HHS Public Access
Author manuscript
Am J Orthod Dentofacial Orthop. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:
Am J Orthod Dentofacial Orthop. 2016 April ; 149(4): 533–542. doi:10.1016/j.ajodo.2015.09.026.

Comparison and reproducibility of two regions of reference for CBCT maxillary regional registration

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Abstract

Introduction—the aim of this study was to evaluate the differences between 2 regions of maxillary voxel-based registration and to test the reproducibility of the registration.

Methods—3D models were built for before treatment (T1) and after treatment (T2) Cone Beam CTs for 16 growing subjects. Landmarks were labeled in all T2 models of the maxilla, and voxel-based registration was performed independently by two observers, at two different times, using two different reference regions: 1) the Maxilla region (MAX) included the maxillary bone clipped inferiorly at the dentoalveolar processes, superiorly at the plane passing through the right and left orbitale points, laterally at the zygomatic processes through the orbitale point, and posteriorly at a plane passing through the distal surface of the second molars. 2) the Palate and Infra-zygomatic region (PIZ) had different posterior and anterior limits (at the plane passing through the distal of the first molar and distal of the canines, respectively). The differences between the registration regions were measured by comparing the distances between corresponding landmarks in the T2 registered models and comparing corresponding x,y,z coordinates from corresponding landmarks. Statistical analysis of the differences between T2 surface models was performed by evaluating the means and standard deviations of the distances between landmarks and by testing the agreement between coordinates from corresponding landmarks (ICC and Bland-Altman method).

Results—The means of the differences between landmarks from PIZ to MAX 3D T2 surface models for all of the regions of reference, times of registrations and observers combinations were smaller than 0.5 mm. The ICC and the Bland-Altman plots indicated adequate concordance.

Conclusions—Both regions of regional maxillary registration (MAX and PIZ) showed similar results and adequate intra- and inter-observer reproducibility.

Keywords

Cone Beam Computed Tomography; Maxilla; Superimposition; Reproducibility of Results

Introduction

Growth and development of the face has an important role in determining overall facial pattern and the nature of the occlusion. Previous studies[1-5] have shed light on the complex mechanisms of maxillary and mandibular growth and remodeling but a better understanding of the direction, amount and pattern of growth, as well response to treatment still is required. A correct jaw relationship depends on adequate interactions among a series of basal and dentoalveolar adaptations in the sagittal, vertical and transverse planes. Serial cephalometric radiographs[1,6,7] have been used for dynamic studies of these interactions in growing children; in particular longitudinal implant studies have indicated stable areas of reference for understanding regional changes during growth.[6,8,9]

Superimposition on these stable maxillary structures can be used to evaluate growth and treatment changes in the maxillary dentoalveolar complex. Multiple registration regions and superimposition methods have been proposed in the literature. The “structural method” based on stable structures of the maxilla (such as the anterior surface and tip of the zygomatic process or “key ridge”)[9] was found to be almost equivalent to the implant method.[10] On the other hand, superimpositions along the palatal plane using the anterior nasal spine as a reference were less reproducible in relation to the structural method.[10] A superimposition using the best fit of internal palatal structures has also been proposed by McNamara.[11] However, Björk’s methods of superimposition on metallic implants still remain the gold standard for superimposition of the maxillary structures[6,9]. Currently, however, there are ethical implications for implant placement for research purposes.

The advent of three-dimensional (3D) cone-beam computed tomography (CBCT) allowed the observation of skeletal and dental changes that could not be attempted with standard 2D radiographs. 3D registrations offer advantage over 2D including volume/regions of interest for registration rather points or lines, lack of distortion of bilateral structures, and head positioning errors. However, anatomical structures reported to be stable on lateral headfilm may not be reliable for 3D analysis that also involves the transverse dimension.[12]

Cevidanes et al. validated a method for voxel-based superimposition of the cranial base to assess post-treatment changes in growing[13] and adult[14] patients. Based on the cranial base registrations, it is possible to quantify the skeletal displacements of both the maxilla and mandible relative to the anterior cranial base used as a stable reference structure. Recently, Schilling et al[15] suggested a regional superimposition method to assess dental changes and subtle bone remodeling within the mandible that considers the symphysis as a stable reference structure. To date, no study in the literature described the 3D voxel-based regional superimposition method for the maxilla.

The current study had two objectives: to evaluate the differences between 2 regions of maxillary voxel-based registration and to test the intra- and inter-observer reproducibility of these registrations.

Subjects and methods

This retrospective study was based on a sample of 16 growing subjects (from 9 to 13 years) comprising of 8 subjects who were treated with rapid maxillary expansion (RME) for crossbite correction and 8 subjects who were treated with the Herbst appliance for the correction of Class II malocclusion. CBCT scans (0.4 mm voxel-size, 16x22 cm FOV) of all subjects were already available at two time points with, at least, six months of interval between them: before (T1) and after treatment (T2) taken using an iCat machine (Imaging Sciences International, Hatfield, PA).

This study was approved by the University of Michigan Institutional Review Board (HUM00095895).

Image analysis

After converting the DICOM files to "Guys Image Processing Lab (gipl)" files using ITK-SNAP open-source software[16] (http://www.itksnap.org), the 3D image analysis procedures followed steps:

1. *Approximation of T1 and T2 scans*

The T1 and T2 gipl files were approximated manually by the same observer with a best fit of the maxillary outlines in 3D multiplanar cross-sections using open-source software (Slicer v4.3.1, http://www.slicer.org).

2. *Construction of* 3D volumetric label maps *of the maxilla (segmentation)*

[17] The construction of 3D volumetric label maps for the T1 and T2 scans was performed using ITK-SNAP software. The automatic segmentation procedures in ITK-SNAP utilize active contour methods to compute feature images based on the CBCT image gray level intensity and boundaries.[18] The threshold was adjusted scan by scan since ITK-SNAP permits the adjustment of the parameters for automatic detection of intensities and boundaries as well as allows user interactive editing of contours. The anatomic structures that were segmented for reference (regions of reference), indicated to the software in which areas it should look for corresponding voxels. The segmentations were also used to build 3D surface mesh models (.stl) that were loaded in the VAM software (VECTRA Analysis Module, version 3.7.6, Canfield Scientific Inc.) to generate the landmarks coordinates and the distances between landmarks.

3. Placement of landmarks on the T2 3D volumetric label maps

One observer labeled six landmarks in all T2 models in different regions of the maxilla in order to eliminate errors of pitch, roll and yaw, and also to avoid any landmark identification errors (Fig. 1). One label different of the 3D volumetric label maps was used to label the landmarks in the following regions: zygomatic process of the maxilla in both sides, buccal surface of the upper first molar in both sides, anterior nasal spine and proximal contact point between upper central incisors. The landmarks were labeled in two consecutive slices using the paintbrush tool. The same 3D volumetric label maps, labeled with landmarks, were used by both observers for the registration procedures to avoid errors due to segmentation or landmark placement.

4. Clipping (cropping) of the masks for each registration region

The T2 3D volumetric label maps, pre-labeled with landmarks, were cropped by two calibrated observers (Obs1 and Obs2). Two observers were trained and calibrated to perform the cropping using a set of ten 3D volumetric label maps not included in this study. The procedures of cropping and registration were performed at two different times (first registration = R1; second registration = R2) with a 3-month interval between both registrations by each of the same two observers working independently. Two different regions of reference (mask) were defined for the voxel-based registration procedures (Figs. 2 and 3): a) the Maxilla (MAX) region of reference included the maxillary bone cropping inferiorly at the dentoalveolar processes; superiorly, the regions above the plane passing through the right and left orbitale points; bilaterally, the zygomatic processes at orbitale points; and posteriorly at a plane passing through the distal surface of the second molars; b) the "Björk-inspired" Palate and Infra-Zygomatic region of reference (PIZ) had different posterior and anterior limits (respectively, the planes passing through the distal of the first molar and distal of the canines).

5. *Voxel-based registration procedures*

These procedures used the anatomic structures described above as masks for reference, indicating to the software in which areas it should look for corresponding voxels to register the T2 scan (with landmarks pre-labeled in a different label) in relation to the T1 scan. After the user had selected the region of reference for registration, a fully automated voxel-based registration method was performed through the Slicer software. The software compares the gray-level values voxel by voxel, within the region of reference,[19,20] in two CBCT images (T1 and T2) maximizing mutual information to compute the rotation and translation parameters between them[18]. Due to the fact that the sample consisted of growing patients, the scans at two time points had different sizes. For this reason, a fully automated voxel-wise rigid growing registration method[13,21] (that takes into account that the images have different sizes but applies only 6 degrees of freedom of rotation and translation to the T2 scan) was performed. The registrations were voxel based on the region of reference and the software generated (as an output file) the 3D volumetric labeled maps registered over T1. The 3D mesh surface models were generated from those output files. Then, the T2 3D volumetric label maps (pre-labeled with landmarks) resulting from the registration based on the MAX and PIZ regions of registration, performed twice (first registration, R1; and second registration, R2) independently by the two observers (Obs1 and Obs2), were saved as 3D surface mesh models (.stl files) with landmarks already placed, using Slicer software.

6. Landmark-based quantitative assessments in VAM software (VECTRA Analysis Module, version 3.7.6, Canfield Scientific Inc.)

The T2 3D surface mesh models (.stl files) with landmarks already placed, registered by two different regions of reference cropped by two different calibrated observers at two different times were loaded in VAM software. The software generated the coordinates for each landmark and the Euclidean distances between corresponding landmarks.[22] These values were statistically analyzed in three different ways to assess the intra- and inter-observer reproducibility and the consistency of the regions of reference.

7. *Color-coded assessment*

Interactive visual analytic evaluation of surface differences was performed by graphical display of color-coded maps and semi-transparent overlays for visual intra- and inter-observers comparisons and to compare the two regions of reference as well.

Statistical analysis

The following statistical tests were carried out to test the consistency of the two regions of reference (MAX and PIZ), the intra- and inter-observer reproducibility: 1) descriptive statistics of the differences between the registered T2 .stl models including means and standard deviations between corresponding pre-labeled landmarks; 2) consistency was tested with intraclass correlation coefficient (ICC, with two way random effect model) by comparison between the corresponding x, y and z coordinates of the corresponding pre-labeled landmarks on the surface of registered T2 .stl models; and 3) Bland-Altman plots of the 95% limits of agreement (average differences ±1.96 of the standard deviation of the differences) evaluating the concordance between the corresponding x, y and z coordinates from corresponding pre-labeled landmarks on the surface of registered T2 .stl models.

All statistical computations were performed with statistical software (SPSS statistical software package, version 21.0, SPSS, Chicago, IL and MedCalc version 14.10.2; MedCalc Software, http://www.medcalc.org).

Results

Table I shows the descriptive statistics for the measurements using the MAX and PIZ registration regions for both observers and both times (first and second registration - R1 and R2). The means of the Euclidean distances between the T2 .stl models after registrations were small at all landmarks for all of the combinations tested (all of the means were smaller than 0.5 mm). Considering the standard deviations, all of the differences between the models registered by two different regions were ≤ 1.0mm.

The statistics to test the concordance (ICC) between regions of reference for registration and for intra- and inter-observer reproducibility revealed excellent consistency (greater than 0.99).

The consistency between regions of registration and intra- and inter-observers reproducibility can be observed in Table II. By using Bland and Altman’s limits of agreement, one would expect that 95% of the differences between corresponding coordinates for all of the six corresponding landmarks obtained from the registrations performed in this study would be within the range −0.82 to 0.77 mm. Figure 5 displays one example of consistency between the two regions used for registration (Fig.5 A), intra- and inter-observer agreement (Fig. 5 B and C, respectively) for the landmark 6.

The visual analytic evaluation between the 3D model surfaces color-coded maps and semi-transparent overlays for comparison between both regions (MAX and PIZ) are shown in Figure 6. The superimpositions of T2 surface models (generated by MAX and PIZ registrations) are almost perfect (Fig 6A), which indicates that both models present with the same spatial position after the registration. The color-coded maps of the T2 models registered by MAX and PIZ registrations (Fig. 6B) confirmed the findings. The color-coded maps from the T2 (MAX and PIZ registrations) superimposed over T1 also display similar pattern of colors (Fig. 6, C and D) between them.

Discussion

Tracing superimposition of serial lateral cephalograms has provided knowledge about craniofacial growth and development as well as dentoskeletal effects produced by orthodontics, orthopedics, and corrective jaw surgical procedures. However, a major disadvantage of using cephalometric tracings includes the fact that a 3D information is compressed into 2D data and often localized to midline structures.

3D registration allows the clinician to evaluate structures that were previously obstructed on lateral cephalograms as well as unilateral/asymmetric anatomic changes to growth or treatment. Furthermore, three-dimensional registration provides more anatomic regions of reference to improve the reliability of the registration. The resulting overlay offers the ability of rotating the 3D surfaces and observing multiple 3D views in the space rather than one sagittal view. Our findings, seen in lateral perspective view are similar to the information provided by 2D cephalograms. However, other views (Fig. 6 and 7) clearly provide clinicians and researchers a better interpretation of growth and treatment changes as well as improved visualization.

Several methods[6,9,10] of 2D maxillary superimposition have been described in the literature such as those published by Björk.[6,9] As metallic implant studies are unrepeatable in humans, the translation of the 2D knowledge from cephalograms superimpositions into a 3D environment is hampered. Studies using dry skulls could be an alternative but they also present problems because they do not display the bone remodeling, eruption, growth and results of treatment based on biological response. Future studies trying to find a gold standard may be necessary to further validate regional bone displacements with treatment.

Promising animal studies on rat mandibles may be helpful to better understand 2D/3D differences[12] but the growth pattern in animal models may not be analogous to humans. Any shift of an area used as reference can cause a misinterpretation in the amount and direction of growth. In addition, tooth movement measurements can be distorted depending on the superimposition method.[1] This study incorporates two commonly used regions for 2D maxillary registration into 3D maxillary registration. Similarly, a published study[19] compared two regions of reference to test the accuracy and reproducibility of voxel based superimposition of CBCT models on the anterior cranial base and the zygomatic arches. Those authors[19] also accepted a reference area from 2D evaluations as reliable to compare a second option for registration.

Clinical implications that can be derived from 3D registrations depend on the structures selected as reference for registration. Cranial base registration has been advocated in different research on growth and follow-up evaluations[16,23-25] but some regional registrations still are controversial. Figure 7 displays findings of maxillary growth and treatment changes seven months after RME using MAX (Fig. 7 A and D) and PIZ (Fig. 7 C and F) regions as reference for the regional registrations and the cranial base registration (Fig. 7 B and E). It demonstrates that differences in interpretation of facial changes can be related to the region of reference used for registration, especially in growing patients.

The concept that the interpretation of the results is relative to the area of reference is an important point for maxillary registration because the maxilla undergoes rotational and translational changes during growth. It is possible to observe alveolar bone and dental changes as well as small areas of remodeling when maxillary regional registration was performed (Figs. 7 A, D and C, F). However, Figure 7 B and E displays the same patient but uses the cranial base as a reference for the registration. Overlay and color maps show a downward displacement of the maxilla and maxillary dentition due to growth. Therefore, the inferences from growth and/or treatment should be made only in relation to the reference structure used for the superimposition method.

For both regions of registration (MAX and PIZ) evaluated in the present study, the dentoalveolar processes were excluded from the mask due to their unstable nature (growth of the alveolus and alternation of deciduous and permanent dentitions according to the development stage of the subjects). The first region was based on the best fit over the entire maxilla (MAX). A second region (PIZ) was a 2D-to-3D attempt to apply Björk's concepts on maxillary regional superimposition using the key ridge as an anatomically stable structure.[6,9,26,27] Both tested regions showed similar results that can be verified by examining Figures 6 and 7 and Table I, II and III as well.

There were no evident differences found for all combinations of observers or regions of reference, as demonstrated by ICC (extremely high coefficient of concordance among them, expressed by ICC > 0.99), and seen in Table I (differences smaller than 0.5 mm between T2 surface models generated after registrations), Table II (excellent inter-observer agreement), and Figure 6 (coincidence of the T2 surface models generated after registrations). Since differences ≤1 mm are clinically insignificant,[28] both the MAX and PIZ regions can be considered clinically comparable and reproducible.

According to the present study, the use of a region corresponding to the key ridge is reproducible for 3D superimposition of the maxilla as well as superimpositions on the entire maxilla. The superimpositions of T2 surface models (generated by MAX and PIZ registrations) are almost perfect (Fig. 6 A), representing remarkable similarity of their surfaces. The color-coded maps from the T2 (MAX and PIZ registrations) superimposed over T1 also display similar pattern of colors (Fig. 6 B). The color-coded maps based on the T2 over T1 express the same interpretation of the results based on the registrations performed by either MAX (Fig. 6C and 7D) or PIZ (Fig. 6D and 7F) regions of reference.

One advantage of PIZ registration is the fact that it does not include maxillary structures distal to the first molar, and therefore is not influenced by the intra-osseous eruption movements of the second molar, if they still do not present occlusal contact at the first time point. In addition, because the PIZ area of reference does not include structures mesial to the distal surface of the canine, this area of reference avoids the influence of ample remodeling of the alveolar process in any cases that may be treated with incisors retraction. Despite the fact that we did not test these situations in the present study, the PIZ registration might be more indicated in cases of ample potential of remodeling.

Our study compared both regions of registration based on the distances between landmarks placed on the 3D volumetric label maps and not in the color maps. The sagittal, axial, and coronal slices, as well as the 3D reconstruction of the image were used for landmark positioning in ITK-SNAP software. The 3D volumetric label maps with identified landmarks were used for the next steps to avoid errors due to segmentation or landmark placement. Color maps are indicated for visual assessment and can be influenced by scans with presence of motion artifacts, large number of metallic artifacts and presence of orthodontic appliances.

The present study investigated voxel-based registration on 3D volumes because it has advantages over surface or landmark based registration methods. Finding a reliable and reproducible area for automatic registration can avoid observer-dependent errors such as training and fatigue[15] and reduce observer-dependent landmark identification errors. Landmark-based registration methods use a limited number of landmarks as reference that is susceptible to landmark identification errors. Surface-based registration can present errors since regions with thin bone are most susceptible to errors in surface reconstruction[30]. However, Almukhtar et al[20] have found no statistical differences between voxel based and surface based registration methods. Voxel based registration, however, showed more consistency in the representation of the actual soft and hard tissue positions. Voxel–based registration compares thousands of voxels including inner structures of the bone including cancellous and cortical bony tissues[13]. This information used for registration suggests that including both cortical and cancellous bone in the registration process would provide to the software a broader region of reference for comparison between two time points. However, in the present study we did not compare neither ‘surface' to ‘voxel registration', nor 'cortical only' to 'cancellous plus cortical' voxel registration.

In summary, this study did not validate the two tested regions used for registration but the region of reference (PIZ) based on Björk structures of reference for 2D superimpositions seems to be applicable to 3D maxillary registration and it displayed similar results when compared to a broader region of reference (MAX). It suggests that 3D interpretation of changes occurring at the level of the maxillary tuberosity, orbital surface of the maxilla, alveolar process, and teeth can be derived from 3D regional superimpositions. The overlay of 3D models at two different time points can provide quantitative and qualitative evaluations of transverse, vertical, and antero-posterior skeletal and dental changes in the maxilla.

Conclusions

The two regions of regional maxillary registration (MAX and PIZ) showed similar results and adequate intra- and inter-observer reproducibility for growing patients.

Acknowledgement

Supported by the National Institute of Dental & Craniofacial Research and the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health (award number R01DE024450). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Highlights

- We evaluate the differences between 2 methods of maxillary voxel-based registration and to test the reproducibility of the methods.
- The differences between the registration methods were measured by the distances between corresponding landmarks in the T2 registered models.
- We tested the Inter-observer reproducibility of the x,y,z coordinates.
- Both methods of regional maxillary registration showed similar results and adequate inter-observer reproducibility.

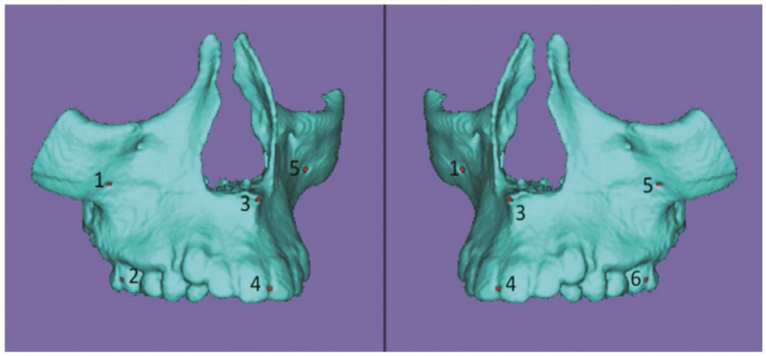

Figure 1.

Images showing T2 3D models with the six pre-labeled landmarks used to obtain the measurements for comparison between the registration methods and between observers.

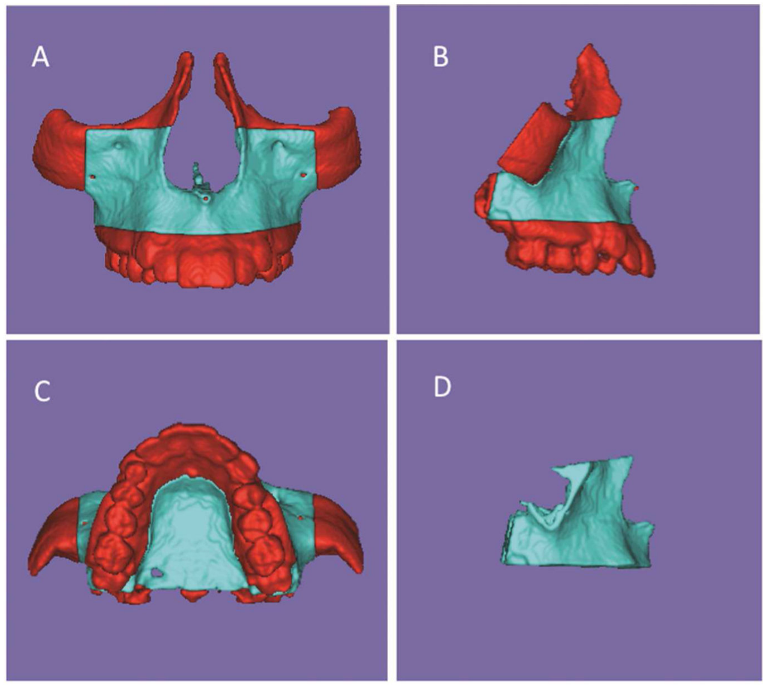

Figure 2.

Images of the cropping to define the MAX region of interest (mask shown in blue) used as reference for the voxel-based MAX registration method. **A**, **B** and **C**, superior, inferior, and lateral limits of the mask (red color refers to regions that will be excluded/cropped); **D**, final mask for MAX registration.

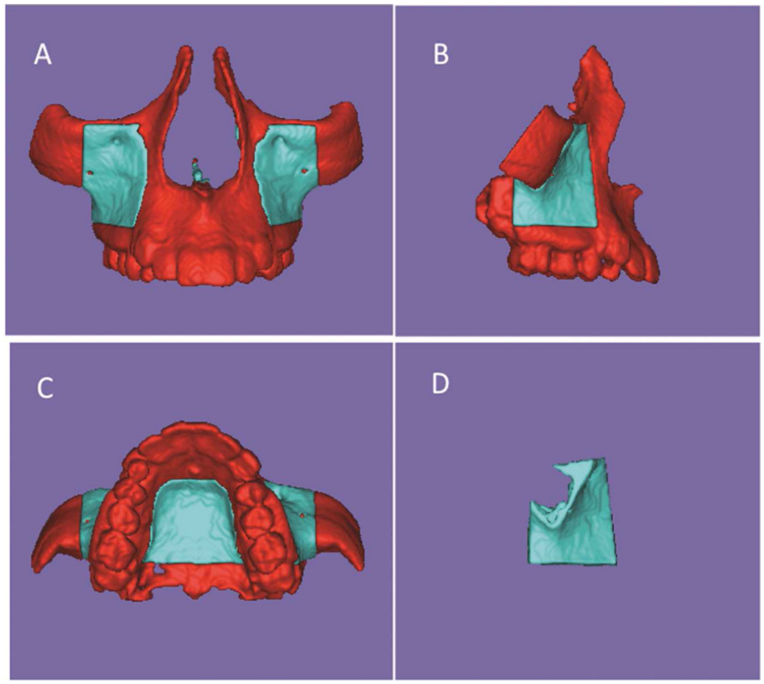

Figure 3.
Images of the cropping to define the PIZ region of interest (mask shown in blue) used as reference for the voxel-based PIZ registration. **A**, **B** and **C**, superior, inferior, and lateral limits of the mask (red color refers to regions that will be excluded); **D**, final mask for PIZ registration.

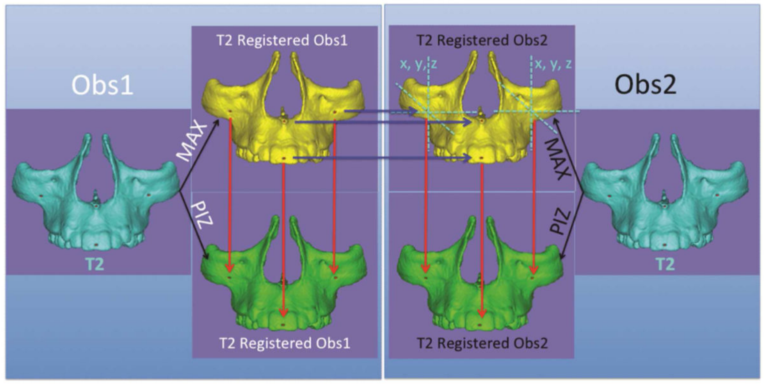

Figure 4.
Flowchart of the study methodology. The light blue box on the left shows the procedures performed by Observer 1 (Obs1), and on the right by observer 2 (Obs2). Both observers used the same maxillary surface model shown in CYAN that was constructed for each Time 2 (T2) CBCT scan and pre-labeled with landmarks. Maxillary surface models shown in YELLOW indicate the registration using MAX reference; and in models in GREEN, the registration using PIZ as reference. The RED arrows indicate the measurements for comparison between the two methods and the BLUE arrows indicate the inter-observer assessments.

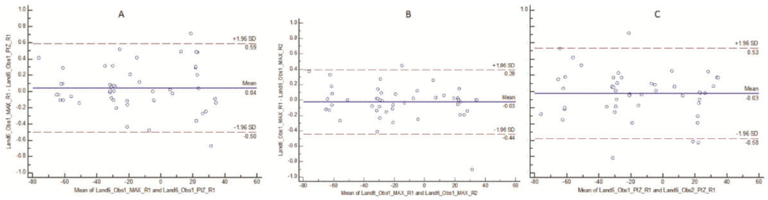

Figure 5.

Bland-Altman plots portraying the agreement between coordinates from corresponding landmarks. **A**, between the two regions used for registration; **B**, intra-observers; **C**, inter-observers. Each circle represents the distance between one coordinate of the landmark 6 placed on T2 models registered by different regions (A), in different times (B) or different observers (C). The solid lines indicate the mean difference, and the dashed lines show the 95% limits of agreement (LOA).

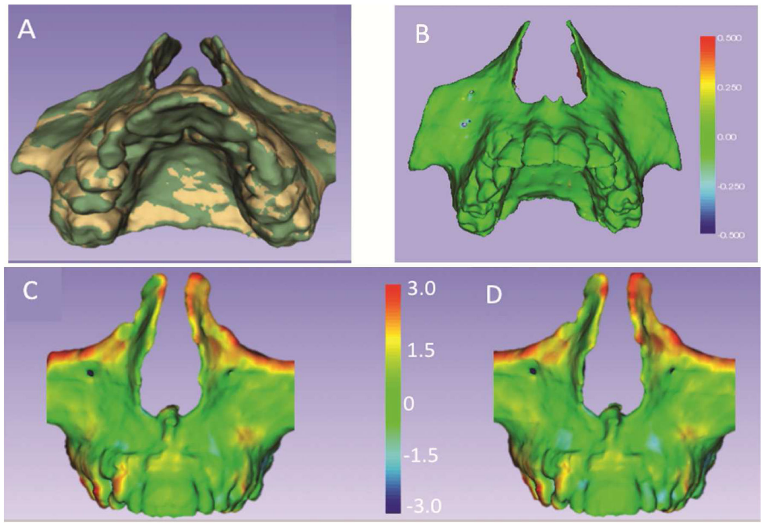

Figure 6.

Visual analytic evaluations (Herbst Patient). **A**, Semi-transparent overlay of the T2 maxilla surface models registered with MAX (yellow) and PIZ (green); **B**, color-coded map of the T2 maxilla surface models generated after being registered using MAX and PIZ regions of reference; **C**, color-coded map of the T2 maxilla surface model over T1 registered using MAX as reference; **D**, color-coded map of the T2 maxilla surface model over T1 registered using PIZ as reference.

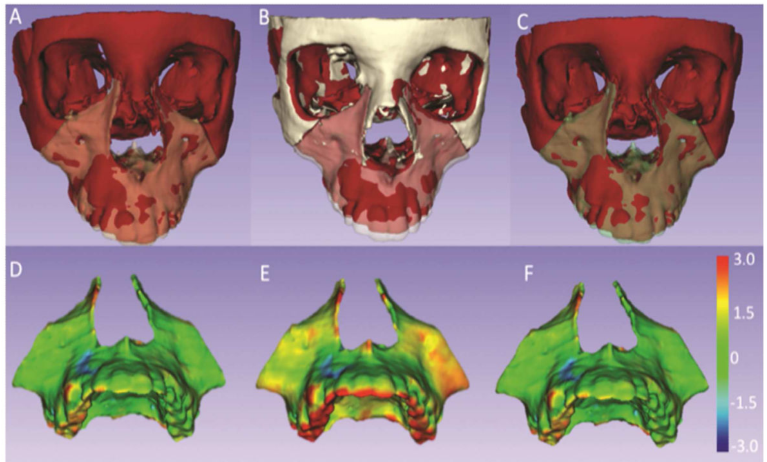

Figure 7.

Comparison of 3D registration methods using different areas of reference (Herbst Patient). **A** and **D,** maxillary registration (MAX as a reference); **B** and **E,** cranial base registration; **C** and **F,** maxillary registration (PIZ as reference)**. A, B,** and **C** show the semi-transparent overlays (T1 is in red, and T2 in yellow in **A**, white in **B,** and green in **C**). **D, E** and **F** show color-coded maps relative to overlays displayed in **A**, **B**, and **C**, respectively.

Table I

Comparison between regions of registration and Intra- and inter-observer comparisons. Descriptive statistics including mean (in mm) and standard deviation (SD) of the Euclidean distances between corresponding landmarks.

		Mean ± SD (mm)
Between regions of registration	MAX Obs1× PIZ Obs1 R1	0.37 (± 0.24)
	MAX Obs1× PIZ Obs1 R2	0.36 (± 0.24)
	MAX Obs2x PIZ Obs2 R1	0.35 (± 0.23)
	MAX Obs2x PIZ Obs2 R2	0.39 (± 0.24)
Intra-Observer	MAX R1 × MAX R2 Obs1	0.31 (± 0.16)
	PIZ R1 × PIZ R2 Obs1	0.33 (± 0.20)
	MAX R1 × MAX R2 Obs2	0.37 (± 0.18)
	PIZ R1 × PIZ R2 Obs2	0.44 (± 0.28)
Inter-Observer	MAX Obs1× MAX Obs2 R1	0.38 (± 0.21)
	MAX Obs1× MAX Obs2 R2	0.36 (± 0.23)
	PIZ Obs1× PIZ Obs2 R1	0.42 (± 0.21)
	PIZ Obs1× PIZ Obs2 R2	0.41 (± 0.24)

Table II

Measurement of the consistency between regions of registration and intra- and inter-observers reproducibility. Bland-Altman means (in mm), standard deviation and 95% limits of agreement (LoA, in mm) for comparison between corresponding x, y, z coordinates from corresponding landmarks (1 to 6).

		Results from Bland-Altman: mean (in mm) and 95% LoA (in mm)											
		Landmark 1		Landmark 2		Landmark 3		Landmark 4		Landmark 5		Landmark 6	
		mean	LoA	mean	LoA	mean	LoA	mean	LoA	mean	LoA	mean	LoA
Between regions of registration	MAX Obs1× PIZ Obs1 R1	0.08	−0.38; 0.54	0.04	−0.51; 0.59	0.05	−0.48; 0.57	0.05	−0.45; 0.55	0.01	−0.37; 0.39	0.04	−0.50; 0.59
	MAX Obs1× PIZ Obs1 R2	0.01	−0.37; 0.39	0.02	−0.65; 0.60	0.00	−0.42; 0.43	0.03	−0.54; 0.61	0.04	−034; 0.42	0.06	−0.47; 0.58
	MAX Obs2x PIZ Obs2 R1	0.04	−0.39; 0.46	−0.06	−0.66; 0.53	−0.01	−0.46; 0.43	−0.03	−0.59; 0.52	0.06	−0.34; 0.46	0.04	−0.44; 0.53
	MAX Obs2x PIZ Obs2 R2	0.05	−0.51; 0.60	0.01	−0.53; 0.55	0.01	−0.47; 0.50	0.01	−0.55; 0.57	0.00	−0.52; 0.52	0.09	−0.48; 0.67
Intra-Observer	MAX R1 × MAX R2 Obs1	0.03	−0.38; 0.43	0.04	−0.37; 0.45	0.00	−0.48; 0.48	−0.03	−0.43; 0.36	0.01	−0.38; 0.40	−0.03	−0.44; 0.39
	PIZ R1 × PIZ R2 Obs1	−0.02	−0.47; 0.43	−0.02	−0.53; 0.48	−0.03	−0.54; 0.47	−0.05	−0.46; 0.36	0.04	−0.27; 0.36	−0.01	−0.34; 0.32
	MAX R1 × MAX R2 Obs2	0.01	−0.46; 0.48	0.00	−0.52; 0.52	0.02	−0.49; 0.52	−0.03	−0.67; 0.62	0.04	−0.36; 0.43	0.00	−0.42; 0.41
	PIZ R1 × PIZ R2 Obs2	0.06	−0.50; 0.62	0.07	−0.65; 0.80	0.05	−0.55; 0.64	0.02	−0.50; 0.54	−0.03	−0.52; 0.47	0.05	−0.51; 0.60
Inter-Observer	MAX Obs1× MAX Obs2 R1	0.04	−0.44; 0.52	0.04	−0.46; 0.54	0.00	−0.51; 0.50	−0.01	−0.53; 0.50	0.00	−0.36; 0.37	0.04	−0.50; 0.59
	MAX Obs1× MAX Obs2 R2	0.03	−0.36; 0.42	0.00	−0.48; 0.48	0.01	−0.58; 0.60	−0.01	−0.62; 0.60	0.03	−0.41; 0.47	−0.01	−0.43; 0.41
	PIZ Obs1× PIZ Obs2 R1	−0.04	−0.63; 0.55	−0.07	−0.82; 0.67	−0.06	−0.57; 0.46	−0.10	−0.66; 0.46	0.06	−0.33; 0.45	−0.03	−0.58; 0.53
	PIZ Obs1× PIZ Obs2 R2	0.04	−0.52; 0.60	0.03	−0.71; 0.77	0.02	−0.59; 0.63	−0.03	−0.56; 0.49	−0.02	−0.41; 0.38	0.03	−0.55; 0.61