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Computer-guided implant placement associated with computer-aided bone regeneration in the treatment of atrophied partially edentulous alveolar ridges: a prospective proof-of-concept study

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If you want to go fast go alone.
If you want to go far go together.
African proverb

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Abstract

Study background

Recent advances in 3D radiological techniques and virtual planning softwares allow the clinician to visualize simultaneously the anatomy of the patient and the prosthetic wax-up directly within the digital environment. This enables ideal planning of the correct position of dental implants considering at the same time anatomical structures and prosthetic demands. The virtual project is then transferred to the surgical site by means of stents realized on the basis of the virtual project. Implants are finally inserted with a computer-guided approach in the desired positions. So far, this technique has been safely used in anatomical situations presenting an adequate amount of bone so that bone augmentation procedures can be avoided and an adequate implant positioning can be achieved.

Aim

The purpose of the present proof-of-concept study was to evaluate the effectiveness of computer-guided implant placement associated to computer-aided guided bone regeneration (GBR) in critical anatomical situations presenting less than ideal quality and quantity of supporting bone to receive dental implants in a prosthetically-driven position.

Materials and methods

Healthy non-smoking patients seeking a fixed rehabilitation were enrolled if presenting partial edentulism characterized by atrophic alveolar bone in the posterior sectors of maxilla or mandible. Patients underwent cone-beam computed tomography (CBCT) exam and impression of the edentulous space was scanned optically. Data of the two acquisitions were imported and matched within dedicated software. At this point, it was possible to plan the ideal position of the implants in a prosthetically-driven position according to a virtual wax-up. The missing bone was virtually augmented according to the position of the implants and the anatomy of the residual alveolar ridge. The project was transferred to the surgical environment by means of stereolithographic model fitted with the augmented bone and tooth-supported guide. Prior surgery, a dense-expanded-polytetrafluoroethylene (d-e-PTFE) membrane was trimmed and contoured based on the said model. Under local anesthesia on outpatient basis, a full-thickness flap was raised and implants were inserted with a computer-aided fully-guided approach. Subsequently, the alveolar ridge was augmented by grafting autogenous bone particles harvested nearby the surgical site with a bone scraper and deproteinized bovine bone mineral (DBBM) granules in a 1:1 ratio. The graft was covered with previously shaped d-e-PTFE membrane fixed with osteosynthesis screws to the underlying bone. A first intention healing was accomplished with horizontal mattresses and single stitches. The duration of the surgery was registered in minutes. Patients were given a questionnaire reporting visual analogue scales (VASs) used to self-register post-operative pain, swelling, bleeding, and perception of the operation during the first post-operative week. Follow-up recalls were scheduled to clinically and radiographically evaluate the post-operative course. Post-operative CBCT scan was acquired to superimpose the position of the implant obtained during the surgical procedure with that planned in the virtual project. The aim was to evaluate the accuracy in terms of linear and angular deviations. To this end, a control group consisting of implants placed with a computer-aided fully-guided approach by means of mucosa-supported screw-retained surgical guides in fully edentulous patients served as reference point. After 6 months from the surgical procedure, the re-entry surgery was carried out to clinically evaluate the quality and quantity of augmented bone. After testing for normality assumption, parametric and non-parametric statistical tests were used to explore the study variables. The significance threshold was set at 0.05.

Results

Overall, 11 patients were considered eligible and were consecutively enrolled and treated, of which 5 in the test group (2 males and 3 females), and 6 in the control group (5 males and 1 female). The mean age was 52.2 ± 6.41 years in the test group, and 60.17 ± 12.73 years in the control group ($p = 0.238$). The mean surgical duration was 92 minutes. No intra- and post-operative complications occurred during the entire study period. Only one patients exhibited a dehiscence of the lingual flap with d-e-PTFE membrane exposure. This was related to an erroneous management of the lingual flap during the surgery, a fact that was not attributable to the experimental procedure itself. Nevertheless, at the re-entry surgery all patients showed complete filling of the bone defect with no clinical and radiological signs of infection or resorption. The newly formed bone-like tissue appeared well vascularized and integrated within the recipient bone. In some cases, implants were completely covered by the regenerated hard tissue. No early losses were observed. In regards to patient-centered outcomes, pain scored exceptionally high with respect to the other variables. The peak was observed at 2 days post-operatively (mean VAS = 64.4 ± 5.17). Swelling peaked the third post-operative day (mean VAS = 56.4 ± 8.14), while the peak of bleeding was registered after 1 day from the surgical procedure (mean VAS = 16.2 ± 2.58). As expected, all variables decreased significantly from their respective peaks up to the seventh post-operative day ($p < 0.05$). The mean VAS score for the patients' perception of the operation was 36 ± 8.63, with no significant correlation with the variables analyzed ($p > 0.05$). A total of 10 and 38 implants in the test and control group respectively were available for the accuracy assessment. No statistically significant differences could be found with respect to linear deviation at coronal and apical points and angular deviation of the long-axis among groups. Mean differences between the two groups were 0.04 ± 0.32 mm; 0.02 ± 0.35; and 0.27° ± 1.71° respectively ($p > 0.05$).

Conclusions

Within the limitations of the present study, computer-guided implant placement and simultaneous computer-aided bone augmentation yielded encouraging results in terms of efficacy and accuracy. No intra- and post-operative complications were observed, therefore the procedure can be considered safe and predictable with respect to surgical and biological aspects at least on a short-term basis. On the other hand, patient-centered outcomes were below the expectations. Further studies are needed to evaluate survival, success, and complication rates of both implants and prostheses on a long-term basis.

Sommario

Background dello studio

I recenti progressi nelle tecniche di imaging diagnostico strumentale 3D e nei software di programmazione virtuale consentono al clinico di visualizzare simultaneamente l'anatomia del paziente e la ceratura protesica direttamente nell'ambiente digitale. Questo rende possibile pianificare in modo ideale la posizione corretta degli impianti dentali, tenendo in considerazione allo stesso tempo le strutture anatomiche e le richieste protesiche. Il progetto virtuale viene poi trasferito alla fase chirurgica tramite dime realizzate sulla base del progetto stesso. Gli impianti vengono infine inseriti con approccio computer-guidato nella posizione desiderata. Ad oggi, l'implantologia computer-guidata è stata utilizzata con sicurezza in situazioni anatomiche caratterizzate da un quantitativo di osso di supporto tale per cui non si rendono necessarie procedure di incremento osseo e, nel contempo, è possibile ottenere una corretta posizione degli impianti.

Obiettivo

L'obiettivo del presente studio tipo "proof-of-concept" è stato quello di valutare l'efficacia dell'inserimento implantare computer-guidato in associazione a procedure di rigenerazione ossea guidata (GBR) computer-assistita in situazioni anatomiche critiche, caratterizzate cioè da un quantitativo e da una qualità ossea di supporto insufficiente a consentire un corretto posizionamento implantare protesicamente guidato.

Materiali e metodi

I criteri di inclusione prevedevano pazienti sani, non fumatori, con desiderio di riabilitazioni proteiche fisse. Tali pazienti venivano arruolati se presentati edentulie parziali caratterizzate da osso alveolare atrofico nei settori posteriori a carico del mascellare superiore o della mandibola. I pazienti venivano sottoposti a tomografia computerizzata a fascio conico (CBCT - cone-beam computed tomography), mentre le impronte dentali venivano scansionate tramite scanner ottico. I dati informatici delle due acquisizioni venivano importanti e sovrapposti con l'ausilio di un software specifico. A questo punto, è stato possibile pianificare la posizione ideale degli impianti protesicamente guidata, sulla base di una ceratura diagnostica virtuale. L'osso mancante è stato aumentato virtualmente in accordo alla posizione degli impianti e all'anatomia della cresta ossea alveolare residua. Il progetto è stato trasferito al campo chirurgico per mezzo di una dima chirurgica e di un modellino stereolitografico dotato dell'incremento osseo pianificato virtualmente. Prima della procedura chirurgica, una membrana in politetrafluoroetilene denso-espanso (d-e-PTFE) è stata sagomata e contornata sulla base del suddetto modellino stereolitografico. Una volta modellata la membrana, si è proceduto all'intervento chirurgico in ambulatorio in anestesia locale. E' stato elevato un lembo a spessore totale e gli impianti sono stati inseriti completamente con approccio computer-guidato. Successivamente, la cresta alveolare è stata rigenerata innestando osso bovino deproteinizzato (DBBM - demineralized bovine bone mineral) e osso autologo particolato prelevato tramite grattino per osso nelle aree adiacenti il sito chirurgico in rapporto 1:1. L'innesto è stato quindi stabilizzato e protetto dalla membrana in d-e-PTFE precedentemente sagomata e modellata. La membrana è stata fissata all'osso nativo con viti da osteosintesi. Una chiusura dei lembi per prima intenzione è stata ottenuta con punti a materassaio orizzontale e punti singoli. La durata della chirurgia è stata cronometrata e registrata in minuti. Durante la prima settimana post-operatoria, ai pazienti è stato chiesto di compilare un questionario riportante una scala visuo-analogica (VAS) per auto-valutare il dolore, il gonfiore, e il sanguinamento post-operatorio, insieme alla percezione dell'operazione chirurgica. Sono stati organizzati dei richiami per valutare clinicamente e radiograficamente il decorso post-operatorio e la guarigione del sito chirurgico.

Una CBCT è stata acquisita prima del rientro chirurgico in modo da valutare l'accuratezza della procedura. In breve, i dati informatici della CBCT post-operatoria sono stati sovrapposti a quelli del progetto virtuale in modo da sovrapporre la posizione degli impianti ottenuta in fase chirurgica con la posizione dei medesimi impianti pianificata virtualmente nel progetto. L'obiettivo era quello di valutare l'accuratezza nel posizionamento degli impianti in termini di deviazioni lineari e angolari. A tal fine, per il confronto con il "gold standard", è stato selezionato un gruppo di controllo usato come punto di referenza. Tale gruppo era caratterizzato da pazienti totalmente edentuli nei quali sono stati posizionati impianti in modo interamente computer-guidato tramite dime chirurgiche a supporto mucoso stabilizzate con pins endossei di fissazione. Dopo 6 mesi dal primo intervento chirurgico, è stata effettuata la seconda fase chirurgica durante la quale è stata valutata la qualità e quantità dell'osso rigenerato.
Per quanto riguarda l'analisi statistica, dopo aver testato la normalità di distribuzione dei dati, test statistici parametrici e non-parametrici sono stati utilizzati per esplorare le variabili dello studio. Il livello di significatività statistica è stato fissato a 0.05.

Risultati
Nel complesso, sono stati arruolati e trattati 11 pazienti, dei quali 5 nel gruppo test (2 maschi e 3 femmine), e 6 nel gruppo controllo (5 maschi e 1 femmina). L'età media è stata di 52.2 ± 6.41 anni nel gruppo test, e 60.17 ± 12.73 anni nel gruppo controllo ($p = 0.238$). La durata media dell'intervento chirurgico è stata di 92 minuti. Non sono state riscontrate complicanze intra- e post-operatorie durante l'intera durata dello studio. L'eccezione è rappresentata da una paziente che ha mostrato una deiscenza del lembo linguale con parziale esposizione della membrana in d-e-PTFE. Questo evento è stato causato da una gestione erronea del lembo linguale durante la chirurgia, un fatto comunque non direttamente attribuibile alla procedura sperimentale. Ciò nonostante, al rientro chirurgico in tutti i pazienti il difetto osseo è stato completamente rigenerato senza segni clinici e radiologici di infezione o riassorbimento. Il tessuto simil-osseo neoformato è apparso ben vascolarizzato e integrato con l'osso ricevente. In alcuni casi, gli impianti erano completamente ricoperti da tessuto simil-osseo rigenerato. Non sono state osservate perdite precoci degli impianti. Riguardo le variabili incentrate sul paziente, i punteggi VAS del dolore sono emersi eccezionalmente alti. Il picco è stato registrato 2 giorni dopo l'atto chirurgico (VAS medio = 64.4 ± 5.17). Il gonfiore ha avuto il picco durante il terzo giorno post-operatorio (VAS medio = 56.4 ± 8.14), mentre il picco del sanguinamento si è avuto dopo il primo giorno post-operatorio (VAS medio = 16.2 ± 2.58). Come previsto, i valori VAS di tutte le variabili si sono ridotti dai rispettivi picchi in modo significativo fino al settimo giorno post-operatorio ($p < 0.05$). Il valore VAS medio riguardante la percezione dell'operazione è stato di 36 ± 8.63, senza una correlazione significativa con le variabili analizzate ($p > 0.05$). Un totale di 10 impianti nel gruppo test e 38 nel gruppo controllo sono stati inclusi nell'analisi sulla accuratezza. Non sono emerse differenze statisticamente significative in termini di deviazioni lineari alla testa e all'apice dell'impianto e angolari tra i due gruppi. Le differenze medie sono state di 0.04 ± 0.32 mm; 0.02 ± 0.35; e 0.27° ± 1.71° rispettivamente ($p > 0.05$).

Conclusioni
Considerando le limitazioni del presente studio, l'inserimento computer-guidato con simultanea ricostruzione ossea computer-assistita hanno mostrato risultati incoraggianti in termini di efficacia e accuratezza. Non sono emerse complicazioni intra- e post-operatorie durante la durata dello studio, di conseguenza questa procedura può essere considerata sicura e predicibile per quanto riguarda gli aspetti chirurgici e biologici per lo meno a breve termine. Tuttavia, le variabili incentrate sul paziente hanno raggiunto punteggi sotto le aspettative. Ulteriori studi sono necessari per valutare a lungo termine i tassi di sopravvivenza, successo, e complicazioni riguardanti sia gli impianti che le protesi implanto-supportate.

1. Introduction

1.1. Consideration on the three-dimensional implant position

1.1.1. Importance of three-dimensional implant position

The use of dental implants to replace missing dental elements is supported by evidence-based data since the understanding of the osseointegration process in the 1960s [1]. Long-term follow-up studies are essential to determine and predict the future clinical course. Encouraging results emerged from studies assessing the survival rates of dental implants over more than 20 years. In some cases, the survival analysis led to percentages close [2, 3] or even higher [4, 5] than 90% with mean follow-ups superior to 20 years of observations.

The correct three-dimensional (3D) positioning of an implant is considered a crucial factor to obtain predictable and reliable long-term clinical results. This is particularly important not only in consideration of biomechanical and functional aspects. Placing an implant in the proper position is essential in order to avoid aesthetic complications in the frontal area. The proper position aims to minimize the resorption of the bundle bone; to respect the correct distances between adjacent teeth/implants, which is vital to preserve the blood supply of hard and soft tissues; to allow a correct prosthetic phase [6].

Malpositioning of implants is an issue that has been given increased attention. It has been identified as one of the most important factor associated to signs and symptoms of peri-implant tissue breakdown. Implants placed too close to the buccal plate or angled too far buccally can lead to mucosal recession. In addition, the mesio-distal position can have a strong impact on crestal bone height and papilla contour. Apart from anatomical and biological concerns, other prosthetic complications may arise when dealing with malpositioned implants. These include the transmission of unfavourable occlusal forces to the implants, the need to fabricate specific prosthetic parts leaving certain implants unrestored, incongruous prosthetic restorations with lack of cleansibility of the reconstruction, and surgical interventions to remove implants or reposition them in a more favourable prosthetic location [7]. The latter is often the only recourse, which restarts the bone-remodelling cascade, further compromising the site and often precluding the placement of another implant.

In this respect, implant insertion should be prosthetically- or "restoration"- driven, with the rationale to follow the prosthetic needs in order to achieve the anticipated treatment outcome [8].

1.1.2. Aesthetic complications due to implant malposition

Research interest has shifted from implant survival toward optimal preservation of hard and soft tissues, focusing on aesthetic outcomes. The health and stability of peri-implant tissues is strictly related to the position of the implant.

An improper mesio-distal position of the implant with respect to the adjacent tooth/implant may cause unsatisfactory interproximal papilla height and peri-implant soft tissue fill. Despite difficulties in defining a value for the optimal horizontal distance between two adjacent implants, there is a tendency for incomplete inter-implant mucosa fill when the implant-tooth distance is < 1.5 mm and the inter-implant distance is < 3 mm [9]. This complication is mainly caused by the development of a crestal bone remodelling process during healing and after implant restoration. As firstly described by Esposito et al., a reduced papilla height will result, since there is not enough space for the soft tissues to develop [10].

Even apico-coronal malpositions are likely to result in aesthetic complications [11]. Basically, two different clinical scenarios might be encountered. If the implant is not inserted deep enough into the tissues, the metal implant shoulder can be visible, causing an unpleasant aesthetic outcome, although no recession of the mucosa is present. More frequently, implants are placed too apically into the bone tissue. This apical malposition can cause recession of the buccal mucosa, particularly in case of a thin facial bone wall. Following restoration, this so-called bundle bone is

resorbed circumferentially during the bone remodelling process. This leads to bone resorption not only at the mesial and distal aspect of the implant, but also on the buccal and oral aspects. Bone resorption on the facial aspect can lead shortly to a recession of the buccal mucosa, with serious impairment of the aesthetic outcome.

Similarly to apico-coronal malpositions, bucco-palatal/lingual deviations from the ideal position can also cause two different complications. The first complication occurs if the implant is positioned too far palatally. This will often lead to a ridge-lap design of the implant crown. While this does not always lead to an aesthetic complication, it may make it difficult for the patient to maintain optimum plaque control, with subsequent long-term implications for the health of the peri-implant tissues. If the palatal malposition is combined with deep placement, it can sometimes be difficult to seat the abutment because of the thick facial and palatal mucosa. The second complication is a recession of the facial mucosa if the implant is clearly positioned too far facially. This can cause severe aesthetic complications, since the harmonious gingival course is significantly disturbed and often requires the removal of the implant.

A further possibility for an aesthetic complication occurs when an implant is inserted with an axis problem. Implants that are inclined too far facially are often associated with recession of the facial mucosa. If the axis problem is minor and the shoulder of the implant lies in an acceptable position, the axis problem can usually be corrected by prosthetic means using angled abutments which are available for most implant systems. If the axis problem is severe and if it is combined with a facial malposition of the implant shoulder the aesthetic complication is usually very difficult to resolve.

1.1.3. Prosthetic complications due to implant malposition

Aesthetic issues proceed in step with prosthetic complications. These sequelae arise when implants are not optimally placed in one or more geometric planes. It is worthy of note that many errors in position are not detected until the prosthetic phase of treatment when a transmucosal component is attached to the implant. This further complicates the clinical situation.

As previously mentioned, buccally malpositioned implants can jeopardize the labial cortical plate of bone. Bone loss may occur at the time of implant placement or as a result of osseous resorption during the healing phase. In general, soft-tissue topography will follow the underlying osseous contour. Therefore, injury to the labial plate of bone may have a detrimental effect on the height of the overlying soft tissue and result in mid-buccal recession. In the aesthetic zone, this can produce an unattractive result. Furthermore, if the buccal malposition of the implant is severe, it may not be possible to incorporate it within the confines of the prosthesis. Implants positioned too far lingually create other problems. In an attempt to restore the crown to its correct position, it may be necessary to create a ridge lap. Lingual positioning of an anterior implant may also cause a problem if there is a deep overbite. In this latter situation, the occlusal relationship may render a palatally placed implant difficult to restore. In addition, a restoration emerging from a palatally placed implant may encroach upon the tongue space, thereby impeding speech.

As for aesthetic complications, an implant can be placed too close or far from a tooth or adjacent implant, or it can be located within the interproximal space. Hence, two different scenarios may occur: too much space or too little space between adjacent teeth or implants. Too little space may cause injury to the interproximal bone and soft tissue, and will necessitate restorations, which are narrower than desired. If there is too much space between implants, an additional pontic can be cantilevered from the implants. However, the mesio-distal dimensions of the teeth may not approximate the contralateral teeth from an aesthetic perspective. Furthermore, cantilevers will increase stress on supporting implants. Implants in close proximity to each other cause other complications. For example, transfer copings on these implants may contact each other or adjacent teeth during the impression phase. Furthermore, at the time of prosthesis insertion, additional effort will be required to remove cement within the

constricted embrasure. There may also be inadequate space to accommodate the horizontal biologic width of an implant, which can result in inter-implant bone resorption and an unaesthetic soft tissue deficiency between adjacent prosthetic teeth.

Lastly, angulation errors remain insidious complications as far as prosthetic components cannot be customized to correct extreme misangulations. Concerning bucco-palatal/lingual angulation issues, if the implant is not placed apically enough, the metal of the angulated component is likely to be visible, creating an aesthetic problem. In addition, high stresses placed on the implant–abutment interface of angled implants can lead to abutment screw loosening, screw fracture, or fracture of the coronal aspect of an implant. The greater masticatory forces that exist in the posterior areas compared to the anterior segments of the mouth can exacerbate these complications. Similarly to bucco-palatal/lingual angulation issues, mesio-distal angulation errors make difficult to develop a gradual emergence profile resulting in a restoration surrounded by a large gingival embrasure, or requiring a circumferential ridge lap, which may be predisposed to food impaction and hygiene difficulties. In addition, mesio-distal angulation issues can result in a metal abutment being exposed, which may be unaesthetic. Moreover, prostheses fabricated on misangulated implants are subject to additional forces, which may contribute to premature mechanical failures.

1.2. Minimize the risk of implant malpositioning: computer-guided implant surgery

1.2.1. Introduction to guided implant surgery

Apart from surgical complications attributed to inadequate operative skills and lack of experience of the surgeon, malposition is mainly related to an improper treatment plan. A thorough preoperative planning is an important requirement for a successful restorative result. Using traditional surgical protocols the pre-surgical planning includes radiographic assessment of accessible bone volume/anatomic structures, which in most cases is determined by periapical and panoramic radiographs. Implant positioning is evaluated by a combined judgement of bone volume on radiographs, by visual inspection of the alveolar crest in the oral cavity and on study casts. In some cases the implant position at surgery can be indicated by using acrylic templates demonstrating the ideal implant placement according to the outline of the permanent prosthesis. However, the final seating of implants depends in general on the skills and experience of the dental surgeon, at the same time taking into account anatomical limitations as well as restrictions in terms of bone availability.

The advances in 3D imaging techniques and computer technology allow to carefully simulate surgical and prosthetic phases importing the 3D data into modern implant planning software. Implant sites can be decided before surgery according to bone volume and quality, location of anatomical structures (nerves, vessels, sinuses), prosthetic and aesthetic evaluations. Accurate one-to-one measurements of the width and height of bone in planned implant sites, as well as distances and angulations between implants from one side of an arch to another, can be predetermined without the distortions that are present in the two-dimensional radiology. Implants and abutments can then be virtually planned, driven by knowledge of the position of the planned restoration. It also allows predetermination of prosthesis path of insertion, placement of screw chambers, componentry space, and pre-surgical abutment choices, as well as pre-surgical fabrication of individual abutments. An accurate virtual surgery planning allows sometimes avoiding bone augmentation procedures, which are associated to an extension of treatment time and sometimes, unfortunately, also to major clinical complications. Moreover, a careful 3D positioning of the implants allows obtaining the best clinical results, especially as regards aesthetic aspects. This preamble briefly summarise the computer-guided implant surgery technology, which basically allows transferring planned rehabilitation project directly into surgical field.

1.2.2. Types of guided implant surgery protocols

Generally, two types of guided implant surgery protocols – static and dynamic – are described in the literature (Figure 1) [12]. The latter are represented by guided navigation methods in which a computer-guided navigation system helps the clinician in real time during the implant positioning through visual imaging tools on a monitor. These methods, although very interesting in future perspective, are currently not particularly widespread, and go beyond the objective of the present study. The static approach refers to the use of a static surgical template. This reproduces the virtual implant position directly from computerized tomographic data to a surgical guide, which does not allow intra-operative modification of the implant position. With the static systems, the planned implant location is usually transferred to the surgical template using computer-milled templates or stereolithographic surgical guides. Surgical guides can be tooth, bone or mucosa supported, with or without stabilization pins. Some guided systems use, for each patient, different templates with different sleeves size, while others use only one template. A further differentiation is given by the modality of implant screwing after implant site preparation: some systems provide fully guided implant insertion through the same drilling template; other methods may require the manual insertion of the implant after removing the surgical template.

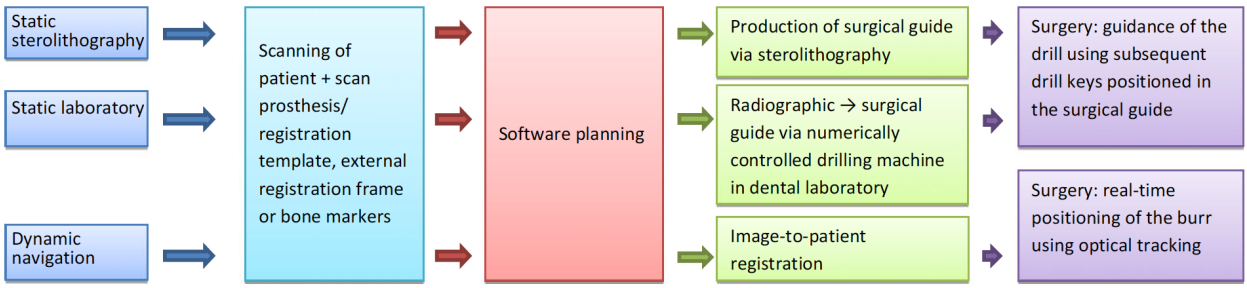


Figure 1. Workflow of static and dynamic guided-surgery systems [12].

1.2.3. Workflow of static computer-guided implant surgery

The methodology of reference has been developed in the mid-1990s by a research team at the University of Leuven. They proposed a double-scan procedure (the patient with the scan prosthesis in the mouth; and the prosthesis alone) followed by integration of the scan prosthesis or radiological template, planned by the dentist, within the craniofacial model [13-15].

Therefore, the scan prosthesis contains small gutta-percha spheres (diameter ± 1 mm). The craniofacial images show the gutta-percha markers with respect to the bone, without visualizing the prosthesis itself. The scan prosthesis is scanned alone, with alerted exposure parameters allowing the denture to be visualized. As the markers are visible in both sets of scans, they can be transformed and realigned to fuse the prosthesis within the maxillofacial structures. Besides an adequate bone model, derived from scanning the patient with the denture in situ, the second scan allows optimal visualization of the prosthesis. Therefore, both models can be presented separately, allowing planning on the bone and/or the prosthetic model. Moreover, by accurate fusion, whilst maintaining excellent image quality, the planning can be carried out and controlled toward the integrated model.

Regardless of the method used, correct positioning of the scan prosthesis is very important. Therefore, an index is strongly recommended to position and stabilize the template in the mouth of the patient during the scanning process. An optimal fit of the scan prosthesis with the patient's soft tissue is crucial. One should determine whether air is visible between the scan prosthesis and the soft tissue. This is especially important for mucosa-supported guides, in which the basis of the future surgical guide will be the same as the basis of the scan prosthesis.

The DICOM (Digital Imaging and COmmunications in Medicine) images are imported in a software program, fusion of the scan prosthesis via the markers is accomplished and the ideal surgical site and optimal implant dimensions are selected. Once planning is complete and has been approved, the digital plan is sent to the manufacturer for production of the guide using stereolithography.

Stereolithography is an additive manufacturing process using a vat of liquid photopolymer resin, curable by ultraviolet light, and an ultraviolet laser that selectively cures resin, layer by layer, into a mass representing the desired three-dimensional object. For each layer, the laser beam traces a part cross-section pattern on the surface of the liquid resin. Exposure to the ultraviolet laser cures or solidifies the pattern traced on the resin and adheres it to the layer below. After a layer is finished (complete pattern has been traced), the object is lowered by one layer of thickness and a new layer of liquid material is applied on top. The subsequent layer pattern is traced by the laser on this new surface and then is joined to the previous layer. This process is repeated until the object is complete. The supports are removed manually after the product is taken from the stereolithography machine. After this process, the sleeves for the drill keys are positioned in the guide.

When the guide is finished, it is sent to the surgeon. Depending on the system, a list with an overview of the planned implants is included, as well as a patient-specific manual. Before surgery, the surgical guide is fitted in the mouth. After applying some compression, the soft tissues underneath the guide should become pale. The correct position of the guide is guaranteed by the use of an index. This index is used to stabilize the guide and to allow fixation. The drilling procedure involves the use of drill keys inserted in the sleeves within the guide, which guide the consecutive drills of different diameters in the correct position and angulation. The drill key can, for some systems, be attached on the drills or can be designed as spoons. Different keys with increasing diameters are available to guide each separate drill. The drills can have a physical or a visual stop. Guidance of the implant is available depending on the system that is used. The tolerance of the drills in the key, of the key in the sleeve or of the implant driver in the sleeve might explain part of the inaccuracy inherent to guided surgery.

1.2.4. Accuracy of computer-guided implant surgery

Computer-guided implant placement is a procedure characterized by several clinical advantages primarily related to the ideal virtually planned implant position [16]. For example, bone augmentation procedures may be avoided or reduced by optimizing implant positioning in accessible bone. By providing the clinician with realistic information of the bony anatomy as well as information of the prosthesis outline, an ideal implant placement can be virtually executed in a prosthetically driven manner limiting the risk of injury at the expenses of anatomic noble structures. As such, an optimal positioning may positively affect the final prosthesis function, speech and aesthetics. A further advantage is to have, at the time of surgery, a prefabricated fixed prosthesis, based on planned implants position, able to connect newly inserted implants and to easily achieve a functional and aesthetic immediate loading. The above-mentioned advantages are essentially dependent on the degree of accuracy of the entire system. Accuracy is defined as matching the position of the planned implant in the software with the actual position of the implant in the mouth of the patient [17]. The accuracy of the implant or the osteotomy site is mostly expressed by four parameters: deviation at the entry point, deviation at the apex, deviation of the long axis, and deviation in height/depth. The first three

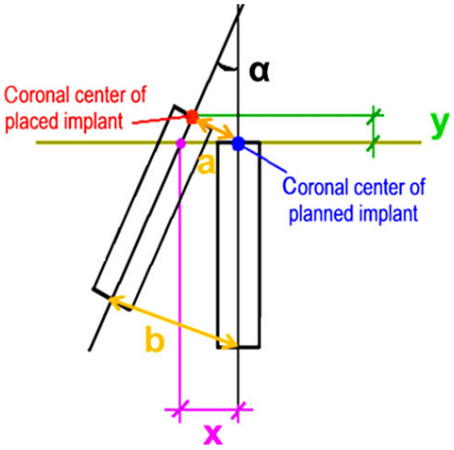


Figure 2. Accuracy evaluation parameters[17] expressed by a) and b): global deviation at neck and apex respectively; x) horizontal/lateral deviation; y) deviation in height/depth; α: angular deviation of the long axis.

parameters are the most frequently reported in the current literature (Figure 2). Matching of the planned with the placed implant position is based on a second cone-beam computed tomography scan allowing matching between preoperative planning and postoperative implant positions. To date, the latest systematic review and meta-analysis developed to assess implant accuracy following static computer-guided surgery has been published in 2018 by Bover-Ramos et al.[18]. In brief, 186 articles were reviewed, and 22 clinical studies fulfilled the inclusion criteria, providing a total of 2.244 dental implants to be analyzed. In case of full-guided implant insertion, the study showed a mean horizontal coronal deviation of 1.08 ± 0.10 mm, a mean horizontal apical deviation of 1.35 ± 0.12 mm, and a mean angular deviation of 3.62° ± 0.29°. It is noteworthy that full-guided implant surgery achieved greater accuracy than half-guided surgery, however the reduced size of the half-guided group compared to the full-guided group must be taken into account as a limitation.

1.2.5. Computer-guided implant surgery versus conventional implant surgery

While the results from the comparison between half- and full-guided implant insertion must be interpreted cautiously, stronger evidence suggests that computer-guided implant surgery achieves more accurate implant positioning with respect to free-hand conventional implant surgery. Free-hand implant placement is intended as implant placement with the aid of a surgical guide for the initial drill (pilot-drill) with or without a drill stop through an integrated guiding sleeve of typically 2 mm in diameter. The rest of implant bed preparation and implant insertion is performed without the use of a surgical guide, i.e. free-handedly.

Aside from *in vitro* studies, this suggestion has been demonstrated by fairly recent *in vivo* randomized clinical trials. Vercruyssen et al. compared computer-guided implant placement by means of mucosa- or bone-supported surgical guides realized following the dual scanning technique [13-15] versus implant placement by means of pilot-drill templates [19]. The primary outcome variable was the deviation at the entry point, at the apex of the implant and the angular deviation. A significant lower mean deviation at the entry point (1.4 mm, range: 0.3–3.7), at the apex (1.6 mm, range: 0.2–3.7) and angular deviation (3.0°, range: 0.2–16°) was observed for the computer-guided group when compared to the pilot-drill template group (3.0 mm, range: 0.6–6.6; 3.4 mm, range: 0.3–7.5 and 8.4°, range: 0.6–21.3°). A subsequent study conducted by the same authors including the latter sample of patient underlined further statistically significant differences even when assessing depth and lateral deviations, with higher inaccuracy detected in the non-guided group [20]. Interestingly, the authors claimed that less mesio-distal and bucco-palatal/lingual deviations in the computer-guided group could indicate that with guided surgery, a more accurate "tooth position" could be achieved. The concept of prosthetically-guided implant insertion for future restorative rehabilitation is therefore strengthened. On the other hand, it is worthy of note that the pilot-drill template consisted of a scan prosthesis transformed into a surgical template. Obviously, such a template cannot be compared to a stereolithographically fabricated pilot-drill guide. In addition, as all patients were edentulous, the surgical guides were either bone-or mucosa-supported, which additionally increased heterogeneity.

To overcome such limitations, a recent randomized controlled study characterized by homogeneous conditions has been designed to evaluate the accuracy of tooth-supported fully guided surgery to free-handed surgery in the posterior maxilla of partially edentulous patients [21]. In brief, partially edentulous patients in need of ≥ 2 implants in the posterior maxilla were randomly allocated to one of the following treatment groups: completely free-handed, pilot-drill guided, and fully guided implant insertion. Ideal implant positions were determined in designated software following the fusion of bony information (CBCT data in DICOM format) to the prosthetic wax-up (optical scan data in STL format). The position of every implant as surgically realized was compared to its "ideal position". The apical global deviation was the primary outcome of the study. Secondary outcome variables were angular deviation, coronal global deviation, coronal lateral deviation, coronal vertical deviation, apical lateral deviation, and apical vertical deviation. In consideration of all deviation variables, fully guided surgery resulted in

higher accuracy, while free-hand insertion provided the lower degree of accuracy. The differences were statistically significant in almost all study variables. It is worth mentioning that a maximum deviation of nearly 2 mm has been found for the computer-guided group. Conversely, free-hand implant insertion showed a maximum deviation of nearly 5 mm which may cause severe biological complications.

2. Study background

2.1. Experience in computer-guided implant surgery

2.1.1. Historical synthesis

The research group to which I belong has always been focused on improving the quality of treatment of patients. As already mentioned, the introduction of CBCT scanning to implant dentistry as a 3D imaging tool has led to a breakthrough in this field, particularly because these scanning devices result in lower radiation dosages than conventional CT scanners. In combination with implant planning software, the use of CBCT images has made it possible to virtually plan the optimal implant position regarding surrounding vital anatomical structures and future prosthetic needs. The primary aim was to improve diagnostic, surgical, and prosthetic precision. This is translated into a technique that is safe, predictable, causing minimal discomfort during periods of healing, in combination with a reduced "chair time" for treatment.

In 2012, we reported a case of full-mouth rehabilitation of a patient with implant-supported fixed dental prostheses carried out with computer-guided implant placement [22]. The treatment protocol consisted of consecutive steps. Clinical and radiological examination by means of CBCT scan was performed to evaluate the residual anatomy of hard and soft tissues (Figure 3A-B).

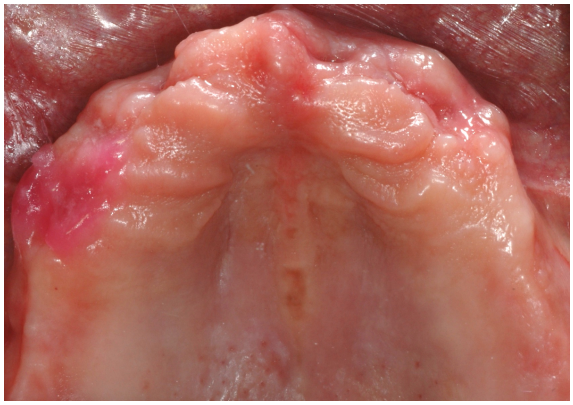


Figure 3A. Pre-operative intraoral clinical view of the bimaxillary edentulism; maxillary arch.

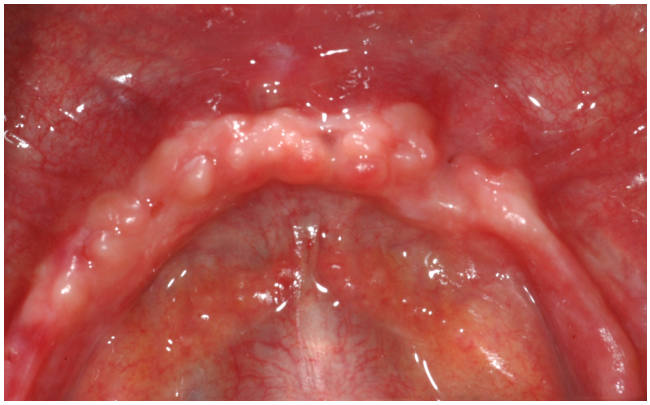


Figure 3B. Pre-operative intraoral clinical view of the bimaxillary edentulism; mandibular arch.

After the evaluation of the articulated chalk models, a preliminary prosthetic wax-up was realized, corresponding to the exact replica of the definitive prostheses accepted by the patient, integrated with aesthetic and functional principles. It was then possible to realize two radiological stents on the basis of the preliminary prosthetic wax-up, as a duplication of the final prostheses. The radiological stents were equipped with an extraoral radiopaque marker for 3D position tracking, required for the subsequent scan overlapping. Subsequently, the patient underwent CBCT scan of the edentulous jaws while wearing the provisory radiopaque stents to integrate the anatomic data with the functional and aesthetic parameters. According to the double-scan procedure, an optical scan of the prostheses alone was conducted, as needed by the specific implant planning data software. At this point, it was possible to import and match the two different scans within the software and perform 3D virtual implant position planning with the data software according to the jawbone anatomy and the prosthetic design. This was made possible by the processing of stereolithography interface (STL)-format data acquired from the optical scan overlapping the data obtained from the CBCT device in a DICOM format, which allowed simultaneous viewing of the axial, 3D, panoramic, and cross-sectional images on the computer monitor (Figure 4). The virtual project was transferred to a 1:1 scale model with a

rapid prototyping technique. This allowed the realization of the surgical stents obtained according to the CBCT scans and pre-operatory chalk models by using the principle of stereolithography (Figure 5).

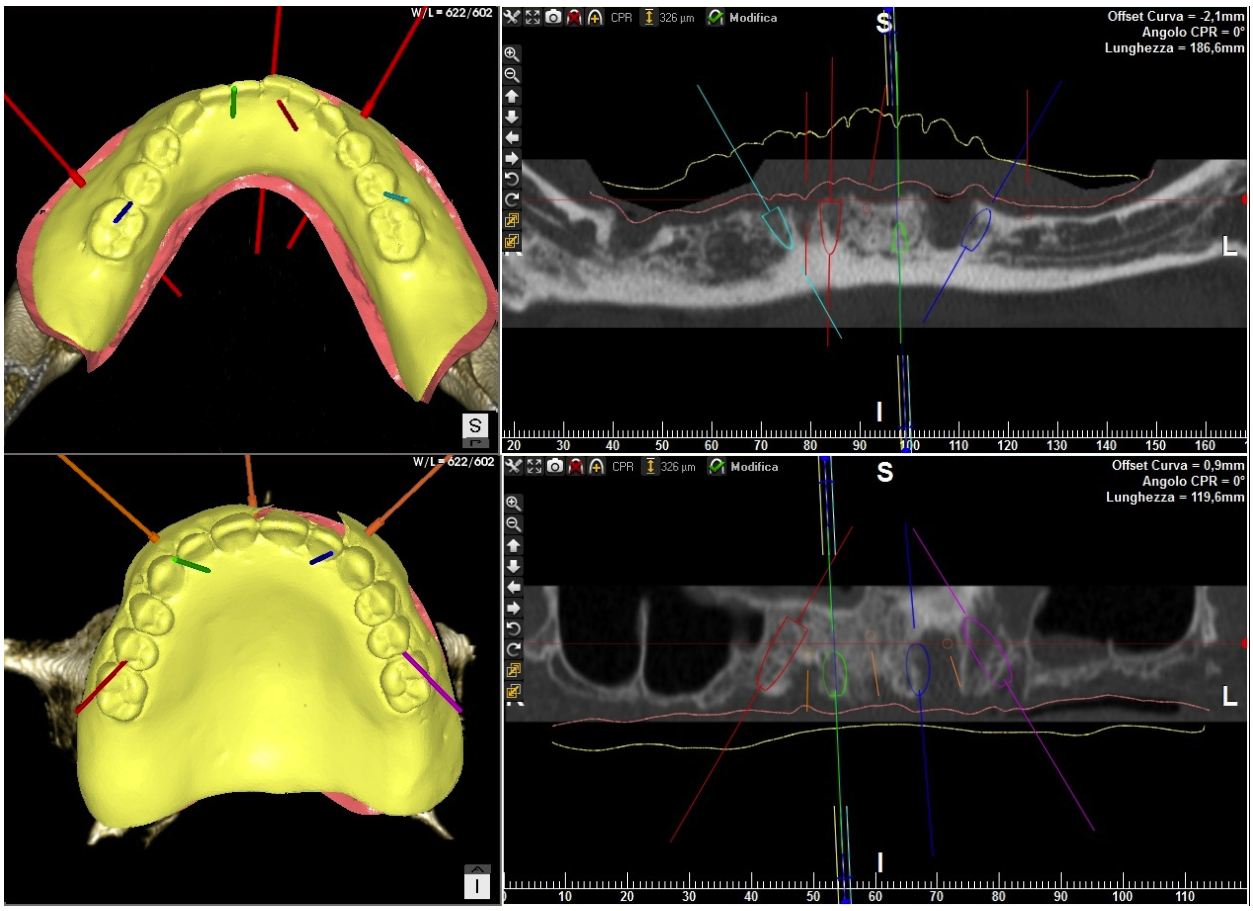


Figure 4. Virtual planning. In both jaws, the optical scans of the prostheses (yellow) have been overlapped to the CBCT scan of the edentulous arches in order to perform a prosthetically-guided implant placement.

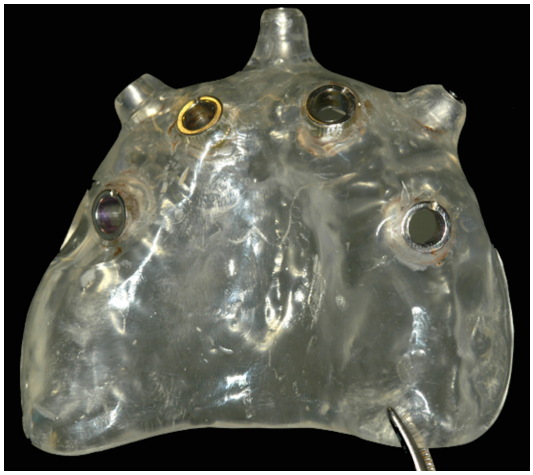


Figure 5. Upper surgical guide for computer-guided implant placement.

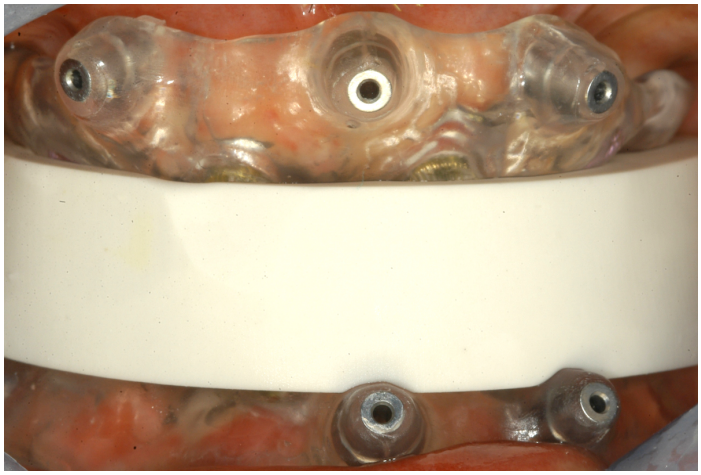


Figure 6. Intra-operative view of the surgical guides positioned with the aid of a silicone index.

Finally, a total of 4 implants per jaw were placed with computer-aided, template-guided flapless technique according to the manufacturer's instructions (Figures 6-8). The healing proceeded uneventfully, and definitive implant-supported screw-retained fixed dental prostheses were delivered 6 months after the implant surgery (Figures 9-10).

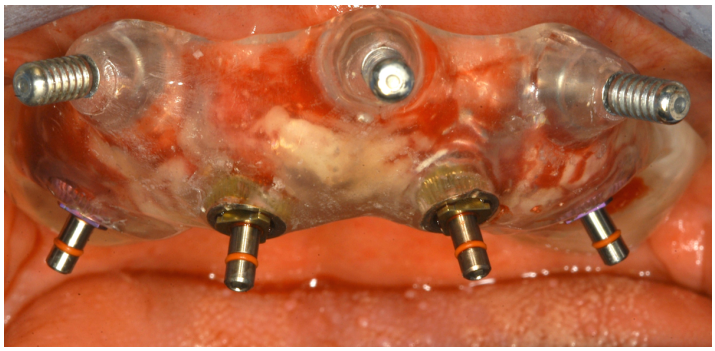


Figure 7. Intraoperative clinical view of the surgical guide stabilized in the proper position with 3 endosseous pins. Four implants have been inserted according to the virtual plan.

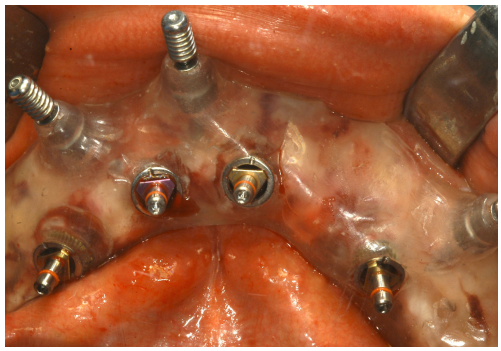


Figure 8. The same surgical procedure performed in the mandible, with four implants inserted with a flapless approach.

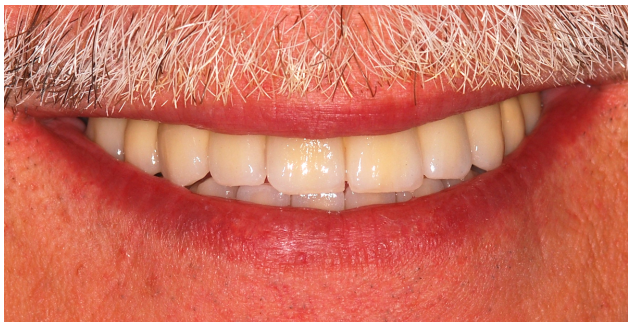


Figure 9. Extraoral view of the definitive screw-retained implant-supported fixed dental prostheses.

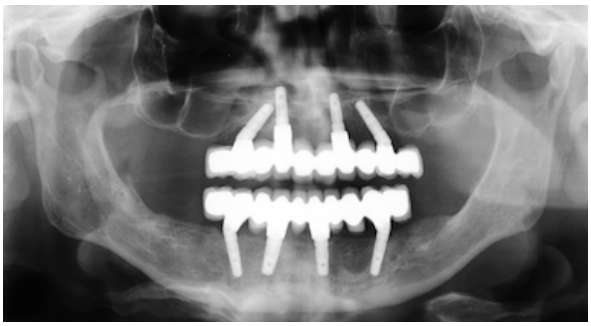


Figure 10. Follow-up orthopantomograph performed after delivery of the definitive prostheses

In 2013 another case-report was published with the purpose to illustrate a full-arch rehabilitation performed with computer-guided implant surgery [23]. Similarly to the previous report, the virtually planned position of the implants was transferred to the surgical environment by means of a surgical template realized with rapid prototyping and stereolithography techniques. A total of four implants were placed in the upper jaw according to anatomic and prosthetic demands. In this case the old denture used by the patient before the surgery and after the extractions, was modified in order to reduce expenses. Six hours after surgery the temporary prosthesis was applied, balanced in the correct occlusion and polished. The patient left the clinic with correct masticatory function and good aesthetics. The final Toronto-bridge prosthesis reinforced with a titanium framework and composite, was inserted four months after the delivery of the temporary prosthesis (Figures 11-18).

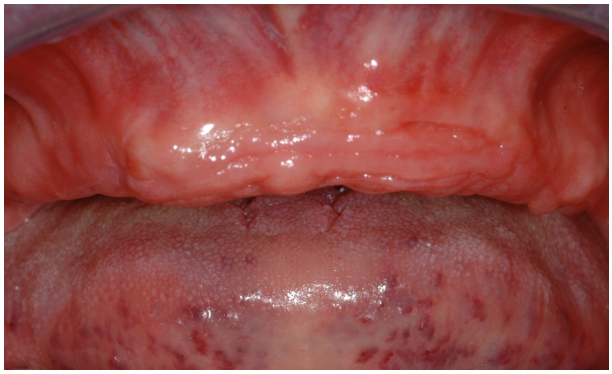


Figure 11. Pre-operative intraoral view of the edentulous maxillary arch.

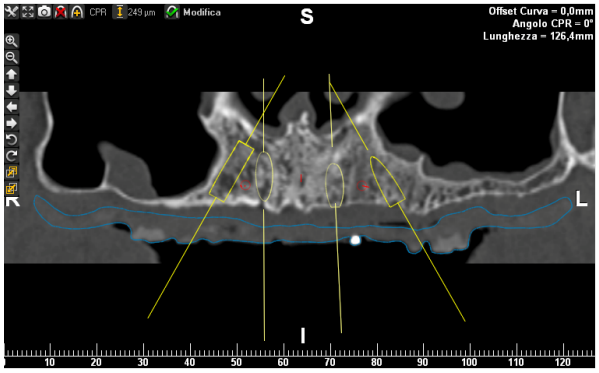


Figure 12. Virtual planning of four implants combining anatomical, functional, and prosthetic aspects.

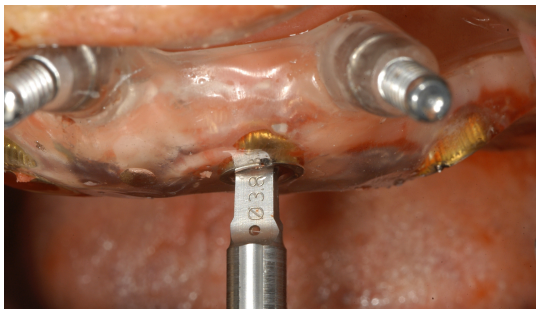


Figure 13. Computer-guided preparation of the implant site with disposable form-drills.

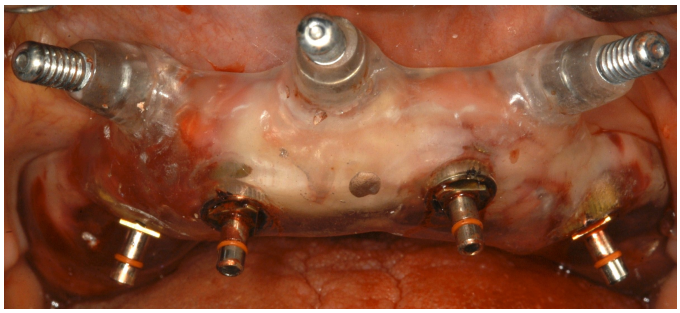


Figure 14. Computer-guided flapless insertion of four implants in the upper jaw by means of a surgical stent.

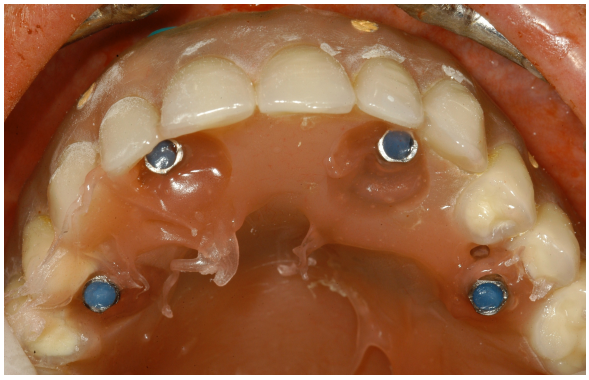


Figure 15. Adaptation of the old prosthesis used by the patient immediately loaded to the implants.

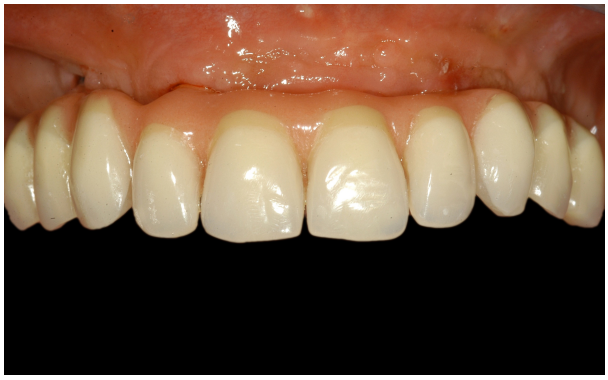


Figure 16. Temporary prosthesis balanced in the right occlusion, refined, and polished.

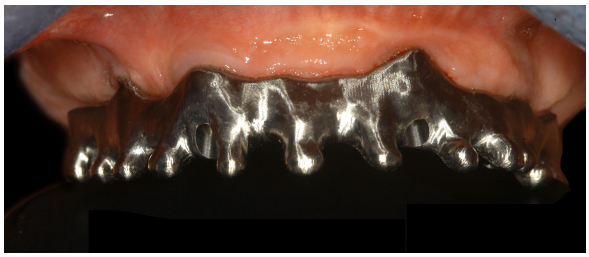


Figure 17. CAD/CAM titanium definitive framework.

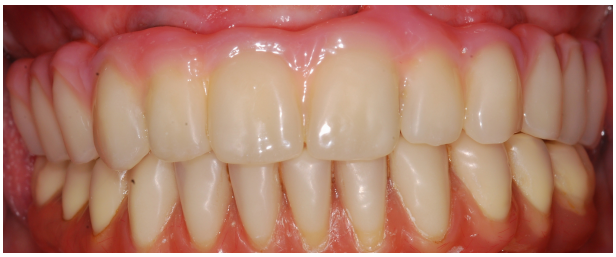


Figure 18. Definitive implant-supported screw-retained fixed dental prosthesis.

The aim of these reports was to stress the advantages of computer guided implant surgery performed with a flapless approach from patient-centered outcomes. These include reduced patient swelling and pain, reduced intra-operative bleeding and surgical time, and no need for suturing, with the preservation of the soft tissue architecture and hard tissue volume at the implant site and maintenance of appropriate blood supply, thereby allowing the patient to restore normal oral hygiene procedures immediately afterwards. Less attention however has been given to the evaluation of the precision of the entire workflow, with respect to a retrospective evaluation of linear and angular deviations.

A little step forward in this direction has been made in 2014, with a study aimed to analyse the accuracy of computer-guided implant placement [24]. Patients demonstrating good general health with no local or systemic contraindications to oral surgery and implant placement were enrolled. Inclusion criteria were both partial and total edentulism in which the teeth were lost at least two months before the date of implant placement, characterized by an adequate quantity of bone, assessed as a minimum of 1 mm buccally and palatally/lingually, and associated with at least 3 mm of keratinized gingiva around the implant. Exclusion criteria were poor oral hygiene, active periodontal infections, uncontrolled systemic pathologies, and presence of a smoking habit (>10 cigarettes/day).

Anatomical situations requiring regenerative procedures prior or contemporaneous to the implant surgery were excluded. In brief, following computer-guided implant surgery patients underwent postoperative CBCT scan with the same apparatus and settings as the preoperative scans. The preoperative and postoperative scans were then overlapped using a dedicated algorithm, which allowed the comparison of the virtually planned and the actual implant positions. Three deviation parameters between each planned and placed implant were measured: linear deviations of the head and apex, and angular deviations of the long axis of the fixture. Such measurements were performed according to other similar studies used as benchmarks at that time [25-29]. Results were encouraging. The comparison of planned and placed implant positions showed a mean linear deviation of the implant head of 0.56 ± 0.23 mm, a mean linear deviation of the implant apex of 0.64 ± 0.29 mm, and a mean angular deviation of the long axis of 2.42° ± 1.02° (Figures 19A-B). These values are still slightly more accurate than the respective means observed in the latest systematic review and meta-analysis previously cited [18]. This might indicate a certain reliability of the protocol adopted herein, however results must be interpreted cautiously due to the limited sample.

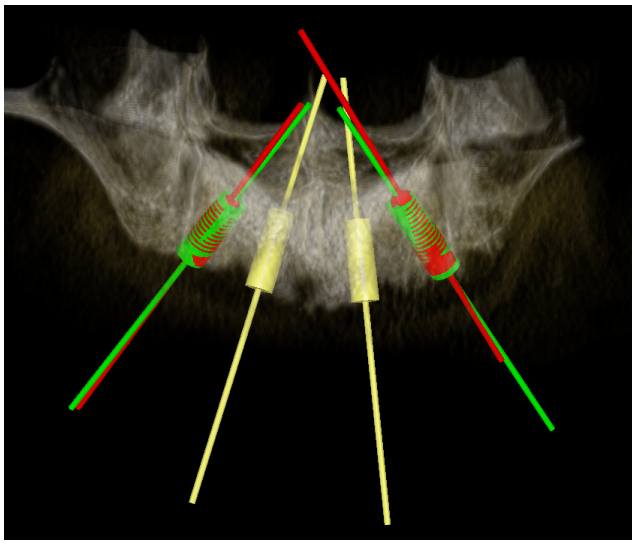


Figure 19A. Superimposition of the pre- and post-operative CBCT scans to evaluate the 3D accuracy of implant positions (red: planned; green: real).

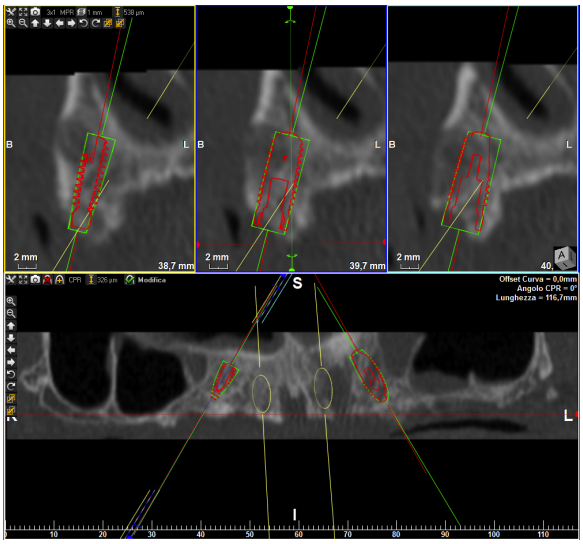


Figure 19B. Accuracy evaluation by assessing coronal and apical linear deviations and long-axis angular deviations (red: planned; green: real).

The survival rate has been used as an estimator to predict the effectiveness of a technique over time. The same applies to implants placed with computer-guided protocols, with recent findings showing a retrospective cumulative survival rate of 97.4% at 10 years [30]. On the other hand evaluating the prosthesis survival, namely the final outcome of the entire treatment, results do not seem to be as impressive, reaching 62% in some cases [16]. Prosthesis fracture, screw loosening, misfit at the time of superstructure connection, and need for extensive occlusal adjustments after placement of the superstructures were the most reported post-surgical complications [31]. A possible explanation might be related to difficulties in fixing the temporary prosthesis in the proper position during relining procedures. Traditionally, prefabricated, screw-retained, fully acrylic, or metal-reinforced acrylic resin provisional restorations are immediately delivered to the patient. The unavoidable small deviation between the planned implant position and axis and the postoperative position is compensated by a small space between the abutments and the cylinders within the prosthesis. However, in the case of partial edentulism converted into total edentulism following tooth and/or implant extractions, all pre-surgical reference points are lost as a consequence of changes in hard and soft tissue contours. In particular, it might be difficult to determine the ideal vertical dimension of occlusion and to obtain balanced occlusion during procedures for relining the temporary prosthesis. Furthermore, the patient could act non-collaboratively due to deep sedation and local anesthesia, hampering the accurate reposition of the fixed

prosthesis on the implants. Therefore, misfit of the prosthesis might result in an accumulation of bending moments and loading stresses, causing possible mechanical complications (loss of retention, fracture of the veneering material, screw loosening, and framework fracture), as well as biological complications (bone remodelling, micro-damage, and loss of osseointegration), which may explain the high rate of postoperative prosthetic complications [32, 33].

In order to minimize the risk of prosthetic failures, in 2016 a technique proposal has been published [34]. The proposed technique has been developed to find a solution that takes account of the reference points lost during the transition from the surgical guide to the fixation of the temporary prosthesis. Differently from the previous techniques, this method allowed the operator to constantly reproduce the transfer of data related to the fixed temporary prosthesis with the same means as used for the surgical template, so that the prosthesis is accurately located, with respect to the implants, according to the pre-existing reference points. The hypothesis was therefore to reduce the risk of prosthetic misfit and consequently the likelihood of developing prosthetic complications, thereby enhancing predictability of the restoration. In summary, once all fixtures have been placed with computer-guided procedures as already described, temporary prostheses were equipped with resin guiding holes corresponding to the exact position of the pin drilling sleeves of the surgical template. The prostheses were consequently stabilized in the proper position with the same bone pins previously used to fix the guiding stent. Thus, greater accuracy and stability was provided to the system during further procedures. A rubber dam was used during the prosthesis relining, in order to prevent infiltration of the liquid resin in the underlying tissues. The temporary resin guiding holes were therefore removed and the prosthesis was properly balanced in the correct occlusion, finished, and polished. The temporary fixed prosthesis with a CAD/CAM fabricated metal framework used to reduce the flexibility of the structure was then connected to the definitive abutments. The screw access openings of the prosthesis were filled with composite resin. Despite the short follow-up, no prosthetic complications were observed (Figures 20-24).

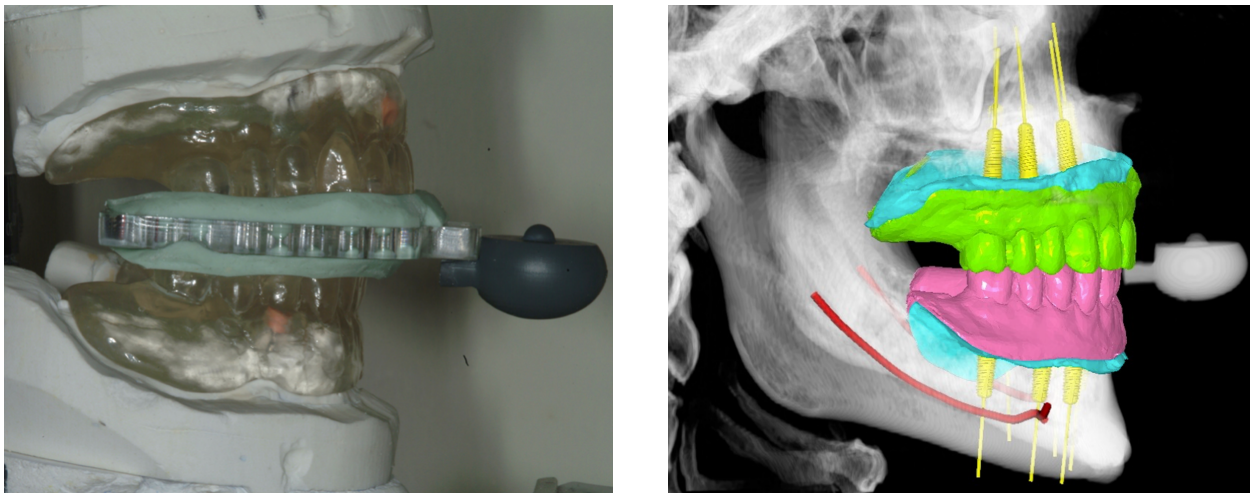


Figure 20A-B. The workflow of computer-guided implant surgery according to the double-scanning technique is summarized herein. Figure 20A shows the radiological guides for both upper and lower jaws, realized on the basis of the prosthetic wax-up replicating the final prostheses. In order to transfer the prosthetic informations to the virtual environment, a customized silicon index equipped with an extra-oral radiopaque marker is used to position the prostheses in the correct interarch position. The same position is subsequently adopted by the patient during the CBCT scan while wearing the radiological guides positioned with the silicone index. At this point, the clinician is able to overlap the optical scan of the prostheses with the DICOM data by superimposing the extra-oral radiopaque marker visible in both sets of scans (Figure 20B). Anatomical data (in red for example the inferior alveolar nerve is shown) together with prosthetic requirements (in green and pink the upper and lower prostheses respectively) allow the clinician to correctly place the implants (in yellow) in the desired position.

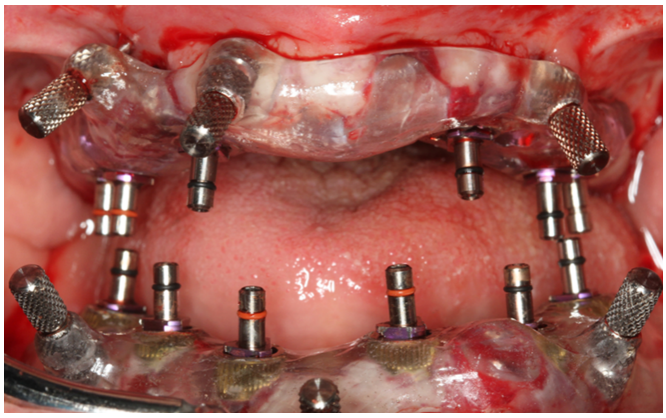


Figure 21. Implant placement with the aid of surgical guides stabilized with anchor pins in the virtually planned position.

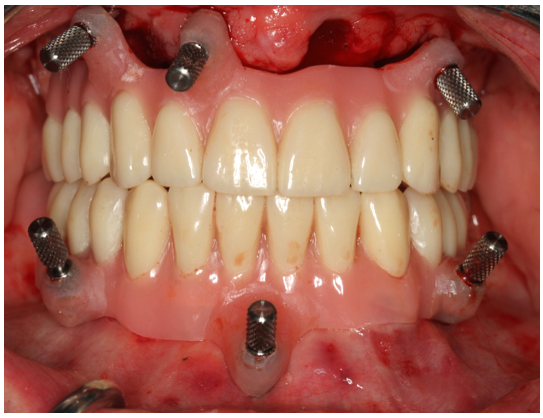


Figure 22. Temporary prostheses positioned in the same position of the surgical stents using resin guides and anchor pins.

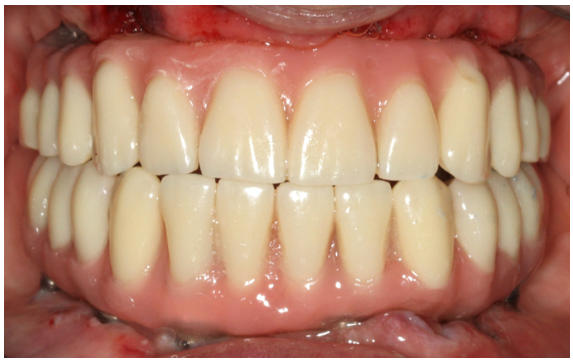


Figure 23. Temporary prostheses relined and fixed in the same position registered previously.

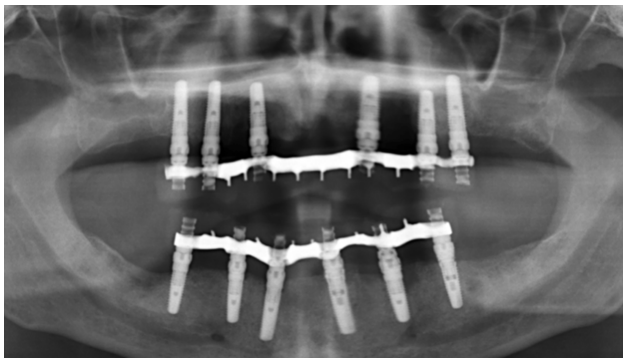


Figure 24. Post-operative panoramic X-ray after the immediate loading.

To further expand the applications of computer-guided implant surgery in clinical scenarios barely explored, in 2017 our research group reported a total rehabilitation of a syndromic patient affected by ectodermal dysplasia [35]. The purpose was to describe a rare as well as complex anamnestic and clinical case managed with fresh frozen bone augmentation and virtual implant planning. As a matter of fact, to our knowledge, this report documented the first time fresh frozen bone allografts and computer-guided implant surgery have been used to replace the missing bone and teeth in a patient affected by ectodermal dysplasia. The patient presented with oligodontia, which precluded the possibility of a conventional tooth-supported fixed bridge. On the other hand, the underdevelopment of the alveolar ridges, consequent to the lack of alveolar bone growth during permanent dentition eruption, made the use of a removable dental prosthesis difficult and esthetically objectionable. As a consequence, implant placement associated with bone augmentation techniques was planned to rehabilitate the patient with an implant-supported fixed dental prosthesis. After alveolar ridge reconstruction by means of fresh frozen bone block allografts, it was possible to perform a virtually guided surgical planning of the implant-supported rehabilitation (Figures 25-26). Innovations included guided removal of the osteosynthesis screws by means of small linear incisions conducted in correspondence of guiding holes equipped in the stent, and the computer-guided insertion of implants in bone reconstructed with fresh frozen bone allografts. The aim was to minimize post-operative discomfort, pain, and swelling, by obtaining at the same time an accurate positioning of the implants in the reconstructed bone without impairing the blood supply. The effectiveness of this procedure has been demonstrated by the accuracy assessment, showing mean linear deviations of less than 1 mm and axial deviations of around 3°.

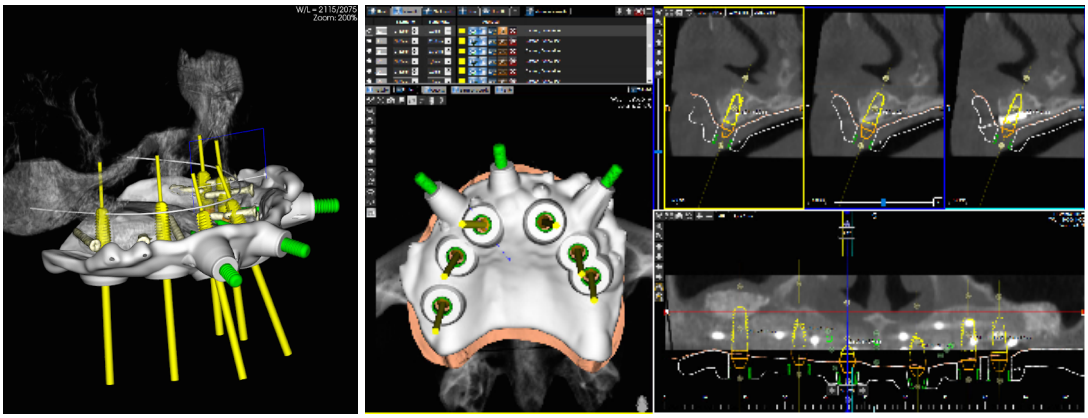


Figure 25. Virtual planning of implants in upper jaw. In some cases the location of the osteosynthesis screws interfered with the ideal position of the implants. This issue was overcome by removing the fixing screws with a flapless approach by means of the guiding holes equipped in the surgical stent. It was also possible to plan the proper axis of the endosseous pins (green).

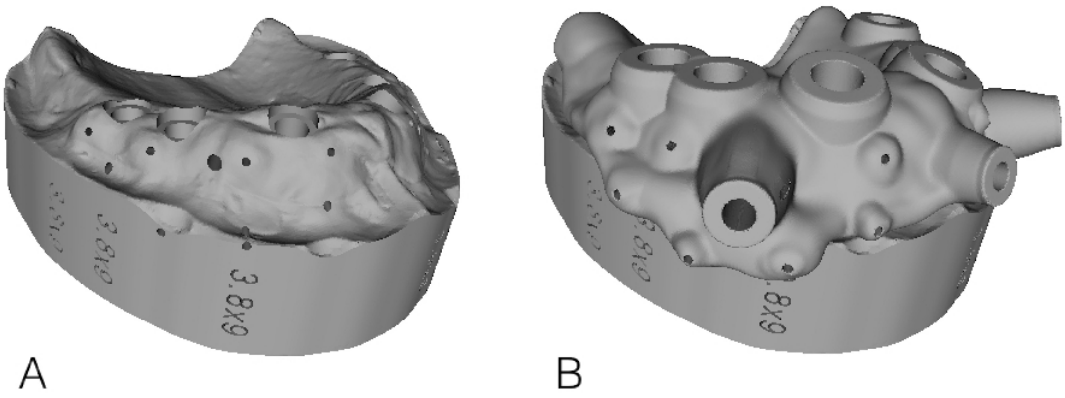


Figure 26A-B. Figure 26A shows the real-size model produced according to virtual planning. The exact position and dimensions of the implants and the location of the osteosynthesis screws were replicated in the model for the subsequent realization of the surgical stent. Figure 26B shows the surgical stent of upper jaw produced on the basis of the real-size model. The guiding holes realized to remove the osteosynthesis screws and to insert the endosseous pins and the implants with a flapless approach corresponded to the simulation obtained in the real-size model.

2.1.2. A new insight

In all the studies mentioned in the previous subchapter, implants have been placed with a flapless procedure in an optimal amount of bone, irrespective of whether the recipient hard tissue was autogenous pristine bone or augmented bone. In other words, the residual bone anatomy allowed placing implants with a flapless computer-guided approach without recurring to bone regeneration or bone recontouring. In some clinical situations, bone remodelling is mandatory to obtain predictable results. This is particularly true in the interforaminal region, where a distance of 8 to 12 mm between the bone crest and the occlusal plane is advisable to provide space for the prosthetic components. In less than ideal situations, additional vertical height and horizontal width may be gained surgically with free-hand osteoplasty. Recent evidence suggested that the use of a surgical guide based on the prospective interim prosthesis and fabricated on a stereolithographic cast permits guided alveolar ridge reduction in a more precise manner [36]. The authors planned a controlled alveolar ridge reduction on the basis of a stereolithographic cast

and transferred the project to the surgical environment by means of a an acrylic resin guide. The implant replicas were then placed freehand on the stereolithographic cast. A surgical guide completed with guiding sleeves and guided pins embedded in autopolymerising acrylic resin, has been fabricated accordingly.

In order to increase the accuracy of both alveolar ridge reshaping and implant insertion, in 2018 our research group presented a novel approach of bone remodelling and implant insertion completely guided by surgical stents fabricated from a virtual plan [37]. The initial phases of virtual implant position planning resembled those provided by the traditional computer-guided protocol. In the mandible, a vertical ridge reduction was planned virtually to obtain a residual crest with optimal anatomy and to position the implants correctly. The entire virtual plan was transferred to the surgical field by means of surgical guides fabricated with a 3D printer and rapid prototyping techniques. After tooth extraction, a stent was accurately placed on the mucosa with a silicone guide to prepare the holes precisely for the subsequent insertion of the anchor pins. A mucoperiosteal flap was then raised to expose the interforaminal region. At this point, a customized bi-component surgical stent was secured in the appropriate position with 4 endosseous pins inserted in the previously prepared reference holes. Thus, the ridge has been remodelled according to the computer-guided virtual plan. Under saline irrigation, the osteoplasty of the residual alveolar ridge was completed with a pear-shaped surgical bur aided by the flat part of the stent corresponding to the virtually planned level of apico-coronal reduction. Thereafter, the upper component of the template was connected to the stent with 3 mini-screws serving as a surgical guide for the forthcoming implant placement. Finally, implants were inserted in compliance with the virtual plan in the interforaminal region with an insertion torque of at least 35 Ncm (Figures 27-30).

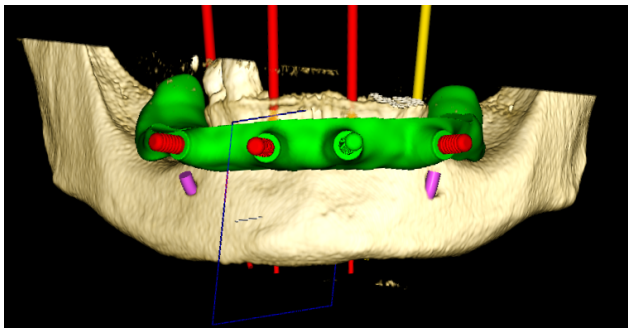


Figure 27. Virtual project of the first surgical stent used to guide the osteotomy allowing for a virtually guided vertical ridge reduction.

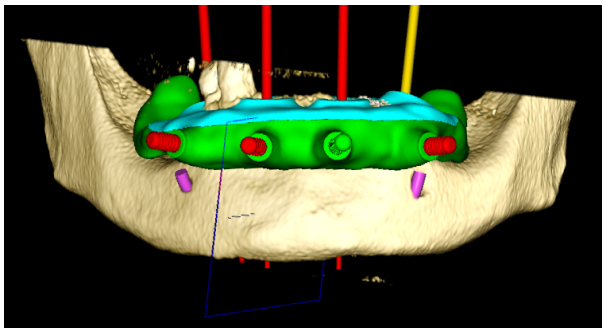


Figure 28. Virtual project of the second surgical stent used to guide the insertion of four dental implants according to the new vertical dimension.

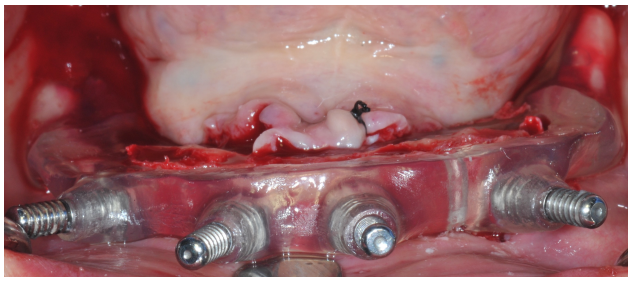


Figure 29. Virtual project transferred to the surgical environment. The first stent has been stabilized in the proper position with anchor pins, and has been used to guide the alveolar ridge vertical reduction in order to allow a prosthetically driven implant insertion.

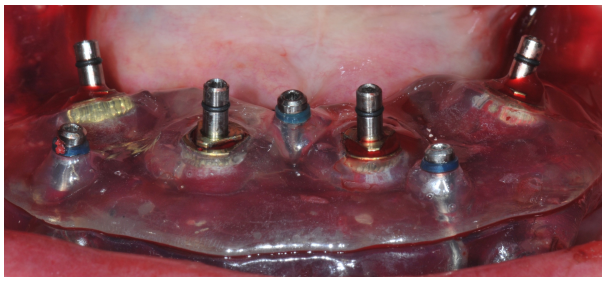


Figure 30. Following alveolar ridge remodelling, the second surgical stent has been screwed with mini-screws to the first surgical stent in order to insert four implants with a fully guided approach according to the new vertical dimension.

The flaps were sutured with 4/0 polyglycolic acid suture. Bar abutments and intermediate abutments were screwed to the implants. An autopolymerizing composite resin was placed over the abutments to fix a polymethyl-methacrylate interim prosthesis precisely with a silicone index. The screw access holes were closed with Teflon tape and light polymerized interim composite resin. Healing proceeded uneventfully, and after 6 months, a definitive impression was made, and chromium-ceramic implant-supported fixed dental prosthesis was delivered (Figures 31-32).

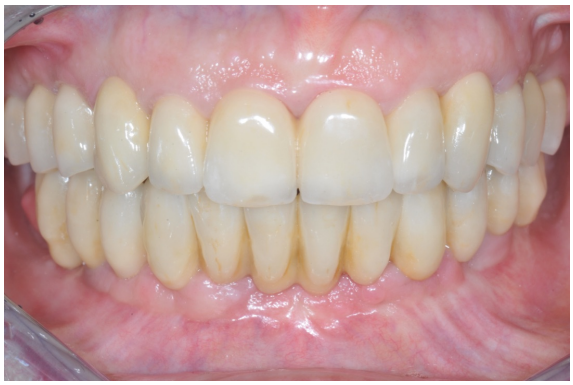


Figure 31. Intraoral clinical view of the definitive screw-retained implant-supported fixed dental prostheses.

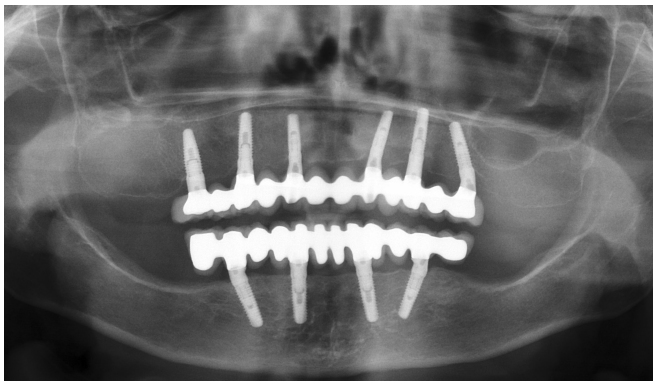


Figure 32. Follow-up orthopantomograph showing stable bone levels with no radiological signs of peri-implant disease.

The focus of the report was to emphasize the possibility to plan the ideal shape of the recipient bone to receive dental implants in a prosthetically driven position in compliance with the prosthetic waxing. Differently from the origin, when computer-guided implant placement was used in case of adequate quality and quantity of supporting bone, the bone tissue is progressively becoming active part of the virtual treatment plan. All is made possible by exploiting current advances in computer tomography and virtual planning software technology.

2.2 Prosthetically-guided bone regeneration

The fact that bone tissue is becoming part of the treatment plan is extensively corroborated by the concept of prosthetically guided bone regeneration [38] as a direct evolution of the restoration-driven implant placement [8].

Differently from the past when implant placement was primarily determined by the location of available bone, current trends suggest to position the implant according to prosthetic needs in order to optimize both function and aesthetics. Indeed, aesthetic outcomes have become more important because implant-supported prostheses have to integrate with the adjacent natural dentition, both from a functional and an aesthetic point of view. Thus, it is no longer sufficient to merely attach a prosthetic device to the underlying fixture, but for optimal function and aesthetics it has become essential to place an implant according to prosthetic demands.

In order to insert implants in the correct prosthetically-guided position, optimal conditions of the recipient alveolar bone in terms of adequate quality and quantity are mandatory in the first instance. However, after tooth loss or other conditions such as sequelae of periodontal disease, traumas, or congenital malformations, alveolar bone inevitably undergoes a variable remodelling phase that in most cases result in a deficient alveolar ridge unable to receive dental implants. In such clinical conditions, the implant site must be augmented with a three-dimensional approach previously or simultaneously with implant placement.

Several techniques have been developed to improve bone volume of segmental defects in the atrophic jaw, including guided bone regeneration (GBR). This surgical procedure has been firstly described in 1959 by Hurley et al., during experimental reconstructive surgery to treat experimental spinal fusion [39]. Subsequently in the mid-90's, GBR has been applied in oral surgery to augment bone volume for implant placement purposes [40-42]. This technique

is based on filling the defect with autogenous bone particles and/or bone substitutes, and covering the graft with a membrane to prevent ingrowth of the epithelial and gingival connective tissue cells. The tissue regeneration promoted allows healing of bony defects within a period of 6 to 10 months. One of the most important aspects in obtaining results with this technique for horizontal and vertical ridge augmentation is the creation and maintenance of a secluded space under the membrane. The development of this space is the prime determinant of the amount of newly formed bone. It is indeed known that without a containment system, a collapse of soft tissues toward the defect can occur, leading to compression or displacement of the graft and consequent inability to achieve the desired results. Several barrier membranes have been proposed in order to avoid membrane collapse and to increase regenerative capabilities of the bone in non space-making situations. Although resorbable membranes are used in most cases due to decreased morbidity, less risk of membrane exposure, and no need of a re-entry surgery, they suffer from low tensile strength and uncontrollable degradation process, which can be a limitation when compared to non-resorbable membranes. This is particularly true in case of extensive vertical bone defects where the space maintaining ability is challenged.

In 2015 our research group evaluated the effectiveness of GBR procedures by performing a retrospective evaluation on a sample of patient treated with bone augmentation and dental implants in a university setting [43]. Patients who presented with partial edentulism and underwent localized horizontal or vertical alveolar ridge augmentation procedures with resorbable and non-resorbable membranes for implant rehabilitation purposes were included. Overall, 192 implants were analyzed with the Kaplan-Meier estimator. Among the 192 implants positioned, 5 implant failures occurred. Over a median follow-up period of 78 months, the cumulative survival rate was 95.6%. No statistically significant differences were obtained from the log rank test with respect to the type of membrane and the timing of implant placement. A standard clinical case has been illustrated in Figure 33.

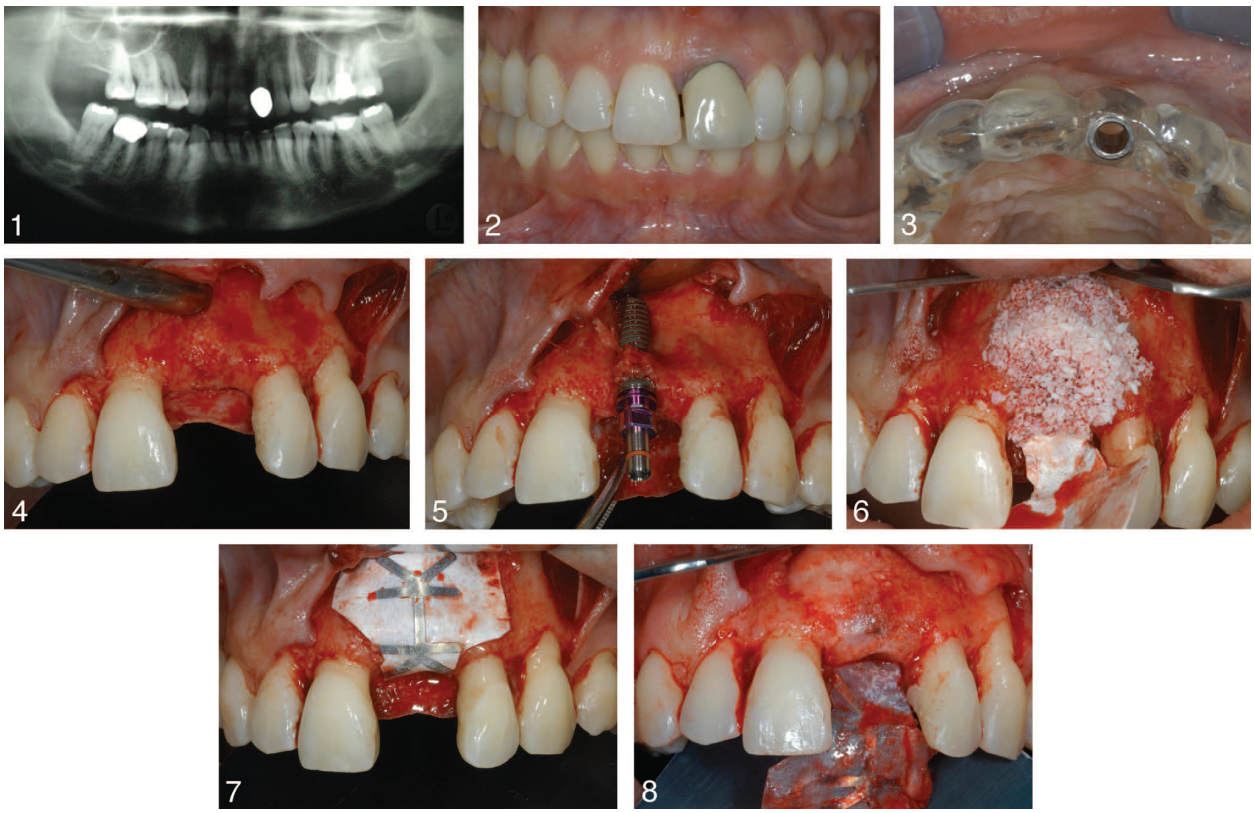


Figure 33. Schematic illustration of a partial edentulism in the frontal aesthetic area of the upper jaw treated with GBR procedures. It is possible to observe a standard surgical guide (Fig-33-1) used to insert the implant with a prosthetically guided approach. The surgical guide was typically equipped with a 2 mm ø hole so that only the first pilot drill was guided by the stent, differently from a fully guided approach where all drills are guided by the stent.

3. Rationale and aim

3.1. Virtually-aided GBR combined with computer-guided implantology

The rationale of the present study arose from the knowledge and experience described in the previous subchapters gained with GBR and computer-guided surgical procedures. The intention was to apply the technology currently available in terms of virtual planning even in critical and demanding anatomical situations. Such clinical conditions included atrophic and resorbed edentulous alveolar ridges characterized by inadequate amount of supporting bone, unsuitable to receive dental implants in a prosthetically guided position without recurring to bone augmentation procedures.

Since the computer-guided implant placement techniques take advantage of the innovations in 3D imaging, they may be advantageous compared to conventional surgical protocols when it comes to patients with limited amount of bone. Theoretically, bone augmentation procedures may be avoided or reduced by optimizing implant positioning in accessible bone [16, 31]. This concept clearly falls into the indications for guided surgery. These may include the following: the need for minimally invasive surgery or flapless approach, optimization of implant planning and positioning, and immediate reconstruction [44].

On the other hand, the current evidence still lacks information concerning the use of computer-guided implant protocols to rehabilitate resorbed edentulous ridges. Fortin et al. in 2009 reported on the use of an image-guided system in severely resorbed posterior maxillae as a viable option to place implants in a very limited amount of bone avoiding at the same time sinus floor elevation procedures. Fifteen resorbed posterior maxillae were treated with a total of 42 implants inserted with half-guided approach together with bone spreading techniques. Implants were placed with a tilted configuration in the palatal curve, or close to the anterior or posterior wall, or in sinus septa. During the 4-year observation period, no complications were recorded, no implants were lost after loading, and there was no infection or inflammation. Only one implant was lost before loading. Unfortunately, according to the latest systematic reviews [16, 17, 45], only the aforementioned paper answered the question whether computer-guided surgery can be used as an alternative to bone augmentation. Obviously, not all residual ridges allow achieving a compromise with respect to the position of the implant. This is particularly true in case of severe horizontal and vertical bone defects where the position of the implant is further limited by anatomical structures such as the maxillary sinus or the inferior alveolar nerve. In this context, GBR has shown successful outcomes in augmentation and reconstruction of alveolar ridge width and height [46].

Hence, the purpose was to merge together prosthetic-guided bone regeneration and computer-guided implant placement techniques within the same surgical phase, in order to exploit the advantages of both procedures simultaneously. Therefore, implants were placed in the ideal prosthetically driven position without recurring to compromises in terms of position or size of the fixture. GBR was subsequently performed to augment peri-implant hard tissue and re-establish the physiological contour of the resorbed ridge. Furthermore, differently from the traditional approach, a secondary goal was to mould and contour the bone to be augmented directly in the virtual environment without recurring to physical wax-ups. The purpose was to perform the entire pre-surgical planning with a computer-guided approach, from the GBR to the implant insertion. This hypothetically allows the creation of a virtual project that takes into account the ideal rehabilitation in terms of implant position and bone architecture.

This aspect constitutes an innovation since the evidence currently available reporting on the combination of virtually-aided GBR and computer-guided implantology is, to the best of our knowledge, extremely under-explored so far.

3.2. Objectives of the study

In view of the aforesaid, the aim was twofold:

1) to evaluate the effectiveness of virtually-aided GBR and simultaneous computer-guided implant placement applied in critical clinical situations presenting an inadequate amount of bone, from clinical and patient-centered outcomes;

2) to test the hypothesis that computer-guided implant placement in such compromised conditions might be able to achieve comparable results in terms of accuracy compared to computer-guided implant insertion in sites presenting an ideal amount of bone.

4. Materials and methods

4.1. Study design

The present study was designed and performed as a prospective mono-centric proof-of-concept study aimed to evaluate the effectiveness and accuracy of a computer-guided protocol developed to assist the operator during simultaneous bone augmentation procedures and implant insertion. All phases of the study were conducted in the same unit (Implant Centre for Edentulism and Jawbone Atrophies, Maxillofacial Surgery and Odontostomatology Unit, Fondazione IRCCS Cà Granda, Maggiore Policlinico Hospital) by the same research group. Surgical procedures were performed by two operators with comparable experience in computer-guided surgery. All patients received thorough explanations and had to complete and sign a written informed consent form prior to being enrolled in the study. All phases of the present study were conducted according to the principles outlined by the World Medical Association Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, as revised, amended, and clarified in its version 2013 [47]. The study protocol was submitted to and approved by the local Institutional Review Board of the Hospital with the reference number RC-2016-420-2.

4.2 Study population

4.2.1. Test group

Patients were recruited as a consecutive sample from 2016 to 2018 after consultation with clinical and radiological examinations by means of orthopantomograph and CBCT. To be enrolled, patients had to fulfil the following inclusion criteria:

1) Male or female patients aged 18 years or older;
2) Partial edentulism with 3 or less missing teeth in the posterior sectors in the upper and/or lower jaw;
3) Loss/extraction of teeth occurred at least 2 months before the date of GBR and implant placement, and complete clinical and radiological healing of the post-extraction socket;
4) Presence of an inadequate amount of bone both in horizontal and vertical dimensions, which impedes an implant placement without recurring to simultaneous GBR procedures. More in detail, only anatomical conditions in which, from the virtual planning, a circumferential peri-implant bone thickness of at least 1 mm cannot be maintained, were considered;
5) Presence of at least 3 natural teeth with no metal restorations that might compromise the subsequent radiological overlapping due to metal-induced radiographic artifacts.
6) Mouth opening of at least 40 mm in order to allow the insertion of the different devices during the surgical phase.

Patients were not included into the present study if any of the following criteria were present.
Local exclusion criteria were as follows:

1) Local mucosal inflammation and possible presence of periodontal disease ascertained clinically (Full-Mouth Plaque Score - FMPS > 25%, and Full-Mouth Bleeding Score - FMBS > 25%);
2) Presence of erosive mucosal disease;
3) Presence of bone lesions;
4) Clinical history of radiotherapy in the head and neck area;
5) Presence of unhealed post-extraction sockets and/or presence of post-extraction socket from less than 2 months from teeth extractions;
6) Patients with parafunctional oral habits;

7) Patients with an unsatisfying oral hygiene or patients not motivated for domestic care.

Systemic exclusion criteria are as follows:
1) Presence of chronic pathological conditions that require prophylactic antibiotics intake (i.e. rheumatic disease, bacterial endocarditis, anomalies of the cardiac valves, etc.);
2) Medical conditions requiring a prolonged intake of steroid drugs and/or bisphosphonates;
3) Clinical history of leukocyte dysfunction or deficiency;
4) Clinical history of coagulation disorders;
5) Clinical history of neoplastic tumors that require or required the use of radio or chemotherapy;
6) Clinical history of renal insufficiency;
7) Clinical history of uncontrolled endocrinopathy;
8) Patients presenting physical and/or mental handicap that impede an adequate oral hygiene;
9) Patients with drinking or drug abuse habits;
10) HIV-infected patients;
11) Patients with smoking habits (> 10 cigarettes per day);
12) Presence of conditions or circumstances that may interfere with the participations of the patient to the study.

4.2.2. Control group

In order to compare the accuracy of the experimental procedure in the test group with the accuracy of the standard computer-guided protocol, another sample of patients was included in the control group serving as a reference point. To this end, an extended population from an initial restricted sample of patients enrolled in a previous study [21] performed in the same Department by the same research group was selected. In this case, subjects were recruited from 2012 to 2014. In brief, only patients demonstrating good general health with no local or systemic contraindications to oral surgery and implant placement were considered suitable for the study. Inclusion criteria were total edentulism in which the teeth were lost at least two months before the date of implant placement. The alveolar ridge had to present an adequate quantity of bone, assessed clinically and radiographically as a minimum of 1 mm buccally and palatally/lingually, and associated with at least 3 mm of keratinized gingiva around the implant. Exclusion criteria were poor oral hygiene, active periodontal infections, local and/or uncontrolled systemic pathologies, and presence of a smoking habit (> 10 cigarettes/day). Anatomical situations requiring bone augmentation procedures prior or simultaneously with the implant surgery were excluded.

4.3. Null hypothesis

The purpose of the present study was to test the null hypothesis that no statistically significant differences would be found in the accuracy level between computer-guided implant insertion in atrophic bone augmented simultaneously versus computer-guided implant placement in optimal bone anatomy, against the alternative hypothesis of a difference.

4.4. Experimental procedure in the test group

4.4.1. Virtual planning

Following the recruitment phase, impressions were taken for each patient with an irreversible hydrocolloid material. After the designated time interval, the impressions were poured with high-precision type IV dental die stone. After impressions, all patients underwent CBCT scan of the localized edentulous space with the same apparatus and settings. DICOM data were subsequently acquired from the CBCT scan and imported into dedicated virtual

planning software. At the same time, the definitive diagnostic stone study cast related to the partially edentulous jaw was scanned with an optical scan. The STL (STereo Lithography interface format) data obtained from the optical scan were imported in the same virtual planning software.

At this point, with an appropriate mathematical algorithm, the software proceeded with a superimposition of the DICOM and STL data. This was made possible by overlapping the selected surfaces of the residual reference teeth free from metal-induced artifacts present in both the CBCT scan and the optical scan. The clinician was therefore able to integrate the contour and thickness of the soft tissues and the precise anatomy of the remaining teeth registered within the stone study cast with the bone architecture and the anatomic structures scanned with the CBCT. According to the prosthetically guided implant placement, the following step consisted in the virtual wax-up of the artificial crowns of the teeth to be replaced. This was accomplished with a specific tool integrated into the software that allowed the clinician to insert and design the desired size and shape of the crowns that best fit the edentulous space according to the modern prosthetic needs.

Once the virtual prosthetic rehabilitation has been validated by the surgeon jointly with the dental prosthetist, it was possible to virtually plan the ideal position of the implants with respect to the virtual wax-up used as the starting point. The ideal length and width of the implants were then selected in the database in order to place each implant in the correct 3D prosthetic position respecting at the same time the anatomical structures and the distances between adjacent teeth and/or implants. The 3D positioning of each implant was further guided by the thickness and contour of the soft tissues in order to predict and respect the peri-implant biologic width.

As soon as the virtual position of each implant has been achieved, it was possible to evaluate the anatomy of the residual bone. Since the test group was characterized by patients presenting with an inadequate amount of hard tissue to receive dental implants, a certain amount of missing bone was always present. Thus, another tool available in the software allowed the clinician to virtually augment and contour the resorbed ridge in order to obtain at least 1 mm of regenerated bone circumferentially around each implant with a physiologic profile.

Once the virtual plan has been checked by the multidisciplinary team, the project was sent for 3D printing with rapid prototyping techniques by the virtual planning software manufacturer. This resulted in 1) stereolithographic real-size model of the partially edentulous jaw with the bone defect and the implant osteotomies; 2) stereolithographic real-size model of the augmented bone with the implant osteotomies easily embeddable to the jaw model; 3) tooth-supported stereolithographic surgical guide.

4.4.2. Surgical procedures

One week before the date scheduled for the experimental surgery, each subject underwent professional oral hygiene session, and was instructed in oral hygiene procedures in order to eliminate any infective complications.

The surgical procedures were performed on an outpatient basis under local anesthesia. The surgical stent was sterilized chemically with an ethylene oxide solution, while the stereolithographic models were sterilized by autoclaving. The latters were used pre-operatively to trim and contour a non-resorbable dense-expanded-polytetrafluoroethylene (d-e-PTFE) so that its shape closely matched the anatomy and shape of the virtually augmented bone transferred in the stereolithographic models.

Before starting the surgical procedure, pre-operative rinsing of the oral cavity with chlorhexidine digluconate 0.2% antiseptic solution, and perioral skin disinfection with 10% povidone-iodine aqueous solution, were performed. Intramuscular injections of 4 mg/mL of dexamethasone sodium phosphate were performed to reduce postoperative edema.

Local anesthesia was induced with infiltrations of mepivacaine 2% with epinephrine 1:100.000. In brief, a mid-crestal horizontal incision extended with intrasulcular incisions at least one tooth mesially and distally, associated with mesial and distal vertical releasing incisions were made to mobilize a full-thickness flap. The bone

crest was then exposed and debrided with a sterile curette and irrigated with saline solution to remove any remnants of fibrous tissue if present, and to prevent connective tissue encapsulation in the implant bed.

At this point, the surgical guide was carefully leaned against the remaining teeth with the aid of guiding grooves carved in the template. Once the optimal adaptation and stability of the surgical guide with the soft tissues in the corresponding edentulous space has been checked for proper seating, it was possible to place the implants with a computer-guided approach.

The surgical stent was equipped with guiding sleeves mounted onto the seating tool that matched the implant diameter. At this point, serial osteotomies were performed using disposable internal coolant pre-drill and subsequent disposable internal coolant form-drills, until the planned depth was reached. Internal cooling was achieved with 5 °C sterile physiological saline solution. Initially, the 5-mm length pre-drill was used to define the drill and implant axis. After pre-drilling, the implant bed is prepared up to the planned implant length in ascending drill length using form-drills. To avoid abrasion of the guide sleeves with drill cutting edges, the drills were not set in rotation until its cylindrical guide shaft was in contact with the inner surface of the guide sleeve. All drills were used with an intermittent technique, i.e. drill the bone for two to three seconds and then withdraw the drill upwards from the bone without stopping the hand motor. The maximum speed drill varied according to the implant diameter: 550 rpm for 3.3 mm Ø; 500 rpm for 3.8 mm Ø; 400 rpm for 4.3 mm Ø. This procedure was repeated until the desired depth has been reached. If during implant bed preparation it was shown that mainly cortical bone was present, the apical portion of the implant bed was widened using the cortical bone form-drill at 300 rpm, with the effect of reduce the insertion torque of the implant. Prior to implant insertion the implant bed was rinsed with sterile physiological saline solution to remove possible soft tissues remnants and titanium chips generated through contact of the drill cutting edge with the guiding sleeve. It was then possible to place the implants in the desired position according to the manufacturer's instructions. The implant reached the planned vertical end position when the shoulder of the insertion post rested on the top of the guide sleeve. All implants were inserted with insertional torque values > 35 Ncm. After reaching the final position, the implant was not rotated further in the template as this could lead to loss of primary stability. Corresponding cover screws were applied to the implants and the surgical template was removed.

Subsequently, GBR could be performed according to the virtual project. Cortical perforations of the recipient bed were performed with a carbide bur under copious irrigation with sterile saline to favor the nourishment and revascularization of the graft. The latter consisted of autogenous bone chips harvested nearby the surgical site by means of bone-scraper mixed with deproteinized bovine bone mineral (DBBM) particles in a 70:30 ratio respectively and wetted with physiological saline solution. The graft was then placed in direct contact with well-vascularized bleeding bone surfaces being careful to avoid an excessive compression to maintain the trabecular architecture. The pre-shaped d-e-PTFE membrane was adjusted to cover the graft maintaining a minimum distance from the periodontium of the neighboring teeth of 1.5 mm in order to prevent possible infiltrations through the gingival sulcus. Endosseous screws were used to fix and stabilize the d-e-PTFE membrane over the graft to the recipient bone at buccal and lingual/palatal aspects.

Finally, periosteal horizontal releasing incisions followed by upper-traction were performed if necessary, to mobilize the buccal flap and obtain a passive closure essential to prevent flap dehiscences and membrane exposure. Horizontal mattresses and single stitches were performed with non-resorbable monofilament e-PTFE suture to seal the surgical wound. Suture was removed after 3 post-operative weeks.

4.4.3. Medications

Medications prescribed for pre- and post-operative domiciliary use by the patient included 1 g amoxicillin-clavulanate twice a day for 6 days starting the day before the scheduled surgical procedure; 80 mg granulated

ketoprofen lysine salt according to patient's needs; 0.2% chlorhexidine digluconate mouthwash rinse solution 1 min three times a day starting 2 days before surgery and up to suture removal. The patients were also asked to apply ice packs for the following 2 days and to consume a soft diet during the first postoperative month.

4.4.4. Clinical case (Figures 34-41)

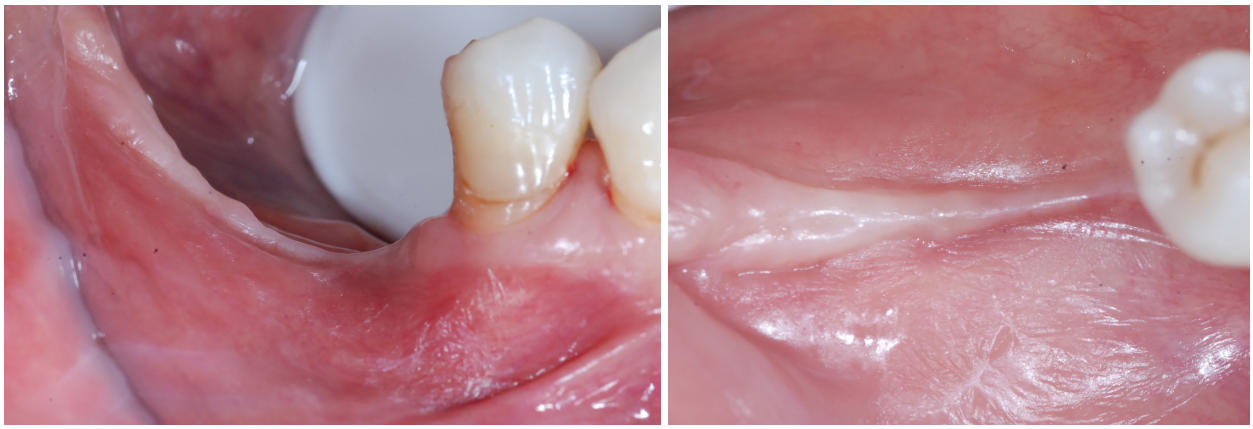


Figure 34. Pre-operative intra-oral view of the partially edentulism from lateral and occlusal aspects.

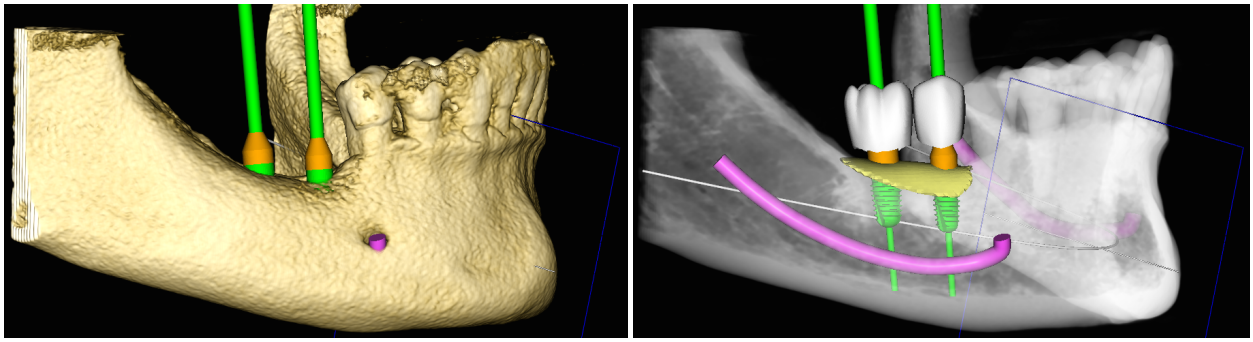


Figure 35A-B. Surgical virtual planning. In Figure 35A, implants were placed in a prosthetically guided position, however horizontal and vertical bone augmentation was required to obtain a predictable result. In Figure 35B, the prosthetically guided position was checked to accomodate the digital wax-up and to prevent injuries to anatomical structures. The bone augmentation was performed virtually (in yellow) in order to recreate the ideal anatomy of the atrophic ridge.

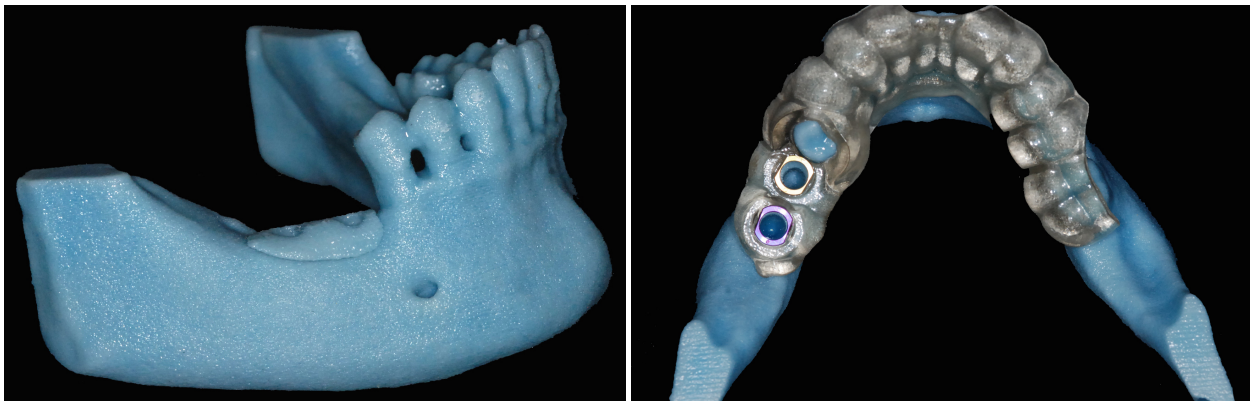


Figure 36A-B. The entire virtual project consisting of implant positions and augmented bone was transferred to a stereolithographic model (A). A surgical guide was realized subsequently with rapid prototyping techniques to place the implants according to the virtual plan before GBR procedures. In all cases treated, the surgical template was tooth-supported by the residual natural dentition (B).

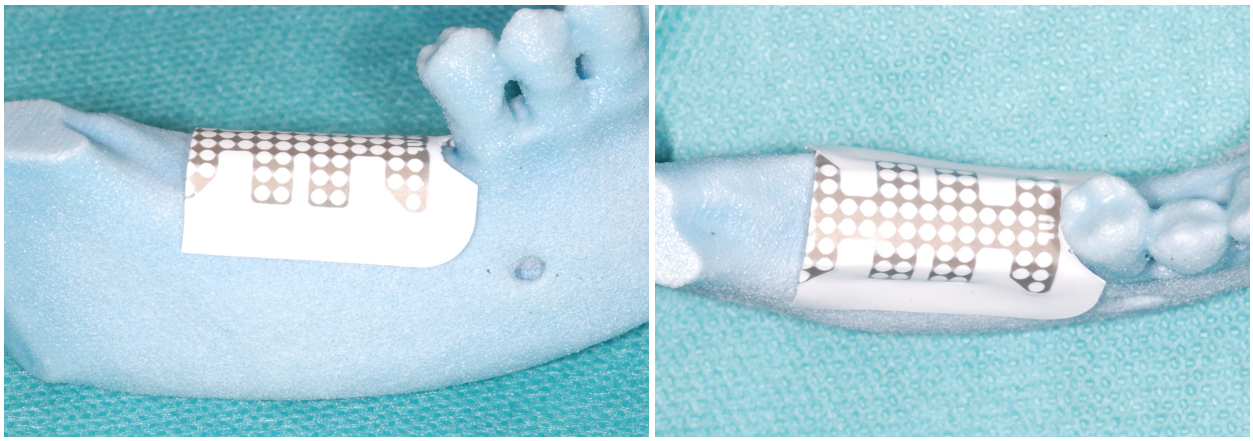


Figure 37. Pre-operative views of the d-e-PTFE membrane trimmed and contoured with the aid of previously sterilized stereolithographic model realized on the basis of the virtual project. The membrane was modeled in order to recreate the physiological profile of the edentulous atrophic ridge after bone augmentation procedure.

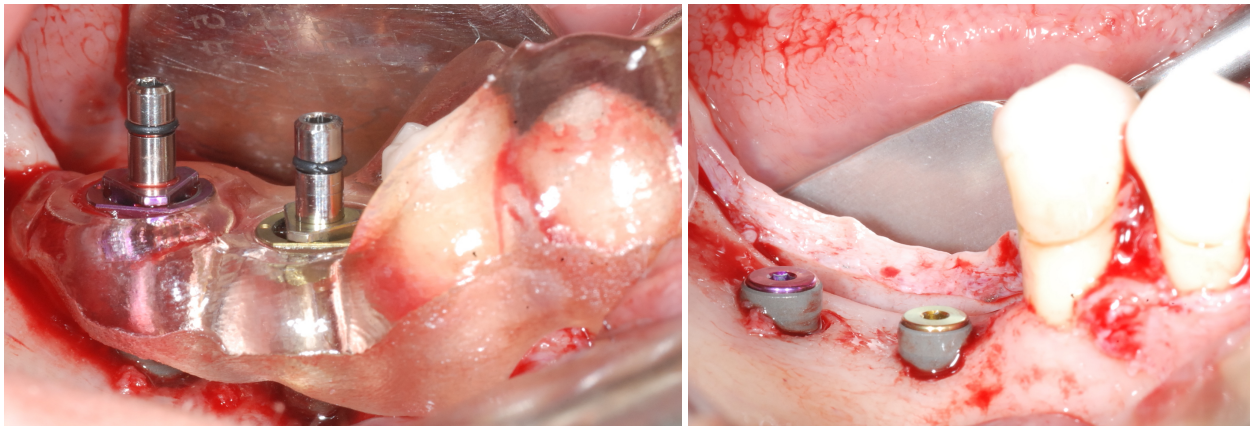


Figure 38A-B. Implants were placed with a computer fully-guided approach by means of tooth-supported surgical stent (A). As pre-visualized in the virtual project, implants were left exposed for subsequent GBR in the correct prosthetically guided position (B).

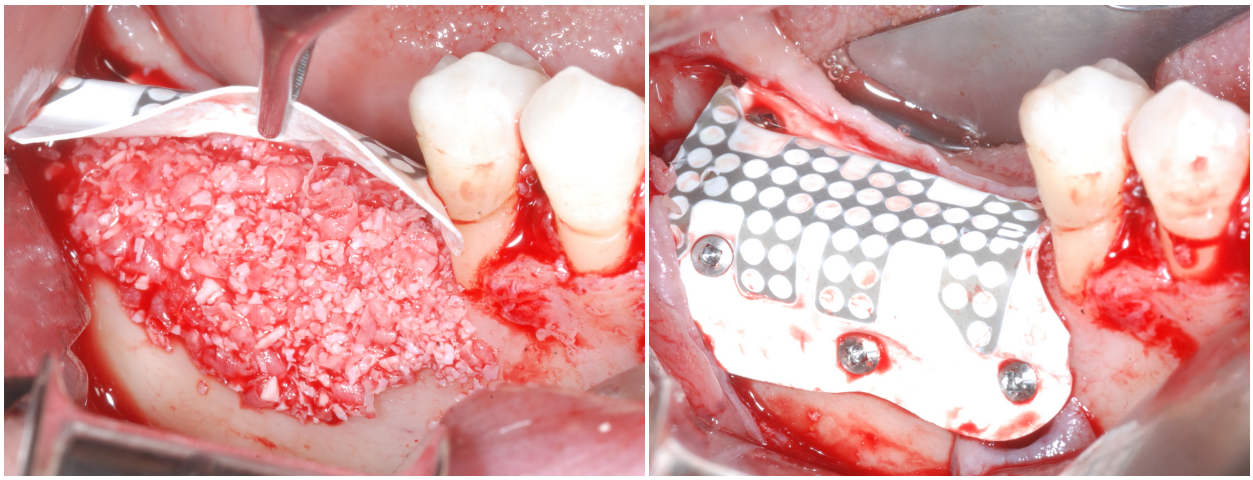


Figure 39A-B. The graft consisting of 70% autogenous bone particles harvested nearby the surgical site by means of bone scraper and 30% DBBM blended in sterile saline, was carefully placed to three-dimensionally augment the atrophic ridge (A). A non-resorbable d-e-PTFE membrane previously fixed to the lingual aspect with osteosynthesis screws was then reflected toward the vestibular side and fixed with additional screws to protect and stabilize the graft during the entire healing period (B).

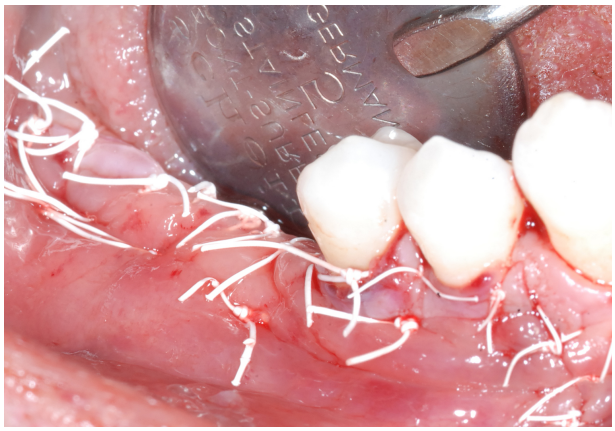


Figure 40. Intra-oral view of the surgical site with flaps sutured with non-resorbable e-PTFE stitches.

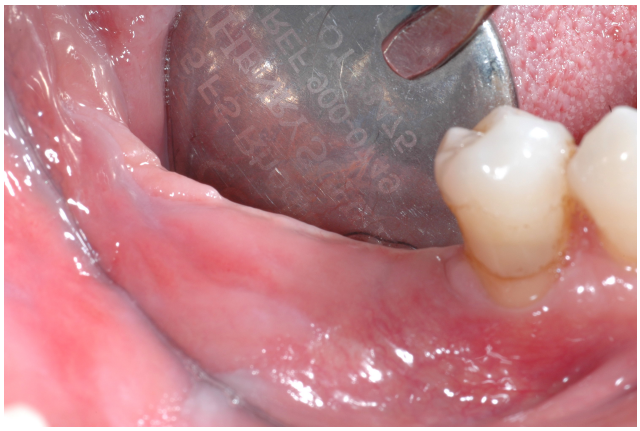


Figure 41. Intra-oral view of the surgical site after 6 months of uneventful healing.

4.4.5. Re-entry surgery

The re-entry surgery to remove the d-e-PTFE membrane was performed on an outpatient basis after 8 months from the bone augmentation and implant placement surgery. Prior surgery, a CBCT scan was acquired to evaluate the healing and the amount of augmented bone.

Briefly, under local anesthesia, a trapezoidal mucoperiosteal flap was raised to expose the d-e-PTFE membrane. Once the fibrous tissue was curetted from the underlying bone, it was possible to identify and remove the osteosynthesis screws used to stabilize the d-e-PTFE membrane. At this point, the d-e-PTFE membrane was carefully detached from the soft tissues and removed gently. Following copious irrigation with physiological saline solution, the overlying soft tissues were repositioned with non-resorbable single stitches.

4.5. Standard procedures in the control group

4.5.1. Virtual planning

After fulfilling inclusion and exclusion criteria, each patient underwent initial complete-arch impressions with an irreversible hydrocolloid material. Record bases and occlusion rims were fabricated to identify the ideal occlusal-vertical dimension from the pre-existing removable dentures. Diagnostic casts and wax rims were mounted on a semi-adjustable articulator in the centric relation position. A preliminary prosthetic wax-up was then realized corresponding to the exact replica of the existing denture accepted by the patient, integrated with aesthetic and functional principles.

A radiographic stent based on the preliminary prosthetic wax-up as a duplication of the final prosthesis was made with a silicone elastomer. The radiological stent was equipped with an extraoral radiopaque 3D marker, required for the subsequent scans overlapping. Each patient underwent CBCT scan with the radiological diagnostic stent secured in the proper intraoral position with the aid of a silicone index. Further optical scans were acquired for the diagnostic casts and the radiological stent alone, with alerted exposure parameters allowing the denture to be visualized.

All the scans were imported and matched within the same planning software used in the test group to integrate the anatomic data with the functional and aesthetic parameters. This was accomplished by superimposing the extraoral radiopaque marker visible in both sets of scans after merging together DICOM and STL data. At this point, it was possible to virtually plan the ideal size and position of the implants according to the jawbone anatomy and the prosthetic design. The virtual project was then transferred on a 1:1 scale model with a rapid prototyping technique, to realize a surgical stent obtained according to the CBCT scan and pre-operatory chalk models using the

principle of stereolithography. The surgical stent was equipped with the sleeves in correspondence with the virtually planned position of the implants, closely matching the diameter of the drills and the implants, as described in the test group.

4.5.2. Surgical procedures

Computer-aided, template-guided, flapless implant placement was carried out on an outpatient basis. Before the surgical procedure, the stent was sterilized chemically with an ethylene oxide solution. Similarly to the test group, pre-operative rinsing of the oral cavity with chlorhexidine digluconate 0.2% antiseptic solution, and perioral skin disinfection with 10% povidone-iodine aqueous solution, were performed.

Local anesthesia was induced with infiltrations of mepivacaine 2% with epinephrine 1:100.000. In this phase, it was important to avoid infiltrations within the area supposed to support the surgical stent. The purpose was to prevent possible thickening of the soft tissues that might hinder the correct seating of the surgical template in the correct position planned in the virtual environment. Hence, infiltrations were performed in alveolar mucosa and not in the attached gingiva. The surgical stent was fitted in the edentulous jaw after application of some compression so that the soft tissues underneath the guide became pale. The stent was then stabilized in the correct position by means of a silicone index and few surgical endosseous pins fixed on the vestibular aspect of the alveolar process according to the virtual project, so as to bypass the anatomic structures. Thereafter, mucosal operculectomies were performed with a circular gingiva punch inserted at 15 rpm into the guiding sleeves to gain access to the implant sites. Serial osteotomies were then performed with disposable internal coolant pre- and form-drills, until the planned depth was achieved, according to the manufacturer's instructions set out in the test group. It was then possible to place the implants in the desired position planned in the software. Implants were inserted without removing the surgical stent, with a fully guided approach in a way identical to the test group.

4.5.3. Medications

Medications prescribed for pre- and post-operative domiciliary use by the patient included 2 g amoxicillin-clavulanate one hour before the scheduled surgical procedure; 80 mg granulated ketoprofen lysine salt according to patient's needs; 0.2% chlorhexidine digluconate mouthwash rinse solution 1 min three times a day for 14 days starting 2 days before surgery. The patients were also asked to apply ice packs for the following 2 days and to consume a soft diet during the first postoperative month.

4.5.4. Clinical case (Figures 42-48)

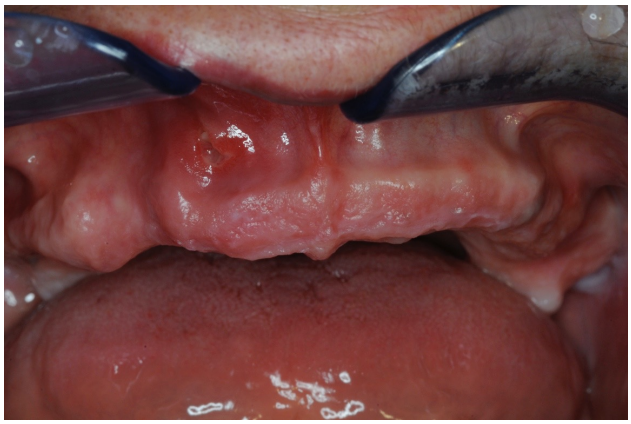


Figure 42. Intra-oral view of the fully edentulous alveolar ridge at baseline.

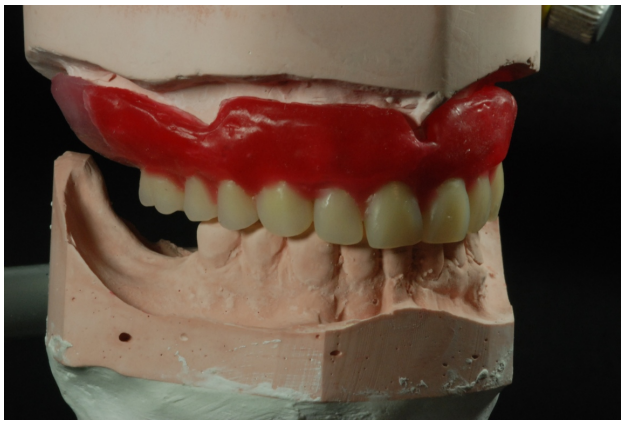


Figure 43. Wax-up of the prosthetic rehabilitation according to functional and aesthetic parameters.

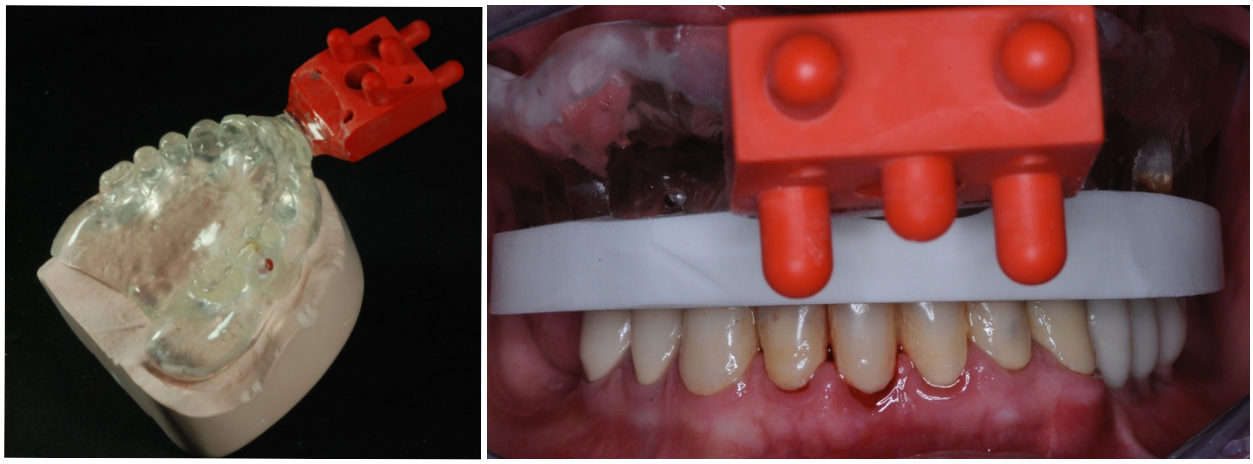


Figure 44A-B. The radiological guide was performed as a duplication of the final wax-up of the prosthetic rehabilitation. The radiological marker (red) consisted in a well-defined extra-oral geometric figure (A). In accordance with the double scanning protocol, the radiological stent was used by the patient during the CBCT acquisition. To place the radiological stent in the correct position during the radiological exam, a silicon index guided by the opposing arch was used (B).

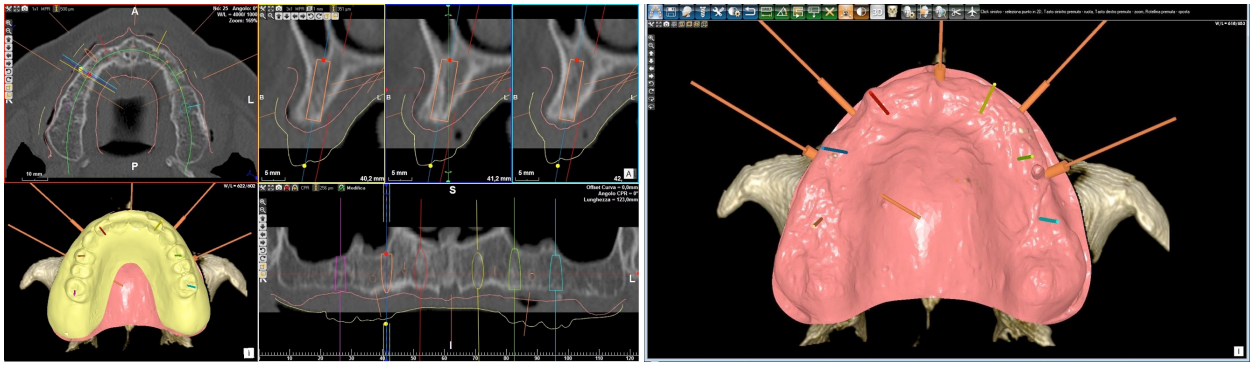


Figure 45. After the superimposition of the DICOM and STL data, it was possible to virtually place the implants in the correct position according to prosthetic (yellow = radiological stent) and anatomical (pink = soft tissues) parameters merged within the pre-existing bone (X-rays).

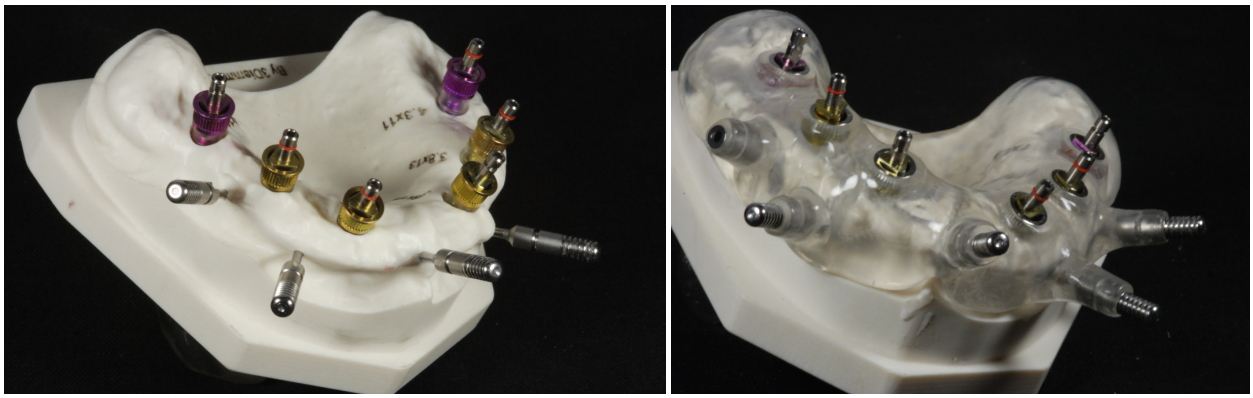


Figure 46A-B. The virtual planning was transferred to a real-size stereolithographic model characterized by the position of the implants (implant replicas and implant mounters were transferred within the model) as well as the position of the endosseous pins used to stabilize the surgical stent (A). The surgical guide was then realized on the basis of the virtual project on the stereolithographic model by means of rapid prototyping techniques. The correct fit of the surgical guide is verified directly on the real-size model by simulating the surgical procedure (B).

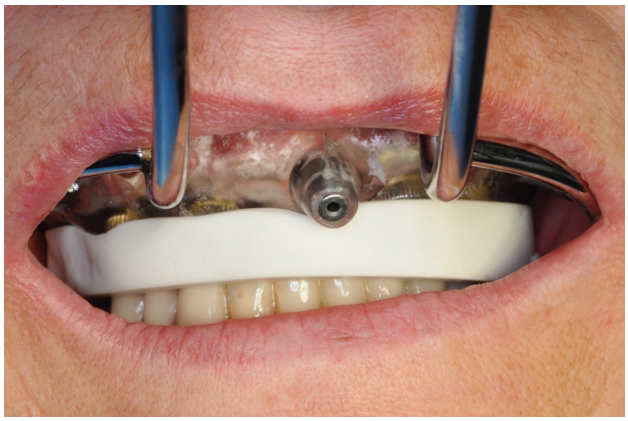
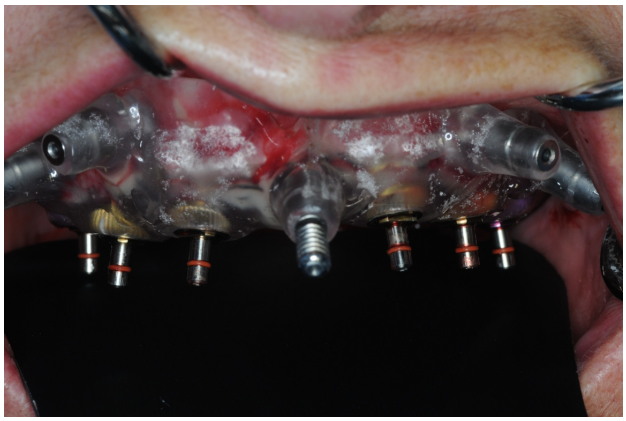



Figure 47A-B. Intra-operative view of the surgical template secured in the proper position by means of a silicone index previously used to stabilize the radiological stent during the CBCT exam (A). Once the surgical stent was fixed to the underlying bone with endosseous pins, implants were placed with a computer-guided flapless approach (B).

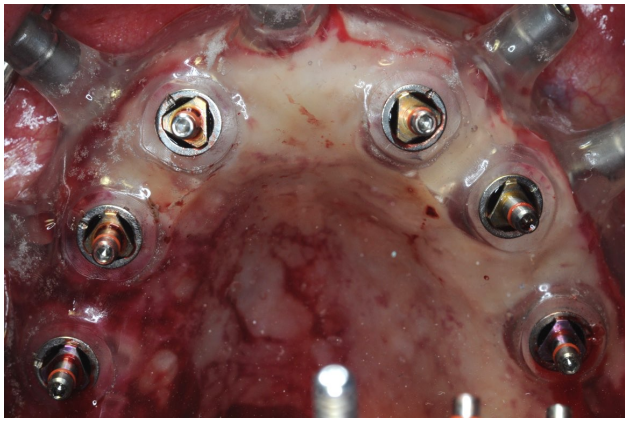
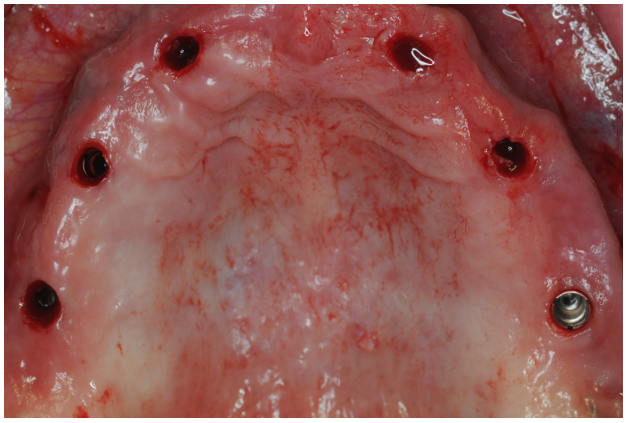



Figure 48A-B. Intra-operative view of the implants placed in the correct prosthetically computer-guided position during (figure 48A) and at the end (figure 48B) of the surgical procedure, before the beginning of the prosthetic phases.

4.6. Prosthetic phases

The aim of the present study was to evaluate an experimental protocol for guided surgery according to specific outcomes that are independent of the type of implant-supported prosthetic rehabilitation. Hence, as the prosthetic phases were not part of the present research study, these will not be described in detail.

In both groups, before the prosthetic phases, or during the transitional period with the patient rehabilitated with temporary prostheses, soft tissues were managed where necessary with periodontal plastic surgery and soft tissue augmentation techniques to enhance quality and quantity of the peri-implant mucosa.

In the test group, implants healed with a submerged approach. Following the re-entry surgery, it was possible to screw the healing abutments and continue with the prosthetic phases. These included impressions with custom impression trays and polyether impression material to realize screw-retained temporary acrylic resin crowns. After 6 months of soft tissues conditioning, definitive impressions were taken to realize definitive ceramic crowns cemented to definitive abutments.

In the control group, based on the primary stability, definitive abutments were screwed to the implants immediately after the implant insertion. The provisional denture was than relined and connected to the intermediate abutments fixed to the definitive ones. Based on the appropriateness of the pre-owned denture used by the patient

before the surgery, it was possible to adapt this prosthesis in order to contain economical costs and expenses. If the initial denture was not suitable for use as a temporary device, a new interim prosthesis was realized as a replica of the radiological stent used during the planning phases. In both cases, a rubber dam was used during the relining of the prosthesis, in order to avoid the infiltration of the liquid resin in the underlying tissues. An autopolymerizing composite resin was placed over the intermediate abutments to fix the interim prosthesis precisely with a silicone index. The screw access holes were closed with Teflon tape and light polymerized interim composite resin. The temporary prosthesis was than applied and balanced in the right occlusion and polished. The patient left the clinic with an immediately loaded prosthesis characterized by a correct masticatory function and a good aesthetic. After 6 months, depending on the treatment plan, implant-supported screw-retained fixed dental prosthesis were delivered to the patients.

4.7. Study outcomes

4.7.1. Primary outcomes

The primary outcome was to evaluate the effectiveness of an experimental protocol consisting of virtually-aided GBR and simultaneous computer-guided implant placement in compromised anatomical situations. To this end, the primary outcome was divided into clinical and patient-centered outcomes.

- The following clinical outcomes were evaluated:

1) Occurrence of intra-operative complications related to the experimental procedure. The evaluation of intra-surgical procedures aimed to analyze possible complications arising during the surgical phase, including but not limited to unstable surgical stent; fracture of the surgical components; low primary implant stability; misplacement of the implant and unwanted fenestrations/perforations; implant fracture; lesion to anatomical structures; and alterations to the surgical plan.

2) Occurrence of post-operative complications related to the experimental procedure. The evaluation of post-operative complications was performed at each follow-up recall scheduled every week during the first month and monthly thereafter up to the re-entry surgery. Possible post-operative complications comprehended infection, fistulae, flap dehiscences and membrane exposure, persistent pain, and early implant failure.

3) Quality and quantity of augmented bone, assessed radiographically with CBCT scans and clinically at the re-entry surgery.

4) Surgical time, measured as the time elapsed between the incision and the end of suture completion.

- The following patient-centered outcomes were evaluated:

1) Post-operative pain;

2) Post-operative swelling;

3) Post-operative bleeding from the surgical wound;

4) Perception of the operation.

The analysis of the patient-centered outcomes was accomplished through a questionnaire given to each patient about the postoperative course from 5 to 6 h postoperatively (before intake of the prescribed analgesics) and until the seventh postoperative day. A 100-mm visual analogue scale (VAS) with extreme end points was used for each variable to record the intensity of postoperative pain on the day of surgery, 1, 2, 3, and 7 days after surgery (no and extreme pain); the severity of swelling on the day of surgery, 1, 2, 3, and 7 days after surgery (no and severe swelling), and the severity of bleeding from the wound on the day of surgery, 1, 2, 3, and 7 days after surgery (no and severe bleeding). Furthermore, on the day of the surgery, the patients scored their satisfaction with their perception of the operation (not and very unpleasant). The questionnaires were collected at the time of suture

removal 14 days after surgery. By means of a ruler, the VAS scores were measured and rounded off to the nearest 1 mm.

4.7.2. Secondary outcome

The secondary outcome aimed to analyze and compare the accuracy of computer-guided implant placement between test and control groups. The accuracy analysis was performed by two experienced process engineers masked to the study design and research protocol.

The locations and axes of planned and placed implants were compared using dedicated software that fused the CBCT images taken before and after implant placement. The first and second CBCT scans were aligned observing the superposition of anatomic landmarks. For each planned and placed implant, two points were located (x, y, and z coordinates) on their long axes. The first point was the neck point (center of the most coronal portion of the implants) of the implant, whereas the second point was the apical point (center of the implant apex) of the implant. The distance between the centers of the simulated and real implants (mm) and the angle (°) that occurred between the long axes of the simulated and real implants were calculated. In particular, to establish the lateral deviation, a plane perpendicular to the longitudinal axis of the planned implant and through its coronal and apical center, was defined and was referred to as reference plane. The lateral deviation was calculated as the distance between the coronal and apical center of the planned implant and the intersection point of the longitudinal axis of the placed implant with the reference plane. The angular deviation was calculated as the angle between the longitudinal axes of the planned and placed implant (Figures 49-50).

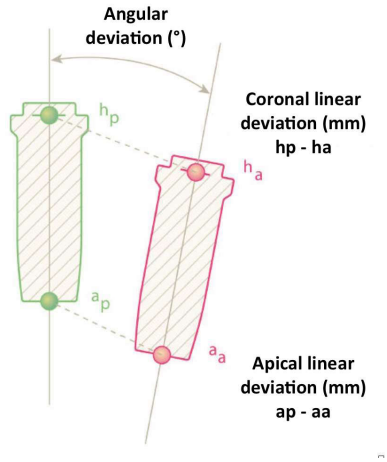


Figure 49. Evaluation of the accuracy in terms of linear and angular deviations.

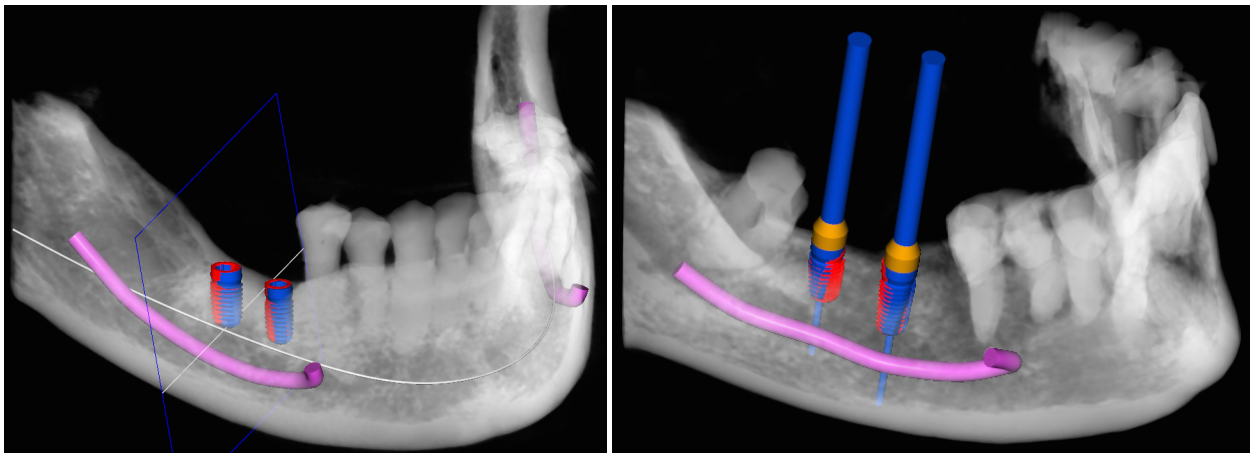


Figure 50. Accuracy evaluations in two different patients in the test group. Pre- and post-operative CBCT scans were overlapped in order to superimpose the planned (blue color) and actual (red color) implant positions and perform the accuracy analysis.

4.8. Statistical analysis

The statistical analyses were done using IBM SPSS Statistics software version 24.0 (IBM Corp., Armonk, NY, USA). Data were expressed as means ± standard deviation (SD), and 95% confidence interval (CI) where appropriate.

The Shapiro-Wilk test was used to assess the normality of data distribution. Because distribution of data in some datasets did not meet the requirements for normality and homogeneity of variance assumptions ($p < 0.05$),

non-parametric quantitative data were compared between groups using non-parametric tests. The rest of the data were investigated with parametric tests.

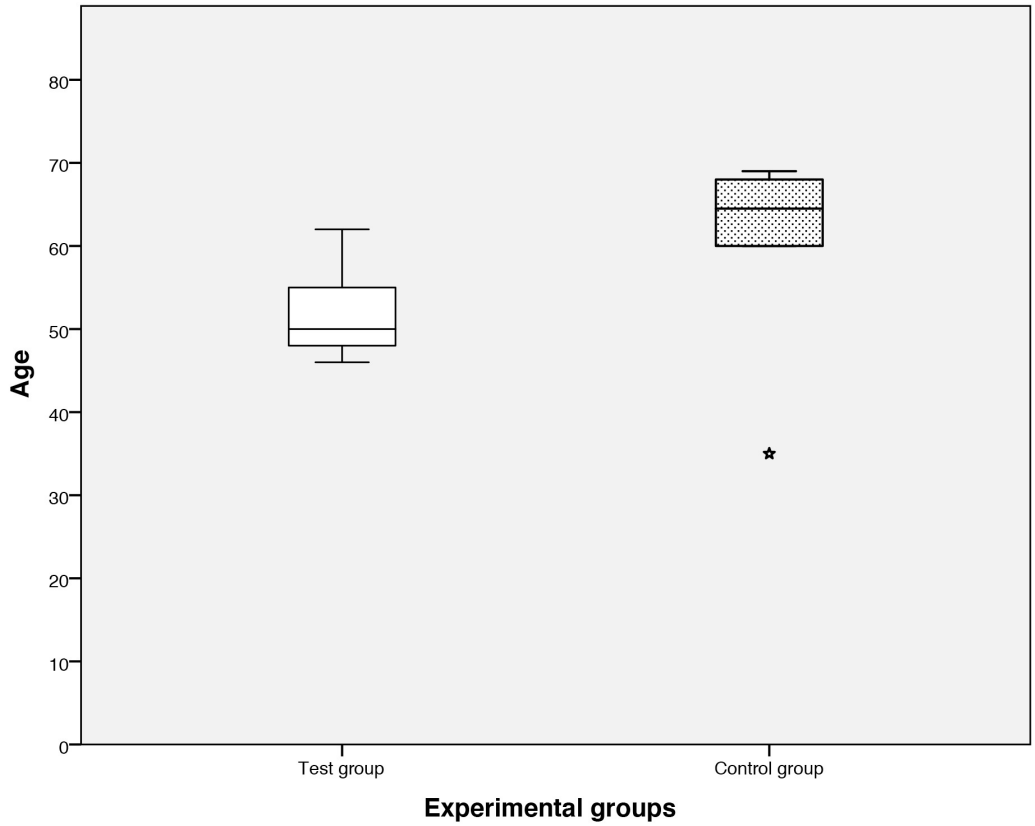
More in detail, the independent samples *t*-test was used to compare the age between test and control groups; the Wilcoxon signed-rank test was used to analyze the VAS scores of pain, swelling, and bleeding between the different study periods; the Spearman's rank correlation coefficient was used to investigate possible correlations between the perception of the operation and pain, swelling, and bleeding VAS scores. The Mann-Whitney U test was used in the accuracy analysis to compare the coronal, apical, and angular deviations between test and control groups. The same statistical test was used to investigate possible intra-group differences in terms of implant location (mandible versus maxilla). In the evaluation of accuracy level, the implant was used as the statistical unit. A significance level of 5% was adopted.

Results obtained from independent samples *t*-test and Mann-Whitney U test were illustrated in box plots showing median, quartile, and extreme values of deviations of implants. Boxes contained 50% of all values, the horizontal lines inside the box indicated the medians, while vertical line were extended to 1.5 of the interquartile range.

5. Results

5.1. Study population

Overall, 12 patients were initially screened for eligibility, 6 in the test group, and 6 in the control group; however, one patient in the test group has finally opted for a removable partial denture and was therefore dropped out of the study. Ultimately, 11 patients were considered eligible and were consecutively enrolled and treated, of which 5 in the test group (2 males and 3 females), and 6 in the control group (5 males and 1 female). The mean age was 52.2 ± 6.41 years in the test group, and 60.17 ± 12.73 years in the control group, with no statistically significant differences between the two groups ($p = 0.238$)(Graph 1).



Graph 1. Box plot showing median, quartile, and range of age comparison between test and control groups. The extreme outlier represent a female patient aged 35 years.

No patients dropped out from the study during the entire study period, and the data from all patients were evaluated in the statistical analysis. A total of 10 implants were inserted in the test group, while 38 implants were placed in the control group.

5.2. Primary outcomes

The primary outcome aimed to evaluate the effectiveness of the experimental protocol from both clinical and patient-centered outcomes. Primary outcomes consisted in the evaluation of intra- and post-operative complications related to the experimental procedure, the duration of the surgical procedure, and the analysis of post-operative patient morbidity, in terms of pain, swelling, bleeding, and perception of the operation.

5.2.1. Clinical outcomes

No intra- and post-operative complications related to the experimental procedure were observed during the study period up to the prosthetic phases.

In one patient, the lingual flap was slightly traumatized during the surgical procedure by the Prichard periosteal elevator used to protect the lingual tissues. This resulted in a partial laceration of the coronal portion of the lingual flap of approximately 7 mm in a mesio-distal direction (Figure 51). The flaps were sutured according to the described procedure so that the laceration was included within the entry and exit points of the horizontal mattress in order to minimize flap tension and promote wound healing. Nevertheless, in that point complete healing was not achieved. Indeed, a dehiscence of roughly 2 mm in ongoing epithelialization phase persisted at the mesial aspect of the lingual flap during the healing period (Figure 52). This complication was managed with 0.12% chlorhexidine mouthwashes and topical application of 1% chlorhexidine gel twice a day until re-entry surgery and recalls every 2 weeks for clinical inspection and plaque removal. In correspondence of the partial laceration, healing resulted in scar tissue with a lack of keratinized tissue at the occlusal aspect. Nevertheless, a fine vascular architecture could be identified in the apical portion of the lingual flap directed toward the overlying keratinized tissue. In view of the position of the dehiscence, close to muscular attachments with consequent continuous traction of the lingual flap and partial exposure of the d-e-PTFE membrane, it was decided to anticipate the re-entry surgery at 5 months to reduce the risk of infection.

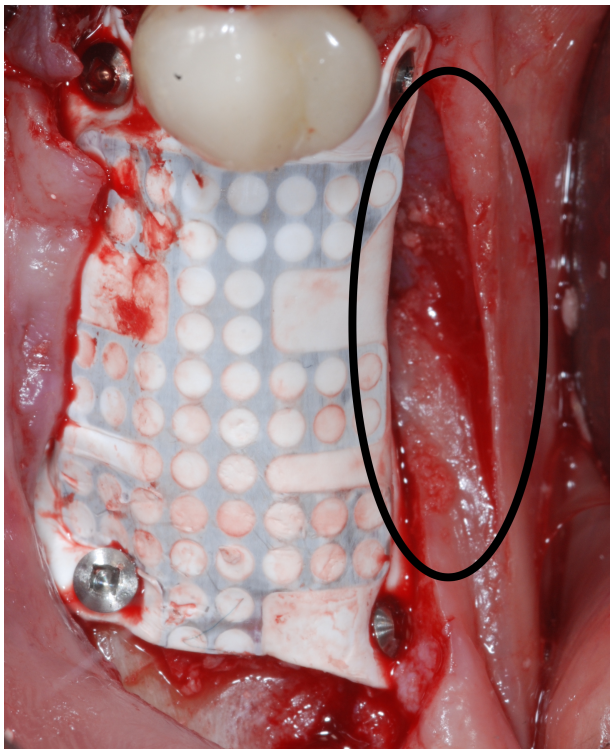


Figure 51. Intraoperative view of the GBR procedure. The black oval highlights the iatrogenic laceration of the lingual flap of roughly 7 mm mesio-distally.

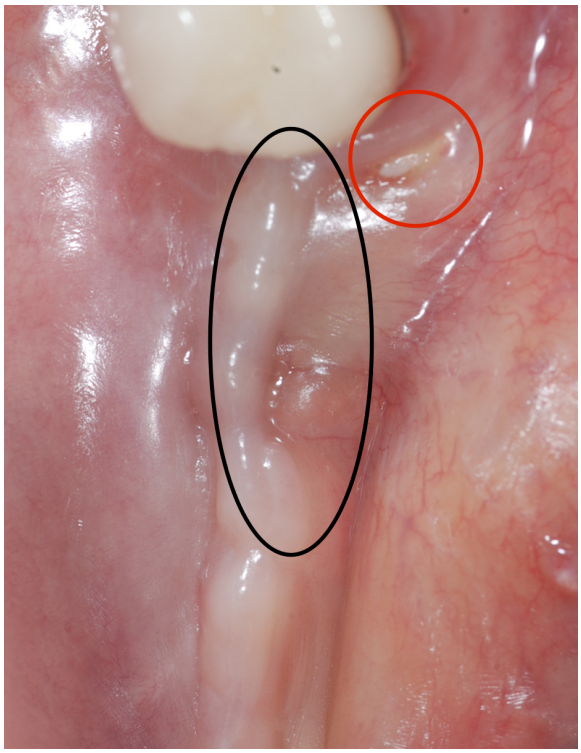


Figure 52. 5-month healing period of the same patient. The black oval highlights the healing in correspondence of the lingual laceration. The red oval underlines a 2-mm dehiscence with partial exposure of the d-e-PTFE membrane.

Macroscopically at the re-entry surgery, in each patient the d-e-PTFE membrane appeared to be surrounded by a dense connective tissue without any clinical signs of infection. The d-e-PTFE membrane appeared to firmly adhere to the newly formed hard tissue. After removal, a whitish inflammation-free periosteal-like tissue was present

underneath. The space under the d-e-PTFE membrane was completely filled by hard tissue with macroscopic features of newly formed bone. Particles of bone substitute not encapsulated in fibrous tissues and integrated within the surrounding hard tissue were hardly distinguishable in some areas. The graft appeared vascularized and well incorporated into the native bone. From a clinical aspect, no residual bone defects were observed and a significant horizontal and vertical bone gain was found circumferentially around the implants in all patients (Figure 53).

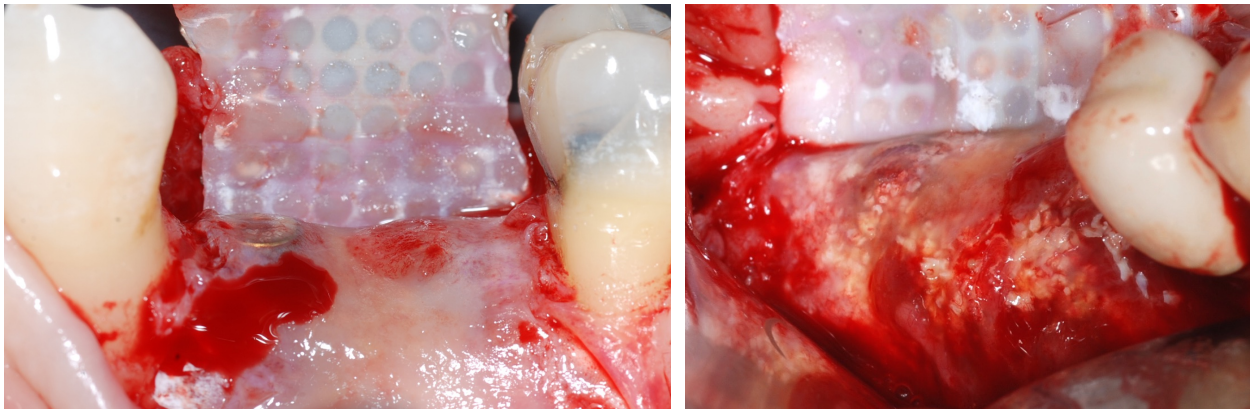


Figure 53A-B. Re-entry surgery at 6 months (A) and 5 months (B). Figure 53A shows newly formed bone-like tissue underneath the d-e-PTFE membrane well integrated within the surrounding tissues. It is possible to appreciate that 1) implants were completely covered by regenerated hard tissue and 2) the vascular ingrowth particularly on the top of the distal implant. Figure 53B illustrates the re-entry surgery in the patient presenting a dehiscence of the lingual flap. In view of a premature exposure, it was possible to observe ongoing bone remodeling phase with granules of bone substitute encapsulated in immature bone matrix. Nevertheless, implants were three-dimensionally surrounded by newly formed hard tissue with no signs of infection or necrosis.

This result was supported by the radiological findings, showing augmented radiopaque hard tissue integrated with the recipient bone. No signs of unusual resorption, infection, and soft tissue ingrowth within the graft were detectable. Dental implants appeared completely surrounded by the remodeled graft, and no radiographic signs of radiolucent regions or peri-implant bone resorption were observed. At the same time, it was possible to identify the d-e-PTFE membrane closely adapted and stabilized to the underlying bone (Figure 54).

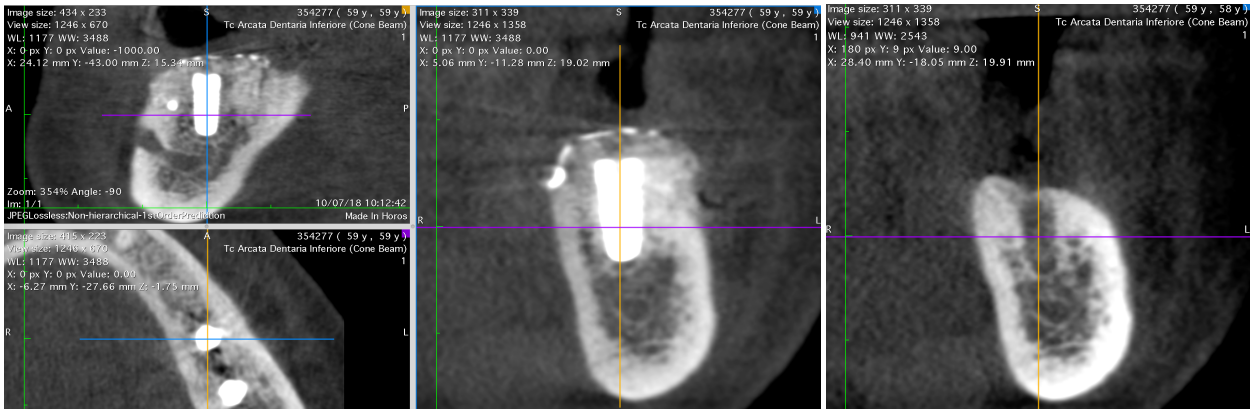
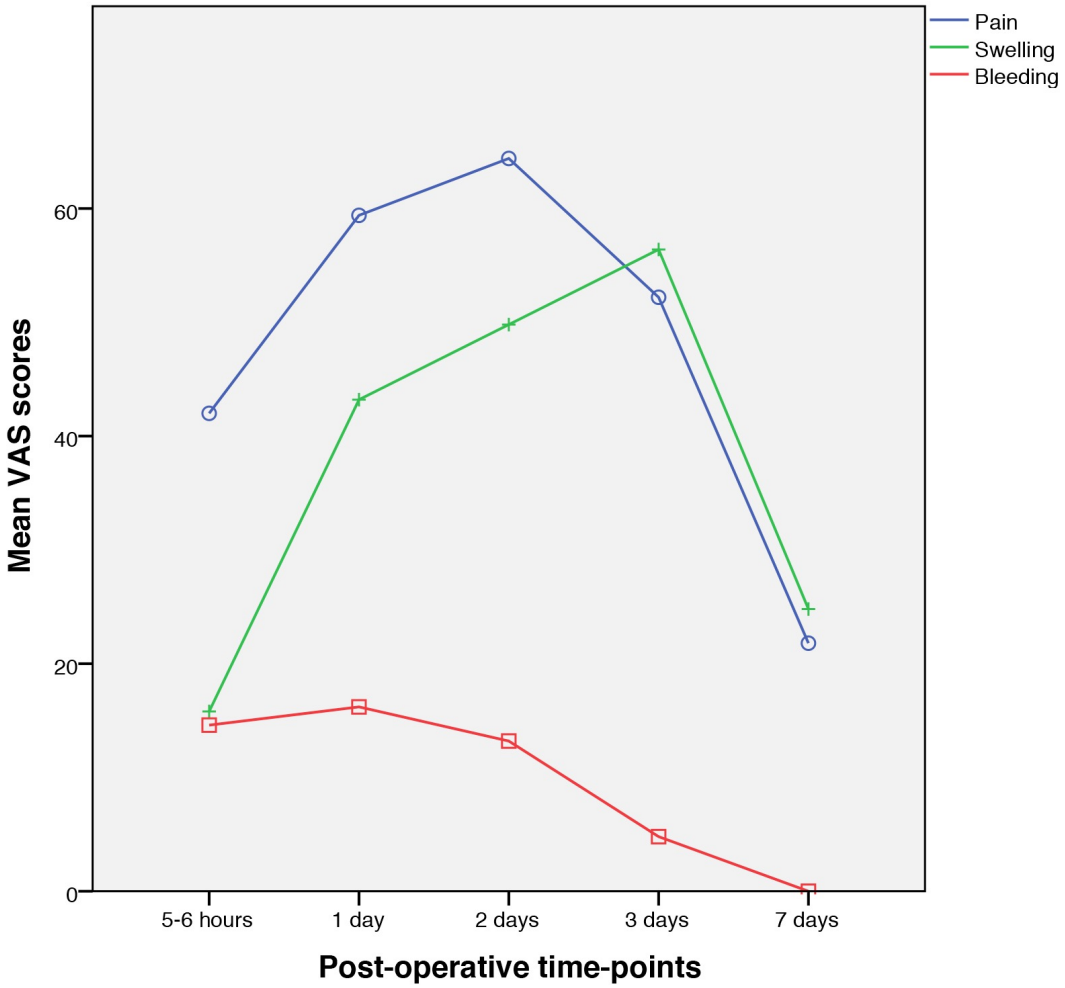


Figure 54. CBCT scan performed after 5 months from the surgical procedure. It is possible to observe the implant completely surrounded by augmented bone-like tissue hardly distinguishable from the recipient bone. The graft is stabilized by a d-e-PTFE membrane closely adapted to the bone defect, shaped in such a way as to re-establish the physiologic contour of the atrophic ridge. CBCT scan at the extreme right shows the pre-operative CBCT scan in the same 3D position as the post-operative CBCT scan, in order to appreciate the initial anatomy of the bone defect and the amount of augmented bone.

The mean duration of the computer-guided bone augmentation and implantation surgery was 92 minutes from first incision to the end of the suture.

5.2.2. Patient-centered outcomes

The trends of mean VAS scores with respect to pain, swelling, and bleeding during the different study periods were illustrated in Graph 2.



Graph 2. Trends of the VAS scores during consecutive study periods for Pain, Swelling and Bleeding.

1) Post-operative pain

The VAS score for pain increased from 5-6 hours post-operatively (mean VAS = 42 ± 6.20) to 1 post-operative day (mean VAS = 59.4 ± 5.94), and peaked 2 days post-operatively (mean VAS = 64.4 ± 5.17). The difference in VAS scores between 5-6 hours and 2 days was statistically significant (Z = -2.023; p = 0.042). The VAS score decreased from 2 to 3 post-operative days (mean VAS = 52.2 ± 2.86) and continued to decrease up to the last assessment at day 7 (mean VAS = 21.8 ± 3.11). The difference in VAS scores between day 2 and day 7 was statistically significant (Z = -2.023; p = 0.043).

2) Post-operative swelling

The VAS score for swelling increased from 5-6 hours post-operatively (mean VAS = 15.8 ± 4.14) to 1 post-operative day (mean VAS = 43.2 ± 6.34), 2 post-operative days (mean VAS = 49.8 ± 7.01) up to the third post-operative day (VAS = 56.4 ± 8.14) when the VAS score reached its peak. The difference in VAS scores between 5-6 hours and 3 days was statistically significant (Z = -2.032; p = 0.042). From this point, VAS score decreased up to the seventh post-operative day (mean VAS = 24.8 ± 4.81) with a statistically significant difference (Z = -2.023; p = 0.043).

3) Post-operative bleeding from the surgical wound

Higher values of VAS scores were found immediately after the surgical procedure (mean VAS = 14.6 ± 3), and within the next 1 (mean VAS = 16.2 ± 2.58) and 2 (mean VAS = 13.2 ± 2.16) post-surgical days. At the third post-operative day, VAS scores decreased substantially (mean VAS = 4.8 ± 0.83) with a statistically significant difference from day 2 (Z = -2.032; p = 0.042). No bleeding was observed at the last assessment 7 days post-operatively.

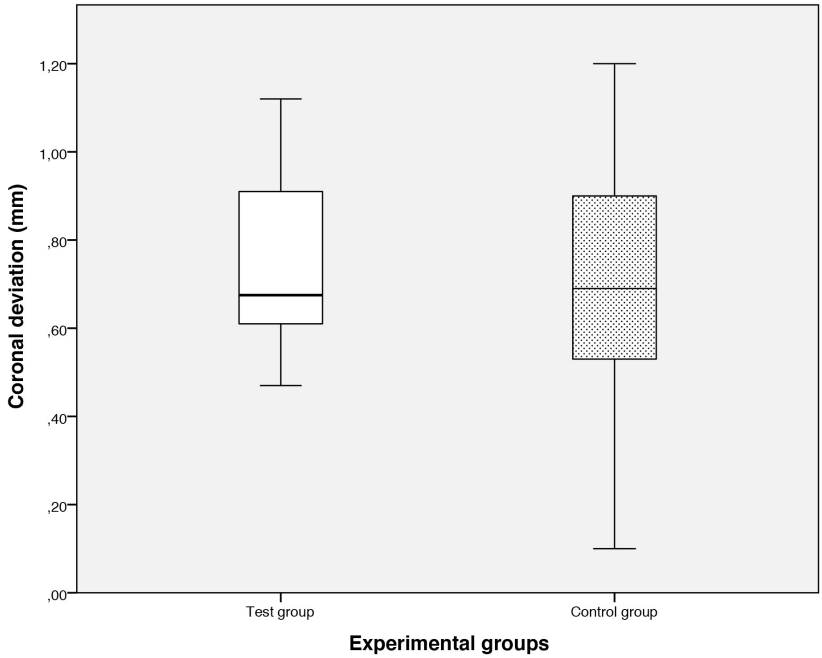
4) Perception of the operation

The mean VAS score for the patients' perception of the operation was 36 ± 8.63. A correlation was not found between the perception of the operation and pain (Spearman's ρ = -0.2; p = 0.74), swelling (Spearman's ρ = 0.5; p = 0.39), and bleeding (Spearman's ρ = 0.3; p = 0.62).

5.3 Secondary outcome

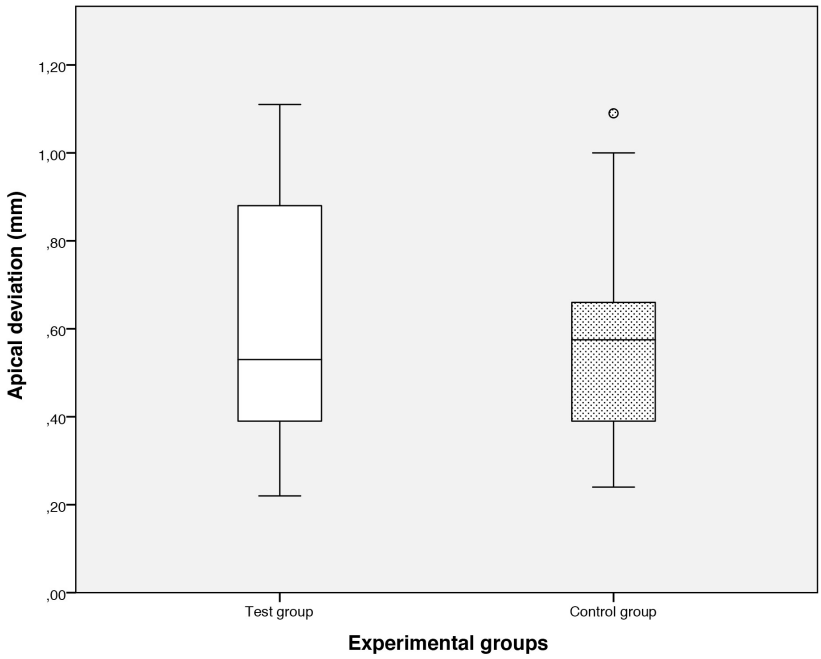
Overall, a total of 48 implants underwent statistical evaluation of the accuracy level by matching the preoperative planning with the in vivo position of the fixtures. A total of 10 and 38 implants were assessed in the test and control group respectively.

Considering the linear deviation at the implant neck, a deviation of 0.73 ± 0.21 mm (95% CI: 0.58 - 0.89 mm) was found in the test group, whereas a deviation of 0.68 ± 0.25 mm (95% CI: 0.60 - 0.77 mm) was observed in the control group. The statistical analysis yielded non-significant differences between the two groups for the coronal deviation (p = 0.76)(Graph 3).



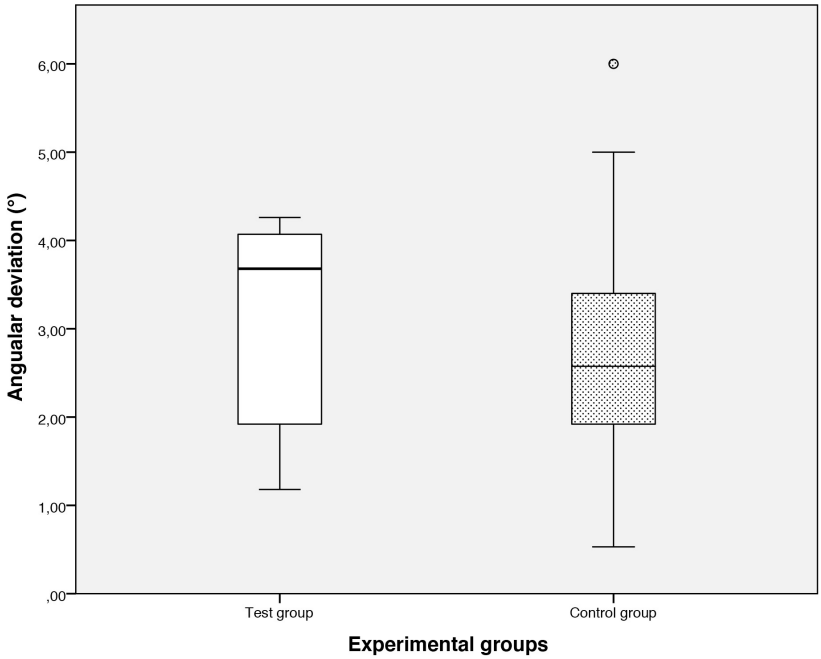
Graph 3. Box plot showing median, quartile, and range of coronal deviations (mm) in test and control groups.

With respect to the linear deviation at the implant apex, a deviation of 0.59 ± 0.28 mm (95% CI: 0.38 - 0.79 mm) was found in the test group, whereas a deviation of 0.57 ± 0.22 mm (95% CI: 0.49 - 0.64 mm) was found in the control group. No statistically significant differences emerged between the two groups for the apical deviation (p = 0.97)(Graph 4).



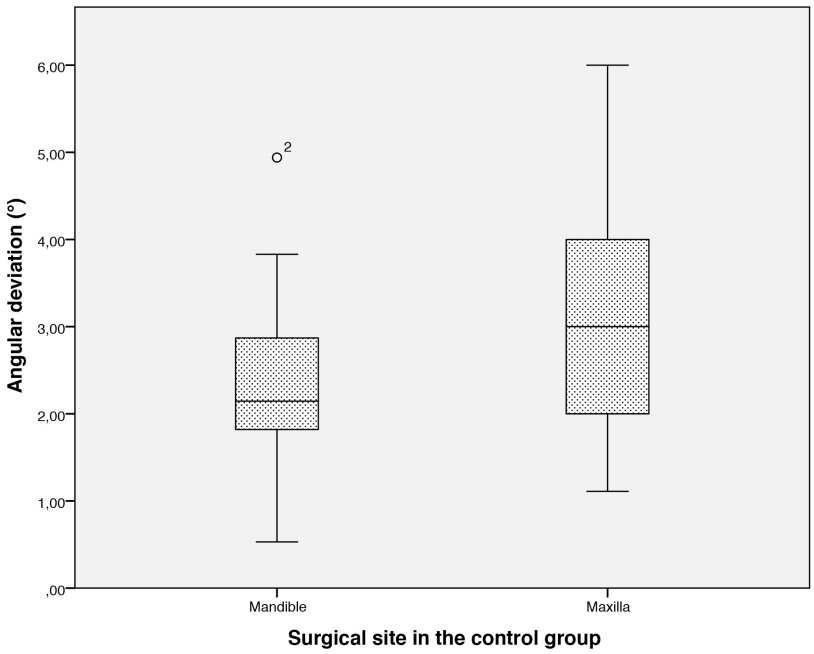
Graph 4. Box plot showing median, quartile, and range of apical deviations (mm) in test and control groups.

The angular deviation of the long axis between the planned and actual positions of the implants was 3.05° ± 1.22° (95% CI: 2.18° - 3.92°) in the test group, and 2.77° ± 1.20° (95% CI: 2.37° - 3.17°) in the control group. The statistical analysis provided non-significant differences between the two groups for the angular deviation (p = 0.36) (Graph 5).



Graph 5. Box plot showing median, quartile, and range of angular deviations (°) in test and control groups.

The intra-group comparison of the accuracy level between implants placed in the mandible versus implants placed in the maxilla in the test group yielded non-statistically significant differences for all considered deviations ($p > 0.05$). On the other hand, while coronal and apical deviations in the control group were similar between the two arches ($p > 0.05$), the corresponding intra-group comparison resulted in statistically significant higher angular deviation for implants placed in the maxilla compared to the mandible (mean difference: 0.87° ± 1.61°; $p = 0.03$) (Graph 6).



Graph 6. Box plot showing median, quartile, and range of angular deviations (°) in the control group according to the location of the implant site (mandible versus maxilla; $p = 0.03$).

6. Discussion

The purpose of the present proof-of-concept experimental study was to evaluate the effectiveness of a computer-guided protocol combining implant surgery and bone augmentation techniques. The sample consisted of patients presenting with a partial edentulism in the mandible and/or in the maxilla, posterior to the canines. The partially edentulous alveolar ridge had to be resorbed in both height and width, so that the resultant horizontal and vertical bone defect jeopardized the correct prosthetically guided implant insertion without recurring to simultaneous GBR procedures. In brief, anatomical and prosthetic information were imported into the virtual environment in order to create a project of the final implant-supported rehabilitation taking into consideration the ideal implant position and the physiological contour of the augmented alveolar ridge. The project was subsequently transferred to the clinical scenario by means of surgical models and templates realized through stereolithography technology and rapid prototyping techniques respectively. Computer-guided implant insertion and virtually-guided bone augmentation was finally carried out on an outpatient basis under local anaesthesia.

6.1. Primary outcomes

No intra-operative complications were encountered during the experimental procedures. However, several complications or unexpected events might be observed during the computer-guided implant insertion. Fracture of the surgical guide has been reported as the most common surgical complication (3.6%) [16]. Other intra-operative adverse events include change in surgical plan (2%), and implants lost during placement because of the lack of primary stability (1.3%) [31]. Evidence suggests an association between low torque values at insertion into type IV bone and implants placed in the maxilla. In contrast, insertion torque values greater than 50 Ncm was associated with fracture of surgical guides and implant platforms [48]. Additional complications include unwanted perforations and improper implant location [49], non-planned grafting [12], implant fracture [50], dehiscences, and soft tissue perforations [17]. Complications can be related to the technical procedure or depending on the used hardware. Complications reflect the accumulation of all errors from imaging over the transformation of data into a guide, to the improper positioning of the latter during surgery. As a matter of fact, the discrepancy between virtual surgery planning and guide manufacturing and prototyping, revealed difficulties in the placement of surgical templates and implant fenestration at the time of placement [51, 52]. Due to a wide heterogeneity of computer-guided protocols, the evaluation of intra-operative complications is difficult to interpret and should be based on the investigation of events occurred in real clinical situations. In this respect it must be noted, however, that the reasons for intra-operative complications are scarcely reported among studies [17].

No post-operative complications strictly related to the experimental procedure were observed during the study period up to the prosthetic phases.

One patient exhibithed a dehiscence of the lingual flap not as a direct consequence of the experimental procedure itself, but rather a surgical complication due to a lack of visibility. The conventional protocol contemplates the use of a Prichard periosteal elevator placed in direct contact with the lingual/palatal jawbone in order to protect the flap from possible injuries during the surgical sequence. At the same time, the conventional protocol involves the use of a surgical stent equipped with a guiding hole of approximately 2 mm in diameter that guides the insertion of the first implant drill. After the first pilot hole has been performed, the surgical stent is normally removed and the drilling sequence is performed free-handedly. The free-hand approach allows better visualization of the surgical site, since the template has a reduced size and is removed after the first pilot drill. On the other hand, in the present study the surgical template has been used during all the drilling sequence up to the implant insertion, in accordance with a fully-guided approach. Once the drilling phase has been initiated, the

surgical stent has no longer been removed in order to maintain the correct 3D axis without changing the position of the template. Furthermore, the size of the surgical stent was more bulky with respect to a conventional free-hand template. This was related to the fact that the dimension of the sleeves equipped within the said stent had to correspond with the diameter of the implants to be inserted. In view of the aforesaid, once the periosteal elevator was introduced between the lingual flap and the jawbone and the stent secured in the proper position, it was extremely difficult to maintain and verify the position of the instrument during the entire procedure. Therefore, it may be presumed that in the case exhibiting flap dehiscence, the periosteal elevator has been inadvertently displaced against the soft tissues instead of the bone, causing a partial laceration of the lingual flap. The partial laceration became evident only after removal of the surgical template after implant insertion. This complication has been initially managed by suturing the flap so that the laceration was included within the entry and exit points of the horizontal mattress. This enabled tight coaptation of the flaps and minimized muscular tension directed apically. During the healing period, chlorhexidine in the form of mouthwashes and gel has been used for domiciliary healthcare. Recalls have been scheduled every 2 weeks for clinical inspection and plaque removal. As expected, a complete healing could not be achieved. For this reason, and to prevent possible infection of membrane and graft, the re-entry surgery has been anticipated at 5 month from the surgical procedure. At the re-entry surgery, it was possible to observe an almost complete filling of the defect by newly formed bone-like tissue. Granules of DBBM were still visible in few areas in ongoing remodelling phase along with dense connective tissue. Nevertheless, implants appeared completely surrounded by regenerated hard tissue. The fact that bone regeneration was not apparently affected by flap dehiscence is consistent with other studies reporting on d-PTFE membrane exposures. In particular, Ghensi et al. reported a case of d-PTFE membrane exposure 14 days after GBR. Similarly to the present study, evidence of an epithelial seal at the site involved, with no detachment on probing or suppuration was observed. The problem was managed by continuing chlorhexidine mouthwashes (0.12%) for 30 days, applying 1% chlorhexidine gel twice a day until the re-opening procedure and removing any plaque once a week at the office. The re-entry surgery took place 4 months after the GBR surgery, and the defect appeared almost completely filled [53]. These findings are consistent with other studies showing that intentionally exposed d-PTFE membranes for socket preservation procedures [54] as well as GBR procedures [55] did not exhibit significantly compromised regeneration outcomes. The reason lies in the pore sizes of d-PTFE membranes which is < 0.3 μm, differently from e-PTFE membranes characterized by pore sizes ranging between 5 to 30 μm. Pore size of < 0.3 μm is impervious to bacterial penetration, as the average size of bacteria is approximately 0.5–5.0 μm [56]. Hence, d-PTFE membranes might prevent bacterial infection when exposed, with consequent less risk of impaired bone augmentation and unsuccessful outcome.

Inappropriate trimming of non-resorbable barrier has been reported as another potential factor attributed to membrane exposure [57]. In order to overcome such drawback, in the present study a stereolithographic real-size model realized with the augmented bone according to the virtual project, has been used before the surgical procedure with a twofold purpose: 1) to trim and contour the non-resorbable d-e-PTFE membrane extraorally directly on the model, providing better access, visualization, and handling with respect to an intra-oral procedure; 2) reduce the risk of contamination by the saliva by reducing the time the membrane was placed in direct contact with the oral fluids. In the traditional approach, the membrane is usually placed several times in the surgical site to verify the correct size, shape, and adaptation. Furthermore, the trimming phase is normally performed before the augmentation procedure. Therefore, the clinician has to contour the membrane on the basis of an empirical evaluation of the future volume of bone that will be grafted in the surgical site. This may lead to possible inconsistencies between the size and shape of the membrane and the underlying graft. Conversely in the present study, the membrane has been trimmed and adapted directly on the model replicating the augmented bone. Hence,

the risk of incongruity between the graft and the contour and dimension of the d-e-PTFE membrane has been reduced.

In the present study, the minimum distance between the d-e-PTFE membrane and the periodontium of the neighbouring teeth was 1.5 mm in order to prevent possible infiltrations through the gingival sulcus. The presence of bacterial contamination compromises the integrity of the membrane and limits the regeneration process. Once compromised, the soft tissue begins to infiltrate the membrane, resulting in a much more difficult removal of the membrane and less favourable outcomes [58]. This aspect has been managed by contouring the membrane with hourglass-shape directly on the model with excellent visualization of both buccal and oral aspects. This represented another advantage compared to the standard procedure, where the correct 1.5 mm-distance between the barrier and the periodontium may be masked by the blood or the surfaces of adjacent teeth.

Other post-operative complications might be expected following computer-guided implant placement. A systematic review and meta-analysis developed to evaluate the complication rate associated with guided surgery identified several post-operative complications reported in studies with follow-up longer than 1 year [48]. Approximately 37.2% of the losses of the implants occurred due to failure in osseointegration (early losses). Other complications including infection and fistulas (7.8%), low primary stability (9.8%), persistent pain (1.9%), and periimplantitis (13.7%), were also reported and associated with losses. Mucositis was the most frequent biological complication and was related to poor hygiene of the patients.

In the present study, the use of a stereolithographic real-size surgical model had an impact on another study variable, which was the duration of the surgical procedure. The fact that the d-e-PTFE membrane has been shaped extra-orally before the beginning of the surgical procedure resulted in a global reduction of the operative time. The mean surgical duration was approximately 1 hour and half. Since no other studies could be found in literature that assessed the operative time in case of computer-guided implant placement and virtually-aided GBR, it is difficult to make comparisons.

Linear regression model analysis clearly demonstrated that prolonged oral surgical intervention might increase postoperative pain and discomfort for the patient and is an important risk factor for the occurrence of complications following oral surgery [59]. Besides parameters such as the severity of surgical procedure and the skill of the surgeon, improved surgical techniques and therapeutic strategies are essential to reduce the operation time. One of the objectives of computer-guided implant placement is to reduce the duration of the surgical procedure by simplifying the technique with the aid of surgical stents. Indeed, a positive correlation has been found between complexity and duration of the surgery, with more difficult and invasive procedures being more time-consuming [60]. The time saved with computer-guided flapless surgery versus conventional open-flap surgery has been quantified by Arisan et al.[61]. The authors found that the duration of the treatment with computer-guided flapless guided surgery was less than half compared to conventional open-flap implant placement (24 minutes versus > 60 minutes respectively). In another trial, the same researchers compared conventional versus computer-assisted stereolithographic template-guided surgery in fully edentulous jaws, and again indicated a significant reduction in surgical time for the guided approach (63 minutes versus 33 minutes, respectively) [62]. Furthermore, the pain intensity and the number of analgesics consumed in the flapless group were lower than the conventional group. In addition, the authors investigated the effect of bacteraemia with relation to conventional and computer-assisted implant surgery and found that computer-guided implant placement reduces the incidence of surgery-related bacteraemia. Thus, the time factor may indeed be a part of the explanation why less pain and discomfort was reported by patients after flapless guided surgery. Obviously, the advantages introduced with the virtual planning such as determination of implant locations, drill-depth control, and pre-contouring of the d-e-PTFE membrane contributed to reduce the operation time in the present study.

Notwithstanding the reduced surgical time, other variables seem to have influenced the patient-centred outcomes evaluated in the present study. As a matter of fact, in the present study pain showed the highest scores compared to the other variables. Pain can be considered to be multifactorial and may thus be influenced by the patient's expectations regarding the forthcoming surgical procedure. Thus, high values of pain perception might be explained by false expectations in view of a procedure believed by the patient to be less painful with respect to a standard surgery. Evidence related to pain and immediate implant placement involving regenerative techniques is extremely underreported in literature.

Similarly to the present study, only one study aimed to assess patient discomfort in terms of pain, swelling and wound oozing following immediate implant placement using regenerative techniques, and further, to evaluate patients' perception of the surgical intervention [63]. Patients provided VAS scores in the range of 30–54 mm, defined as being equivalent to moderate pain according to Collins et al. [64]. Conversely, in the present study patients reported mean VAS score for pain > 64, consistent with severe pain. Differences might be related to the fact that the previous study performed immediate post-extraction implants to replace a single molar, and used a collagen membrane to cover the graft. In the present study, two implants per patient were inserted into more extensive horizontal and vertical defects that required the use of non-resorbable membrane to stabilize the graft. Thus, it might be inferred that extensive harvest of autogenous bone, extended flap design and horizontal periosteal releasing incisions to mobilize and passivate the flaps, could have caused a more intense pain. Interestingly, in the present study swelling scored lower with respect to the previous study. This probably might not reflect the real outcome considering the different invasiveness of the two surgical approaches. This indicates that aspects other than merely the surgical procedure may be involved in the process of pain intensity perception. As a matter of fact, pain was perceived more compared to swelling, which can be regarded as an indicator of how invasive the performed surgery was and thereby the succeeding trauma to the soft tissue.

As already mentioned, large flap had to be passivate and mobilized in order to gain soft tissue closure. Periosteal incisions have significant impact in post-operative swelling, which could explain high VAS scores recorded up to the third post-operative day. One may further expect that postoperative bleeding would be an issue of concern following extensive periosteal incisions. This was, however, not the case because the mean VAS regarding oozing from the wound, which peaked on 1 day postoperative, was rather low and declined rapidly. Topical infiltrations of dexamethasone sodium phosphate, and application of cold packs for 48 hours post-operatively may have helped to avoid postsurgical bleeding and reduce postoperative swelling.

The perception of the operation was moderate. It is noteworthy that no correlation could be found between perception of the operation and the study variables. Thus, it might be speculated that subjective emotional component rather than the outcome of the surgical procedure itself led to a moderate perception of the operation, particularly with respect to exceptionally higher scores for pain. The perception of pain is an integrated process including the perception of a potentially noxious sensorial input, rapid evaluation of the noxious stimulus, the elaboration of a biological response, and the construction of an attitude towards the pain [65]. There was a general feeling that patients had a worst attitude to pain because they were told they would have undergone shorter and less invasive surgical procedure. However, the surgery still remained invasive and longer compared to their expectations and hopes. In view of the aforesaid, the patients obviously cannot be promised they will have no pain by using the computer-guided approach, especially if implants are to be placed near a vital structure. Moreover, telling to the patient that they will experience less pain, and that their pain will be shorter in duration could be hazardous and misleading in consideration of the present surgical approach. Contrariwise, minimally invasive surgical procedures such as computer-guided flapless implant surgery showed decrease pain experience by patients when compared to the conventional procedure [66]. This was corroborated by a randomized controlled trial including also partially edentulous patients requiring at least 2 implants to be restored with a single prosthesis [67]. Patients were randomised

according to a parallel group study design into two arms: computer-guided implant placement aided with templates versus conventional implant placement without templates. Statistically significant more postoperative pain was reported by patients of the conventional group.

6.2. Secondary outcome

The secondary outcome of the present study aimed to evaluate the accuracy of the experimental procedure. Matching of the planned with the placed implant position was expressed by three parameters: deviation at the entry point; deviation at the apex; and deviation of the long axis. These parameters are currently used as references to calculate the overall deviation reflecting the clinical accuracy [68].The evaluation was performed by overlapping the virtually planned position with the surgical position of the implant acquired on the post-operative CBCT scan. Mean coronal, apical, and angular deviations were 0.73 ± 0.21 mm; 0.59 ± 0.28 mm; and 3.05° ± 1.22° respectively.

To evaluate the level of accuracy, a control group has been introduced. The characteristics of the control group included computer-guided implant placement in fully edentulous patients, presenting ideal amount of bone tissue to place implants in a prosthetically driven position, without recurring to GBR procedures. Surgical stents were mucosa-supported guides stabilized to the jawbone with anchor pins, allowing fully-guided implant insertion. Notably, considering at least one parameter in terms of coronal, apical, and angular deviations, flapless computer-guided surgery resulted in greater accuracy than open-flap procedures [68]; full-guided surgery achieved greater accuracy than half guided surgery [18, 68]; mucosa-supported guides indicated a statistically significant greater reduction in deviation when compared to the bone-supported guides [44, 69]; when mucosa-supported guides were additionally stabilized by endosseous pins, results were even better compared to non-fixed mucosa-supported guides [31]. Hence, based on the evidence reported herein, it may be assumed that the control group could represent the reference procedure with adequate reliability. Thus, when implants were placed flaplessly in ideal surgical conditions, mean coronal, apical, and angular deviations were 0.68 ± 0.25 mm; 0.57 ± 0.22 mm; and 2.77° ± 1.20° respectively.

To assess the accuracy of the experimental procedure, the deviations were compared with those obtained in the control group. To avoid possible bias, all the procedures from data acquisition to realization of the surgical stent were performed with the same devices and settings. Between the two groups, mean differences of coronal, apical, and angular deviations were 0.04 ± 0.32 mm; 0.02 ± 0.35; and 0.27° ± 1.71° respectively. None of the parameters showed a statistically significant difference, therefore it appeared that the experimental procedure achieved a degree of accuracy comparable with the reference procedure. Up to now, it remains unclear how much inaccuracy can be accepted. Unreported *t*-test showed that the coronal, apical, and angular deviations in both groups were statistically different from zero. This might underline a certain level of inaccuracy from a mathematical point of view. The question whether this level of accuracy is clinically acceptable has been answered by several paper, at least with respect to linear deviations. The literature seems to indicate that one has to accept an inaccuracy of ± 1.5 mm [31, 45, 70], which is clearly less than that observed in the present study in both test and control groups.

The placement of endosseous implants has many pitfalls, such as movement of the patient while drilling, limited surgery time related to the use of local anesthesia, a restricted visualization of the operation field, and transfer of two-dimensional radiographs into the 3D surgical environment to name a few. Thus, during a limited time span and with a restricted view, the surgeon has to take numerous decisions while approaching a conscious patient under aseptic conditions. Therefore, the aim of the present study was to introduce virtual planning and computer-guided surgery as an aid in critical anatomical situations, where the conventional free-hand approach would be more difficult.

Data on the accuracy of free-handed implant surgery in partially edentulous patients are completely lacking, even though the technique is by many still considered the standard approach. Notwithstanding the fact that

no randomized controlled trials are currently available comparing computer-aided GBR and implant placement versus the conventional protocol, increasing evidence strengthened the use of computer-guided surgery to achieve greater accuracy. Similarly to the present study, Younes et al. evaluated the accuracy of tooth-supported fully guided surgery in the posterior sectors of partially edentulous patients [21]. The authors compared the accuracy with tooth-supported pilot-drill guided implant placement and free-handed surgery. Fully-guided surgery was the most accurate, followed by the pilot-drill guided implant insertion, which achieved higher accuracy when compared to free-handed surgery, specifically in the horizontal plane. For such reason, the authors claimed that the use of a pilot-drill guide might not be obsolete, particluarly in those cases where a fully guided surgery is not feasible (e.g. a thin alveolar crest). This assumption has been undermined by the present study, in which a fully guided implant insertion has been successfully accomplished in resorbed and atrophic alveolar ridges. Interestingly, although screw-retained restorations were planned for all implants, the authors reported cement-retained restorations in 19.2% and 4.2% of implants placed with a free-hand or pilot-drill guided approach respectively. This emphasizes the fact that inaccuracy is a risk factor not only for biological, but also for prosthetic complications as previously mentioned herein.

Within the field of prosthetic complications due to malpositioning, the apico-coronal position is of major importance when it comes to aesthetic and functional outcomes. It is worth mentioning that implants placed without guiding systems had a tendency to be positioned more coronal than planned [20]. This could indicate that considering the bone volume in the planning software, implants were placed more apical than one would do judging the bone volume in the clinical situation. Thus, based on the ideal position planned within the software, an underestimation of the available bone volume was made, with increasing risk of implant malpositioning in apico-coronal dimension. Other authors reported difficulties with the freehand method related to the complete uncertainty and lack of information regarding the implant-prosthesis relation [62]. This led the surgeons to place the implants where the bone volume appeared the most abundant, which is in contrast with a prosthetically- and not bone-driven implant insertion.

Similarly to the present study, other authors evoked the use of guided surgery to improve accuracy for multiple-implant cases in partially edentulous sites [71]. The authors also indicated that in cases with incomplete bone remodelling and splayed roots, such as in lower molars, guided surgery should be used to counteract the tendency of the drill to be driven off course toward the newly formed bone. This concept has been exploited also in the present study, as the bur sleeves equipped in the template permitted rigidly guided and highly controllable drillings, which represented an advantage in areas of irregular and/or immature bone.

Another issue related to free-hand implant placement relies on the primary stability, which is a crucial factor in achieving implant success and is often related to the surgical protocol. Free-hand implant bed preparation is likely to produce an elliptical rather than perfectly round site, hindering the achievement of proper primary stability. Contrarily, higher primary stability can be achieved by taking advantage of the ability to pre-plan implant design (tapered or straight) and drilling sequence, and to use the digitally produced surgical template to precisely guide drills and the implant to final position [72]. Accordingly, in the present study all of the implants were placed with insertion torque values > 35 Ncm.

One of the crucial factors for precision is the stability of the template position during implant placement. In the present study, tooth-supported surgical guides stabilized by the residual dentition were used. In the literature, it is recommended to have at least two or more teeth without mobility to improve template stability and thus accuracy [29]. In the present study none of the patients exhibithed tooth mobility, a fact that might have had an impact on the correct seating of the surgical guide. Previously reported systematic reviews clustered the outcomes of implant deviation when using different types of guided support from cadaver, laboratory, and clinical studies, not necessarily within the same study. This made it difficult to evaluate the present results with other guided supports. Actually, the

proper comparison should be made between tooth-supported and bone-supported surgical guides, since the latter involve the elevation of a full-thickness flap to access the underlying bone according to the present study. Raico-Gallardo et al. performed a systematic review including into the meta-analysis data of only clinical trials that compared within the same study the accuracy of surgical guides with different supporting tissues [69]. An important finding of this meta-analysis was that the bone-supported guides provided lower accuracy than did the tooth-supported stents. It is worth mentioning that between mucosa- and tooth-supported guides, no statistically significant differences could be found for any of the outcome measures, namely coronal, apical, and angular deviations. This outcome is consistent with the result observed in the present study, with no statistically significant differences between tooth- and mucosa-supported guides. However, differences between the surgical approaches do not allow drawing final conclusions since a direct comparison cannot be made.

Other factors inherent to the surgical protocol itself might have had a remarkable role in the degree of accuracy obtained with the present experimental procedure. Among these, the use of single-guide system that, differently from multiple-guides, allowed placing the implant without changing the template for each drill diameter throughout the surgery, thus reducing the likelihood of deviations from the planned position. In addition, the reported protocol contemplated the use of disposable drills that may have improved the accuracy of the system, thereby enhancing the cutting potential and consequently preventing possible deviations originating from excessive wear. Moreover, drills had a physical and not a visual stop, with better control of the preparation depth. The accuracy of implant position was further increased by using a fully-guided approach, which assisted the clinician in every step of the surgery, starting from the first drill up to the implant insertion without switching the guiding sleeves in the said stent. The advances in digital technology allowed a virtual superimposition of the diagnostic stone study cast with the CBCT scan by a matching process on the corresponding structures (teeth). Thus, both the osseous and prosthetic structures were visible in one single 3D application. This made it possible to consider surgical and prosthetic aspects in the virtual environment without recurring to a radiological template. The elimination of a radiological template reduced the number of steps required to complete the virtual planning. A reduced number of steps might be interpreted in light of the fact that deviations may reflect the sum of all errors occurring from imaging to the transformation of data into a guide, to the improper positioning of the latter during surgery. Thus, all errors, although seldom occurring, can be cumulative. For this reason, reducing the number of steps needed to plan the surgical and prosthetic phase could have played a substantial role in increasing the accuracy of the workflow.

6.3. Limitations of the study

The present proof-of-concept study has some limitations that need to be addressed.

First of all, the sample size represented an issue of no little significance. Unfortunately, after an extensive review of the literature, no studies were available using computer-aided GBR and implant placement to rehabilitate partially edentulous patients. Actually, no studies were found applying computer-guided implant placement in clinical situation presenting an inadequate amount of bone that needed to be augmented simultaneously with implant insertion. Therefore, the calculation of the sample size could not be performed properly. This was probably due to the nature of the present study, namely a proof of principle study. On the other hand, sample size calculation seems to be a common pitfall in dental research. Surprisingly, Lucena et al. reported that just 2 (1%) of the 226 research articles they reviewed in operative dentistry reported an a priori sample size calculation or effect size estimation [73].

As a consequence of the small sample size enrolled in the present study, this may have hidden some differences between treatments. In other words, this study may have been underpowered to detect statistically significant differences between the treatment groups in terms of linear and angular deviations. A retrospective

sample-size calculation has been performed considering the higher discrepancy between the study variables. More in detail, the mean difference in angular deviation between test and control group has been adopted. Two-tailed Wilcoxon-Mann-Witney test was used to compute the required sample size with statistical software (G*Power 3.1, Heinrich-Heine University, Dusseldorf, Germany). To detect a difference of 0.27° ± 1.71° between test and control group, with a precision of 5%, and a confidence level of 80%, a total of 309 implants per group were needed.

It must be noted however that, depending on how retrospective power is calculated, it might be legitimate to use the statistical power calculation and sample size in planning future study, but cannot legitimately be used as describing the power of the study from which it is calculated. Post-hoc power calculation performed when obtaining a non-statistically significant result has been demonstrated to be a flawed approach and should be performed to plan future researches instead of retrospectively evaluate the observed data [74].

Another limitation is related to the convenience sample used in the present study rather than large randomly selected population sample, which bears the risk of selection bias. The study has been carried out in a University setting with strict inclusion criteria that might not reflect the real condition of the general population. Moreover, the test and control groups were unmatched, treated differently, and seen by the same research team. Even the operator experience might be considered a cofounding factor. Indeed, guided implant surgery is technically demanding and not free from specific procedure-related complications. Surgical skills and experience of the clinician using this surgical technique go above and beyond those necessary for providing regular implant surgery [75]. All of these concerns recognize the absence of external validity and demand that the reported results should be interpreted with caution.

Within the context of selection bias, another concern might be related to the inclusion criteria for partially edentulous sites. All partial edentulisms in the posterior sectors of both maxilla and mandible were included. The fact that some patients presented a partial edentulism included within remaining teeth while other patients were treated in areas not presenting teeth distally to the edentulous site might have provided fallacious results in terms of accuracy. Unreported data of the present study showed slightly higher angular deviations when implants were placed in edentulous ridges not presenting distal teeth. This might be explained by the fact that the surgical guides were probably more stable when supported by at least one tooth distally with respect to the edentulous site. On the contrary, when no supporting teeth were present distally, the guides may have incurred twisting moments while applying some pressure during the drilling phase at the distal site. This supposition may explain the slightly higher deviations observed for the distal implants to a certain extent. This speculation could not be confirmed due to the restricted sample, however it should be taken into account for future studies.

The fact that the duration of the surgery was registered assumed that all surgeries had to be performed with the same techniques and procedures. In the present study, all procedures were standardized in terms of protocols and number of implants. On the other hand it was not possible to equalize the number of osteosynthesis screws needed to stabilize the d-e-PTFE membrane. Some membranes were secured with four screws, while others were fixed with five devices. This might have prolonged the surgical time of the latter of approximately 5 minutes. Consequently, the overall mean duration of the surgical time could have been misreported. The question whether this difference might have had an impact on the patient-centred outcomes remained unanswered.

The present study has been designed as a proof-of-concept study aimed to provide preliminary results with respect to an innovative application of virtual planning. Hence, not all the study variables have been explored in detail. For example, in the evaluation of the patient-centred outcomes, the effect of anxiety on pain perception has not been investigated. The same applies to other variables such as the gender, the age of the patients, the smoking habits, and the location of the surgical site. All of these factors have been reported to affect the post-operative patient-centred outcomes [63]. Due to the limited sample, however, the analysis of these variables was not considered significant for the general purposes of the study.

7. Conclusions

Within the limitations of the present study, it might be concluded that computer-guided implant placement associated with computer-aided guided bone regeneration has proven to be an effective technique in the treatment of partially edentulous patients seeking a fixed implant-supported rehabilitation. Indeed, no biological and technical intra-operative complications were observed in all cases treated with the experimental protocol. Only one post-operative biological complication occurred, however this was not strictly related to the experimental procedure itself but rather related to iatrogenic fault. Nonetheless, in all cases an adequate quality and quantity of augmented bone was found at the re-entry surgery. Prosthetic procedures were therefore carried out according to the treatment plan.
In consideration of patient-centred outcomes, some concerns still persist with respect to the perception of the operation reported by the patients. Although the procedure has been developed to minimize the post-operative patient morbidity, this advantage could not be validated in the present study. Therefore, stating that computer-guided implant placement and GBR was able to reduce post-operative pain, swelling, and bleeding could be misleading.
Lastly, the application of computer-guided implant placement in demanding anatomical situations characterized by less than ideal availability of residual bone resulted in acceptable degrees of accuracy. This assumption has been verified by comparing the experimental procedure with the "gold standard" technique consisting of flapless mucosa-supported screw-retained computer-guided implant placement in fully edentulous patients presenting ideal amount of supporting bone.
In conclusion, computer-guided implant placement with computer-aided guided bone regeneration may be considered a viable tool in case of atrophic partially edentulous ridges to correctly place implants in a prosthetically guided position in association with prosthetically-driven GBR. This procedure however might not guarantee reduced post-operative morbidity and improved perception of the operation by the patients.
Further short-, medium-, and long-term studies are required to evaluate the outcomes of this protocol in terms of early and late survival, success, and complication rates of both implants and prostheses.

References

1. Branemark PI, Adell R, Breine U, et al. Intra-osseous anchorage of dental prostheses. I. Experimental studies. *Scand J Plast Reconstr Surg*. 1969;3(2):81-100.
2. Horikawa T, Odatsu T, Itoh T, et al. Retrospective cohort study of rough-surface titanium implants with at least 25 years' function. *Int J Implant Dent*. 2017;3(1):42.
3. Chrcanovic BR, Kisch J, Albrektsson T, et al. A retrospective study on clinical and radiological outcomes of oral implants in patients followed up for a minimum of 20 years. *Clin Implant Dent Relat Res*. 2018;20(2): 199-207.
4. Knofler W, Barth T, Graul R, et al. Retrospective analysis of 10,000 implants from insertion up to 20 years-analysis of implantations using augmentative procedures. *Int J Implant Dent*. 2016;2(1):25.
5. Simion M, Nevins M, Rasperini G, et al. A 13- to 32-Year Retrospective Study of Bone Stability for Machined Dental Implants. *Int J Periodontics Restorative Dent*. 2018;38(4):489-493.
6. Testori T, Weinstein T, Scutella F, et al. Implant placement in the esthetic area: criteria for positioning single and multiple implants. *Periodontol 2000*. 2018;77(1):176-196.
7. Hammerle CHF, Tarnow D. The etiology of hard- and soft-tissue deficiencies at dental implants: A narrative review. *J Periodontol*. 2018;89 Suppl 1S291-s303.
8. Garber DA, Belser UC. Restoration-driven implant placement with restoration-generated site development. *Compend Contin Educ Dent*. 1995;16(8):796, 798-802, 804.
9. Jung RE, Heitz-Mayfield L, Schwarz F. Evidence-based knowledge on the aesthetics and maintenance of peri-implant soft tissues: Osteology Foundation Consensus Report Part 3-Aesthetics of peri-implant soft tissues. *Clin Oral Implants Res*. 2018;29 Suppl 1514-17.
10. Esposito M, Ekestubbe A, Grondahl K. Radiological evaluation of marginal bone loss at tooth surfaces facing single Branemark implants. *Clin Oral Implants Res*. 1993;4(3):151-157.
11. Mailoa J, Miron RJ, Wang HL. Risk Indicators and Prevention of Implant Soft-Tissue Complications: Interproximal Papillae Loss and Midfacial Implant Mucosal Recessions. *Compend Contin Educ Dent*. 2017;38(7): 436-443; quiz 444.
12. D'Haese J, Ackhurst J, Wismeijer D, et al. Current state of the art of computer-guided implant surgery. *Periodontol 2000*. 2017;73(1):121-133.
13. Verstreken K, Van Cleynenbreugel J, Martens K, et al. An image-guided planning system for endosseous oral implants. *IEEE Trans Med Imaging*. 1998;17(5):842-852.
14. Verstreken K, Van Cleynenbreugel J, Marchal G, et al. Computer-assisted planning of oral implant surgery. An approach using virtual reality. *Stud Health Technol Inform*. 1996;29423-434.
15. Verstreken K, Van Cleynenbreugel J, Marchal G, et al. Computer-assisted planning of oral implant surgery: a three-dimensional approach. *Int J Oral Maxillofac Implants*. 1996;11(6):806-810.
16. Hultin M, Svensson KG, Trulsson M. Clinical advantages of computer-guided implant placement: a systematic review. *Clin Oral Implants Res*. 2012;23 Suppl 6124-135.
17. Vercruyssen M, Hultin M, Van Assche N, et al. Guided surgery: accuracy and efficacy. *Periodontol 2000*. 2014;66(1):228-246.
18. Bover-Ramos F, Vina-Almunia J, Cervera-Ballester J, et al. Accuracy of Implant Placement with Computer-Guided Surgery: A Systematic Review and Meta-Analysis Comparing Cadaver, Clinical, and In Vitro Studies. *Int J Oral Maxillofac Implants*. 2018;33(1):101-115.

19. Vercruyssen M, Cox C, Coucke W, et al. A randomized clinical trial comparing guided implant surgery (bone- or mucosa-supported) with mental navigation or the use of a pilot-drill template. *J Clin Periodontol*. 2014;41(7):717-723.

20. Vercruyssen M, Coucke W, Naert I, et al. Depth and lateral deviations in guided implant surgery: an RCT comparing guided surgery with mental navigation or the use of a pilot-drill template. *Clin Oral Implants Res*. 2015;26(11):1315-1320.

21. Younes F, Cosyn J, De Bruyckere T, et al. A randomized controlled study on the accuracy of free-handed, pilot-drill guided and fully guided implant surgery in partially edentulous patients. *J Clin Periodontol*. 2018;45(6): 721-732.

22. Beretta M, Stoffella E, Poli PP, et al. Chirurgia flapless guidata per la riabilitazione immediata di edentulie totali: descrizione di un caso clinico. *Quintessenza Internazionale Speciale implantologia*. 2012;28(3bis):38-46.

23. Beretta M, Poli PP, Maridati P, et al. Computer-aided flapless surgery for implant prosthodontic rehabilitation of edentulous patients: a clinical case report. *European Journal of Oral Surgery*. 2013;4(3):57-63.

24. Beretta M, Poli PP, Maiorana C. Accuracy of computer-aided template-guided oral implant placement: a prospective clinical study. *J Periodontal Implant Sci*. 2014;44(4):184-193.

25. Di Giacomo GA, Cury PR, de Araujo NS, et al. Clinical application of stereolithographic surgical guides for implant placement: preliminary results. *J Periodontol*. 2005;76(4):503-507.

26. Ersoy AE, Turkyilmaz I, Ozan O, et al. Reliability of implant placement with stereolithographic surgical guides generated from computed tomography: clinical data from 94 implants. *J Periodontol*. 2008;79(8):1339-1345.

27. Ozan O, Turkyilmaz I, Ersoy AE, et al. Clinical accuracy of 3 different types of computed tomography-derived stereolithographic surgical guides in implant placement. *J Oral Maxillofac Surg*. 2009;67(2):394-401.

28. D'Haese J, Van De Velde T, Elaut L, et al. A prospective study on the accuracy of mucosally supported stereolithographic surgical guides in fully edentulous maxillae. *Clin Implant Dent Relat Res*. 2012;14(2):293-303.

29. Arisan V, Karabuda ZC, Ozdemir T. Accuracy of two stereolithographic guide systems for computer-aided implant placement: a computed tomography-based clinical comparative study. *J Periodontol*. 2010;81(1):43-51.

30. Tallarico M, Meloni SM. Retrospective Analysis on Survival Rate, Template-Related Complications, and Prevalence of Peri-implantitis of 694 Anodized Implants Placed Using Computer-Guided Surgery: Results Between 1 and 10 Years of Follow-Up. *Int J Oral Maxillofac Implants*. 2017;32(5):1162-1171.

31. Tahmaseb A, Wismeijer D, Coucke W, et al. Computer technology applications in surgical implant dentistry: a systematic review. *Int J Oral Maxillofac Implants*. 2014;29 Suppl25-42.

32. Abduo J, Lyons K, Bennani V, et al. Fit of screw-retained fixed implant frameworks fabricated by different methods: a systematic review. *Int J Prosthodont*. 2011;24(3):207-220.

33. Jemt T, Book K. Prosthesis misfit and marginal bone loss in edentulous implant patients. *Int J Oral Maxillofac Implants*. 1996;11(5):620-625.

34. Baruffaldi A, Poli PP, Baruffaldi A, et al. Computer-aided flapless implant surgery and immediate loading. A technical note. *Oral Maxillofac Surg*. 2016;20(3):313-319.

35. Maiorana C, Poli PP, Poggio C, et al. Oral Rehabilitation of a Patient With Ectodermal Dysplasia Treated With Fresh-Frozen Bone Allografts and Computer-Guided Implant Placement: A Clinical Case Report. *J Oral Maxillofac Surg*. 2017;75(5):939-954.

36. Faeghi Nejad M, Proussaefs P, Lozada J. Combining guided alveolar ridge reduction and guided implant placement for all-on-4 surgery: A clinical report. *J Prosthet Dent*. 2016;115(6):662-667.

37. Beretta M, Poli PP, Tansella S, et al. Virtually guided alveolar ridge reduction combined with computer-aided implant placement for a bimaxillary implant-supported rehabilitation: A clinical report. *J Prosthet Dent*. 2018.

38. Chiapasco M, Casentini P. Horizontal bone-augmentation procedures in implant dentistry: prosthetically guided regeneration. *Periodontol 2000*. 2018;77(1):213-240.
39. Hurley LA, Stinchfield FE, Bassett AL, et al. The role of soft tissues in osteogenesis. An experimental study of canine spine fusions. *J Bone Joint Surg Am*. 1959;41-a1243-1254.
40. Simion M, Trisi P, Piattelli A. Vertical ridge augmentation using a membrane technique associated with osseointegrated implants. *Int J Periodontics Restorative Dent*. 1994;14(6):496-511.
41. Simion M, Dahlin C, Trisi P, et al. Qualitative and quantitative comparative study on different filling materials used in bone tissue regeneration: a controlled clinical study. *Int J Periodontics Restorative Dent*. 1994;14(3):198-215.
42. Simion M, Baldoni M, Rossi P, et al. A comparative study of the effectiveness of e-PTFE membranes with and without early exposure during the healing period. *Int J Periodontics Restorative Dent*. 1994;14(2):166-180.
43. Beretta M, Cicciu M, Poli PP, et al. A Retrospective Evaluation of 192 Implants Placed in Augmented Bone: Long-Term Follow-Up Study. *J Oral Implantol*. 2015;41(6):669-674.
44. Hammerle CH, Cordaro L, van Assche N, et al. Digital technologies to support planning, treatment, and fabrication processes and outcome assessments in implant dentistry. Summary and consensus statements. The 4th EAO consensus conference 2015. *Clin Oral Implants Res*. 2015;26 Suppl 1197-101.
45. Vercruyssen M, Laleman I, Jacobs R, et al. Computer-supported implant planning and guided surgery: a narrative review. *Clin Oral Implants Res*. 2015;26 Suppl 1169-76.
46. Milinkovic I, Cordaro L. Are there specific indications for the different alveolar bone augmentation procedures for implant placement? A systematic review. *Int J Oral Maxillofac Surg*. 2014;43(5):606-625.
47. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
48. Moraschini V, Velloso G, Luz D, et al. Implant survival rates, marginal bone level changes, and complications in full-mouth rehabilitation with flapless computer-guided surgery: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg*. 2015;44(7):892-901.
49. Campelo LD, Camara JR. Flapless implant surgery: a 10-year clinical retrospective analysis. *Int J Oral Maxillofac Implants*. 2002;17(2):271-276.
50. Landazuri-Del Barrio RA, Cosyn J, De Paula WN, et al. A prospective study on implants installed with flapless-guided surgery using the all-on-four concept in the mandible. *Clin Oral Implants Res*. 2013;24(4):428-433.
51. Pomares C. A retrospective study of edentulous patients rehabilitated according to the 'all-on-four' or the 'all-on-six' immediate function concept using flapless computer-guided implant surgery. *Eur J Oral Implantol*. 2010;3(2):155-163.
52. Gillot L, Noharet R, Cannas B. Guided surgery and presurgical prosthesis: preliminary results of 33 fully edentulous maxillae treated in accordance with the NobelGuide protocol. *Clin Implant Dent Relat Res*. 2010;12 Suppl 1e104-113.
53. Ghensi P, Stablum W, Bettio E, et al. Management of the exposure of a dense PTFE (d-PTFE) membrane in guided bone regeneration (GBR): a case report. *Oral Implantol (Rome)*. 2017;10(3):335-342.
54. Greenstein G, Carpentieri JR. Utilization of d-PTFE Barriers for Post-Extraction Bone Regeneration in Preparation for Dental Implants. *Compend Contin Educ Dent*. 2015;36(7):465-473.
55. Waasdorp J, Feldman S. Bone regeneration around immediate implants utilizing a dense polytetrafluoroethylene membrane without primary closure: a report of 3 cases. *J Oral Implantol*. 2013;39(3): 355-361.
56. Bartee BK, Carr JA. Evaluation of a high-density polytetrafluoroethylene (n-PTFE) membrane as a barrier material to facilitate guided bone regeneration in the rat mandible. *J Oral Implantol*. 1995;21(2):88-95.

57. Gher ME, Quintero G, Assad D, et al. Bone grafting and guided bone regeneration for immediate dental implants in humans. *J Periodontol*. 1994;65(9):881-891.

58. Rakhmatia YD, Ayukawa Y, Furuhashi A, et al. Current barrier membranes: titanium mesh and other membranes for guided bone regeneration in dental applications. *J Prosthodont Res*. 2013;57(1):3-14.

59. Shigeishi H, Ohta K, Takechi M. Risk factors for postoperative complications following oral surgery. *J Appl Oral Sci*. 2015;23(4):419-423.

60. Sato FR, Asprino L, de Araujo DE, et al. Short-term outcome of postoperative patient recovery perception after surgical removal of third molars. *J Oral Maxillofac Surg*. 2009;67(5):1083-1091.

61. Arisan V, Karabuda CZ, Ozdemir T. Implant surgery using bone- and mucosa-supported stereolithographic guides in totally edentulous jaws: surgical and post-operative outcomes of computer-aided vs. standard techniques. *Clin Oral Implants Res*. 2010;21(9):980-988.

62. Arisan V, Karabuda CZ, Mumcu E, et al. Implant positioning errors in freehand and computer-aided placement methods: a single-blind clinical comparative study. *Int J Oral Maxillofac Implants*. 2013;28(1):190-204.

63. Urban T, Wenzel A. Discomfort experienced after immediate implant placement associated with three different regenerative techniques. *Clin Oral Implants Res*. 2010;21(11):1271-1277.

64. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? *Pain*. 1997;72(1-2):95-97.

65. Gomez-de Diego R, Cutando-Soriano A, Montero-Martin J, et al. State anxiety and depression as factors modulating and influencing postoperative pain in dental implant surgery. A prospective clinical survey. *Med Oral Patol Oral Cir Bucal*. 2014;19(6):e592-597.

66. Fortin T, Bosson JL, Isidori M, et al. Effect of flapless surgery on pain experienced in implant placement using an image-guided system. *Int J Oral Maxillofac Implants*. 2006;21(2):298-304.

67. Pozzi A, Tallarico M, Marchetti M, et al. Computer-guided versus free-hand placement of immediately loaded dental implants: 1-year post-loading results of a multicentre randomised controlled trial. *Eur J Oral Implantol*. 2014;7(3):229-242.

68. Zhou W, Liu Z, Song L, et al. Clinical Factors Affecting the Accuracy of Guided Implant Surgery-A Systematic Review and Meta-analysis. *J Evid Based Dent Pract*. 2018;18(1):28-40.

69. Raico Gallardo YN, da Silva-Olivio IRT, Mukai E, et al. Accuracy comparison of guided surgery for dental implants according to the tissue of support: a systematic review and meta-analysis. *Clin Oral Implants Res*. 2017;28(5):602-612.

70. Van Assche N, Vercruyssen M, Coucke W, et al. Accuracy of computer-aided implant placement. *Clin Oral Implants Res*. 2012;23 Suppl 6112-123.

71. Choi W, Nguyen BC, Doan A, et al. Freehand Versus Guided Surgery: Factors Influencing Accuracy of Dental Implant Placement. *Implant Dent*. 2017;26(4):500-509.

72. Schnitman PA, Hayashi C, Han RK. Why guided when freehand is easier, quicker, and less costly? *J Oral Implantol*. 2014;40(6):670-678.

73. Lucena C, Lopez JM, Abalos C, et al. Statistical errors in microleakage studies in operative dentistry. A survey of the literature 2001-2009. *Eur J Oral Sci*. 2011;119(6):504-510.

74. Hoenig JM, Heisey DM. The Abuse of Power. *The American Statistician*. 2001;55(1):19-24.

75. Sicilia A, Botticelli D. Computer-guided implant therapy and soft- and hard-tissue aspects. The Third EAO Consensus Conference 2012. *Clin Oral Implants Res*. 2012;23 Suppl 6157-161.

Appendix

List of materials used in the present proof-of-principle study:

High-precision type IV dental die stone: Fuji Rock®; GC Europe, Leuven, Belgium;

Virtual planning software: 3Diagnosys®, 3DIEMME®; Como, Italy;

Dental implants: Guide System CONELOG® Screw-line Implant, Promote® plus; Camlog Biotechnologies, Basel, Switzerland;

Deproteinized bovine bone mineral: Bio-Oss®; Geistlich Pharma AG, Wolhusen, Switzerland;

Non-resorbable d-e-PTFE membrane: NeoGen™; Neoss®, Milan, Italy;

Endosseous osteosynthesis screw: Maxil®, inner square ø 1.5 mm, length 4-5 mm; Omnia® S.p.A., Fidenza, Italy;

Non-resorbable suture: CV-5 and CV-7 GORE-TEX® sutures, W. L. Gore & Associates S.r.l, Verona, Italy.