

Recently, the authors proposed a design for the lateral window based on rational considerations and observations.¹⁷ This design involves positioning the window as low and mesially as possible (Fig. 1), and it has been named the “low window sinus lift technique.” The lower osteotomy line is always placed flush with the sinus floor, and the mesial line is always flush with the sinus anterior wall. Additionally, the window never exceeds 6 mm in height, to avoid the intraosseous anastomosis. The distal osteotomy is positioned to correspond to the most distal planned implant.

The design and position of such an anastomosis requires the use of 3-dimensional (3D) digital software. This enables creation of a surgical template that helps the surgeon to perform the osteotomies accurately. In the low window design, the lower and mesial osteotomy lines play a fundamental role. As the lower osteotomy line is placed flush with the sinus floor, it follows that even when the A angle of the patient’s sinus is narrow (eg, $A < 30$ degrees, a condition with an increased risk of membrane tearing during detachment¹⁵), the surgical angle of approach, A_{LW} , will always be greater than 90 degrees (Fig. 2A), potentially reducing the risk of membrane perforation. Similarly, because the mesial line is positioned flush with the anterior sinus wall, it follows that on the coronal

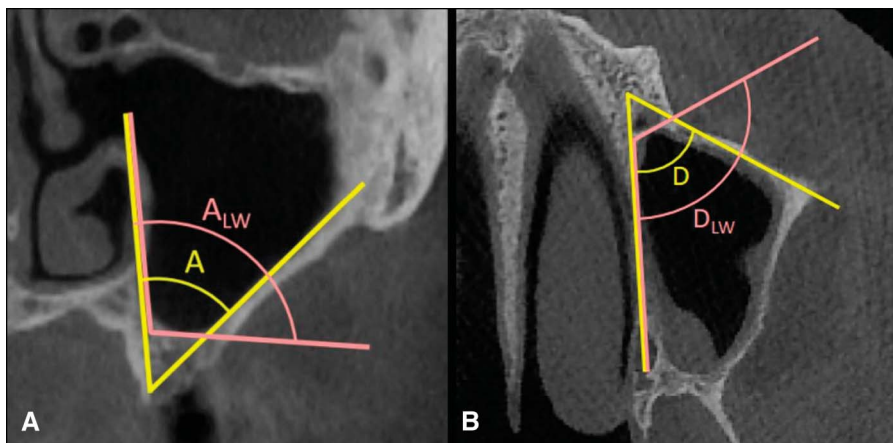


Fig. 2. (A) As in the low window anastomosis design, the lower osteotomy line is always placed flush with the sinus floor. The surgical angle when approaching the sinus membrane to detach it (A_{LW}) will always be independent from the anatomical angle. Even if the A angle were <30 degrees, the A_{LW} angle would still be >90 degrees. (B) Similarly, on the coronal plane, as the mesial osteotomy line is always placed flush with the anterior sinus wall, the surgical angle D_{LW} will always be greater than the D angle, again facilitating elevation of the sinus membrane.

plane, the surgical angle of approach D_{LW} (Fig. 2B) will always be greater than the D angle of the patient’s sinus

in the horizontal plane, even if that angle is narrow. Again, this reduces the risk of membrane perforation. Both

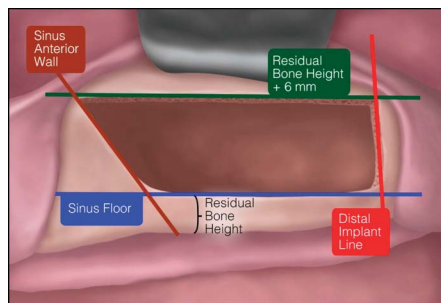


Fig. 1. The low window sinus lift anastomosis. The lower osteotomy line (blue) is positioned flush with the sinus floor. The upper one (green) is 6 mm higher, that is, it is placed at a distance from the ridge equal to the residual bone height plus 6 mm. The mesial line (brown) is flush with the sinus anterior wall. The distal one (red) should be placed to correspond to the position of the most distal implant.

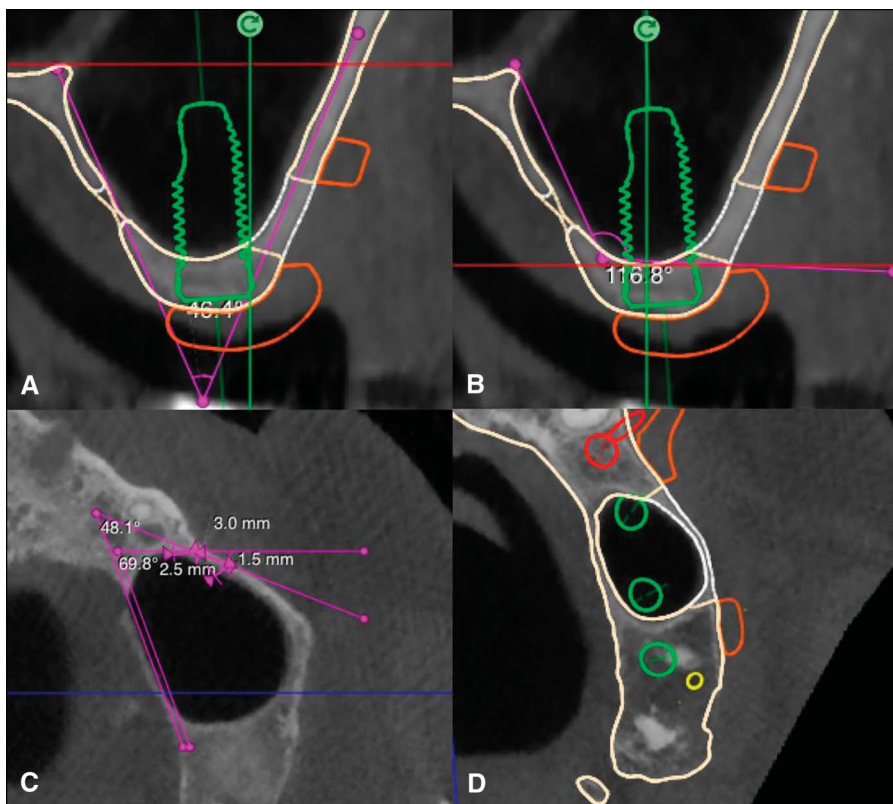


Fig. 3. When planning the position of the anastomosis for the low window design, the surgeon may easily measure the A angle (A) and the A_{LW} angle (B) (in the case shown 46.4 and 116.8 degrees, respectively). The A_{LW} angle is defined by the coronal anastomosis line, placed flush with the sinus floor. The surgeon also can easily measure both the D (C) and the D_{LW} angle (D) (in the case shown, 48.1 and 69.8 degrees, respectively). The D_{LW} angle is defined by the mesial osteotomy line, which is placed flush with the sinus anterior wall.

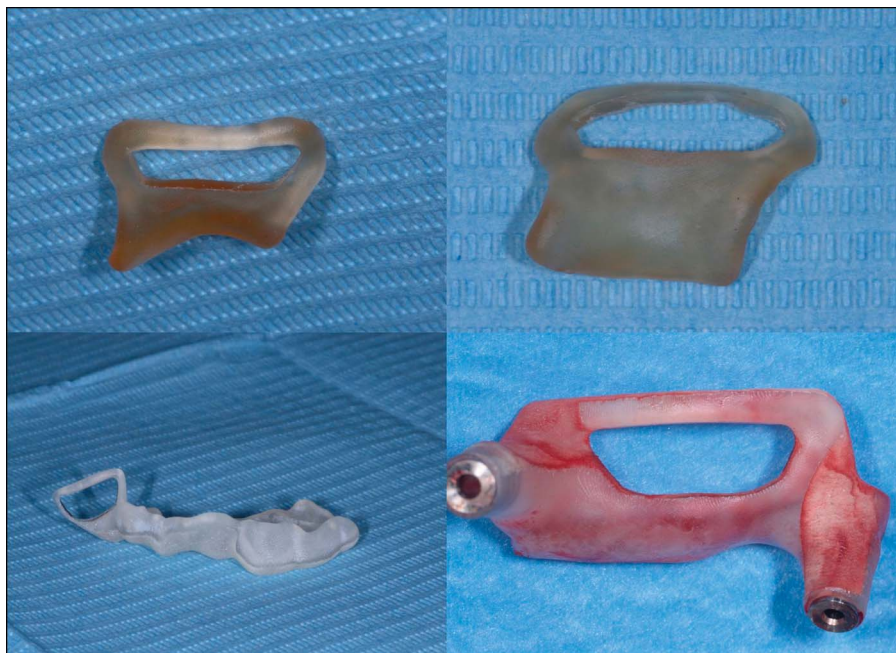


Fig. 4. The surgical guide is manufactured by 3D printing.

the A_{LW} and D_{LW} angles for any patient can be easily measured when planning the surgery and designing the template using any standard 3D digital software (Fig. 3, A–D). The surgical guide (Fig. 4) is then produced using 3D printing technology.

This approach allows preparation of the flap to be limited to a linear incision, preserving the attached gingiva of the most distal residual element present. Release incisions are not performed, potentially sparing the patient later discomfort. Additionally, the position of the mesial osteotomy

line, flush with the anterior sinus wall, allows for easier access to the sinus recess, that is, the zone where detaching the sinus membrane is usually more difficult, possibly minimizing again the risk of membrane tearing. At present, the benefits or pitfalls of this approach have never been systematically investigated; the only evidence concerning its application has been anecdotal. This article therefore aimed at retrospectively investigating the short-term safety and effectiveness of the low window technique for a group of patients.

MATERIALS AND METHODS

Clinical records were selected among those of patients with atrophic ridges who presented between January 2011 and December 2013 seeking implant-supported rehabilitation because of partial or total maxillary edentulism. Patients were included in the retrospective study if (a) they underwent sinus augmentation according to the low window sinus lift approach, (b) had 1- or 2-stage implant placement, (c) had sinuses augmented using equine-derived cortical-cancellous graft material, (d) had a cone beam computed tomography (CBCT) scan performed before surgery, and (e) had been followed after functional loading of the definitive prosthesis for a minimum of 24 months. The records also reported the patients' subjective evaluation of their postsurgical progress.

Other inclusion criteria were an age between 35 and 75 years and the lack of any systemic diseases. All patients were eligible for regenerative treatment, not presenting any of the following: pregnancy; osteoporosis, neoplasia, or psychiatric disease; acute oral infections; acute maxillary sinusitis; coagulation disorders; history of chemotherapy or radiotherapy in the head or neck region; immunocompromised status; current bisphosphonate therapy; chronic alcohol or drug abuse; or smoking more than 10 cigarettes per day.

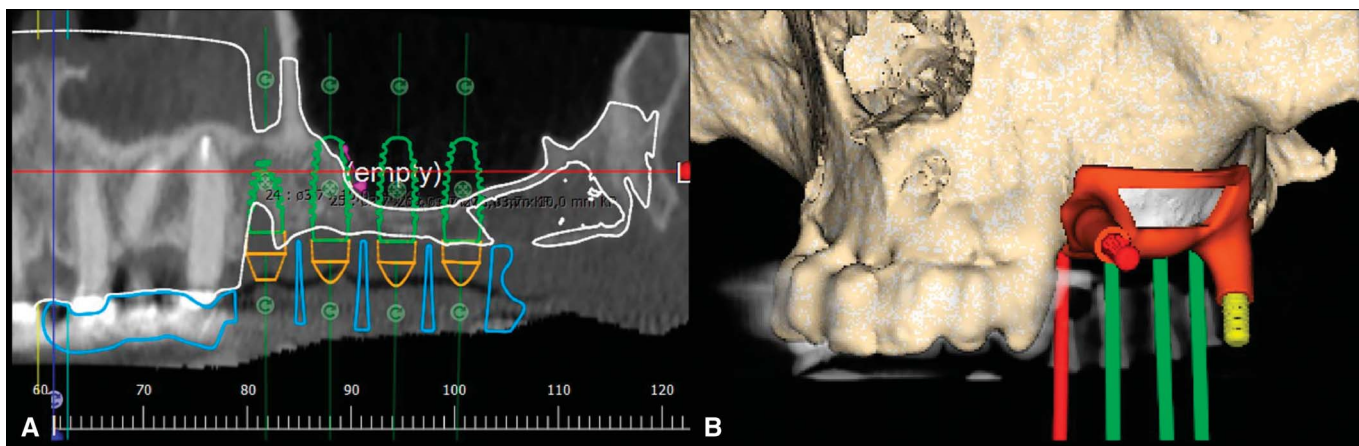


Fig. 5. The case is first studied on CBCT scans. The implant position is planned, and a surgical guide, incorporating a template to guide the surgeon during the antrotomy, is designed. The guide will later be fabricated with stereolithography.

Implant Planning and Surgical Guide Manufacturing

A CBCT examination was performed to evaluate the health and anatomical status of each sinus (Fig. 5). The position of implants was preplanned using the CBCT scan to have a surgical guide manufactured. The design of the surgical guide also included a guide for carrying out the lateral antrostomy according to the low window scheme previously described.¹⁷

Surgical Procedure

Antibiotic prophylaxis (amoxicillin/clavulanic acid, Augmentin; GlaxoSmithKline, Verona, Italy, 1 g 1 hour before surgery and then every 12 hours for 6 days) was initiated. Patients also were instructed to rinse with chlorhexidine 0.2% (Corsodyl; GlaxoSmithKline) for 2 weeks after the surgery. Ketoprofen 80 mg (Oki; Dompé, L'Aquila, Italy) was prescribed for pain as needed but not to exceed every 8 hours for 7 days.

To get easier access to the surgical area, a flexible aid (Opragate; Ivoclar Vivadent AG, Schaan, Liechtenstein) was placed. The surgical area was anesthetized with articaine hydrochloride 40 mg/mL with adrenaline 1:100,000. A full-thickness flap was then elevated, which enabled the apical osteotomy line to be drawn at a distance of 6 mm plus the residual bone height from the ridge. Mesially, the incision was paramarginal to the more distal residual element to preserve its attached gingiva. No releasing incisions were performed either distally or mesially, that is, the incision had no vertical components (Fig. 6A). The access window was then drawn on the vestibular bone using a dermographic pencil and the surgical guide (Fig. 6B). Using standard piezoelectric tips (Mectron, Carasco, Italy) under sterile saline irrigation, the window in the maxillary sinus lateral wall was then created. The sinus membrane was carefully elevated using dedicated sinus elevation hand instruments (Hu-Friedy, Chicago, IL) (Fig. 6, C–D), and equine-derived cortical-cancellous granules, sized 0.5 to 1 or 2 to 3 mm (OsteOxendon; Bioteck, Arcugnano, Italy), were hydrated with sterile saline and inserted into

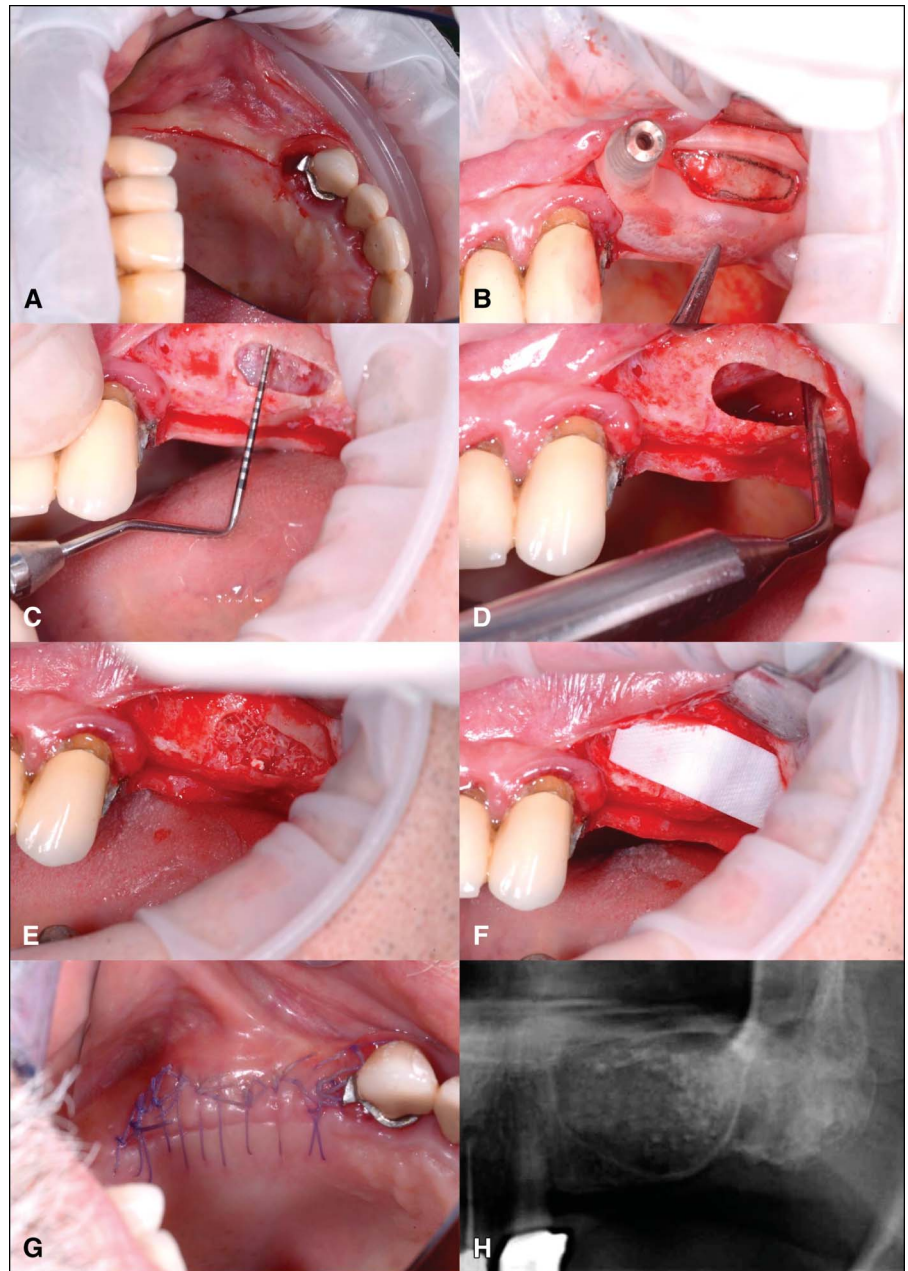


Fig. 6. First surgery. The photographs refer to the case shown in Figure 4. (A) A mucoperiosteal flap is elevated. The flap is limited to a linear incision, preserving the attached gingiva of the most distal residual element present. Release incisions are not performed. The antrostomy is carried out (B) with the help of the surgical guide. C, The window height is 6 mm. (D) The membrane is lifted, and the sinus is grafted (E). Before suturing, (F) a collagen membrane is placed to protect the antrostomy. (G) Finally, suturing is carried out. (H) The radiograph shows the extent of filling performed.

the cavity, applying gentle pressure to stabilize them (Fig. 6E). A membrane (Ossix Plus; Datum Dental, Lod, Israel) was placed to protect the graft (Fig. 6F). In 1-stage procedures, the planned number of osseointegrated implants was placed in the positions indicated by the surgical guide before the

cavity was full. Filling of the cavity was completed after the implant placement(s), and the mucoperiosteal flaps were sutured using nonresorbable 5.0 sutures (Fig. 6, G–H).

Sutures were removed after 10 days. Patients were then recalled monthly. Patients undergoing 2-stage

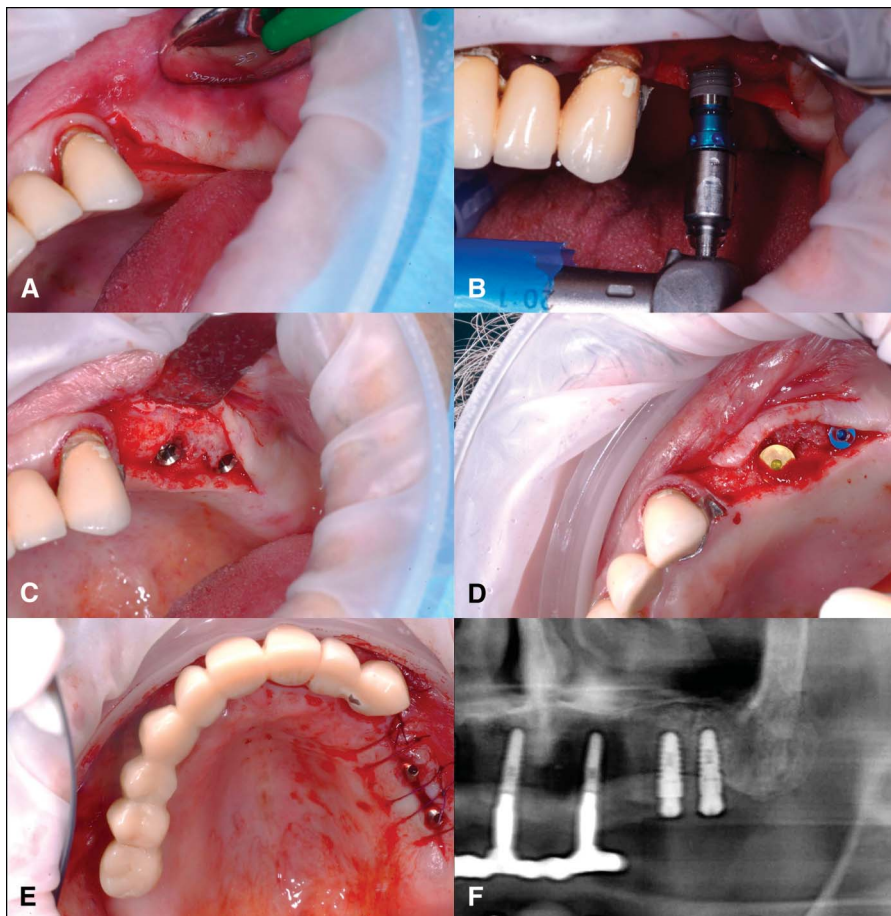


Fig. 7. Second surgery. (A) A very limited mucoperiosteal flap is elevated, and the implants are placed (B and C). (D–F) They are not submerged. The definitive prosthesis will be delivered approximately 4 months later.

implant placement had their implants placed 4 to 6 months after sinus grafting, after undergoing the same antibiotic prophylaxis and antibiotic and analgesic treatment as in the first surgery (Fig. 7). Four to 6 months after the sinus lift and concomitant implant placement or after implant placement, only for the 2-stage patients, implants were uncovered, and healing screws were attached. Three weeks later, radiographs were taken, and dental impressions were made using pick-up impression copings to manufacture the provisional prostheses. These were delivered after approximately 10 days, and the patients wore them for approximately 3 months, at which point definitive prostheses were delivered. All final prostheses were porcelain-fused-to-metal or metal-composite, implant-supported bridges.

Follow-up

After definitive prosthetic rehabilitation, patients were recalled for control visits every 6 months. At each visit, they received professional hygiene and a thorough oral examination. Radiographs were taken at each follow-up control.

Subjective Patient Satisfaction

At the 10-day suture-removal visit, patients were asked to assess subjectively their postsurgical progress on a qualitative basis, considering their perception of pain and swelling on a 4-level scale (poor, fair, good, excellent).

Alveolar Ridge Height, Sinus Angle, and Membrane-Thickness Measurements

The preoperative CBCT scans were independently analyzed by 3 physicians (T.Z., A.Z., S.R.), who measured the residual vertical ridge height

at the site of implant insertion. Each operator compared the postoperative radiograph with the preoperative CBCT scans to determine on the latter the position of implant insertion. The ridge height (R) and sinus angle (A)^{16,18} were measured for each position with the aid of the software provided with the CBCT device. Each measurement was repeated twice. All R values and all A values were then averaged to provide a single estimate of the ridge height R and sinus angle A for each patient.

The sinus membrane thickness M was measured as described by Rapani et al.¹⁸ Briefly, the thickness of the sinus membrane was measured to the nearest 0.1 mm at 3 different sites in the maxillary sinus. To define these sites on the panoramic CBCT view, the most anterior and posterior points adherent to the sinus wall were drawn vertically, and then the median point of the 2 was drawn. For each of these 3 sites, the corresponding cross-sectional CBCT image was retrieved, and 3 different measurements were made. Finally, a mean of 3 measurements was recorded, and the thickness of the sinus mucosa was measured (in millimeters).

Implant Survival and Success Rate

Implant success was evaluated according to criteria described by Buser et al.¹⁹ and modified by Albrektsson and Zarb²⁰ including (1) absence of persistent pain, dysesthesia, or paresthesia in the implant area; (2) absence of periimplant infection with or without suppuration; (3) absence of perceptible mobility of the implant; and (4) absence of periimplant bone resorption greater than 1.5 mm during the first year of loading and 0.2 mm/y in the following years. For the analysis of periimplant bone loss, digitally taken intraoral radiographs were analyzed using a dedicated software (ImageJ; National Institute of Health, Bethesda, MD). The software was calibrated using the known implant length. The distance from the implant-abutment interface to the most apical point of crestal bone observed to be in intimate contact with the implant was measured to the nearest 0.01 mm on both the mesial and distal sides. The mesial and distal periimplant bone levels were averaged to get a single

Table 1. Patient's Identification Number, Patient's Demographic Characteristics (Gender, Age), and Sinus Characteristics: Sinus Angle (A), Ridge Height (R) and Sinus Membrane Thickness (M)

Patient #	Gender	Age	Sinus Angle A (Degrees)	Residual Ridge Height R (mm)	Membrane Thickness (Type)
1	F	52	A < 30	R > 4	III
2	M	48	30 ≤ A ≤ 60	R < 2	II
3	M	65	30 ≤ A ≤ 60	R < 2	I
4	F	58	A < 30	R < 2	IV
5	F	46	A < 30	R < 2	I
6	F	72	30 ≤ A ≤ 60	R = 3	III
7 (bilateral, right)	M	51	A > 60	R = 3	II
7 (bilateral, left)	M	51	A > 60	R > 4	II
8	M	60	A > 60	R < 2	II
9	M	47	30 ≤ A ≤ 60	R < 2	IV
10 (bilateral, right)	M	52	30 ≤ A ≤ 60	R = 3	II
10 (bilateral, left)	M	52	30 ≤ A ≤ 60	R < 2	II
11	M	64	A > 60	R > 4	IV
12 (bilateral, right)	F	63	30 ≤ A ≤ 60	R > 4	II
12 (bilateral, left)	F	63	30 ≤ A ≤ 60	R < 2	III
13	F	63	A < 30	R < 2	I
14 (bilateral, right)	M	75	A > 60	R > 4	IV
14 (bilateral, left)	M	75	A > 60	R < 2	I
15	M	55	30 ≤ A ≤ 60	R > 4	I
16 (bilateral, right)	F	55	30 ≤ A ≤ 60	R < 2	IV
16 (bilateral, left)	F	55	30 ≤ A ≤ 60	R < 2	III
17	F	70	A < 30	R < 2	II
18 (bilateral, right)	F	57	30 ≤ A ≤ 60	R = 3	IV
18 (bilateral, left)	F	57	30 ≤ A ≤ 60	R > 4	III
19	M	55	A > 60	R < 2	IV
20	M	65	A > 60	R > 4	II
21	M	60	30 ≤ A ≤ 60	R < 2	IV
22	F	64	A < 30	R < 2	II

A and R were measured twice and then averaged. M was measured at 3 different sites in the maxillary sinus: for each of the 3 sites, the corresponding cross-sectional CBCT image was retrieved, and 3 different measurements were made and then averaged. The thickness of the Schneiderian membrane was classified as type I (nonrecordable), type II (0–2 mm), type III (3–4 mm), or type IV (>4 mm), according to the classification given by Rapani et al.¹⁸

mean value per implant. For each implant, bone loss after the first year of loading and at the final follow-up was then calculated as the difference between the bone levels at the time point under consideration and that at baseline (implant insertion). Implants were considered successful when all the conditions were met.

Statistical Analysis

Descriptive statistics (absolute and relative frequencies, means, and corresponding standard deviations) concerning the following variables of interest were calculated: (1) patients' gender and age; (2) sinus angle A and membrane thickness M; (3) residual ridge height R; (4) surgical time; (5) patient satisfaction; intraoperative and postoperative complications; (6) implant diameter and length; (7) implant survival and success; and (8) total follow-up time. Statistical calculations were performed

using standard statistical software (Origin 9.0; Northampton, MA: Originlab). All values in this work are provided as mean ± standard deviation.

RESULTS

Records of 22 patients (10 women and 12 men; 59.0 ± 8.6 years old) were retrieved and analyzed. Average follow-up was 38.4 ± 13.2 months. Demographic and anatomical data concerning the patients are provided in Table 1. There were 13 one-stage interventions, in which 36 implants were placed. In the remaining 15 two-stage interventions, 43 implants were placed. A total of 79 osseointegrated implants were thus placed, their length and diameter varying from patient to patient as described in Tables 2 and 3. The average implant length was 11.0 ± 1.3 mm, and most of the implants (83.5%) were shorter than 13 mm. No cases of sinus membrane

tearing or of other intrasurgical complications occurred. The sinus lift procedure was then completed successfully. All patients healed uneventfully and reported a good (n = 10; 45.5%) or excellent (n = 12; 54.5%) degree of satisfaction concerning postsurgical side effects (pain and swelling). Minimal facial swelling is confirmed by photographs of the patients taken at 1 to 3 days after the surgery. At the final follow-up, all prostheses were fully functional, and all implants were successful according to the Albrektsson and Zarb²⁰ criteria. Mean bone loss after 1 year of loading was 0.48 mm ± 0.43 mm (range, 0.1–1.3 mm); the mean annual bone loss after that was 0.05 mm ± 0.06 mm (range, 0.0–0.2 mm).

DISCUSSION

To the authors' knowledge, no investigators have systematically

Table 2. Patients Identification Number, Position in Which Each Implant Has Been Inserted for Each Patient, Details of the Implants Placed

Patient	Position	Implant Size (Length × Diameter, mm)
1	24, 25, 26, 27	4.0 × 11.5; 4.0 × 10.0; 4.0 × 10.0; 4.0 × 10.0
2	17, 16, 15	4.0 × 8.5; 4.0 × 8.5; 5 × 10.0
3	15, 16, 17	4.0 × 13; 5 × 11.5; 5 × 11.5
4	16	4.0 × 11.5
5	16, 17	4.0 × 10.0; 4.0 × 10.0
6	15, 16, 17	4.0 × 10.0; 4.0 × 10.0; 4.0 × 10.0
7	16, 17	4.0 × 10.0; 5 × 8.5
7	24, 25, 26, 27	4.0 × 13; 4.0 × 11.5; 4.0 × 10.0; 5 × 8.5
8	25, 26	4.0 × 13; 4.0 × 11.5
9	25, 26, 27	4.0 × 13; 4.0 × 11.5; 5 × 11.5
10	14, 15, 16	4.0 × 13; 4.0 × 11.5; 4.0 × 11.5
10	24, 25, 26	4.0 × 11.5; 4.0 × 10.0; 4.0 × 10.0
11	16, 15	4.0 × 13; 4.0 × 11.5
12	14, 15, 16	4.0 × 11.5; 4.0 × 10.0; 4.0 × 8.5
12	24, 25, 26	4.0 × 11.5; 4.0 × 11.5; 4.0 × 10.0
13	25, 26, 27	4.0 × 11.5; 4.0 × 11.5; 4.0 × 10.0
14	14, 15, 16	4.0 × 10.0; 4.0 × 10.0; 5 × 10.0
14	24, 25, 26, 27	4.0 × 11.5; 4.0 × 10.0; 5 × 10.0; 5 × 10.0
15	16, 15	4.0 × 11.5; 4.0 × 11.5
16	14, 15, 16	4.0 × 11.5; 4.0 × 11.5; 4.0 × 10.0
16	24, 25, 26	4.0 × 11.5; 4.0 × 10.0; 4.0 × 10.0
17	24, 25, 26	4.0 × 13; 4.0 × 11.5; 4.0 × 11.5
18	14, 15, 16	4.0 × 11.5; 4.0 × 11.5; 4.0 × 10.0
18	24, 25, 26	3.4 × 13; 3.4 × 13; 3.4 × 11.5
19	16, 15	3.4 × 13; 3.8 × 11.5
20	24, 25	3.4 × 13; 3.4 × 13
21	14, 15, 16, 17	3.4 × 13; 3.4 × 11.5; 3.4 × 11.5; 3.8 × 10
22	24, 25, 26, 27	3.4 × 11.5; 3.8 × 10; 3.8 × 8.5; 3.8 × 8.5

Details are expressed as length × diameter (in millimeters).

Table 3. Distribution of Implants According to Their Length

Length (mm)	n	%
8.5	7	8.9
10	27	34.2
11.5	27	34.2
13	13	16.5

Descriptive statistics indicate the absolute (n) and relative frequencies (%) of the implants placed for each implant length.

investigated the effect of the window design, size, and position on complication rates or effort required to perform sinus lift surgeries. Different authors provide different indications concerning the window size and the position of the lower antrostomy line. Although some advise placing it flush with the sinus floor, others suggest a position up to 2 to 3 mm higher.^{21–27} The current clinical literature on lateral sinus augmentation reveals great variability in the recommended window shape, design, size, and position.^{1,12,28–30} Some authors suggest

positioning the window based on each specific patient's anatomy,¹ but in most publications, the window position seems to be chosen by the surgeon only on the basis of his/her personal habits.

Standardized window preparation instead might provide significant advantages. Any standardized technique is less prone to operative errors and is associated with a faster learning curve. Second, a well-defined technique is by definition more reproducible in its execution and, accordingly, should provide more reproducible results. Last but not

least, if the standardization is based on a solid rationale, a reproducible technique should provide significant operative and clinical advantages. The authors have designed the “low window” antrostomy based on their clinical observation that the more apical and distal the window, the more difficult the surgical access and the greater the risk of tearing the sinus membrane. Accordingly, they have proposed the creation of a low window at the most coronal and mesial position possible, to facilitate access to the sinus and provide other specific surgical advantages. Placement of the lower horizontal osteotomy flush with the sinus floor eliminates any residual bone wall that could hinder detachment of the sinus membrane.

The position of the distal osteotomy line is determined by the position of the most distal implant; extending it more distally provides no advantage and may result in elevation of a wider mucoperiosteal flap. Placing it more mesially forces the surgeon to detach a portion of the membrane in a “blind” condition, with no reference points. A window height of 6 mm is the minimum that allows for easy access of the membrane elevators, thus minimizing the risk of damaging the membrane. A smaller height would create an obstacle to membrane elevation, whereas a greater one would not provide any significant advantage but would require elevation of a wider mucoperiosteal flap,³⁰ increasing the risk of intercepting the intraosseous anastomosis between the infraorbital and superior alveolar arteries.^{31,32} A reduction in the antrostomy size is in line with a recent randomized, split-mouth, clinical trial by Baldini et al²⁷ who showed that a reduction of window dimensions did not affect the safety of the surgical procedure. Moreover, patients had a preference for such procedures at 7 and 14 days after operation.

Finally, when the maxillary ridge is more atrophic, the upper horizontal osteotomy will be lower (because the distance from the upper osteotomy to the sinus floor must be 6 mm). Less detachment of the mucoperiosteal flap will be required, reducing the overall invasiveness of the surgery. Current evidence shows that effective rehabilitation may

be achieved with implants significantly shorter than those that were initially used to rehabilitate patients undergoing sinus augmentation. In this sense, the low window approach is consistent with the aim of reducing invasiveness. It allows for the use of the same amount of graft material as in traditional approaches, enabling placement of implants of the desired size, as planned.^{33,34}

Results of the present study suggest that when the window is designed and prepared following this rationale, the patient's subjective evaluation of satisfaction was good, and the risk of intra-surgical or postsurgical complications does not increase. In the present study, no cases of membrane perforation were observed, whereas the rate of membrane tearing usually reported in the literature varies from approximately 18% to 35%.^{15,35–38} Proper studies should be carried out on a larger number of patients to investigate if this technique is really associated with a lower rate of intra-surgical membrane tearing.

Patients expressed a high degree of satisfaction, and no surgical or postsurgical complications were observed even in those patients who, because of their sinus anatomy, were regarded as being at risk (ie, they had a small residual bone ridge, a thin sinus membrane, and a narrow sinus angle).^{1,15,16,18,39} Although carrying out the sinus augmentation surgeries, invasiveness appeared to be reduced because a smaller flap was usually necessary than with other lateral antrostomy preparations. The approach allowed access to the surgical site to be gained easily, usually reducing the need for the surgical assistant to provide retraction of lips and cheeks. In most cases, a flexible aid alone was enough to provide sufficient retraction. Osteotomy preparation seemed to require less time than with traditional approaches, likely because the cortical layer that had to be removed was thinner because of the low window position. In all cases, the sinus membrane could be detached quite easily, as the elevating movement of the surgical instruments could be easily carried out not only laterally but also upward, performing an inferior-lateral Schneiderian membrane lifting. This also may have contributed to avoid

sinus membrane tearing. In this series, no cases of maxillary sinus septa were observed. Although we do not expect that this anatomical variation should have a significant impact on the outcomes of the low window technique, further studies should confirm this. In addition, further studies including objective assessments are needed to confirm the benefits of this technique on the reduction of patient discomfort and surgical time.

It should be noted that the effectiveness of this technique depends at least in part on the use of computer-aided design and manufacturing technology, that is, the surgeon, to carry out the technique properly, will need to have a CT or CBCT scan performed and a surgical guide manufactured. Other authors have already proposed modification of a surgical guide for implant insertion by incorporating the window frame in it^{40,41} to improve precision in window outlining. The low window design enables any surgical guide to be used effectively. In contrast, a higher window position tends to hinder correct positioning of any such guide because of the inclination of the vestibular ridge.

The present study is retrospective in nature, included a small number of subjects, and had limited follow-up. The results thus cannot be generalized, and no definitive conclusion can be drawn about the validity of this novel approach to sinus lift window design. However, the reduced number of complications and excellent implant success rate indicate that further investigations should be carried out on a larger number of subjects and for a longer time through prospective comparative trials.

CONCLUSION

Results of the present retrospective case series indicate that the low window sinus lift technique appears to be a replicable, rational approach to sinus lift augmentation that may entail significant advantages for both patients and surgeons. Controlled, prospective studies should be undertaken to investigate whether this technique provides significant improvements over alternative window designs and sinus augmentation approaches.

DISCLOSURE

Authors have no conflict of interest. Data belonged to the authors, and none of the manufacturers cited in the study interfered with its execution or results.

APPROVAL

Each author approves the present manuscript for publication.

ROLES/CONTRIBUTIONS BY AUTHORS

T. Zaniol: Devised the project and the main conceptual ideas. He acquired and processed clinical and experimental data, performed the analysis, drafted the manuscript, and designed the figures. A. Zaniol: Acquired and processed clinical and experimental data, performed the analysis, and contributed to drafting the manuscript. A. Tedesco and S. Ravazzolo: Contributed to the design and implementation of the research and to the writing of the manuscript. S. Ravazzolo also contributed to performing the analysis. All authors discussed the results and commented on the manuscript.

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