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Customized CAD/CAM Titanium meshes for the guided bone regeneration of severe alveolar ridge defects: preliminary results of a retrospective clinical study in humans

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Abstract

Objectives: To present the results of Guided Bone Regeneration (GBR) of atrophic edentulous ridges with customized CAD/CAM Titanium meshes.

Materials and methods: 41 patients, presenting with 53 atrophic sites were enrolled between 2018 and 2019. GBR was obtained with titanium meshes filled with autogenous bone chips and bovine bone mineral (BBM). After a mean of 7 months (range: 5-12 months), meshes were removed and 106 implants placed. After a mean of 3.5 months (range: 2-5 months), implants were uncovered and prosthetic restorations started. The outcomes were vertical and horizontal bone augmentation changes, biological complications and implant survival.

Results: out of 53 sites, 11 underwent mesh exposure: 8 of them were followed by uneventful integration of the graft, while 3 by partial bone loss. The mean vertical and horizontal bone gain after reconstruction was 4.78±1.88mm (range 1.00 to 8.90mm), and 6.35±2.10mm (range 2.14 to 11.48 mm), respectively. At the time of implant placement, mean changes of initial bone gain were -0.39±0.64mm (range -3.1 to +0.80mm), and -0.49±0.83mm (range –3.7 to +0.4mm), in the vertical and horizontal dimensions, respectively. Reduction of bone volume was significantly higher ($P<0.001$ for both dimensions) in the exposed sites. The mean follow-up of implants after loading was 10.6±6.5months (range: 2 to 26months). The survival rate of implants was 100%.

Conclusion: customized titanium meshes can represent a reliable tool for GBR of severely atrophic sites, with simplification of the surgical phases.

1. INTRODUCTION

In case of severe bone defects of edentulous ridges, implant placement may result impossible or not compatible with an acceptable prosthetic outcome from a functional and/or aesthetic point of view.

To restore adequate bone volumes, different reconstructive techniques have been proposed, including: a) autogenous bone grafts (Chiapasco, et al., 2009; Milinkovic, & Cordaro, 2014; Chiapasco, et al.,2018; Chiapasco, et al.,2020); b) distraction osteogenesis (Chin & Toth 1996; Chiapasco, et al.; 2004) and, c) guided bone regeneration - GBR (Lang, et al., 1994; Milinkovic, & Cordaro, 2014; Benic, et al., 2014; Wessing, et al., 2018).

Among these, GBR procedures are well documented. According to the extent and/or type of defect (horizontal and/or vertical), GBR can be performed using autogenous bone particles or non-autogenous bone substitutes in association with resorbable or non-resorbable membranes, including titanium meshes.

However, it is worth noting that the use of resorbable membranes, because of their insufficient space-maintaining capacity, might be inadequate for relevant vertical defects. Conversely, non-resorbable membranes, such as Titanium reinforced PTFE membranes, offer a very good space-maintaining effect, but are prone, in case of exposure, to a non-negligible risk of infection with subsequent partial or total loss of the initial bone gain (Chiapasco, et al., 2009; Esposito, et al., 2009; Milinkovic & Cordaro, 2014; Elnayef, et al., 2017). Moreover, non-resorbable membranes must be adapted “in situ” to the defect by modelling and trimming in a precise way: this requests special skills and results are very technique-sensitive.

The traditional titanium meshes (TM) have shown good clinical and radiological results. However, some drawbacks and complications have been reported: the available meshes are generally rectangular foils of different thickness which must be trimmed and bended according to the defect to be reconstructed, requiring clinical skill and experience. This procedure can be time consuming and the final shape not ideal; furthermore, angles and edges created during modelling, if irregular and sharp, may expose soft tissues to mechanical trauma, which may lead to perforation of the flap and exposure of the mesh. This can be followed by infection and partial or total loss of the initial bone augmentation (Roccuzzo, et al., 2007; Her, et al., 2012; Miyamoto, et al., 2012; Briguglio, et al., 2019).

As an alternative to membranes and traditional titanium meshes and to provide a solution to the over-mentioned disadvantages, in particular in the presence of vertical / three-dimensional defects with “very irregular” morphology - where adaptation of membranes or bone blocks might be complex - a new generation of titanium meshes have been recently proposed. These latter, in order to be precisely

adapted to the bone defects, are created with a CAD/CAM technology. This makes it possible to produce a precise three-dimensional scaffold by means of laser sintering (Sumida, et al., 2015; Sagheb, et al., 2017; Seiler, et al., 2018).

The aims of this clinical study are to evaluate: a) the effectiveness of digitally customized titanium meshes in association with autologous bone particles and BBM and covered with collagen membranes the regeneration of atrophic edentulous sites; and, b) the survival rate of implants placed in the regenerated areas.

2. MATERIALS AND METHODS

2.1 - Study design

This retrospective, single arm study included patients presenting with atrophic ridges and asking for fixed implant-supported restorations. They were treated with customized titanium meshes obtained through a CAD-CAM technology (Yxoss CBR® by Reoss, Filderstadt, Germany) used in association with autogenous bone particles, deproteinized bovine bone mineral (Bio-Oss®- Geistlich Biomaterials AG- Wolhusen – Switzerland), in a 1:1 ratio, and covered with collagen membranes (Bio-Gide®- Geistlich Biomaterials AG- Wolhusen – Switzerland). Patients received dental implants after a mean period of 7.3 months (range: 5-12 months; median: 7.3; SD: 1.45), to obtain a good consolidation of the grafted material. Implants were uncovered after a mean period of 3.5 months (range: 2-5 months; median: 3.45; SD: 0.89) and were rehabilitated with implant-supported prostheses after another mean time of 1.8 months (range: 1-3.5 months; median: 1.78; SD: 0.71)

An informed consent was obtained from all patients prior to treatment, including: a) the purpose of the treatment; b) a detailed description of the procedure; c) the potential side effects and complications; c) reconstructive alternatives with advantages and disadvantages (GBR with non-resorbable membranes, autogenous bone blocks, and distraction osteogenesis); d) the necessity of clinical and radiographic controls; e) and the patients' authorization to use their data for statistical analysis.

The study was performed in accordance with Guidelines ISO Standard 14155:2011 (Clinical Investigation of Medical Devices for Human Patients with the Appendixes VIII and X of the Medical Devices Directive 93/42/EEC) and following the principles stated in the Declaration of Helsinki.

The study was approved by the Ethics Committee of the University of Milan, Italy (Registration No. 2019/ST/197; Protocol of Final Approval No. 47470/2019).

This manuscript was prepared according to the STROBE guidelines.

2.2 - Study Population

In a 2- year period (January 2018- December 2019), 41 patients (10 males, 31 females) aged between 20 and 81 years (mean: 53.98 years, SD 14.32), presenting with 53 severely atrophic edentulous sites in the upper and lower jaw, and requesting implant-supported prosthetic restorations, were enrolled in this study. Details of type of defects and distribution in the jaws are reported in table 1. Further information of anagraphic data and main clinical features (dates of GBR procedure, implant placement, loading, etc) are reported in the supplementary table 1.

Initial patient screening included: a) evaluation of the residual dentition and periodontal status (Plaque Index – PI; Probing Depth – PD; and Bleeding On Probing BOP); b) intra-oral photographs; c) panoramic and peri-apical radiographs; d) preoperative impressions, study models, and manufacturing of a diagnostic wax-up to optimize the final prosthetic restoration.

Inclusion criteria included: a) systemically healthy patients; b) a minimum age of 18 years; c) relevant or severe bone atrophy at the edentulous sites incompatible with placement of even short (≤6 mm) or narrow (<3 mm) implants in an appropriate and prosthetically guided position; d) adequate compliance of patients, both in terms of oral hygiene and respect the follow-up recalls; and e) ability to understand the proposed surgical treatment and to understand and sign the informed consent.

Exclusion criteria included: a) severe kidney and/or liver disease; b) congenital or acquired immunodeficiency; c) ongoing antiblastic chemotherapy at the time of first examination; d) sequelae of radiotherapy in the head and neck area; e) oral mucosa disease, such as lichen planus; f) full mouth plaque score (FMPS) and full mouth bleeding score (FMBS) > 20%; g) non-compliant patients; h) tobacco (>10 cigarettes per day) or alcohol abuse; i) non compensated diabetes; j) active periodontal disease at the time of first examination (in these cases, patients underwent etiologic therapy and motivation in personal oral hygiene and were re-evaluated for surgical treatment); k) bisphosphonate chemotherapy in progress; and, l) pregnant women.

2.3 - Clinical Protocol

2.3.1 Pre-operative planning

In every patient, dental impressions were taken and study casts constructed: on these latter, a diagnostic wax-up with ideal position and dimension of the teeth to be prosthetically substituted was performed and a diagnostic template including radiopaque teeth was created.

All patients received a CBCT wearing the radiological templates, and the DICOM files obtained were sent to the Ti-mesh manufacturer (Yxoss CBR® by Reoss, Filderstadt, Germany). These digital files were used to create a three-dimensional model reproducing both the edentulous and the neighbouring dentate areas. These CBCTs were considered the reference point (time 0=T0) to which the following ones were compared to calculate bone volume changes over time.

A digital model of the Ti-mesh was provided by the manufacturer for final approval. Any modification of the mesh shape, if needed, was communicated by the surgeons to obtain the appropriate morphology.

After final approval, it was possible to produce with CAD/CAM technology a precise three-dimensional class IV titanium scaffold by means of laser sintering (Yxoss CBR® by Reoss, Filderstadt, Germany).

2.3.2 – Preoperative ancillary procedures

Two out of 41 patients presented previously failed attempts of implant placement in association with GBR procedures which were followed by implant removal because of infection, lack of osseointegration, or malposition. Healing was followed by bone defects and an insufficient quality of the residual soft tissues. It was therefore decided to create a more favourable environment by means of autogenous connective tissue grafts taken from the palate.

2.3.3 - Pre-operative Patients Preparation

All patients were prepared to both the regeneration procedure (T1) and the second stage implant surgery (T2) according to the following protocol: a) professional oral hygiene (1-2 weeks prior to T1-T2); b) local antisepsis with 0.2% chlorhexidine mouthwashes starting 3 days before T1-T2; c) antibiotic prophylaxis consisting of oral administration of amoxicillin and clavulanate (2 g), 1 hour before T1-T2; and d) an antioedema medication (Bromelina Plus® Solgar Italia Multinutrient SpA – Padova - Italy) to be assumed 3 days before T1-T2 (3 tabs per day). In case of intravenous sedation or general anaesthesia, antibiotics were infused at the time of induction. In case of allergy or intolerance, amoxicillin was substituted with macrolids or cephalosporins.

2.3.4 - Reconstructive Procedure

All patients were treated by the same surgical and prosthetic team (MC e PC). The regeneration procedure was performed in sterile conditions under local anaesthesia, intravenous sedation, or general anaesthesia, according to patient's compliance and defect extent**.**

A mid-crestal incision with mesial and distal releasing incisions at least 1.5 cm from the area to be reconstructed and the elevation of a full-thickness flap was performed to expose the edentulous area. Any residual soft tissues over the site to be regenerated were accurately removed to avoid interposition of connective tissue between the recipient site and the grafting material.

As a relevant augmentation was expected, periosteal releasing incisions on the buccal and lingual sides were performed in the mandible and only on the buccal side in the maxilla.

Bone harvesting was performed with disposable bone scrapers (SafeScraper Twist®-C.G.M. SPA Divisione Medicale Meta, Reggio Emilia, Italia) from the mandibular body and ramus in the majority of patients. In the case of atrophy in the posterior mandible, one single incision allowed access to both the harvesting and recipient sites. In the other cases, two independent incisions were performed. The amount of bone particles needed was calculated taking into account that approximately 50% of the grafting material was represented by BBM. It is worth noting that the Ti-mesh manufacturers were able to calculate pre-operatively in cubic centimetres the volume of grafting material.

In 9 patients, presenting with extended severe atrophy, autogenous bone was collected with the same scraper from the parietal bone of the calvarium through a short full-thickness, parasagittal incision.

The Ti-mesh was checked to control adequacy of shape and fitting to the atrophic site, filled with the grafting material, and placed over the defect area.

Stabilization of the mesh was obtained with dedicated titanium micro-screws, 1.4 mm in diameter and 5 to 13 mm long, according to surgical needs.

A collagen membrane (Bio-Gide®- Geistlich Biomaterials AG- Wolhusen – Switzerland) was applied over the mesh to reduce the risk of soft tissue ingrowth through the mesh during the early phases of healing.

Patients presenting with bone atrophy of the posterior maxilla requiring sinus grafting in addition to bone augmentation, received a sinus lift with BBM via a lateral approach.

The surgical procedure was concluded with a water-tight and tension-free closure with polyglactin resorbable 5/0 sutures, alternating horizontal mattress and single sutures.

The following post-surgical instructions were prescribed: a) application of ice packs for 6–8 hours after surgery; b) oral antibiotics (amoxicillin and clavulanate - 3 g per day for 6 days) or macrolids /

cephalosporins in case of allergy; c) nonsteroidal anti-inflammatory (NSAIDs) or paracetamol for 3–5 days after surgery; d) an antioedema medication (Bromelina Plus® Solgar Italia Multinutrient SpA – Padova - Italy) - 3 tabs per day for 5 days; e) cold and liquid diet for the first 2 days after surgery and a soft diet until suture removal; f) 0.2% chlorhexidine mouthrinses, twice per day for 21 days, combined with normal oral hygiene manoeuvres on the remaining dentition (if present). When a concomitant maxillary sinus floor elevation was performed, patients were instructed to avoid any pressure peak in the upper respiratory tract for at least 15 days not to potentially damage the Schneiderian membrane (i.e. sneezing with their mouth closed, blow their nose, flying in the post-operative day, etc). Patients were not allowed to wear removable prostheses that could traumatize the reconstructed area for at least 6 weeks. Vacuform retainers including resin teeth, Maryland bridges, or conventional bridges, were fabricated to provide a purely cosmetic restoration and to avoid any compression on the operated area.

A CBCT was done in all patients immediately after T1, to control the outcome of the surgery and to obtain a reference point for the following measurements. A dedicated software (Plamneca Romexis Viewer® Planmeca OY – Helsinki - Finland) was used to measure bone volume changes. Sutures were removed 2-3 weeks after surgery.

2.3.5 – Ti-Mesh removal and implant placement

After a mean waiting time of 7.3 months (median: 7.3; range: 5-12 months; SD: 1.45), patients were re-evaluated with a new CBCT (T2) performed with the aid of the same radiological templates to check bone volumes of the regenerated tissues and to plan implant placement according to the prosthetically guided project. An average waiting period of 7 months was judged a congruous time for obtaining a good integration of the graft, also on the basis of available literature on this type of technique (Sumida, et al., 2015; Sagheb, et al., 2017; Seiler, et al., 2018) and the available literature on horizontal/vertical GBR with non-resorbable barriers (Chiapasco et al., 2009; Milinkovic & Cordaro, 2014; Urban et al., 2019). Longer waiting times were determined only because a very limited number of patients did not respect the recall schedule for personal reasons. Variations in waiting times were not related to site (maxilla/mandible) or type (horizontal/vertical) of the defect.

Removal of the meshes and implant placement was performed under local anaesthesia, sedation, or general anaesthesia according to patients' compliance and extent of surgery. Access was obtained following the previous incisions. Ti-meshes and fixation screws were exposed and removed, surgical templates applied and implant site preparation started.

A total of 106 pure titanium or titanium zirconium alloys, root-form, and bone level implants were placed in the regenerated areas and they were left to heal in a submerged fashion. Post-operative instructions and medications were the same ones used after T1.

In 12 randomly chosen sites, one implant site was prepared with a 2.5 mm trephine drill to obtain a bone biopsy for histomorphometric analysis of the regenerated tissue. Histomorphometric results will be published in detail in another, dedicated, paper, while in the results section of this paper only a short summary will be reported. Briefly, the bone biopsies were fixed in a 10% buffered formalin for a maximum of 5 days. The specimens were dehydrated in an increasing ratio alcohol-water solution (from 70% to 100%). Once the dehydration was completed, samples were included in pure methylmethacrylate resin (Technovit 7200 VLC, Exact Kultzer, Bio-Optica, Milano, Italy) by light polymerization.

The polymerized resin blocks were abraded until reaching a thickness of about 100μm, and then stained with Toluidine Blue and Pyronin Yellow to differentiate the bone tissue components. A qualitative analysis was performed following the indications of ISO-10993-6:2007 annex E to evaluate cell type response. The tissue composition of the regenerated area was assessed by means of stereological principles.

2.3.6 – Implant re-opening and prosthetic phases

After a mean waiting time of 3.5 months (range 2-5 months; median: 3.45; SD: 0.89), implants were uncovered and healing abutments placed (T3). At this time, the quality and quantity of peri-implant soft tissues were evaluated.

Following the regeneration procedure, relevant releasing incisions were needed with modification of the position of the residual band of the keratinized mucosa and reduction of the buccal sulcus. If these latter were judged inadequate to guarantee a sufficient seal around implant abutments, a vestibuloplasty in association with a free gingival graft harvested from the palate was performed.

In patients presenting with adequate keratinized mucosa, but with insufficient thickness of peri-implant soft tissues, residual concavities were corrected with autogenous connective tissue taken from the palate or with porcine-derived collagen matrices (FibroGide® - Geisltlich Biomaterials AG- Wolhusen – Switzerland).

After a mean waiting time of 1.8 months (range: 1-3.45; median:1.78; SD:0.71) patients started the prosthetic phases. Provisional restorations were delivered first (T4), and after adequate conditioning of peri-implant soft tissues, the final prostheses (screw-retained or cemented) were delivered.

2.4- Follow-up

After the start of prosthetic loading, patients were recalled 3, 6, 12 months later, and annually thereafter, to assess peri-implant hard and soft tissue conditions, the stability of the reconstructed bone, and the onset of implant-related complications. The recall frequency for patients' maintenance and clinical evaluation was established through a continuous multilevel assessment of the patients risk profile for periodontal and peri-implant disease (Lang, & Tonetti, 2003).

Peri-apical radiographs were taken immediately after implant placement (T2), at the time of implant loading with prosthetic restoration (T4), six (T5) and 12 (T6) months after the start of prosthetic loading, and annually thereafter. A flowchart describing the timing of planning and treatment is shown in figure 1.

2.5 – Analysis

The following parameters were analysed after the regeneration procedures.

2.5.1 – Bone gain

Vertical and horizontal bone gain were evaluated on a CBCT (Planmeca ProMax 3D Max® - Planmeca OY – Helsinki - Finland) taken immediately after surgery with a dedicated software (Planmeca Romexis Viewer® Planmeca OY – Helsinki - Finland) using as reference points the internal margins of the Ti-mesh and the profile of the residual bone before the reconstruction. More in detail, it was possible to identify the different radiolucency between residual bone and the regenerated one on CT scans. Only the maximum value (expressed in mm) of horizontal and vertical augmentation was calculated. In order to repeat measurements in the same points at T1 and T2, the final, computer guided position of "virtual" implants obtained by the dedicated software according to the indication of the diagnostic template, was used as a reference point. In such a way, 2 independent examiners (GT and MDF) were able to measure vertical and horizontal bone gains (in mm) in repeatable and comparable points. Intra-examiner calibration was performed on the first ten consecutive patients using the kappa intra-class correlation coefficient. The arithmetic mean of the two examiners measurements was done.

Six months later, at the time of implant planning, a new CBCT, as well as the same measurement following the previously described modalities, was performed.

Any difference between the two CBCTs as regards height and width of bone gains was recorded for comparison.

As regards bone volume modifications, the residual basal and alveolar bone of the atrophic edentulous areas were not measured, but considered as baseline (T0). Only the volumes of the regenerated areas were measured at T1 and T2 in cubic centimetres.

As regards bone volume gains, CBCTs were segmented at T0, T1 and T2 with a dedicated software (3d Slicer 4.1 - Free Open Source Software https://www.slicer.org). After segmentation, 3D models were obtained, exported as stl files and imported on Blender (free and open source software - https://www.blender.org). Thanks to the plug-in Object Alignment (Author Plug-In: Patrick Moore, DDS), a superimposition of the 3d models at T0,T1 and T2 was performed. Then, a Boolean difference between volume at T0 and T1, and from T0 and T2 was performed to obtain only the bone volume increase at T1 and T2. The two different volumes obtained through this Boolean subtraction (T0-T1 and T0-T2) were imported again on 3d Slicer (3d Slicer 4.1 - Free Open Source Software https://www.slicer.org) and measured in cubic centimeters.

2.5.2 - Complication rate of the reconstructive procedure

During the time following bone grafting and prior to implant placement, short-term complications regarding the donor and/or grafting sites were recorded in the patients' chart.

2.5.3 - Implant survival rate and implant-related complications

Criteria used to determine implant survival were absence of: (a) persistent pain or dysesthesia; (b) mobility; (c) continuous peri-implant radiolucency.

Failed implants were considered those presenting: (a) continuous peri-implant radiolucency; (b) implant mobility or fracture; (c) symptoms of persistent paresthesia/dysesthesia or chronic pain; (d) presence of peri-implant infection not responding to medical/surgical treatment.

Cases of peri-implant mucositis and peri-implantitis in which disease resolution was achieved by non-surgical and/or surgical means were considered as implant-related complications.

2.5.4 - Peri-implant bone resorption

Marginal peri-implant bone loss was evaluated on periapical radiographs using a dedicated image processing software (ImageJ® 1.38v U. S. National Institutes of Health, Bethesda, MD, USA). The analysis was performed on digital radiographs by measuring the distance between the implant shoulder and the first bone-to-implant contact, at the mesial and distal aspect of each implant. Dimensional distortion was corrected by setting the known length and diameter of each implant. Radiographs taken immediately

after implant placement were considered as the baseline. All measurements were rounded to the nearest half millimetre. A mean bone resorption value was then calculated for each implant and for each patient. All measurements were evaluated by the same examiners and with the same modalities used for bone gain measurements.

2.6 - Statistical analysis

Sample size was calculated using the free tool at https://clincalc.com/stats/samplesize.aspx, considering as outcome variable the vertical bone gain. A previous study was taken as comparison (Troeltzsch et al. 2016). For augmentation procedures with a mixture of autogenous bone with allogeneic/xenogeneic grafting materials, that study provided a mean vertical gain of 3.7±1.4 mm. It was assumed to achieve a mean value of 4.4mm in the present study (about 15% better than the literature control). Considering a power of 80% and an alpha =0.05, 31 patients would be required to observe a difference of 0.7mm. Assuming a dropout rate of 15%, it was established to enroll at least 36 patients.

Statistical evaluation was performed using GraphPad Prism 5.03 (GraphPad Software, Inc., La Jolla, CA, USA), and IBM SPSS Statistics software (Version 24, SPSS Inc., Chicago, IL, USA).

Descriptive statistics of data were done using means, medians, ranges, and standard deviation (SD) for quantitative variables normally distributed. Normality of distribution was evaluated through the d'Agostino and Pearson omnibus test. Occurrence of complications were expressed in percentages and analysed by means of Kaplan–Meier curve. Implants and cases (reconstructed sites), respectively, were considered the statistical unit of analysis. Fisher's exact test was used to evaluate the effect of patients' gender, age (> or <60y at the time of surgery), area of edentulism, number of sites involved per patient, co-interventions (e.g. maxillary sinus augmentation), harvesting site, on the occurrence of complications. Either the patient or the reconstructed sites (cases) were considered as the unit of analysis. Fisher's exact test was used because the incidence of complications was less than five in at least one subgroup. Descriptive statistical methods were used for vertical and horizontal bone changes at the reconstructed site, and peri-implant marginal bone level (MBL) changes at mesial and distal aspect after 6 months of loading.

Means ± SD, median, minimum and maximum values were calculated utilizing the patient as the statistical unit of analysis. The effect of mesh exposure on bone changes was evaluated by comparing exposed versus non-exposed groups of patients, by means of unpaired Student's t-test. Significance threshold was set at $p = 0.05$.

A multilevel mixed-effects linear regression model was used to evaluate the relationship between exposure, vertical bone loss, horizontal bone loss and the following variables, using the patient as the unit: age, number of sites per patient, number of implants per patient, sinus lift. For vertical and horizontal bone loss, also the occurrence of exposure was considered. The estimates of coefficients' standard errors and confidence intervals were adjusted using a robust variance-covariance estimator. The same model was used to evaluate the relationship between bone volume loss and the following variables, using the case as the unit: n. of implants per case, exposure, sinus lift. The analyses were performed using Stata 16.1 (StataCorp LLC, 4905 Lakeway Drive College Station, TX 77845, USA).

3.RESULTS

3.1 – Bone gain

Changes in vertical and horizontal dimensions at T1 and T2, were measured both in percentage and mm: the Kappa intra-class correlation coefficient calculated on repeated measurements collected from the first 10 patients was 0.85. Data are reported in table 2.

Volume changes between T1 and T2 measured in terms of variations of cubic centimetres and in percentage are reported in table 2. More details are available in supplementary table 2 and, as box plots, in figures 2 and supplementary figures 1-2-3-4.

On average, the comparison between initial bone gain and the one at the time of implant placement demonstrated very limited contraction of bone volumes.

It is worth noting that in 5 sites, an overgrowth of bone covered the mesh in some areas. The growth of bone through and even over the "open spaces" of the meshes may also explain the relative complexity in removing them at T2. In these patients, the areas of the meshes completely covered by new bone were left "in situ" as they never interfered with implant placement, as shown in the clinical case presented.

3.2 - Complication rate of the reconstructive procedures

In none of the patients the Ti-meshes had to be adapted as they fitted perfectly.

The number of treated sites was considered the unit of statistical analysis, as many patients presented with multiple atrophic sites at the same time. Out of 53 sites (33 in the maxilla and 20 in the mandible), 42 healed uneventfully, while 11 presented with a variable degree of Ti-mesh exposure which occurred 15 to 150 days after surgery.

Out of these, in 3 sites the exposure was very limited and no reduction of the initial bone gain was observed at T2.

In another 3 sites, exposure was followed by a minimal reduction of initial bone gain, but implant-supported restoration was completed according to the initial program.

Another 3 sites in 2 patients underwent partial bone loss, but it was still possible to deliver the planned prosthetic restorations, although supported by shorter implants.

In one site, the Ti-mesh had to be removed prior to the planned timing, but it was still possible to complete restoration because of limited bone loss.

Finally, one site, treated with GBR and sinus lift, underwent dehiscence and relevant infection 30 days after surgery, not responsive to local and systemic antibiotic therapy. It was decided to remove the Ti-mesh and all the infected graft. The patient healed by secondary intention with preservation of the sinus graft only and the more apical part of the residual ridge. This patient has been considered the only one failure of the procedure and prosthetic rehabilitation has not been started yet.

The follow-up after the reconstructive procedure (T1-November 2020) ranged from 13 to 34,20 months (mean and median=22.24 months; SD=6.56).

Overall, a successful outcome of the regeneration procedure was obtained in 42 out of 53 sites. Occurrence of distribution of dehiscences and number of cases without complications are reported in fig. 3 (Kaplan-Meier curve).

No statistically significant correlation was found between exposures and: a) gender; b) age; c) number of sites treated; d) mandibular or maxillary sites; e) GBR in association with sinus lift; and f) the harvesting site (ramus vs calvarium), as shown in table 3.

It is however worth noting that Ti-mesh exposures were more frequent in the maxilla, in particular when maxillary reconstruction was associated with sinus lift. On the contrary, no correlation was found between the extent of the defect in mesio-distal direction and the quantity of augmentation and the incidence of exposures.

Moreover, Ti-mesh exposures were positively correlated with bone resorption in the regenerated areas and the difference as compared to non-exposed sites was statistically significant ($p=2.66x10^{-6}$ and $2.94x10^{-4}$ for vertical and horizontal bone resorption respectively) as it is shown in table 4.

Finally, two patients, treated in two mandibular sites, reported a transient paraesthesia of the inferior alveolar nerve: all signs and symptoms disappeared spontaneously within 4 to 12 weeks.

The multilevel linear regression analysis showed a significant relationship between exposure and bone graft linear horizontal/vertical dimension loss, and volumetric loss. Sinus lift also had a significant effect on vertical bone loss (for details see supplementary tables 3-4-5-6).

Table 6 compares bone loss in sites with/without exposure and with/without sinus lift. Data are expressed as mean values and standard deviation.

3.3 – Histomorphometric analysis

As specified in the materials and methods section, only a brief summary of histomorphometric results is here presented, while an extensive analysis of results will be discussed in another publication. In all sites, no signs of necrosis, fibrosis, and ectopic infiltration of fatty cells were observed. Histomorphometric analysis of the regenerated bone in patients with uneventful healing revealed that a 77% of the tissue was completely calcified or in phase of mineralization or occupied by biomaterial particles divided in the following proportion: 35.88%±13.53% of new lamellar bone, 16.42%±6.41% of woven bone, 10.88%±6.41% of osteoid matrix and 14.10%±7.54% of grafted remnants. The 22.72%±9.72% of the regenerated area was occupied by medullary spaces.

In sites where soft tissue dehiscence occurred, morphological features of the newly formed bone were resembling sites healed in a physiological way. At morphometric analysis, tissue was composed on average by 32.67% of lamellar bone, 11.80% of woven bone, 10.46% of osteoid matrix, 16.64% of biomaterial and 28.42% of medullary spaces. The mean percentage of the regenerated area occupied by vessels was 3.64%.

3.4 - Implant survival and implant related complications

Out of 106 implants placed in the regenerated areas in 40 patients, one was removed in a patient who received 7 implants because of loss of integration before loading. Out of the remaining 105 implants, 90 in 36 patients were loaded with fixed prosthetic restorations. Fifteen implants in 4 patients are still waiting prosthetic restoration, as inserted more recently. One patient (2 mandibular sites and 4 implants) interrupted clinical and radiographic controls after having received the final restoration. Therefore, at the end of the observation period (November 2020), 105 implants before loading, and 86 implants in 35 patients after prosthetic restoration were available for statistical analysis. The mean follow-up after implant placement and after delivery of prosthetic restorations were 14.99 months (range: 6.6 - 29; median= 14.99; SD=6.29), and 10.6 months (median= 10.6 months; range: 2-26.02; SD=6.49), respectively. No implants developed biological complications such as peri-implantitis.

The survival rate of loaded implants at the end of the observation period was 100%. No prosthetic complications were reported during the observation period.

3.5 - Peri-implant bone resorption

Peri-implant bone loss per patient before and after the start of prosthetic loading was very limited and never >1.5 mm at the end of the observation period (see Table 5). The Kappa intra-class correlation coefficient calculated on repeated measurements collected from the first 10 patients was 0.87.

A representative case is reported in supplementary figures 5a-d.

4.DISCUSSION

Non customized titanium meshes in association with particulated bone have been successfully used for many decades for the regeneration of bone defects involving edentulous jaws (Gongloff, et al., 1986; Roccuzzo, et al., 2007; Myamoto, et al., 2012; Briguglio, et al., 2019).

Myamoto et al. (2012), in 27 combined vertical and horizontal defects, reported a mean horizontal and vertical gain of 3.7mm (SD: 2) and 5.4 mm (SD:3.4), respectively. As regards the complication rate, the incidence of mesh exposures was 40.7% and in 33% of these cases they were associated with partial or total graft loss.

A systematic review by Briguglio et al. (2019), reported mesh exposures ranging from 0 to 80% (mean 34.8%), and necessity of early Ti-mesh removal of 22.8%. Similar results were reported by other Authors (Roccuzzo et al 2007).

The analysis of this data seems to indicate that the main problem of this procedure is represented by mesh exposures at different times after surgery with a variable degree of bone resorption. Moreover, trimming, modelling, adaptation to the defect morphology, and stabilization of these meshes can be technically demanding.

Customized Ti-meshes have been recently introduced as an alternative to the traditional Ti-meshes (Sumida, et al., 2015; Sagheb, et al., 2017; Seiler, et al., 2018) with these potential advantages: a) no need of modelling and trimming “in situ”; b) possibility of filling the Ti-mesh with grafting material outside of the oral cavity, with elimination of the risk of graft dispersion/contamination intra-orally; c) easy stabilization with a reduced number of screws, thanks to the rigidity of the mesh.

Sagheb et al. (2015), in a retrospective study involving 17 patients and 21 atrophic sites, reported 100% success of the regeneration procedures, despite a relevant incidence of Ti-mesh exposures (33% of the sites between 5 to 12 weeks after surgery).

Sumida et al. (2017), in a comparative study between conventional (13 sites) and customized Ti-meshes (13 sites), reported more favourable results with customized Ti-meshes as regards: a) operation times (75.4 vs 111.9 minutes); b) number of exposures (7.7% vs 23.1%); and, c) infection rate (7.7% vs 23.1%).
Seiler et al. (2018), in a retrospective study on 100 patients and 115 defects treated with customized Ti-meshes in association with autogenous bone particles and DBBM, despite a 22.6% of exposures, reported no loss of graft in 60% of the defects and in 21.7% of them even an overgrowth of new bone on the non-exposed areas of the meshes.
Despite the relevant percentage of mesh exposures (range: 22.6 to 33%), it has been shown by the previously cited articles that bone regeneration can be anyhow obtained thanks to the low rate of infection and the spontaneous and early re-epithelization below the exposed mesh. This phenomenon may create a natural barrier protecting the graft and thus make it possible an efficient bone regeneration.

Results from the present study seem to confirm data reported by the previously mentioned publications. Customized Ti-meshes made it possible to obtain relevant bone augmentations, up to 11.48 mm (mean 6.35) and 8.90 mm (mean 4.78) in width and height, respectively. Moreover, it is worth noting that none of the meshes had to be modified in shape and dimensions at the time of surgery, thanks to their precision and easy adaptability to the defect areas. Another advantage, as compared to other types of barriers (non-customized meshes or membranes), was the very limited number of screws necessary for stabilization. Up to 4-5 teeth edentulous areas, only 2 screws were used in the majority of cases, while for fully edentulous arches the maximum number of screws was 4. Even if operating times were not one of the outcomes, the precision and easy adaptability of customized meshes and the reduced number of fixation screws simplified surgery. An uneventful healing was observed in 42 out of 53 sites.
Results from this study seems also to confirm that the rate of exposures (11 out 53 sites – 20.75%) is still a relevant drawback of this technique. However, it is worth noting that, despite exposures, 6 of them were associated with no significant reduction of initial bone gain at T2 and implant-supported restoration was completed according to the initial program (42+6 sites=48; 90.57%). Four sites underwent partial bone loss, but it was still possible to deliver the planned prosthetic restorations, although supported by shorter implants (7.55%). Only one site (1.89%) underwent infection, early mesh removal and relevant bone loss, rendering implant placement impossible.
In all these cases, a spontaneous and fast re-epithelization beneath the inner part of the mesh was observed. This phenomenon may explain the limited reduction of initial bone gain, as reported by other authors (Sagheb, et al., 2015; Sumida, et al. 2017; Sailer, et al. 2018). Moreover, the quality of the residual

graft was very good, as demonstrated by both the briefly described histomorphometric results and the possibility to prosthetically restored these patients.

Results from this study are consistent with those reported by Authors (Sagheb, et al., 2015; Sumida, et al. 2017; Sailer, et al. 2018) using customized Ti-meshes.

Another interesting aspect is that exposures were never associated (besides the only one case in which the mesh was early removed) to local infection/suppuration below the mesh: this may have contributed to the maintenance of the graft (see table 4).

However, it has been shown that both vertical and horizontal bone volume changes were higher in the exposed sites, and the difference was statistically significant (see table 4).

Since the exposures occurred even months after surgery, and in the majority of cases not at the level of the incisions lines, one may presume that these exposures were not related to an insufficient flap release or suturing technique, but rather to the mechanical trauma caused by the rigid structure of the mesh on the overlying mucosa.

In accordance with other Authors (Sagheb, et al., 2017; Seiler, et al., 2018), results from this study showed that a higher incidence of exposures occurred in the maxilla. As the palatal mucosa cannot be released, 100% of the releasing procedure was performed on the buccal flap with consequent “thinning” and potential reduction of vascularization of the flap. On the contrary, releasing incisions in the mandible can be equally distributed on both the buccal and lingual sides. This makes it possible to maintain thicker flaps, less exposed to mechanical trauma. Finally, one may speculate if the gingival phenotype (thin or thick) may influence the percentage of exposures. However, this data is lacking at present.

It is also interesting to compare the incidence of complications following GBR with customized ti-meshes with the one following GBR with non-resorbable membranes and autogenous bone blocks for the correction of three-dimensional defects. In two systematic reviews by Milinkovic & Cordaro, 2014 and Urban et al., 2019, the complication rates of GBR were 13.1%, and 12.1%, respectively. Therefore, results from this study are consistent with those reported in the cited reviews.

As regards the reconstruction with autogenous bone blocks, the complication rate from the same systematic reviews (Milinkovic & Cordaro, 2014; Urban et al., 2019) was 8.1% and 23.9%, respectively. Again, it appears that the complication rate of regeneration with customized Ti-meshes is consistent with that reported in the previously cited publications.

As regards bone gains, results from this study demonstrated a vertical increase up to 8.9mm (mean:4.78; median:5.12; SD: 1.88) can be obtained. In the systematic review by Urban et al., the mean bone gain was 4.31 mm and 4.99 mm for expanded and dense PTFE membranes, respectively.

As regards bone gain obtained with autogenous bone blocks, the mean value reported by Urban et al. 2019, was ~ 3.5 mm, thus demonstrating the non-superiority of these procedures as compared to GBR with customized titanium meshes.

It is however worth noting that also in case of uneventful healing, the elevation of flaps to expose the underlying meshes was more complex and more time consuming as compared to cases treated with autogenous bone blocks or GBR procedures with non-resorbable membranes such as the PTFE ones.

Despite the limited number of loaded implants and the short follow-up, the survival rate of loaded implants (100%) and the limited mean mesial and distal peri-implant bone resorption (0.57 and 0.59 mm 1 year after loading, respectively) seem to confirm the reliability of this GBR technique (Sumida, et al., 2015; Sagheb, et al., 2017; Seiler, et al., 2018). Results were also consistent with those related to other GBR procedures with resorbable and non-resorbable membranes (Hämmerle, et al., 2002; Chiapasco, et al., 2009; Esposito, et al., 2009; Milinkovic & Cordaro, et al., 2014; Cucchi, et al., 2017; Urban, et al., 2019), and with those related to implants placed in native bone (Moraschini et al., 2015).

5. CONCLUSION

Preliminary results of this study, despite the limited number of patients, implants, short follow-up, and the non-negligible incidence of Ti-mesh exposures, seem to demonstrate that CAD-CAM customized Ti-meshes may represent a reliable GBR option for the correction of severely atrophic edentulous ridges in terms of vertical bone gain, limited peri-implant bone resorption and survival rate of implants. It is however worth noting that if on one hand it is possible to simplify the reconstructive procedure thanks to the customization of Ti-meshes, on the other hand surgeons have to face the non-negligible incidence of Ti-mesh exposures and the higher complexity of their removal at the time of implant placement. Therefore, studies involving a higher sample of patients and with longer follow-ups are necessary.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of the article.

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Table 1. Distribution and type of edentulism in the upper and lower jaws

	No. missing teeth: 1	No. missing teeth: 2	No. missing teeth: 3-5	No. missing teeth: >5	No. missing teeth: edentulous arch
Maxilla 1 site	3+ 1 §	5+1 §	7 + 1# + 1¶	3	1
Maxilla 2 sites	3	0	1+1*	0	0
Mandible 1 site	1 #	3+ 1¶	8	1	0
Mandible 2 sites	0	0	2 + 1*	0	0

Legenda:

* one patient presented at the same time 4 sites (2 mandibular and 2 maxillary) with more than 3 teeth missing per site

one patient presented at the same time 2 sites (1 mandibular and 1 maxillary) with 1 and 3 teeth missing, respectively

¶ one patient presented at the same time 2 sites (1 mandibular and 1 maxillary) with 2 and 3 teeth missing, respectively

§ one patient presented at the same time 2 maxillary sites with 1 and 2 teeth missing, respectively

Table 2. Changes in bone height and width of the regenerated areas at T1 and T2; volume changes at T1 and T2 .

	N. pat	mean	SD	median	min	max
Vertical bone gain (T1), mm	41	4.78	1.88	5.12	1.00	8.90
Horizontal bone gain (T1), mm	41	6.35	2.10	6.24	2.14	11.48
Vertical bone resorption (T2), mm	40	-0.39	0.64	-0.27	+0.80	-3.10
Vertical bone resorption (T2), %	40	-8.09%	12.27%	-5.00	+12.54%	-48.66%
Horizontal bone resorption (T2), mm	40	-0.49	0.83	-0.30	+0.40	-3.70
Horizontal bone resorption (T2), %	40	-6.17%	11.11%	-4.40	+14.76%	-42.05%
Volume at T1 (cc)	41	1.49	1.36	1.15	0.20	6.86
Volume at T2 (cc)	40	1.37	1.27	1.12	0.20	6.80
Volume changes between T1-T2 (%)	40	- 6.34%	10.14	-2.86	-41.67	+ 5.00

Legenda:

T1= values of bone gains at the end of reconstructive procedure

T2 = values of bone gains at the time of mesh removal and implant placement

Table 3. Effect of different variables on the occurrence of mesh exposure (Fisher's exact test).

Variable (unit)	Feature	No exposure	Exposure	P-value
Gender (patient)	Male	7	3	0.28
	Female	24	7	
Age at reconstructive surgery (patient)	<60y	18	6	0.29
	>60y	13	4	
Number of sites treated (patient)	1	23	8	0.32
	>1	8	2	
Site location (case)	Mandible	19	2	0.08
	Maxilla	23	9	
Site location (case)	Anterior (13-23, 33-43)	13	3	0.28
	Posterior	29	8	
Sinus lift (maxillary case)	Yes	7	6	0.10
	No	16	3	
Harvesting site (patient)	Ramus	25	7	0.25
	Calvarium	6	3	

Table 4. Effects of mesh exposure on bone parameters change.

Parameter		N. pat	Mean(SD)	median	min	max	P-value*
Vertical bone resorption, mm	Exp	9	-1.10(0.79)	-0.84	-0.2	-3.10	$2.7x10^{-6}$
	Non-exp	31	-0.19(0.26)	-0.23	0.40	-0.80	
Horizontal bone resorption, mm	Exp	9	-1.27(1.18)	-0.85	0.03	-3.70	$2.9x10^{-4}$
	Non-exp	31	-0.25(0.49)	-0.23	0.40	-2.04	
MBL at 6m post-load, mm	Exp	7	0.25(0.32)	0.00	0.00	0.75	0.185
	Non-exp	17	0.42(0.26)	0.44	0.00	1.00	
MBL at 1y post-load, mm	Exp	4	0.56 (0.43)	0.63	0.00	1.00	0.915
	Non-exp	9	0.59 (0.42)	0.50	0.00	1.25	

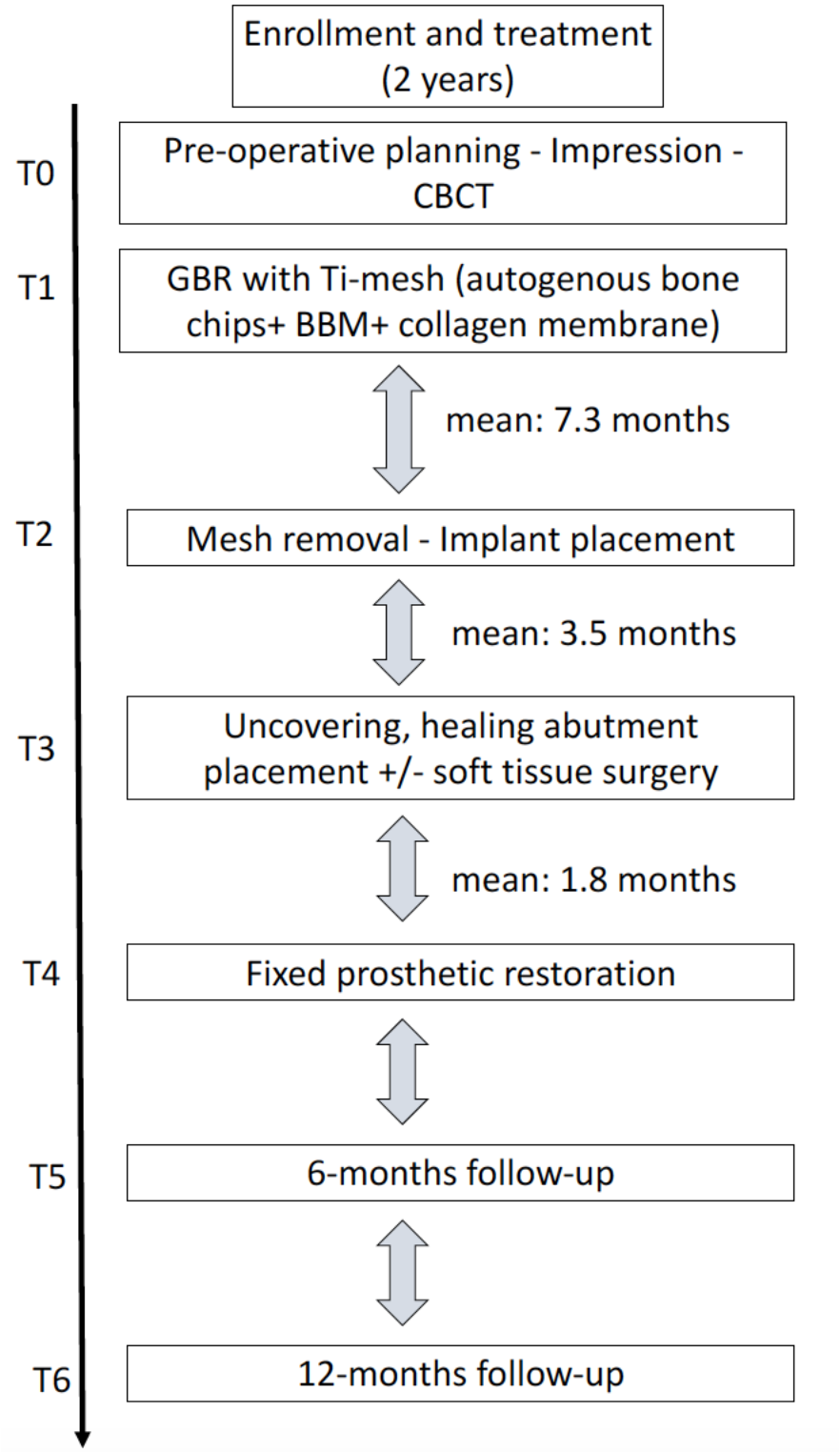
*unpaired Student's t-test; Pat= patients; Exp= exposed; Non-exp= non-exposed; SD=standard deviation

Table 5. Marginal Bone Loss (MBL) around implants placed in the regenerated areas

	N. pts	mean	SD	median	min	max
MBL (mesial) at 6m post-load (T5), mm	24	0.33	0.34	0.50	0.00	1.00
MBL (distal) at 6m post-load (T5), mm	24	0.37	0.41	0.50	0.00	1.50
MBL (mesial) at 1y post-load (T6), mm	13	0.54	0.34	0.50	0.00	1.00
MBL (distal) at 1y post-load (T6), mm	13	0.56	0.42	0.50	0.00	1.50

Table 6: bone loss in sites with/without exposure and with/without sinus lift. Data are expressed as mean values and standard deviation.

	exposure	No exposure	Sinus lift	No sinus lift (maxilla+mandible)	No sinus lift (only maxilla)
Vertical loss, mm	-1.10±0.84	-0.19±0.25	-0.89±0.91	-0.23±0.29	-0.27±0.25
n	10	31	11	30	16
P-value	<0.001		0.001		0.015
Horizontal loss, mm	-1.27±1.18	-0.24±0.49	-1.01±1.27	-0.30±0.52	-0.42±0.63
N	10	31	11	30	16
P-value	<0.001		0.014		0.12
Volume loss, mm3	-14.07±13.54	-3.61±5.30	-10.79±14.44	-4.23±5.54	-4.76±5.84
N	10	42	11	41	20
P-value	0.0002		0.02		0.11



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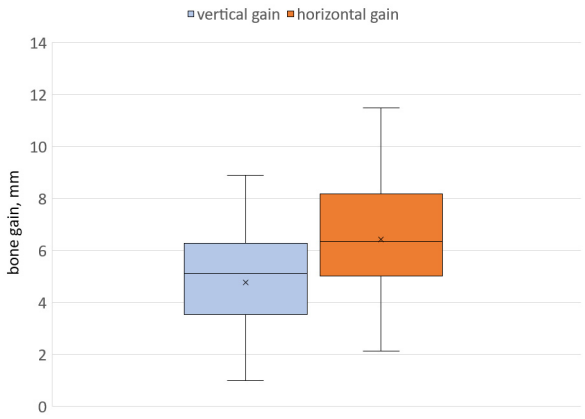

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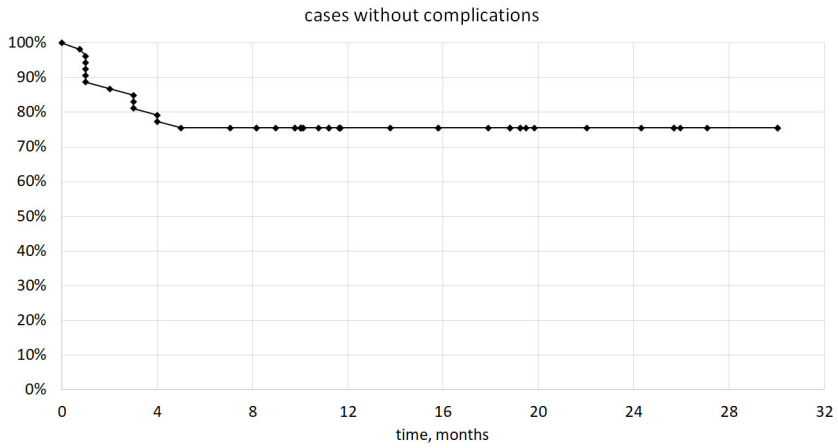

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