

Article

A Case Treated with Maxillary Molar Distalization through the Maxillary Sinus: Three-Dimensional Assessment with a Cone-Beam Computed Tomography Superimposition

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Abstract: In this report, we describe a successful orthodontic treatment through the maxillary sinus and show the utility of cone-beam computed tomography (CBCT) for this procedure. A 20-year-old man with Class I molar relationships and crowding of the maxillary and mandibular anterior teeth came to us to improve his malocclusion. Maxillary molar distalization was necessary to reduce the crowding of the teeth. This was achieved by the use of temporary anchorage devices (TADs) and the uprighting of the mandibular molars. However, several roots of the maxillary molars protruded into the maxillary sinus. The maxillary sinus is a known barrier to orthodontic tooth movement, leading to root resorption and/or tipping movement. We aimed to distalize the maxillary molars through the maxillary sinus by bodily movement. The findings were three-dimensionally confirmed by using the superimposition of CBCT obtained before and after the treatment.

Keywords: maxillary molar distalization; temporary anchorage devices; CBCT superimposition; maxillary sinus



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1. Introduction

In the nonextraction orthodontic treatment of Angle Class I, II, or both malocclusion(s), the treatment procedure occasionally involves distalization of the maxillary molars to ensure an ideal occlusion [1,2]. The use of temporary anchorage devices (TADs) techniques in recent years has made maxillary molar distalization efficient and feasible [3–7]. However, orthodontists are often faced with anatomical limitations, such as the maxillary sinus, that may compromise successful orthodontic tooth movement [4,8,9].

The maxillary sinus is the largest paranasal sinus, and histology has shown that most radiographically observed roots protruding into the maxillary sinus are surrounded by a thin cortical bone layer [10]. The maxillary sinus is known to prevent orthodontic movement; therefore, for the purpose of planning an appropriate treatment strategy, it is important to establish the anatomical relationship between the maxillary teeth roots and maxillary sinus floor [8]. When the latter protrudes into the maxillary sinus, apical root resorption and tipping may occur as the tooth horizontally moves across the sinus floor [11]. Furthermore, when the roots of the maxillary teeth intrude into the maxillary sinus, root resorption may be induced when the teeth vertically move [12]. In contrast with this general knowledge, several studies have demonstrated that teeth can be moved through the maxillary sinus without inducing any root resorption [4,9,13]. In other words, there is still no consensus on the association between the maxillary sinus and orthodontic treatment. It is thus necessary to evaluate the results of orthodontic treatment through the maxillary sinus using a reproducible, quantitative evaluation to establish an evidence-based safety protocol [8].

In orthodontics, the evaluation of treatment results, such as tooth movement and root resorption, is generally performed using two-dimensional (2D) panoramic radiography

and lateral and anteroposterior cephalometric measurements. Given the limitations of 2D radiography in assessing the topographic relationship between the roots of the maxillary teeth and sinus floor, it has been difficult to accurately establish the relationship between the three-dimensional (3D) tooth movement and root resorption [14,15]. Although some studies have reported successful orthodontic treatment through the maxillary sinus, only a few researchers have used a 3D evaluation method [4,9]. Instead, 3D analysis using cone-beam computed tomography (CBCT) images can provide a detailed and accurate assessment of root apices of the maxillary teeth and maxillary sinus [15,16].

In this report, we describe the treatment of a man with a skeletal Class I pattern and demonstrate the possibility of moving teeth through the maxillary sinus, which was confirmed on 3D evaluation using CBCT. We are the first to evaluate orthodontic tooth movement through the maxillary sinus using CBCT superimposition. Additionally, the results of this study support the usefulness of the pretreatment, post-treatment, and superimposition CBCT images for diagnosis and evaluation. Our findings provide valuable insights and can be used to avoid orthodontic treatment-related complications.

2. Materials and Methods

2.1. Case Report

A 20-year-old Japanese man presented with a chief complaint of the crowding of his anterior teeth. His pretreatment facial profile was straight with a mild retrusive upper lip that receded the E-line, and a mild protruded lower lip that exceeded the E-line (Figure 1). The frontal view was almost symmetrical, and the maxillary and mandibular dental midline almost coincided with the facial midline. When smiling, the gums were mildly exposed. Model analysis revealed Class I molar and Class II canine relationships on both sides, an overjet of 3.8 mm, an overbite of 5.3 mm, arch length discrepancies of -3.5 mm on the maxillary arch and -5.5 mm on the mandibular arch, a narrow maxilla, and buccal inclination of the maxillary second molars due to the posterior crowding. The maxillary third molars on both sides had erupted. The mandibular incisors had protruded, and a Spee curve was observed. The anterior tooth size ratio indicated that the size of the mandibular anterior teeth was slightly larger than that of the maxilla (Figure 2). Before treatment, panoramic and lateral cephalometric radiographs were obtained for diagnosis (Figure 3). The lateral cephalometric radiographs revealed the end of the skeletal growth period according to the cervical vertebral maturation, indicating that the patient was an adult [17]. Panoramic radiography revealed bilateral horizontally impacted third molars in the mandible, a mesial inclination of mandibular molars, and a maxillary sinus floor located inferiorly and close to the roots of the maxillary molars. After the panoramic radiography, CBCT was performed for a more detailed anatomical examination to extract the maxillary and mandibular third molars. The CBCT findings revealed that several roots of the maxillary molars protruded into the maxillary sinus (Figure 4). The cephalometric analysis (Table 1), compared with the Japanese norm, showed a skeletal Class I relationship (ANB angle, 3.5°). The mandibular plane was large (FMA, 32.4°). The maxillary incisor was labially inclined (U1 to FH, 116.5°), whereas the inclination of the mandibular incisors was within the normal range (FMIA, 56.0°).

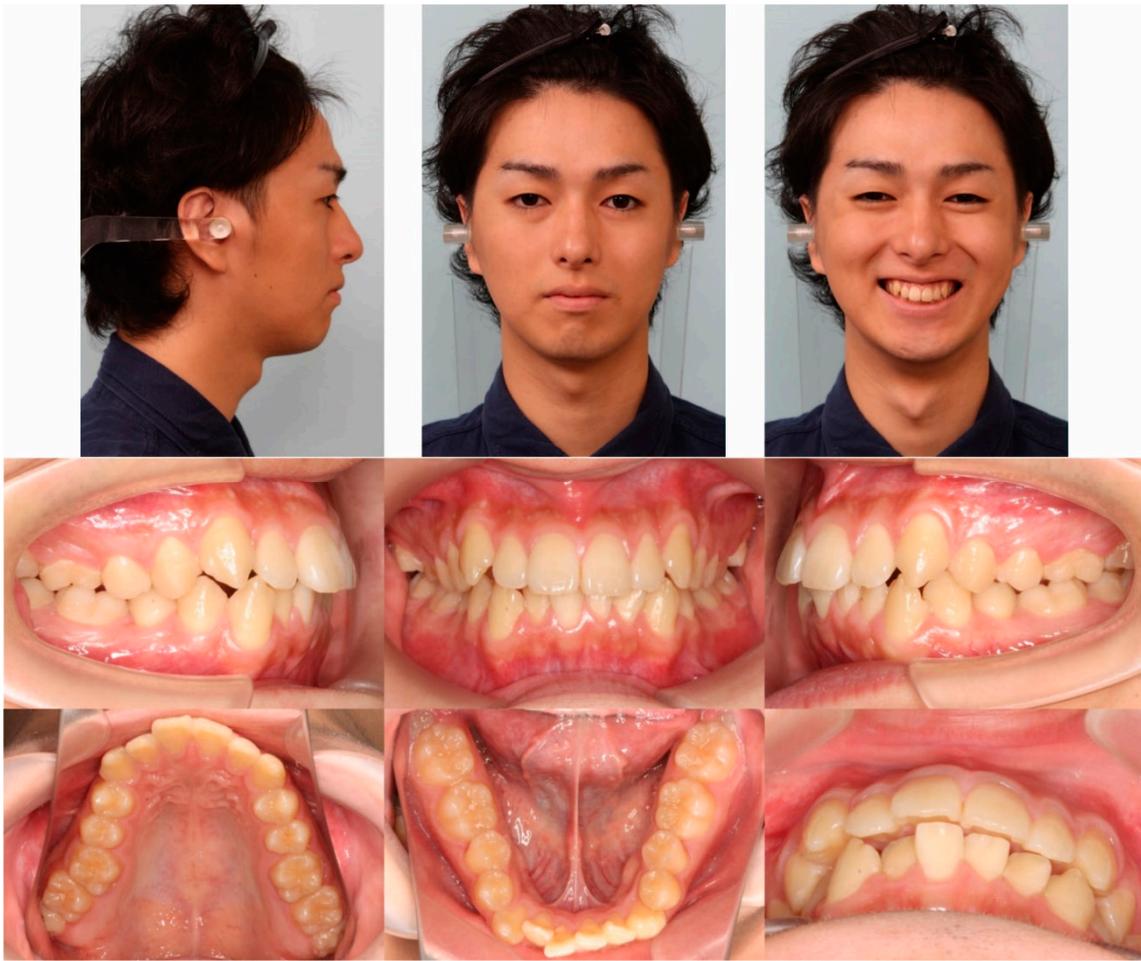


Figure 1. Pretreatment facial and intraoral photographs.



Figure 2. Pretreatment dental casts.

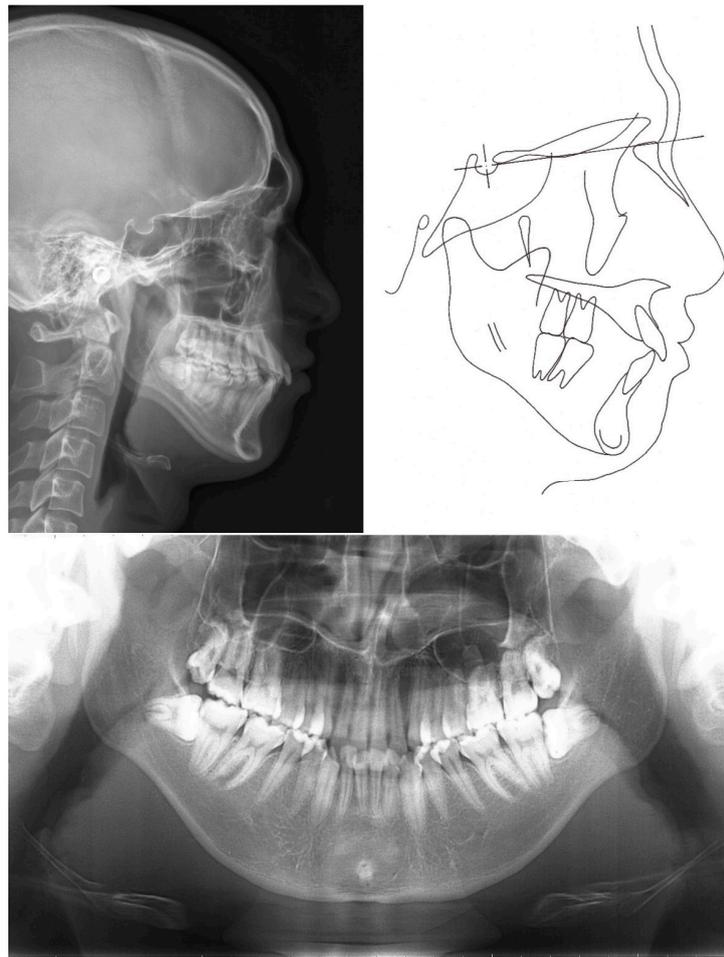


Figure 3. Pretreatment lateral cephalometric, cephalometric tracing, and panoramic radiographs.

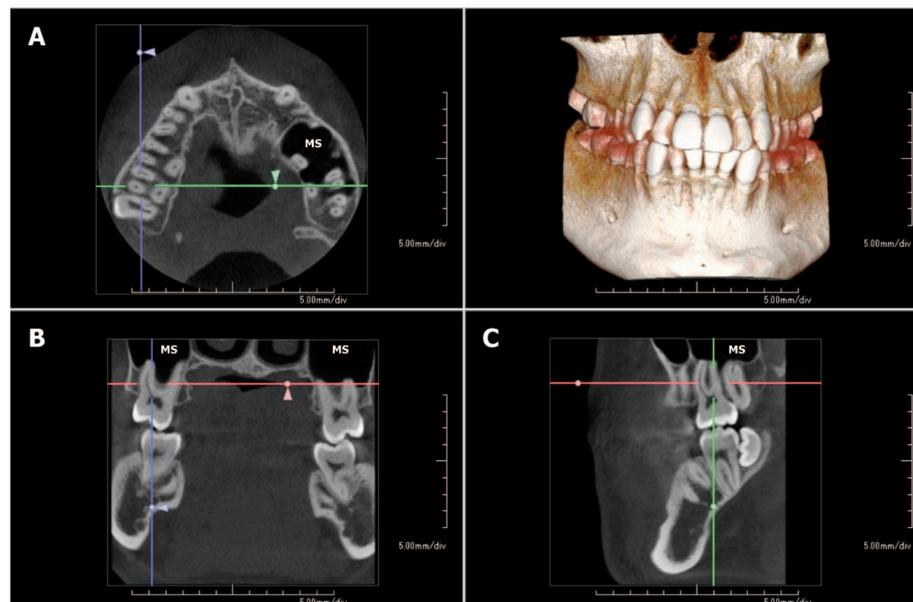


Figure 4. Pretreatment cone-beam computed tomography (CBCT) images of the relationships between the maxillary molars and the maxillary sinus. (A) Axial image; (B) coronal image; (C) sagittal image simultaneously. Abbreviation: MS, maxillary sinus.

Table 1. Cephalometric analysis.

Variables (Degrees)	Japanese Norm	Pretreatment	Post-Treatment	Retention
SNA	82.3 ± 3.5	79.8	79.8	79.8
SNB	78.9 ± 3.5	76.3	76.0	76.0
ANB	3.4 ± 1.8	3.5	3.9	3.9
FMA	28.8 ± 5.2	32.4	33.0	33.0
U1 to FH	111.1 ± 5.5	116.5	107.2	108.0
IMPA	96.3 ± 5.8	91.6	92.2	92.6
FMA	54.6 ± 6.5	56.0	54.8	55.3
Interincisal angle	121.4 ± 7.6	119.4	127.6	127.3

The treatment objectives were to (1) reduce the crowding, (2) establish a satisfactory occlusion with stable anterior and posterior supports, (3) establish the relationship between the Class I molar and canine on both sides, (4) align the maxillary incisors with the appropriate axis, (5) improve the patient's previously gum-revealing smile, and (6) induce appropriate overbite and overjet. To eliminate crowding and achieve Class I occlusion, distalization of the maxillary molars and making the mandibular molars upright were necessary. To distally move these molars, it was necessary to extract the maxillary and mandibular third molars because distal spacing with cancellous bone was required. TADs (Dualtop; Jeil Medical, Seoul, Korea) were used to achieve anchorage for the intrusion of the maxillary anterior teeth and distalization of the maxillary molars.

The following alternative treatment was presented to the patient: To eliminate the crowding of the incisors, we considered extracting the premolars. However, in the diagnostic setup model with the extraction of the maxillary premolars, the amount of movement of the maxillary molars through the maxillary sinus increased compared with the distalization of the maxillary molars without premolars extraction. In the present case, the maxillary sinus was extended to the mesial side of the maxillary molars, similarly to the distal side. This raised the concern that a large amount of mesial movement through the maxillary sinus could increase the risk of root resorption.

A treatment alternative that involved the extraction of the maxillary and mandibular premolars was also presented to the patient. The diagnostic setup model indicated that the required mesial movement of the molars was large and unrealistic. Moreover, the amount of retraction of the incisors was large, and there was a concern that the patient's lip would be retracted too much. The patient had a straight profile with a mildly retrusive upper lip. Because the patient was worried that his lip might retract as a result of the premolar extraction, he refused this option [18]. Therefore, we decided to extract only the maxillary and mandibular third molars and establish the Angle Class I molar relationships with molar distalization.

Prior to orthodontic treatment, the patient was referred to a maxillofacial surgeon for extraction of all of his third molars. For initial leveling, the 0.022 in preadjusted edgewise appliances (Tomy international, Tokyo, Japan) that were bonded to his maxillary and mandibular lateral teeth and 0.016 × 0.022-in improved super elastic nickel-titanium alloy archwires (ISW) were used. In addition, TADs were inserted between the maxillary first molar and second premolar on both sides to anchor them down better and to move the molars distally (Figure 5A). Four months later, there was clear progressions in the leveling and expansion of the maxillary and mandibular lateral teeth; the brackets were further bonded to the anterior teeth as well.



Figure 5. Progressive intraoral photographs. (A) Leveling of maxillary and mandibular lateral teeth; (B) distalization of the maxillary molars and uprighting of the mandibular molars; (C) distalization of the maxillary canines and premolars.

After leveling the maxillary teeth, the distalization of the maxillary molars was started using 0.018×0.025 inch stainless-steel archwires (SSWs). The maxillary second molars were distalized using 50 g nickel–titanium open-coil springs placed between the first and second molars on both sides, while tip-forward bends were incorporated into the archwire to prevent any further distal tipping of the second molars. In addition, we incorporated a step-up bend, toe-in bend, and torque into the archwire to prevent extrusion and rotation. At the same time, distalization of the maxillary first molars was started using 100 g nickel–titanium open-coil springs placed between the second premolars and first molars on both sides. Similar to the movement of the second molars, we controlled the movement of the maxillary first molars using bends. We used long hooks with elastic chains from the TADs that were placed in contact with the mesial aspect of the maxillary first premolars to prevent any reciprocal reaction. These long hooks were loosely crimped to the SSW such that they could slide distally, which successfully moved the maxillary premolars distally (Figure 5B). The maxillary first premolars and canines were also moved distally, in the same order, by the same method (Figure 5C). The buccal inclination of the maxillary second molars was also improved. Additionally, the anterior tooth crowding of the mandible was relieved by expanding and uprighting the molars using intermaxillary Class III elastics and an ISW with a reversed curve (Figure 5B). Finally, moderate stripping was performed on the mandibular anterior teeth to improve crowding and anterior tooth size ratio.

Fourteen months later, the molar and canine relationships were successfully corrected from Class II to Class I. Finally, retraction and intrusion of the maxillary anterior teeth were performed to induce appropriate overbite and overjet using TADs. The arch of dentition was gradually molded into the form of an ideal arch to tighten the occlusal relationships. Twenty-five months later, the multibracket appliances and TADs were removed. For retention, immediately following removal, a fixed lingual retainer was applied between the maxillary first premolars, and a circumferential-type retainer was placed in the maxilla. Moreover, a fixed lingual retainer was applied between the mandibular canines on both arches, and a Hawley-type retainer was placed in the mandible.

2.2. CBCT Superimposition

CBCT images were acquired pre- and post-treatment with approval from the Institutional Ethical Committee of the Tokyo Medical and Dental University (approval number: 1254). The purpose of using CBCT was explained to the subjects, and written consent was obtained thereafter from all subjects. All work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). CBCT images were acquired using the following settings: normal mode (16.8 s, 4.10 mGy, 90 kV, and 4 mA); slice thickness, 0.147 mm; field of view, 81 × 74 mm; and voxel size, 0.146 mm. Images were saved as digital imaging and communication in medicine (DICOM) files. CBCT images were reconstructed using 3D imaging software (OsiriX; Pixmeo, Geneva, Switzerland). The pre- and post-treatment CBCT DICOM dates were manually approximated by the same observer using best fits of the maxillary outlines in 3D multiplanar cross-sections using OsiriX [19,20]. Regions corresponding to anatomically stable structures were used as landmarks, such as the bilateral zygomatic processes of the maxilla (i.e., key ridge) and the anterior nasal spine because their consistency was amenable to the 3D superimposition of the maxilla [21].

3. Results

3.1. Treatment Results

Post-treatment facial photographs showed that the patient's profile was well-maintained without excessive receding of the lips and that his previously gum-revealing smile was improved as a result of the intrusion of his maxillary incisors. The patient's chief complaint, crowding of his maxillary and mandibular anterior teeth, was improved by orthodontic treatment consisting of maxillary and mandibular molar distalization (Figure 6). The post-treatment model analysis revealed that the patient achieved Class I molar and canine relationships, an overjet of 1.3 mm, and an overbite of 1.5 mm (Figure 7). When comparing the pre- and post-treatment dental cast model, the maxillary intercanine arch width increased by −1.2 mm, the inter-first-molar width increased by 2.7 mm, and the inter-second-molar width increased by −3.8 mm from pre- to post-treatment. The mandibular intercanine arch width increased by −1.5 mm, the inter-first-molar width increased by 2.9 mm, and the inter-second-molar width increased by 1.5 mm from pre- to post-treatment. Additionally, the anterior tooth size ratio improved with 1.8 mm stripping of the mandibular incisors. The post-treatment lateral cephalometric radiograph is shown in Figure 8, and the post-treatment cephalometric analysis is shown in Table 1. The post-treatment panoramic radiograph revealed no significant root resorption and demonstrated that root parallelism was successfully established (Figure 8). The pre- and post-treatment cephalometric superimposition (Figure 9) showed that the extents of distalization of the maxillary and mandibular first molars were 2.2 and 2.0 mm, respectively. The maxillary incisors had a 3.7 mm retraction and 1.6 mm intrusion, and the mandibular incisors had a 1.2 mm retraction and 2.2 mm intrusion.

After two years of retainer use, no significant relapse and change was observed (Figures 10–12). The occlusion was stable, and appropriate guidance of lateral movement and grinding was confirmed.

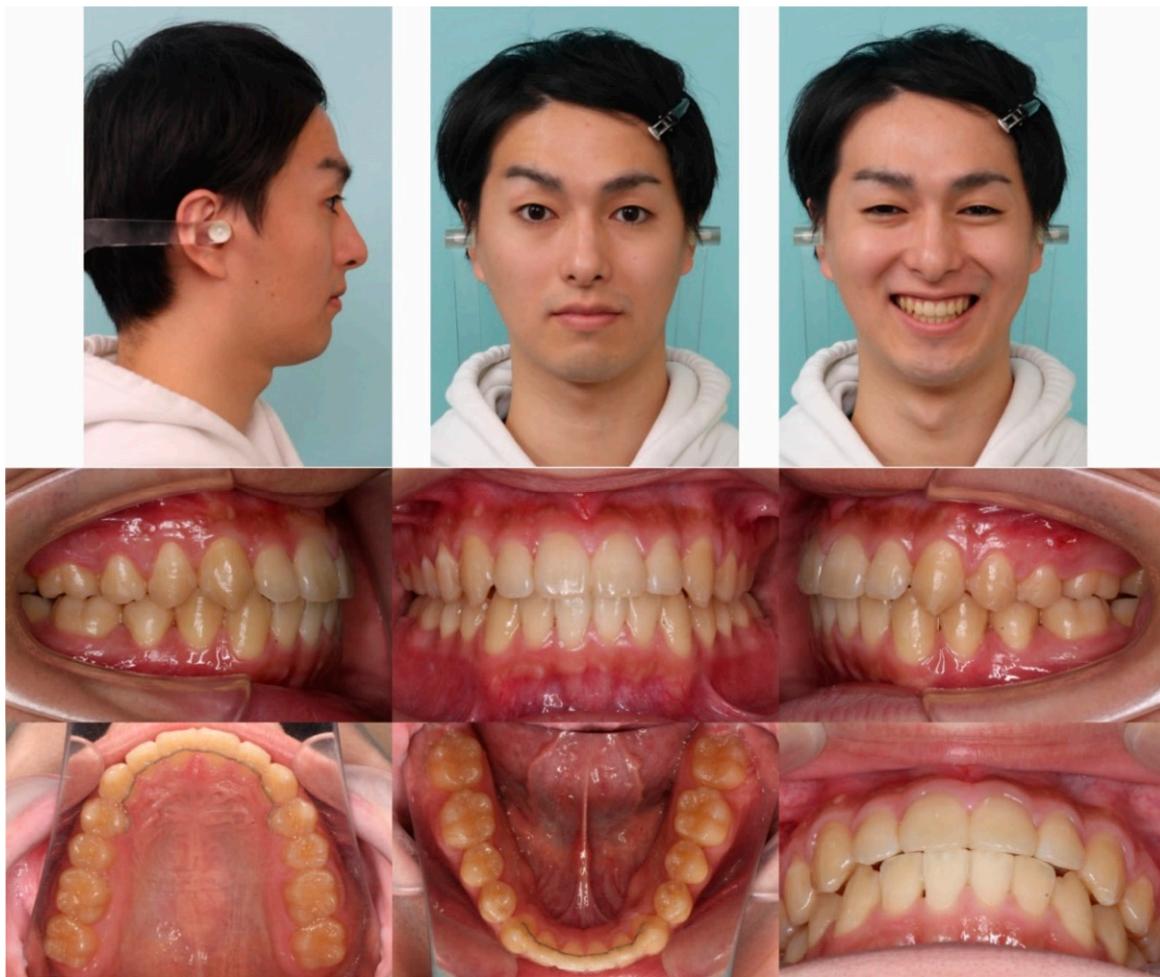


Figure 6. Post-treatment facial and intraoral photographs.

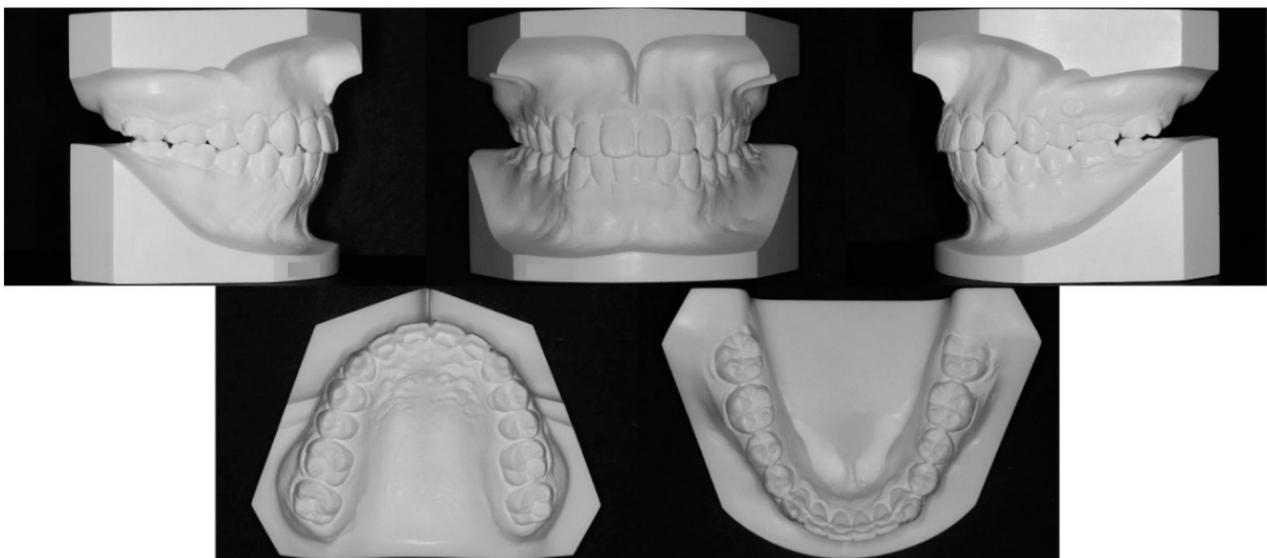


Figure 7. Post-treatment dental casts.

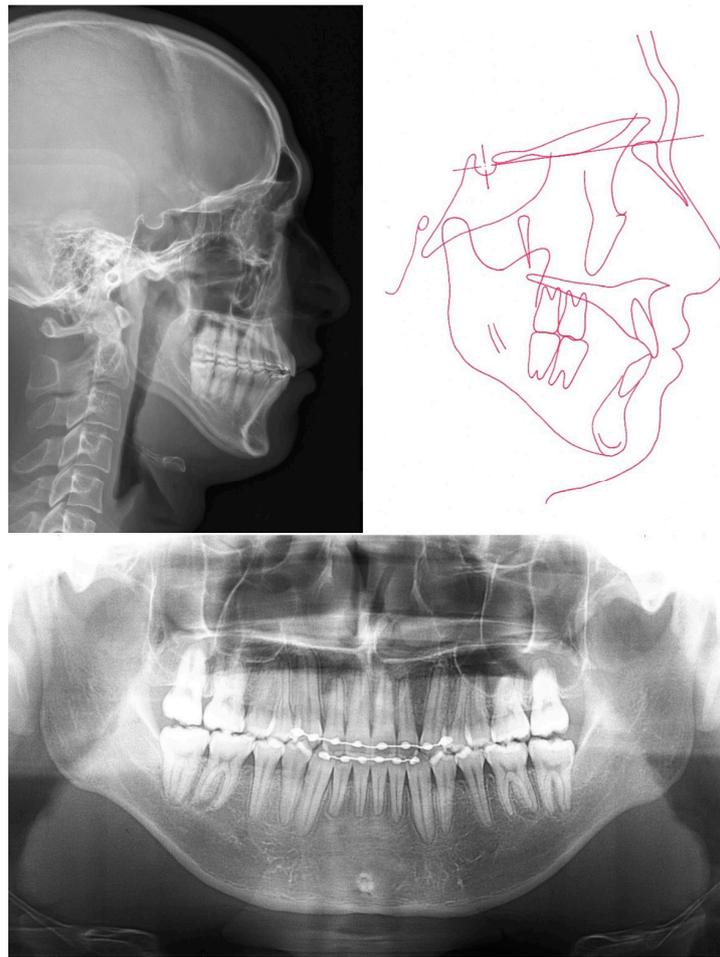


Figure 8. Post-treatment lateral cephalometric, cephalometric tracing, and panoramic radiographs.

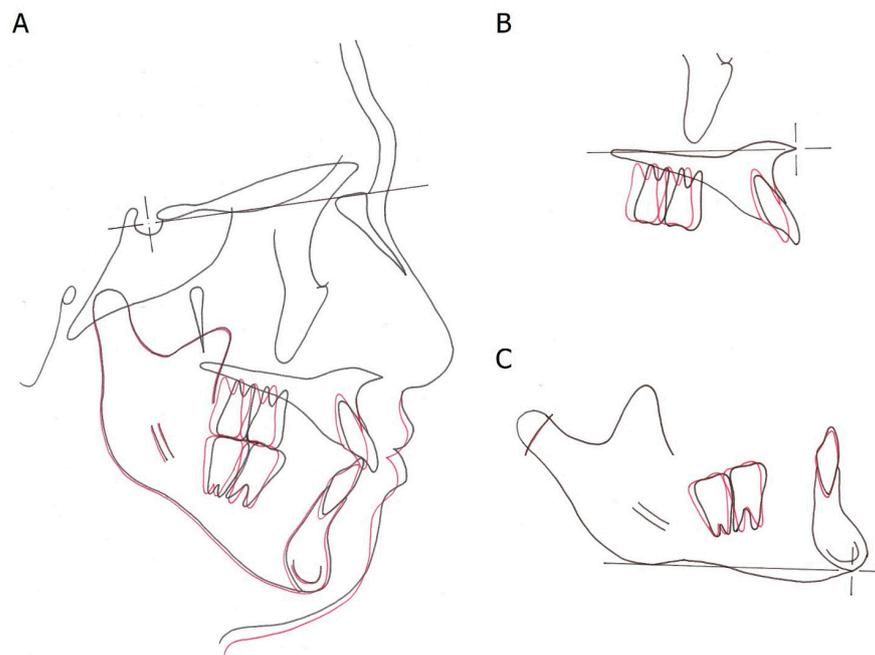


Figure 9. Superimposed tracings of the pre- and post-treatment lateral cephalometric radiographs. (A) on the sella-nasion plane at sella; (B) on the palatal plane at ANS; (C) on the mandibular plane at menton.



Figure 10. Facial and intraoral photographs after 2 years of retention.



Figure 11. Two-year retention dental casts.

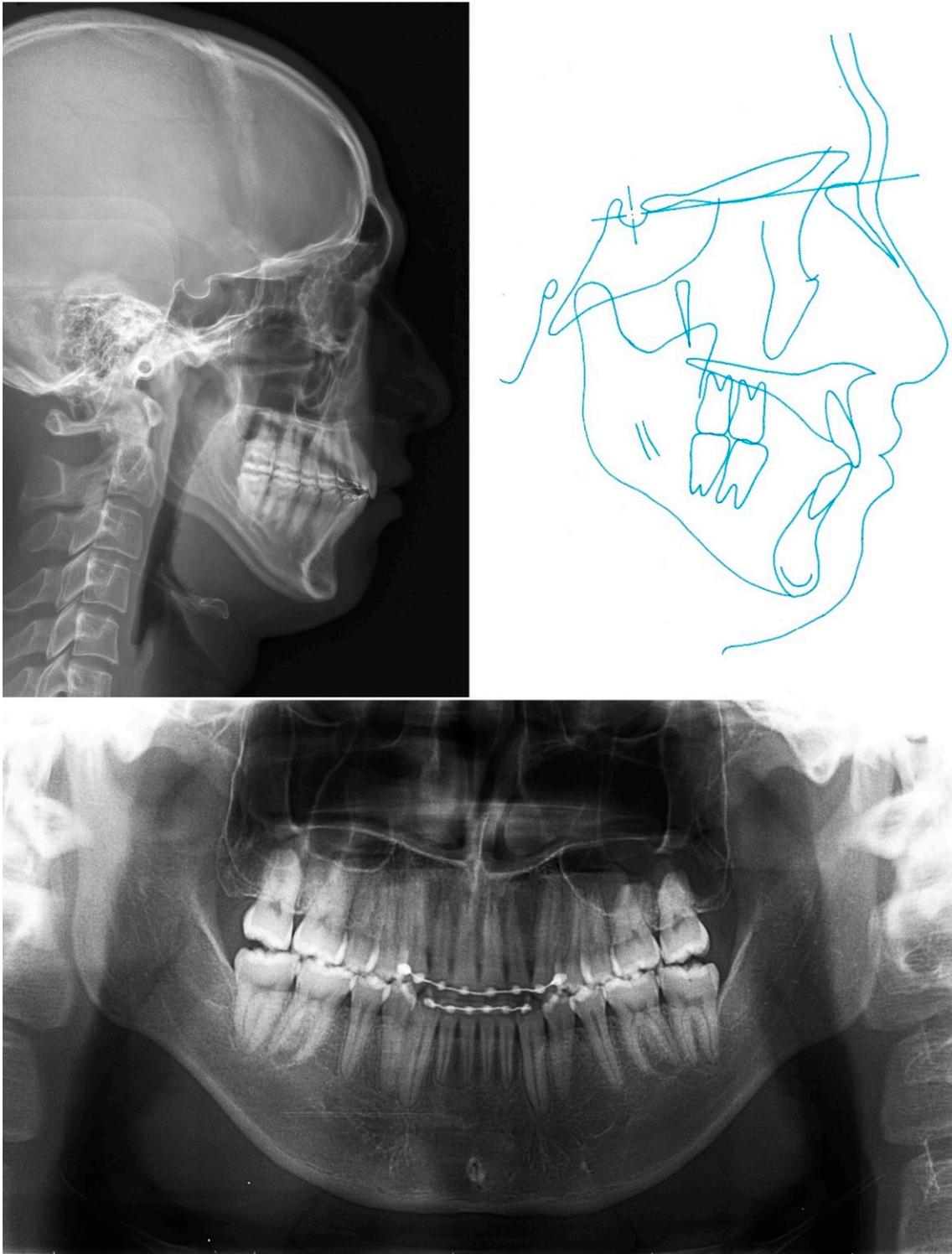


Figure 12. Lateral cephalometric, cephalometric tracing, and panoramic radiographs after 2 years of retention.

3.2. CBCT Superimposition

Pre- and post-treatment CBCT images and 3D superimposition of the maxilla from the CBCT images are shown in Figures 13 and 14, respectively. The pretreatment CBCT indicated that the roots of the maxillary premolars and molars protruded into the maxillary sinus (Figure 13F,J; Figure 14B,F,J,N). The post-treatment CBCT showed that these maxillary

roots had moved without inducing any root resorption (Figure 13G,K; Figure 14C,G,K,O). CBCT superimposition showed that the crowns and roots of the maxillary teeth had distally moved (Figure 13D,H,L; Figure 14D,H,L,P). CBCT superimposition showed that the roots of the maxillary molars on both sides had disto-palatally moved (Figure 13H,L). When the movement of the roots in the right first molar was measured using Figure 13L as an example, the mesio-buccal root had moved 1.49 mm distally and 0.47 mm palatally, the disto-buccal root had moved 2.28 mm distally and 0.92 mm palatally, and the palatal root had moved 0.48 mm distally and 0.49 mm palatally. In the right second molar, the mesio-buccal root had moved 3.08 mm distally and 0.53 mm palatally, the disto-buccal root had moved 3.19 mm distally and 1.55 mm palatally, and the palatal root had moved 1.96 mm distally and 1.63 mm palatally (Table 2). After a 3-month interval, the pre- and post-treatment CBCT images were superimposed again, and all measurements were repeated to check the intraexaminer reliability. All operations were performed by a single examiner. A paired t-test performed using SPSS software (version 20; IBM, Armonk, NY, USA) showed no significant differences between the two measurements. Dahlberg's formula was used to calculate the method error [22]. Thus, pre- and post-treatment CBCT image evaluations provide detailed treatment results that are not visible in the 2D radiographic images and are useful information for future treatment.

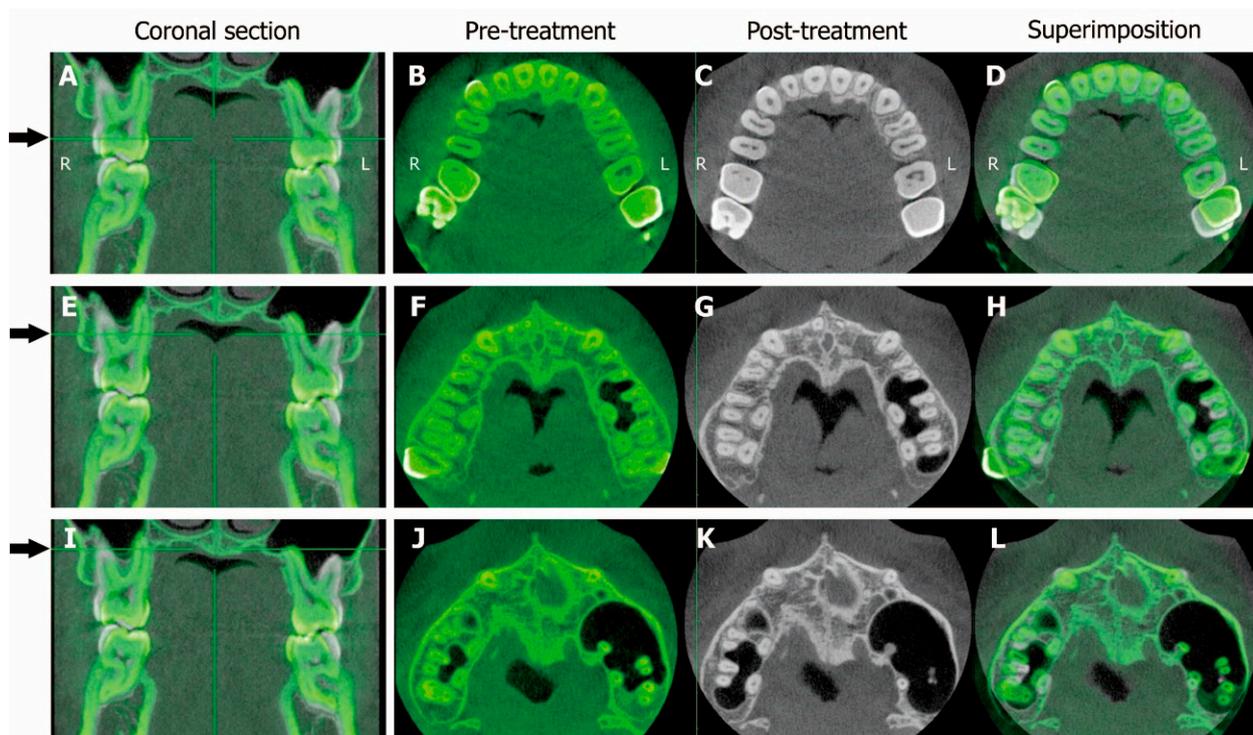


Figure 13. Three-dimensional cone-beam computed tomography (CBCT) images of the relationships between the maxillary molars and maxillary sinus. (A–D) CBCT coronal section at the crown level of the maxillary first molars (*arrow*), CBCT axial sections at post-treatment (*gray*) and pretreatment (*green*), and their superimposition; (E–H) CBCT coronal section at the root level of the maxillary first molars (*arrow*), CBCT axial sections at post-treatment (*gray*) and pretreatment (*green*), and their superimposition; (I–L) CBCT coronal section at the root apex level of the maxillary first molars (*arrow*), CBCT axial sections at post-treatment (*gray*) and pretreatment (*green*), and their superimposition.

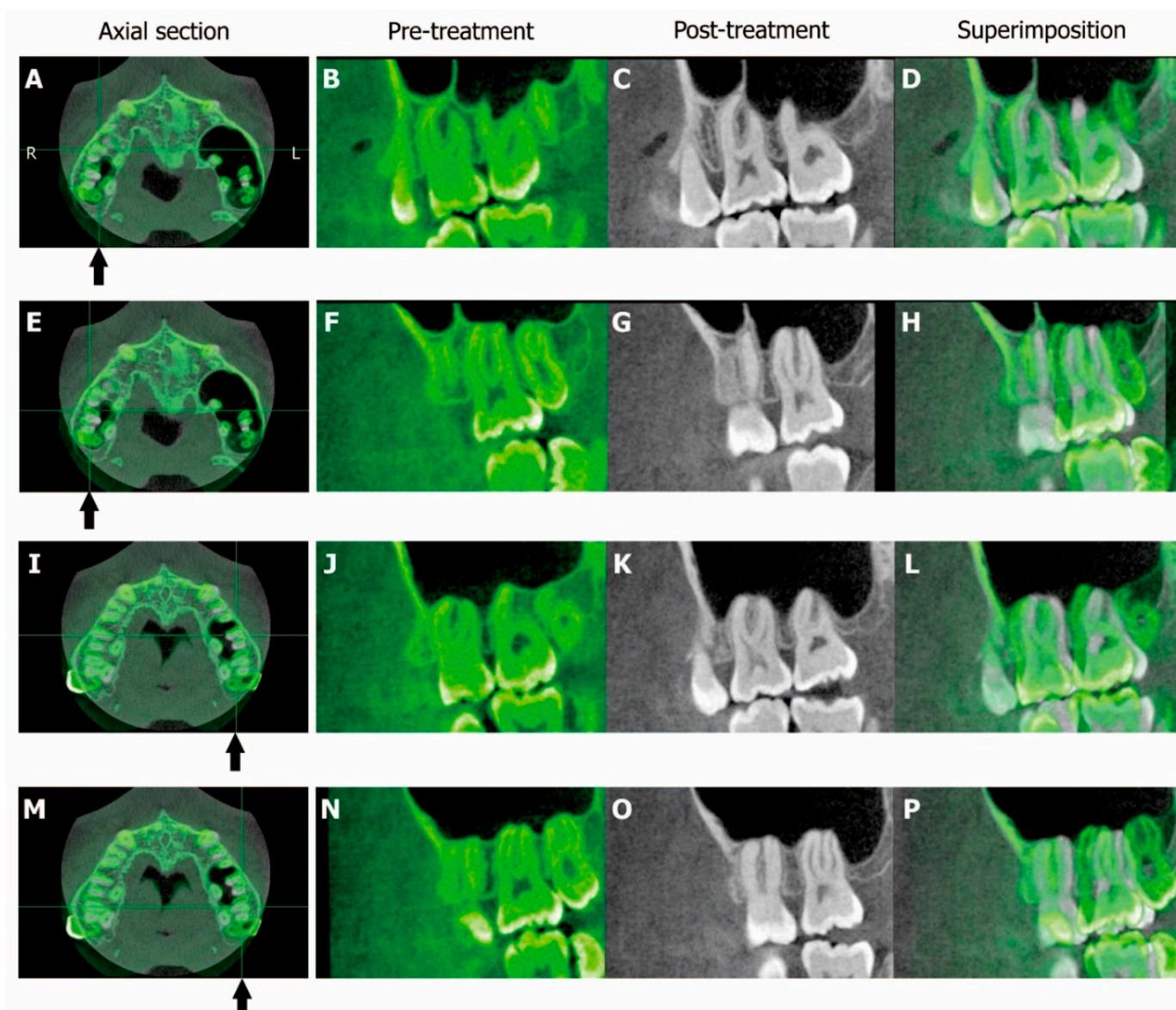


Figure 14. Three-dimensional cone-beam computed tomography (CBCT) images of the relationships between the maxillary molars and maxillary sinus. (A–D) CBCT axial section at the right first molar level (*arrow*), CBCT sagittal sections at post-treatment (*gray*) and pretreatment (*green*), and their superimposition; (E–H) CBCT axial section at the right second molar level (*arrow*), CBCT sagittal sections at post-treatment (*gray*) and pretreatment (*green*), and their superimposition; (I–L) CBCT axial section at the left first molar level (*arrow*), CBCT sagittal sections at post-treatment (*gray*) and pretreatment (*green*), and their superimposition; (M–P) CBCT axial section at the left second molar level (*arrow*), CBCT sagittal sections at post-treatment (*gray*) and pretreatment (*green*), and their superimposition.

The distances were recorded on cone-beam computed tomography images as positive values if the crowns or roots moved palatally and negative values if the crown or root moved buccally. Abbreviations: 6C, the crown of the right first molar; 7C, the crown of the right second molar; 6MB, the mesio-buccal root of the right first molar; 6DB, the disto-buccal root of the right first molar; 6P, the palatal root of the right first molar; 7MB, the mesio-buccal root of the right second molar; 7DB, the disto-buccal root of the right second molar; 7P, the palatal root of the right second molar; UM, unmeasurable.

Table 2. Distal and palatal movement of the maxillary first and second molars measured with superimposed CBCT images.

Superimposition	Figure 13D		Figure 13H						Figure 13L					
	6C	7C	6MB	6DB	6P	7MB	7DB	7P	6MB	6DB	6P	7MB	7DB	7P
Right side														
Distal movement (mm)	2.06	3.01	2.12	2.25	0.76	2.42	3.10	2.91	1.49	2.28	0.48	3.08	3.19	1.96
Palatal movement (mm)	−1.97	2.67	0.31	0.35	0.46	1.14	1.56	2.07	0.47	0.92	0.49	0.53	1.55	1.63
Left side														
Distal movement (mm)	2.23	2.61	2.58	2.35	0.46	2.49	2.78	2.23	UM	UM	UM	UM	UM	UM
Palatal movement (mm)	−1.15	2.80	0.88	1.56	0.34	0.94	1.24	1.80	UM	UM	UM	UM	UM	UM

4. Discussion

In this patient, we performed distal movement of the maxillary molars, premolars, and canines to reduce the crowding using TADs [1,2,4]. In addition, we performed uprighting of the mandibular molars to eliminate mandibular anterior crowding and established Angle Class I relationships [1]. Because we had extracted the third molars, there was enough bone in the posterior maxilla and mandible to induce molar distalization [1,2,5]. Previous clinical reports have suggested a treatment plan that includes distalization of the mandibular or maxillary dentition to correct Class I or Class II malocclusion is preferred because this method avoids extraction [1,2,4,23]. However, in this patient, the maxillary sinus floor was inferiorly located and appeared to be in the vicinity of the roots of the maxillary molars, according to the pretreatment panoramic radiograph [14]. Furthermore, 3D analysis based on the CBCT images indicated that most roots of the maxillary molars contacted or protruded into the maxillary sinus floor [15,16]. Thus, the risks of tipping and root resorption during orthodontic treatment were high [10,11].

The maxillary floor and bone-deficient areas of the sinus are known barriers to successful orthodontic tooth movement [4,8,10–12]. Tipping and root resorption may be induced while the tooth horizontally moves across the sinus floor [11]. Therefore, orthodontic treatment through the maxillary sinus is considered challenging [10–12]. However, several recent case reports have shown that bodily movement can be achieved during orthodontic treatment through the maxillary sinus to close a tooth extraction space [4,9,13,24]. Additionally, a previous animal study indicated that bone reduction of the maxillary sinus and root resorption could be avoided by applying an optimum force [25]. In contrast, excessive orthodontic force was suggested to induce root resorption during orthodontic treatment through the maxillary sinus [26]. In general, the degree of root resorption depends on both the orthodontic force strength and the duration [27]. The application of heavy forces during orthodontic tooth movement causes increases in the severity and incidence of root resorption [25,26]. According to previous reports, applying a constant force of 50–200 g is recommended during orthodontic treatment through the maxillary sinus [4,9,13,24].

Therefore, we used the ISW for the initial leveling of maxillary posterior crowding, especially for the buccal inclination of the second molars. An ISW can maintain the shape into which it is molded, is superelastic, and is amenable to applying light, continuous orthodontic force [2,3,28,29]. After leveling the maxillary teeth using the ISW, distalization of the maxillary molars was initiated with 100 g and 50 g nickel–titanium open-coil springs (the first and second molars, respectively) on both sides, using the SSW. As a result, tooth movement was achieved through the maxillary sinus using light force throughout the orthodontic treatment, as referred to in previous reports [4,9,13,24]. However, evidence to date related to orthodontic treatment through the maxillary sinus is based on only a few case reports [8]. In this case, based on the superposition of CBCT, we confirmed that the roots of the maxillary molars not only distally moved through the maxillary sinus but also moved in the palatal direction without inducing any considerable root resorption. Changes in the surrounding tissues of the roots were also confirmed with the tooth movement

through the maxillary sinus. Alveolar bone remodeling was visible around the roots after moving through the maxillary sinus.

In general, the evaluation of orthodontic treatment has been performed using panoramic and cephalometric radiographs. Although these radiographs are widely available and allow visualization of the various anatomic structures at low doses of radiation [30], they lack 3D information [14,30]. CBCT images overcome these limitations by providing multiplanar images in three dimensions with high spatial resolution [15]. In particular, an evaluation of the movement in coronal and bucco-palatal directions is considered useful because it cannot be obtained using the 2D images from lateral cephalometric radiographs. In addition, it can visually confirm the bodily movement of the maxillary teeth through the maxillary sinus in the pre- and post-treatment CBCT superimposition. This is one of the few reports of distal movement of the maxillary molars through the maxillary sinus [8] and the first report of orthodontic bodily movement in the palatal direction. To the best of our knowledge, this is the first report of the evaluation of palatal root movement through the maxillary sinus. According to a cross-sectional study [20], the proportion of the palatal roots protruding into the maxillary sinus showed a high probability. However, even in previous studies in which the tooth moved through the maxillary sinus [4,9,13,24], the movement of the mesial and distal buccal roots of the molars could be confirmed, but the movement of the palatal roots was not evaluated. In other words, the movement of the molars was not accurately understood. Therefore, the accurate evaluation of the palatal root movement can provide useful information for clinicians.

As reported in the results, the pre- and post-treatment CBCT images were helpful for diagnosis and evaluation of treatment. However, cases need to be cautiously selected because using CBCT is associated with radiation exposure. CT imaging should be performed for safety when several roots seem to protrude to the maxillary sinus according to the 2D radiographs. There is a high possibility of root resorption during 3D tooth movement, such as molar intrusion to the maxillary sinus or mesio-distal and bucco-palatal directional movement through the maxillary sinus [11,12]. The degree of intrusion through the maxillary sinus can affect the difficulty of orthodontic treatment [20,31]. Therefore, knowledge of the proximity of the maxillary root apices to the sinus floor is important for the safe delivery of orthodontic treatment and the prevention of any associated problems.

5. Conclusions

We demonstrated that bodily movement of the maxillary molars through the maxillary sinus could be performed in the distal and palatal directions. Additionally, the pre- and post-treatment CBCT images were useful for the diagnosis and evaluation of the patient, respectively. In particular, CBCT superimposition image evaluations provided detailed treatment results that were not visible in 2D radiographic images and useful information.

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Informed Consent Statement: Informed consent was obtained from all the individuals involved in the study.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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