Contemporary Approaches in Osas: Orthognathic Surgery & Crucial Role of Digital Planning

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To Cite This Chapter

Erdemgil, D. İ., & Ak, K. B. (2024). Contemporary Approaches in Osas: Orthognathic Surgery & Crucial Role of Digital Planning. In F. Zerrin Saltan, H. Arıkan & Y. Uzun (Eds.), *Current Studies in Basic Sciences, Engineering and Technology 2024* (pp. 1-16). ISRES Publishing.

Introduction

Sleep-disordered breathing (SDB) refers to a group of conditions characterized by abnormal respiratory patterns during sleep, which includes obstructive sleep apnea (OSA) and central sleep apnea (CSA). These conditions can lead to significant morbidity and mortality, affecting individuals of all ages, from children to adults. OSA is the most prevalent form, primarily caused by direct physical airway blockage. In contrast, CSA is caused by a lack of respiratory effort due to failure in the central nervous system's respiratory control centers. CSA is often associated with various comorbidities, including heart failure, opioid use, and neurological disorders (Foldvary-Schaefer & Waters, 2017; Sateia, 2014).

Obstructive Sleep Apnea Syndrome (OSAS) is a clinical condition marked by repeated episodes of complete (apnea) or partial (hypopnea) blockage of the upper airway during sleep, each lasting more than 10 seconds, despite ongoing thoracoabdominal movements. Apnea episodes lead to improper nocturnal alveolar ventilation, resulting in decreased oxygen saturation and increased blood pressure. Consequently, this condition disrupts sleep, causes hypoxia, and leads to a range of cognitive, behavioral, and metabolic consequences (Sateia, 2014).

The diagnosis of OSAS primarily relies on polysomnography (PSG), considered the gold standard. Comprehensive sleep evaluations and follow-ups are essential for accurate diagnosis.

The management of OSAS requires a multidisciplinary approach. Treatments for obstructive sleep apnea syndrome include continuous positive airway pressure (CPAP), weight loss, exercise, myofunctional therapy, and various surgical options such as maxillomandibular advancement (MMA) and uvulopalatopharyngoplasty. CPAP remains the most effective and widely recommended treatment, significantly improving symptoms and quality of life. Exercise and weight loss are beneficial adjuncts, particularly for overall health. Myofunctional therapy offers a promising alternative for reducing symptoms, especially for those who cannot tolerate CPAP. Surgical options are available but vary in effectiveness, with maxillomandibular advancement showing the highest success rates. Further research is needed to optimize treatment strategies and explore new therapeutic avenues (Abbasi et al., 2021, Foldvary-Schaefer & Waters, 2017).

Orthognathic surgery (OS) can be performed via Le Fort I osteotomy (LFIO) and bilateral sagittal split ramus osteotomy (BSSRO) with or without genioplasty, which is a highly effective surgical treatment for OSAS. This procedure significantly reduces the apnea-hypopnea index (AHI) and respiratory disturbance index (RDI) scores, high surgical success and cure rates, and long-term improvements in sleep quality and overall health. While MMA is more effective than some other surgical options, its complication rate is higher than that of standard orthognathic surgery procedures. Overall, MMA is a valuable option for patients with OSA, particularly those who are intolerant to CPAP therapy (Gottsauner-Wolf et al., 2018; Spyropoulou et al., 2022).

MMA increases upper airway volume by repositioning muscle attachments, which repositions the tongue and hyoid bone. However, this procedure can cause unesthetic results in patients without maxillary hypoplasia, especially in the paranasal regions. In this context, OS aims to enlarge the airway in OSAS patients while ensuring facial aesthetics. To achieve this, counterclockwise rotation (CCWR) of the maxillomandibular complex is used to treat OSAS patients where maxillary advancement is not required (Caples et al., 2010; Wei et al., 2017).

Virtual surgical planning (VSP) has revolutionized orthognathic surgery, particularly in treating patients with skeletal-dental abnormalities and OSAS. Computed tomography (CT) based VSP illustrates the postoperative outcomes in a three-dimensional plane before the operation. It allows the surgeon to analyze these data to optimize facial aesthetics and functional outcomes by exploring and simulating different surgical options without risking the patient. Therefore, it provides accurate and predictable movements of the maxillofacial skeleton (Alkhayer et al., 2020; Chen et al., 2021).

VSP based on patient-specific 3D reconstructed CT scans allows for the identification of anatomic sites of obstruction, aiding in determining the extent of airway obstruction and the necessary advancements and impactions during skeletal surgery for OSA. Moreover, VSP can assist in establishing target endpoints for distraction procedures, such as mandibular distraction, by enhancing precision and reducing complications (Ha et al., 2023; Resnick, 2018).

Customized surgical treatment planning is essential for patients with OSAS, considering diverse skeletal-dental and soft-tissue patterns to achieve favorable changes in facial esthetics and sleep function. Integrating VSP with maxillofacial surgery has significantly improved surgical planning for patients with OSAS, enabling more accurate and predictable postoperative outcomes. Additionally, VSP has been shown to decrease surgical time and increase surgical accuracy in various medical fields, including maxillofacial surgery (Hua et al., 2019). By utilizing VSP, surgeons can perform complete virtual planning for operations, leading to simplified and more accurate surgical procedures (Klasen et al., 2022).

In conclusion, VSP is crucial in enhancing surgical planning and outcomes for patients with OSAS. Its ability to provide precise preoperative simulations, individualized treatment plans, and improved surgical accuracy makes it a valuable tool in modern healthcare, benefiting patients and healthcare providers (Ha et al., 2023).

This chapter focuses on the impact of digital planning on the success and aesthetic outcomes of orthognathic surgery in patients diagnosed with OSAS with/without dentofacial deformities.

Obstructive Sleep Apnea Syndrome (OSAS)

OSAS is a severe and widespread condition that affects both adults and children with a higher prevalence in men and the elderly, leading to significant cognitive, psychological, and physiological consequences. It is characterized by repeated episodes of upper airway obstruction during sleep, causing disrupted sleep, intermittent hypoxemia, and impacting daytime functioning and cognitive abilities (Sforza & Roche, 2012; Vaessen et al., 2015).

This condition's prevalence is on the rise due to increasing obesity rates and improved diagnostic tools. Common symptoms include snoring, difficulty breathing during sleep, and excessive daytime sleepiness in adults, while children may exhibit hyperactivity and behavioral problems (Lyons et al., 2020; Prajsuchanai et al., 2022).

OSAS leads to intermittent hypoxia, triggering oxidative stress and inflammation, which contributes to cardiovascular and metabolic health issues. Furthermore, the condition is linked with increased risks of hypertension, cardiovascular diseases, and overall mortality. Cognitive impairments associated with OSAS, particularly in attention, working memory, episodic memory, and executive functions, are partially reversible with treatment, but some residual impairments may persist. It is also worth noting that there is a significant overlap between OSAS and psychiatric comorbidities, especially depressive symptoms and anxiety disorders (May & Mehra, 2014).

Effective diagnosis and treatment are crucial, with CPAP being the most common therapy. However, a multidisciplinary approach encompassing lifestyle changes and alternative treatments is often necessary to manage the condition and improve patients' quality of life (Randerath et al., 2021).

Airway Anatomy in OSAS and Dentofacial Deformities

The respiratory system, consisting of the airways, lungs, and associated structures, plays a vital role in gas (O2 & CO2) exchange. Understanding the intricate details of airway anatomy and physiology is critical to comprehending respiratory health and diseases (Strohl et al., 2012).

Mechanical forces acting on the airways are also pivotal in airway physiology. They influence airway development, health, and disease, showcasing the profound impact of the mechanical environment on airway structure and function. Moreover, airway compliance, cartilage, and smooth muscle collectively contribute to the overall mechanical properties of the airways, influencing their responsiveness and ability to uphold patency (Abramson et al., 2010).

OSAS patients have higher upper airway resistance, which is correlated with anatomical variables such as the length of the soft palate and the position of the hyoid bone, also lung cancer has been reported (Sircu et al., 2023).

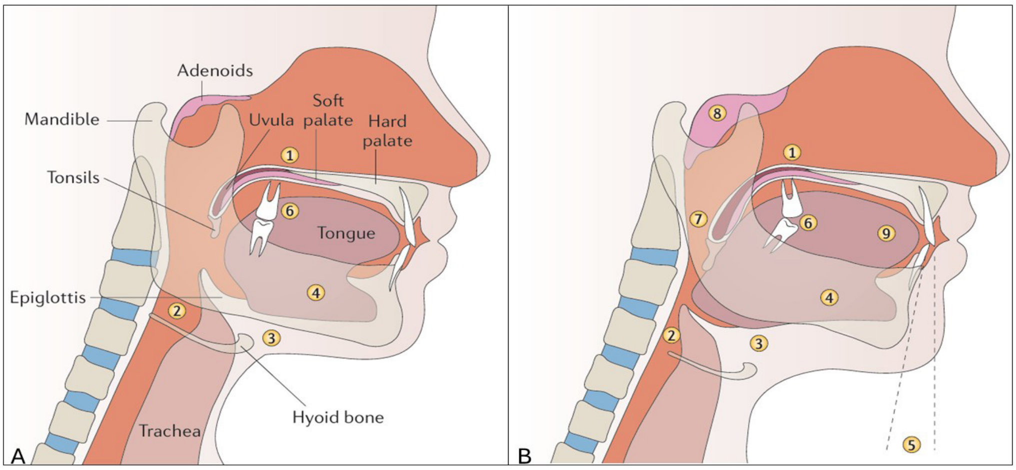
Obstructive sleep apnea (OSA) and other sleep disorders are often present with various oral health issues, including gingivitis, periodontitis, dry mouth, halitosis, and recurrent throat infections. The Mallampati classification, which evaluates the visibility of the soft palate and uvula, is commonly used to assess the risk of OSA and for pre-anesthetic evaluation, particularly when intubation may be necessary. Bruxism (teeth grinding) is often an early indicator of sleep apnea. This grinding can result in tooth attrition and wear facets on the incisors, suggesting the patient may be pushing the mandible forward to help open the airway during sleep. Clenching can damage teeth, leading to regressive changes in tooth structure, gingival inflammation, recession, and an increased risk of dental caries due to weakened enamel (Jokubauskas et al,2017).

Tongue crenulations, or scalloped borders, indicate that the patient is habitually pressing the tongue against the mandibular teeth, possibly to improve airflow. This can also result in anterior or lateral open-bite relationships between opposing teeth. Additionally, dimpling on the functional cusps and the lingual or palatal surfaces of the teeth can indicate gastroesophageal reflux disorder, which is associated with OSA. Other oral features linked to OSA include orofacial pain, reduced jaw size, and erythema in the larynx and pharynx due to snoring and mouth breathing (Padmanabhan et al., 2020).

In OSA patients, the most common physical examination finding is narrowing of the oropharyngeal airway, with or without soft tissue deposition. Other factors that contribute to airway narrowing include retrognathia, micrognathia, tonsillar hypertrophy, macroglossia, and an inferiorly displaced hyoid bone (Biradar et al., 2023; Deegan & McNicholas, 1995).

Figure 1

Maxillofacial and Soft Tissue Changes Occurring in OSAS



a. Normal anatomy. B. Typical anatomical changes in obstructive sleep apnea syndrome (OSAS): a long soft palate and enlarged uvula (1); a reduced retroglossal pharyngeal airway space (2); an increased distance between the hyoid bone and the mandible (3); a shorter and more vertical mandible (4); a retro-position of the mandible, which is measured by the angle (retrognathia) (5); dental overbite or loss of normal dental occlusion (6); tonsillar hypertrophy (7); adenoid hypertrophy (8); and macroglossia (unusual large tongue) (9). (Lévy et al., 2015)

Mandibular hypoplasia and vertical growth patterns are strongly linked to airway obstruction, particularly in the oropharyngeal and hypopharyngeal regions. Recent Computed Tomography (CT) studies have shown that individuals with mandibular hypoplasia exhibit narrower pharyngeal airways compared to those with Class I skeletal relationships. Additionally, longitudinal studies confirm that these patients maintain smaller airway volumes throughout pre- and post-pubertal periods. Key anatomical features of mandibular hypoplasia, including mandibular retrognathia, a shortened mandibular corpus or ramus, and posterior mandibular rotation, contribute to nasopharyngeal and oropharyngeal narrowing. This narrowing can lead to improper tongue positioning and respiratory issues such as snoring, increased upper airway resistance, and a heightened risk of obstructive sleep apnea (OSA) (Jung & Kim, 2015; Kurbanova et al., 2021).

The position of the hyoid bone in individuals with Class II malocclusion and obstructive sleep apnea syndrome (OSAS) is a critical area of study due to its implications for airway management and treatment outcomes. Class II malocclusion is characterized by a retruded mandible, which can influence the positioning of the hyoid bone and subsequently affect the airway space. Research indicates that the hyoid bone is often positioned lower in patients with OSAS, which can exacerbate airway obstruction during sleep (Anand et al, 2020; Jung & Kim, 2015).

Studies have demonstrated a strong correlation between the hyoid bone's position and OSAS severity, highlighting that a lower hyoid position is often associated with a narrower retro-lingual space and increased airway obstruction due to the tongue base's downward displacement. Inferior hyoid positioning is commonly observed in severe

OSAS cases, suggesting that this anatomical change may result from the disorder rather than being a predisposing factor. Additionally, findings indicate that the hyoid bone tends to sit lower in OSAS patients than in healthy individuals, underscoring a notable anatomical alteration linked to the condition (Cho et al., 2019; Wang et al., 2012).

The interaction between facial morphology and hyoid position further underscores airway compromise risks, especially in Class II malocclusion, where features such as increased facial height and clockwise mandibular rotation contribute to a lower hyoid position. This positioning correlates with a higher apnea-hypopnea index (AHI), indicating its role in exacerbating sleep apnea severity. Moreover, caudal displacement of the hyoid during sleep is a defining characteristic of OSAS, often contributing to impaired swallowing and heightened aspiration risk. In adults, six anatomical factors correlate with OSA severity: the size of the hypopharynx and oropharynx, the inferior position of the hyoid bone, mandibular rotation, sagittal maxillomandibular position, and BMI. Studies indicate that adult OSA patients often have longer airways, shorter skull bases, macroglossia, or elongated soft palates (Kurbanova et al., 2021; Tanellari et al., 2022).

Obstructive Sleep Apnea Syndrome Treatment with Orthognathic Surgery (OS)

OS, particularly the maxillary Le Fort I osteotomy combined with bilateral mandibular ramus sagittal split osteotomy, is widely used to treat OSAS. The combined use of these maxillary and mandibular osteotomies often results in greater advancement of jaw structures, leading to improved outcomes. Notably, Wolford and colleagues emphasized that a counterclockwise advancement of both the maxilla and mandible not only maximizes the posterior airway space (PAS) but also enhances facial aesthetics. Additional procedures such as septoplasty, turbinectomies, nasal reconstruction, and uvulopalatopharyngoplasty can be performed alongside these procedures (Brunetto et al., 2014; Caples et al., 2010).

Maxillomandibular advancement surgery, which advances both the maxilla and mandible, relocates the hyoglossus muscle insert (Sakamoto, 2017) and increases buccopharyngeal volume, leading to the enlargement of the velo-oropharyngeal and hypopharyngeal airways, as well as the advancement of the tongue and hyoid bone. MMA is highly effective in increasing airway dimensions and reducing pharyngeal collapsibility during inspiration, making it the most effective craniofacial surgical technique for treating OSAS in adults. Of the upper airway dilator muscles, the musculus uvulae, tensor veli palatini, levator veli palatini, and palatoglossus are attached to the jaw and comprise the soft palate muscles. These muscles strongly influence the morphology of the velopharynx. Jaw advancement affects the soft palate muscles, and the velopharyngeal space is expanded 3 dimensionally by each of those muscles. The surgery advances the anterior pharyngeal tissues, including the soft palate, tongue base, and suprahyoid musculature, without directly manipulating the pharyngeal tissues. Even without maxillomandibular horizontal deficiency, MMA is effective in patients with hypopharyngeal or velo-orohypopharyngeal narrowing. Especially the advancement of the maxilla results in the maximal expansion of the velopharyngeal space in patients with OSA (Gokce et al., 2014; Okushi et al., 2011).

There is no universally accepted standard for maxillomandibular advancement amount, and no direct correlation has been established between the degree of advancement and the reduction in the apnea-hypopnea index (AHI). However, in most cases, advancements are typically within the range of 5–10 mm for the maxilla and 10–12 mm for the mandible (Patel et al., 2024).

Maxillomandibular advancement surgery may be recommended for OSA patients based on three key criteria:

1-OSA Diagnosis During Orthodontic-Surgical Assessment: When OSA is diagnosed during the routine evaluation of a patient being considered for orthognathic surgery, it may necessitate a change in the surgical plan. This could involve extending mandibular advancement beyond the original plan and including the maxilla in the procedure.

2-Presence of Maxillomandibular Deformities: In patients with OSA and maxillomandibular deformities, orthognathic surgery can be justified to address both the skeletal deformity and the OSA.

3-Failure or Intolerance to Medical Treatments: In cases where patients do not tolerate or fail to respond to treatments such as continuous positive airway pressure (CPAP) or mandibular advancement devices (MAD), maxillomandibular advancement surgery may be considered, even if the patient does not exhibit a retrusive facial profile. However, patients should be informed about the potential morphological changes resulting from surgery (Barrera, 2018; Liu et al., 2017, 2019).

Role of Digital Planning

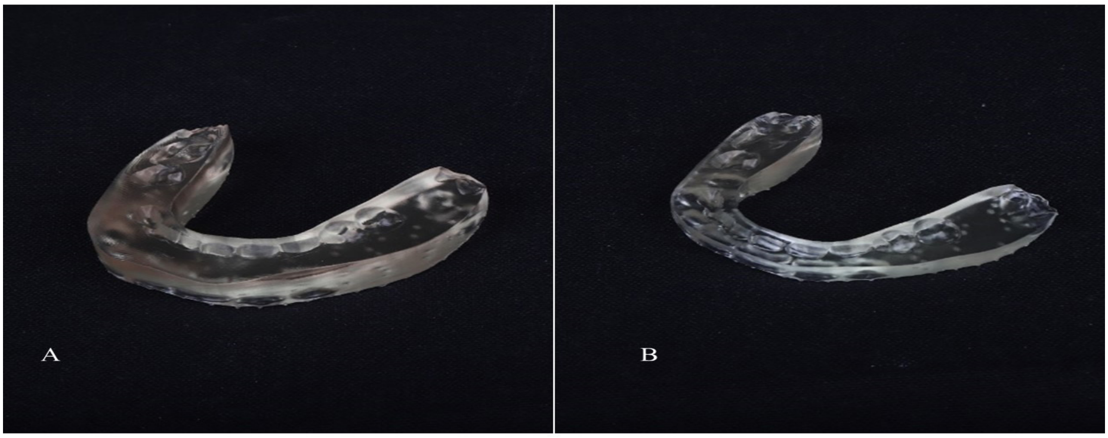
Traditional OS preoperative workflow primarily focused on achieving ideal occlusion, with cephalometric analysis as the primary planning tool. However, cephalometric analysis is limited in detecting asymmetries, as it largely relies on the sagittal plane. This occlusion-centered approach often overlooked crucial aspects of facial symmetry and aesthetics. Consequently, treatment outcomes prioritized functional alignment overachieving balanced facial harmony (Stokbro et al., 2014).

The reliance on sagittal plane analysis in traditional cephalometric techniques limited the ability to evaluate facial symmetry and proportionality fully. This method provided a two-dimensional view, making it nearly impossible to address differences between the left and right sides in the lateral view. As a result, the surgical team often had to choose one side as the basis for planning, leading to potential deviations from the ideal treatment plan. These limitations hindered comprehensive planning and impacted the aesthetic outcomes of orthognathic surgeries (Chen et al., 2021; Stokbro et al., 2014).

As orthognathic planning advances and societal perceptions of aesthetics evolve, there is a noticeable shift towards considering soft tissue in addition to skeletal corrections. In the past, surgical planning was primarily based on the Frankfort horizontal plane, often resulting in inaccurate diagnoses and suboptimal surgical plans. However, with the introduction of approaches like the Arnett analysis (Arnett et al., 1999) is, True Vertical Line (TVL), and Natural Head Position (NHP), a more patient-specific framework for accurate diagnosis and treatment planning has emerged. Advanced 3D analysis and planning software, supported by computer-assisted simulations, now allow for a comprehensive assessment of facial symmetry and skeletal relationships (Arnett et al., 1999; Chen et al., 2021; K. J. C. Lee et al., 2022; Leung et al., 2016).

The virtual OS planning process is comprehensive, beginning with the collection of clinical records, including photographs taken in the Natural Head Position (NHP), assessments of muscle dynamics, temporomandibular joint function, and facial measurements. A CT scan is then captured with the patient in centric occlusion, often stabilized with a wax bite plate, followed by a 3D dental scan using an intraoral scanner. A 3D facial photograph is also taken to capture external facial features. These images—dental scan, CT, and facial scan—are then merged within specialized software, allowing for a virtual simulation of the planned surgery. Based on this digital model, surgical guide splints (Figure 2) are custom-designed, and 3D printed to ensure precise execution during the procedure (Chen et al., 2021). This process ensures that every aspect of the patient’s condition is considered, providing a thorough and reassuring approach to orthognathic surgery planning (Alkhayer et al., 2020; Farrell et al., 2014; Hua et al., 2019).

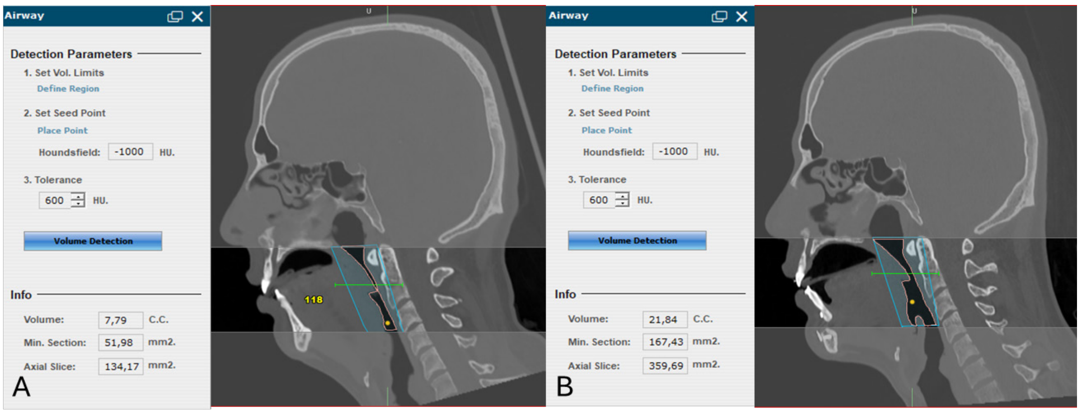
Figure 2
Surgical guide splints



A. Intermediate splint *B. Final splint*

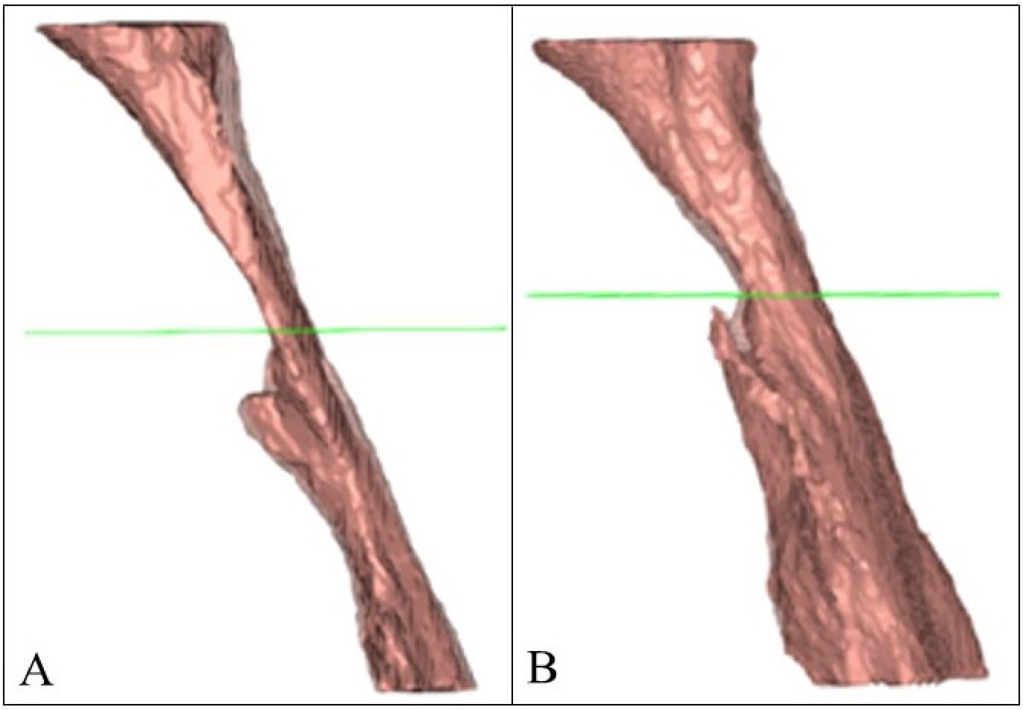
Digital planning software enables clinicians to simulate both preoperative and postoperative conditions, providing a clear visualization of expected surgical outcomes. By virtually adjusting skeletal structures and soft tissues, the surgical team can accurately predict changes in facial aesthetics and function. This simulation capability helps anticipate potential challenges, allowing for adjustments to be made before surgery begins. Ultimately, this leads to greater surgical precision and helps align the procedure with patient expectations (Alkhayer et al., 2020; Gagnier et al., 2024). It also provides better postoperative mandibular condyle position in the articular fossa than traditional orthognathic surgery planning (Alkhayer et al., 2020).

Figure 3
Airway Assessment



A. Preoperative airway assessment of a Class II patient with severe OSAS (Ahi:86.1) B. Postoperative airway assessment of the same patient 6 months after Le Fort I osteotomy and BSSRO with maxillomandibular advancement and counterclockwise rotation of maxillomandibular complex and additional wing genioplasty.

Figure 4
Airway Assessment



A.Preoperative airway, B.ostoperative airway

Integrating 3D airway modelling in digital planning allows for an in-depth assessment of airway structure and patency, which is particularly critical for patients with OSAS and other airway-compromising conditions. This technology enables the surgical team to visualize and measure airway dimensions accurately, ensuring that treatment plans address not only aesthetic and functional goals but also airway health. 3D modelling helps tailor surgical interventions to maintain or improve respiratory function by identifying potential obstructions or narrow regions. This targeted approach not only enhances patient safety and optimizes treatment outcomes for OSAS patients but also provides a proactive benefit for younger orthognathic surgery patients who may not yet have an OSAS diagnosis. With 3D airway visualization, potential airway restrictions can be identified early, allowing the surgical plan to be adjusted to prevent future health issues (Abramson et al., 2010). Modifications such as advancing the maxillomandibular complex further or incorporating more counterclockwise rotation (CCWR) can help safeguard the patient's respiratory health over the long term (Louro et al., 2018; Stokbro et al., 2014).

Digital planning provides patients with a clearer understanding of their treatment by offering 3D visualizations of expected surgical outcomes. Patients gain confidence in the procedure by reviewing virtual models of their facial structures and projected changes and feel more involved in their care. This transparency allows for better communication between the patient and surgical team, as potential adjustments can be discussed and tailored to meet both aesthetic and functional expectations. This collaborative approach helps align patient goals with surgical planning, leading to higher satisfaction and a smoother recovery process (S. J. Lee et al., 2021).

Despite the enhanced predictability offered by digital planning, accurately simulating postoperative soft tissue changes remains challenging. Variations in soft tissue thickness, muscle activation, fat distribution, and tissue elasticity among individuals can lead to differences in how skeletal adjustments translate to soft tissue outcomes. These factors underscore the need for further advancements in soft tissue modelling to achieve even more precise predictions. As technology continues to evolve, the goal is to enhance the accuracy of these simulations, improving both aesthetic and functional results (Alkhayer et al., 2020; Awad et al., 2022; Chantaraaumporn et al., 2023; Knoops et al., 2019).

Figure 5

Three-dimensional changes of the reference points in preoperative digital planning

Models Measurements

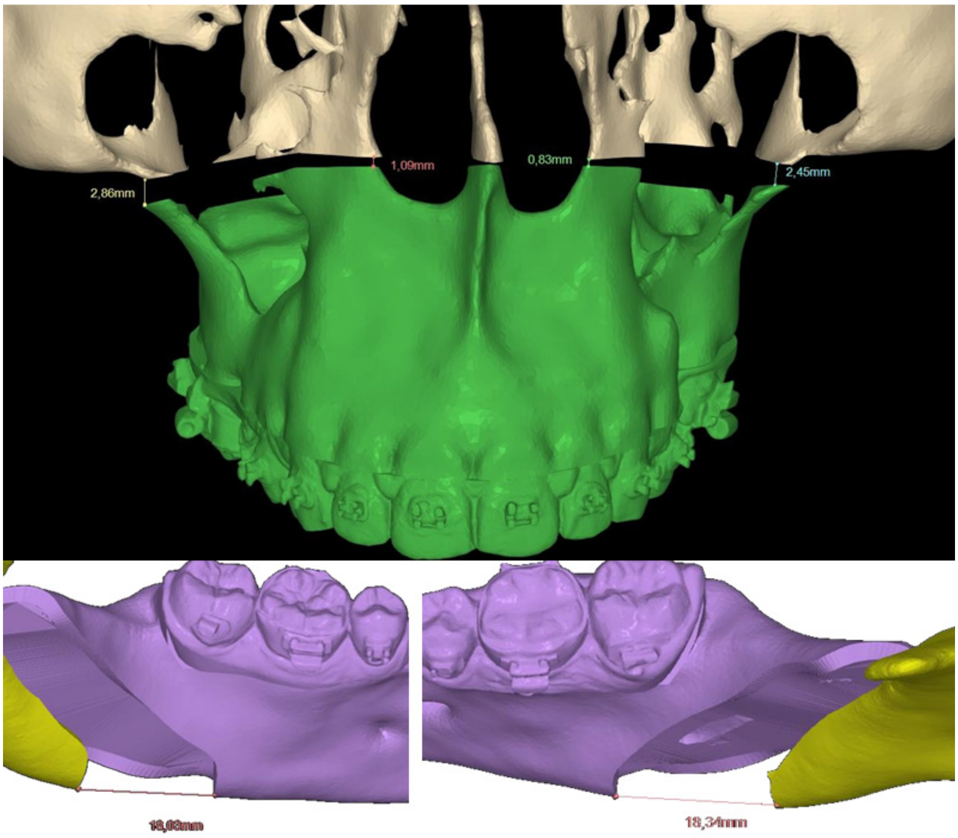
Maxilla		A-P		Vert		Side
ANS	→	3,28	↑	0,74	←	0,43
PNS	→	4,68	↓	4,15	←	0,31
Mx1 tip	→	7,51	↑	1,00	→	0,01
R Canine	→	7,35	↑	0,01	←	0,01
L Canine	→	7,26	↑	0,27	←	0,02
Right Molar MB cusp tip	→	6,94	↓	2,15	←	0,06
Left Molar MB cusp tip	→	6,69	↓	1,75	←	0,09

Mandible		A-P		Vert		Side
Md1 tip	→	12,89	↑	0,23	←	0,02
B Point	→	16,65	↓	0,42	→	0,21
Pogonion	→	18,27	↓	0,55	→	0,30
R Chin	→	18,16	↓	1,74	→	0,29
L Chin	→	18,36	↓	1,56	→	0,31
L Canine	→	12,80	↓	0,49	←	0,03
R Canine	→	12,84	↓	0,64	←	0,03
Left Molar MB cusp tip	→	12,65	↓	1,84	←	0,04
Right Molar MB cusp tip	→	12,75	↓	2,27	←	0,03

Measurement	Ini	Dif	Surg
NASION SCREW			
Screw to Mx1 R	96,0	-0,8	95,2
OCCLUSAL PLANES			
MxOccPl	106,4°	-5,7°	100,7°
MxOP R	104,5	-6,1	98,4
MxOP L	107,9	-5,4	102,5
MdOccPl	98,1°	-6,6°	91,5°
MdOP R	96,9	-7,0	89,9
MdOP L	99,3	-6,2	93,0
HT PROJECTIONS T...	+		
MIDLINES			
Mx Dental Midline	1,4	0,0	1,4
Md Dental Midline	1,3	0,0	1,4
Chin Midline	2,0	-0,3	1,7
CANT +R DOWN -...			
Mx33	0,6	0,3	0,9
Md33	0,2	0,2	0,4
Chin Cant	-1,9	0,2	-1,7
Body Cant	-0,8	0,3	-0,4
Gonion Cant	-1,7	-0,4	-2,1
L 2nd Molar Cant	0,6	0,4	1,0

Figure 6

Preoperative osteotomy planning and distances between bony segments

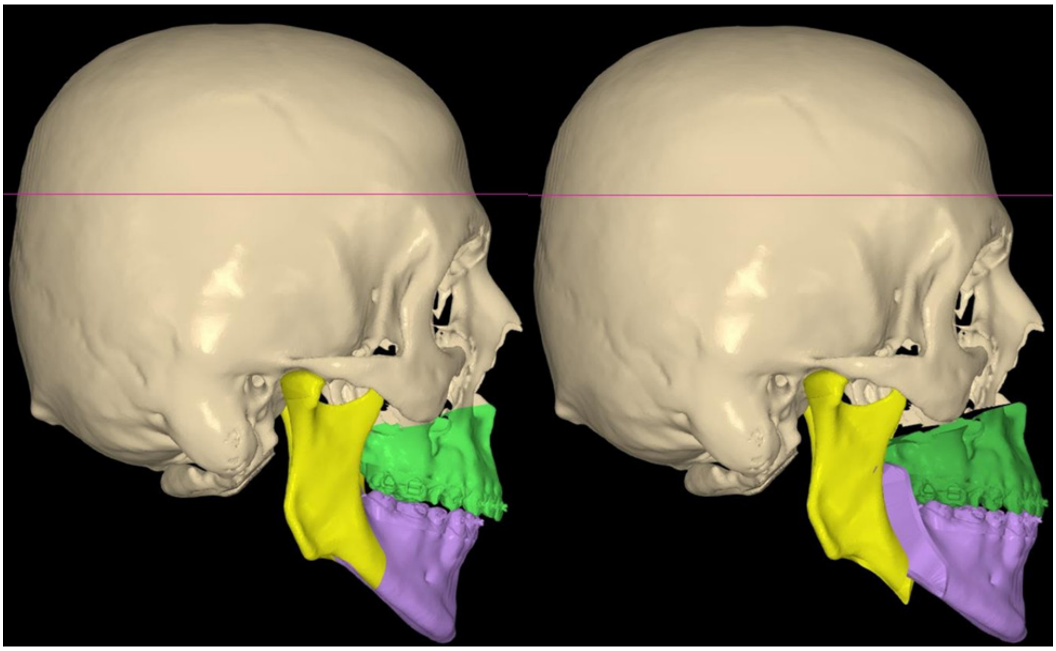


Digital planning has greatly enhanced the precision of identifying airway obstructions in patients with OSAS and other respiratory conditions. By visualizing the specific sites of obstruction, surgeons can tailor their interventions to address these critical areas directly, avoiding unnecessary tissue manipulation. This targeted approach ensures that both functional and aesthetic aspects are addressed, leading to more effective treatment outcomes (Abramson et al., 2010).

It also enables a more refined surgical strategy by clearly identifying obstruction points. Each intervention can be adapted to the patient's unique needs, ensuring that the procedure improves respiratory function and facial aesthetics. Digital tools that support precise mapping of airway structures help maintain or improve airway patency in the long term. This patient-centred approach prioritizes airway health and maximizes the effectiveness of orthognathic surgeries, especially for those at risk of respiratory obstruction (Christino et al., 2021; Vidal-Manyari et al., 2022).

Maxillomandibular advancement and counterclockwise rotation (CCWR) of the maxillomandibular complex significantly enhance airway patency, a crucial benefit for OSAS patients. However, advancing the jaw structures excessively can result in compromised facial aesthetics, especially for those without inherent dentofacial deformities (Brevi et al., 2011; Knudsen et al., 2015; Yu et al., 2017).

Figure 7
Simulation of maxillomandibular counterclockwise rotation



Digital planning and simulation are essential to achieve an optimal balance, allowing the surgical team to predict aesthetic outcomes while addressing functional needs. For OSAS patients with or without dentofacial deformities, these tools ensure that both the airway and facial profile are considered, ultimately reducing complication risks and enhancing overall treatment effectiveness (Farrell et al., 2014; Piombino et al., 2022).

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