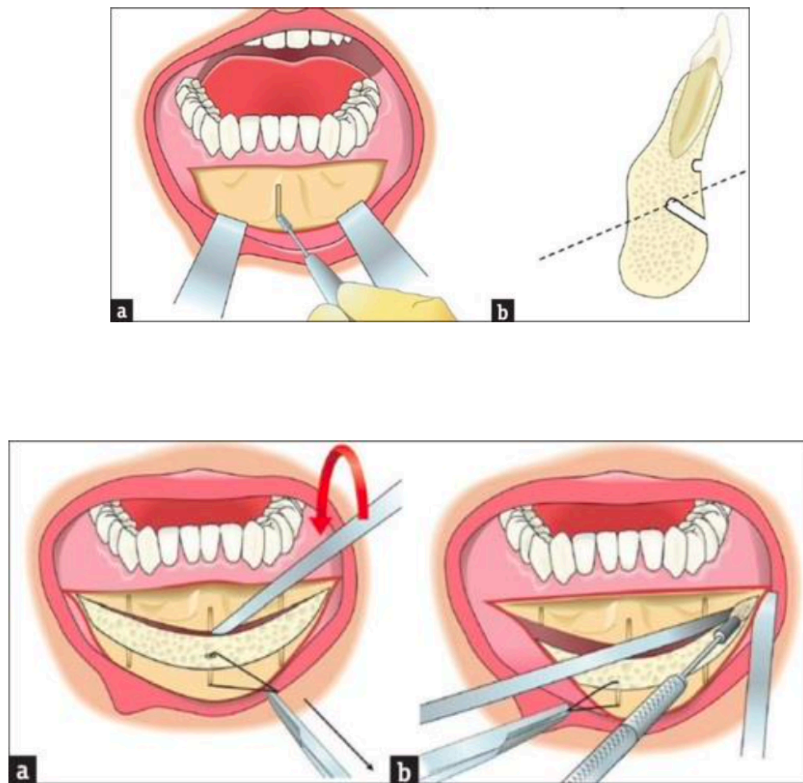


Figure 11-12.ab

Nowadays, alternatively, it is possible to use both cutting guides and patient-specific synthesis devices made with additive manufacturing technology using CT scan data and CAD/CAM technology. [24]. In particular, the creation of genioplasties with custom-made surgical guides produced by 3D printing technology improves predictability and accuracy, providing safer results. [25]

The reason for these statements is that custom-made cutting guides allow for the safe and precise identification of the correct direction of bone resection to be performed for the specific clinical case.

Advances in virtual surgical planning and CAD/CAM technologies will continue to provide reliable solutions to ensure the correct position of the chin and a good aesthetic result.

1.4 Traditional surgical planning (TSP) and its limitations

Traditional surgical planning has been a widely used system in orthognathic surgery to treat dentoskeletal malocclusions. In order to study the individual clinical case and intervene surgically, it was necessary to acquire clinical evaluations together with photographs of the patient's face, two-dimensional (2D) radiographs (Figure 13) and build plaster models (Figure 14-15). [26]

The steps therefore included an accurate clinical evaluation of the face integrated with frontal, profile and three-quarter photographs both at rest and with a smile to best define the type of facial dysmorphism present.

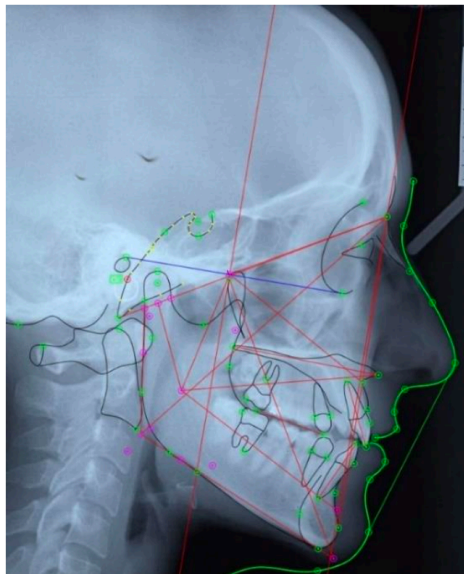


Figure 13.Cephalometrics 2-D

To all this it was necessary to add radiographic evaluations through teleradiography, cephalometry and dental panoramics. Through the study of the images, the bone and dental points are traced to define the cephalometric tracings: it is clear how the localizations obtained with these methods were rougher and less precise than the points currently acquired with modern radiological techniques (cranial-facial CT and oral scanner). In any case, the final aim of the work was to obtain a quantitative analysis of the occlusal relationships between the maxillary and mandibular bones.



Figura 14. Semi-adjustable articulator



Figura 15. Anatomical articulator

Subsequently, impressions of the maxillary and mandibular arches were taken to create plaster models, which in turn were mounted on an anatomical and/or semi-adjustable joint to study the more complex combined interventions (Figure 14, 15).

[27]. On the plaster models it was possible to study the shape and characteristics of the intermediate and final splints in order to ensure the best oral occlusion.

Despite its widespread use, important limitations have been observed over time, first of all the occurrence of errors given the complexity of preoperative preparation and the presence of numerous steps between the hospital department and industrial laboratories for the manufacture of the materials necessary for the intervention. [28]

The errors at the end of the surgical procedure were the result of the sum of small, numerous and hidden errors that arose during traditional planning, including the imprecision of the cephalometric points obtained from the x-rays, the preoperative study of the “raw” operation on the plaster models, the extra-hospital production of the materials (splints, plates) and the long correspondence between the surgeon and

the engineer in the planning and preparation phase of the materials necessary for the operation. In addition, the lack of control in the third dimension and the absence of evaluation of the changes in position of the temporomandibular joint were denounced. [29]

Not to mention the fact that there were intrinsic intraoperative errors that did not depend on traditional planning. In order to reduce errors and improve treatment planning and outcome, “virtual surgical planning” was introduced.

1.5 3D printing in CMF

This chapter aims to present the historical evolution and subsequent use in the surgical field of new available technologies such as 3D printing and CAD/CAM system. These are virtual surgical planning aids that have been developed and implemented over time within the department due to their multiple advantages compared to traditional planning.[30-31]

Virtual planning and 3D printing have improved not only the ability to visualize complex cranial anatomy, allowing for the simulation and execution of correct bone movements, but also the ability to create precise splints, plates, and cutting guides [32].

3D printing is a technology born in the 80s, precisely in 1983, thanks to the contribution of Chuck Hull: the purpose of this technology is the creation of physical objects starting from a virtual 3D image obtained thanks to radiological methods such as CT or MRI.

The principle of rapid prototyping is to use 3D computer models for reconstruction of a 3D physical model by the addition of material layers [33]. With additive fabrication, the machine reads in data from a CAD drawing and lays down successive layers of liquid, powder, or the sheet material, and in this way builds up the model from a

series of cross sections. These layers, which correspond to the virtual cross section from the CAD model joined.

Stereolithography (SLA) is the oldest 3D printing technique but nowadays is still widely used thanks to excellent surface details obtained. SLA uses photopolymers that can be cured by UV laser beams which are guided according to the CAD cross-sectional data (Figure 16). In Maxillofacial surgery SLA technique is used to create cutting guides and anatomical models as a support tool in the operating room.

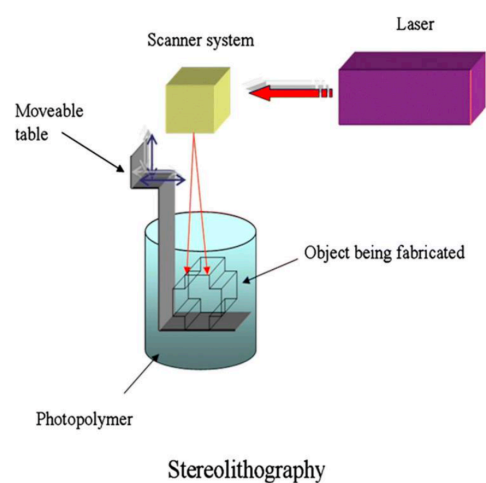
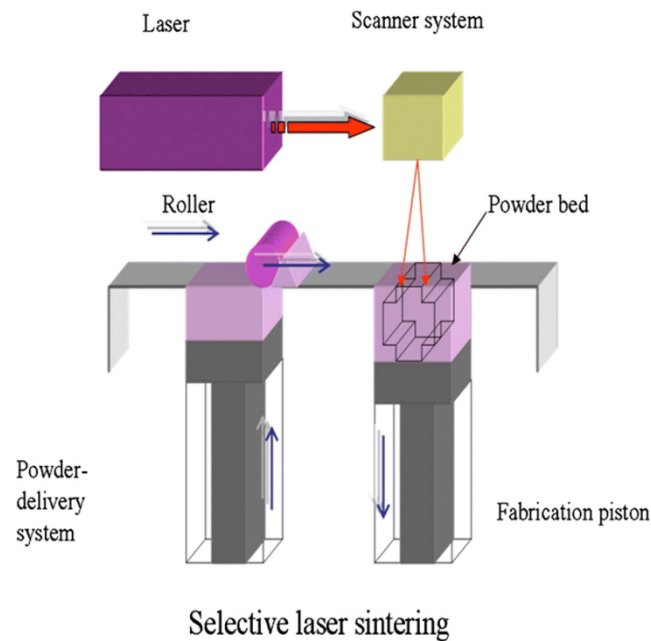


Figure 16. Schematic representation of the stereolithography (SLA) system.

Selective Laser Sintering (SLS) is strongly used for creating bone tissue engineering constructs for sites such as the temporomandibular joint: it consists of small particles of thermoplastic, metal, ceramics or glass powders that are fused by a high power laser. Based on this process, any powdered biomaterial that will fuse but not decompose under a laser beam can be used to fabricate scaffolds by SLS (Figure 17).

Figure 17. Scheme of selective laser sintering (SLS) technique.

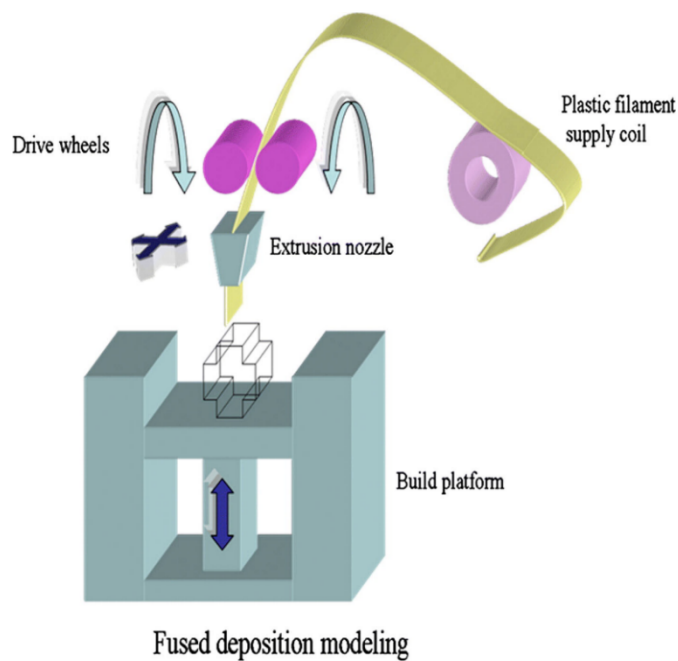


In the final analysis the Fused Deposition Modeling (FDM) process forms objects by operating the extrusion small beads of fused thermoplastic material that immediately bond to the layer below.

The head extrudes the semiliquid state thermoplastic polymer in ultrathin layers precisely into place. The extruded material solidifies and adheres to the preceding layer.

In Maxillofacial surgery, FDM technology is typically used too print anatomical replicas, prototypes of cutting guide, and in generale all devices supporting programming and not used in the operating room[34] .

Figure 18. Scheme of the fused deposition modeling (FDM) system.



Thus, thanks to the combined use of 3D printing with CT images, the digital environment has been greatly improved: its application is in fact widely exploited in the surgical field and, in our case, at the level of maxillofacial surgery in the orthognathic field.

The result obtained is a 3D computerized composite image of the skull, including the occlusion, which is the basis of virtual planning of orthognathic surgery.

3D objects can be produced based on CT (Computed Tomography) or MRI (Magnetic Resonance Imaging) volumetric medical images according to precise steps which will be analyzed in the subchapter“Workflow”.

1.6 On-site VSP and 3D printing in CMF

In recent years, surgeons have begun to adopt CAD/CAM systems as an aid in the planning and execution of complex surgical procedures. As the name suggests, CAD/CAM software is used for the design and fabrication of prototypes or finished products, such as anatomical replicas or surgical devices.

The main disadvantages of adopting this system are costs, delivery times, and difficulties in communication between the medical team and the company. To overcome these issues, the first in-house laboratories have been established, fostering close collaboration between surgeons and engineers and making use of low-cost 3D printers thanks to technological development and their widespread adoption, particularly FDM technology. As introduced in the previous section, the choice of printing technology and material is closely related to the intended application, with associated advantages and disadvantages such as accuracy, mechanical strength, and material properties (e.g., biocompatibility, sterilizability, transparency).

Among the many advantages of the CAD/CAM method, it is important to mention the reduction in operative time and the increase in effectiveness and precision of the surgical outcome compared to conventional methods [35]. These advantages are maintained and further enhanced with an in-house approach, in which the surgeon has the opportunity to work and collaborate with a team of engineers to develop patient-specific devices that also take into account the surgeon's habits and the instruments used during the procedure. As reported in a study by Legocki et al. [36], with the necessary know-how and one or more 3D printers available, it is possible to manufacture medical devices tailored to the patient's anatomy at a lower cost than professionally produced ones, with greater benefits in terms of customization. The same study also demonstrated a cost advantage in the production of anatomical 3D models, comparing in-house manufacturing costs with those of commercial providers.

Overall, the in-house approach, with the ability to visualize the virtual 3D model and to have access to the printed object at a low production cost, represents a valuable tool for learning and information exchange. Planning is an effective method for teaching both technical and non-technical skills in a safe environment. The virtual model allows junior, less experienced surgeons to easily simulate the procedure by following a virtual guide and to share the decision-making process and surgical indications with senior surgeons during virtual planning.

Concerning craniofacial dysmorphoses, such as retrognathism and prognathism, are clinically significant conditions as they can cause both functional impairments—affecting mastication, respiration, and phonation—and aesthetic alterations, leading to a considerable impact on patients' quality of life. Orthognathic surgery currently represents the main treatment option for these conditions, as it enables the three-dimensional repositioning of skeletal structures to restore occlusal balance and facial harmony [33].

In recent years, the introduction of Virtual Surgical Planning (VSP) has marked a major advancement in maxillofacial surgery. This approach allows the surgeon to simulate skeletal movements in a three-dimensional environment, optimize the sequence of surgical manoeuvres, and design patient-specific guides through rapid prototyping techniques [37].

Numerous studies have demonstrated that VSP improves the predictability and precision of surgical procedures, while reducing operative time and enhancing procedural reliability [336-37].

However, despite these technological advances, a discrepancy still exists between the planned and the actual postoperative skeletal positions. These differences are often more pronounced along the vertical and anteroposterior directions and may be attributed to intraoperative variability, osteotomy complexity, or limitations of predictive models [37].

Another critical aspect concerns the prediction of soft tissue behavior, which plays a central role in determining the final aesthetic outcome. Unlike hard tissues, soft tissues exhibit complex mechanical properties influenced by individual factors such

as elasticity, skin thickness, and muscle tension. Consequently, their response to skeletal displacements is neither linear nor uniform. Current models implemented in clinical software tend to underestimate changes in delicate areas such as the upper lip, nose, and chin, leading to systematic errors that reduce the accuracy of aesthetic simulations [37].

Recently, alongside advances in biomechanical modeling, more sophisticated statistical and computational approaches have been introduced to improve the prediction of soft tissue movements. Multivariate regression and “shallow” machine learning methods—such as Partial Least Squares (PLS) regression—have proven more robust than traditional linear regression models. These approaches are especially suitable for studies with limited sample sizes, as commonly encountered in clinical contexts, since they can handle multicollinearity among variables and reduce the risk of overfitting [36-37].

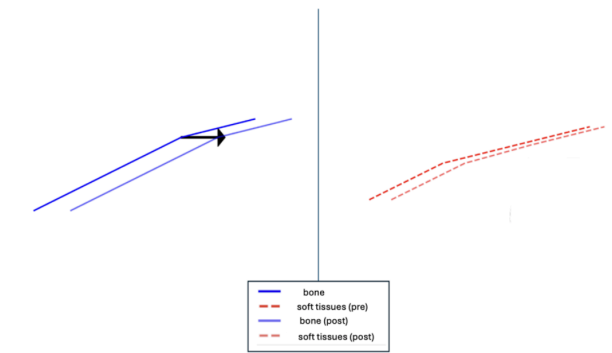
1.7 Soft Tissue Behavior and Prediction

One of the most complex aspects of orthognathic surgery concerns the prediction of soft tissue modifications resulting from skeletal movements. Unlike bone structures, which follow linear and predictable geometric and biomechanical laws, soft tissues exhibit nonlinear, anisotropic, and patient-specific behavior, making it difficult for the surgeon to precisely estimate the postoperative aesthetic appearance of the face [38].

Patient satisfaction following surgery depends not only on functional improvement but also on the aesthetic outcome [38]. It has been demonstrated that the ability to provide the patient with a realistic simulation of the postoperative aesthetic result significantly enhances surgeon–patient communication [39-40]. However, literature reports show that current predictive tools are still unable to provide highly accurate predictions when compared with actual postoperative results [39-40]. The facial regions showing the largest predictive discrepancies are the upper lip, perioral region,

and chin, where the complex interaction among musculature, skin, and tissue elasticity strongly influences the final aesthetic outcome [41].¹²

Figure 19 Difference between bone displacement and soft tissue adaptation.



Initially, soft tissue prediction relied on empirical ratios between skeletal displacement and cutaneous response. However, these empirical relationships were shown to be neither constant nor universally reliable, as interindividual variability was too large to ensure clinically valid predictions [40-41].

The introduction of Finite Element Models (FEM) marked a significant advancement in this field. FEM approaches allow simulation of soft tissue deformation by incorporating the mechanical properties of skin and muscles. Clinically validated FEM models have been shown to provide more accurate predictions than empirical approaches, as they can describe regional differences in skin thickness and stiffness and offer a more realistic simulation [40]. Nevertheless, their use remains limited due to their high computational cost and long processing times.

In recent years, several statistical and machine learning approaches have been proposed to predict soft tissue changes. Among these, the Partial Least Squares (PLS) method has been applied to directly correlate skeletal displacements with surface facial changes [42]. Results have shown mean prediction errors below 3 mm in

regions such as the zygomatic and cheek areas, demonstrating the effectiveness of the PLS approach even in studies with small datasets.

Despite these advances, soft tissue prediction remains a challenging task. The main limitations are:

- Individual variability: differences in skin elasticity, soft tissue thickness, and muscle characteristics across patients;
- Intraoperative factors: tension applied during suturing and the degree of postoperative edema can influence the final result;
- Trade-off between accuracy and complexity: more sophisticated models require higher computational resources.

The integration of 3D digital planning, FEM modeling, and machine learning algorithms represents a promising direction for the future [42-43]. Furthermore, the literature emphasizes the importance of patient-specific models, which incorporate individual soft tissue characteristics to reduce prediction errors and improve the reliability of postoperative outcome simulations [44].

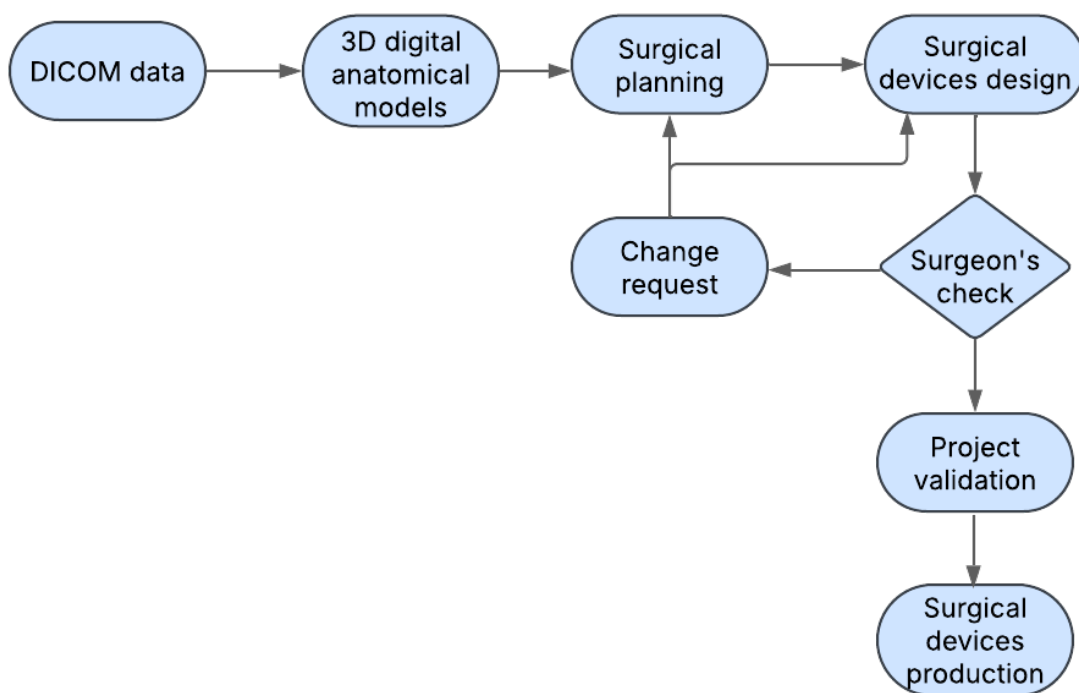
1.8 VSP in-house workflow

This work was developed in close collaboration with the surgeons of the Maxillofacial Surgery Department, director Prof. G. Ramieri, of the University Company “Città della Salute e della Scienza di Torino” and engineers of the Department of Management and Production Engineering, Politecnico di Torino, Turin, Italy.

Digital planning is managed by a work team made up of different professional figures, doctors and engineering, who work together to obtain the best clinical result in terms of precision and accuracy.

To ensure the best possible result reduce as possible costs and times, it has defined a specific workflow.

Figure 20. "Workflow" shows, through a flowchart, the path that is followed from the moment the DICOM data is acquired up to the production of the specific patient materials needed for the surgical intervention.



1. IMAGE ACQUISITION

Process starts with the DICOM data elaboration. 3D models are derived from anatomical structures of interest, both hard and soft tissues.

2. VIRTUAL SURGICAL PLANNING

A “report” is then developed, divided into several pages, containing 3D images of the skeleton in the pre-operative position, that is the malocclusion pathological picture.

This is followed by the modified 3D images in which the bone movements to be performed at the maxillary, mandibular and/or chin level are represented virtually and chromatically depending on the individual clinical case. The splints and cutting guides are graphically depicted within the “final position” (Figure 21).

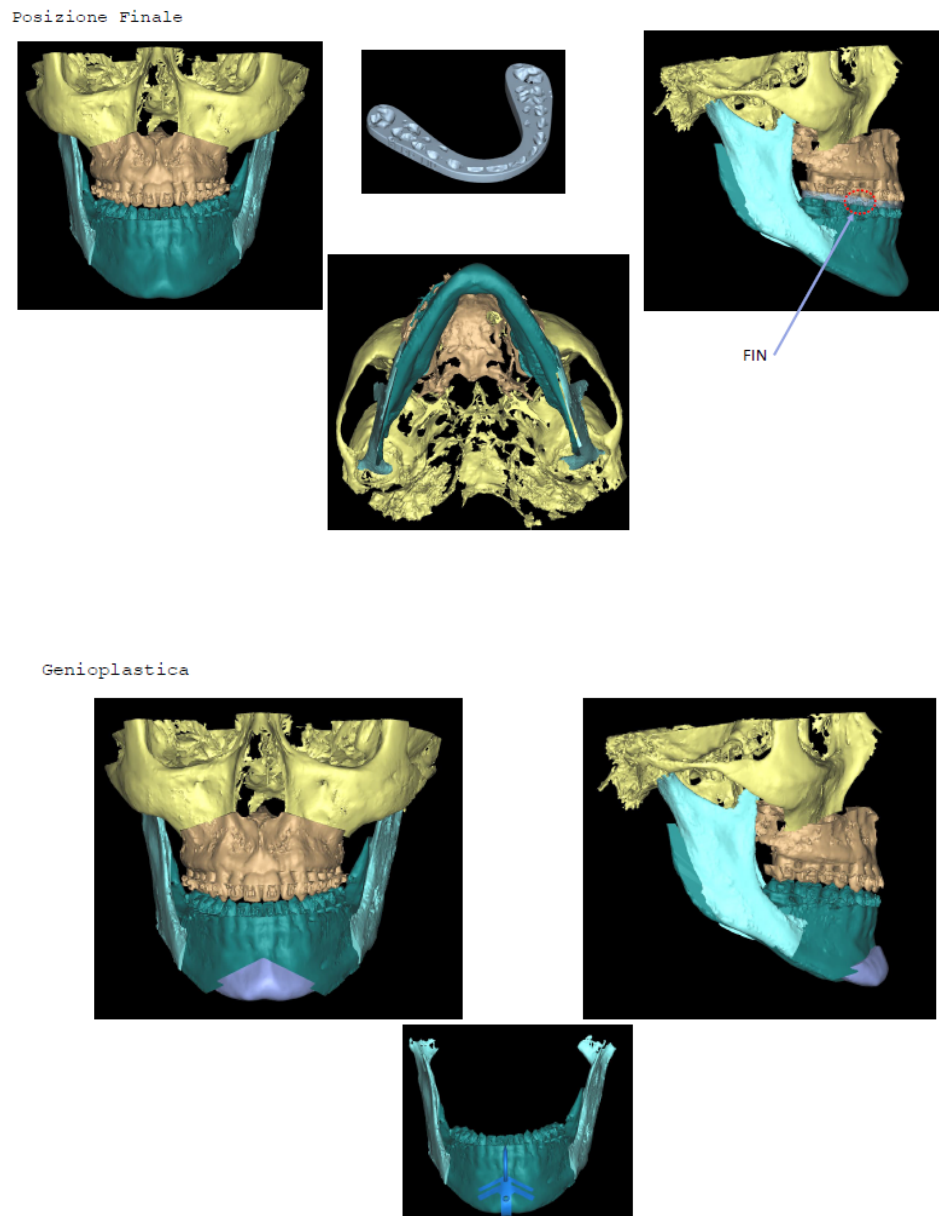
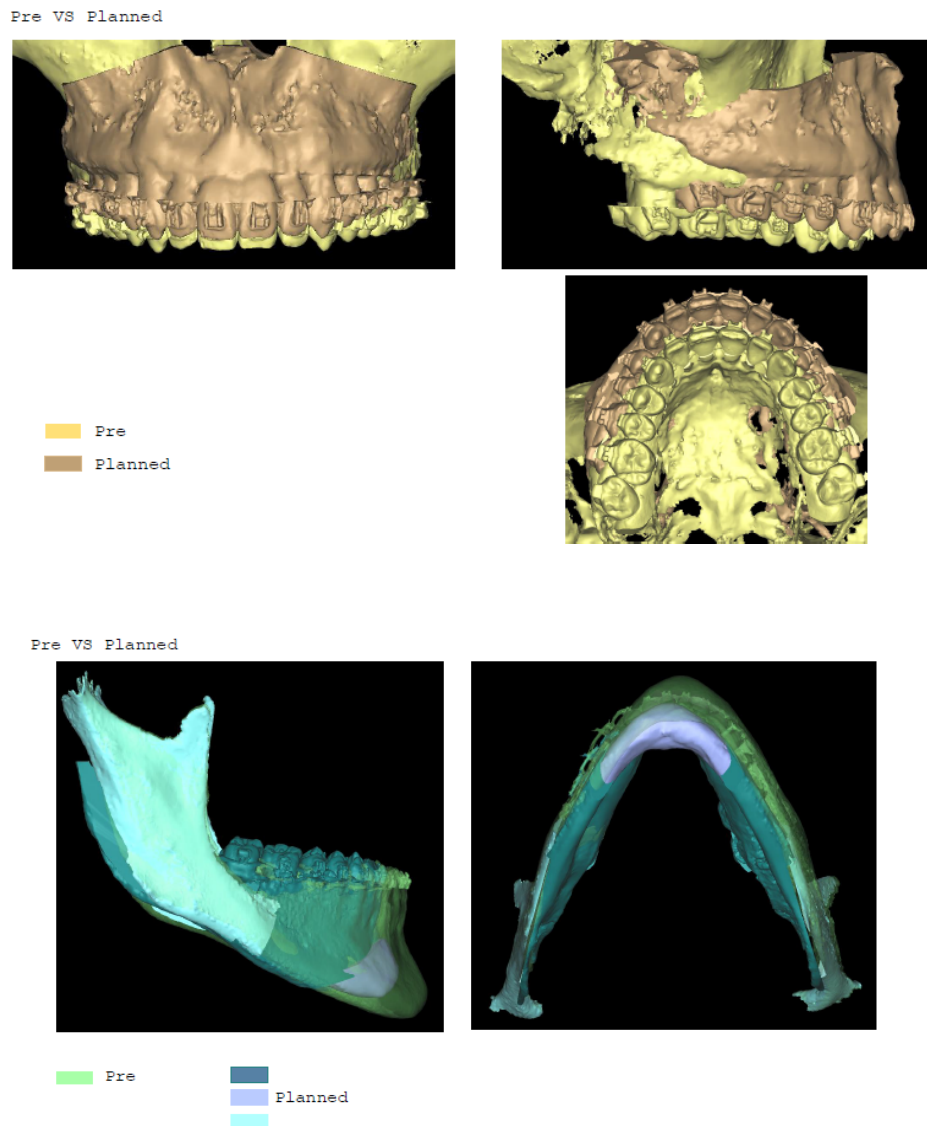


Fig.21

The images of the pre-operative and final positions are then superimposed (Figure 22-23), marking them with different colors respectively to better visualize the differences and have a comprehensive picture of the movement at a graphic level.

Fig.22-23



Finally, the cephalometric analysis table is included containing the anatomical reference points and the relative millimetric measurements of the bone movements to be performed within the three-dimensional space. Each of the cephalometric points presents its own physical position in the space defined in the "Delta 3D". (Fig.24)

This geometric point is thus broken down into its three components that follow the antero-posterior (Ant/Post), medio-lateral (Left/Right) and vertical (Up/Down)

reference axes, orthogonal to each other and perpendicular in turn to their respective cardinal plane.

Fig.24

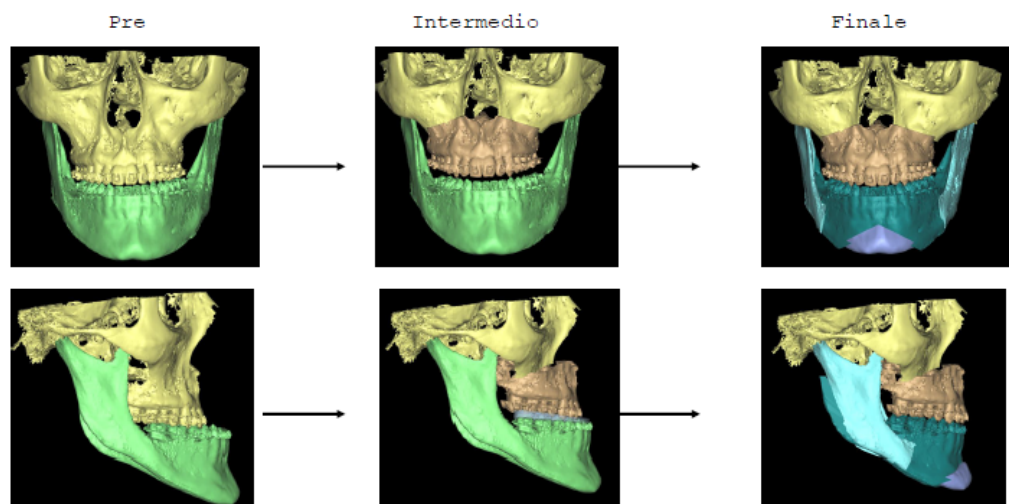
Point	Delta 3D	Left / Right [mm]		Ant / Post [mm]		Up / Down [mm]	
ANS	10.08	0.03	L	9.88	Ant	2.00	Up
PNS	11.43	1.76	R	10.06	Ant	5.15	Up
Maxilla incisormidline	8.25	0.00		8.00	Ant	2.00	Up
Maxilla canine L	7.70	0.26	R	7.30	Ant	2.43	Up
Maxilla canine R	8.77	0.30	R	8.39	Ant	2.54	Up
Pog	11.20	4.19	R	8.68	Post	5.71	Up
Mandible incisormidline	8.34	4.15	R	6.92	Post	2.10	Up
Mandible canine L	7.85	3.98	R	6.30	Post	2.47	Up
Mandible canine R	8.59	4.00	R	7.26	Post	2.26	Up

3. CHECK AND PROJECT VALIDATION

The surgeon and the engineer define the entire planning by evaluating the clinical and technical aspects associated with the pathology and the related surgical devices that will have to be created (Figure 25). This concludes the planning phase.

Then follows the project verification phase from which requests for modifications may arise, both of a "clinical" type, that is associated with evaluations related to the pathology, or of a "technical" type, taht is associated with critical issues that emerged

Pre VS Planned



during the simulation phase of the surgical treatment with the prototype guides. Once the modifications have been made, the project is subjected to verification again.

4. 3D PRINTING: SURGICAL DEVICE PRODUCTION

Once approval has been obtained, we move on to the production phase of the surgical devices using 3D printers, in particular with FDM and SLA techniques within the department.

1.9 Comparison between VSP and TSP

In-hospital planning has allowed us to compare traditional surgical planning (TSP) with the new virtual surgical planning (VSP) to study its positive impact, not only at a purely clinical level, but also in terms of costs and organization within the department and therefore hospital structure. The purpose of VSP includes the reduction of costs, errors and planning times.

Correct preoperative planning is therefore the most important step for an excellent postoperative result.

Traditional surgical planning (TSP) is done on the basis of clinical recordings, two-dimensional (2D) radiographs, photographs, and plaster model surgeries, represented in the past years the standard procedure.

However, TSP had several limitations: first of all the complexity of the preoperative preparation, which in turn represented a cause of errors and a lack of control in the 3 dimensions and finally the absence of evaluation of the position of the temporomandibular joint.

Towards the end of the 90s, thanks to the advent of 3D technologies and CAD/CAM software, a rapid development of Virtual Surgical Planning (VSP) was observed. Virtual planning, based on a virtual model, allows not only to have a three-dimensional view of the craniofacial structures, but at the same time, it allows to simulate the changes in spatial position of the maxillary and mandibular structures in real time.

In 2017 Gaber et al systematically reviewed the evaluation tool for assessing the accuracy of VSP and suggested a universal protocol with the lowest margin of error. [45]

This demonstrates that in the field of orthognathic surgery VSP will replace TSP in view of the improved surgical accuracy for hard tissues and prediction accuracy for soft tissues.

Further confirming this thesis, in a recent systematic review of 2020, Nilsson et al reported that computer-aided planning has shown advantages in shortening the surgical time and the ischemia time for maxillofacial reconstruction and in shortening the preoperative planning time for orthognathic surgery compared to the traditional approach. The saving of time in the operating room subsequently translates into a shorter hospital stay with a reduction in costs and an economic advantage, despite this, however, it is good to remember that the average length of postoperative hospitalization depends on different variables [45-46]

In conclusion of what has been said the VSP technique is significantly more accurate in certain reference areas, especially in the anterior area, showing clinically significantly greater precision for soft tissue prediction in the sagittal plane of the maxilla. The VSP technique required more time for software planning, but it showed an advantage in time savings when considering the entire preoperative process. Accompanied by the use of an accurate computer-aided splint, the VSP technique could effectively reduce the operative time. Apart from the initial financial investment of software and hardware, the total cost of the VSP technique was similar to that of the TSP technique. [47]

2. AIM and OBJECTIVES

The aim of the study was to:

1. To describe the in-hospital surgery pianification within the department structure
2. To assess advantages, solutions and eventually critical points within the workflow
3. To evaluate the accuracy of this new working methods and to analyze discrepancies between the planned and actual postoperative skeletal displacements
4. To investigate the relationship between hard and soft tissue movements, proposing apredictive method based on inter-patient similarity and PLS regression models, with thegoal of improving the accuracy of postoperative aesthetic simulations.

From a clinical perspective, the work aims to provide more accurate decision-support tools for surgical planning, reducing uncertainties in simulations and enhancing surgeon–patient communication, as a realistic prediction of aesthetic outcomes has a direct impact on patient acceptance and satisfaction.

From an engineering perspective, the thesis introduces the development of an experimental pipeline integrating 3D segmentation, geometric registration, statistical analysis, and predictive modeling using multivariate methods. This framework allows a systematic assessment of the reliability of algorithms used in clinical practice and the exploration of new strategies for soft tissue prediction.

3. MATERIAL and METHODS

3.1 Patient collection

This study included 20 selected patients who underwent bimaxillary orthognathic surgery from October 2023 to July 2024 at the Department of Maxillofacial surgery of university of Torino. The patients were aged between 18 and 42 year, and all provided written informed consent. The patients included 14 women and 6 men, with a mean age of 26 years (range 18–42 years). (Tab 1)

Inclusion criteria were as follows:

1. skeletal maturity;
2. presence of dentoskeletal malocclusion requiring bimaxillary orthognathic surgery;
3. Availability of preoperative computed tomography (CT) scans and intraoral digital scans.

Exclusion criteria included:

1. syndromic craniofacial anomalies;
2. history of facial trauma or previous orthognathic surgery;
3. history of prior aesthetic (cosmetic) facial surgery.

All subjects were in good general health and had no systemic pathologies, previous craniofacial surgeries, or trauma that interfered with skeletal symmetry.

Tab1 Demographic and clinical characteristics of the patients included in the study.

<i>Parameter</i>	<i>Value / Distribution</i>
<i>Total number of patients</i>	20
<i>Patients-Object 1</i>	13
<i>Patient-Object 2</i>	5
<i>Mean age (years)</i>	26,1 ± 7,2 (18–42)
<i>Sex (F/M)</i>	12 (66,7 %) / 6 (33,3 %)
<i>Dentoskeletal pattern</i>	Class I (1); Class II (4); Class III (8)
<i>Mean follow-up (months)</i>	6,6 ± 1,0
<i>General conditions</i>	No systemic diseases or craniofacial anomalies

Patients were classified according to their dentoskeletal pattern:

- 1 class I case;
- 5 class II cases;
- 14 class III cases.

For the present study, radiological data were provided by the Maxillofacial Surgery Department of Le Molinette Hospital in Turin. Craniofacial CT scans in DICOM format (Digital Imaging and Communications in Medicine) were obtained for each patient in both preoperative and postoperative phases. These datasets provided three-dimensional information on both skeletal structures and soft tissues, necessary for comparing the virtual surgical planning with the actual postoperative outcome.

The DICOM format represents the international standard for the storage and exchange of medical imaging data, developed by ACR-NEMA and universally adopted across hospital systems [48]. Each file contains not only the image data but also metadata related to the patient, imaging protocol, and acquisition parameters, which are essential for ensuring traceability and reproducibility of the datasets.

The CT examinations used in this study were acquired using standard clinical protocols optimized for the investigation of craniofacial structures. The use of Cone Beam CT (CBCT), compared to conventional CT, reduces radiation dose while maintaining high spatial resolution [49-51]. This aspect is particularly important in

longitudinal studies or for younger patients, where minimizing radiation exposure is a critical consideration.

The image quality depends on several technical parameters, including:

- Slice thickness, which determines axial resolution and the accuracy of 3D reconstructions;
- Field of View (FOV), which influences the anatomical area included in the study;
- Radiation dose, which must balance diagnostic quality with patient safety.

From the DICOM datasets, 3D models of craniofacial structures were reconstructed through segmentation performed in 3D Slicer. The resulting models were exported in STL (Standard Tessellation Language) format, which represents surface geometry using triangular meshes. This format is widely used in maxillofacial surgery for surgical planning and for the fabrication of surgical splints through 3D printing technologies.

The overall data processing workflow can be summarized as follows:

1. CT acquisition → data stored in DICOM format;
2. Segmentation of craniofacial structures in 3D Slicer;
3. Mesh cleaning and optimization in MeshLab;
4. Export of the STL model for subsequent analyses.

Using CT imaging as the acquisition method ensures high morphological fidelity and allows for an accurate representation of both bony structures and soft tissues [12,19].

However, several critical factors must be taken into consideration:

- Motion artifacts: may compromise the quality of the reconstructions, particularly in the mandibular region;
- Metal artifacts: commonly found in patients with orthodontic appliances or prosthetic devices, which generate local distortions in the images;
- Protocol variability: differences in radiological parameters that may affect the comparability of datasets [48].

To minimize these effects, only datasets meeting predefined quality criteria were included in the study, while those affected by significant artifacts or incomplete anatomical structures were excluded.

3.2. Software Tools Used: 3D Slicer, MeshLab, MATLAB

The analytical workflow of the present study involved the combined use of three software platforms: 3D Slicer, MeshLab, and MATLAB. Each tool was employed for its specific features, making their use complementary across the different stages of the processing pipeline.

3D Slicer

3D Slicer is an open-source platform for the visualization and analysis of 3D medical images, developed with the support of the National Institutes of Health (NIH). It is widely used in both clinical and research contexts due to its modularity and the fact that it has been validated in numerous studies on craniofacial surgery [52].

In the present work, 3D Slicer was used to:

- Import data in DICOM format;
- Perform semi-automatic segmentation of bone structures;
- Reconstruct 3D models;

- Export geometries in STL format for subsequent processing.

One of the main advantages of this platform is its capability to apply advanced segmentation algorithms, allowing the level of detail to be adapted to specific clinical requirements.

MeshLab

MeshLab is an open-source software designed for the manipulation and optimization of three-dimensional meshes[53]. It is particularly useful for managing large STL files generated from volumetric segmentations. Moreover, it allows for:

- Surface cleaning, by removing residual polygons or artifacts;
- Decimation, reducing the number of mesh faces without compromising geometric accuracy;
- Topology uniformization, improving model stability in subsequent processing steps.

In this study, MeshLab was used during the intermediate phase to ensure that the STL models derived from 3D Slicer were optimized, lightweight, and free of artifacts.

MATLAB

MATLAB is a widely used tool in biomedical engineering for numerical and statistical dataanalysis. In this study, it played a key role in two main areas:

1. Geometric analysis and registration
 - o Implementation of alignment algorithms;
 - o Calculation of linear and angular discrepancies between preoperative, postoperative, and planned models.

2. Statistical data processing o Analysis of correlations between skeletal displacements and soft tissue deformations; o Organization of results for quantitative comparison between surgical planning and actual outcomes.

The use of MATLAB allowed for the automation of several procedures and the efficient processing of complex datasets within reasonable computation times.

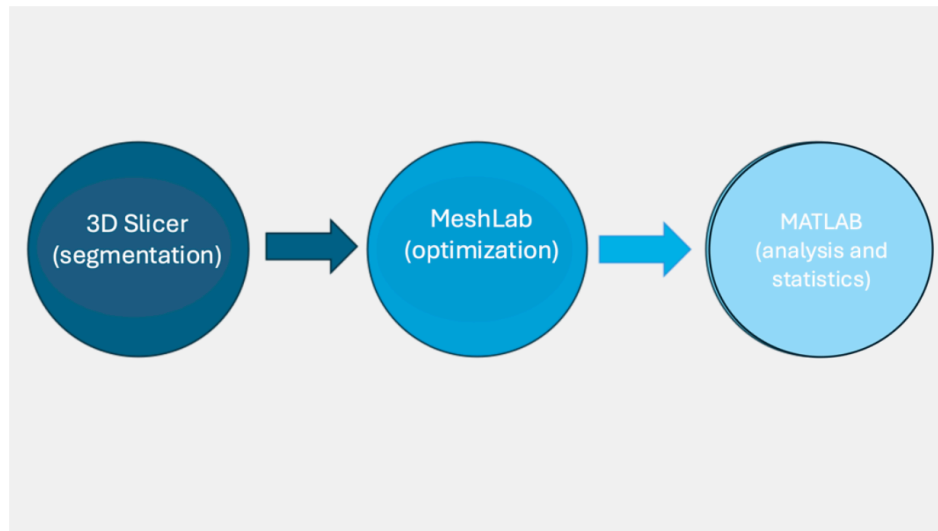


FIG. 26: Illustrative diagram of the software used in this study. CT data in DICOM format were imported and segmented in 3D Slicer, the 3D models were then cleaned and optimized in MeshLab and finally analyzed and statistically processed using dedicated MATLAB scripts. Personal reworking.

3.3 Preoperative procedure

1. First Patient Assessment

The clinical process begins with an initial clinical-surgical evaluation at the craniofacial dysmorphology outpatient clinics of the Maxillofacial Surgery Department at the “Città della Salute e della Scienza di Torino”. The evaluation includes:

- A detailed medical and dental history (both remote and recent);
- Assessment and classification of dentoskeletal deformity;

- Discussion of potential therapeutic approach with the patient;
- Issuance of the referral for craniofacial CT or CBCT (Cone Beam Computed Tomography), to be performed after the completion of orthodontic treatment – ideally one month prior to surgery;
- Acquisition of informed consent for participant in the study.

2. Second Patient Assessment

The second evaluation is performed after the patient has completed orthodontic therapy and CT images have been acquired. This includes:

- Extraoral photographs (frontal, profile and three-quarter views) at rest and during smiling, using cheek retractors;
- Intraoral photographs with cheek retractors and dental mirrors;
- Acquisition of DICOM files from CT/CBCT;
- Collection of all preoperative assessments;
- Preoperative anaesthesiology consultation.

3. Image Acquisition

Craniofacial CT scans are acquired externally, while intraoral digital scans are obtained within the hospital using Shining 3D Aosalscan Elite. CT image acquisition must follow a strict protocol to ensure data uniformity:

- a. Removal of removable metallic prostheses or jewelry that could interfere with the scanned area;
- b. Non-metallic prostheses may be retained;
- c. Patient are instructed to avoid movements (including head tilt or rotation) to prevent motion artifacts;

d. A thin “bite wafer” is used during scanning to stabilize occlusion without altering interarch relationships.

Image are reconstructed using appropriate matrices depending on whether a CT or a CBCT scans was performed and are saveed in lossless DICOM format to preserve data integrity.

4. Virtual Surgical Planning (VSP)

The planning process begins with processing the DICOM and STL files. Preoperative CT scan of the craniofacial skeleton and intraoral digital scan are imported into the CAD/CAM software using the InVesalius software. Within the department, virtyal surgical planning is carried out Materialise Enlight CMF (Figure 20).

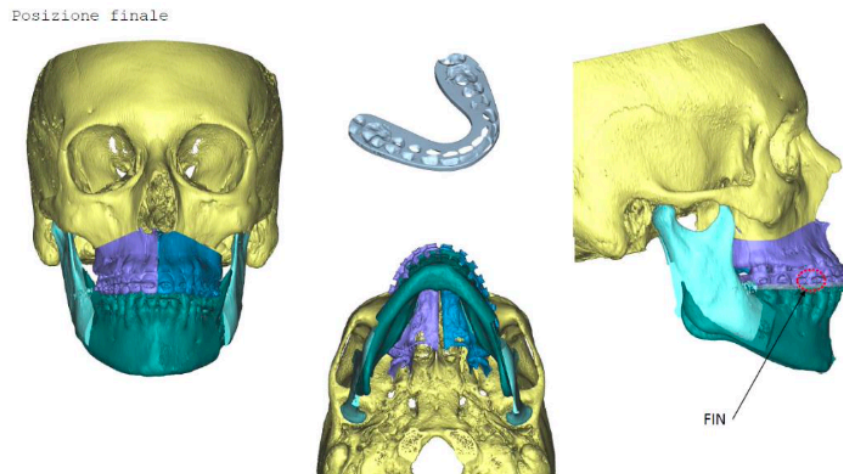
This software is an intuitive orthognathic planning tool that allows a wide range of osteotomies and provides acurate outcome simulations.

Two additional software tools are used in the development of the Virtual Surgical Planning (VSP): 3D Slicer and Meshmixer. Although they serve different purposes, they are both essential and complementary within the overall planning process.

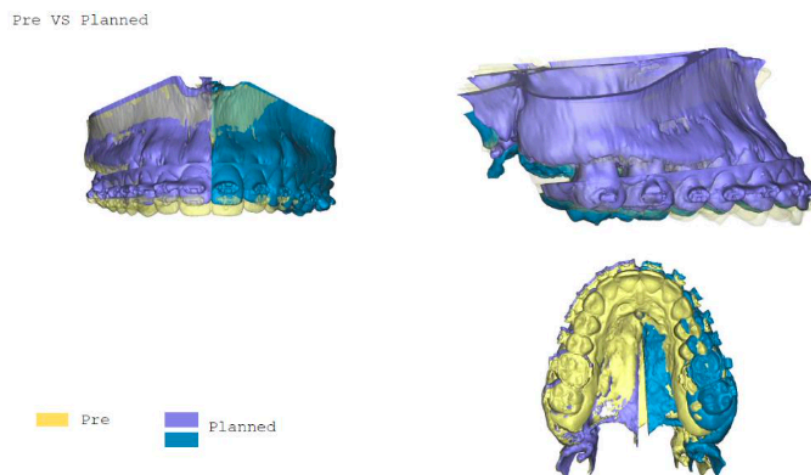
Specifically, 3D Slicer enables the anatomical segmentation and three-dimensional reconstruction of bone and dental structures.

Meshmixer, on the other hand, is a software tool used to clean and optimize artifacts resulting from 3D Slicer segmentation, as well as to design cutting guides and custom prostheses tailored to bone structures.

Thus STL (stereolithography) model are extracted to define osteotomy plans, based on relevant anatommmical structures (both hard and soft tissues). Virtual resections of the maxilla and mandible are planned, with surgical margins guided by clinical and radiological assessments. Final bone segment positioning is precisely defined in three spatial dimensions (anteroposterior, vertical, and transverse axes). To translate the



3D visualizations of the final position, incorporating final splint



virtual plan into the operating room, surgical cutting guides and occlusal splints are designed according to the specific clinical and surgical requirements

Preoperative and final images are superimposed (Figure 27, 28) using distinct colors to visually highlight the surgical changes.

The report also includes a cephalometric table listing anatomical landmarks and the

corresponding bone displacements, each quantified in millimeters in the “Delta 3D” table (Figure 28). Each movement is broken down into components along orthogonal axes: antero-posterior (Ant/Post), medio-lateral (Left/Right) and vertical (Up/Down).

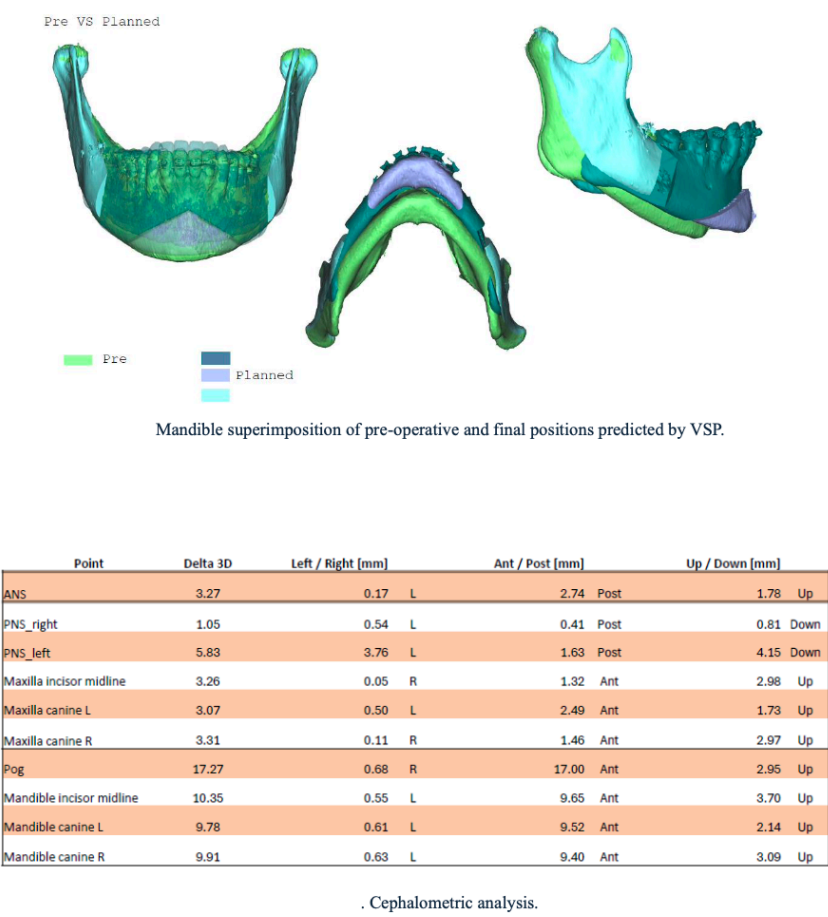


FIG. 28 Maxillary superimposition of preoperative position and final positions predicted by VSP

Pre VS Planned

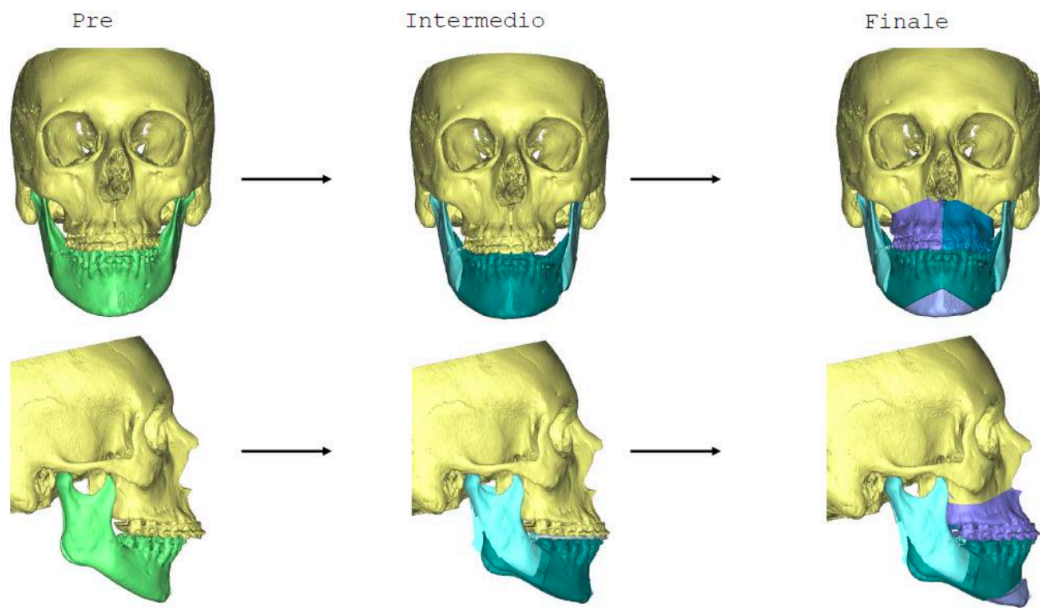


FIG. 29 Pre VS Post VSP

5. Project Review and Validation

The planning is jointly reviewed by the surgeon and the biomedical engineer to evaluate both clinical and technical aspects. This step may lead to modifications, either clinical (e.g., pathology-related changes) or technical (e.g., challenges identified during simulation). After implementing revisions, the updated plan is revalidated (Figure 29).

6. 3D Printing: Surgical Device Production

Upon final approval, surgical guides, intermediate/final splints, and osteosynthesis plates are converted from STL format into G-code instructions using Ultimaker Cura software: 3D printer can execute and fabricate physical object.

At our institution's 3D lab, the Formlabs Form 3B printer is used, employing biocompatible, autoclave-sterilizable resins. This printer uses Low Force Stereolithography (LFS)TM to produce high-resolution prints with smooth surfaces – ideal for precise anatomical replication and surgical applications.

The guides, splints, and plates are printed and finalized by the surgical team, who verify the design and screw positioning using the final 3D printed surgical model.

3.4 Surgical Procedure

All osteotomies and osteosynthesis were performed by two maxillofacial surgeons operating jointly. The surgical procedures were performed by different maxillofacial surgeons with varying years of experience. The operating team was not fixed, and surgeons rotated based on availability and case complexity. Each procedure was planned in detail using VSP, and surgical guides and splints ensured precise transfer of the plan to the operating fields.

All surgeries were conducted under general anesthesia with nasotracheal intubation. The surgical approach (i.e. “maxilla first” or “mandible first”) was chosen based on case-specific requirements.

3.5 Analysis of Rating Scales

FACE-Q|Aesthetics © scale

FACE-Q is a modern patient-reported outcome (PRO) instrument comprising a series of independently functioning scales designed to measure facial aesthetic outcomes

that are significant to patients. The accurate and reliable measurement of patient-centered outcomes is essential for the continuous improvement of clinical practice and research in facial aesthetics. As such, FACE-Q represents a next-generation tool capable of providing clinically meaningful and scientifically valid data that reflect the patient's perception of the outcome. These type of questionnaires have become fundamental in clinical research across in all fields of medicine and surgery.

Since its development in 2010, the FACE-Q Aesthetic module has been widely adopted in both clinical practice and research settings, evaluating quality of life and patient satisfaction.

It quantifies the impact of, and changes resulting from, various form of facial aesthetic surgery and minimally invasive treatments.

Thanks to its modular structure, researchers and clinicians can select the scales most appropriate for their specific clinical questions or study contexts.

In this thesis work, a customized version of the FACE-Q Aesthetic questionnaire was used, composed of four distinct sections designed to assess:

- Satisfaction with the result (6 items)
- Life's quality (20 items)
- Post-operative course (11 items)
- Analysis of adverse symptoms (11 items), assessed in two timeframes:

.6 immediately after the surgery

.7 six months post-surgery.

Each section consists of a set of statements rated using a four-point Likert scale (from “not at all in agreement” to “very much in agreement”). Each level of agreement is assigned a numerical value from 1 to 4, allowing the data to be objectified and analyzed statistically.

The questionnaire was administered six months after the surgical procedure, during the final follow-up visit. This timing allowed for a comprehensive review of the postoperative journey and the identification of any persistent symptoms or complications. Patients were asked to indicate their level of agreement with each statement, thereby providing insight into their subjective experience and satisfaction.

VAS: Visual Analogue Scale

The Visual Analogue Scale (VAS) is a widely utilized instrument for assessing postoperative pain, designed to capture a broad range of patient responses with high sensitivity. Unlike the

categorical format of the Likert scale, the VAS employs a continuous linear scale, enabling the collection of more nuanced data.

Typically, the VAS is represented as a horizontal line, anchored by two verbal descriptors at either ends -for example, “no pain” on the left and “worst possible pain” on the right. Equal numerical distances along the scale are intended to reflect equal increments in the perceived intensity of the symptom being measured. Respondents indicate their condition by placing a mark along the line at the most appropriate point.

The continuous nature of the VAS scale allows for more precise and variable responses, thereby enhancing the scale’s theoretical reliability and making the data more amenable to statistical analysis.

In this study, the VAS was employed to assess both perceived pain and patient satisfaction with facial aesthetic outcomes, by marking a value between 0 and 10 at two time points: preoperatively and six months postoperatively.

Katsuragy Scale and Our Proposed Symmetry Assessment Scale

The clinical morpho-functional outcome was assessed through both the surgeon's visual assessment and patient-reported satisfaction. The Katsuragy scale is a validated tool that assesses the symmetry of the facial contour and the visibility of scars on the face both before and after surgery.

In this study, a modified version of the Katsuragy scale -referred as the Symmetry Assessment Scale (Table 2) - was introduced to both patients and surgeons. This adapted scale focused specifically on the subjective perception of facial contour symmetry, the primary variable of interest in the current analysis.

Cosmetic outcomes were categorized as follows:

- 'Excellent': complete symmetry of the mandible and cheek contours;
- 'Good': slight asymmetry, such as minor cheek depression or lip irregularities;
- 'Fair': moderate asymmetric of soft-tissue contours;
- 'Poor': significant mandibular asymmetry or poor mental projection.

Tab. 2 **Symmetry Assessment Scale.**

<i>Rating</i>	<i>Symmetry of the contour, including mental projection (both bone and soft tissue)</i>
<i>Excellent</i>	Completely symmetrical
<i>Good</i>	Slightly asymmetrical
<i>Acceptable</i>	Slightly asymmetrical
<i>Poor</i>	Asymmetrical or poor mental projection

GAIS

The overall aesthetic result was assessed with a modified version of the Global Aesthetic Improvement Scale (GAIS)

The final satisfaction with the aesthetic outcome was evaluated using a modified version of the Global Aesthetic Improvement Scale (GAIS), which consists of five descriptive categories ranging from "Great improvement" -indicating a significant enhancement in facial appearance compared to the pre-surgical condition- to "Severe deterioration" -denoting a markedly worsened appearance. Each category is assigned a numerical score from 5 (Great improvement) to 1 (Severe deterioration).

The evaluation was carried out by the patient and two independent maxillofacial surgeons who were not involved in the surgical procedure. In case of disagreement, a consensus was reached through discussion. This dual-perspective approach provided

Tab.3 **Modified Global Aesthetic Improvement Scale (GAIS).**

<i>Rating</i>	<i>Description</i>
<i>Large improvement</i>	The facial appearance is much better than before surgery
<i>Slight improvement</i>	The facial appearance is slightly better than before surgery
<i>No change</i>	The facial appearance is essentially the same as prior to surgery
<i>Mild worsening</i>	The facial appearance is slightly worse than before surgery
<i>Severe worsening</i>	The facial appearance is severely worse than before surgery

a more objective and comprehensive assessment of the final facial aesthetic outcome.

3.6 Analysis of Discrepancies Between Surgical Planning and Postoperative Outcome

The aim of this chapter is to describe the methodology used to quantitatively evaluate the 3D differences between the virtual surgical plan and the actual postoperative

outcome within Objective 1 of the present work. The experimental approach includes the following steps:

1. Segmentation and three-dimensional reconstruction of bone models from DICOM data;
2. Geometric alignment of pre- and postoperative models using rigid landmarks and rigid registration algorithms;
3. Calculation of three-dimensional displacements and comparison with the planned movements;
4. Statistical analysis of the obtained results.

This workflow enables the identification and quantification of systematic biases, directional errors, and anatomical regions that are more prone to inaccuracies. It also provides a basis for comparing the quality and reliability of digital surgical planning with the actual postoperative outcomes.

Input Data and Image Format

For each patient, Computed Tomography (CT) scans of the maxillofacial region were acquired and stored in DICOM format. The DICOM format preserves all metadata related to acquisition settings and maintains the spatial relationships among individual slices—an essential requirement for accurate volumetric reconstruction [54].

Segmentation of Hard and Soft Tissues

The DICOM images were imported into 3D Slicer (version 5.2), an open-source software platform that allows semi-automatic volumetric segmentation of anatomical structures [51].

Within the Segment Editor module, two distinct sets of masks were generated:

- One for hard tissues (bone structures), including the mandible and maxilla;
- One for soft tissues, including the cutaneous surface and facial covering tissues.

Segmentation of both tissue types was performed using intensity thresholding based on Hounsfield Unit (HU) values, followed by manual refinement in the axial, sagittal, and coronal planes. For the soft tissue mask, an additional manual refinement step was applied to isolate the external facial profile and remove non-relevant regions of the neck and cranial vault that were not pertinent to the analysis.

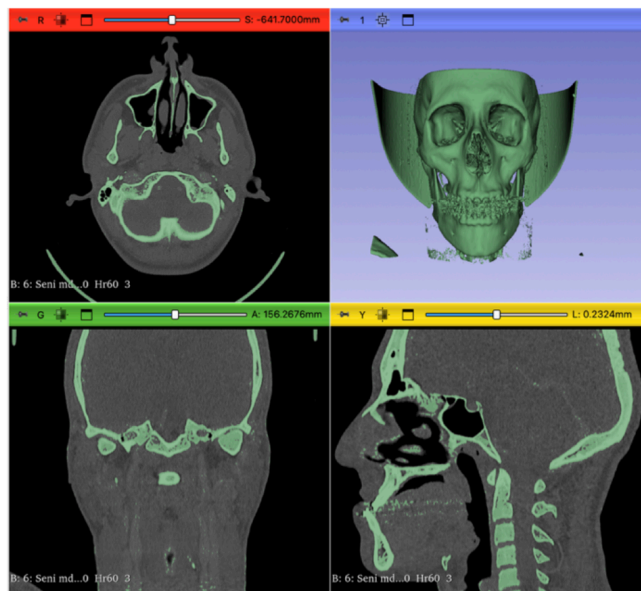


Fig 30 Example of segmentation of pre-operative hard tissue of one patient included in the study, using the thresholding technique in 3D Slicer. Personal reworking.

This procedure ensures the generation of morphologically realistic and artifact-free surfaces, which are essential conditions for an accurate geometric comparison in the subsequent analysis phases.

Reconstruction and Export of 3D Models

From the segmented masks, three-dimensional surface reconstructions were generated using the Show3D module in 3D Slicer, which converts the binary regions into triangular meshes.

Each model was then exported in STL (Standard Tessellation Language) format, which is

compatible with the software MeshLab and MATLAB, both used in the following steps of

the workflow.

During the export phase, the following parameters were verified:

- Topographic consistency (absence of holes or discontinuities);
- Orientation of surface normal;
- Metric scale accuracy.

The resulting STL files constitute the reference models for both preoperative and postoperative dataset.

These models were subsequently subjected to a cleaning and decimation process to optimize mesh quality and reduce computational load without compromising geometric accuracy.

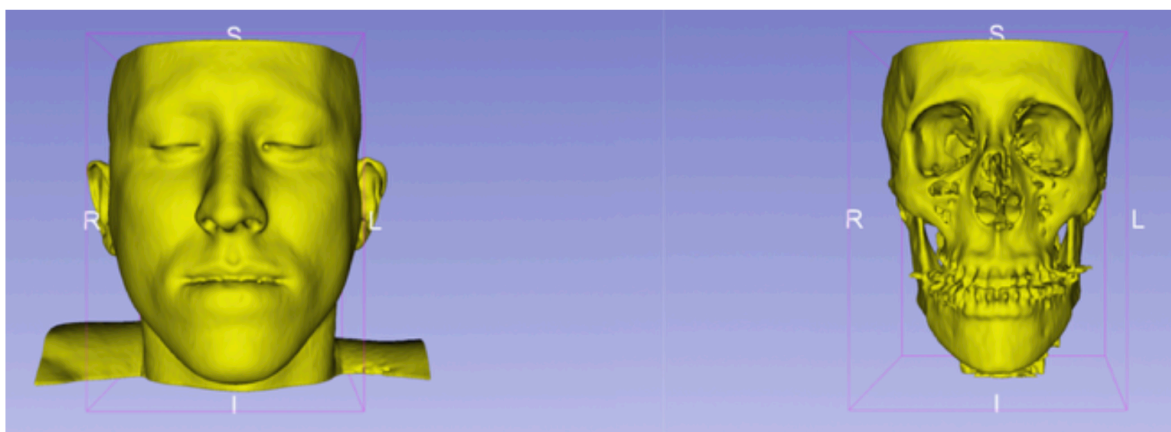


Fig. 31 : Pre-operative STL models of soft and hard tissues of one of the subjects in the study, obtained after the segmentation and 3D reconstruction phase. Personal reworking.

Mesh Cleaning and Reduction

After reconstructing and exporting the three-dimensional models in STL format, a geometric optimization step was performed. The purpose of this phase was to remove topological imperfections and reduce the mesh complexity, while preserving the geometric accuracy required for subsequent alignment procedures.

Pre-processing and Topological Correction

The triangular meshes generated from segmentation may contain errors resulting from image noise, thresholding artifacts, or volume interpolation. These imperfections can appear as small discontinuities, isolated surfaces, or degenerate triangles and must be corrected before proceeding to the following steps [55].

Mesh cleaning was performed using MeshLab (Visual Computing Lab, ISTI-CNR, Pisa, Italy), an open-source software widely used for mesh processing in medical and engineering applications.

The following filters were applied:

- Removal of isolated pieces: automatic deletion of small disconnected components, using a threshold of 100 faces;
- Remove duplicate and unreferenced vertices: correction of redundant vertices and unreferenced triangles.

These operations ensured topological consistency, a necessary condition for accurate alignment in the next phase.

Vertex Reduction

The surfaces exported from 3D Slicer typically contain a high number of triangles, many of which are unnecessary for analytical purposes and lead to increased computational load during registration.

Therefore, a controlled mesh simplification was carried out to reduce the number of vertices while maintaining the overall morphology of the model.

The reduction was performed using the Quadratic Edge Collapse Decimation filter in MeshLab, with a simplification factor of 30% relative to the initial number of vertices.

The algorithm proposed by Garland and Heckbert [56] minimizes the local quadratic error produced by edge collapse operations, thereby preserving geometric fidelity even in regions with local curvature.

Selection of the Anatomical Region of Interest

To focus the analysis on the facial areas relevant to orthognathic surgery, the models were trimmed to retain only the anterior facial region.

This selection was performed directly in MeshLab using region selection tools.

Non-relevant areas—such as the posterior neurocranium, upper cranial vault, and basal portions of the neck—were excluded, while preserving the structures between the orbital margins and the inferior mandibular border. The same region selection procedure was applied to both preoperative and postoperative models, for both hard and soft tissue datasets, to ensure geometric consistency during registration.

The outcome of this phase consisted of clean, lightweight, and optimized 3D models, ready for the rigid alignment procedure described in the following section.

Alignment of Pre- and Postoperative 3D Models

The three-dimensional alignment of pre- and postoperative models is a crucial step in

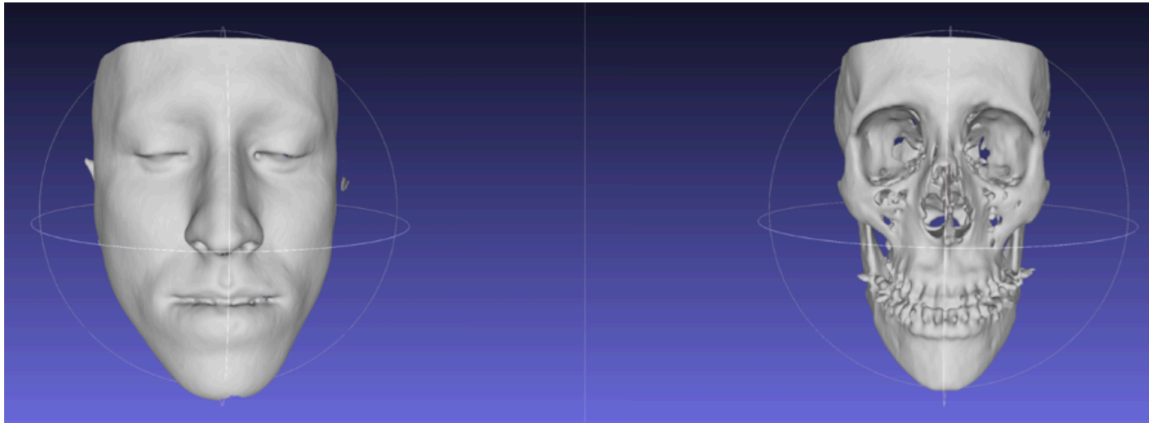


Fig 32 STL models of pre-operative soft and hard tissues of one subject in the study, obtained after cleaning and optimization and ready for the next processing phase. Personal reworking.

assessing the discrepancies between the virtual surgical planning and the actual postoperative outcome.

The objective of this procedure is to achieve an accurate superimposition of the cranial regions that remain unaffected by surgery, so that the measured displacements of the mobile skeletal segments (mandible, maxilla, chin) reflect only the surgical effect and not registration errors [57,58].

The alignment process was carried out in two sequential stages:

1. An initial rigid registration based on stable anatomical landmarks using Procrustes analysis;
2. An optimization step performed with the Iterative Closest Point (ICP) algorithm applied to a rigid cranial region delimited by a bounding box.

Selection of Rigid Reference Landmarks

To identify a common reference system between the pre- and postoperative models, a set of cranio-orbital landmarks was selected. These landmarks are located in stable bony regions not affected by surgical movements and characterized by high repeatability in three- dimensional localization.

The selection of these landmarks was based on the guidelines proposed by Jung et al. [59] and the anatomical reference manual Three-Dimensional Cephalometry by Swennen [60], which provides a detailed description of the main craniofacial reference structures used for model registration.

All landmarks were manually annotated on both pre- and postoperative STL models using the Markups module in 3D Slicer.

Selected Landmarks

1. Nasion (Na)

The nasion is the intersection point between the frontonasal suture and the midsagittal plane. It is located at the superior boundary of the nasal bridge, marking the anterior end of the junction between the nasal bones and the inferior margin of the frontal bone.

2. Right and Left Frontozygomatic Points (FZD, FZS)

The frontozygomatic points represent the upper lateral limits of the orbit, located at the intersection between the frontal and zygomatic margins. They correspond to the junction between the zygomatic process of the frontal bone and the frontal process of the zygomatic bone.

3. Right and Left Endocanthion (EnD, EnS)

Located at the medial commissures of the eyelids, these points represent the internal contact between the upper and lower eyelids. At the skeletal level, they correspond to the lacrimal margin of the orbit .

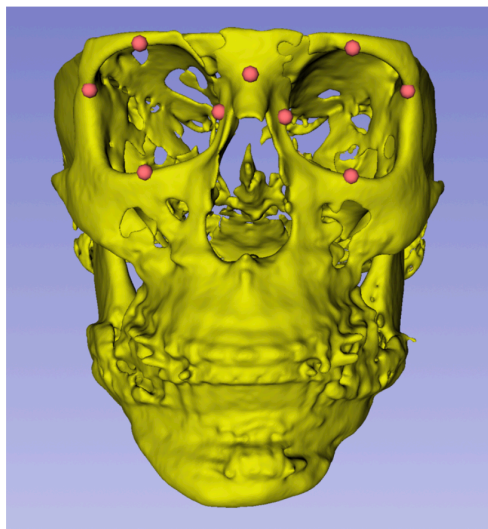
4. Right and Left Superior Orbitale (OrSupD, OrSupS)

These points are located at the most cranial position of the superior orbital rim, along the inferior border of the frontal bone.

5. Right and Left Inferior Orbitale (OrInfD, OrInfS)

Situated at the lowest point of the inferior orbital rim, they correspond to the junction between the inferior orbital wall and the infraorbital margin.

Figure 33 Three-dimensional visualization



Practical Implementation and Application to 3D Models

In the present work, rigid Procrustes registration was used to obtain an initial three-dimensional alignment between the preoperative and postoperative models, based solely on the rigid cranio-orbital landmarks previously selected.

The alignment was implemented in MATLAB, using the built-in `procrustes()` function, which computes the rigid transformation (rotation and translation) that minimizes the total squared distance between two corresponding point sets.

The following matrices were defined:

- **X**: an $N \times 3$ matrix containing the coordinates of the preoperative landmarks;

- Y: an $N \times 3$ matrix containing the coordinates of the postoperative landmarks.³³

The MATLAB function performs the following steps:

1. Centering both point sets with respect to their centroids;
2. Computing the optimal rotation that minimizes the Euclidean distance between corresponding points;
3. Applying the translation required to best superimpose YY onto XX.

In the implementation, the parameters 'Scaling' = false and 'Reflection' = false were set to enforce a strictly rigid transformation. To obtain the aligned model according to the rigid landmarks, the rotation matrix and translation vector were then applied to all vertices of the postoperative model.

This step enabled the rigid alignment of the two 3D models while preserving the original geometry and avoiding any deformation of the structures.

The accuracy of the rigid registration obtained through Procrustes analysis was verified visually.

A custom MATLAB script was implemented to display the superimposition of the pre- and postoperative models, allowing for qualitative inspection of the alignment accuracy.

ICP Registration on the Rigid Region (Bounding Box)

Following the initial registration, a fine alignment was performed using the Iterative Closest Point (ICP) algorithm. This step allows for further optimization of the superimposition between pre- and postoperative models and enables an automatic alignment of surfaces based on local geometric correspondences.

The algorithm follows these main steps:

1. For each point of the moving model (postoperative), the closest point on the surface of

the reference model(preoperative) is identified;

2. The rigid transformation that minimizes the mean squared distance between corresponding point pairs is computed;
3. The transformation is applied to the moving model;
4. The process is repeated iteratively until the mean change in error between two consecutive iterations falls below a predefined convergence threshold.

Definition of the rigid region (bounding box)

The alignment cannot be applied to the entire face but only to the portion of the skull not subject to surgical modifications, so a limited area was selected around the previously chosen rigid landmarks.

The rigid region was defined by constructing a three-dimensional bounding box of ± 10 mm around the pre-operative landmarks, so as to include only the vertices belonging to the upper part of the face, which is considered stable with respect to orthognathic surgery [34,35].

The bounding box was applied by implementing a MATLAB code that calculates the minimum and maximum limits of the 3D box and selects only the vertices located within it for both models.

This way, subsequent registration occurs only on the stable portion of the skull.

Application of the ICP Algorithm

Once the rigid region was obtained, the rigid ICP algorithm was applied between the points belonging to the bounding box of the two models that had already undergone an initial alignment.

The MATLAB code used the `pcregistericp` function from the Computer Vision Toolbox, with a `pointToPoint` metric and a maximum of 50 iterations.

The algorithm calculated the optimal rigid transformation that minimizes the distance between the corresponding points of the two surfaces in the rigid region.

The resulting transformation was applied to the entire post-operative model to obtain the final, perfectly aligned model.

Calculation of Actual vs. Planned Displacements

Once the pre- and post-operative model registration phase was completed, the study continued with the calculation of the actual displacements of anatomical points of interest based on the aligned pre- and post-operative models and the comparison with the planned values of these displacements provided by the surgeons within the surgical planning.

The calculation was performed using a MATLAB code that processes the landmarks extracted from the aligned STL models in `.fcsv` format and organizes the results in Excel tables structured by patient.

The process involves four phases:

1. Extraction and reading of the landmark files in `.fcsv` format;
2. Vector calculation of the actual three-dimensional displacements between the corresponding pre- and post-operative points in the aligned models;
3. Organization of the results in a table with directional components and total magnitude of the displacement, which was then exported to Excel format. These tables also reported the directional and magnitude components of the displacements planned by the surgeons during the planning phase;
4. Comparison between these two data sets, i.e., the actual displacements calculated

between the aligned pre- and post-operative models and the planned displacements, which allowed us to determine the three-dimensional error for each landmark and for each spatial direction.

Extraction of Landmarks from Pre- and Postoperative Models

The landmarks used to calculate three-dimensional discrepancies were chosen to correspond to the cephalometric points indicated in the surgical plans provided by the maxillofacial surgeons, thus ensuring consistency between the virtual and real comparisons.

These are anatomical references widely used in orthognathic literature because they are easily identifiable and clinically relevant for describing the movements resulting from the surgery.

For each patient, the following nine landmarks were manually identified in 3DSlicer in both the pre- and post-operative models using the software's Markups tool.

The three-dimensional coordinates were exported in .fcsv format, which was then imported into MATLAB for displacement calculations.

The landmarks used are as follows:

- Maxillary landmarks:

- o ANS (Anterior Nasal Spine)

Anterior point of the nasal spine, located at the lower end of the intermaxillary suture [60].

- o PNS (Posterior Nasal Spine)

Most posterior point of the hard palate, defined by the intersection of the midline of the baseplate with the posterior margin of the horizontal plate of

the palatine bone [60].

- o Maxilla canine R/L

Points corresponding to the cusps of the right and left canines of the maxilla [10,35].

- o Maxilla incisor midline

Midline point between the upper central incisors, located on the incisal edge [35].

- Mandibular landmarks:

- o Pog (Pogonion)

Most anterior point of the mental symphysis in the sagittal projection, identified on the cortical bone of the chin [35].

- o Mandible canine R/L Points placed on the cusps of the right and left canines of the mandible [35].

- o Mandible incisor midline

Midline point between the lower incisors, used to measure the horizontal and vertical deviation of the mandibular median plane [60].

All the landmarks were placed on the rigid bone surface using the three-dimensional visualization in 3DSlicer in order to have greater accuracy. Calculation of 3D Displacements and Directional Components (LR, AP, UD)

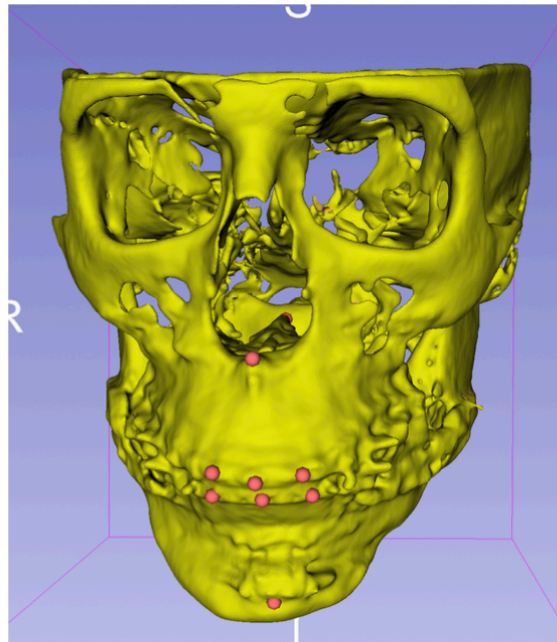


Fig 34 Visualization of the nine cephalometric landmarks selected on the post-operative model of a patient included in the study, used for calculating the discrepancies between surgical planning and the actual outcome. Personal reworking.

Calculation of 3D Displacements and Directional Components (LR, AP, UD)

To calculate the three-dimensional displacements and compare them with the planned values, a MATLAB code was used that allows the landmark coordinates exported from 3DSlicer in .fcsv format to be processed.

The goal of this phase is to determine the actual distance between the real pre- and post- operative positions for each landmark and then compare them with the planned distance, thus obtaining a measure of the error in the virtual surgical planning.

Two files were used for each patient:

- A file containing the three-dimensional coordinates of the landmarks in the preoperative model;
- A file containing the coordinates of the landmarks in the rigidly registered postoperative model.

The files were read into MATLAB using a specific function and returned as Nx3 matrices (N = number of landmarks, 3 = x, y, and z coordinates).

Calculating Real Three-Dimensional Distances

Once the coordinates are imported, the code calculates the real displacement vector for each landmark, defined as:

$$\vec{V}_i = \overrightarrow{L_{post,i}} - \overrightarrow{L_{pre,i}}$$

Where are the three-dimensional coordinates of the i-th point in the pre-operative and aligned post-operative models respectively.

From this vector, the following are then derived:

- Total three-dimensional distance (D3D) described by:

$$\Delta 3D = \sqrt{(x_{post,i} - x_{pre,i})^2 + (y_{post,i} - y_{pre,i})^2 + (z_{post,i} - z_{pre,i})^2}$$

- Directional components along the axes:
 - o LR (x-axis) - transverse displacement;
 - o AP (y-axis) - anteroposterior displacement;
 - o UD (z-axis) - vertical displacement.

In addition to the absolute value of the distances, the directional sign for each axis is also reported, which is determined based on the LPS (Left-Posterior-Superior) reference system, where:

- Positive values indicate Left (L), Posterior (P), and Superior (S);
- Negative values indicate Right (R), Anterior (A), and Inferior (I).

This information is saved in a MATLAB table containing, for each landmark: point name, total distance $\Delta 3D$, displacements ΔLR , ΔAP , ΔUD , and their respective

directions. For each patient, both the actual distances obtained and the planned distances, i.e., the displacements assumed in the surgical plans, were combined in an Excel file.

The Excel file contains 13 sheets, one for each subject in the sample, and each sheet contains all the analyzed landmarks, the actual and planned distances in the three spatial directions (LR, AP, UD), with their respective directional signs according to the reference system adopted.

Point	Delta3D_real	Delta_LR_real	LR_Dir_real	Delta_AP_real	AP_Dir_real	Delta_UD_real	UD_Dir_real	Delta3D_plan	Delta_LR_plan	LR_Dir_plan	Delta_AP_plan	AP_Dir_plan	Delta_UD_plan	UD_Dir_plan
ANS	1.05	0.32	R	0.66	Ant	0.75	Up	6.75	0.99	L	6.01	Ant	2.90	Up
PNS	3.63	0.49	R	2.74	Ant	2.33	Up	6.65	2.30	L	6.08	Ant	1.39	Up
Maxilla canine R	4.86	0.43	R	4.61	Ant	1.47	Up	7.45	0.39	R	6.45	Ant	3.70	Up
Maxilla canine L	7.77	3.54	R	6.86	Ant	0.82	Up	7.92	0.48	R	7.66	Ant	1.94	Up
Maxilla incisor midline	3.11	2.01	R	1.35	Ant	1.95	Up	7.70	0.62	R	7.05	Ant	3.03	Up
Pog	9.17	0.62	R	1.51	Post	9.02	Up	8.35	0.00	NaN	3.76	Ant	7.45	Up
Mandible canine R	3.70	0.00	L	0.92	Ant	3.59	Up	4.91	0.00	NaN	2.35	Ant	4.30	Up
Mandible canine L	5.16	0.16	L	0.71	Ant	5.11	Up	4.91	0.00	NaN	2.42	Ant	4.27	Up
Mandible incisor midline	3.77	0.81	L	1.98	Post	3.10	Up	5.14	0.00	NaN	2.46	Ant	4.51	Up

Fig 35 Example of an Excel sheet containing real and planned distances for one patient in the study. Extract from the file generated by MATLAB scripts, showing for each landmark the real ($\Delta 3D_real$) and planned ($\Delta 3D_plan$) three-dimensional distances, along with their directional components along the LR (latero-lateral), AP (antero-posterior), and UD (supero-inferior) axes and their respective movement directions (Right/Left, Anterior/Posterior, Up/Down). These values serve as input for the subsequent computation of three-dimensional and directional errors between planning and actual results.

3.7 Predictive Analysis of Soft Tissue Behavior

Accurate modeling of soft tissue behavior is a crucial step in surgical planning because it allows for the anticipation of the aesthetic effects of the procedure and supports the surgeon in choosing the most appropriate surgical strategy. However, the complex and nonlinear nature of soft tissues is influenced by individual biomechanical and morphological variables, necessitating the use of an advanced statistical approach that captures these multidimensional relationships. The following chapter describes the methodology adopted for the construction and validation of a predictive model based on Partial Least Squares (PLS) regression, integrating the geometric information obtained from the pre- and post-operative 3D models of 18 patients.

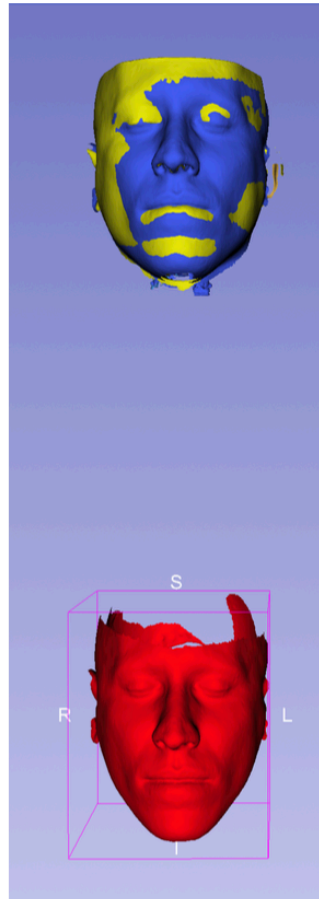


Fig 36 Alignment of pre- and post-operative soft tissue models. The yellow model represents the pre-operative condition, the red model the original post-operative condition, while the blue model shows the post-operative condition after alignment using the combined Procrustes + ICP matrix computed on hard tissues.

Data Preparation and Model Alignment

The first step in building the predictive model is preparing the pre- and post-operative soft tissue dataset obtained from 3D reconstructions of patients undergoing orthognathic surgery.

The goal of this phase is:

1. To ensure precise alignment between the pre- and post-operative soft tissue models to isolate actual displacements due to surgery;
2. To ensure consistent reference systems across all subjects, which is necessary to compare data and develop a common statistical model.

These operations are essential to avoid systematic errors due to arbitrary rotations or

translations of the STL models exported from segmentation software and to obtain a normalized and morphometrically comparable database.

Pre- and Post-operative Alignment of Soft Tissue Models

The three-dimensional models of the soft tissues were obtained from the same DICOM images and with the same segmentation procedure described in Subchapters, in which the mesh generation and cleaning phases in 3DSlicer and MeshLab are explained in detail.

Unlike what was done in Aim 1, at this stage it was not necessary to repeat the landmark selection or the manual registration of the soft models. In fact, to ensure that the soft tissues followed the same rigid displacements as the hard tissues, the exact same transformation matrix (obtained from the Procrustes + ICP combination) already calculated to align the bone models was reused.

In practice, for each patient:

- The Procrustes transformation and the ICP transformation obtained on the hard tissues were saved in MATLAB structures;
- These transformations were then applied to the vertices of the post-operative soft tissue model, thus rigidly aligning it with the respective pre-operative soft tissue model in the same reference system.

This approach allows for perfect spatial consistency between the two tissue types and avoids introducing differences due to new interpolations or point marking errors.

Using the same rigid transformation applied to the hard tissues ensures that the alignment of the soft tissues respects the previously obtained spatial position and preserves the anatomical relationship between the two compartments.

The validity of the process was verified for each patient by visualization in 3DSlicer and by numerically checking the RMSE, which was kept below 2 mm.

In this way, for each patient, two perfectly superimposed soft tissue models (pre- and post- aligned) were obtained in the same reference system, ready for the calculation of the displacements and for the subsequent predictive analysis.

After aligning the pre- and post-operative three-dimensional models of the soft tissues, it was necessary to define the geometric reference elements to be used to describe and quantify the facial response to surgery.

These elements, consisting of landmarks and surface patches, allow for localized analysis of the most significant morphological changes and to obtain, for each patient, the spatial information necessary for the subsequent predictive model.

Selected Facial Soft Tissue Landmarks

Soft tissue landmarks were manually selected on each three-dimensional model using the Markups module of 3DSlicer and following a standardized and reproducible approach already validated in the literature for facial analysis studies.

The selection was made by considering the most representative anatomical points of the facial regions affected by the movements produced by orthognathic surgery, with particular attention to the mid-lower portion of the face, where the main perceived aesthetic variations are concentrated.

The selected regions include the nose, lips and chin, which are areas that directly reflect the movements of the maxilla and mandible. In particular:

- The nasolabial complex is strongly influenced by the position of the maxilla, especially during advancement and impaction movements;
- The lower lip and maxilla, on the other hand, respond primarily to mandibular movements;
- The perioral areas represent a biomechanical transition zone between the two regions, often the site of complex interactions between the bony planes.

The identified landmarks and their anatomical description are reported in Table 4 according to the nomenclature of the Three-Dimensional Cephalometry manual by Swennen et al. [60].

<i>Acronym</i>	Name	Anatomical description and rationale for selection
<i>Prn</i>	Pronasale	The most anterior point of the nasal tip; represents nasal protrusion and reflects changes in the upper maxilla and nasal septum.
<i>Alr_dx/Alr_sx</i>	Right/Left Alare	The most lateral points of the nasal alae; sensitive to transverse and vertical variations of the maxilla and to the rotation of the nasolabial complex.
<i>Ls</i>	Labrale superius	The most anterior point of the upper lip on the midline; indicative of the degree of maxillary advancement and lip tissue tension.
<i>Li</i>	Labrale inferius	The most anterior point of the lower lip; reflects anteroposterior movement and mandibular rotation.
<i>Ch_dx/Ch_sx</i>	Right/Left Chelion	Corners of the mouth; represent horizontal and vertical mobility of the labial complex and postoperative symmetry.
<i>Pg'</i>	Cutaneous Pogonion	The most anterior point of the chin at the skin level; sensitive to mandibular movements and indicative of the lower facial profile.
<i>Go'dx/sx</i>	Right/Left Cutaneous Gonion	The most lateral point on the cutaneous contour of the mandibular angle (cutaneous projection of the skeletal Gonion). Useful for detecting changes in mandibular width and angle definition following mandibular movements and rotations; supports the assessment of lateral asymmetries.
<i>Zy'dx/sx</i>	Right/Left Cutaneous Zygion	The most lateral point on the cutaneous contour of the zygomatic arch (cutaneous projection of the skeletal Zygion). Sensitive to variations in zygomatic width and malar fullness; useful for monitoring possible transverse asymmetries of the midface.

These points were selected to cover the main clinical and biomechanical areas of interest in the face, ensuring a balanced analysis between the central and lateral components.

Furthermore, by selecting bilateral landmarks, it is possible to assess any post-surgical asymmetries or differences in soft tissue response.

Each landmark was positioned on both the pre-operative and post-operative aligned models so that the actual three-dimensional displacement of each point could be subsequently calculated. The coordinates were exported in .fcsv format for processing in MATLAB.

Patches (Regions of Interest) and Criteria for Subdivision

To add a more robust and continuous representation of local deformations to the point-based landmark information, the face was divided into patches (areas of interest) defined around key anatomical points.

The patches allow us to describe the average displacement of soft tissues in large, topologically coherent regions, reducing the influence of local noise and surface micro-irregularities.

The selected regions correspond to the most morphologically relevant areas for evaluating post-operative aesthetics:

- Right and left nasal wings (Right_wing, Left_wing) → represent the variations of the nasal base and the rotation of the nasolabial complex.
- Upper lip (Upper_lip) → region influenced by the advancement or retraction of the maxilla, which modifies the labial projection and nasolabial opening.
- Lower lip (Lower_lip) → reflects the response to mandibular movements and lip closure.

- Chin (Chin) → crucial area for the harmony of the lower profile and highly sensitive to mandibular translations and rotations.

The patches were defined by manually selecting landmarks representing the anatomical area of interest and positioned on the face in 3DSlicer. These landmarks represent the centre or seed of the section, around which the MATLAB code used identifies the mesh vertices belonging to the same region, according to the geodesic distance or oriented bounding box criteria. The landmarks were chosen to provide uniform coverage consistent with the morphology of the face, including only vertices relevant to the anatomical region of interest.

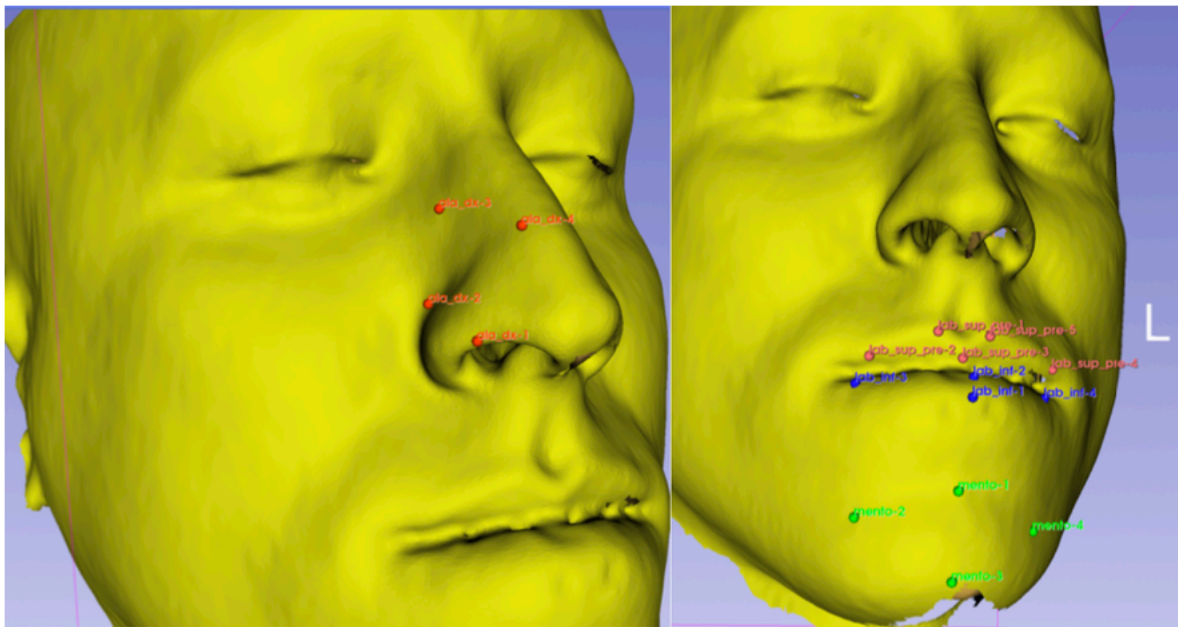


Fig 37 Example of landmark placement used for defining anatomical patches on the face.

The dedicated script uses the aligned pre- and post-operative soft tissue meshes and generates subregions based on:

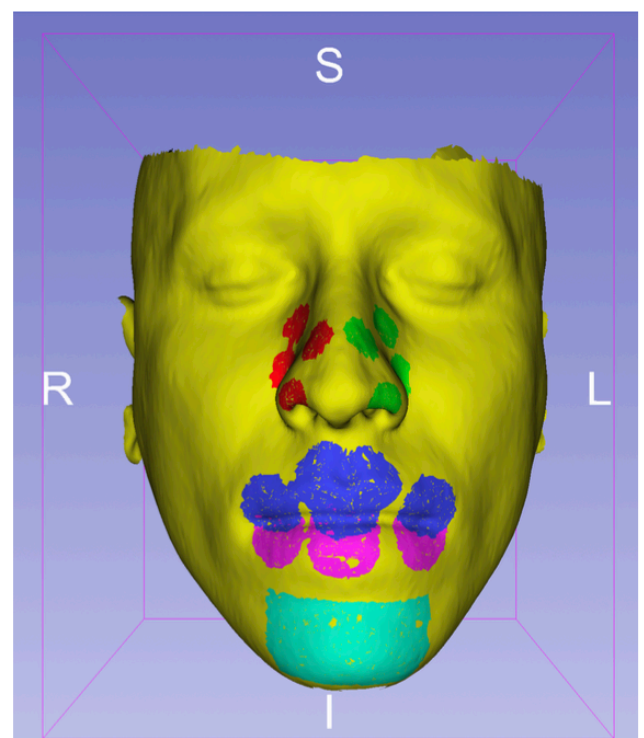
- Geodesic distance of the reference point (for curved surfaces such as the nose and lips);
- Or an oriented bounding box (OBB) for more regular but asymmetric regions such as the chin.

This choice allows the patch definition to be adapted to the local morphology and preserves the geometric consistency of the mesh.

The entire process was applied to all patients and both models, resulting in the following for each patch:

- The .stl file;
- The .csv file with the coordinates of the patch vertices;
- A preview image highlighting the patch on the facial surface.

A total of 10 patches were obtained for each patient (5 for the pre-aligned and 5 for the post-aligned models), which will then be used to calculate the actual three-dimensional displacements. (Fig.38)



Calculation of Actual Soft Tissue Displacements

After aligning the three-dimensional models and defining the landmarks and reference patches, the actual displacement calculation phase was performed.

The purpose of this phase was to objectively quantify the spatial variation of the soft tissues following the bone repositioning achieved by surgery.

The analysis, conducted in MATLAB, involved:

- Reading the files containing the three-dimensional coordinates of the pre- and post-operative points (in .fcsv or .csv format);
- Calculating the change in position in space for each point or vertex;
- Extracting the directional components of the displacement along the three principal axes (L/R, A/P, U/D);
- Obtaining the total three-dimensional magnitude (
- Identifying the anatomical direction of movement based on the sign of each component.

All calculations were performed in the LPS (Left-Posterior-Superior) reference system, which is consistent with the format of the .fcsv files exported from 3DSlicer, where the positive axes correspond to left (L), posterior (P), and superior (S).

The final results were collected in two separate Excel files:

- One containing the distances calculated for each landmark for each patient;
- One containing the distances calculated for each patch for each patient.

Displacement Calculation for Landmark

For each patient, .fcsv files containing the 3D coordinates of the pre- and post-operative skin landmarks were imported.

For each point, the three-dimensional displacement was calculated as the vector difference between the two configurations.

From this vector, the following were derived:

- The three-dimensional Euclidean distancespatial variation of the point in millimeters;
- The directional components along the three main axes:
 - o X-axis: lateral-lateral displacement (LR);
 - o Y -axis: anteroposterior-posterior displacement (AP);
 - o Z-axis: up-down displacement (UD);
- The anatomical direction of movement, which is determined by the sign of the component.

This method allows for the direct and intuitive quantification of how much and in which direction each landmark has moved, providing three-dimensional information that can be interpreted clinically

Once the soft tissue patches for the pre- and post-operative conditions were defined, the actual displacements of the vertices in each region were quantified.

For each patch, the three-dimensional coordinates of the vertices belonging to the pre- and post-operative meshes were read.

Each vertex of the pre-model was matched to the closest vertex of the post-mesh, obtaining an estimate of the displacement vector.

Since these models are already aligned, these differences directly indicate the actual

displacement of soft tissues in the patient's anatomical space, without alterations due to additional rigid transformations.

For each patch, the directional displacement was estimated as the median of the Δx , Δy and Δz components, resulting in a representative and robust measure of regional motion, less sensitive to surface noise and local sampling discrepancies between meshes.

In addition to the magnitude of the displacement, the anatomical directions of movement

were obtained along the main axes of the LPS system:

- X-axis: Lateral-lateral displacement (LR);
- Y -axis: Anterior-posterior displacement (AP);
- Z-axis: Up-down displacement (UD);

By applying robust statistics to the mesh vertices, it was possible to obtain a more accurate and anatomical estimate of the soft tissue displacement than methods based solely on the patch centroid.

The calculated distances represent the actual translation of each facial region.

Construction of the Predictive Model

The construction of the soft tissue predictive model is a multi-stage process and aims to estimate the expected facial changes in a patient (the "target") based on the transformations that have occurred in patients who have already undergone surgery (the "reference patients").

The approach is inspired by data-driven methods recently introduced in maxillofacial surgery [24,32,60] and is based on the principle that patients with similar morphological characteristics tend to show comparable soft tissue responses following orthognathic surgery.

The steps are:

1. Determine the similarity between patients using morphometric indices;
2. Normalize the parameters and calculate the z-scored Euclidean distances;
3. Predict the baseline for each target patient as a weighted average of the actual displacements observed in the most similar patients;
4. Preliminary evaluation of the predictive capacity of the similarity model.

Determination of Patient Similarity

Quantifications of morphological similarities between patients were obtained by selecting a set of morphometric features derived from the three-dimensional coordinates of the preoperative soft tissue landmarks.

These features were chosen to concisely represent the main proportions and volumes of the face and provide a numerical basis useful for similarity analysis.

The selection of indices was conducted in accordance with the three-dimensional cephalometric literature [60] and previous studies on morphometric comparisons between orthognathic patients.

The indices were chosen to ensure:

- anatomical completeness, covering the three fundamental dimensions of the head (width, height, and projection);
- geometric robustness, based on reliable and reproducible landmarks;
- non-redundancy, avoiding excessive correlations between parameters derived from adjacent anatomical regions.

The 10 features used to define inter-patient similarity are shown in Table 5.

They include linear distances and normalized ratios calculated between pairs or groups of soft facial landmarks with precise morphological significance.

Tab 5 Pre-operative soft tissue morphometric measurements used to define similarity between patients.

ID	MORPHOMETRIC FEATURE	GEOMETRIC DEFINITION	ANATOMICAL- FUNCTIONAL MEANING
F1	Bizygomatic distance (Zy'-Zy')	Euclidean distance between the right and left cutaneous zygion points	Width of the midface; represents the transverse amplitude of the zygomatic region.
F2	Bigonial distance (Go'-Go')	Distance between the right and left cutaneous gonion points	Lower facial width; sensitive to mandibular position and rotation.
F3	Total facial height (Tr-Me')	Vertical distance between the trichion and the cutaneous menton	Global index of facial verticality.
F4	Lower facial height (Sn-Me')	Distance between the subnasale and the cutaneous menton	Lower facial proportion; measures the vertical mandibular component.
F5	Naso-labial projection (Prn-Sn)	Sagittal distance between the pronasale and the subnasale	Anterior projection of the nasolabial complex.
F6	Upper lip projection (Sn-Ls)	Distance between the subnasale and the labrale superius	Prominence of the upper lip.
F7	Lower lip projection (Sn-Li)	Distance between the subnasale and the labrale inferius	Prominence of the lower lip.
F8	Transverse labial distance (Ch'-Ch')	Distance between the right and left cheilion points	Transverse width of the mouth.
F9	Zygomatic index	Ratio F1 / F3	Relationship between facial width and height (vertical harmony).
F10	Mandibular index	Ratio F2 / F4	Relationship between mandibular width and lower facial height.

The combination of these ten features allows for a compact yet informative three-dimensional description of the preoperative morphology. Features F1-F4 represent the absolute linear dimensions of the face, while F5-F8 indicate the sagittal projection and transverse symmetry of the perioral and nasal regions.

Finally, F9 and F10 are proportional indices that summarize the harmony between vertical and transverse components.

This combination balances anatomical specificity with morphometric generality and ensures that morphologically similar patients are effectively identified as such in the subsequent similarity calculation. The set of selected features was found to be sufficient to discriminate the main facial variants without introducing numerical redundancies.

Normalization and Computation of Z-Scored Euclidean Distances

To compare morphometric characteristics between patients objectively and without the influence of different feature measurement units, data normalization was performed using z-score standardization.

This operation allows each variable to be centered on a common scale with a zero mean and a unit standard deviation, thus ensuring that all features contribute equally to the similarity calculation.

The standardization of a generic feature was performed by applying the formula

$$z_i = \frac{x_i - \mu}{\sigma}$$

Where μ represents the sample mean and σ the standard deviation.

This way, each feature is unitless and comparable across subjects with different proportions or metric scales. This step is essential in distance-based models and machine learning methods because it prevents numerically larger variables from dominating the overall distance calculation [61].

Once the data were normalized, an inter-patient similarity matrix was constructed based on the weighted Euclidean distance between z-scored morphometric vectors of pre-operative soft tissues described by the formula:

$$D_{ij} = \sqrt{\sum_{k=1}^n w_k \cdot (z_{ik} - z_{jk})^2}$$

For this calculation, a uniform weighting ($VD = 1/T$) was adopted to avoid bias due to specific anatomical assumptions and to ensure that each district contributes equally to defining the overall similarity.

The resulting matrix D is symmetric and of dimension $N' N$, where N is the total number of patients.

For each target subject, the $k=3$ most similar "reference patients" were identified, corresponding to the rows with the smallest distance values.

This choice of k represents an optimal compromise between statistical robustness and morphological specificity and is consistent with suggestions in similar studies [60,61].

Baseline Prediction via Weighted Mean of Similar Reference Patients

Based on the defined similarity matrix, a baseline prediction of soft tissue displacements was constructed for each target patient, calculated as a weighted average inversely proportional to the similarity distances with respect to the three most similar reference patients as described in formula

$$\Delta S_{target}^{pred} = \frac{\sum_{k=1}^3 w_k \cdot \Delta S_{donatore k}}{\sum_{k=1}^3 w_k}, \text{ con } w_k = \frac{1}{D_{target, donatore k}}$$

This way, greater influence is attributed to the most similar patients and the impact of distinct subjects in the morphometric space is reduced [62-64]

The baseline prediction was calculated separately for:

- landmarks, providing a precise assessment of local deformations;
- patches, allowing for a more robust regional average analysis against geometric noise.

To avoid data leakage and obtain a realistic estimate of the model's predictive capacity, a Leave-One-Out Cross-Validation (LOOCV) validation was implemented.

In each iteration, the target patient was excluded from the similarity matrix calculation and was predicted using only the remaining patients as reference patients. In this way, each target was independent from the training set, simulating a real generalization condition of the model and reducing the risk of overestimating the performance and possible self-similarity effects between patients. Furthermore, it allowed to obtain more prudent and methodologically solid results.

4. RESULTS

4.1 Analysis of study sample

A total of 20 patients underwent orthognathic surgery between October 2023 and July 2024. One patient was excluded due to the absence of preoperative virtual surgical planning. Four patients not undergoing postoperative CT scans, which are essential for overlap analysis and comparison of pre- and post-operative results, were also excluded. Two additional patients were excluded as their follow-up period exceeded the study's timeframe required for completion of orthodontic treatment and postoperative imaging. Ultimately, 13 patients (10 women and 3 men) were included. The mean age at surgery was 26.1 years old (SD [standard deviation], 7.2 years) (range: 18-42 years). Patients were categorized into three dentoskeletal pattern: ID 1 was class I, IDs 2-5 were class II and IDs 6-13 were class III (Table 1 and Table 2).

4.2 Surgical analysis

Twelve patients underwent bimaxillary surgery (Le Fort I + BSSO) while only one patient performed Le Fort I osteotomy alone. Genioplasty was performed in 6 interventions (46.2%).

A maxilla-first approach was used in 8/13 (61.5%) patients, while a mandible-first approach was selected for the remaining patients. Maxillary segmentation was performed in 3 patients (2 bipartitions and 1 tripartition).

Of the total of 12 patients who underwent the combined "Le Fort I + BSSO" procedure, 11 intermediate splints (91.7%) were designed in the planning and produced. The final splints were designed and produced for all 13 patients. For the single case of maxillary tripartition (patient ID 2), a palatal plate was designed and produced.

In 9 of 13 surgeries (69.2%) all planned surgical guides and splints were utilized. In one case (7.7%) the intermediate splint was omitted; in two cases (15.4%) the final

splint was not used and out of three cutting guides produced only one was not used (33.3%).

The mean operating time was 168 min (SD, 46) (approximately 2 hours and 48 min).

One intraoperative complication (7.7%) occurred - a bleeding event required resuturing. The mean follow-up duration was 6.6 months (SD, 1.0) (range, 6-9 months). No complications occurred in the first 30 postoperative days.

All surgical details were summarized in Table 6 and Table 7

Tab 6 **Overview of patient characteristics and surgical intervention.**

<i>Patient ID</i>	<i>Age (y)</i>	<i>Gender (M, F)</i>	<i>Dentoskeletal pattern</i>	<i>Type of surgery</i>	<i>Maxilla or Mandible first approach</i>	<i>Maxilla segmentation</i>
1	18	F	I	LE FORT I + BSSO + GENIOPLASTY	Mandible	-
2	34	F	II	LE FORT I + BSSO + GENIOPLASTY	Maxilla	Tripartition
3	21	F	II	LE FORT I + BSSO	Maxilla	Bipartition
4	42	F	II	LE FORT I + BSSO	Maxilla	-
5	27	F	II	LE FORT I + BSSO + GENIOPLASTY	Mandible	Bipartition
6	20	F	III	LE FORT I + BSSO	Mandible	-
7	20	F	III	LE FORT I + BSSO	Mandible	-
8	20	M	III	LE FORT I + BSSO + GENIOPLASTY	Maxilla	-
9	35	F	III	LE FORT I + BSSO	Maxilla	-
10	23	F	III	LE FORT I + BSSO + GENIOPLASTY	Maxilla	-
11	28	M	III	LE FORT I + BSSO + GENIOPLASTY	Maxilla	-
12	23	F	III	LE FORT I + BSSO	Maxilla	-
13	28	M	III	LE FORT I	-	-

Tab 7 Summary of patient demographic and clinical characteristics, surgical data and follow-up times.

	<i>Mean ± SD, or n (%), N=13</i>
<i>Age (years)</i>	26.1 (7.2) (range, 18 – 42)
<i>Sex</i>	
<i>Female</i>	10 (76.9%)
<i>Male</i>	3 (23.1%)
<i>Type of surgery</i>	
<i>Le Fort I + BSSO</i>	12 (92.3%)
<i>Genioplasty</i>	6 (50 %)
<i>Le fort I</i>	1 (7.7%)
<i>“Le Fort I + BSSO” ‘s approach</i>	12
<i>Maxilla first</i>	8 (66.7%)
<i>Mandible first</i>	4 (33.3%)
<i>Bipartition</i>	2
<i>Tripartition</i>	1
<i>Palatal plate</i>	1
<i>Intermediate splint</i>	11
<i>Final splint</i>	13
<i>Guide custom made</i>	3
<i>Unused materials</i>	
<i>Intermediate splint</i>	1
<i>Final splint</i>	2
<i>Guide custom made</i>	1
<i>Intraoperative complications</i>	1
<i>Bleeding</i>	1
<i>Postoperative (0-30 days) complications</i>	0
<i>Operating times (min)</i>	168 ± 46 min
<i>Follow Up (Months)</i>	6.6 ± 1.0 months (range, 6 - 9)

4.3 Follow-up visit at 6 months follow-up

No infections and/or reoperations were reported during follow-up.

None of the patients reported pain on palpation of the condylar pole or temporalis muscles. Masseter palpation elicited pain in 2 patients (15.4%). However, deep intraoral palpation revealed pain in the pterygoid region in 9 of 13 patients (69.2%). No pain was reported on palpation of the sternocleidomastoid muscles (Table 3).

Temporomandibular joint (TMJ) sounds (“clicks”) during mandibular opening or lateral movements were noted in 5 of 13 patients (38.5%). Mandibular protrusive

movements were preserved in 11 out of 13 patients (84.6%), while 2 patients exhibited mild lateral deviation.

All patients denied sensory deficits, including both partial (hypoesthesia) or complete (anesthesia) loss of sensation. However, 7 patients (53.9%) reported positive sensory symptoms in the form of tingling (paraesthesia and/or dysesthesia).

The MIO (maximum interincisal opening) mean was 42.2 mm (SD, 6.7).

The mean estimated duration of post-operative orthodontic treatment was 3.3 months (SD, 2.6). Notably, patient ID 13 had completed orthodontic treatment at the time of follow up, thus contributing a value of zero to the cohort average.

All described results obtained from the 6-month follow-up visit are summarized in Table 8.

Tab 8 **Summary of the clinical results during the postoperative clinical visit.**

<i>Variables</i>	<i>Number (%), N=13</i>
<i>Reintervention</i>	0
<i>Postoperative infections (0-6 Months)</i>	0
<i>Pain on palpation</i>	
<i>Mandibular condyle</i>	0
<i>Temporal muscles</i>	0
<i>Masseter muscles</i>	2 (15.4%)
<i>Pterygoid muscles</i>	9 (69.2%)
<i>Sternocleidomastoid muscles</i>	0
<i>TMJ sounds (mandible opening and/or lateralization)</i>	5 (38.5%)
<i>Mandibular movements</i>	
<i>No deviations</i>	11 (84.6%)
<i>Lateral deviation or deflection on opening</i>	2
<i>Paresthesia and/or dysesthesia (lower lip and chin)</i>	7 (53.9%)
<i>Hypoesthesia and/or anesthesia (lower lip and chin)</i>	0
<i>MIO (maximum interincisal opening)</i>	42.2 ± 6.7 mm
<i>Post-operative orthodontic treatment duration (months)</i>	3.3 ± 2.6 months

4..4 Analysis of rating scales

Patients reported a mean pain score during mandibular function of 2.2 (SD, 3.3) before surgery, which did not change significantly at the 6-month follow-up (mean, 3.5; SD, 2.7) (p , 0.337, paired Student t-test) (Table 8).

General aesthetic assessment showed a significant improvement from 3.8 points (SD, 2.3) to 8.4 points (SD, 1.0) after treatment ($p < 0.001$, paired Student t-test), according to the VAS scale (Table 9).

When patients were asked to evaluate the outcome of the treatment according to the FACE- Q scale, a mean score of 157.4 point (SD, 11.2) was reported. The partial scores of the individual test components are shown in the Table 10.

Tab 9 **Rating scales results before and after orthognathic surgery.**

<i>Variables</i>	<i>before orthognathic surgery mean (SD)</i>	<i>after orthognathic surgery mean (SD)</i>	<i>mean difference (95% IC)</i>	<i>p</i>
<i>VAS functional pain</i>	2.2 (3.3)	3.5 (2.7)	1.2 (-1.4, 3.9)	0.337*
<i>VAS aesthetic</i>	3.8 (2.3)	8.4 (1.0)	4.6 (3.2, 6.0)	< 0.001*

* Paired Student t-test

Abbreviations: CI, confidence interval; VAS, visual analogue scale.

Tab 10 **Assessment with FACE-Q scale**

<i>Test components</i>	<i>mean (SD)</i>
<i>Satisfaction with the result</i>	20.5 (2.8)
<i>Life's quality</i>	63.8 (9.5)
<i>Post-operative course</i>	29.7 (3.7)
<i>Analysis of adverse symptoms</i>	43.4 (9.9)
<i>Face Q (total)</i>	157.4 (11.2)

Abbreviations: SD, standard deviation.

The results of the evaluation of facial symmetry before and after orthognathic surgery are summarized in Table 11. Scores according to the Symmetry assessment scale showed a significant difference between the two time points, for both patient (p, 0.002, related-samples Wilcoxon signed rank test) and surgeon evaluations (p, 0.003, related-samples Wilcoxon signed rank test) (Table 6). Cohen's Kappa coefficient for inter-observer agreement was 0.148 (proportion in agreement 46%, P=0.299 slight agreement) and 0.217 (proportion in agreement 62%, P=0.429 fair moderate agreement) for the pre- and postoperative evaluations, respectively.

Tab 11 **Aesthetic outcome assessment with the Symmetry Assessment Scale**

	<i>before orthognathic surgery</i>	<i>after orthognathic surgery</i>	<i>p</i>
	<i>n (%)</i>	<i>n (%)</i>	
<i>Patient</i>	Excellent: 1 (7.7)	Excellent: 5 (38.5)	0.002°
	Good: 1 (7.7)	Good: 8 (61.5)	
	Acceptable: 3 (23.1)	Acceptable: 0	
	Poor: 8 (61.5)	Poor: 0	
<i>Surgeon</i>	Excellent: 0	Excellent: 6 (46.2)	0.003°
	Good: 6 (46.2)	Good: 7 (53.8)	
	Acceptable: 3 (23.1)	Acceptable: 0	
	Poor: 4 (30.7)	Poor: 0	
	Cohen's Kappa coefficient: 0.148	Cohen's Kappa coefficient: 0.217	
	Proportion in agreement: 46%	Proportion in agreement: 62%	
	P=0.299	P = 0.429	

Abbreviations: GAIS, Global Aesthetic Improvement Scale

° related-samples Wilcoxon signed rank test

According to the GAIS scale (Table 11), 10 (76.9%) patients reported a large improvement and 3 (23.1%) a slight improvement in facial appearance. The surgeons classified the outcome as largely improved in 7 (53.8%) and slightly improved in 6 (46.2%) Cohen's Kappa coefficient for inter-observer agreement was 0.198 (proportion in agreement 62%, P=0.416, slight agreement). (Tab 13).

Tab 12. **Aesthetic outcome assessment with GAIS scale**

	<i>Variables</i>
<i>Patient</i>	Large improvement: 10 (76.9%) Slight improvement: 3 (23.1%) No change: 0 Mild worsening: 0 Severe worsening: 0
<i>Surgeon</i>	Large improvement: 7 (53.8%) Slight improvement: 6 (46.2%) No change: 0 Mild worsening: 0 Severe worsening: 0 Cohen's Kappa coefficient: 0.198 Proportion in agreement: 62% P=0.416

Abbreviations: GAIS, Global Aesthetic Improvement Scale

Tab 13 **Cohen's Kappa coefficient values**

<i>Kappa (k) value</i>	<i>Interpretation</i>
< 0	Disagreement
$0 - 0.20$	Slight agreement
$0.21 - 0.40$	Fair agreement
$0.41 - 0.60$	Moderate agreement
$0.61 - 0.80$	Substantial agreement
$0.81 - 1.00$	Almost perfect agreement

4.5. Accuracy Analysis

4.5.1 Descriptive Analysis of Signed and Absolute Metrics

The signed and absolute descriptive metrics were calculated for each landmark in all three spatial directions, resulting in the mean, standard deviation, median, and interquartile ranges.

Tables 14 and 15 show the main mean values in millimeters obtained for the signed and absolute errors, respectively.

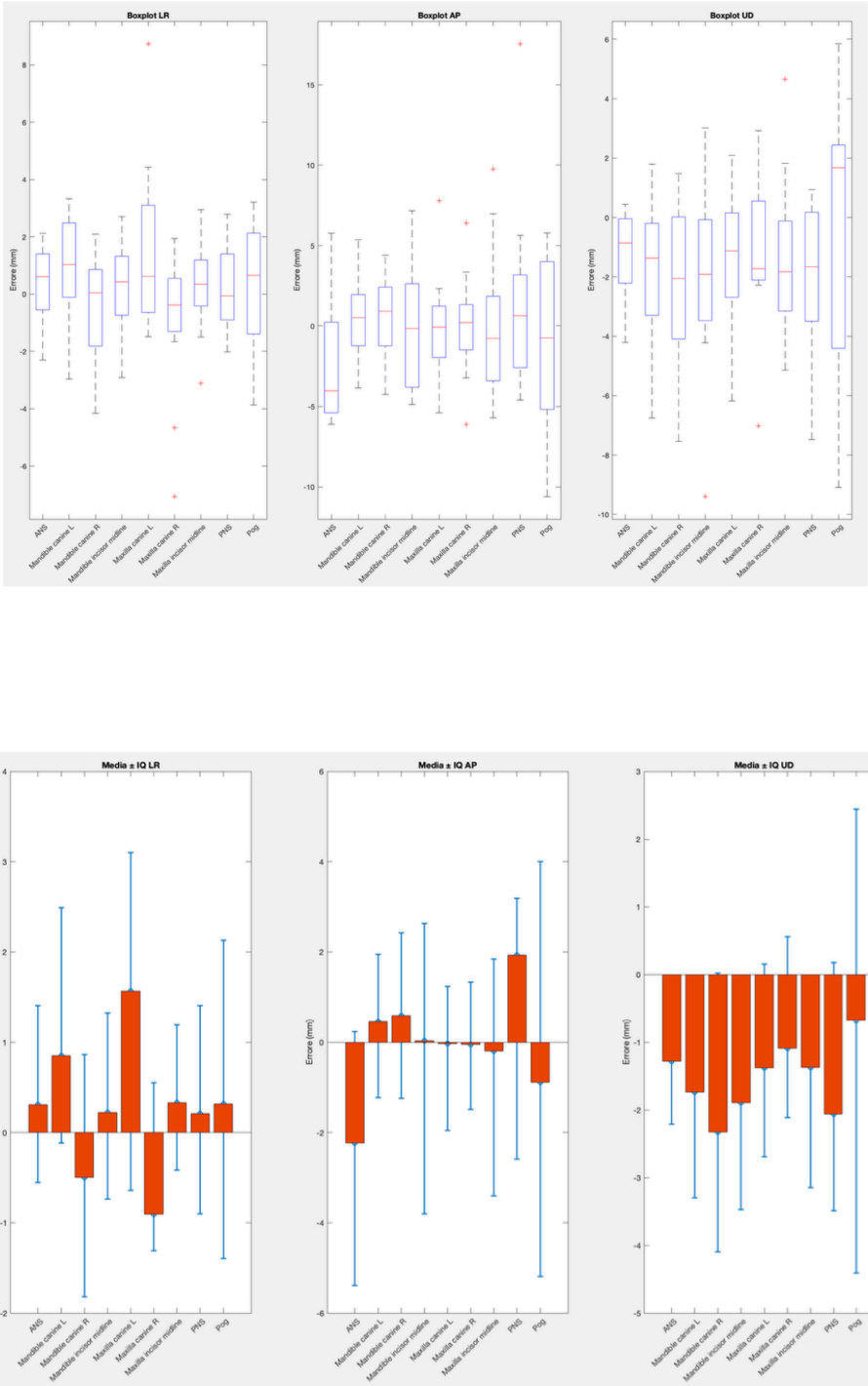
The results show that the mean deviations are generally less than 2 mm in all directions, with a greater dispersion for the mandibular region points than for the maxillary region.

Landmark	Mean_LR	Median_LR	Std_LR	IQ_LR_1	IQ_LR_2	Mean_AP	Median_AP	Std_AP	IQ_AP_1	IQ_AP_2	Mean_UD	Median_UD	Std_UD	IQ_UD_1	IQ_UD_2
ANS	0,31	0,61	1,36	-0,55	1,41	-2,23	-4,03	4,23	-5,39	0,24	-1,28	-0,86	1,43	-2,21	-0,04
Mandible canine L	0,85	1,04	1,85	-0,12	2,49	0,46	0,52	2,76	-1,23	1,95	-1,74	-1,37	2,40	-3,30	-0,20
Mandible canine R	-0,50	0,04	2,09	-1,82	0,87	0,59	0,92	2,54	-1,24	2,43	-2,33	-2,06	2,87	-4,10	0,02
Mandible incisor midline	0,22	0,43	1,79	-0,74	1,33	0,03	-0,16	3,92	-3,81	2,63	-1,90	-1,91	3,36	-3,47	-0,07
Maxilla canine L	1,57	0,62	2,80	-0,64	3,10	-0,03	-0,08	3,15	-1,96	1,23	-1,38	-1,12	2,31	-2,69	0,16
Maxilla canine R	-0,90	-0,38	2,49	-1,31	0,55	-0,04	0,22	3,08	-1,49	1,33	-1,09	-1,72	2,56	-2,11	0,56
Maxilla incisor midline	0,33	0,35	1,54	-0,42	1,20	-0,19	-0,77	4,52	-3,41	1,85	-1,37	-1,82	2,64	-3,15	-0,12
PNS	0,21	-0,06	1,64	-0,90	1,41	1,93	0,64	7,04	-2,59	3,19	-2,06	-1,66	2,85	-3,49	0,18
Pog	0,32	0,66	2,26	-1,40	2,13	-0,89	-0,75	5,29	-5,19	4,01	-0,68	1,68	4,70	-4,41	2,44

Descriptive metrics in millimeters in absolute value for each landmark and direction.

Landmark	Mean_LR	Median_LR	Std_LR	IQ_LR_1	IQ_LR_2	Mean_AP	Median_AP	Std_AP	IQ_AP_1	IQ_AP_2	Mean_UD	Median_UD	Std_UD	IQ_UD_1	IQ_UD_2
ANS	1,14	1,31	0,74	0,53	1,72	4,32	4,98	1,76	3,09	5,61	1,40	0,86	1,30	0,36	2,21
Mandible canine L	1,60	1,42	1,18	0,53	2,7	2,115	1,57	1,72	0,81	3,76	2,18	1,49	1,97	0,87	3,30
Mandible canine R	1,52	1,01	1,46	0,31	2,39	2,13	1,64	1,38	1,12	3,33	2,68	2,06	2,52	0,64	4,10
Mandible incisor midline	1,43	1,10	1,02	0,53	2,51	3,09	2,82	2,20	1,23	4,61	2,83	2,11	2,54	1,54	3,47
Maxilla canine L	2,12	0,88	2,37	0,64	3,10	2,21	1,42	2,16	0,90	2,74	2,02	1,86	1,73	0,79	2,69
Maxilla canine R	1,69	1,14	2,00	0,52	1,73	2,24	1,37	2,01	1,01	3,26	2,20	2,00	1,61	1,43	2,36
Maxilla incisor midline	1,19	0,97	0,97	0,35	1,59	3,37	2,58	2,85	1,08	5,15	2,54	1,95	1,44	1,49	3,38
PNS	1,27	0,99	0,94	0,47	2,08	4,37	2,59	5,65	0,73	5,12	2,38	1,97	2,54	0,34	3,49
Pog	1,86	2,02	1,21	0,67	2,78	4,32	5,19	2,91	2,02	5,77	3,95	3,09	2,36	2,29	5,51

Figures 39 and 40 show the boxplots and bar graphs (media±IQR) of the directional errors, respectively.



From the analysis of these figures, a tendency towards negative errors can be observed along the UD axis (downward direction), indicating an underestimation of the vertical displacement compared to what was planned.

Along the AP axis, the errors are on average larger, particularly for the Pog and PNS points, which represent greater inter-patient variability.

These results are consistent with the literature, where the anteroposterior direction is the most critical in terms of predictive accuracy due to the influence of mandibular rotation and soft tissue deformation [51,62,63].

4.6 Inferential Analysis and Significance Testing

To assess the statistical significance of the differences obtained, a Shapiro-Wilk test was initially performed on each set of errors to verify whether the distribution was normal.

Depending on the outcome ($p > 0.05$ indicates normal distribution, otherwise non-normal), a one-sample t-test was applied in the normal case, or a non-parametric Wilcoxon test, considering 0 mm as the expected reference value.

Table 16 shows the test applied for each landmark and direction, the Shapiro-Wilk and inferential test p-values, and their interpretation in terms of significance.

Tab 16 Results of normality and inferential tests.

Landmark	Direction	used test	p_Shapiro	p_value	interpretation
ANS	LR	t-test	0,55	0,43	Not significant
ANS	AP	Wilcoxon	0,01	0,17	Not significant
ANS	UD	t-test	0,17	0,01	Significativo
Mandible canine L	LR	t-test	0,71	0,14	Not significant
Mandible canine L	AP	t-test	0,90	0,58	Not significant
Mandible canine L	UD	t-test	0,80	0,03	Significativo
Mandible canine R	LR	t-test	0,17	0,43	Not significant
Mandible canine R	AP	t-test	0,96	0,44	Not significant
Mandible canine R	UD	t-test	0,45	0,02	Significativo
Mandible incisor midline	LR	t-test	0,66	0,69	Not significant
Mandible incisor midline	AP	t-test	0,65	0,98	Not significant
Mandible incisor midline	UD	t-test	0,35	0,09	Not significant
Maxilla canine L	LR	Wilcoxon	0,04	0,13	Not significant
Maxilla canine L	AP	t-test	0,14	0,97	Not significant
Maxilla canine L	UD	t-test	0,93	0,05	Not significant
Maxilla canine R	LR	Wilcoxon	0,02	0,41	Not significant
Maxilla canine R	AP	t-test	0,59	0,96	Not significant
Maxilla canine R	UD	t-test	0,06	0,15	Not significant
Maxilla incisor midline	LR	t-test	0,57	0,46	Not significant
Maxilla incisor midline	AP	t-test	0,16	0,88	Not significant
Maxilla incisor midline	UD	t-test	0,29	0,09	Not significant
PNS	LR	t-test	0,82	0,73	Not significant
PNS	AP	Wilcoxon	0,02	0,74	Not significant
PNS	UD	t-test	0,27	0,08	Not significant
Pog	LR	t-test	0,60	0,64	Not significant
Pog	AP	t-test	0,56	0,57	Not significant
Pog	UD	t-test	0,22	0,63	Not significant

The results obtained suggest that:

- In a few landmarks, the data do not follow a normal distribution and are based on the Wilcoxon test;
- Most of the differences are statistically not significant, indicating a good correspondence between the planned and the actual movement;
- In some isolated cases, in the UD direction, significant deviations are observed, suggesting a directional bias.

This approach is consistent with the recommendations of statistical analyses of accuracy in orthognathic surgery.

4.7 Results of Clinical Significance (Effect Size)

In addition to statistical significance, the effect size (Cohen's d) was also calculated for each landmark and direction, which quantifies the clinical relevance of the errors obtained.

The results, reported in Table 17, show the d values and the related qualitative classification

Most landmarks have a d value between 0.2 and 0.5, which is small, indicating that the errors do not have a clinically relevant impact.

In the LR and AP displacements, we mostly find small values, meaning minimal clinical relevance and accurate planning.

In the UD displacements, we find large values, meaning clinically relevant, indicating significant discrepancies between the two models

Only a few landmarks reach values of $d > 0.8$, indicating a moderate to large difference, due to individual variations in mandibular rotation or difficulty positioning them in the model.

This assessment highlights the importance of distinguishing between statistical and clinical significance.

Tab 17 Cohen's d values and classification of effect size magnitude.

Landmark	Direction	Cohens_d	Magnitude
ANS	LR	0,23	Small
ANS	AP	-0,53	Medium
ANS	UD	-0,90	Big
ANS	3D	3,28	Big
Mandible canine L	LR	0,46	Small
Mandible canine L	AP	0,16	Negligible
Mandible canine L	UD	-0,72	Medium
Mandible canine L	3D	1,86	Big
Mandible canine R	LR	-0,24	Small
Mandible canine R	AP	0,23	Small
Mandible canine R	UD	-0,81	Big
Mandible canine R	3D	1,81	Big
Mandible incisor midline	LR	0,12	Negligible
Mandible incisor midline	AP	0,01	Negligible
Mandible incisor midline	UD	-0,56	Medium
Mandible incisor midline	3D	1,79	Big
Maxilla canine L	LR	0,56	Medium
Maxilla canine L	AP	-0,01	Negligible
Maxilla canine L	UD	-0,60	Medium
Maxilla canine L	3D	1,57	Big
Maxilla canine R	LR	-0,36	Small
Maxilla canine R	AP	-0,01	Negligible
Maxilla canine R	UD	-0,43	Small
Maxilla canine R	3D	1,61	Big
Maxilla incisor midline	LR	0,21	Small
Maxilla incisor midline	AP	-0,04	Negligible
Maxilla incisor midline	UD	-0,52	Medium
Maxilla incisor midline	3D	2,36	Big
PNS	LR	0,13	Negligible
PNS	AP	0,27	Small
PNS	UD	-0,72	Medium
PNS	3D	1,12	Big
Pog	LR	0,14	Negligible
Pog	AP	-0,17	Negligible
Pog	UD	-0,15	Negligible
Pog	3D	2,34	Big

4.8 Results of agreement Analysis (Bland–Altman)

To assess the agreement between actual and planned values, Bland-Altman plots were constructed for each spatial direction.

They indicate, for each observation, the difference between actual and planned values as a function of their mean, allowing for the identification of any systematic biases and limits of agreement.

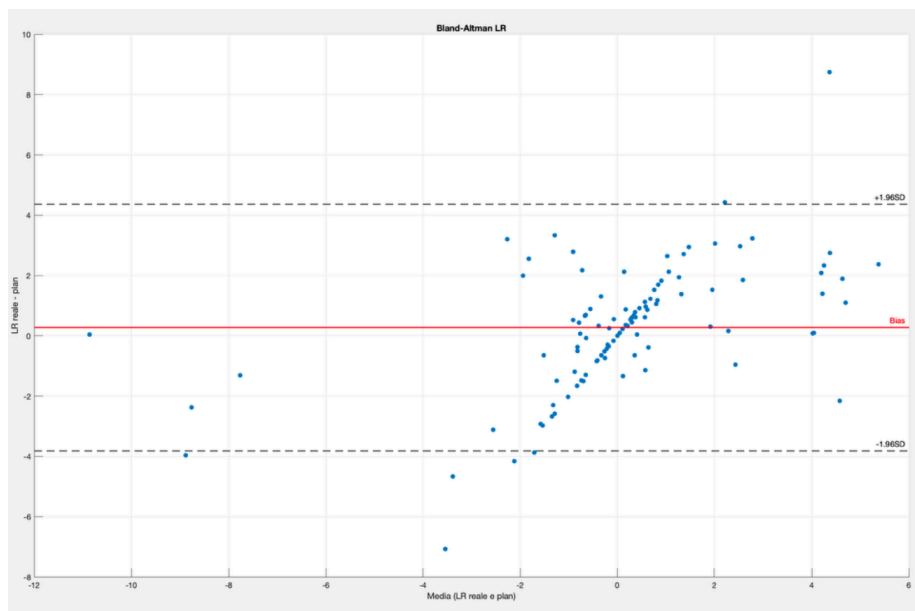


Fig 41 Bland–Altman plot for the LR direction.

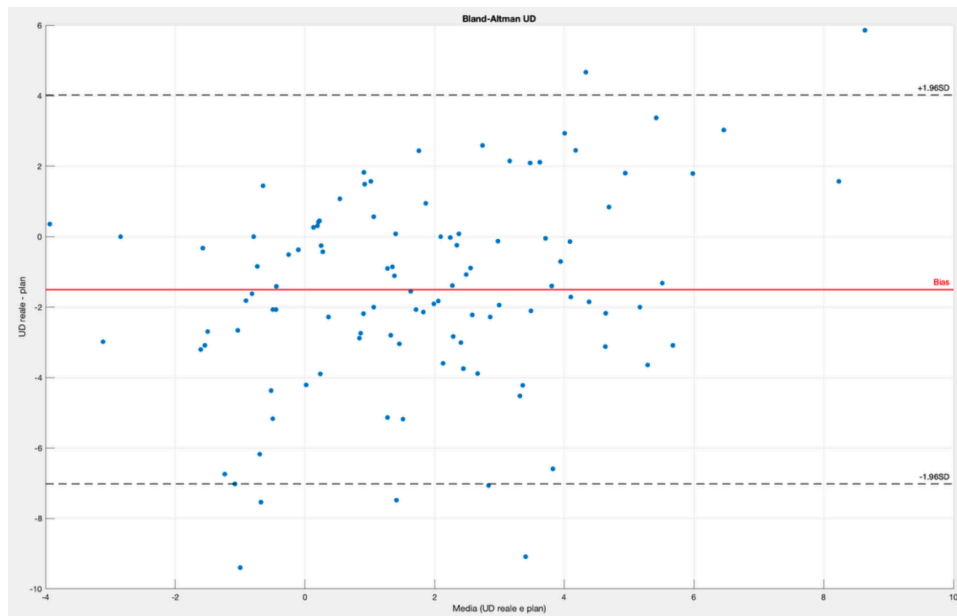


FIG 42 Bland–Altman plot for the AP direction.

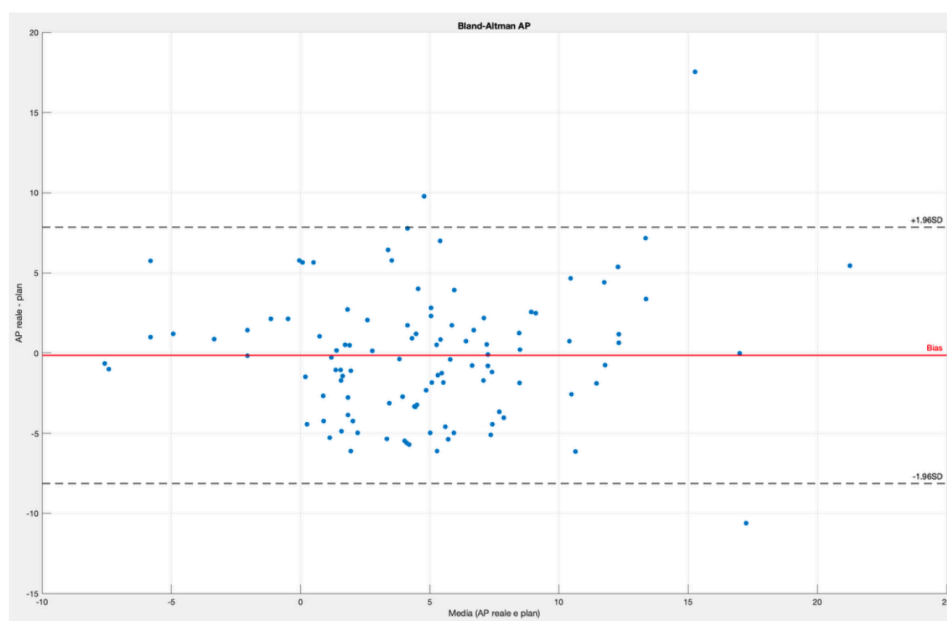


FIG 43 Bland–Altman plot for the UD direction.

In all cases, most points fall within the limits of agreement (good reliability of the virtual planning process).

The average bias is close to zero for the LR direction, slightly negative for the AP, and more marked for the UD.

This observation is compatible with what is found in the literature, where average vertical errors are around 1-2 mm [53,58]

4.9. Predictive Analysis of Soft Tissue Behavior

Preliminary Evaluation of the Similarity Model Performance

An evaluation of the baseline model was conducted to analyze the ability of the morphometric similarity method to predict three-dimensional postoperative soft tissue displacements based on preoperative morphology.

The analysis was developed simultaneously on two levels:

- a quantitative evaluation, to estimate the numerical accuracy of the predictions compared to actual values;
- a graphical evaluation, to interpret similarity relationships between patients and understand the spatial and directional distribution of errors.

The results obtained allow us to define the model's global behavior and verify its robustness as a reference for subsequent PLS-based predictive models.

Morphological Distribution of the Sample (PCA)

As a first analysis, a principal component analysis (PCA) was performed on the z-scored morphometric features of the preoperative soft tissues.

The first two principal components explain approximately 5% of the total variance.

The distribution of points in the PC1-PC2 plane highlights a high level of morphological heterogeneity among patients, with recognizable local clusters reflecting similar facial configurations.

This dispersion confirms the need for an approach based on individual similarity, rather than a single generalized model, because patients exhibit different facial geometries even when undergoing the same surgery [7,15].

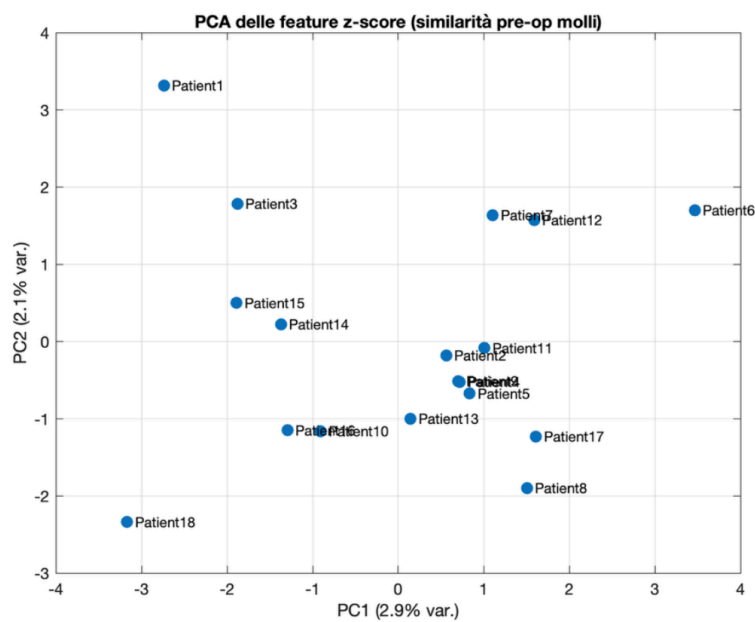


FIG 43 Distribution of patients in the morphometric space defined by the first two principal components (PCA). The highlighted areas indicate local clusters of subjects with similar morphologies.

Correlations between Morphometric Features

The correlation matrix of the z-scored morphometric vectors was calculated to verify the presence of linear relationships or redundancies between the features.

The color distribution is predominantly neutral and without homogeneous blocks with high correlation, indicating that the selected variables are weakly correlated and therefore independent in their information.

This result confirms the validity of the feature selection because they represent the different facial regions in a complementary manner and allow for a balanced assessment of similarity.

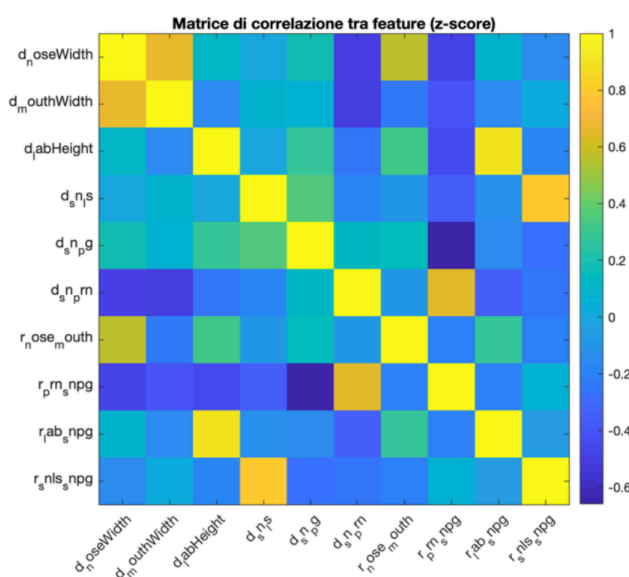


FIG 44 Correlation matrix of z-scored morphometric features. The absence of high-correlation blocks indicates that the variables capture distinct morphological aspects.

Patient Similarity Matrix

The weighted distance matrix calculated between pairs of patients shows patterns consistent with the PCA observations.

In the heatmap sorted by hierarchical clustering, blue regions along the diagonal represent smaller distances and therefore groups of morphologically similar subjects.

Clusters consistent with the visual similarity between the pre-operative models, characterized by comparable facial proportions, were identified. This behavior confirms that the z-scored similarity metric effectively discriminates morphological similarities and generates a distance structure consistent with anatomical perception.

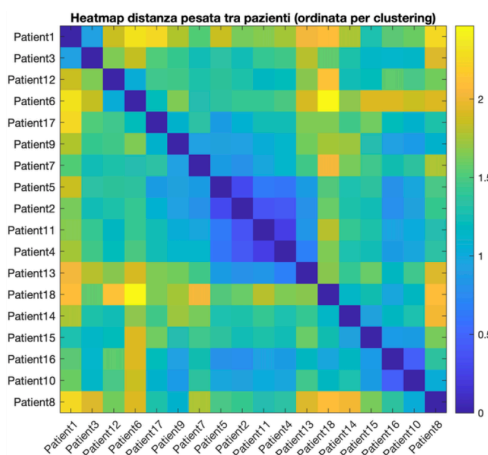


FIG 45 Weighted patient similarity matrix (heatmap) ordered by hierarchical clustering. The blue regions along the diagonal identify local morphologic clusters.

Reference Patients Weight Distribution

For each target patient, the distribution of weights assigned to the three selected reference patients in the inverse-distance weighted average was analyzed.

The normalized vertical bars show uniform balance, without a single dominant reference patient.

This indicates that the weighted combination works well, giving greater weight to the most similar subjects and maintaining a stable distribution among the three contributions.

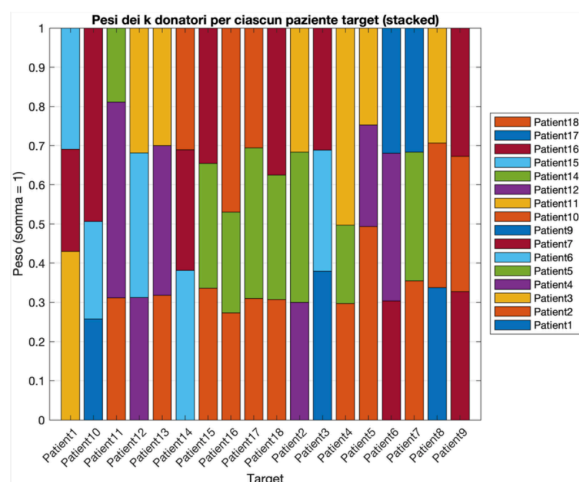


FIG 46 Distribution of the weights of the three reference patients for each target patient. The total height of the bars is normalized to 1; the balance among contributions confirms the stability of the weighted combination model.

Predictive Performance: Predicted-Actual

The relationships between predicted and actual displacements were analyzed separately for landmarks and patches.

In the predicted-actual plots, the predictions for landmarks show a weak correlation and a wider dispersion, due to the greater sensitivity of individual points to local variations or individual asymmetries.

In contrast, patches show a positive correlation and a distribution of points more aligned with the bisector, indicating better stability and directional consistency of the prediction.

The spatial aggregation of patches reduces the influence of local noise and provides a more robust representation of the overall facial deformation.

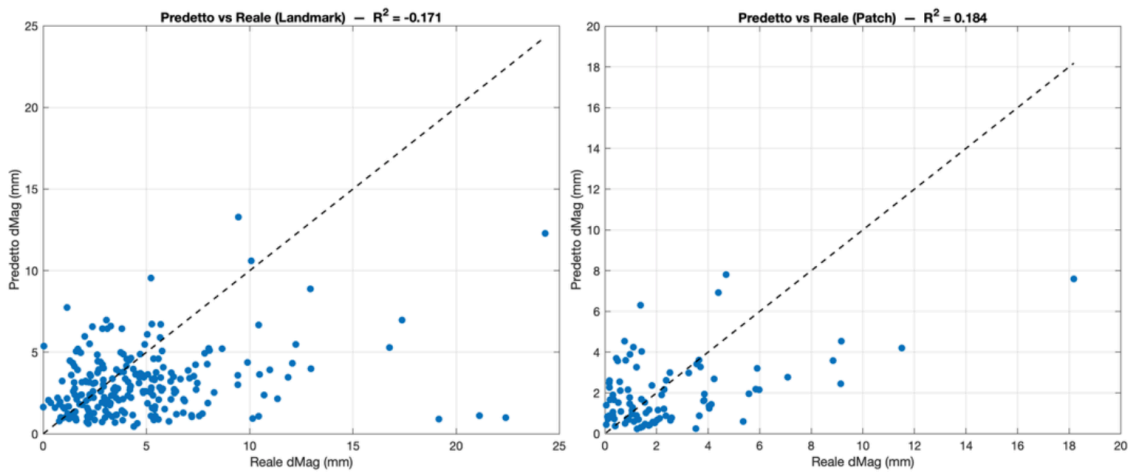


FIG 47 Predicted–Actual plots for landmarks and patches. The patches show greater consistency with the bisector compared to landmarks, indicating a more stable prediction.

Bland-Altman Concordance Analysis

The agreement between predicted and actual values was assessed using Bland-Altman plots, which allow us to quantify bias and limits of agreement (LoA).

Most points fall within the limits of agreement, with no systematic trends as a function of displacement magnitude, suggesting no systematic directional errors.

The patches are therefore confirmed to be more reliable and less susceptible to outliers than landmarks.

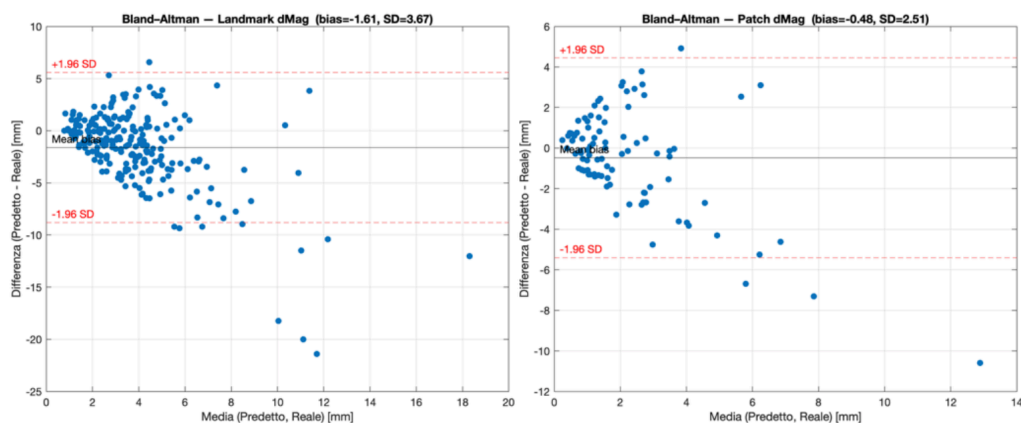


FIG 48 Bland–Altman plots for landmarks and patches. The patches show reduced bias and narrower limits of agreement, confirming higher predictive stability.

Overall, the baseline model demonstrates good stability and internal consistency, producing predictions free of significant directional bias and a low mean error.

Graphical analyses demonstrate that z-weighted morphometric similarity effectively identifies significant reference patients, while the inverse-distance weighted average provides a realistic and robust estimate of postoperative deformation.

The greater reliability of patches compared to landmarks suggests that the regional scale of analysis represents a more appropriate level for the statistical modeling of soft tissue. These results consolidate the validity of the similarity method as a quantitative baseline on which to build the PLS model described in the next chapter.

Construction of the Geometric Prediction of the Target and Normalization of reference systems

To ensure proper comparability between reference and target patients, a preliminary reference system normalization procedure was introduced, which is necessary to avoid orientation and translation errors due to the different postures acquired during CBCT scanning and segmentation.

In this phase, each subject was described within his or her own facial frame, defined on the basis of rigid and reproducible anatomical landmarks and according to criteria similar to those proposed by Swennen et al. [60]

The facial frame was constructed from the following reference points:

- X-axis: straight line passing through the right and left cheilion (transversal direction of the face);
- Y -axis: orthogonalization with respect to the X-Z plane and defined starting from the Subnasal-Pronal vector;
- Z-axis: obtained as the vector product between X and Y and with an upward

direction.

This orthonormal basis, referred to as the rotation matrix R , represents the transformation from the facial frame to the MATLAB system.

To standardize the axes conversion to those of the RAS (Right-Anterior-Superior) system, a flip was applied on X and Y using the reflection matrix $S = \text{diag}(-1, -1, 1)$, thus obtaining the rotation in the RAS system described by relation:

$$R_{RAS} = S \cdot R$$

Each real displacement vector from the reference patients (previously calculated in the LPS system) was then:

1. Converted from the LPS frame to the reference patient's facial frame;
2. Transported to the target facial frame;
3. Converted back to the target RAS system for final application.

This procedure allows for an anatomical and locally consistent reference, regardless of the absolute coordinates of the models or their global orientation in space.

In this way, the displacement maps from the reference patients can be combined and transferred with geometric accuracy, preserving the real spatial relationships of hard and soft tissues.

Combination of Displacement Maps from Reference Patients

Once normalization was performed, the displacement maps derived from the three similar reference patients, determined based on the morphometric distance calculated in the similarity phase were combined for each target.

The goal is to obtain an average three-dimensional prediction of soft tissue behavior, separated by landmark and patch.

a) Landmarks

For each landmark considered (Pronasal, Subnasal, Upper/Lower Labial, Right/Left Cheilion, Pogonion, Right/Left Gonion, Right/Left Zygion), the actual displacement vectors of the three selected reference patients were retrieved. These vectors were converted into the facial frame of the respective reference patient and then transferred to the target facial frame, where a weighted average was performed with coefficients proportional to the inverse of the morphological distance to give greater weight to the reference patients, from the most similar to the least similar.

Finally, the average vectors were converted back to the target's RAS system and applied to the preoperative landmarks to generate the predicted postoperative coordinates.

b) Patches

For each of the five anatomical patches (right nasal wing, left nasal wing, upper lip, lower lip, and chin), a local rigid approach was applied.

In the presence of the reference patients' pre- and post-operative STL models, the rigid transformation from pre- to post-operative was estimated for each subject, obtaining the rotation R_d and t_d .

These transformations were converted into the reference patient's facial frame and then subsequently transferred to the target's facial frame and its RAS, where they were combined with weighting inversely proportional to the morphometric distances.

Transfer of Predicted Maps onto the Target

In the final step, the predicted displacement maps obtained were applied to the preoperative target models to construct the geometric prediction of the postoperative face.

For landmarks, the mean vectors of the predictions obtained were added to the preoperative coordinates to produce the configuration of the predicted postoperative points and saved in .fcsv format.

For the patches, the rigid average was applied to the corresponding pre-operative STL models of the target, thus generating predicted versions representing the estimated surgical transformation.

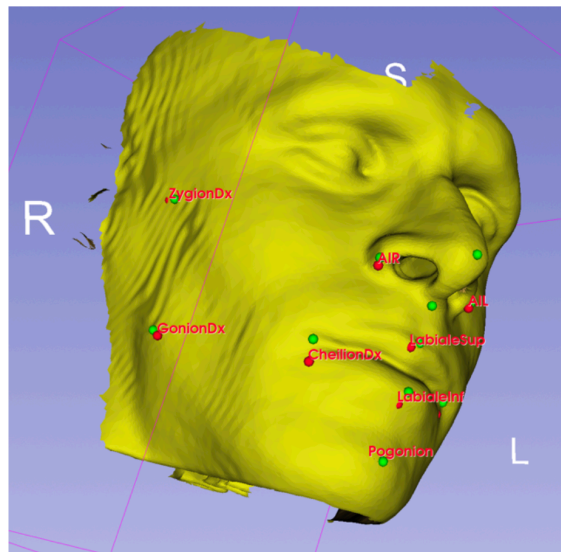


FIG 49 Post-operative model of a patient from the dataset, showing in green the actual post-operative landmarks and in red the predicted post-operative landmarks.

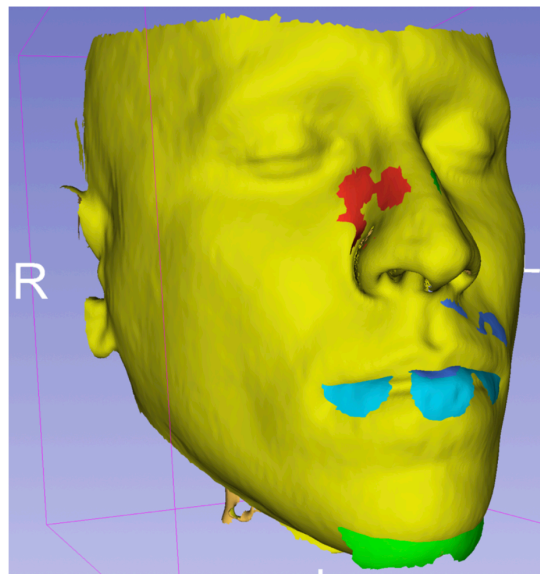


FIG 50 Actual post-operative model of a patient from the dataset showing the predicted post-operative patches obtained in this phase.

The resulting models allow for immediate visualization and comparison with the real post-operative face, both using 3D Slicer and derived quantitative measures (Δx , Δy , Δz , magnitude, rotation).

Quality and Variability Analysis of Residuals

Descriptive indicators were calculated for each patient, landmark, and patch to assess the quality of the baseline and characterize residual variability.

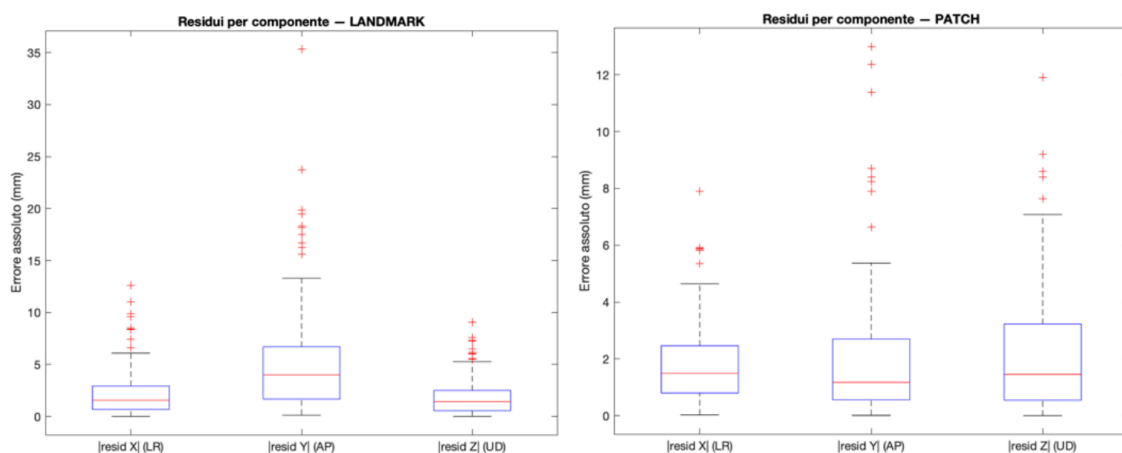
Furthermore, directional patterns by axis (LR, AP, UD) were analyzed and outliers, i.e., anomalous values, were identified using the IQR rule [41].

a) Residual distribution by component (LR, AP, UD)

The boxplots show that the anterior-posterior (AP) axis remains the most critical for landmark-based registration, while for patches, no marked differences between the components are observed.

Higher MAE and RMSE values are found for landmarks compared to patches, which describe greater variability.

These results indicate that the areal representation of the patches allows for a more stable capture of local deformations, reducing the impact of sagittal movements.



b) Directional Biases

The average of the residuals per axis shows limited directional bias for both methods.

For landmarks, the bias is more negative along the anteroposterior (AP) axis (−3.99 mm), indicating a tendency to underestimate sagittal displacement, while the LR and UD components are substantially balanced.

Patches, on the other hand, show small biases, close to zero, along all axes, suggesting better compensation for local deformations.

This bias distribution indicates that the areal representation of the patches reduces systematic directional errors compared to discrete points, confirming the stability of the registration model.

Tab 18 Mean residual bias per axis (mm) for landmarks and patches.

	LR	AP	UD
<i>Landmark</i>	+0.11 mm	-3.99 mm	-0.01 mm
<i>Patch</i>	-0.39 mm	-0.15 mm	+0.07 mm

c) Outlier Identification

Outliers were identified on the magnitude $|r|$ using the IQR (interquantile range) rule:

- Landmarks: 10 outliers;
- Patches: 4 outliers.

The outliers are mainly concentrated in highly mobile regions, such as the lips and chin, or in patients with large sagittal excursions.

No patterns attributable to systematic errors or sign reversals emerged, and the values are clinically interpretable.

In summary, the baseline is stable in all directions, with low bias for patches and higher bias for landmarks along the sagittal axis. The limited number of outliers and the absence of anomalous patterns confirm the robustness of this process.

This guides the construction of the PLS model with Y = residuals and X = z-scored morphometric features, both of which will be centered and scaled on the training folds to avoid leakage.

5. DISCUSSION

5.1 Summary

This study presents a streamlined and efficacious workflow for virtual surgical planning (VSP) and in-hospital fabrication of patient-specific surgical devices -including intermediate and final splints, as well as osteotomy cutting guides, aimed at optimizing the individualization of surgical procedures for both patients and surgeons.

The implementation of virtual surgical planning (VSP) has led to substantial advancements in preoperative strategy by improving procedural efficiency, reducing intraoperative variability, and enhancing postoperative outcomes.

The integration of in-hospital manufacturing capabilities further contributes to this improvement by significantly decreasing both the preoperative lead time and overall surgical duration, without compromising clinical accuracy or result reproducibility.

A comprehensive evaluation was conducted on the performance of CAD/CAM software systems and 3D printing technologies integrated into the digital workflow, with particular focus on their reliability in supporting the planning and execution of complex craniofacial procedures.

Furthermore, a critical review of accuracy assessment methodologies described in current literature was performed to identify prevalent limitations and methodological biases.

Drawing from this analysis, we proposed a standardized, reproducible protocol for orthognathic surgical planning, developed through interdisciplinary collaboration between surgical and biomedical engineering domains.

Finally, the integration of an innovative comparative analysis protocol between the 3D

models derived from preoperative and six-month postoperative CT/CBCT scans, developed by the Polytechnic University of Turin, allowed verification of the accuracy and strengthened the overall robustness of the proposed workflow.

5.2 Analysis

According to the literature, the main reasons that lead patients with dentofacial deformities to undergo orthodontic and orthognathic treatment are primarily aesthetic and functional in nature.⁵⁷ Pain, on the other hand, is not considered a primary motivating factor. Previous studies confirm that aesthetic improvement and its associated psychosocial benefits are perceived by patients as more relevant than functional aspects, indicating that orthognathic surgery is often sought for aesthetic purposes.[65,66]

In particular, the facial changes resulting from orthognathic surgery are perceived as improvements by the vast majority of patients, with this perception often emerging as early as two months postoperatively. [67]

Given the critical role of facial aesthetics in patients' quality of life and interpersonal relationships, our objective was to quantify changes in self-perceived aesthetics using a subjective indicator (VAS scale) pre- and post-operatively.

Patient-reported aesthetic self-assessment via VAS showed a statistically significant improvement, increasing from a mean of 3.8 preoperatively to 8.4 postoperatively.

Additionally, 76.9% of patients reported high levels of aesthetic satisfaction (VAS scores of 8, 9, or 10), indicating a substantial perceived improvement. These findings align with those of Rustemeyer et al., who reported high post-surgical aesthetic satisfaction in most patients, reinforcing that aesthetic outcome is a primary determinant of patient satisfaction following orthognathic surgery. [68]

Regarding pain, the literature suggests that residual temporomandibular joint (TMJ) pain may result from dysfunctional remodeling of the joint. The TMJ, being a load-sensitive anatomical structure, may undergo morphological changes in response to mechanical stress variations induced by orthodontic-surgical treatment. Orthodontic mechanics employed to correct skeletal malocclusions can cause significant changes in condylar positioning, potentially leading to compression and resorption. [69]

Although orthognathic surgery provides both aesthetic and functional benefits, joint pain may persist or, in some cases, worsen postoperatively. Our findings show that six months after surgery, self-reported pain during mandibular function did not change significantly compared to the preoperative period (mean VAS score increased from 2.2 to 3.5).

Nevertheless, 3 out of 13 patients reported complete absence of postoperative pain. The mean age of patients with TMJ pain was approximately 26 years, consistent with the literature, which reports a higher prevalence of TMJ disorders among young and middle-aged adults. [70,71].

We also conducted a comparative analysis of aesthetic perception between patients and surgeons. Facial Symmetry Assessments Scale showed significant improvement after surgery from both perspectives. However, the inter-observer agreement, measured using Cohen's Kappa coefficient, was 0.148 preoperatively and 0.217 postoperatively, indicating only slight agreement.

Objective evaluation using the Global Aesthetic Improvement Scale (GAIS) revealed that 10 patients (76.9%) reported a marked improvement in facial appearance, while 3 patients (23.1%) noted only a mild improvement. Surgeons rated the outcome as "very much improved" in 7 cases (53.8%) and "slightly improved" in 6 cases (46.2%). The inter-rater agreement between patients and surgeons (Kappa = 0.198) also reflected a slight level of concordance.

Cohen's Kappa coefficient is a statistical measure used to assess the degree of agreement between two raters when classifying qualitative variables. It is particularly useful in clinical research for evaluating consistency in subjective judgments beyond

chance agreement. The low concordance observed in both the symmetry assessment and GAIS scores may be attributed to differing perceptions of “quality” in aesthetic outcomes between clinicians and patients.

Clinical examination at the six-month follow-up revealed that none of the patients reported sensory deficits, including partial (hypoesthesia) or complete (anesthesia) loss of sensation.

However, 53.9% reported persistent tingling in the lower lip and chin (paresthesia). This finding supports existing literature, which recognizes neurosensory disturbance as a well-known and often unavoidable complication of orthognathic surgery. Nerve injury can be direct—due to surgical instruments—or indirect, related to edema or hematoma formation.

In general, nerve damage is associated with the type of mandibular osteotomy, placement of rigid fixation devices, concomitant procedures, and the surgeon’s experience. [72]

Sensory alterations following orthognathic surgery may include hypoesthesia, paresthesia, and dysesthesia. [73]

The recovery timeline for neurosensory injury varies between individuals, typically progressing more rapidly in the first six postoperative weeks and more slowly thereafter. [74] Although most patients experience gradual recovery, some sensory changes may be permanent.

Sensory retraining therapy—consisting of simple facial exercises performed daily with a soft cosmetic brush and a mirror—has proven to be an effective cognitive-behavioral strategy to reduce residual numbness. At six months postoperatively, patients who performed these exercises reported fewer complaints of persistent numbness and sensory loss. [75]

The six-month follow-up data confirmed that no patients required revision surgery, supporting the absence of both early (within 30 days) and late (up to six months)

complications. Furthermore, none reported infectious episodes necessitating antibiotic therapy or specialist reevaluation.

The scientific literature emphasizes that virtual surgical planning represents a fundamental tool in supporting the surgeon in translating the operative plan into a clinical outcome that is as accurate and reproducible as possible.[76,77].

By superimposing preoperative and postoperative three-dimensional (3D) models derived from DICOM files of the corresponding computed tomography (CT) acquisitions, it was possible to assess the extent of skeletal displacements using specific anatomical reference landmarks: the Anterior Nasal Spine (ANS), the Mandibular Incisor Midline (MIM), and the Pogonion (Pog). The magnitude of genioplasty movement was determined by calculating the difference between the Pogonion and MIM positions ($\text{Genioplasty} = \text{Pog} - \text{MIM}$).

Overall, the results demonstrate that the average three-dimensional error remains below 2 mm, a threshold widely regarded as clinically acceptable for orthognathic surgery [3,38,44]. The most pronounced directional biases are observed along the anteroposterior (AP) and up–down (UD) axes, where individual anatomical variability and the inherent difficulty in accurately simulating mandibular rotation may introduce deviations [78]. It is important to emphasize that ensuring precision in the vertical movement of the maxillary complex is more challenging than in advancement. Unlike horizontal movements, there are currently no intraoperative devices capable of reliably controlling and verifying vertical displacements. As a result, the amount of movement cannot be objectively measured during surgery and is instead assessed clinically by the surgeon. This makes vertical displacement less aligned with the virtual plan.

For genioplasty, the difference between the postoperative value (5.68 mm) and the planned value (4.03 mm) showed a mean discrepancy of 1.65 mm (SD, 3.03), which also falls within the 95% confidence interval (CI: -0.27 to 3.57). However, the result is not statistically significant due to the inclusion of zero within the interval. Despite this, the skeletal discrepancy remains within the ± 2 mm threshold established by the

literature. The relatively large standard deviation (3.03 mm) reflects high variability within the cohort, which can be partly explained by the technical nature of genioplasty. Unlike maxillary and mandibular movements, genioplasty is often performed “freehand” without rigid surgical guides [78]. Supporting this, it was observed that among the six virtual genioplasty plans, only two included the use of cutting guides. To enhance accuracy and fidelity in genioplasty, the systematic production and adoption of specific surgical guides is advisable, even though the literature reports no statistically significant differences between guided and freehand techniques. [78]

Pogonion (10.83 mm) exceeded the planned value (8.74 mm) by 2.09 mm (SD, 4.08). The high standard deviation indicates a wide dispersion of values within the sample. This variability is expected, as the Pogonion is indirectly influenced by the extent of genioplasty itself. Although the discrepancy falls within the confidence interval—which includes zero and is thus not statistically significant—it suggests that the obtained displacement was not significantly greater than planned.

All three parameters (maxillary advancement, mandibular advancement, and genioplasty) showed a trend toward greater postoperative values compared to the planned values, with the most notable increases observed in the chin (genioplasty) and Pogonion, followed by the mandible. Although a consistent trend of postoperative increase is evident across all three parameters, none of the differences reached statistical significance.

Inter-patient variability is greatest for mandibular landmarks, a finding that is consistent with previously published studies [63]. Furthermore, the strong concordance between the virtual planning and postoperative outcomes, as evidenced by the Bland–Altman analyses, confirms the high reliability of the adopted workflow.

An important part of this thesis focuses on the development of a predictive model capable of quantitatively and three-dimensionally estimating the response of facial soft tissues following orthognathic surgery. The aim is to understand and predict how

skeletal movements translate into changes in the skin surface, with the ultimate goal of improving the accuracy and aesthetic predictability of postoperative outcomes.

Accurate modeling of soft tissue behavior represents a crucial step in surgical planning, as it allows for the anticipation of the aesthetic effects of the intervention and supports the surgeon in selecting the most appropriate surgical strategy. However, the complex and nonlinear nature of soft tissues, influenced by multiple individual biomechanical and morphological variables, necessitates the use of advanced statistical approaches capable of capturing these multidimensional relationships.

Accurate prediction of soft tissue response is one of the most complex aspects of orthognathic surgical planning. Although modern Virtual Surgical Planning (VSP) techniques have greatly improved the accuracy of simulating bone displacements, prediction of soft tissue behavior remains an open problem due to its biomechanical nonlinearity and interindividual variability related to anatomical, elastic, and surgical factors [60,63].

Several studies have shown that, for the same skeletal displacement, soft tissue deformations do not follow constant proportions but depend on the degree of local skin tension, the relative position of the fascial planes, and the mechanical properties of the dermis and subcutaneous tissue [4,19,27]. This makes it difficult to transfer bone transformations to the facial surface without introducing systematic errors.

In clinical practice, visual prediction of the aesthetic outcome is based on simplified geometric simulations or commercial "black-box" approaches, which provide qualitatively good results but are difficult to interpret from an engineering perspective [12,28]. For this reason, scientific interest has focused on quantitative and data-driven models capable of learning the statistical relationships between preoperative morphology and actual post- surgical changes.

The prediction results showed that the morphometric similarity model

combined with PLS regression provided a consistent and quantitatively valid estimate of postoperative facial displacements.

The average errors below 3 mm for most landmarks and patches confirm the model's ability to capture the fundamental geometric relationships between hard and soft tissues.

It was also observed that the patch-based approach was more stable than the landmark-based one, likely due to the local averaging effect of the deformations, as also highlighted in the literature [79]. In direct comparison, a conceptual coherence emerges between the two purposes: the vertical underestimation observed in planning is also reflected in the soft tissue prediction, suggesting a direct correlation between residual skeletal error and simulated skin response.

From a clinical perspective, the results demonstrate that VSP can be considered reliable and clinically relevant, with discrepancies below the accepted threshold of 2 mm [38].

However, vertical variability suggests the need for improved intraoperative control of vertical movements and rotations of the maxilla.

Regarding soft tissue, the PLS model's ability to reproduce the direction and magnitude of movements provides a useful tool to support the surgeon in preoperative communication with the patient and improves the perception of the aesthetic result.

From an engineering perspective, the developed workflow stands out for:

- The automatic integration of geometric analysis, statistics, and machine learning techniques;
- The reproducibility of results, thanks to the use of open-source software;
- The scalability of the predictive model, which can be expanded to include new subjects or morphometric variables without modifying the pipeline.

This approach represents a step towards quantitative and data-driven surgical planning, overcoming the empirical limitations of traditional models.

The entire experimental workflow proved to be robust, traceable, and repeatable, confirming the validity of the proposed approach for quantitatively analyzing the relationships between bone displacements and soft tissue responses.

The combination of rigid alignment and subsequent ICP optimization provided consistent results, with low registration errors and high reproducibility. The use of orbital and canthal landmarks as references ensured a reliable rigid base and minimized the propagation of local errors to mobile facial areas.

The baseline based on the weighted average of the three most similar patients showed low mean MAE errors and also the absence of significant systematic biases in the Bland-Altman plots. Patch analysis showed stable improvement compared to individual landmarks, suggesting that the distributed spatial representation attenuates local variations due to individual anatomical differences.

The integration of the PLS model with the baseline model allowed us to identify robust linear relationships between hard tissue displacements and soft tissue responses.

The R^2 and Q^2 values, less than 0.5, indicate the absence of overfitting and adequate model complexity for the small sample, in line with what is reported in the literature for small datasets [5,45,49].

Although these values do not represent high correlations, the stability of the LOOCV performance and the absence of anomalous oscillations in the component error curves confirm the goodness of the fit and the model's ability to generalize to subjects in the same domain.

VIP analysis allowed us to identify the most relevant morphometric predictors, highlighting the facial areas most involved in transmitting bone movements to soft

tissues. The limited number of latent components used ensured a balance between accuracy and clinical interpretability of the model.

Overall, the validity of the workflow is supported by:

- Methodological consistency across the different phases (segmentation, registration, statistical analysis, modeling);
- Stable predictive performance free of overfitting, with low MAE and minimal directional bias;
- Scalability and reproducibility of the process, thanks to the use of open-source software and a standardized calculation flow.

These elements make the proposed workflow a reliable foundation for future data-driven predictive developments, while maintaining strong clinical consistency and anatomical interpretability.

5.3 Study Limitations

Despite the encouraging results, this work presents some limitations:

- Small number of subjects

The sample size represents the main limitation of the study, affecting the statistical robustness of the analyses and the ability of the PLS model to capture interindividual variability. This large sample size, however, is consistent with most methodological studies on soft tissue prediction in orthognathic surgery [4,5,18,45], in which the primary goal is workflow validation rather than clinical generalization.

- Heterogeneity of radiological data

Slight differences in CT protocols can introduce minor geometric discrepancies between subjects. This condition is common in studies integrating real-world clinical

data [21,35], but the impact is limited thanks to the uniform application of the segmentation and registration pipeline, which reduces systematic deviations below the clinical threshold of 2 mm [80,81].

- Absence of dynamic or biomechanical modeling

The proposed model is static and based on linear morphometric relationships, without including muscle behavior or time-dependent tissue response. This choice is intentional and consistent with the goal of maintaining an interpretable and data-driven workflow, as already adopted in Suh et al. [5] and Ruggiero et al. [18].

However, it represents a simplification that limits the ability to describe local nonlinear phenomena.

- Sample and anatomical variability

The model was trained and validated on patients belonging to a specific category of surgically treated malocclusion. Although the PLS method reduces the impact of collinearity and handles small datasets well [49], the lack of subjects belonging to different skeletal classes limits the possibility of generalizing the observed relationships to more heterogeneous populations.

5.4 Conclusions

For the first time within the Department of Maxillofacial Surgery at Hospital (Molinette), University of Turin, the implementation of a fully digital, in-hospital virtual surgical planning (VSP) protocol for orthognathic surgery. The establishment of the three-dimensional printing laboratory, “Lab 3D,” enabled the development of an integrated and synergistic collaboration between maxillofacial surgeons and biomedical engineers, fostering the translation of digital planning into routine clinical practice.

The proposed workflow is based on a fully digital and in-house process, starting from the acquisition of craniofacial computed tomography (CT) DICOM data and digital intraoral scans, and extending to the design and fabrication of patient-specific surgical devices, including intermediate and final splints as well as cutting guides. This approach ensured a high-fidelity transfer of the virtual surgical plan to the operating room, resulting in a standardized, accurate, and reproducible surgical workflow.

The accuracy and reliability of the virtual surgical planning process were confirmed through the analysis of radiological and clinical outcomes, demonstrating both temporal stability and reproducibility. In addition, patient-reported outcomes indicated high levels of postoperative aesthetic satisfaction, further supporting the clinical validity of the proposed protocol.

Beyond its clinical implications, virtual surgical planning proved to be a valuable educational and training tool. By reducing the gap between expert and less experienced surgeons, the digital workflow contributes to the standardization of surgical outcomes and enhances procedural consistency. The in-hospital 3D platform facilitates the acquisition of competencies in imaging interpretation, surgical simulation, and preoperative decision-making within a controlled and risk-free environment, promoting active collaboration between junior and senior surgeons.

Overall, the results of this work demonstrate that the integration of virtual surgical planning and in-hospital additive manufacturing represents a reliable, scalable, and clinically meaningful advancement in orthognathic surgery. The proposed approach lays a solid foundation for future developments in data-driven surgical planning, personalized treatment strategies, and advanced predictive modeling of hard and soft tissue responses.

Regarding the prediction of the soft tissue the results obtained in this study demonstrated the possibility of modeling soft tissue response through a statistical approach based on Partial Least Squares (PLS), applied to the residuals between geometric prediction and actual post-operative configuration.

Even though it is based on a limited number of cases, the model showed consistent behavior without overfitting, confirming the validity of the method and the robustness of the implemented alignment, normalization, and validation procedures.

5.5 Future Perspectives

Future developments may focus on several areas:

- Expanding the dataset with new patients to improve the statistical robustness of the model and include different malocclusion patterns.
- Applying advanced machine learning techniques (e.g., Random Forest, interpretable neural networks) to explore nonlinear relationships while maintaining clinical traceability.
- Implementing the developed workflow in a clinical setting, with a simplified interface for real-time predictive visualization.
- Prospective multicenter validation to compare the model's predictive accuracy across different maxillofacial surgery departments.

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